Histology- and molecularly-driven medical therapy of STS

Silvia Stacchiotti
silvia.stacchiotti@istitutotumori.mi.it

Disclosure:

Bayer, Glaxo, Novartis, Pfizer

- Research funds, travel coverage

Amgen

- Honoraria, research funds

Plexxicon/Daiichi, Karyopharm, Lilly, Pharmamar

- Advisory role, Honoraria, research funds

Adipocytic tumours
- Well deifferentiated / dedifferentiated liposarcoma
- Myxoid / round cell liposarcoma
- Pleomorphic liposarcoma
- …..

Fibroblastic / myofibroblastic tumours
- Fibromatosis (desmoid)
- Solitary fibrous tumour / haemangiopericytoma
- Low grade myofibroblastic tumour
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Mixofibrosarcoma
- …..

So-called fibrohistiocytic tumours
- Pleomorphic MFH / Undifferentiated pleomorphic sarcoma
- …..

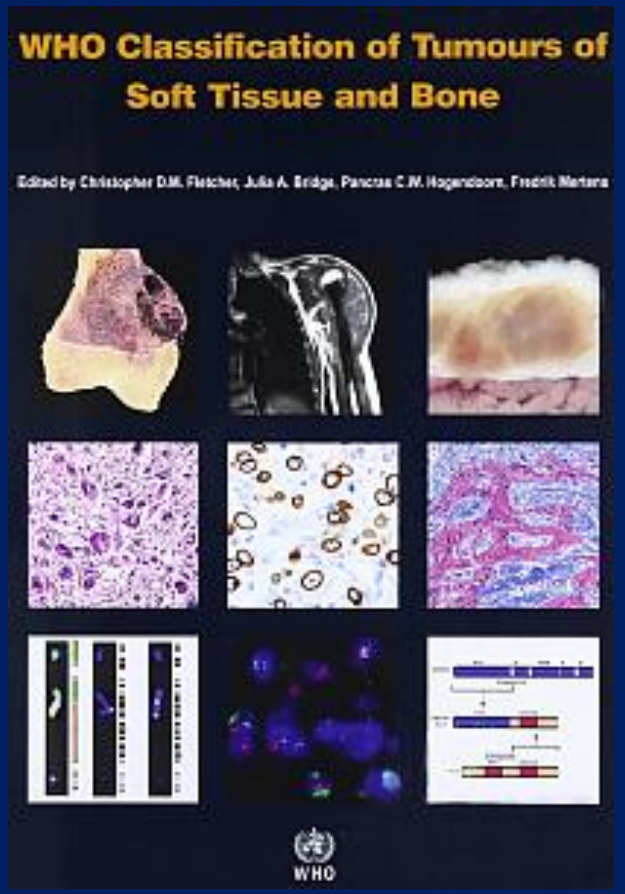
Smooth muscle tumours
- Leiomyosarcoma
- …..

Skeletal muscle tumours
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

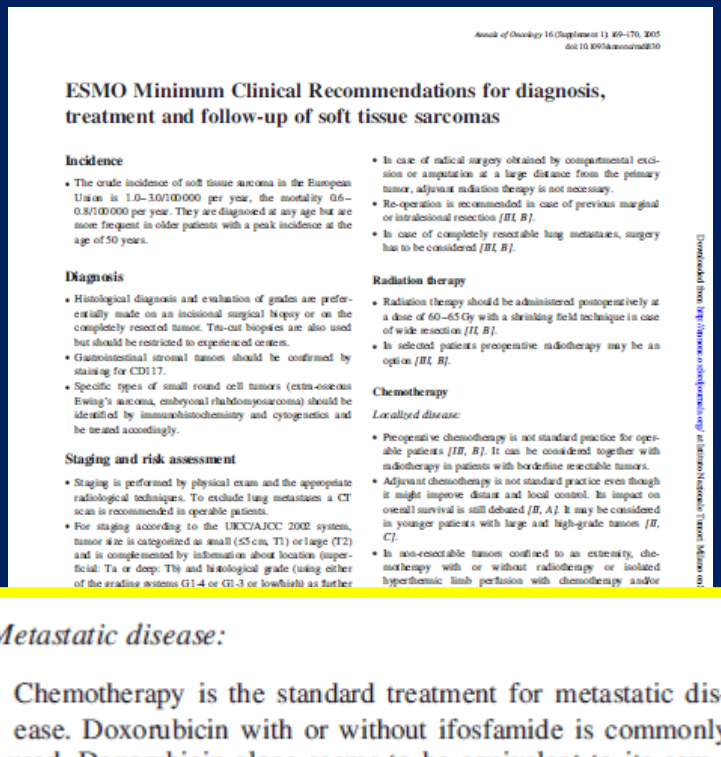
Vascular tumours
- Epithelioid haemangioendothelioma
- Angiosarcoma of soft tissue
- …..

Chondro-osseous tumours
- Mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

Tumours of uncertain differentiation
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing tumour
- Desmoplastic small round cell tumour
- Extra-renal rhabdoid tumour
- Malignant mesenchymoma
- Neoplasms with perivascular epithelioid cell differentiation (PEComa)
- Intimal sarcoma



Fletcher C et al, WHO 2013



Annals of Oncology 16 (Supplement 1): i59–i70, 2005
doi:10.1093/annonc/mdi830

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of soft tissue sarcomas

Incidence

- The crude incidence of soft tissue sarcoma in the European Union is 1.0–3.0/100 000 per year, the mortality 0.6–0.8/100 000 per year. They are diagnosed at any age but are more frequent in older patients with a peak incidence at the age of 50 years.

Diagnosis

- Histological diagnosis and evaluation of grades are preferentially made on an incisional surgical biopsy or on the completely resected tumor. Tru-cut biopsies are also used but should be restricted to experienced centers.
- Gastrointestinal stromal tumors should be confirmed by staining for CD117.
- Specific types of small round cell tumors (extra-osseous Ewing's sarcoma, embryonal rhabdomyosarcoma) should be identified by immunohistochemistry and cytogenetics and be treated accordingly.

Staging and risk assessment

- Staging is performed by physical exam and the appropriate radiological techniques. To exclude lung metastases a CT scan is recommended in operable patients.
- For staging according to the UICC/AJCC 2002 system, tumor size is categorized as small (≤5 cm, T1) or large (T2) and is complemented by information about location (superficial: Ta or deep: Tb) and histological grade (using either of the grading systems G1-4 or G1-3 or low/high) as further

- In case of radical surgery obtained by compartmental excision or amputation at a large distance from the primary tumor, adjuvant radiation therapy is not necessary.
- Re-operation is recommended in case of previous marginal or intralesional resection *[III, B]*.
- In case of completely resectable lung metastases, surgery has to be considered *[III, B]*.

Radiation therapy

- Radiation therapy should be administered postoperatively at a dose of 60–65 Gy with a shrinking field technique in case of wide resection *[II, B]*.
- In selected patients preoperative radiotherapy may be an option *[III, B]*.

Chemotherapy

Localized disease:

- Preoperative chemotherapy is not standard practice for operable patients *[III, B]*. It can be considered together with radiotherapy in patients with borderline resectable tumors.
- Adjuvant chemotherapy is not standard practice even though it might improve distant and local control. Its impact on overall survival is still debated *[II, A]*. It may be considered in younger patients with large and high-grade tumors *[II, C]*.
- In non-resectable tumors confined to an extremity, chemotherapy with or without radiotherapy or isolated hyperthermic limb perfusion with chemotherapy and/or

Metastatic disease:

- Chemotherapy is the standard treatment for metastatic disease. Doxorubicin with or without ifosfamide is commonly used. Doxorubicin alone seems to be equivalent to its combinations with other agents with regard to survival, despite a higher response rate with combination regimens *[II, B]*.
- Imatinib (STI 571, a tyrosine kinase receptor inhibitor) is the treatment of choice for gastro-intestinal stromal tumors (GIST).

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii21–iii26, 2014
doi:10.1093/annonc/mdu255

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ES

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

incidence

Adult soft tissue and visceral sarcomas (excluding gastrointestinal stromal tumour) are rare tumours, with an estimated incidence averaging 4–5/100 000/year in Europe [1].

diagnosis

Soft tissue sarcomas (STSs) are ubiquitous in their site of origin and are often managed with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists, organ-based specialists, as applicable). Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which sarcoma patients' enrolment is common. This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with a unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm. Quality criteria are needed for sarcoma reference centres and, all the more, reference networks. These criteria may vary from country to country but, among others, should be based on: multidisciplinarity (incorporating tools such as weekly

Extraskeletal Ewing sarcoma is covered by other ESMO Guidelines in general, the same principles for these tumours in children apply to adults. This is also the case for embryonal and alveolar rhabdomyosarcoma, which are exceedingly rare in adults. On the other hand, pleomorphic rhabdomyosarcoma is viewed as a high-grade adult-type soft tissue sarcoma. Gastrointestinal stromal tumours are covered by the dedicated ESMO Clinical Practice Guidelines. Kaposi's sarcoma is excluded.

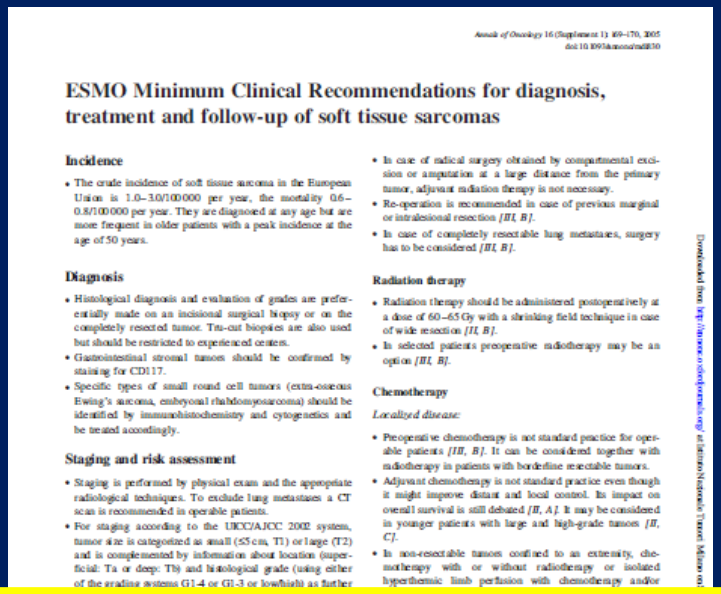
tumour boards discussing new cases), volume of patients, availability of facilities needed to properly apply clinical practice guidelines, recording and publication of outcomes.

In soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk. Standard radiographs may be useful to rule out a bone tumour, to detect bone erosion with a risk of fracture and to show calcifications. Computed tomography (CT) has a role in calcified lesions to rule out a myositis ossificans, and in retroperitoneal tumours, where the performance is identical to MRI. Ultrasound may be the first exam, but it should be followed by CT or MRI.

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies, possibly by using 2/14–16 G needles. However, an excisional biopsy may be the most practical option for <3 cm superficial lesions. An open biopsy may be another option in selected cases, as decided within reference centres. An immediate evaluation of tissue viability may be considered, to ensure that the biopsy is adequate at the time it is carried out. However, a frozen-section technique for immediate diagnosis is not encouraged, because it generally does not allow a complete diagnosis, particularly when preoperative treatment is planned. Fine needle aspiration is used only in some institutions, which have developed specific expertise on this procedure, and is not recommended outside these centres. A biopsy may underestimate the tumour malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging (including positron emission tomography, PET) may be useful, in addition to pathology, in providing the clinician with information that helps to estimate the malignancy grade (i.e. necrosis). The biopsy should be carried out by a surgeon or a radiologist, after multidisciplinary discussion, as needed, within reference centres. It should be planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery (except for retroperitoneal sarcomas, RPS). The biopsy entrance point can be tattooed. The tumour sample should be fixed in 4% buffered formalin in due time (Bouin fixation should not be used, since it prevents molecular analysis). The collection of fresh/frozen tissue and tumour imprints (touch preps) is encouraged, because new molecular pathology assessments could be made at a later stage in the patient's interest. In this perspective, the availability of a blood sample could add to the value of tumour tissues. Informed consent for biobanking should be sought, enabling later analyses and research, as long as this is allowed by local and international rules.

clinical practice guidelines

2005 2014



Annals of Oncology 16 (Supplement 1): i69–i70, 2005
doi:10.1093/annonc/mdi830

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of soft tissue sarcomas

Incidence

- The crude incidence of soft tissue sarcoma in the European Union is 1.0–3.0/100 000 per year, the mortality 0.6–0.8/100 000 per year. They are diagnosed at any age but are more frequent in older patients with a peak incidence at the age of 50 years.

Diagnosis

- Histological diagnosis and evaluation of grades are preferentially made on an incisional surgical biopsy or on the completely resected tumor. Tru-cut biopsies are also used but should be restricted to experienced centers.
- Gastrointestinal stromal tumors should be confirmed by staining for CD117.
- Specific types of small round cell tumors (extra-osseous Ewing's sarcoma, embryonal rhabdomyosarcoma) should be identified by immunohistochemistry and cytogenetics and be treated accordingly.

Staging and risk assessment

- Staging is performed by physical exam and the appropriate radiological techniques. To exclude lung metastases a CT scan is recommended in operable patients.
- For staging according to the UICC/AJCC 2002 system, tumor size is categorized as small (≤5 cm, T1) or large (T2) and is complemented by information about location (superficial: Ta or deep: Tb) and histological grade (using either of the grading systems G1-4 or G1-3 or low/high) as further

- In case of radical surgery obtained by compartmental excision or amputation at a large distance from the primary tumor, adjuvant radiation therapy is not necessary.
- Re-operation is recommended in case of previous marginal or intralesional resection *[III, B]*.
- In case of completely resectable lung metastases, surgery has to be considered *[III, B]*.

Radiation therapy

- Radiation therapy should be administered postoperatively at a dose of 60–65 Gy with a shrinking field technique in case of wide resection *[II, B]*.
- In selected patients preoperative radiotherapy may be an option *[III, B]*.

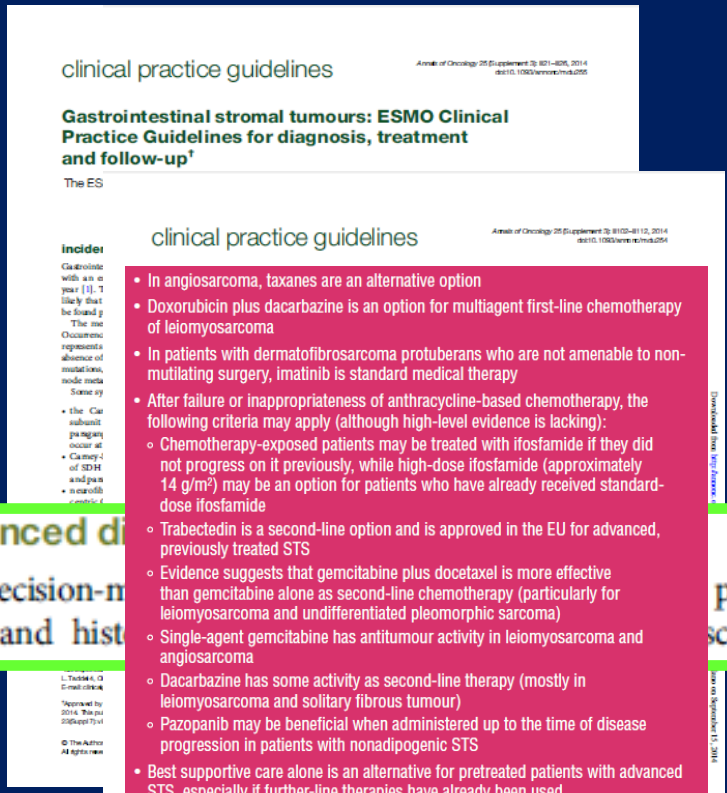
Chemotherapy

Localized disease:

- Preoperative chemotherapy is not standard practice for operable patients *[III, B]*. It can be considered together with radiotherapy in patients with borderline resectable tumors.
- Adjuvant chemotherapy is not standard practice even though it might improve distant and local control. Its impact on overall survival is still debated *[II, A]*. It may be considered in younger patients with large and high-grade tumors *[II, C]*.
- In non-resectable tumors confined to an extremity, chemotherapy with or without radiotherapy or isolated hyperthermic limb perfusion with chemotherapy and/or

Metastatic disease:

- Chemotherapy is the standard treatment for metastatic disease. Doxorubicin with or without ifosfamide is commonly used. Doxorubicin alone seems to be equivalent to its combinations with other agents with regard to survival, despite a higher response rate with combination regimens *[II, B]*.
- Imatinib (STI 571, a tyrosine kinase receptor inhibitor) is the treatment of choice for gastro-intestinal stromal tumors (GIST).



clinical practice guidelines

Annals of Oncology 25 (Supplement 3): 821–826, 2014
doi:10.1093/annonc/mdu255

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ES

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

- In angiosarcoma, taxanes are an alternative option
- Doxorubicin plus dacarbazine is an option for multiagent first-line chemotherapy of leiomyosarcoma
- In patients with dermatofibrosarcoma protuberans who are not amenable to non-mutilating surgery, imatinib is standard medical therapy
- After failure or inappropriateness of anthracycline-based chemotherapy, the following criteria may apply (although high-level evidence is lacking):
  - Chemotherapy-exposed patients may be treated with ifosfamide if they did not progress on it previously, while high-dose ifosfamide (approximately 14 g/m²) may be an option for patients who have already received standard-dose ifosfamide
  - Trabectedin is a second-line option and is approved in the EU for advanced, previously treated STS
  - Evidence suggests that gemcitabine plus docetaxel is more effective than gemcitabine alone as second-line chemotherapy (particularly for leiomyosarcoma and undifferentiated pleomorphic sarcoma)
  - Single-agent gemcitabine has antitumour activity in leiomyosarcoma and angiosarcoma
  - Dacarbazine has some activity as second-line therapy (mostly in leiomyosarcoma and solitary fibrous tumour)
  - Pazopanib may be beneficial when administered up to the time of disease progression in patients with nonadipogenic STS
- Best supportive care alone is an alternative for pretreated patients with advanced STS, especially if further-line therapies have already been used
- Radiotherapy should be used on a palliative basis in all cases, as appropriate to the clinical need
- In general, previously treated patients with advanced STS are candidates for clinical trials
- There is anecdotal evidence of activity for crizotinib, sunitinib and cediranib in selected histological types

advanced di

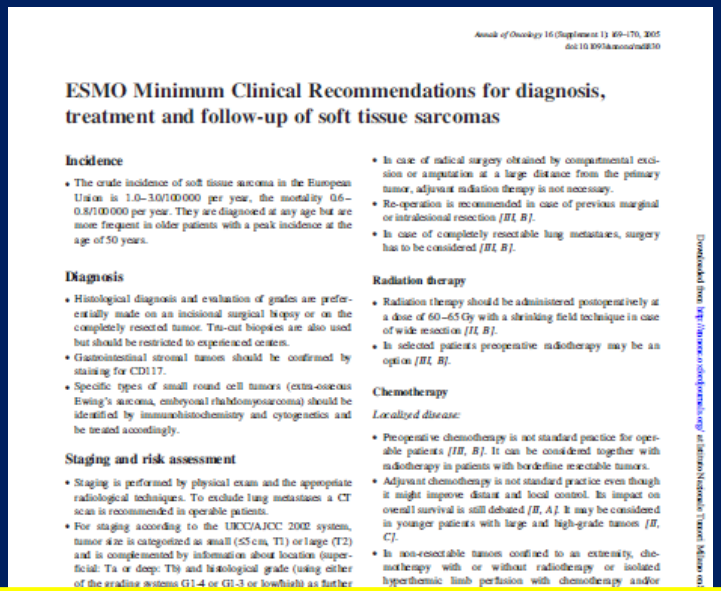
The decision-m

tions and hist

presenta-

sciplinary.

2005 2014



Annals of Oncology 16 (Supplement 1): i59–i70, 2005
doi:10.1093/annonc/mdi830

ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of soft tissue sarcomas

Incidence

- The crude incidence of soft tissue sarcoma in the European Union is 1.0–3.0/100 000 per year, the mortality 0.6–0.8/100 000 per year. They are diagnosed at any age but are more frequent in older patients with a peak incidence at the age of 50 years.

Diagnosis

- Histological diagnosis and evaluation of grades are preferentially made on an incisional surgical biopsy or on the completely resected tumor. Tru-cut biopsies are also used but should be restricted to experienced centers.
- Gastrointestinal stromal tumors should be confirmed by staining for CD117.
- Specific types of small round cell tumors (extra-osseous Ewing's sarcoma, embryonal rhabdomyosarcoma) should be identified by immunohistochemistry and cytogenetics and be treated accordingly.

Staging and risk assessment

- Staging is performed by physical exam and the appropriate radiological techniques. To exclude lung metastases a CT scan is recommended in operable patients.
- For staging according to the UICC/AJCC 2002 system, tumor size is categorized as small (≤5 cm, T1) or large (T2) and is complemented by information about location (superficial: Ta or deep: Tb) and histological grade (using either of the grading systems G1-4 or G1-3 or low/high) as further

- In case of radical surgery obtained by compartmental excision or amputation at a large distance from the primary tumor, adjuvant radiation therapy is not necessary.
- Re-operation is recommended in case of previous marginal or intralesional resection *[III, B]*.
- In case of completely resectable lung metastases, surgery has to be considered *[III, B]*.

Radiation therapy

- Radiation therapy should be administered postoperatively at a dose of 60–65 Gy with a shrinking field technique in case of wide resection *[II, B]*.
- In selected patients preoperative radiotherapy may be an option *[III, B]*.

Chemotherapy

Localized disease:

- Preoperative chemotherapy is not standard practice for operable patients *[III, B]*. It can be considered together with radiotherapy in patients with borderline resectable tumors.
- Adjuvant chemotherapy is not standard practice even though it might improve distant and local control. Its impact on overall survival is still debated *[II, A]*. It may be considered in younger patients with large and high-grade tumors *[II, C]*.
- In non-resectable tumors confined to an extremity, chemotherapy with or without radiotherapy or isolated hyperthermic limb perfusion with chemotherapy and/or

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii21–iii26, 2014
doi:10.1093/annonc/mdu255

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ES

Metastatic disease:

- Chemotherapy is the standard treatment for metastatic disease. Doxorubicin with or without ifosfamide is commonly used. Doxorubicin alone seems to be equivalent to its combinations with other agents with regard to survival, despite a higher response rate with combination regimens *[II, B]*.
- Imatinib (STI 571, a tyrosine kinase receptor inhibitor) is the treatment of choice for gastro-intestinal stromal tumors (GIST).

advanced disease

The decision-making is complex, depending on diverse presentations and histologies, and should always be multidisciplinary.

special presentations and entities

retroperitoneal sarcomas

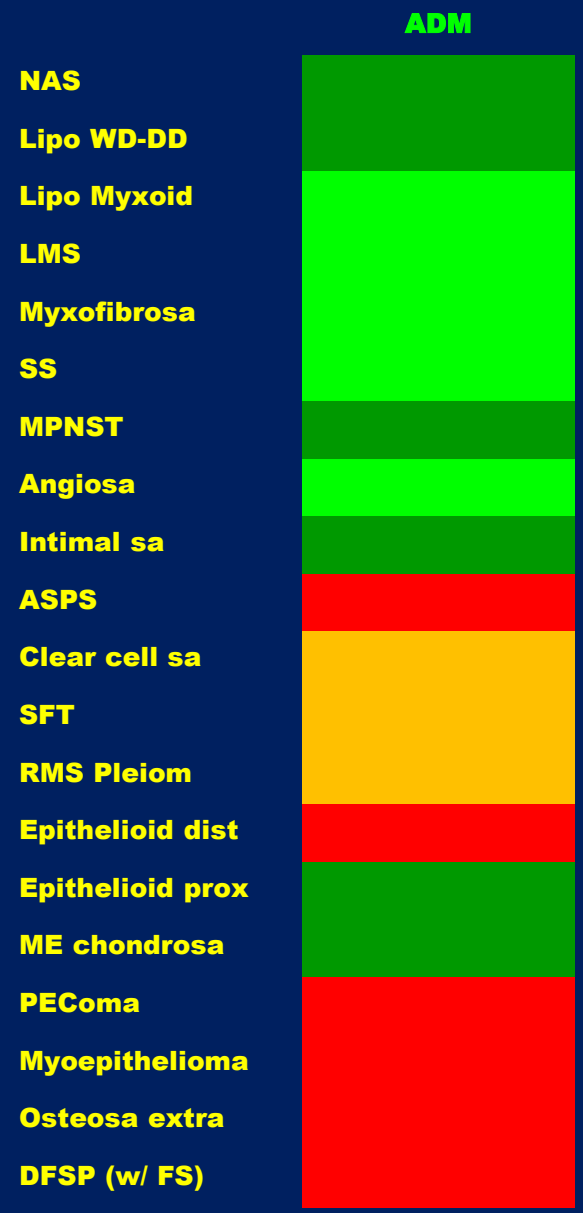
uterine sarcomas

desmoid-type fibromatosis

breast sarcomas

2005 2014

- Standard chemotherapy is based on anthracyclines as first-line treatment



clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

Extraskeletal Ewing sarcoma is covered by other ESMO Guidelines in general, the same principles for these tumours in children apply to adults. This is also the case for embryonal and alveolar rhabdomyosarcoma, which are exceedingly rare in adults. On the other hand, pleomorphic rhabdomyosarcoma is viewed as a high-grade adult-type soft tissue sarcoma. Gastrointestinal stromal tumours are covered by the dedicated ESMO Clinical Practice Guidelines. Kaposi's sarcoma is excluded.

incidence

Adult soft tissue and visceral sarcomas (excluding gastrointestinal stromal tumour) are rare tumours, with an estimated incidence averaging 4–5/100 000/year in Europe [1].

diagnosis

Soft tissue sarcomas (STSs) are ubiquitous in their site of origin and are often managed with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists, organ-based specialists, as applicable). Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which sarcoma patients' enrolment is common. This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm. Quality criteria are needed for sarcoma reference centres and, all the more, reference networks. These criteria may vary from country to country but, among others, should be based on: multidisciplinarity (incorporating tools such as weekly tumour boards discussing new cases), volume of patients, availability of facilities needed to properly apply clinical practice guidelines, recording and publication of outcomes.

In soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk. Standard radiographs may be useful to rule out a bone tumour, to detect bone erosion with a risk of fracture and to show calcifications. Computed tomography (CT) has a role in calcified lesions to rule out a myositis ossificans, and in retroperitoneal tumours, where the performance is identical to MRI. Ultrasound may be the first exam, but it should be followed by CT or MRI.

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies, possibly by using 2/14–16 G needles. However, an excisional biopsy may be the most practical option for <3 cm superficial lesions. An open biopsy may be another option in selected cases, as decided within reference centres. An immediate evaluation of tissue viability may be considered, to ensure that the biopsy is adequate at the time it is carried out. However, a frozen-section technique for immediate diagnosis is not encouraged, because it generally does not allow a complete diagnosis, particularly when preoperative treatment is planned. Fine needle aspiration is used only in some institutions, which have developed specific expertise on this procedure, and is not recommended outside these centres. A biopsy may underestimate the tumour malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging (including positron emission tomography, PET) may be useful, in addition to pathology, in providing the clinician with information that helps to estimate the malignancy grade (i.e. necrosis). The biopsy should be carried out by a surgeon or a radiologist, after multidisciplinary discussion, as needed, within reference centres. It should be planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery (except for retroperitoneal sarcomas, RPS). The biopsy entrance point can be tattooed. The tumour sample should be fixed in 4% buffered formalin in due time (Bouin fixation should not be used, since it prevents molecular analysis). The collection of fresh/frozen tissue and tumour imprints (touch preps) is encouraged, because new molecular pathology assessments could be made at a later stage in the patient's interest. In this perspective, the availability of a blood sample could add to the value of tumour tissues. Informed consent for biobanking should be sought, enabling later analyses and research, as long as this is allowed by local and internal/oral rules.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: August 2003, last update July 2014. This publication supersedes the previously published version—Ann Oncol 2012; 23(Suppl 7):vii80–vii84.

- Standard chemotherapy is based on anthracyclines as first-line treatment

Doxo (1 st, ...)
DTIC (1 st, ...)
IFX (1 st, ...)
GEM (1 st, ...)
TAX (1 st, ...)
Trabectedin (2 nd, ...)
VP16 (1 st, ...)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Imat... (1 st, DFSP)
Pazo (2 nd, non-adipocitic)
Sirolimus (1 st, LAM)

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii102–iii112, 2014
doi:10.1093/annonc/mdu254

Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

Extraskeletal Ewing sarcoma is covered by other ESMO Guidelines in general, the same principles for these tumours in children apply to adults. This is also the case for embryonal and alveolar rhabdomyosarcoma, which are exceedingly rare in adults. On the other hand, pleomorphic rhabdomyosarcoma is viewed as a high-grade adult-type soft tissue sarcoma. Gastrointestinal stromal tumours are covered by the dedicated ESMO Clinical Practice Guidelines. Kaposi's sarcoma is excluded.

incidence

Adult soft tissue and visceral sarcomas (excluding gastrointestinal stromal tumour) are rare tumours, with an estimated incidence averaging 4–5/100 000/year in Europe [1].

diagnosis

Soft tissue sarcomas (STSs) are ubiquitous in their site of origin and are often managed with multimodality treatment. A multidisciplinary approach is therefore mandatory in all cases (involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, as well as nuclear medicine specialists, organ-based specialists, as applicable). Management should be carried out in reference centres for sarcomas and/or within reference networks sharing multidisciplinary expertise and treating a high number of patients annually. These centres are involved in ongoing clinical trials, in which sarcoma patients' enrolment is common. This centralised referral should be pursued as early as at the time of the clinical diagnosis of a suspected sarcoma. In practice, referral of all patients with a lesion likely to be a sarcoma would be recommended. This would mean referring all patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm. Quality criteria are needed for sarcoma reference centres and, all the more, reference networks. These criteria may vary from country to country but, among others, should be based on: multidisciplinarity (incorporating tools such as weekly tumour boards discussing new cases), volume of patients, availability of facilities needed to properly apply clinical practice guidelines, recording and publication of outcomes.

In soft tissue tumours, magnetic resonance imaging (MRI) is the main imaging modality in the extremities, pelvis and trunk. Standard radiographs may be useful to rule out a bone tumour, to detect bone erosion with a risk of fracture and to show calcifications. Computed tomography (CT) has a role in calcified lesions to rule out a myositis ossificans, and in retroperitoneal tumours, where the performance is identical to MRI. Ultrasound may be the first exam, but it should be followed by CT or MRI.

Following appropriate imaging assessment, the standard approach to diagnosis consists of multiple core needle biopsies, possibly by using 2/14–16 G needles. However, an excisional biopsy may be the most practical option for <3 cm superficial lesions. An open biopsy may be another option in selected cases, as decided within reference centres. An immediate evaluation of tissue viability may be considered, to ensure that the biopsy is adequate at the time it is carried out. However, a frozen-section technique for immediate diagnosis is not encouraged, because it generally does not allow a complete diagnosis, particularly when preoperative treatment is planned. Fine needle aspiration is used only in some institutions, which have developed specific expertise on this procedure, and is not recommended outside these centres. A biopsy may underestimate the tumour malignancy grade. Therefore, when preoperative treatment is an option, radiological imaging (including positron emission tomography, PET) may be useful, in addition to pathology, in providing the clinician with information that helps to estimate the malignancy grade (i.e. necrosis). The biopsy should be carried out by a surgeon or a radiologist, after multidisciplinary discussion, as needed, within reference centres. It should be planned in such a way that the biopsy pathway and the scar can be safely removed by definitive surgery (except for retroperitoneal sarcomas, RPS). The biopsy entrance point can be tattooed. The tumour sample should be fixed in 4% buffered formalin in due time (Bouin fixation should not be used, since it prevents molecular analysis). The collection of fresh/frozen tissue and tumour imprints (touch preps) is encouraged, because new molecular pathology assessments could be made at a later stage in the patient's interest. In this perspective, the availability of a blood sample could add to the value of tumour tissues. Informed consent for biobanking should be sought, enabling later analyses and research, as long as this is allowed by local and international rules.

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: August 2003, last update July 2014. This publication supersedes the previously published version—Ann Oncol 2012; 23(Suppl 7):vii80–vii84.

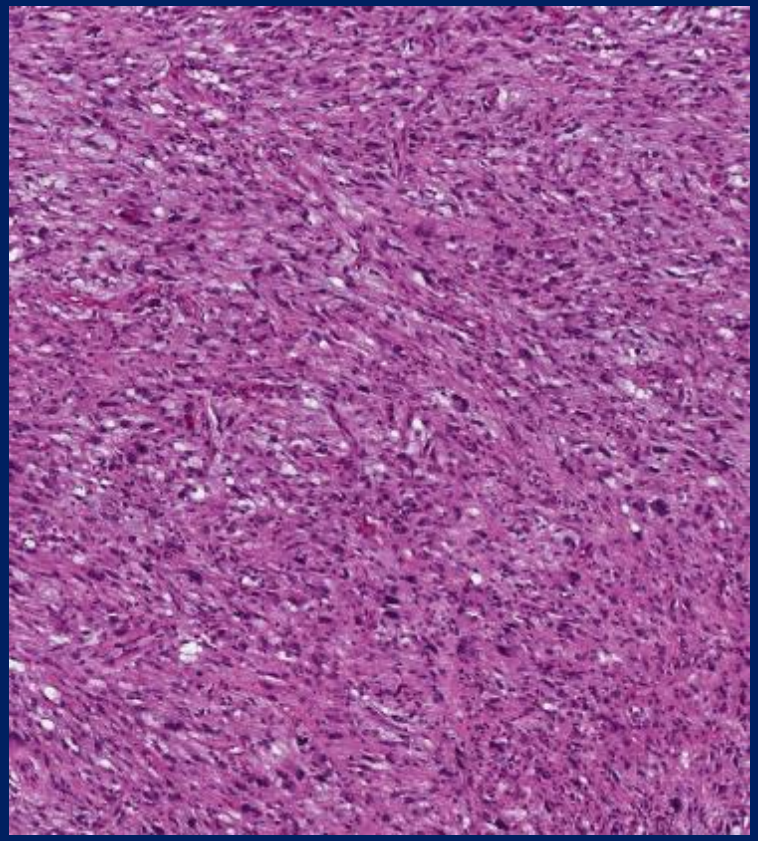
- Standard chemotherapy is based on anthracyclines as first-line treatment

Doxo	(1 st, …)
DTIC	(1 st, …)
IFX	(1 st, …)
GEM	(1 st, …)
TAX	(1 st, …)
Trabectedin	(2 nd, …)
VP16	(1 st, …)

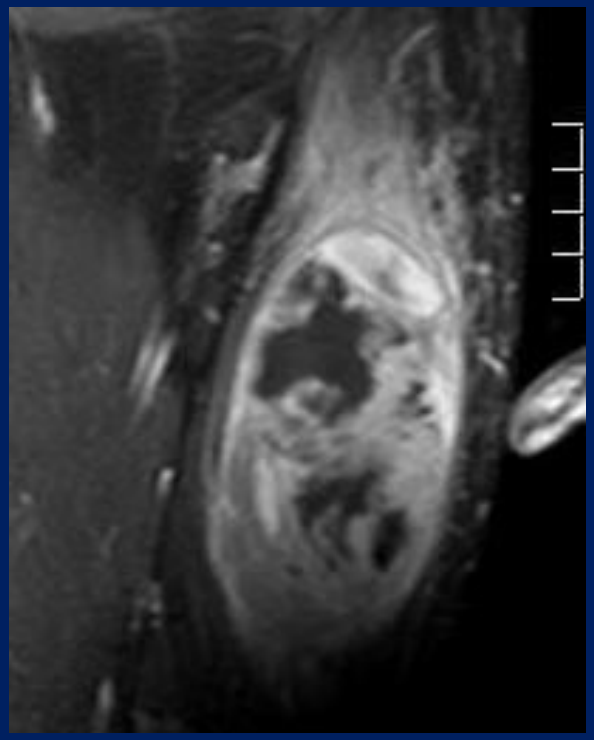
Imat…ib	(1 st, DFSP)
Pazo	(2 nd, non-adipocitic)
Sirolimus	(1 st, LAM)

Sunitinib
Sorafenib
Sirolimus / Everolimus
Bevacizumab
Imatinib
Crizotinib
Vemurafenib
Temozolomide
Interferon
Figitumumab
Palpociclib
…

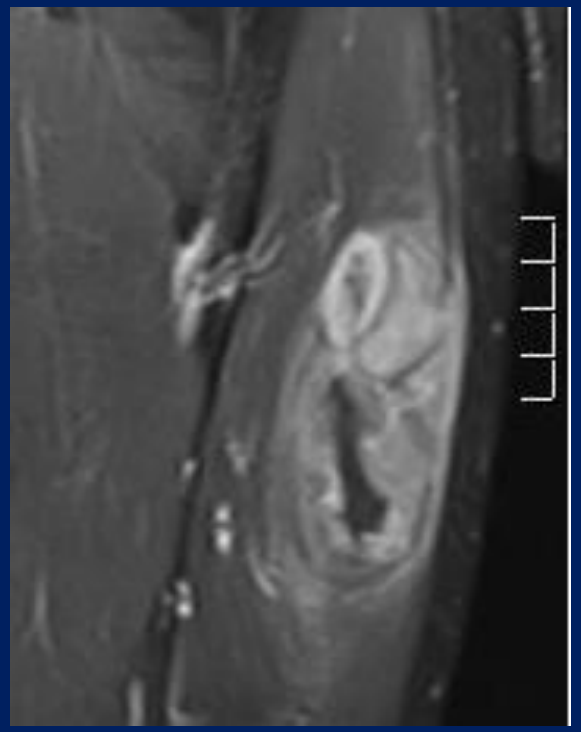
Leiomyosarcoma



… epirubicin (+ ifosfamide)

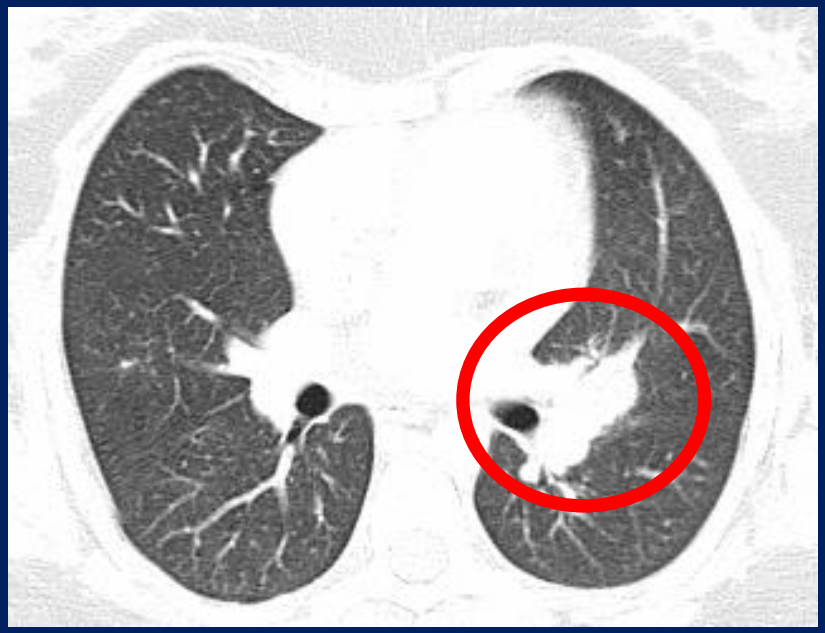


0

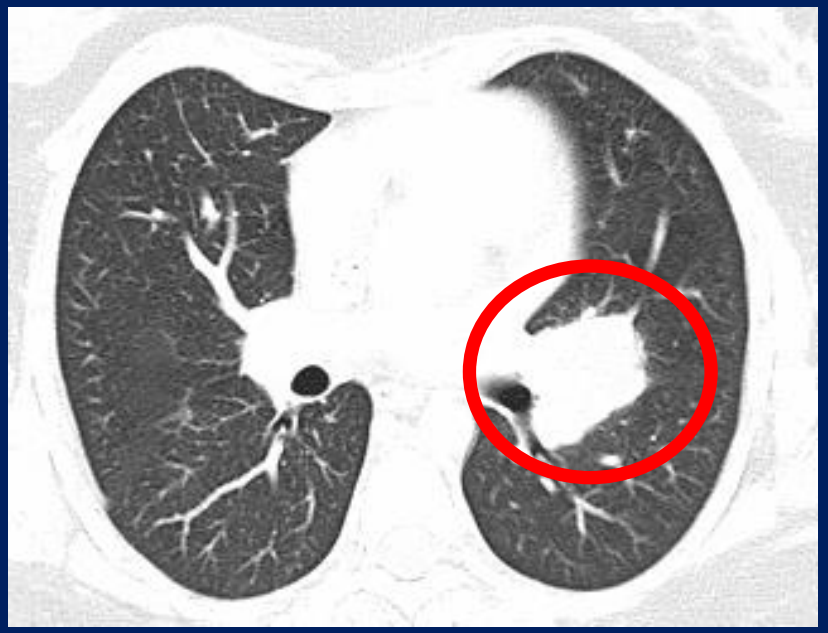


+3 cycles

… high-dose ifosfamide

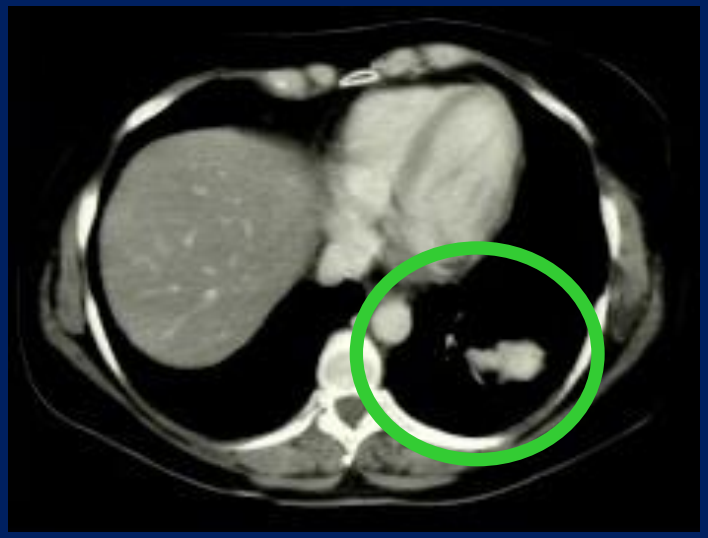


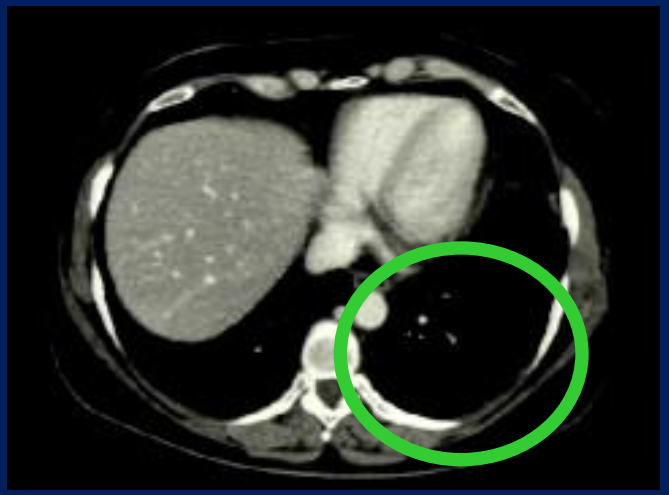
0



+3 mos

… dacarbazine

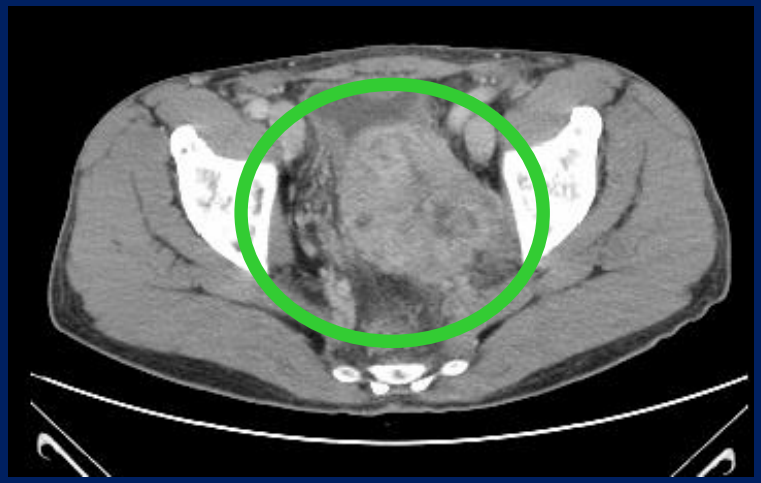


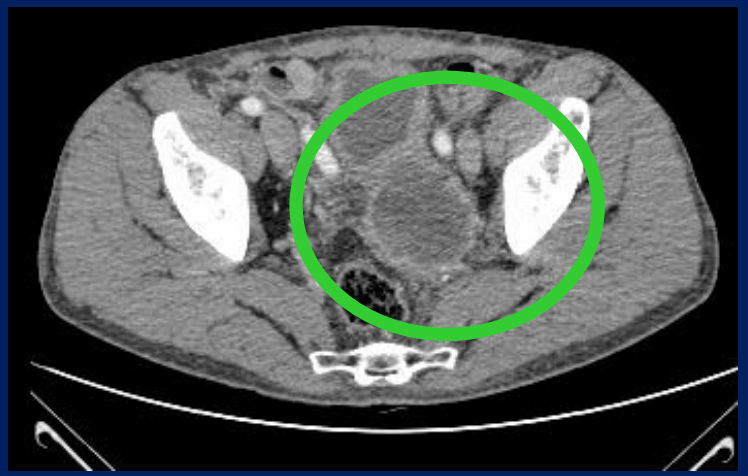


0

+2 mos

… adria + dacarbazine

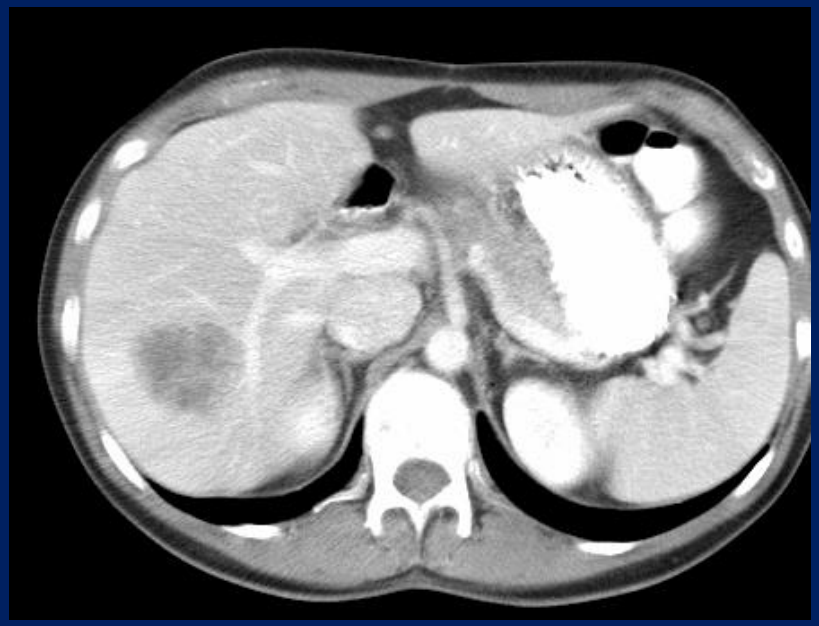




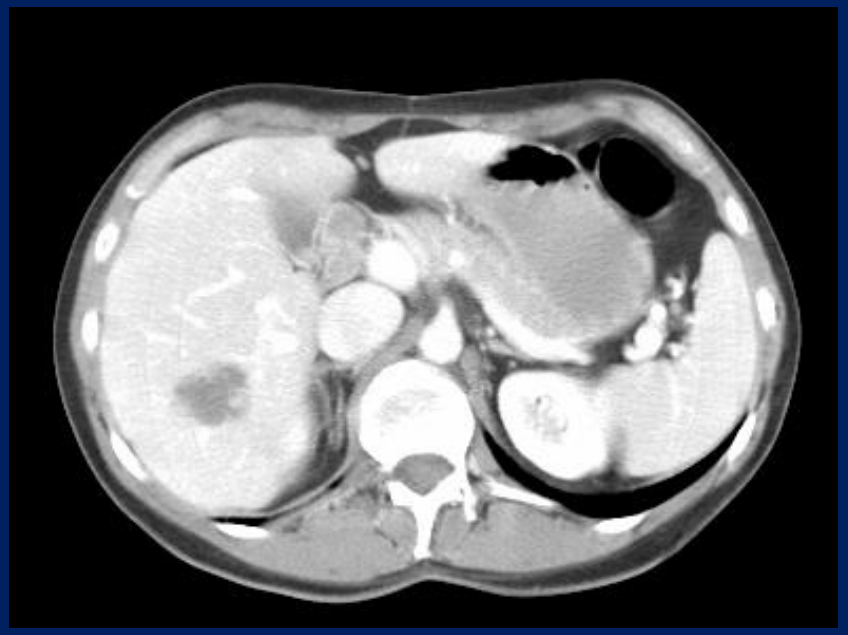
0

+4 mos

… gem + docetaxel



0

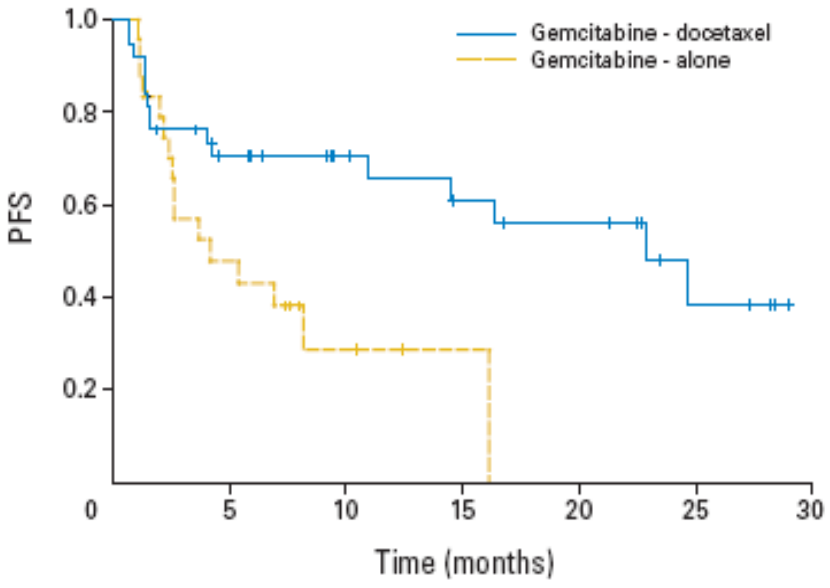


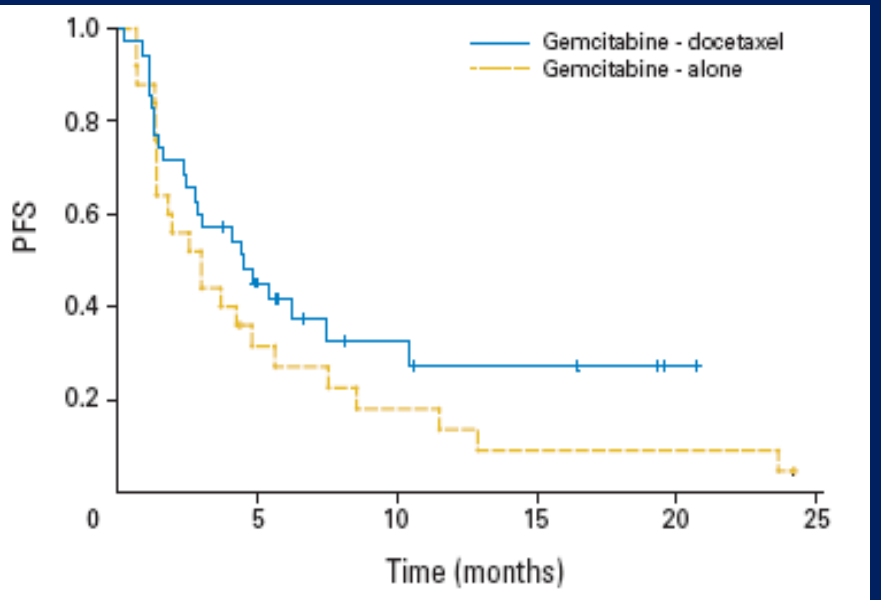
+2 mos

gem +/- docetaxel

VOLUME 25 · NUMBER 19 · JULY 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Study of Gemcitabine and Docetaxel Compared With Gemcitabine Alone in Patients With Metastatic Soft Tissue Sarcomas: Results of Sarcoma Alliance for Research Through Collaboration Study 002





maki@mskcc.org

0732-183X/07/2519-2755/$20.00
DOI: 10.1200/JCO.2006.10.4717

used for larger primary extremity tumors.[4] Despite good local control, 40% to 50% of patients will develop distant recurrence, which is nearly always fatal.

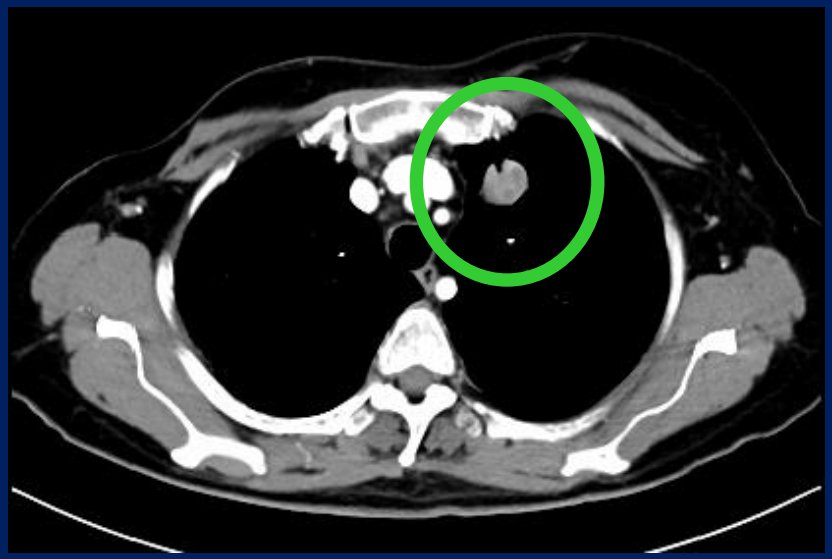
The most active chemotherapy agents for metastatic soft tissue sarcoma are doxorubicin and ifosfamide.[2] Gemcitabine and docetaxel each have modest activity in sarcomas alone.[5-7] Gemcitabine other soft tissue sarcomas.[8,9] However, it is unclear if the activity of the combination is due to the prolonged infusion of gemcitabine or synergy between the two drugs.

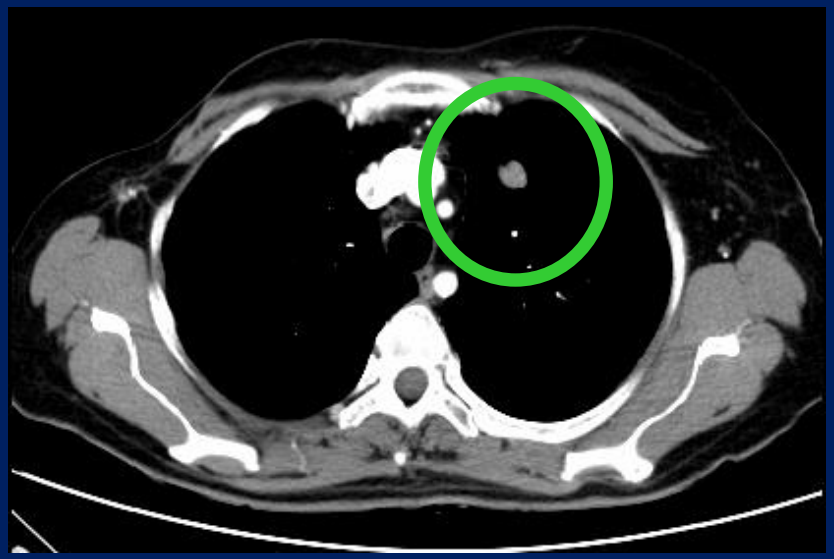
We therefore conducted a multicenter, open-label, phase II study of gemcitabine given via fixed dose rate infusion versus a lower dose of fixed dose

- **RR: CR/PR GEM+TAX 16%; GEM 8%**
- **median PFS GEM+TAX 6 mos; GEM 3 mos**

Maki R et al, JCO 2007

… gemcitabine





0

+4 mos

... gem + dacarbazine

Published Ahead of Print on May 23, 2011 as 10.1200/JCO.2010.33.6107
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.33.6107

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized Phase II Study Comparing Gemcitabine Plus Dacarbazine Versus Dacarbazine Alone in Patients With Previously Treated Soft Tissue Sarcoma: A Spanish Group for Research on Sarcomas Study

Xavier García-del-Muro, Antonio López-Pousa, Joan Maurel, Javier Martín, Javier Martínez-Trufero, Amancio Casado, Auxiliadora Gómez-España, Joaquín Fra, Josefina Cruz, Andrés Poveda, Andrés Mesana, Carlos Pericay, Ricardo Cubedo, Jordi Rubió, Ana De Juan, Nuria Lainez, Juan Antonio Carrasco, Raquel de Andrés, and José M. Buesa†

A B S T R A C T

Purpose
To assess the activity and toxicity of the combination of gemcitabine plus dacarbazine (DTIC) in patients with advanced soft tissue sarcoma (STS) in a randomized, multicenter, phase II study using DTIC alone as a control arm.

Patients and Methods
Patients with previously treated advanced STS were randomly assigned to receive either fixed-dose rate gemcitabine (10 mg/m²/min) at 1,800 mg/m² followed by DTIC at 500 mg/m² every 2 weeks, or DTIC alone at 1,200 mg/m² every 3 weeks. The primary end point of the study was progression-free rate (PFR) at 3 months.

Results
From November 2005 to September 2008, 113 patients were included. PFR at 3 months was 56% for gemcitabine plus DTIC versus 37% for DTIC alone ($P = .001$). Median progression-free survival was 4.2 months versus 2 months (hazard ratio [HR], 0.58; 95% CI, 0.39 to 0.86; $P = .005$), and median overall survival was 16.8 months versus 8.2 months (HR, 0.56; 95% CI, 0.36 to 0.90; $P = .014$); both favored the arm of gemcitabine plus DTIC. Gemcitabine plus DTIC was also associated with a higher objective response or higher stable disease rate than was DTIC alone (49% *v* 25%; $P = .008$). Severe toxicities were uncommon, and treatment discontinuation for toxicity was rare. Granulocytopenia was the more common serious adverse event, but febrile neutropenia was uncommon. Asthenia, emesis, and stomatitis were the most frequent nonhematologic effects.

Conclusion
The combination of gemcitabine and DTIC is active and well tolerated in patients with STS, providing in this phase II randomized trial superior progression-free survival and overall survival than DTIC alone. This regimen constitutes a valuable therapeutic alternative for these patients.

J Clin Oncol 29: © 2011 by American Society of Clinical Oncology

INTRODUCTION

In patients with advanced soft tissue sarcoma (STS) not amenable to surgery, chemotherapy is the only available treatment.[1] Until recently, a limited number of drugs have been available for these patients. Doxorubicin[2] and ifosfamide[3] are agents with well-established activity that, given sequentially or in combination, constitute the standard treatment of advanced STS. Dacarbazine (DTIC) also is a drug with some classically known activity.[4] The results obtained by using these standard agents, however, remain disappointing, with a median overall survival (OS) close to 12 months.[2,3] Therefore, there is a necessity to identify new active agents and combinations to improve therapy for patients with advanced STS.

In the last few years, a small number of drugs have been incorporated into the second-line treatment of sarcomas. Trabectedin[5] and temozolomide,[6] as well as gemcitabine,[4,7] are promising drugs that have shown variable degrees of efficacy in phase II studies. Although gemcitabine and DTIC appear to have modest activity given as monotherapy, a phase I trial and a subsequent phase II trial that explored the combination of

Xavier García-del-Muro, Institut Català d'Oncologia L'Hospitalet, IDIBell; Antonio López-Pousa, Hospital Sant Pau; Joan Maurel, Hospital Clínic, Barcelona; Javier Martín, Hospital Son Dureta, Palma de Mallorca; Javier Martínez-Trufero, Hospital Miguel Servet; Raquel de Andrés, Hospital Lozano Blesa, Zaragoza; Antonio Casado, Hospital Universitario San Carlos; Ricardo Cubedo, Hospital Puerta de Hierro, Madrid; Auxiliadora Gómez-España, Hospital Reina Sofía, Córdoba; Joaquín Fra, José M. Buesa, Hospital Central de Asturias, Oviedo; Josefina Cruz, Hospital Universitario de Canarias, Tenerife; Andrés Poveda, Instituto Valenciano de Oncología, Valencia; Andrés Mesana, Hospital General de Alicante, Alicante; Carlos Pericay, Hospital Parc Taulí, Sabadell; Jordi Rubió, Institut Català d'Oncologia, Girona; Ana De Juan, Hospital Marqués de Valdecilla, Santander; Nuria Lainez, Hospital de Navarra, Pamplona; Juan Antonio Carrasco, Hospital Xeral Cíes, Vigo, Spain.

Submitted November 12, 2010; accepted March 28, 2011; published online ahead of print at www.jco.org on May 23, 2011.

Supported in part by Lilly.

†Deceased.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

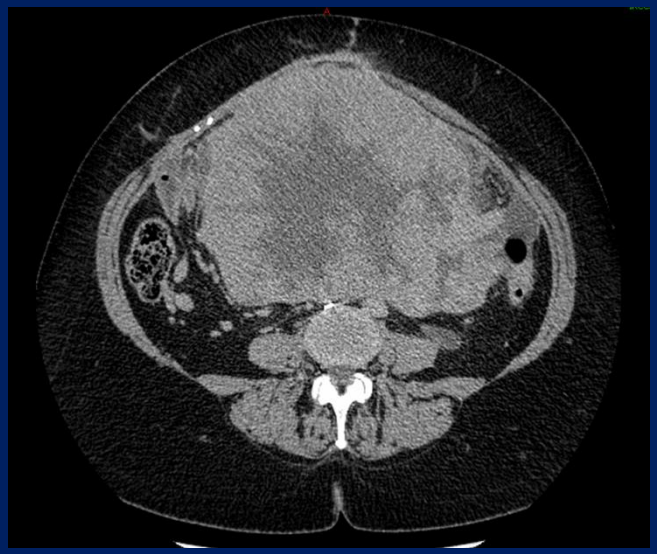
Corresponding author: Xavier García del Muro, MD, PhD, Sarcoma Multidisciplinary Unit, Institut Català d'Oncologia L'Hospitalet, Avda Gran Via Km 2.7, 08907 L'Hospitalet, Barcelona, Spain; e-mail: garciadelmuro@cmoncologia.net.

0732-183X/11/2999-1/$20.00

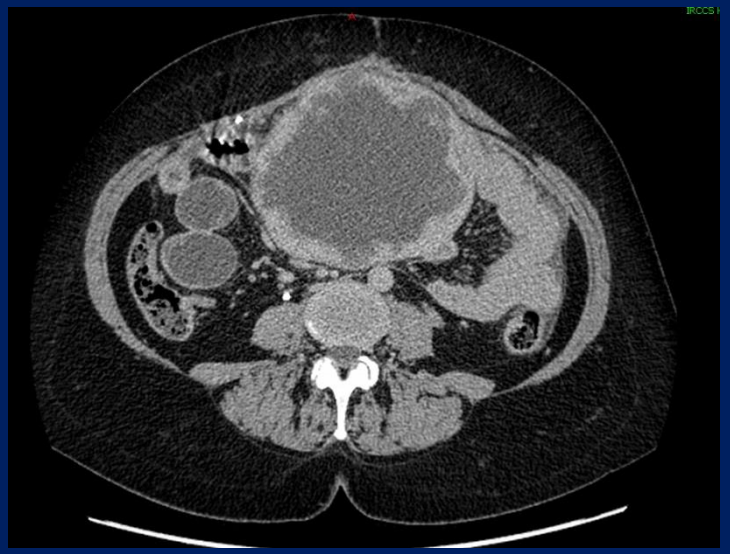
DOI: 10.1200/JCO.2010.33.6107

Del Muro G et al , JCO 2011

… gem + dacarbazine

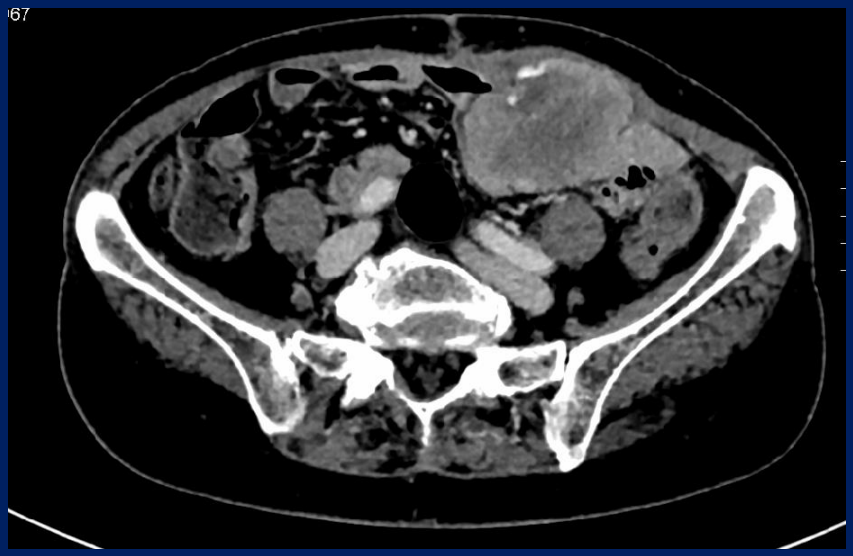


0

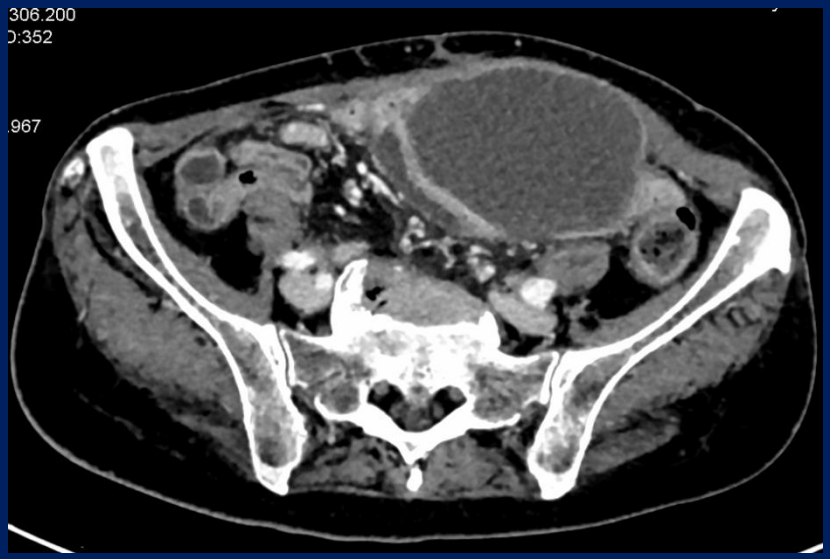


+5 mos

… trabectedin



0



+4 mos

Published Ahead of Print on September 14, 2015 as 10.1200/JCO.2015.62.4734
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.62.4734

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

George D. Demetri, Margaret von Mehren, Robin L. Jones, Mariee L. Hensley, Scott M. Schuetze, Arthur Staddon, Mohammed Milhem, Anthony Elias, Kristen Ganjoo, Hussein Tawbi, Brian A. Van Tine, Alexander Spira, Andrew Dean, Nashwa Z. Khokhar, Yoon Chot Park, Roland E. Knoblauch, Trilok V. Parekh, Robert G. Maki, and Shreyaskumar R. Patel

See accompanying editorial doi:10.1200/JCO.2015.63.5838

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on September 14, 2015.

Written on behalf of the SAR-3007 investigators.

Processed as a Rapid Communication manuscript.

Supported by Janssen Pharmaceuticals, and supported in part by the Adelson Medical Research Foundation (G.D.D.).

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01343277.

Corresponding author: George D. Demetri, MD, Ludwig Center at Harvard, Harvard Medical School, and Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; e-mail: george_demetri@dfci.harvard.edu.

0732-183X/15/2699-1/$20.00

DOI: 10.1200/JCO.2015.62.4734

ABSTRACT

Purpose
This multicenter study, to our knowledge, is the first phase III trial to compare trabectedin versus dacarbazine in patients with advanced liposarcoma or leiomyosarcoma after prior therapy with an anthracycline and at least one additional systemic regimen.

Patients and Methods
Patients were randomly assigned in a 2:1 ratio to receive trabectedin or dacarbazine intravenously every 3 weeks. The primary end point was overall survival (OS), secondary end points were disease control—progression-free survival (PFS), time to progression, objective response rate, and duration of response—as well as safety and patient-reported symptom scoring.

Results
A total of 518 patients were enrolled and randomly assigned to either trabectedin (n = 345) or dacarbazine (n = 173). In the final analysis of PFS, trabectedin administration resulted in a 45% reduction in the risk of disease progression or death compared with dacarbazine (median PFS for trabectedin *v* dacarbazine, 4.2 *v* 1.5 months; hazard ratio, 0.55; $P < .001$); benefits were observed across all preplanned subgroup analyses. The interim analysis of OS (64% censored) demonstrated a 13% reduction in risk of death in the trabectedin arm compared with dacarbazine (median OS for trabectedin *v* dacarbazine, 12.4 *v* 12.9 months; hazard ratio, 0.87; $P = .37$). The safety profiles were consistent with the well-characterized toxicities of both agents, and the most common grade 3 to 4 adverse effects were myelosuppression and transient elevation of transaminases in the trabectedin arm.

Conclusion
Trabectedin demonstrates superior disease control versus conventional dacarbazine in patients who have advanced liposarcoma and leiomyosarcoma after they experience failure of prior chemotherapy. Because disease control in advanced sarcomas is a clinically relevant end point, this study supports the activity of trabectedin for patients with these malignancies.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

INTRODUCTION

After GI stromal tumors, leiomyosarcomas and liposarcomas are the most common subtypes of soft tissue sarcomas (STS), a heterogeneous group of malignancies that arise from tissues of mesenchymal origin and together compose approximately 1% of all solid tumors.[1,2]

The prognosis for patients with advanced or metastatic STS is poor, with an estimated median survival of 12 to 15 months.[3-5] Treatment is palliative in nature, and the goal is delay of the progression and severe morbidity that can arise when tumor growth compromises organ function.[6] Initial therapy for patients with STS that is unresectable for cure typically includes cytotoxic chemotherapy that is most commonly anthracycline based (mainly doxorubicin) or gemcitabine based.[7,8] Other chemotherapeutic agents, including dacarbazine, ifosfamide, and unapproved analogs, have been investigated.[9-13] In metastatic STS, combination chemotherapy with dose-intensive doxorubicin

... trabectedin

Leio, median PFS 4.3 mos

Demetri et al, JCO 2015

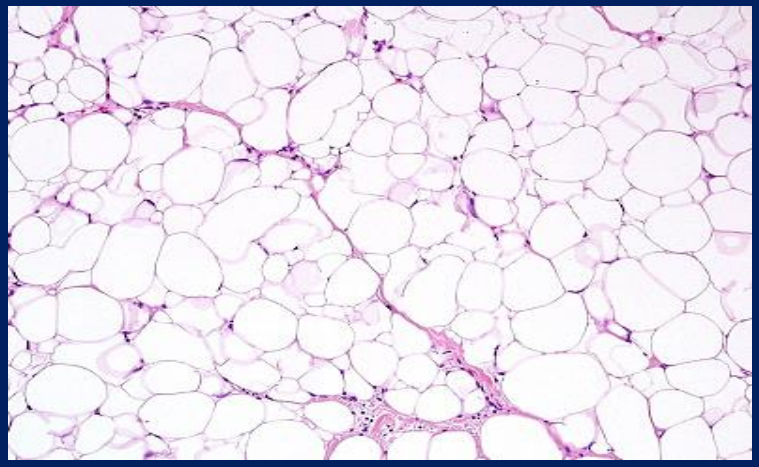
… pazopanib

RR?
median PFS?
mech action?

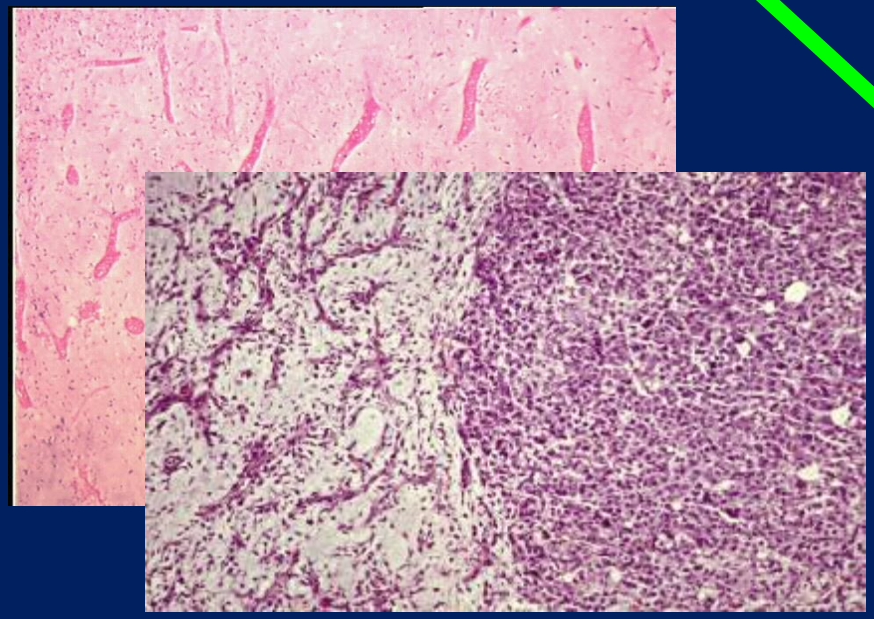
0

+2 mos

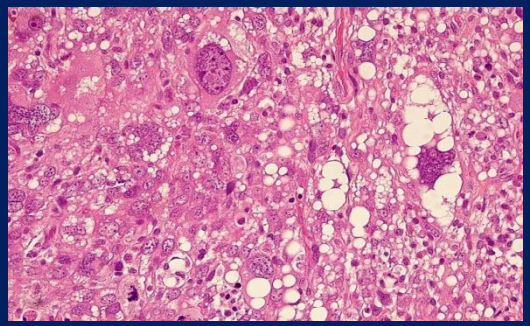
Liposarcoma



Well diff → dediff

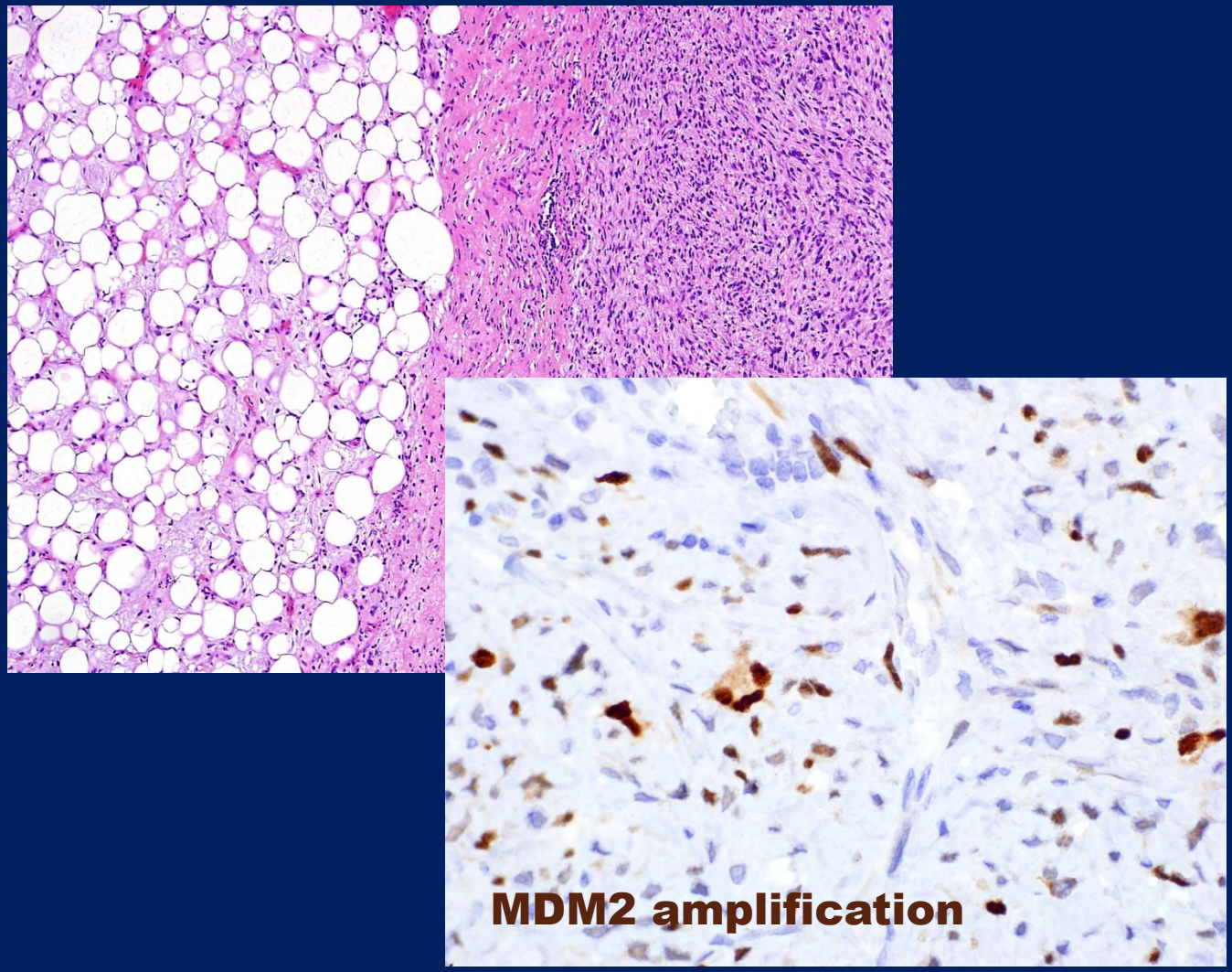


Myxoid

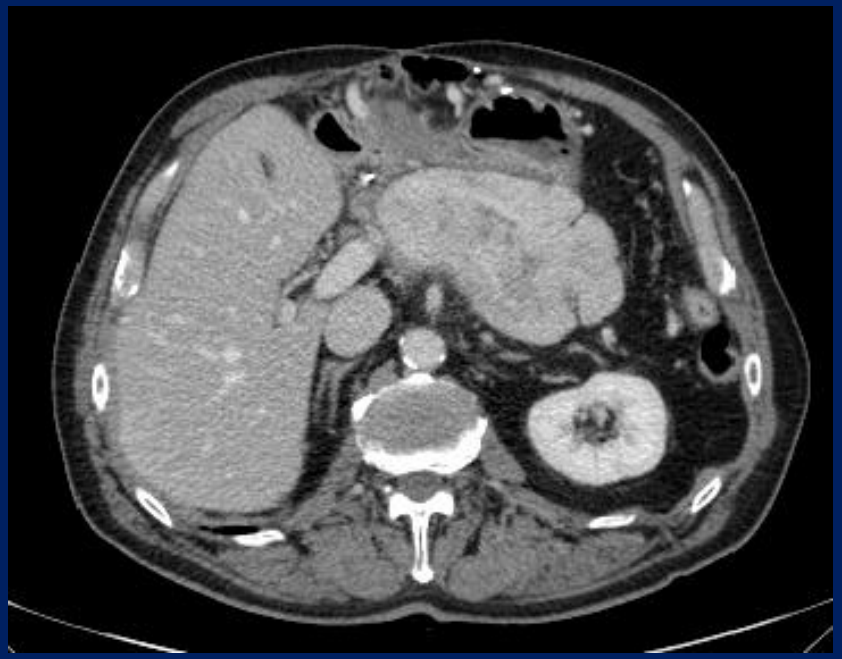


Pleomorphic

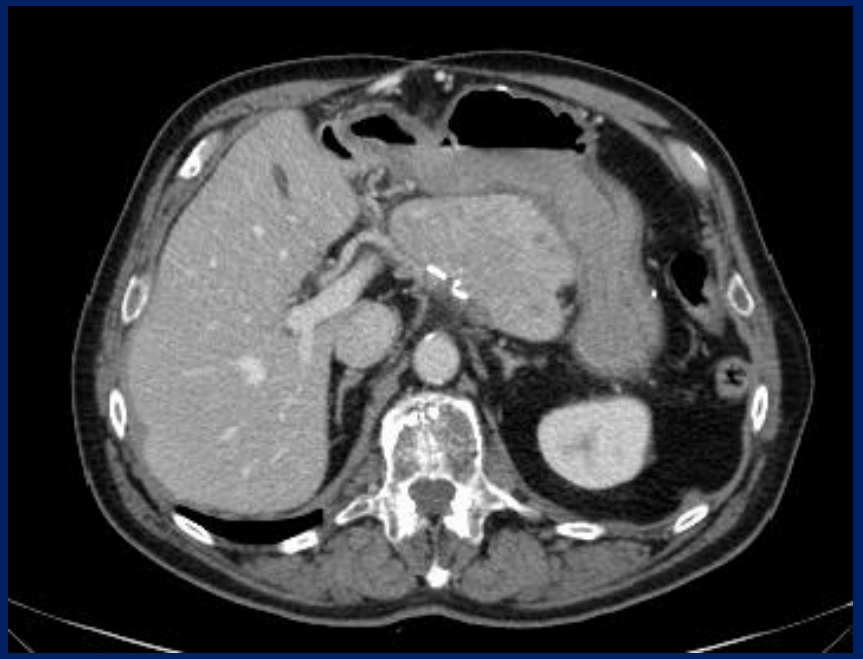
WD/Dediff Liposarcoma



… doxo

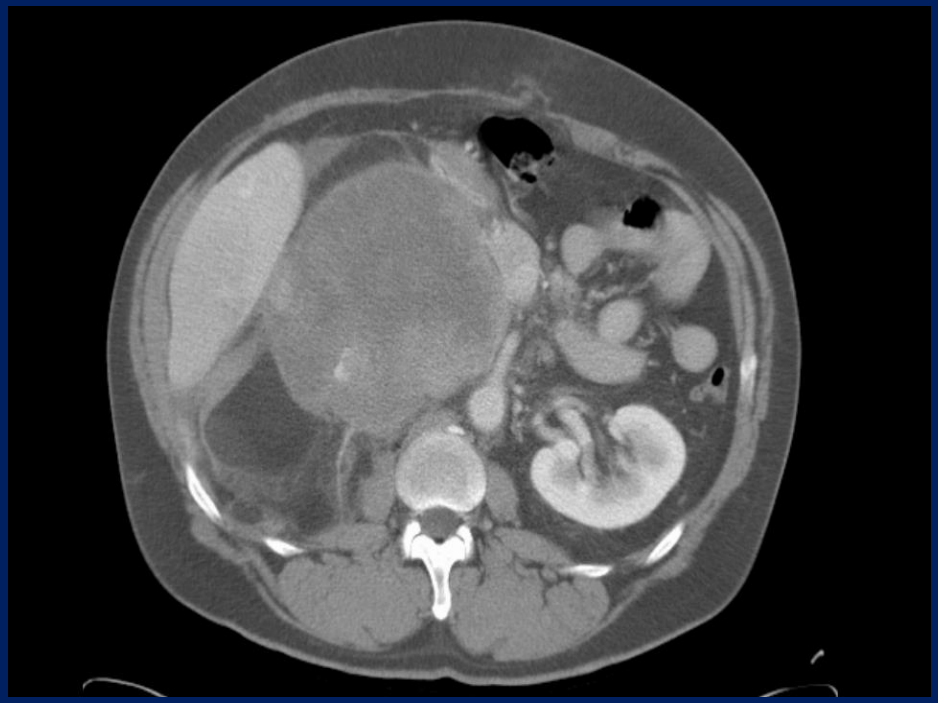


0

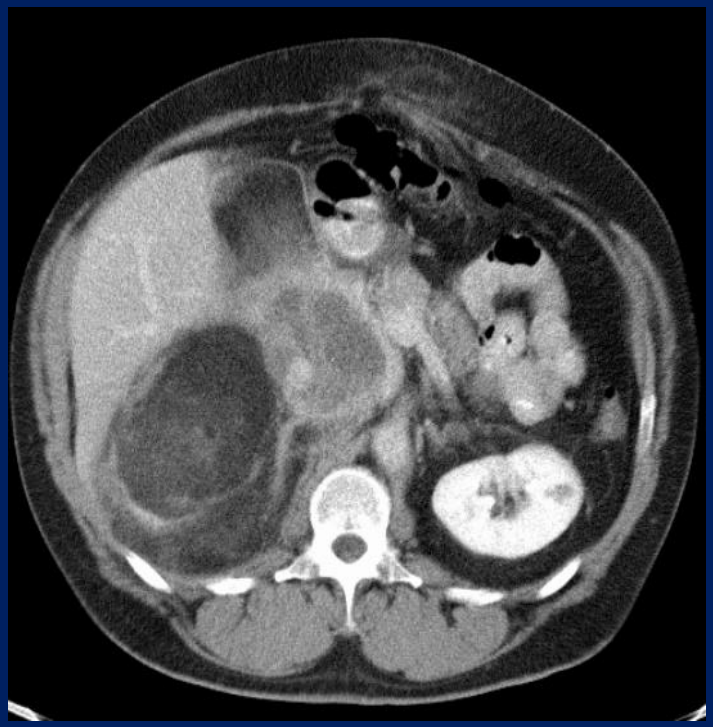


+5 mos

… high-dose ifosfamide



0



+5 mos

ORIGINAL ARTICLE

Successful Ifosfamide Rechallenge in Soft-Tissue Sarcoma

Jonathan Noujaim, MD, Anastasia Constantinidou, MD, Christina Messiou, MD, PhD, Khin Thway, MBBS, BSc, Aisha Miah, MD, PhD, Charlotte Benson, MD, Ian Judson, MD, and Robin L. Jones, MD

Objectives: Treatment options for metastatic soft-tissue sarcomas are limited. The aim of this study was to investigate the clinical activity of ifosfamide rechallenge in synovial sarcoma (SS), liposarcoma (LPS), leiomyosarcoma (LMS), and high-grade sarcomas not otherwise specified.

Methods: A retrospective search of the Royal Marsden Sarcoma Unit Database was performed to identify patients initially treated with ifosfamide (as single agent or in combination) and who were subsequently rechallenged with single-agent ifosfamide. Baseline demographics and response assessment were retrospectively obtained.

Results: Sixty-seven patients were identified and the median age at diagnosis was 41 years (range, 18 to 71 y). There were 29 cases of SS, 17 of LPS, 12 of LMS, and 9 of sarcomas not otherwise specified. First-line ifosfamide-containing therapy was given to 14 patients as adjuvant therapy (adjuvant group) and 53 patients as palliative therapy (palliative group). Clinical activity (partial response or stable disease) with single-agent ifosfamide rechallenge was documented in 50.0% of

evidence base is limited.[4,5] Chemotherapy continues to be considered palliative for patients with metastatic or locally advanced inoperable disease.

Single-agent doxorubicin remains the accepted first-line therapy for most STS.[6] Besides doxorubicin, ifosfamide has also been extensively studied in STS and is commonly used in practice. Ifosfamide can be given either as part of a combination therapy[7] or as a single agent (3 daily divided doses with doses ranging from 2 to 4 g/m^2/d given as an inpatient every 3 weeks[8,9] or as a prolonged continuous infusion over 14 consecutive days in cycles of 28 days[10]). Reported overall response rates (ORR) for single-agent ifosfamide are approximately 20% to 25%. In the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) trial that randomized patients to doxorubicin or to 2 different ifosfamide schedules, data were suggestive of a higher likelihood of response in SS (ORR = 40%) compared with LMS (ORR = 5%) and LPS

TABLE 3. Overall Response to First-line Ifosfamide Treatment and Subsequent Rechallenge According to Histology in the Palliative Group

	n (%)			
	Synovial	Liposarcoma	Leiomyosarcoma	Sarcoma NOS
First-line therapy				
CR	0	0	1 (8.3)	0
PR	10 (58.8)	9 (52.9)	5 (41.7)	5 (71.4)
SD	6 (35.3)	5 (29.4)	6 (50.0)	2 (28.6)
PD	1 (5.9)	3 (17.6)	0	0
Ifosfamide rechallenge				
CR	0	0	0	0
PR	4 (23.5)	3 (17.6)	3 (25.0)	1 (14.3)
SD	4 (23.5)	0	2 (16.7)	1 (14.3)
PD	9 (52.9)	13 (76.5)	7 (58.3)	5 (71.4)
NA	0	1 (6.3)	0	0

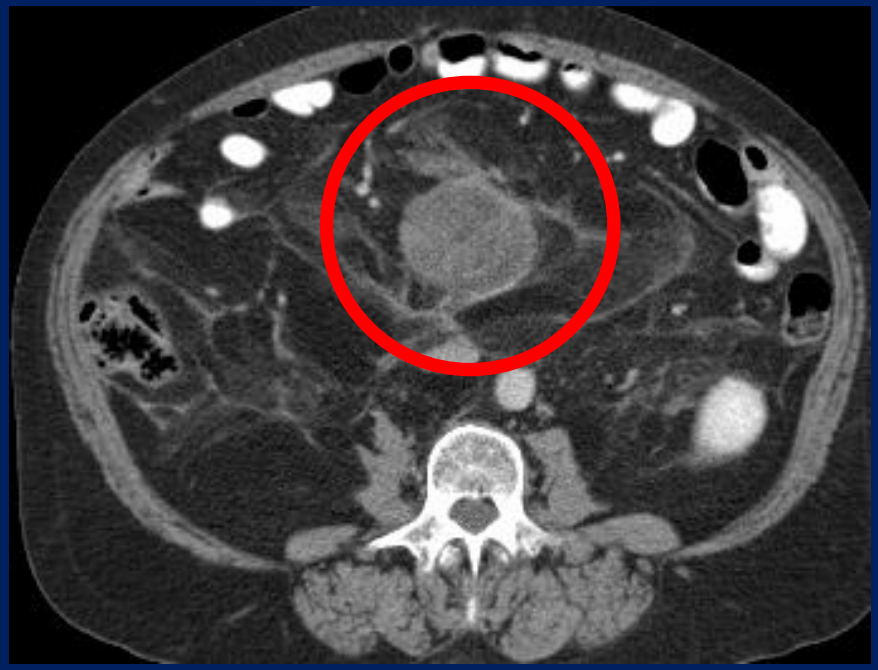
CR indicates complete remission; NA, not available; NOS, not otherwise specified; PD, progressive disease; PR, partial remission; SD, stable disease.

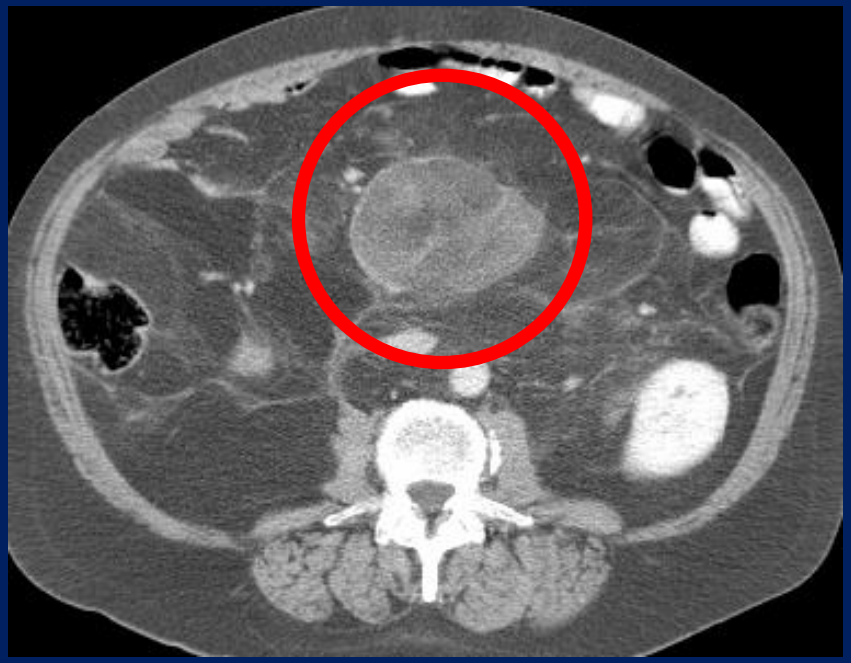
DOI: 10.1097/COC.0000000000000243

the histologic diagnosis was confirmed by an experienced

Nouejan J et al, Am J Clin Oncol 2015

… gemcitabine

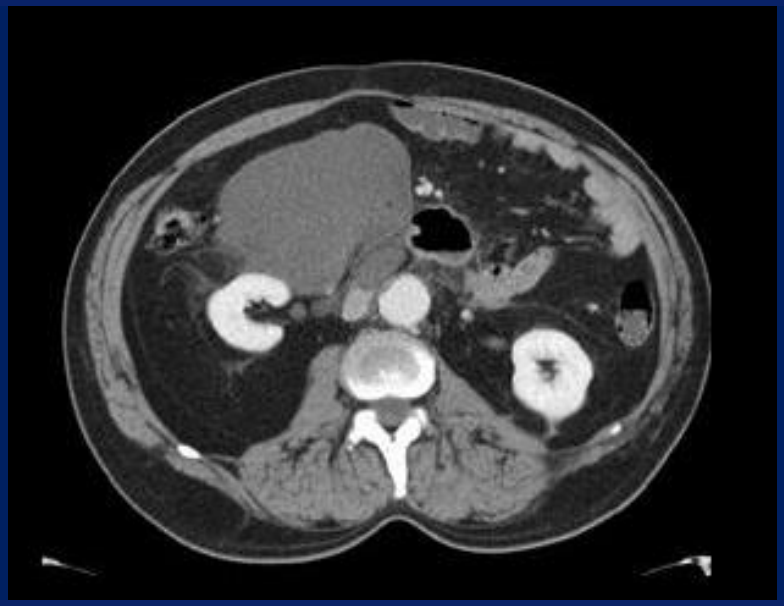


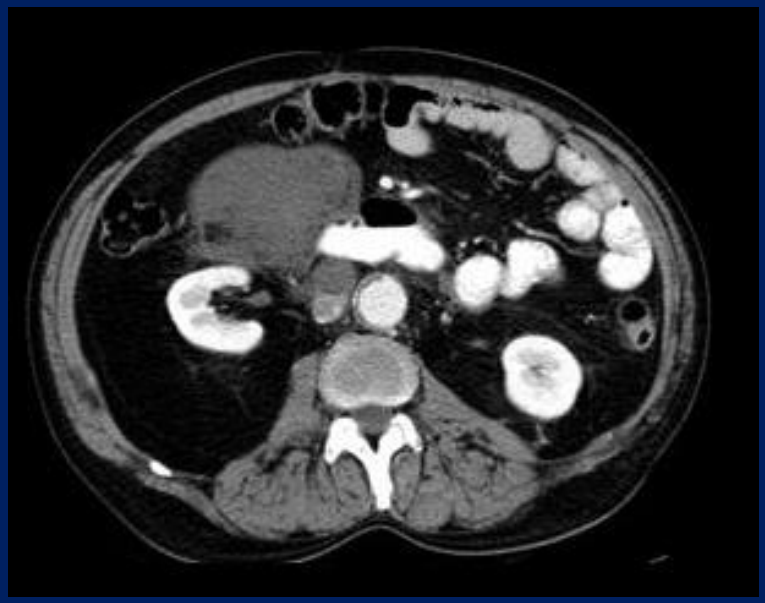


0

+3 mos

… trabectedin





0

+3 mos

… eribulin

Randomized, open-label, multicenter, phase 3 study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI)

Patrick Schöffski, MD, MPH
Department of General Medical Oncology
University Hospitals Leuven, Leuven Cancer Institute
KU Leuven, Leuven, Belgium

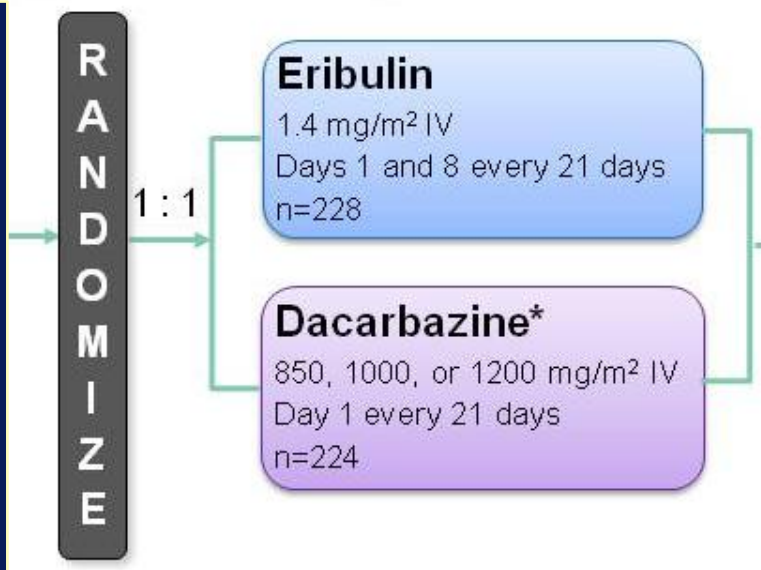
Abstract # LBA10502 submitted by **P Schöffski**, R Maki, A Italiano, H Gelderblom, E Choy, G Grignani, V Camargo, S Bauer, SY Rha, S Chawla, JY Blay, P Hohenberger, DR D'Adamo, B Wang, B Chmielowski, A LeCesne, GD Demetri, and S Patel.
Clinicaltrials.gov identifier: NCT01327885.

PRESENTED AT: ASCO Annual '15 Meeting

Schoffski P, ASCO 2015

Study design and objectives

leio, lipoSA G2-3 advanced >2 line ...

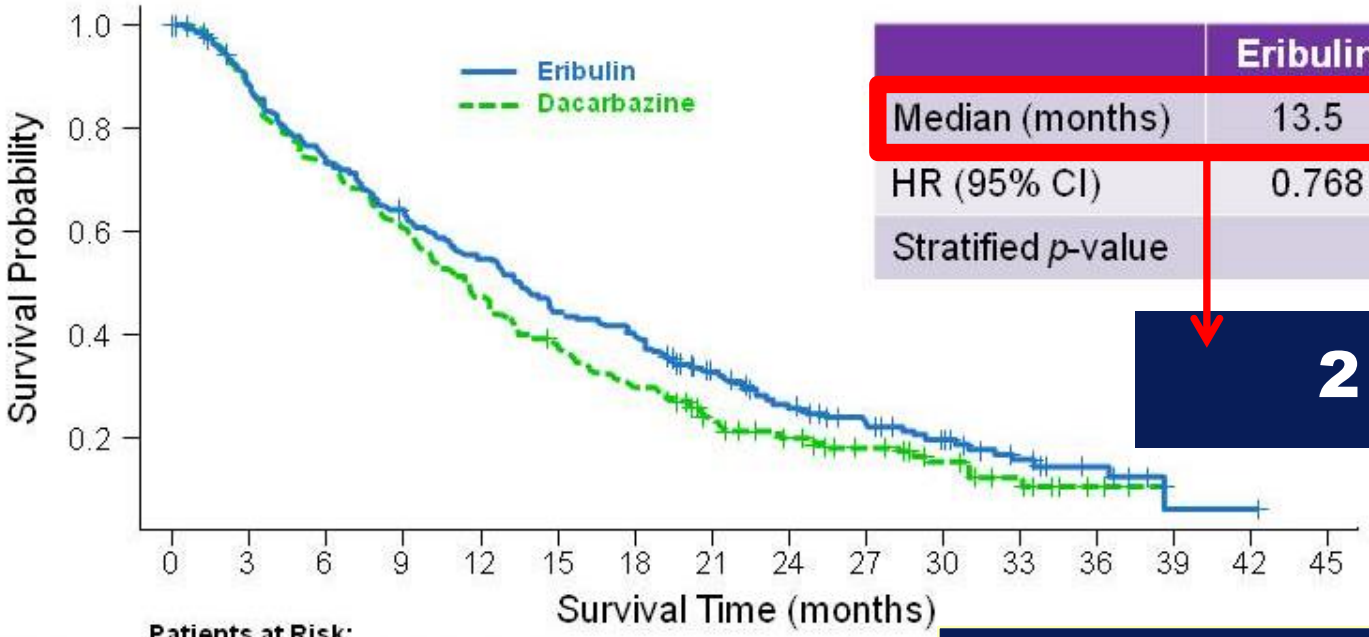


Primary endpoint
- Overall survival (OS)

Selected Secondary endpoints
- Progression-free survival (PFS)
- Progression-free rate at 12 weeks (PFR_{12wks})†
- Safety and tolerability (AE assessment based on CTCAE v4.02[2])

Selected exploratory endpoints
- Objective response rate (ORR; CR or PR)
- Health-related quality of life

Primary endpoint: OS



Patients at Risk:

Eribulin	228	197	162	138	120	97	88	64	45	34	2
Dacarbazine	224	190	158	130	103	81	64	45	32	24	1

	Eribulin	Dacarbazine
Median (months)	13.5	11.5
HR (95% CI)	0.768 (0.618, 0.954)	
Stratified *p*-value	0.0169	

2 mos

7-mos OS benefit in lipoSA

(15 vs 8 mos)

Preplanned OS subgroups ana

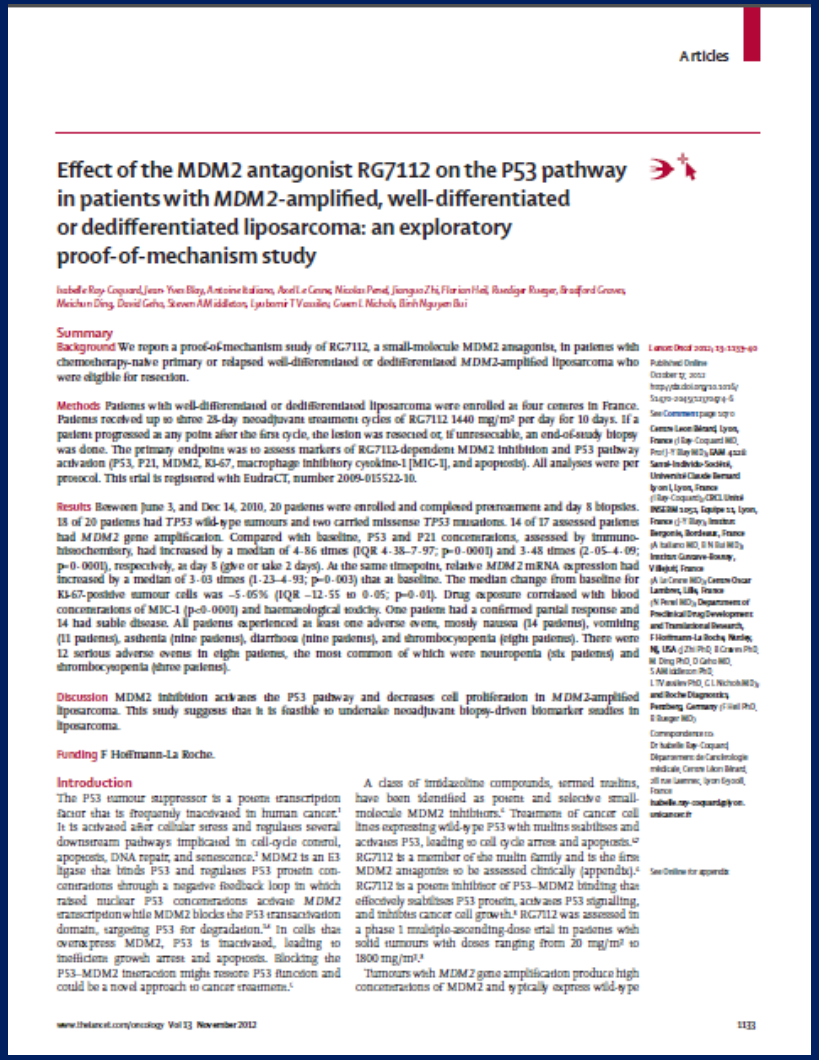
Group/Subgroup	Events/n — Eribulin	Events/n — Dacarbazine	HR (95% CI)	Median (months) — Eribulin	Median (months) — Dacarbazine
Histology					
ADI	52/71	63/72	0.511 (0.346, 0.753)	15.6	8.4
LMS	124/157	118/152	0.927 (0.714, 1.203)	12.7	13
AJCC sarcoma tumor grade score at the date of diagnosis					
High	118/150	125/152	0.796 (0.607, 1.042)	12.7	11.5
Intermediate	57/77	55/69	0.649 (0.439, 0.961)	14.8	10.1

28 January, 2016 FDA approved eribulin mesylate (Halaven)

1. unresectable or advanced liposarcoma

2. after prior anthracycline-based chemotherapy

… pazopanib



Articles

Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with *MDM2*-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study

Isabelle Ray-Coquard, Jean-Yves Blay, Antoine Italiano, Axel Le Cesne, Nicolas Penel, Jiangxia Zhi, Florian Heil, Ruediger Rueger, Bradford Graves, Meichun Ding, David Geho, Steven AM Middleton, Lyubomir T Vassilev, Gwen L Nichols, Binh Nguyen Bui

Summary

Background We report a proof-of-mechanism study of RG7112, a small-molecule MDM2 antagonist, in patients with chemotherapy-naive primary or relapsed well-differentiated or dedifferentiated *MDM2*-amplified liposarcoma who were eligible for resection.

Methods Patients with well-differentiated or dedifferentiated liposarcoma were enrolled at four centres in France. Patients received up to three 28-day neoadjuvant treatment cycles of RG7112 1440 mg/m² per day for 10 days. If a patient progressed at any point after the first cycle, the lesion was resected or, if unresectable, an end-of-study biopsy was done. The primary endpoint was to assess markers of RG7112-dependent MDM2 inhibition and P53 pathway activation (P53, P21, MDM2, KI-67, macrophage inhibitory cytokine-1 [MIC-1], and apoptosis). All analyses were per protocol. This trial is registered with EudraCT, number 2009-015522-10.

Results Between June 3, and Dec 14, 2010, 20 patients were enrolled and completed pretreatment and day 8 biopsies. 18 of 20 patients had *TP53* wild-type tumours and two carried missense *TP53* mutations. 14 of 17 assessed patients had *MDM2* gene amplification. Compared with baseline, P53 and P21 concentrations, assessed by immunohistochemistry, had increased by a median of 4·86 times (IQR 4·38–7·97; p=0·0001) and 3·48 times (2·05–4·09; p=0·0001), respectively, at day 8 (give or take 2 days). At the same timepoint, relative *MDM2* mRNA expression had increased by a median of 3·03 times (1·23–4·93; p=0·003) that at baseline. The median change from baseline for KI-67-positive tumour cells was −5·05% (IQR −12·55 to 0·05; p=0·01). Drug exposure correlated with blood concentrations of MIC-1 (p<0·0001) and haematological toxicity. One patient had a confirmed partial response and 14 had stable disease. All patients experienced at least one adverse event, mostly nausea (14 patients), vomiting (11 patients), asthenia (nine patients), diarrhoea (nine patients), and thrombocytopenia (eight patients). There were 12 serious adverse events in eight patients, the most common of which were neutropenia (six patients) and thrombocytopenia (three patients).

Discussion MDM2 inhibition activates the P53 pathway and decreases cell proliferation in *MDM2*-amplified liposarcoma. This study suggests that it is feasible to undertake neoadjuvant biopsy-driven biomarker studies in liposarcoma.

Funding F Hoffmann-La Roche.

Introduction

The P53 tumour suppressor is a potent transcription factor that is frequently inactivated in human cancer.[1] It is activated after cellular stress and regulates several downstream pathways implicated in cell-cycle control, apoptosis, DNA repair, and senescence.[2] MDM2 is an E3 ligase that binds P53 and regulates P53 protein concentrations through a negative feedback loop in which raised nuclear P53 concentrations activate *MDM2* transcription while MDM2 blocks the P53 transactivation domain, targeting P53 for degradation.[3,4] In cells that overexpress MDM2, P53 is inactivated, leading to inefficient growth arrest and apoptosis. Blocking the P53–MDM2 interaction might restore P53 function and could be a novel approach to cancer treatment.[5]

A class of imidazoline compounds, termed nutlins, have been identified as potent and selective small-molecule MDM2 inhibitors.[6] Treatment of cancer cell lines expressing wild-type P53 with nutlins stabilises and activates P53, leading to cell cycle arrest and apoptosis.[6,7] RG7112 is a member of the nutlin family and is the first MDM2 antagonist to be assessed clinically (appendix).[8] RG7112 is a potent inhibitor of P53–MDM2 binding that effectively stabilises P53 protein, activates P53 signalling, and inhibits cancer cell growth.[8] RG7112 was assessed in a phase 1 multiple-ascending-dose trial in patients with solid tumours with doses ranging from 20 mg/m² to 1800 mg/m².[8]

Tumours with *MDM2* gene amplification produce high concentrations of MDM2 and typically express wild-type

Lancet Oncol 2012; 13: 1133–40
Published Online October 17, 2012
http://dx.doi.org/10.1016/S1470-2045(12)70474-6
See Comment page 1070

Centre Léon Bérard, Lyon, France (I Ray-Coquard MD, Prof J-Y Blay MD, EAM 4218 Santé-Individu-Société, Université Claude Bernard Lyon I, Lyon, France (I Ray-Coquard), CRCL Unité INSERM 1052, Equipe 12, Lyon, France (J-Y Blay), Institut Bergonié, Bordeaux, France (A Italiano MD, B N Bui MD), Institut Gustave-Roussy, Villejuif, France (A Le Cesne MD), Centre Oscar Lambret, Lille, France (N Penel MD), Department of Preclinical Drug Development and Translational Research, F Hoffmann-La Roche, Nutley, NJ, USA (J Zhi PhD, B Graves PhD, M Ding PhD, D Geho MD, S AM Middleton PhD, L T Vassilev PhD, G L Nichols MD), and Roche Diagnostics, Penzberg, Germany (F Heil PhD, R Rueger MD)

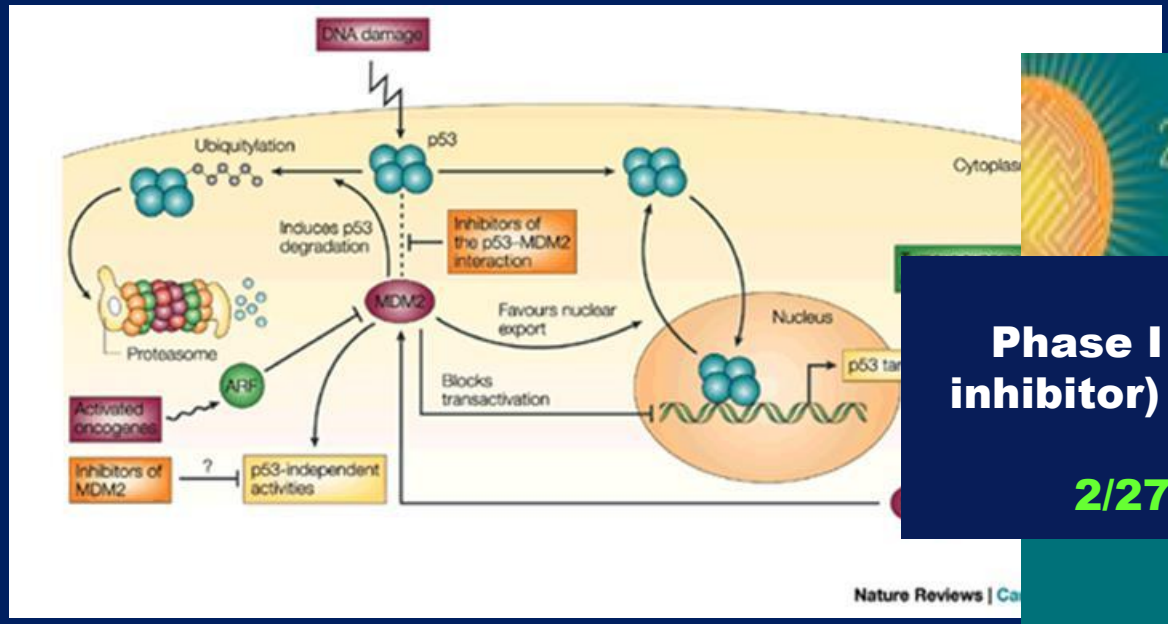
Correspondence to: Dr Isabelle Ray-Coquard, Département de Cancérologie médicale, Centre Léon Bérard, 28 rue Laennec, Lyon 69008, France
isabelle.ray-coquard@lyon.unicancer.fr

See Online for appendix

… MDM2 inhibitor

Ray Coquard I et al, Lancet 2013

… MK-8242 (HDM2 inhibitor)



2015 ASCO Annual Meeting
Illumination&Innovation

Phase I trial of MK-8242 (HDM2 inhibitor) in advanced solid tumors

2/27 RECIST PR (lipoSA)

ASCO

ASCO 2015, abs 10564

… CDK4 inhibitor

VOLUME 31 · NUMBER 16 · JUNE 1 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase II Trial of the CDK4 Inhibitor PD0332991 in Patients With Advanced *CDK4*-Amplified Well-Differentiated or Dedifferentiated Liposarcoma

Mark A. Dickson, William D. Tap, Mary Louise Keohan, Sandra P. D'Angelo, Mrinal M. Gounder, Cristina R. Antonescu, Jonathan Landa, Li-Xuan Qin, Dustin D. Rathbone, Mercedes M. Condy, Yelena Ustoyev, Aimee M. Crago, Samuel Singer, and Gary K. Schwartz

All authors: Memorial Sloan-Kettering Cancer Center, New York, NY.

Published online ahead of print at www.jco.org on April 8, 2013.

Supported by Pfizer and in part by National Cancer Institute, National Institutes of Health, Soft Tissue Sarcoma Program Project Grant No. P01 CA047179 (C.R.A., S.S., G.K.S.).

Presented in part at the 48th Annual Meeting of the American Society for Clinical Oncology, Chicago, IL, June 1-5, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT01209598.

Corresponding author: Mark A. Dickson, MD, 300 E 66th St, New York, NY 10065; e-mail: dicksonm@mskcc.org.

0732-183X/13/3116w-3026w/$20.00

DOI: 10.1200/JCO.2012.46.5670

A B S T R A C T

Purpose

CDK4 is amplified in > 90% of well-differentiated (WDLS) and dedifferentiated liposarcomas (DDLS). The selective cyclin-dependent kinase 4 (CDK4)/CDK6 inhibitor PD0332991 inhibits growth and induces senescence in cell lines and xenografts. In a phase I trial of PD0332991, several patients with WDLS or DDLS experienced prolonged stable disease. We performed an open-label phase II study to determine the safety and efficacy of PD0332991 in patients with advanced WDLS/DDLS.

Patients and Methods

Patients age ≥ 18 years experiencing disease progression while receiving systemic therapy before enrollment received PD0332991 200 mg orally once per day for 14 consecutive days in 21-day cycles. All were required to have *CDK4* amplification by fluorescence in situ hybridization and retinoblastoma protein (RB) expression by immunohistochemistry (≥ 1+). The primary end point was progression-free survival (PFS) at 12 weeks, with 12-week PFS of ≥ 40% considered promising and ≤ 20% not promising. If ≥ nine of 28 patients were progression free at 12 weeks, PD0332991 would be considered active.

Results

We screened 48 patients (44 of 48 had *CDK4* amplification; 41 of 44 were RB positive). Of those, 30 were enrolled, and 29 were evaluable for the primary end point. Grade 3 to 4 events included anemia (17%), thrombocytopenia (30%), neutropenia (50%), and febrile neutropenia (3%). At 12 weeks, PFS was 66% (90% CI, 51% to 100%), significantly exceeding the primary end point. The median PFS was 18 weeks. There was one partial response.

Conclusion

Treatment with the CDK4 inhibitor PD0332991 was associated with a favorable progression-free rate in patients with *CDK4*-amplified and RB-expressing WDLS/DDLS who had progressive disease despite systemic therapy.

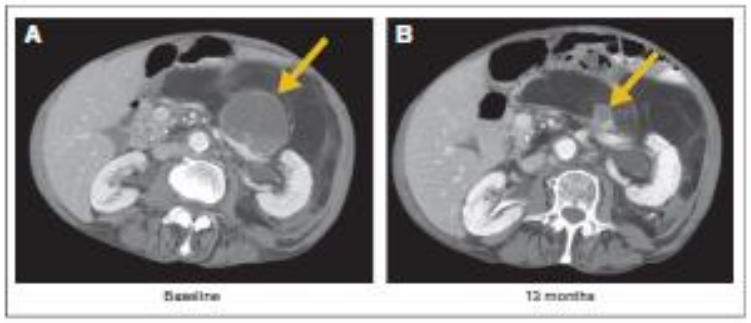
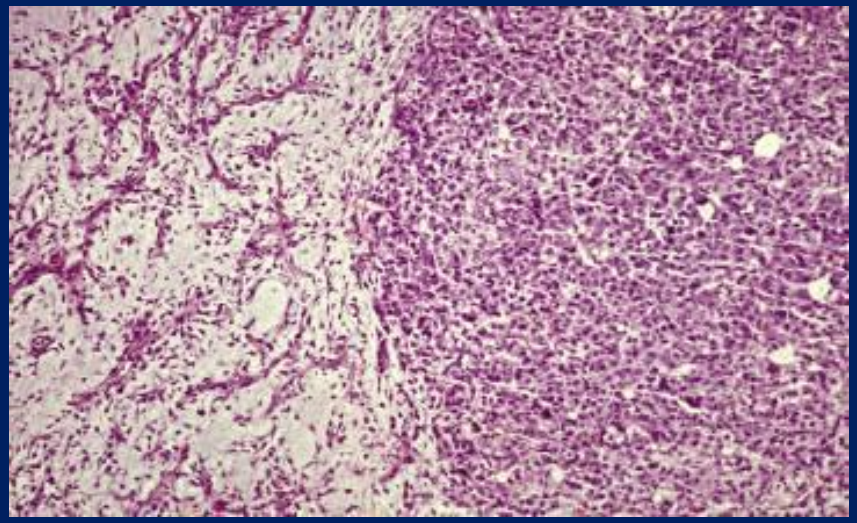


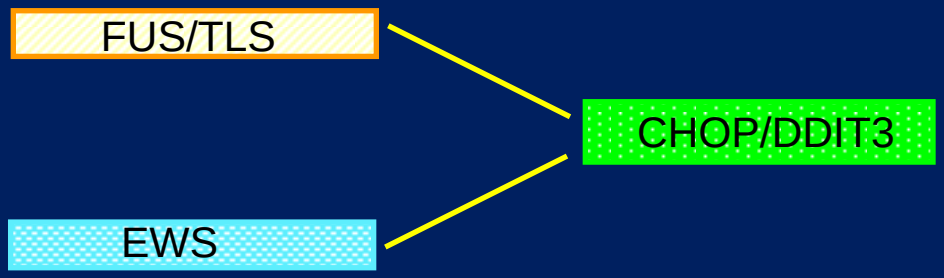
Fig 4. Computed tomography scans at (A) baseline and (B) after 13 months of treatment with PD0332991, demonstrating favorable tumor response (arrows) in dedifferentiated liposarcoma surrounded by well-differentiated liposarcoma.

Dickson MA et al, JCO 2013

Myxoid Liposarcoma



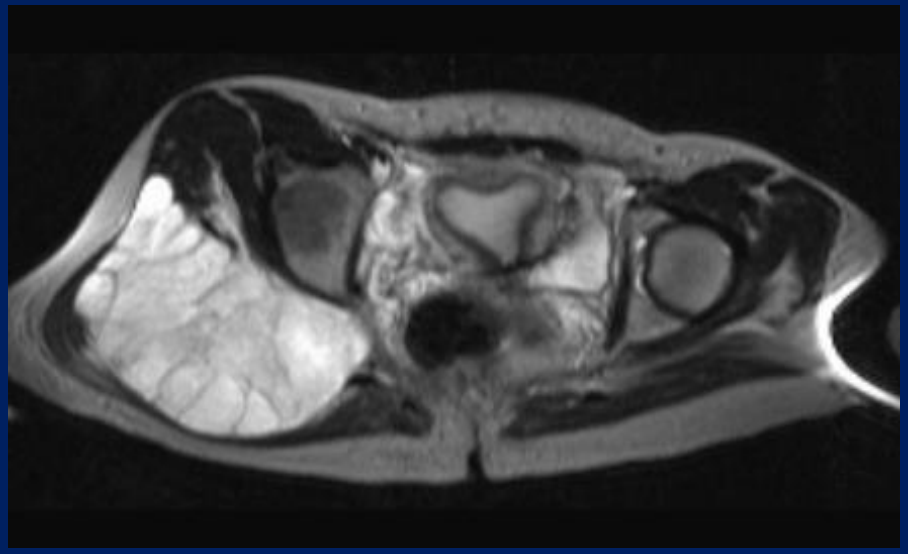
FUS/CHOP t(12;16)(q13;p11) **(95%)**

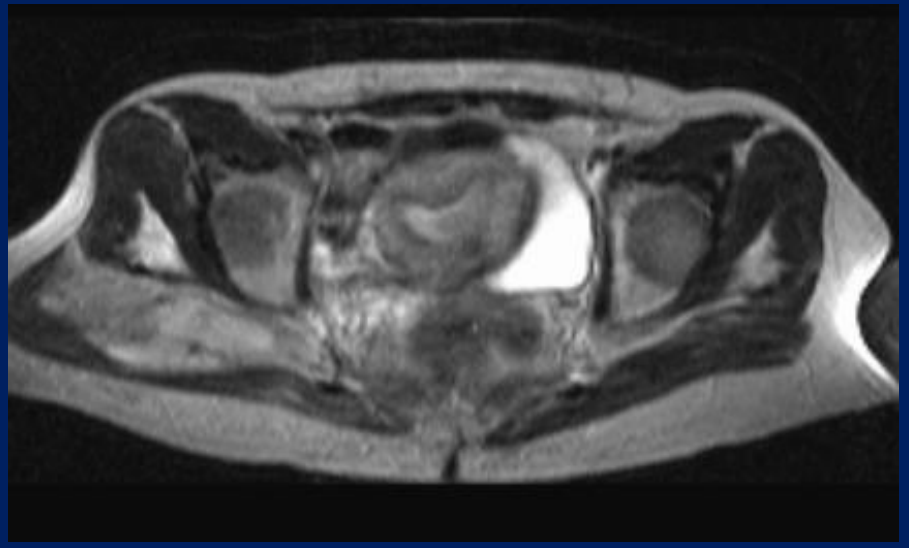


EWS/CHOP t(12;22)(q13;q12) **(5%)**

Rabbitts et al, Nat Genet 1993

… epirubicin +/- ifosfamide

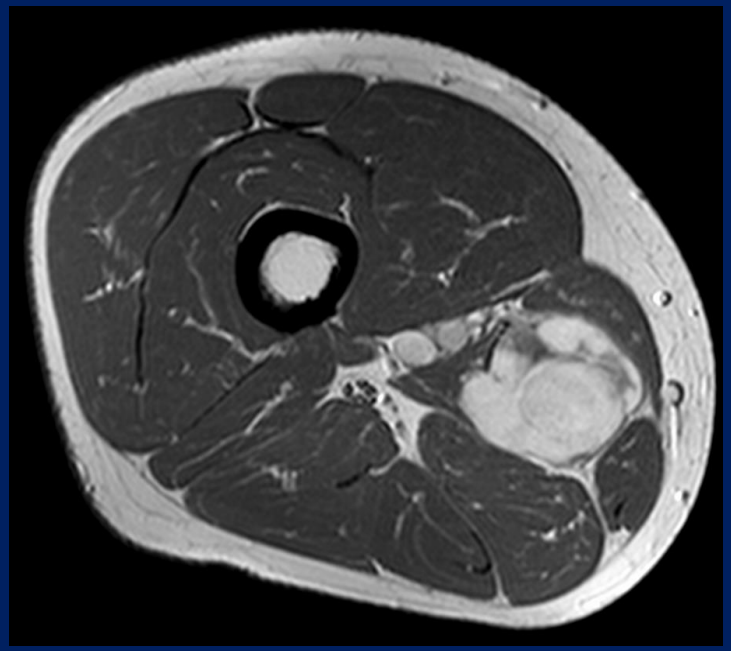




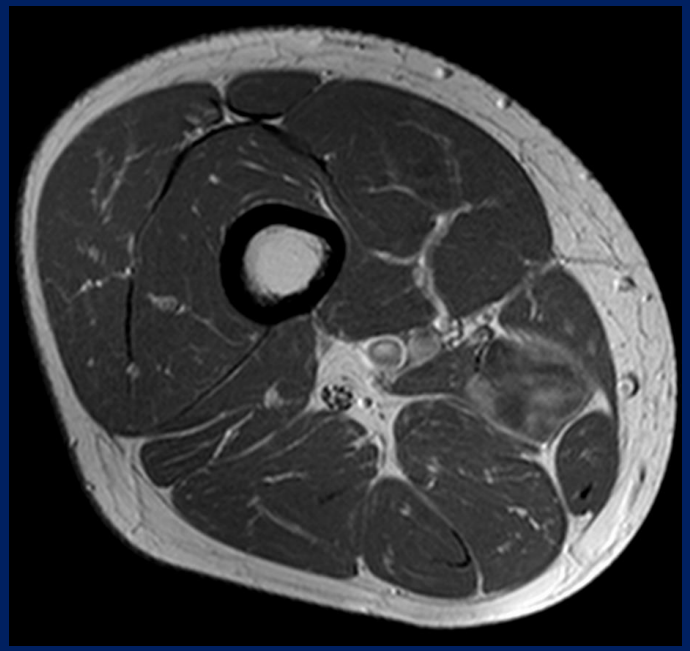
0

+3 cycles

… trabectedin



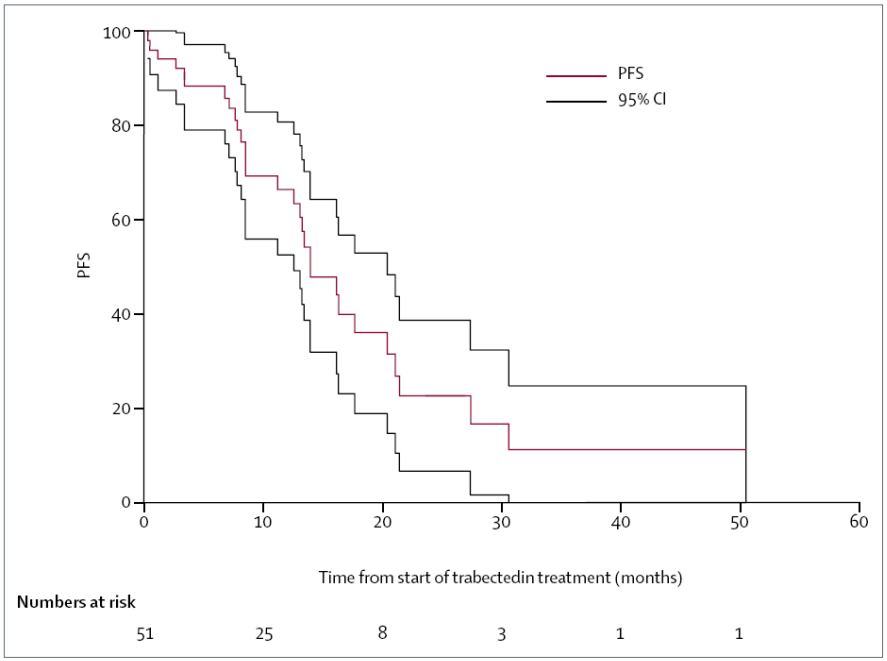
0



+3 mos

Efficacy of trabectedin (ecteinascidin-743) in advanced pretreated myxoid liposarcomas: a retrospective study

Federica Grosso, Robin L Jones, George D Demetri, Ian R Judson, Jean-Yves Blay, Axel Le Cesne, Roberta Sanfilippo, Paola Casieri, Paola Collini, Palma Dileo, Carlo Spreafico, Silvia Stacchiotti, Elena Tamborini, Juan Carlos Tercero, Josè Jimeno, Maurizio D'Incalci, Alessandro Gronchi, Jonathan A Fletcher, Silvana Pilotti, Paolo G Casali



- **32 pts**
- **MRCL**
- **RR 50%**
- **median PFS 18 mos**

Grosso F et al, Lancet Oncol 2007

Oncogene (2014) 33, 5201–5210
© 2014 Macmillan Publishers Limited All rights reserved 0950-9232/14
www.nature.com/onc

ORIGINAL ARTICLE

Mode of action of trabectedin in myxoid liposarcomas

S Di Giandomenico[1,*], R Frapolli[1,*], E Bello[1], S Uboldi[1], SA Licandro[1], S Marchini[2], L Beltrame[1], S Bitch[2], V Mauro[2], E Tamborini[2], S Pilotti[2], PG Casali[3], F Grosso[4], R Sanfilippo[4], A Gronchi[5], R Mantovani[6], R Gatta[6], CM Galmarini[7], JMF Sousa-Faro[7] and M D'Incalci[1]

To elucidate the mechanisms behind the high sensitivity of myxoid/round cell liposarcoma (MRCL) to trabectedin and the suggested selectivity for specific subtypes, we have developed and characterized three MRCL xenografts, namely ML017, ML015 and ML004 differing for the break point of the fusion gene FUS-CHOP, respectively of type I, II and III. FUS-CHOP binding to the promoters of some target genes such as Pentraxin 3 or Fibronectin 1, assessed by chromatin immunoprecipitation, was strongly reduced in the tumor 24 h after the first or the third weekly dose of trabectedin, indicating that the drug at therapeutic doses causes a detachment of the FUS-CHOP chimera from its target promoters as previously shown *in vitro*. Moreover, the higher sensitivity of MRCL types I and II appears to be related to a more prolonged block of the transactivating activity of the fusion protein. Doxorubicin did not affect the binding of FUS-CHOP to target promoters. Histologically, the response to trabectedin in ML017 and ML015 was associated with a marked depletion of non-lipogenic tumoral cells and vascular component, as well as lipidic maturation as confirmed by PPARγ2 expression in western Blot. By contrast, in ML004 no major changes either in the cellularity or in the amount of mature were found, and consistently PPARγ2 was null. In conclusion, the data support the view that the selective mechanism of action of trabectedin in MRCL is specific and related to its ability to cause a functional inactivation of the oncogenic chimera with consequent derepression of the adypocytic differentiation.

Oncogene (2014) **33**, 5201–5210; doi:10.1038/onc.2013.462; published online 11 November 2013

Keywords: trabectedin; myxoid liposarcoma; xenografts; differentiation; transcription regulation

INTRODUCTION

Myxoid liposarcoma is a specific histological type within the family of adult soft tissue sarcomas.[1] It accounts for one-third of liposarcomas and mostly arises in the deep soft tissues of the extremities of adult younger than other sarcomas histotypes.

Microscopically, myxoid liposarcoma is characterized by the presence of myxoid stroma, branching capillary pattern, round/oval-shaped primitive non-lipogenic mesenchymal cells and a variable number of monovacuolated lipoblasts. Better defined by its synonym: myxoid/round cell liposarcoma (MRCL), this tumor represents a morphological continuum of a single biologic entity that differs in the fraction of round cell component. The usual myxoid variant (ML) shows low cellularity, conspicuous vascular network and myxoid stroma, whereas the round cell variant (RCL) shows high cellularity made up of closely packed roundish cells, little or no intervening stroma and a capillary pattern not easy to be visualized. Diagnosis of RCL requires the presence of a round cell component exceeding 5%.[2] This amount is of prognostic relevance as within the MRCL spectrum, the 5-year survival varies between 20 and 70%, and RCL falls in the shortest figures. Recently, the increase in aggressiveness of RCL has been correlated with the activation of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway[3] or via activating mutations of phosphoinositide 3-kinase (PI3K)[4] or inactivation of phosphatase and tensin homolog (PTEN).[5,6]

In line with the morphological continuum and the concept of single biological entity, the ML and RCL share the same balanced translocation, most commonly t(12;16)(q13;p11) fusing FUS (also named as TLS) with CHOP (also named as DDIT3) and rarely t(12;22)(q13;q12), where EWS (Ewing's Sarcoma protein) substitutes for its homologous FUS. The fusion FUS-CHOP- and EWS-CHOP-encoded proteins are believed to function as abnormal transcription factors. FUS-CHOP oncogene consists of the NH2-terminal domain of FUS fused to the entire coding sequence of CHOP.[5,7] The NH2-terminal domain of FUS confers the transactivation domain to the fusion protein.[8,9] CHOP is a member of the C/EBP family of transcription factors that contain a basic leucine zipper domain and a DNA-binding domain.[10,11] CHOP takes part in many processes that involve a response to noxious stimuli, particularly the endoplasmic reticulum stress response. Its expression is tightly regulated and the protein is also implicated in developmental programs.[12,13] One of the most important functions of CHOP is to heterodimerize with other members of the family, serving as a dominant-negative protein by altering their transcriptional potential.[12] Within the constitutively active FUS-CHOP or EWS-CHOP chimeras, CHOP retains the heterodimerization and DNA-binding domains affecting the normal C/EBP activities.[14,15] Genetic and biochemical experiments established the key role of three members C/EBP-α, -β and -γ in adipocyte differentiation. C/EBPβ and C/EBPγ have redundant roles in the early phases of lineage commitment,

[1]Department of Oncology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [3]Adult Sarcoma Medical Treatment Unit; Cancer Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [4]Department of Oncology, SS Antonio e Biagio General Hospital, Alessandria, Italy; [5]Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [6]Dipartimento di Bioscienze, Università degli Studi di Milano, Milan, Italy and [7]Pharmaethic SA, Madrid, Spain. Correspondence: Dr M D'Incalci, Department of Oncology, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', via La Masa 19, Milan 20156, Italy.
E-mail: maurizio.dincalci@marionegri.it
*These authors contributed equally to this work.
Received 24 June 2013; revised 4 September 2013; accepted 5 September 2013; published online 11 November 2013

Microenvironment and Immunology

Cancer Research

Antitumor and Anti-inflammatory Effects of Trabectedin on Human Myxoid Liposarcoma Cells

Giovanni Germano[1], Roberta Frapolli[2], Matteo Simone[2], Michele Tavecchio[2], Eugenio Erba[2], Samantha Pesce[1], Fabio Pasqualini[1], Federica Grosso[3], Roberta Sanfilippo[3], Paolo G. Casali[3], Alessandro Gronchi[4], Emanuela Virdis[5], Eva Tarantino[5], Silvana Pilotti[5], Angela Greco[6], Manuela Nebuloni[7], Carlos María Galmarini[8], Juan Carlos Tercero[8], Alberto Mantovani[1,9], Maurizio D'Incalci[2], and Paola Allavena[1]

Abstract

Inflammatory mediators present in the tumor milieu may promote cancer progression and are considered promising targets of novel biological therapies. We previously reported that the marine antitumor agent trabectedin, approved in Europe in 2007 for soft tissue sarcomas and in 2009 for ovarian cancer, was able to downmodulate the production of selected cytokines/chemokines in immune cells. Patients with myxoid liposarcoma (MLS), a subtype characterized by the expression of the oncogenic transcript *FUS-CHOP*, are highly responsive to trabectedin. The drug had marked antiproliferative effects on MLS cell lines at low nanomolar concentrations. We tested the hypothesis that trabectedin could also affect the inflammatory mediators produced by cancer cells. Here, we show that MLS express several cytokines, chemokines, and growth factors (CCL2, CCL3, CCL5, CXCL8, CXCL12, MIF, VEGF, SPARC) and the inflammatory and matrix-binder protein pentraxin 3 (PTX3), which build up a prominent inflammatory environment. *In vitro* treatment with noncytotoxic concentrations of trabectedin selectively inhibited the production of CCL2, CXCL8, IL-6, VEGF, and PTX3 by MLS primary tumor cultures and/or cell lines. A xenograft mouse model of human MLS showed marked reduction of CCL2, CXCL8, CD68+ infiltrating macrophages, CD31+ tumor vessels, and partial decrease of PTX3 after trabectedin treatment. Similar findings were observed in a patient tumor sample excised after several cycles of therapy, indicating that the results observed *in vitro* might have *in vivo* relevance. In conclusion, trabectedin has dual effects in liposarcoma: in addition to direct growth inhibition, it affects the tumor microenvironment by reducing the production of key inflammatory mediators. *Cancer Res 70(6); 2235–44. ©2010 AACR.*

Introduction

Trabectedin (ET-743; Yondelis) is the first marine-derived anticancer drug that has reached the market. It was approved in Europe in 2007 for second line treatment of soft tissue sarcomas and in 2009 for relapsed ovarian cancer in combination with pegylated liposomal doxorubicin. Studies are in progress to ascertain its efficacy in other neoplastic diseases, including breast and prostate cancer, as suggested by the early clinical trials. Originally derived from the marine tunicate *Ecteinascidia turbinata*, it is now obtained by a semisynthetic method starting from cyanosafracyn B, an antibiotic that can be produced in large quantities by fermentation of *Pseudomonas fluorescens* (1). Trabectedin is a DNA-binding agent interfering with gene transcription, regulation, and DNA repair machinery (2, 3), and is able to induce cell cycle perturbation with a delayed S phase progression and accumulation of cells in G_2 phase (4). Its mechanism of action is incompletely understood and presents some unique features. Unlike most conventional antitumor agents, it binds the minor groove of DNA at the N2 position of guanines, bending the DNA sharply towards the major groove (3, 5, 6); its cytotoxicity seems to be dependent on the efficiency of transcription-coupled nucleotide excision repair, a deficiency of which makes cells less sensitive to the drug instead, cells carrying defects of homologous recombination repair, eg., for *BRCA* gene mutations, are especially sensitive (7–9).

A distinct histologic subtype of soft tissue sarcoma is the myxoid liposarcoma (MLS) which is particularly susceptible to trabectedin (10–12). Second line treatment in patients with MLS was reported to be exceptionally effective with

Authors' Affiliations: [1]Department of Immunology and Inflammation, IRCCS Istituto Clinico Humanitas, Rozzano, [2]Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri, [3]Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine and Departments of [4]Surgery, [5]Pathology, and [6]Experimental Oncology, National Cancer Institute; [7]Pathology Unit, L. Sacco Department of Clinical Sciences and [8]Department of Translational Medicine, University of Milan, Milan, Italy; and [9]Humanitas, Madrid, Spain

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

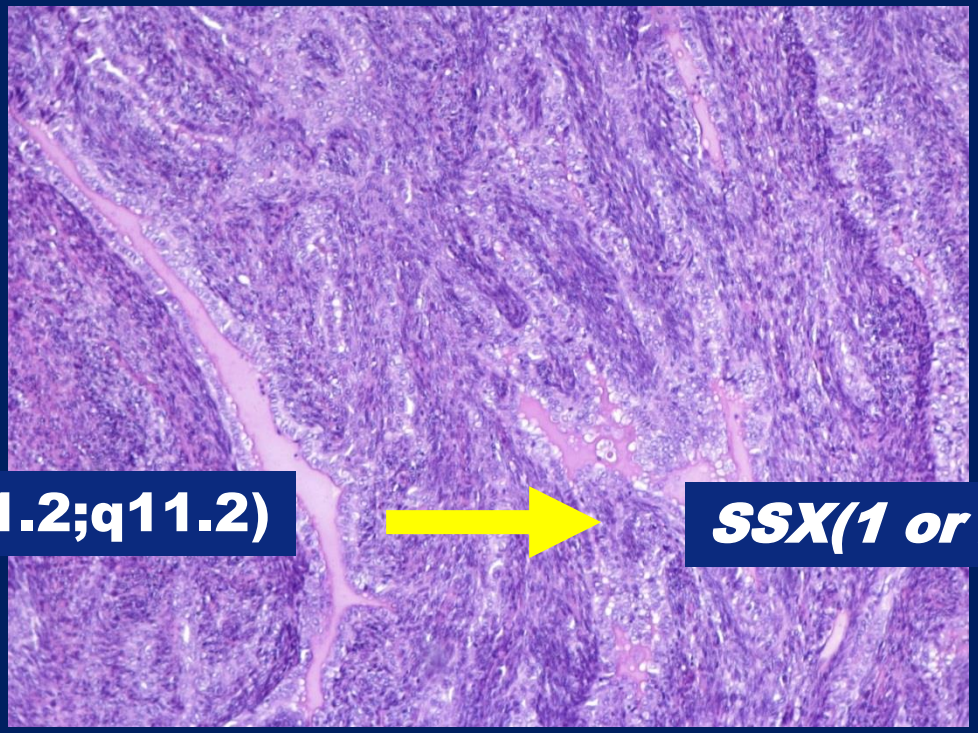
Corresponding Author: Paola Allavena, Istituto Clinico Humanitas, Via Manzoni, 56 Rozzano-Milano, Milan 20089, Italy. Phone: 39-0822-45112; Fax: 39-0822-45101; E-mail: paola.allavena@humanitasresearch.it and Maurizio D'Incalci, Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy. E-mail: maurizio.dincalci@marionegri.it.

doi: 10.1158/0008-5472.CAN-09-2305

Di Giandomenico et al, Oncogene 2014
Germano et al, Cancer Cell 2010

… pazopanib

Synovial Sarcoma

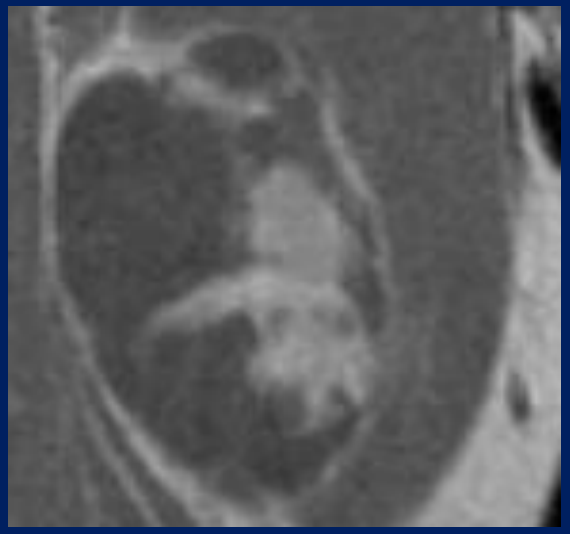


t(X;18)(p11.2;q11.2)

SSX(1 or 2 or 4)/SS18

BAF complex disruption

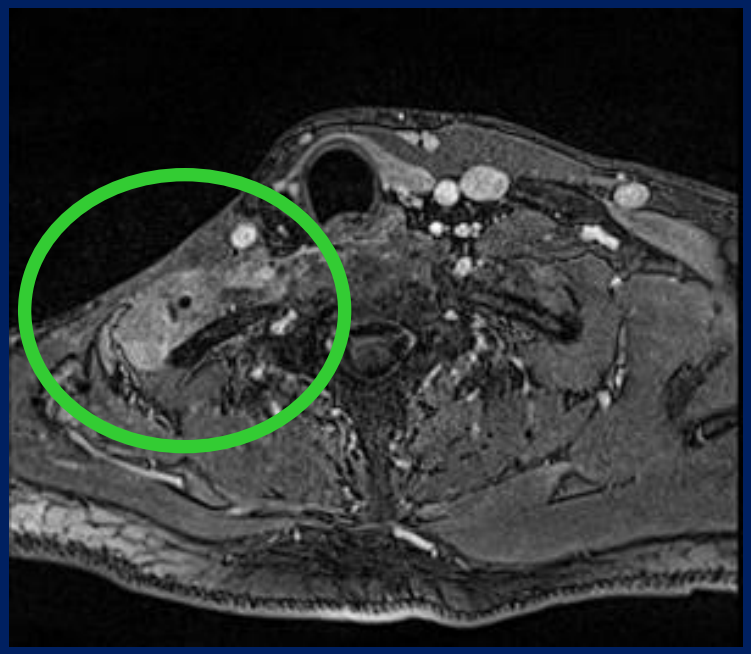
… epirubicin + ifosfamide



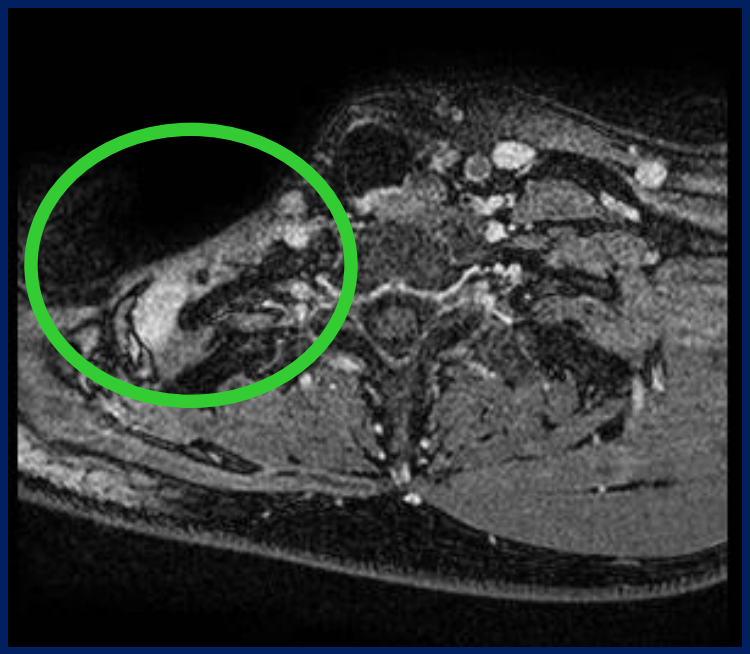
0

+3 cycles

… high-dose ifosfamide



0



+6 mos

Trabectedin in advanced synovial sarcomas: a multicenter retrospective study from four European institutions and the Italian Rare Cancer Network

Roberta Sanfilippo[a], Palma Dileo[a,f], Jean-Yves Blay[h], Anastasia Constantinidou[g], Axel Le Cesne[i], Charlotte Benson[g], Laura Vizzini[b], Marianna Contu[c], Giacomo G. Baldi[d], Angelo P. Dei Tos[e] and Paolo G. Casali[a]

Treatment options for patients with metastatic synovial sarcoma are limited. Over recent years, trabectedin has emerged as an effective agent for patients with advanced soft tissue sarcomas resistant to anthracyclines and ifosfamide. The aim of this retrospective analysis was to study the efficacy of trabectedin in the subgroup of synovial sarcomas. A retrospective analysis was carried out on patients with advanced synovial sarcoma treated with trabectedin at four European reference sarcoma centers and within the Italian Rare Cancer Network between 2000 and 2013. Radiological response, progression-free, and overall survival, as well as serious and unexpected adverse events were retrospectively assessed. Sixty-one patients with metastatic synovial sarcoma were identified. The median number of previous chemotherapy regimens was 2 (range 1–6). Nine patients had a partial response, in addition to two minor responses, and 19 patients had stable disease, for an overall response rate of 15% and a tumor control rate of 50%. The median progression-free survival was 3 months, with 23% of patients free from progression at 6 months. The median progression-free survival in responding patients was 7 months. Trabectedin is a therapeutic option for palliative treatment of a subset of patients with metastatic synovial sarcoma. *Anti-Cancer Drugs* 00:000–000 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Anti-Cancer Drugs 2015, 00:000–000

Keywords: chemotherapy, soft tissue sarcoma, synovial sarcoma, trabectedin

[a]Adult Mesenchymal Tumor Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, [b]Department of Oncology, General Hospital of Agrigento, Agrigento, [c]Department of Oncology, Ospedale Civile SS. Annunziata Sassari, Sassari, [d]Medical Oncology Unit, University Hospital S. Chiara, Pisa, [e]Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy, [f]Department of Oncology, University College of London Hospital, [g]Sarcoma Unit, Royal Marsden, London, UK, [h]Centre Leon Berard, Lyon and [i]Institut Gustave Roussy, Villejuif, France

Correspondence to Roberta Sanfilippo, MD, Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan, Italy
Tel: +39 02 23903 207; fax: +39 0 2239 0280 4;
e-mail: roberta.sanfilippo@istitutotumori.mi.it

Received 30 October 2014 Revised form accepted 10 February 2015

Introduction

Synovial sarcoma accounts for ~10% of all soft tissue sarcomas [1]. The most frequent anatomic location is represented by the limbs; however, it can arise everywhere in the body including visceral sites. Synovial sarcoma presents morphologically as three main variants, namely, spindle cell monophasic, biphasic, and poorly differentiated. A characteristic chromosomal translocation, namely t(X; 18), resulting in the fusion of SYT with either SSX1 or SSX2 (very rarely with SSX4) is observed in the vast majority of cases [1]. Synovial sarcomas can arise at any age, but mainly occur during adolescence and early adulthood [1]. Surgery alone or in combination with radiotherapy, depending on prognostic factors, is the main treatment for localized synovial sarcoma [2]. Despite adequate localized treatment, about 50% of patients relapse, with a median survival after first documented metastases of about 1 year [3].

Synovial sarcomas are considered to be more chemosensitive than some other soft tissue sarcoma subtypes. Doxorubicin and ifosfamide have been considered the drugs most active in synovial sarcoma, with an objective response rate of ~30% or more and better prognosis in responding patients [4-6]. In addition to anthracyclines ± ifosfamide, recommended treatment for patients with advanced disease includes trabectedin and, most recently, pazopanib [2,7]. Trabectedin is approved in Europe for the treatment of adult patients with advanced soft tissue sarcoma after failure of anthracyclines and ifosfamide, or those who are unfit to receive these agents. The benefit has been mainly documented in liposarcoma and leiomyosarcoma [8, 9]. Among others, there are reported cases of partial responses in patients with synovial sarcoma in clinical studies or retrospective series evaluating the activity of trabectedin [10]. The aim of this retrospective analysis was to review all patients with advanced synovial sarcoma treated with trabectedin at four European sarcoma reference centers and within the Italian Rare Cancer Network (RTR; 'Rete Tumori Rari'), a clinical collaborative effort aimed at improving the quality of care in adult rare solid cancers in Italy.

Methods

A retrospective analysis of all cases of advanced synovial sarcoma treated with trabectedin at four sarcoma referral

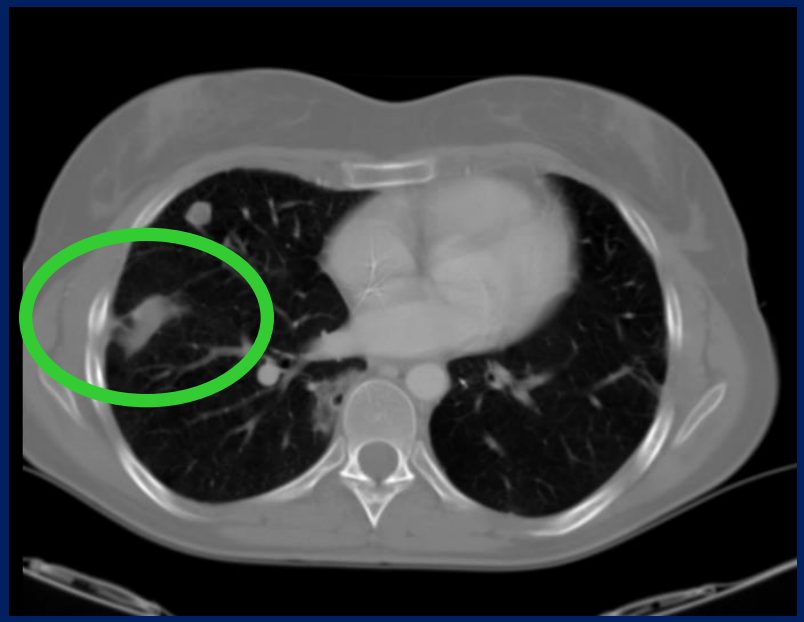
DOI: 10.1097/CAD.0000000000000228

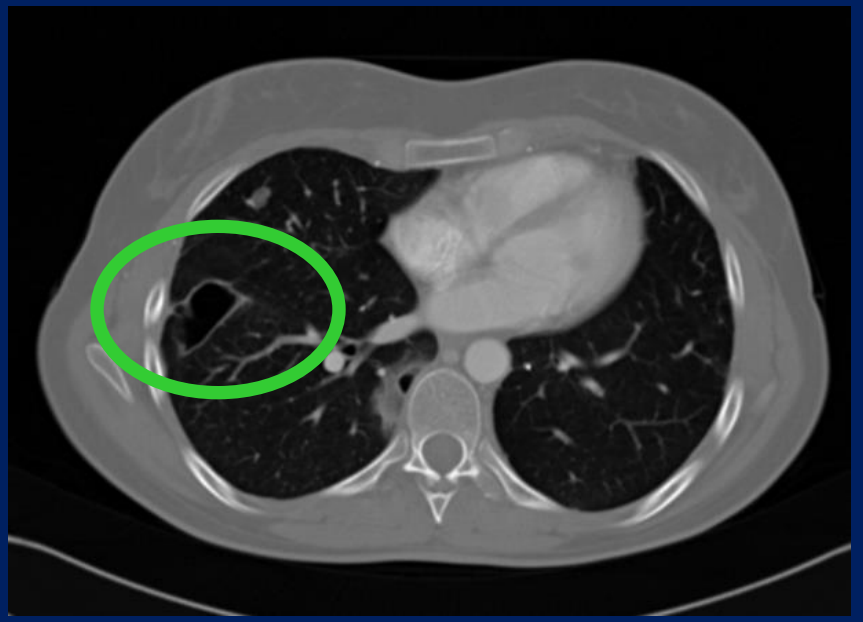
... trabectedin

61 pts
RR: PR 9 (15%); SD 19
median PFS 7 mos

Sanfilippo R et al, Anticancer drugs 2015

… pazopanib





0

+2 mos

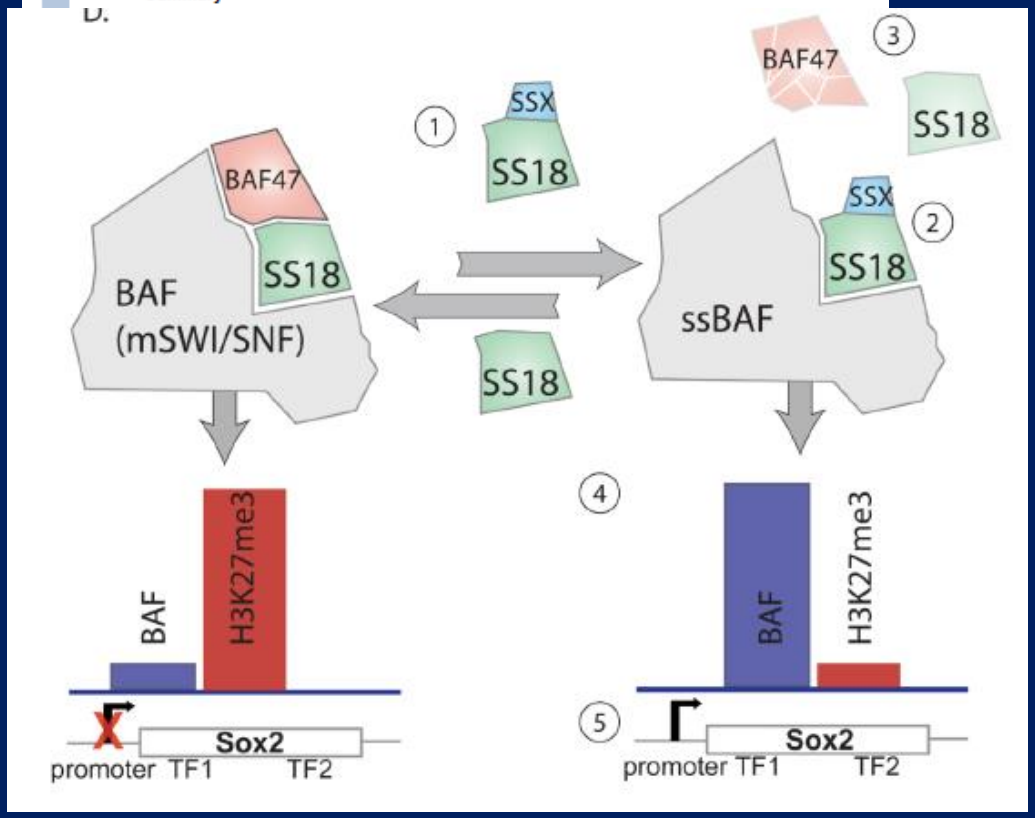
...EZH2 inhibitor, tazemetostat

Published in final edited form as:
Cell. 2013 March 28; 153(1): 71–85. doi:10.1016/j.cell.2013.02.036.

Reversible Disruption of mSWI/SNF (BAF) Complexes by the SS18-SSX Oncogenic Fusion in Synovial Sarcoma

Cigall Kadoch[1,2] and Gerald R. Crabtree[2]
[1]Program in Cancer Biology, Stanford University School of Medicine, Stanford, CA, USA
[2]Howard Hughes Medical Institute and Departments of Pathology and Developmental Biology, Stanford University School of Medicine, Stanford, CA, USA

Summary



Epizyme, Inc. Protocol EZH-202
Amendment 2: 02-Oct-2015

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma
Compound Name (Number):	Tazemetostat (EPZ-6438)
Protocol Number:	EZH-202
Effective Date:	02-Oct-2015
IND Number:	124608
EudraCT Number:	2015-002469-41
Sponsor:	Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA
Sponsor Medical Monitor:	Blythe Thomson, MD Epizyme, Inc. 400 Technology Square, 4th Floor Cambridge, MA 02139 USA Phone: (617) 674-1795 Fax: (617) 349-0707
North America Medical Monitor:	Franklin O. Smith, M.D. Medpace Inc. 5375 Medpace Way Cincinnati, Ohio 45227 USA Phone: (513) 579-9911 Ext. 2087 Mobile: (513) 659-8298 Fax: (513) 579-0444 Email: f.smith@medpace.com
SAE Hotline for North American/Australian sites only:	Phone: +1-800-730-5779 Ext. 2999 or +1-513-579-9911 Ext. 2999 Fax: +1-866-336-5320 or +1-513-579-0444 E-mail: medpace-safetynotification@medpace.com
EU Medical Monitor:	Jamal Gasmi, M.D. Medpace Inc. Phone: +33 1 47 72 98 82 Mobile: +33 677 259 597 E-mail: j.gasmi@medpace.com
SAE Hotline for EU sites only:	Phone: +49 89 89 55 718 44 Fax: +49 89 89 55 718 104 E-mail: medpace-safetynotification@medpace.com

This protocol has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by an Institutional Review Board or Ethics Committee and the performance of all aspects of the study, including the methods used to obtain informed consent, must also be in accordance with the principles enunciated in the declaration, ICH E6 (R1) guidelines of Good Clinical Practice, US FDA CFR Part 50 Protection of Human Subjects and 21 CFR Part 56 Institutional Review Boards, and all applicable regulatory authority requirements.

Kadoch C et al, Cell 2013

...Adoptive T-cell therapy, NY-ESO antigen

VOLUME 29 · NUMBER 7 · MARCH 1 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Tumor Regression in Patients With Metastatic Synovial Cell Sarcoma and Melanoma Using Genetically Engineered Lymphocytes Reactive With NY-ESO-

Paul F. Robbins, Richard A. Morgan, Steven A. Feldman, James C. Yang, Richard M. Sherry, Mark E. Dudley, John R. Wunderlich, Azam V. Nahvi, Lee J. Helman, Crystal L. Mackall, Udai S. Kammula, Marybeth S. Hughes, Nicholas P. Restifo, Mark Raffeld, Chyi-Chia Richard Lee, Catherine L. Levy, Yong F. Li, Mona El-Gamil, Susan L. Schwarz, Carolyn Laurencot, and Steven A. Rosenberg

ABSTRACT

From the National Institutes of Health, National Cancer Institute, Bethesda, MD.

Submitted August 19, 2010; accepted October 21, 2010; published online ahead of print at www.jco.org on January 31, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available at JCO.org.

Corresponding author: Paul F. Robbins, PhD, National Institutes of Health, National Cancer Institute, Surgery Branch, CRC 3-5744, 10 Center Dr, Bethesda, MD 20892-1201; e-mail: Paul_Robbins@nih.gov.

Published by the American Society of Clinical Oncology

0732-183X/11/2907-911/$20.00

DOI: 10.1200/JCO.2010.32.2537

Published OnlineFirst December 23, 2014; DOI: 10.1158/1078-0432.CCR-14-2708

Cancer Therapy: Clinical

Clinical Cancer Research

A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Paul F. Robbins[1], Sadik H. Kassim[1], Thai L.N. Tran[2], Jessica S. Crystal[1], Richard A. Morgan[1], Steven A. Feldman[1], James C. Yang[1], Mark E. Dudley[1], John R. Wunderlich[1], Richard M. Sherry[1], Udai S. Kammula[1], Marybeth S. Hughes[1], Nicholas P. Restifo[1], Mark Raffeld[3], Chyi-Chia R. Lee[3], Yong F. Li[1], Mona El-Gamil[1], and Steven A. Rosenberg[1]

Abstract

Purpose: Although adoptive cell therapy can be highly effective for the treatment of patients with melanoma, the application of this approach to the treatment of other solid tumors has been limited. The observation that the cancer germline (CG) antigen NY-ESO-1 is expressed in 70% to 80% and in approximately 25% of patients with synovial cell sarcoma and melanoma, respectively, prompted us to perform this first-in-man clinical trial using the adoptive transfer of autologous peripheral blood mononuclear cells that were retrovirally transduced with an NY-ESO-1–reactive T-cell receptor (TCR) to heavily pretreated patients bearing these metastatic cancers.

Experimental Design: HLA-A*0201 patients with metastatic synovial cell sarcoma or melanoma refractory to standard treatments and whose cancers expressed NY-ESO-1 received autologous TCR-transduced T cells following a lymphodepleting preparative chemotherapy. Response rates using Response Evaluation Criteria in Solid Tumors (RECIST), as well as immunologic correlates of response, are presented in this report.

Results: Eleven of 18 patients with NY-ESO-1+ synovial cell sarcomas (61%) and 11 of 20 patients with NY-ESO-1+ melanomas (55%) who received autologous T cells transduced with an NY-ESO-1–reactive TCR demonstrated objective clinical responses. The estimated overall 3- and 5-year survival rates for patients with synovial cell sarcoma were 38% and 14%, respectively, whereas the corresponding estimated survival rates for patients with melanoma were both 33%.

Conclusions: The adoptive transfer of autologous T cells transduced with a retrovirus encoding a TCR against an HLA-A*0201 restricted NY-ESO-1 epitope can be an effective therapy for some patients bearing synovial cell sarcomas and melanomas that are refractory to other treatments. *Clin Cancer Res*; 21(5); 1019–27. ©2014 AACR.

Introduction

The in vitro expansion of tumor-infiltrating lymphocytes (TIL) from fresh melanoma samples frequently leads to the generation of T cells reactive with autologous tumor cells. The administration of these TILs following lymphodepleting chemotherapy can mediate objective tumor regressions in 50% to 70% of patients with metastatic melanoma, with some patients achieving durable complete regressions (1). Although there is evidence that T cells derived from additional tumor types can recognize autologous tumors (2–4), tumor-reactive TILs are less frequently obtained from other tumors. One strategy for addressing the difficulty in generating tumor-reactive T cells is the genetic modification of autologous T cells to express cloned T-cell receptors (TCR) directed against shared tumor antigens. Cancer germline (CG) antigens, molecules expressed in a wide variety of tumor types but often not expressed in any adult tissues with the exception of germline cells that lack HLA class I and class II expression, represent attractive targets for these therapies (5). The CG antigen NY-ESO-1 is expressed in 10% to 50% of metastatic melanomas, lung, breast, prostate, thyroid, and ovarian cancers (6–9) as well as between 70% and 80% of synovial cell sarcomas (10). In 2011, we reported preliminary results of this first-in-man clinical trial utilizing the adoptive transfer of autologous peripheral blood mononuclear cells (PBMC) that were transduced with a high-affinity TCR directed against an HLA-A*0201–restricted NY-ESO-1 epitope in 6 and 11 patients with metastatic synovial cell sarcoma and metastatic melanoma, respectively (11). In the current study, we present clinical response data for 12 additional synovial cell sarcoma patients and 9 additional patients with melanoma enrolled in this trial, updated response data for the 17 patients characterized in the first report, and analyses of the in vitro antitumor reactivity and in vivo persistence following adoptive transfer of the administered T cells.

[1]NIH, National Cancer Institute, Surgery Branch, Bethesda, Maryland. [2]University of California, Irvine, California. [3]Laboratory of Pathology, NIH, National Cancer Institute, Bethesda, Maryland.

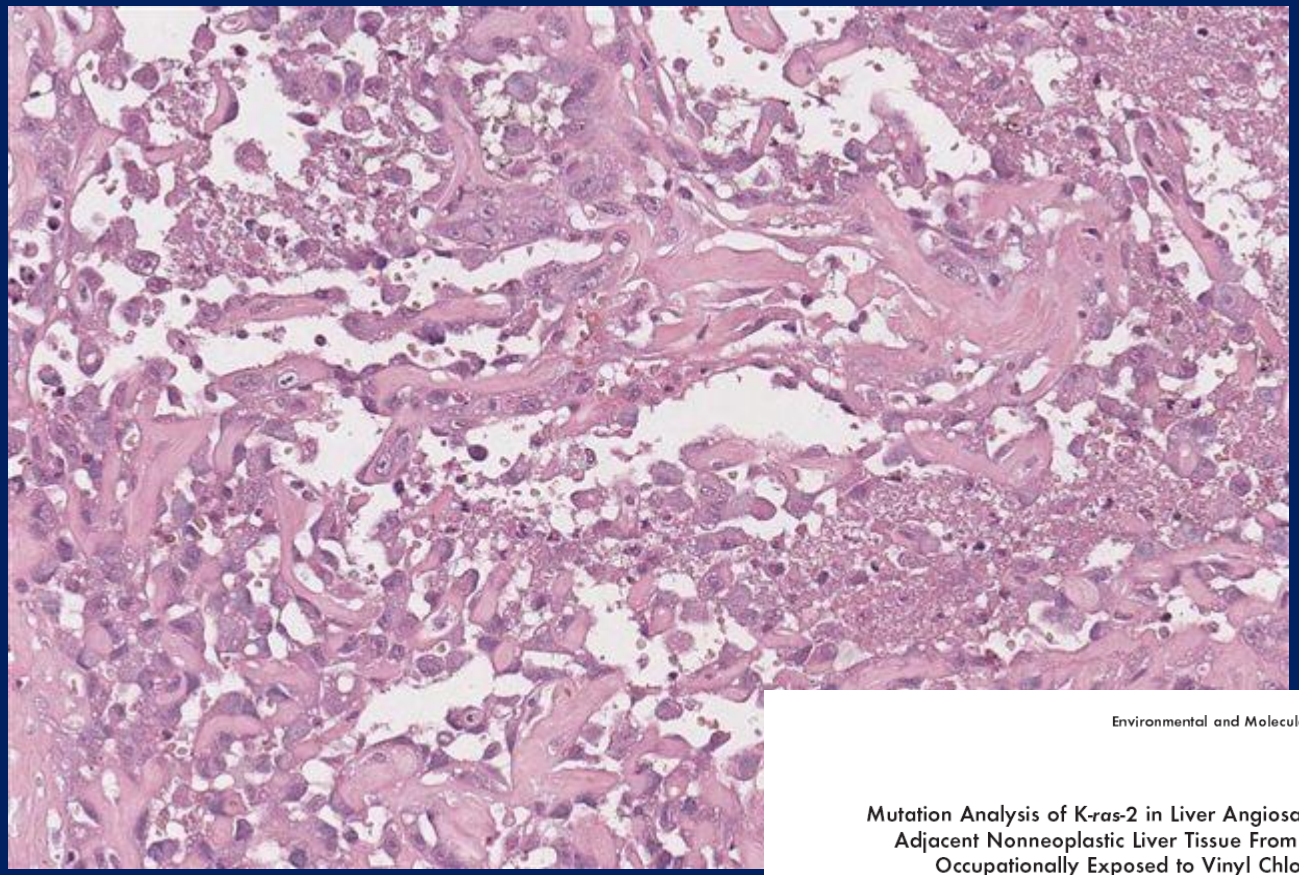
Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Paul F. Robbins, NIH, National Cancer Institute, Surgery Branch, CRC 3-5744, Bethesda, MD 20892. Phone: 301-402-3068; Fax: 301-451-6949; E-mail: Paul_Robbins@nih.gov

doi: 10.1158/1078-0432.CCR-14-2708

Robbins et al JCO 2011
Robbins et al clin Cancer res 2015

Angiosarcoma



Environmental and Molecular Mutagenesis 40:36–40 (2002)

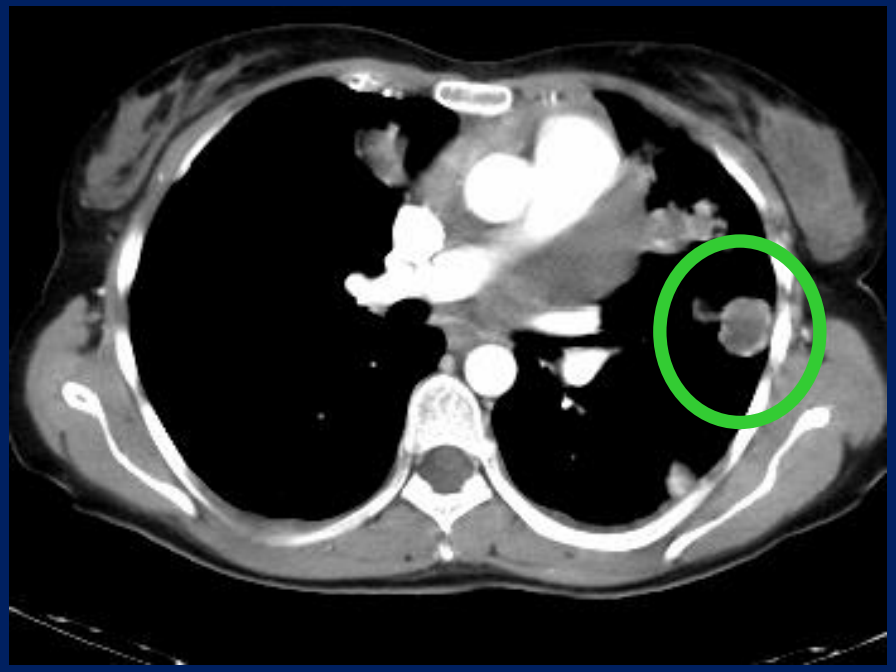
Mutation Analysis of K-*ras*-2 in Liver Angiosarcoma and Adjacent Nonneoplastic Liver Tissue From Patients Occupationally Exposed to Vinyl Chloride

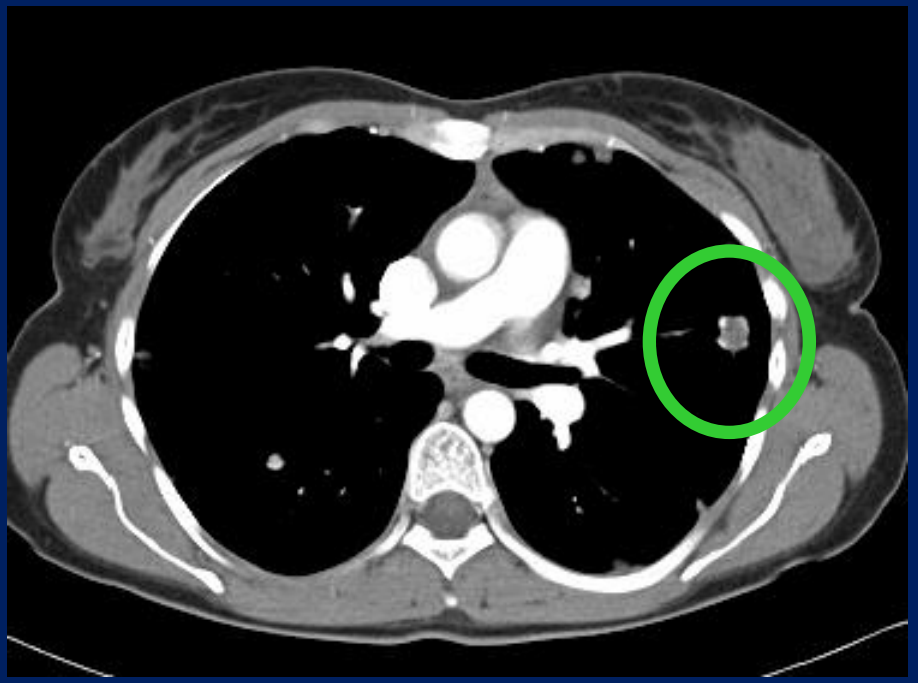
Markus Weihrauch,[1]* Michael Bader,[1] Gerhard Lehnert,[2] Bernd Koch,[3] Christian Wittekind,[4] Renate Wrbitzky,[1] and Andrea Tannapfel[4]*

[1]*Institute of Occupational Medicine, University of Hannover, Germany*
[2]*Institute of Occupational, Social and Environmental Medicine, University of Erlangen, Nuremberg, Germany*
[3]*German Industrial Professional Association for the Chemical Industry, Cologne, Germany*
[4]*Institute of Pathology, University of Leipzig, Germany*

Weihrouch et al, Env and Mol Mutagenesis 2002

... doxo

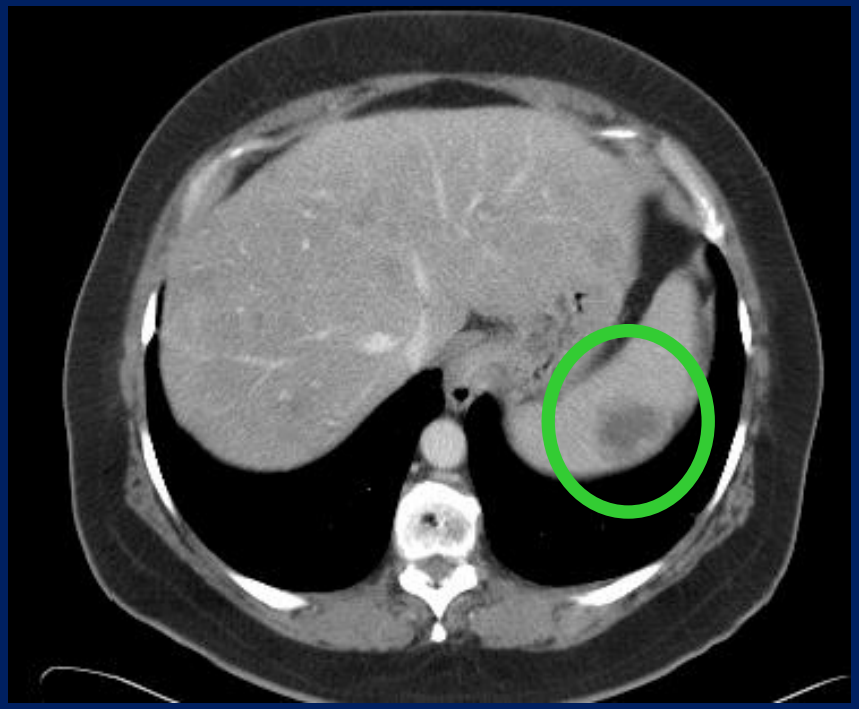




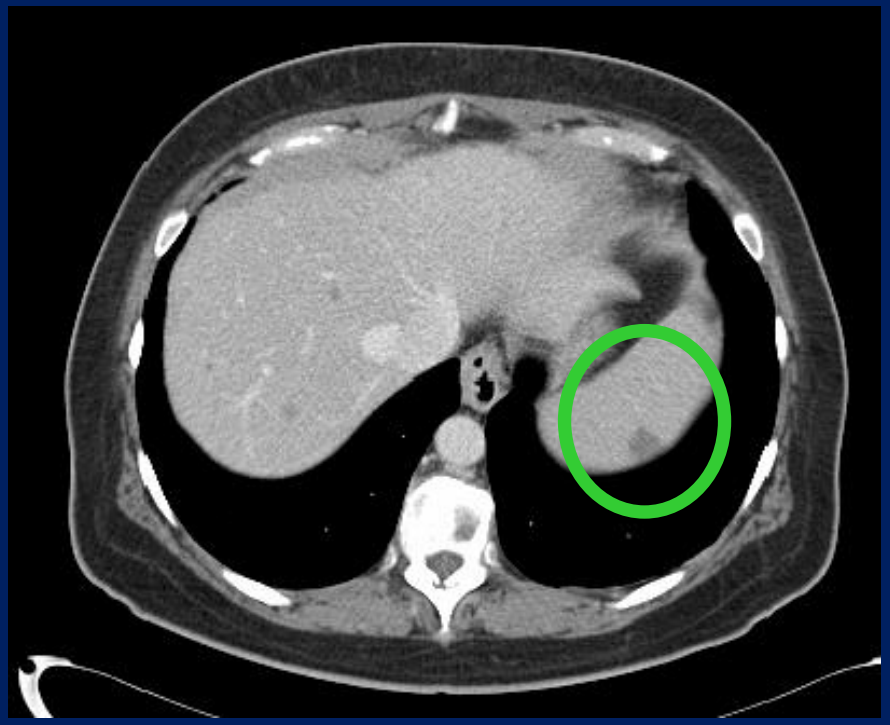
0

+4 mos

… high-dose ifosfamide

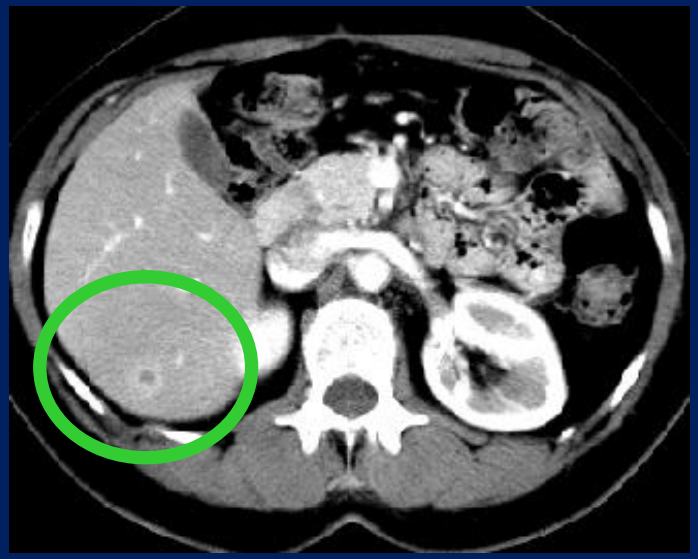


0

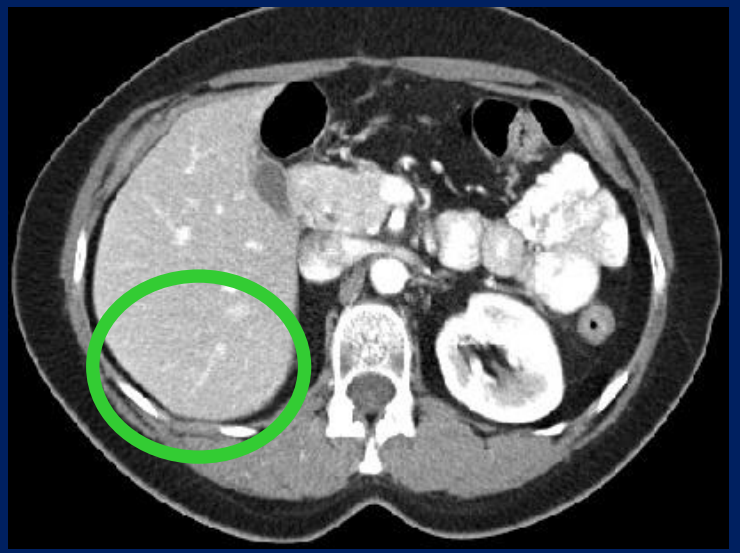


+4 mos

... taxanes



0



+5 mos

VOLUME 26 · NUMBER 32 · NOVEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study

Nicolas Penel, Binh Nguyen Bui, Jacques-Olivier Bay, Didier Cupissol, Isabelle Ray-Coquard, Sophie Piperno-Neumann, Pierre Kerbrat, Charles Fournier, Sophie Taieb, Marta Jimenez, Nicolas Isambert, Frédéric Feyrade, Christine Chevreau, Emmanuelle Bompas, Etienne G.C. Brain, and Jean-Yves Blay

From the Département de Cancérologie Générale, Unité de Biostatistiques, and Département d'Imagerie Médicale, Centre Oscar Lambret; Equipe d'Accueil 2694, Santé Publique, Epidémiologie et modélisation des maladies chroniques, Université Lille II, Lille; Département d'Oncologie Médicale, Institut Bergonié, Bordeaux; Département d'Oncologie Médicale, Centre Jean Perrin, Clermont-Ferrand; Département d'Oncologie Médicale, Centre Val d'Aurelle, Montpellier; Département d'Oncologie Médicale, and Unité U Institut National de la Santé et de la Recherche Médicale 590, Centre Léon Bérard; Service d'Oncologie Médicale, Hôpital Edouard Herriot, Lyon; Département d'Oncologie Médicale, Institut Curie; Bureau des Etudes Cliniques et Thérapeutiques, Fédération Nationale des Centres de Lutte Contre le Cancer, Paris; Département d'Oncologie Médicale, Centre Eugène Marquis, Rennes; Département d'Oncologie Médicale, Centre Georges-François Leclerc, Dijon; Département d'Oncologie Médicale, Centre Antoine Lacassagne, Nice; Département d'Oncologie Médicale, Institut Claudius Regaud, Toulouse; Département d'Oncologie Médicale, Centre René Gauducheau, Nantes; and the Département d'Oncologie Médicale, Centre René Huguenin, Saint-Cloud, France.

Submitted April 7, 2008; accepted June 16, 2008; published online ahead of print at www.jco.org on September 22, 2008.

Supported by La Ligue National Contre le Cancer, Mayne Pharma France, and Chugai Pharma France.

Presented in oral format at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-4, 2007, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Nicolas Penel, MD, Département de Cancérologie Générale, Centre Oscar Lambret, 3 rue Frédéric Combemale, 59020, Lille, France; e-mail: n-penel@o-lambret.fr.

0732-183X/08/2632-5269/$20.00

DOI: 10.1200/JCO.2008.17.3146

A B S T R A C T

Purpose
The objective of this phase II trial was to assess the efficacy and toxicity of weekly paclitaxel for patients with metastatic or unresectable angiosarcoma.

Patients and Methods
Thirty patients were entered onto the study from April 2005 through October 2006. Paclitaxel was administered intravenously as a 60-minute infusion at a dose of 80 mg/m² on days 1, 8, and 15 of a 4-week cycle. The primary end point was the nonprogression rate after two cycles.

Results
The progression-free survival rates after 2 and 4 months were 74% and 45%, respectively. With a median follow-up of 8 months, the median time to progression was 4 months and the median overall survival was 8 months. The progression-free survival rate was similar in patients pretreated with chemotherapy and in chemotherapy-naïve patients (77% *v* 71%). Three patients with locally advanced breast angiosarcoma presented partial response, which enabled a secondary curative-intent surgery with complete histologic response in two cases. One toxic death occurred as a result of a thrombocytopenia episode. Six patients presented with grade 3 toxicities and one patient presented with a grade 4 toxicity. Anemia and fatigue were the most frequently reported toxicities.

Conclusion
Weekly paclitaxel at the dose schedule used in the current study was well tolerated and demonstrated clinical benefit.

J Clin Oncol 26:5269-5274. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Angiosarcomas represent a rare type of visceral and soft tissue sarcoma, accounting for less than 2% of all visceral and soft tissue sarcomas.[1,2] Various clinical forms have been described include primary angiosarcoma of the scalp,[3] angiosarcoma associated with lymphedema,[4,5] primary breast angiosarcoma,[6,7] angiosarcoma arising in irradiated areas,[6-8] and vinyl chloride–induced liver angiosarcomas.[9] These clinical presentations share an aggressive behavior, leading to a short median survival (15 to 30 months) with a less than 12% survival rate at 5 years.[1,6-9]

Recently, a retrospective study has suggested the efficacy of paclitaxel in the treatment of primary angiosarcoma of the scalp,[3] with an objective response reported in eight of nine patients and a median progression-free survival of 5 months. This objective response rate seemed to be superior to the results previously obtained with doxorubicin-based chemotherapy.[3] Moreover, weekly paclitaxel demonstrated significant activity on Kaposi's sarcoma, another vascular-derived tumor.[10,11]

The mode of action of paclitaxel involves the stabilization of microtubules through the inhibition of the depolymerization process.[12,13] This inhibition of depolymerization is observed during the metaphase/anaphase transition of mitosis.[12] Paclitaxel exhibits a wide spectrum of antitumoral activity, including breast cancers (even those refractory to anthracyclines), lung cancers, squamous cell carcinomas of the upper respiratory/digestive tracts, stem cell tumors, lymphomas, and Kaposi's tumors.[13-20]

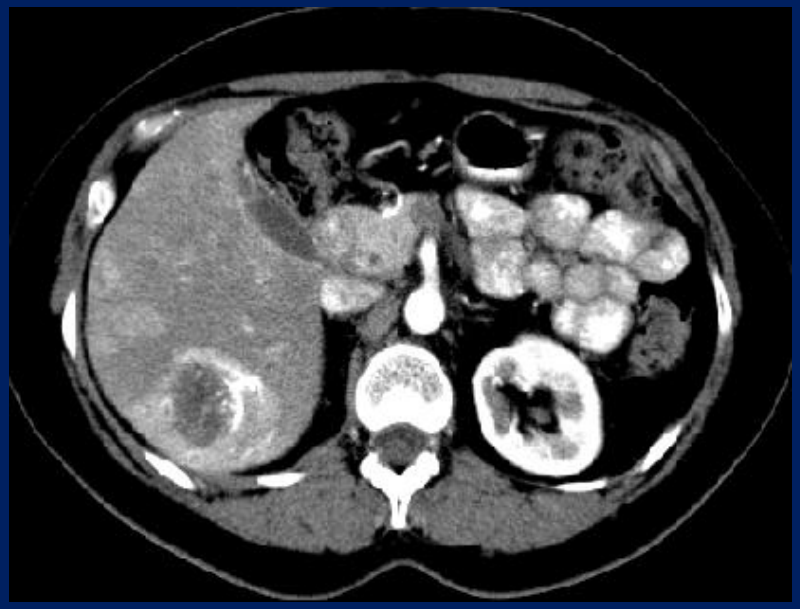
Weekly administration of paclitaxel induces a clear increase in dose-intensity, without significant enhancement of toxicity, for fragile or heavily pretreated patients with ovarian,[16,17] lung,[18,20] or gastric cancers.[19] Therefore, we conducted a multicenter phase II trial to assess the efficacy and toxicity of the weekly paclitaxel regimen in patients with metastatic or unresectable angiosarcomas.

... taxanes

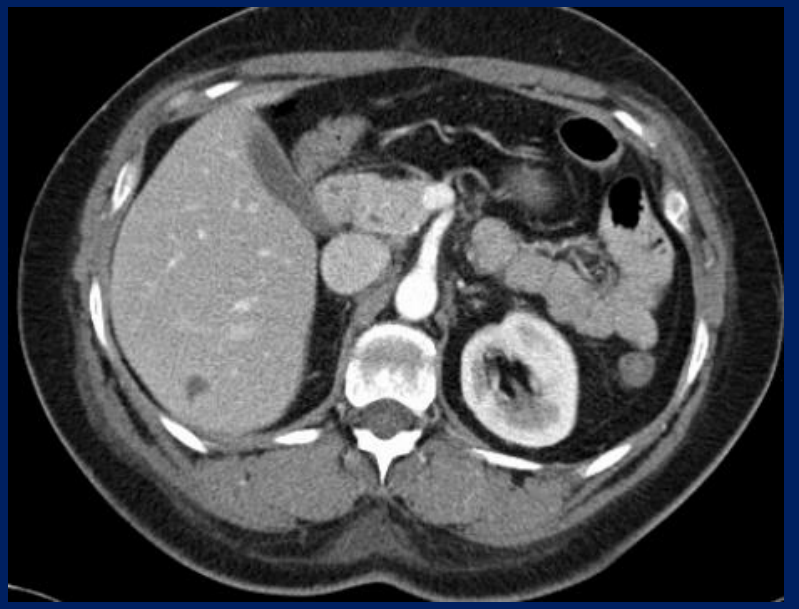
- 30 pts
- weekly low dose, day 1-8-15@28
- advanced angioSA
- RR: 3/30 PR (10%)
- median TTP 4 mos

Penel N et al, JCO 2009

… gem + docetaxel

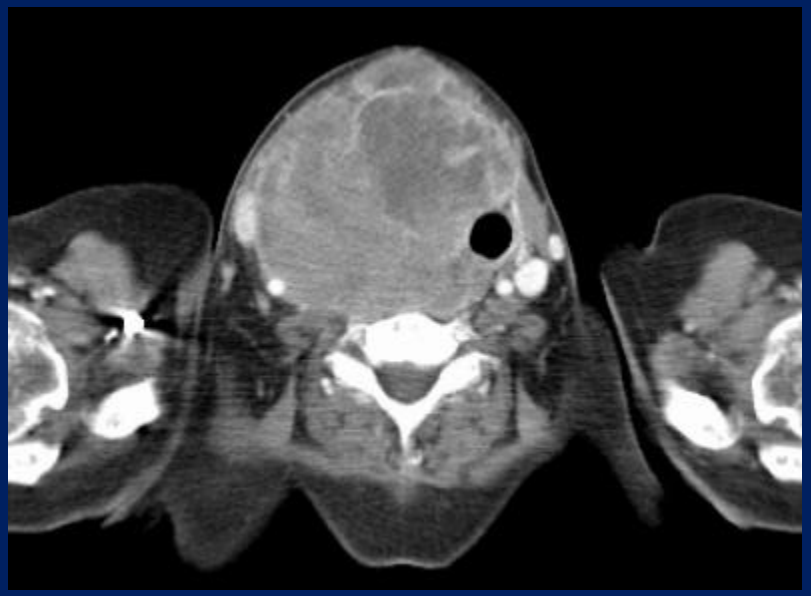


0

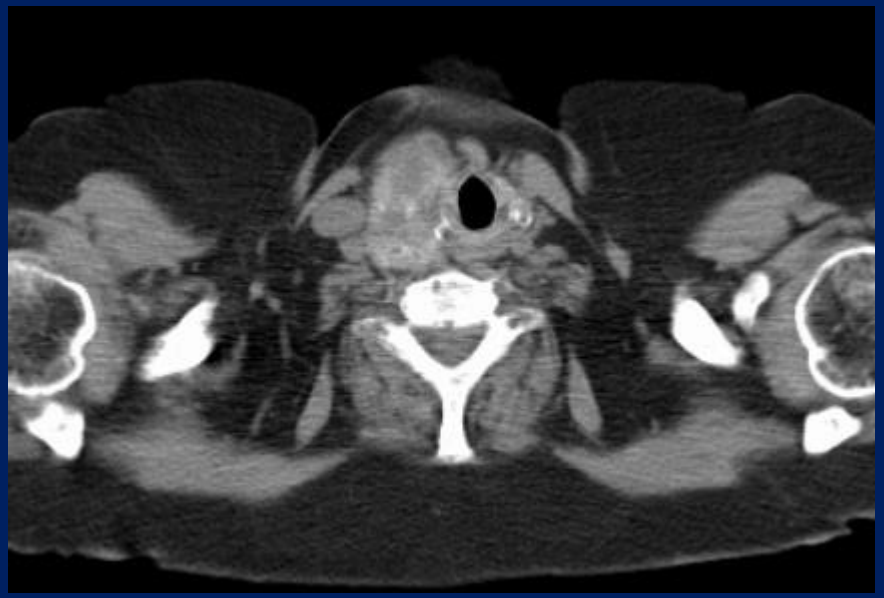


+4 mos

… gemcitabine



0



+4 mos

original article

Annals of Oncology
doi:10.1093/annonc/mdr066

Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network

S. Stacchiotti[1], E. Palassini[1], R. Sanfilippo[1], B. Vincenzi[2], M. G. Arena[3], A. M. Bochicchio[4], P. De Rosa[5], A. Nuzzo[6], S. Turano[7], C. Moros[8], A. P. Dei Tos[9], S. Pilotti[9] & P. G. Casali[10]

[1]Department of Cancer Medicine, Fondazione istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale dei Tumori, Milano; [2]Department of Medical Oncology, University Campus Bio-Medico, Roma; [3]Department of Cancer Medicine, Ospedale Ignazio Tonrlab, Tropea; [4]Department of Cancer Medicine, Istituto di Ricovero e Cura a Carattere Scientifico Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture; [5]Unit of Medical Oncology and Innovative Therapy, Istituto Nazionale Tumori Fondazione G. Pascale, Napoli; [6]Department of Cancer Medicine, Ospedale Renzetti, Lanciano; [7]Department of Cancer Medicine, Ospedale Mariano Santo, Cosenza; [8]Department of Radiology, Fondazione istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milano; [9]Department of Anatomic Pathology, General Hospital of Treviso, Treviso; [10]Department of Pathology and Molecular Biology, Fondazione istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori, Milano, Italy

Received 8 February 2011; accepted 10 February 2011

Background: Angiosarcoma is a highly aggressive soft tissue sarcoma. Responses to anthracyclines plus/minus ifosfamide, and taxanes alone or in combination with gemcitabine are well documented. Very few data are available on gemcitabine as a single agent.

Patients and methods: We retrospectively reviewed all cases of advanced progressive angiosarcoma treated with gemcitabine as a single agent (1000 mg/m^2 i.v. every week for 3 weeks every 4 weeks), at Istituto Nazionale Tumori and within the Italian Rare Cancers Network from January 2008 to November 2010.

Results: Twenty-five patients (mean age: 52 years; radiation therapy (RT)-related: 8) received gemcitabine. Best tumor response by RECIST was as follows: complete response = 2, partial response = 14, stable disease = 2, progressive disease = 7 cases, for an overall response rate (PR + CR) of 68%. Six of eight post-RT angiosarcomas responded to treatment. Median overall survival (OS) was 17 months. Median progression-free survival (PFS) was 7 months (range 1–40 months). One patient with a locally advanced thyroid angiosarcoma became resectable after 5 months of gemcitabine, with <10% residual viable tumor cells seen on surgical specimen. Overall, gemcitabine was well tolerated.

Conclusions: Gemcitabine is active in both RT- and non-RT-related angiosarcoma, with dimensional and possibly long-lasting responses. A formal phase II study on gemcitabine as a single agent is warranted.

Key words: angiosarcoma, chemotherapy, gemcitabine, sarcoma

introduction

Angiosarcoma is a very rare sarcoma (incidence <0.1/100 000/year) of vascular or lymphatic origin, whose cells variably recapitulate the morphological and functional features of normal endothelium [1]. In fact, angiosarcoma expresses vascular antigens, including CD31, CD34, D2-40, FLI-1, and vascular endothelial growth factor [1, 2]. Skin is the most common primary site, followed by deep soft tissues, viscera, and bone [1, 3–7]. Etiology is unknown. Yet, several risk factors for angiosarcoma have been described, such as a previous exposure to vinyl chloride [8–12] or radiation therapy (RT) [3, 13–16], preexisting benign vascular lesions [17], chronic lymphoedema [18], chronic infection/inflammation [3, 19–21], and prolonged immunosuppression [22, 23]. Angiosarcoma is usually regarded as a high-grade tumor, aside from morphology [1], being marked by one of the highest metastatic potentials among sarcomas, with an overall median survival of <4 years and a cure rate of <40% at 5 years. Series with a more favorable outcome after wide surgery and RT have been reported [3–5, 24, 25]. In fact, wide surgery followed by RT is the treatment of choice [25]; however, if primary site and the multifocality of local disease are, considered negative margins are often difficult to achieve [4, 25]. Sometimes, a less aggressive behavior can be seen in skin and breast angiosarcomas. These are the only two locations where angiosarcomas could be classified histologically as low, intermediate, or high grade. Nevertheless, an unfavorable outcome has been recently reported even for skin and breast angiosarcomas, especially in presence of necrosis or of an epithelioid morphology or in post-RT cases, even if the primary tumor is small in size [5, 6, 26–28]. The prognosis of

Correspondence to: Dr S. Stacchiotti, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, 20133 Milano, Italy. Tel: +39-02-2390-2923; Fax: +39-02-2390-2804. E-mail: silvia.stacchiotti@istitutotumori.mi.it

... gemcitabine

- 35 pts
- advanced angioSA
- RR: 2 CR, 14 PR, 2 SD (50%)
- median PFS 7 mos

Stacchiotti S et al, Ann Oncol 2011

Published Ahead of Print on May 18, 2009 as 10.1200/JCO.2008.20.4495
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2008.20.4495

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of Sorafenib in Patients With Metastatic or Recurrent Sarcomas

Robert G. Maki, David R. D'Adamo, Mary L. Keohan, Michael Saulle, Scott M. Schuetze, Samir D. Undevia, Michael B. Livingston, Matthew M. Cooney, Martee L. Hensley, Monica M. Mita, Chris H. Takimoto, Andrew S. Kraft, Anthony D. Elias, Bruce Brockstein, Nathalie E. Blachère, Mark A. Edgar, Lawrence H. Schwartz, Li-Xuan Qin, Cristina R. Antonescu, and Gary K. Schwartz

From the Departments of Medicine, Pathology, Radiology, and Biostatistics and Epidemiology, Memorial Sloan-Kettering Cancer Center, Rockefeller University, New York, NY; Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago; Evanston Northwestern Health Care, Evanston, IL; Carolinas Hematology-Oncology and University of North Carolina, Charlotte, NC; Division of Hematology and Oncology, University Hospitals Case Medical Center, Case Comprehensive Cancer Center, Cleveland, OH; Institute for Drug Development, Cancer Therapy and Research Center at the University of Texas Health Science Center, San Antonio, TX; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC; and the University of Colorado Cancer Center, Aurora, CO.

Submitted October 9, 2008; accepted January 27, 2009; published online ahead of print at www.jco.org on May 18, 2009.

Supported by the National Cancer Institute (NCI) Program Project Grant No. CA47179; NCI phase II contract CM62202; Cycle for Survival; the Shuman Family Fund for GIST research, and the Sarcoma Research Fund.

Presented in part in oral format at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Robert G. Maki, MD, PhD, Melanoma-Sarcoma Program, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, Howard 908, New York, NY 10065; e-mail: makir@mskcc.org.

0732-183X/09/2799-1/$20.00

DOI: 10.1200/JCO.2008.20.4495

ABSTRACT

Purpose
Since activity of sorafenib was observed in sarcoma patients in a phase I study, we performed a multicenter phase II study of daily oral sorafenib in patients with recurrent or metastatic sarcoma.

Patients and Methods
We employed a multiarm study design, each representing a sarcoma subtype with its own Simon optimal two-stage design. In each arm, 12 patients who received 0 to 1 prior lines of therapy were treated (0 to 3 for angiosarcoma and malignant peripheral-nerve sheath tumor). If at least one Response Evaluation Criteria in Solid Tumors (RECIST) was observed, 25 further patients with that sarcoma subtype were accrued.

Results
Between October 2005 and November 2007, 145 patients were treated; 144 were eligible for toxicity and 122 for response. Median age was 55 years; female-male ratio was 1.8:1. The median number of cycles was 3. Five of 37 patients with angiosarcoma had a partial response (response rate, 14%). This was the only arm to meet the RECIST response rate primary end point. Median progression-free survival was 3.2 months; median overall survival was 14.3 months. Adverse events (typically dermatological) necessitated dose reduction for 61% of patients. Statistical modeling in this limited patient cohort indicated sorafenib toxicity was correlated inversely to patient height. There was no correlation between phosphorylated extracellular signal regulated kinase expression and response in six patients with angiosarcoma with paired pre- and post-therapy biopsies.

Conclusion
As a single agent, sorafenib has activity against angiosarcoma and minimal activity against other sarcomas. Further evaluation of sorafenib in these and possibly other sarcoma subtypes appears warranted, presumably in combination with cytotoxic or kinase-specific agents.

J Clin Oncol 27. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Sarcomas are a heterogeneous family of malignancies of soft tissue, with biologic behavior and clinical outcomes distinct for each subtype. For soft tissue sarcomas other than gastrointestinal stromal tumors (GIST), doxorubicin and ifosfamide remain the most active agents against these diseases.[1] Gemcitabine and docetaxel are an active chemotherapy combination against selected sarcoma histologies as well.[2-7]

Patients with metastatic GIST show notable sensitivity to kinase inhibitors imatinib and sunitinib.[8,9] However, the activity of tyrosine kinase inhibitors is less well examined in patients with other soft tissue sarcomas. Imatinib has only anecdotal activity in non-GIST sarcomas except for dermatofibrosarcoma protuberans,[10-12] and studies of inhibitors of mammalian target of rapamycin (mTOR) show only low Response Evaluation Criteria in Solid Tumors (RECIST) response rates.[13-16]

Sorafenib, a small molecule B-raf and vascular endothelial growth factor (VEGF) receptor inhibitor, is potentially useful in several specific sarcoma subtypes, such as malignant peripheral-nerve sheath tumors (MPNST) with loss of *NF1* and activation of the ras-raf signaling pathway.[17-19] Angiosarcomas are inherently a target for antiangiogenic agents. Further, a phase I study of sorafenib in patients with solid tumors indicated a promising 30% 12-week nonprogression rate in patients with metastatic sarcomas.[20]

... sorafenib

RECIST CR/PR: 5/37 angioSA

median PFS 3.2 mos

Maki R et al, JCO 2008

… pazopanib

Correspondence

Low-dose administration of oral pazopanib for the treatment of recurrent angiosarcoma

doi: 10.1111/cod.12575

Angiosarcoma is an aggressive tumour, characterized by a rapid and fatal course.[1] Pazopanib, a multitargeted tyrosine kinase inhibitor (TKI), has been shown to be effective in patients with angiosarcoma.[2–4] Although an advantage of pazopanib is that it can be administered orally, unlike taxanes (currently the standard chemotherapy regimen for angiosarcoma), the frequency of hypertension as an adverse event of pazopanib administration (800 mg/day) is relatively high (approximately 40%).[4] We report two cases of recurrent angiosarcoma successfully treated with low-dose pazopanib.

Patient 1 was an 88-year-old man, who had undergone excision and 70 Gy of electron radiation therapy for angiosarcoma of the scalp 2 years previously (Fig. 1a), as well as excision of metastatic angiosarcoma of the right parotid gland 3 months prior to presentation. He presented with a 2-month history of nodules and purpura on his right cheek (Fig. 1b). He was undergoing treatment for hypertension with amlodipine 10 mg, therefore we started him on oral pazopanib 400 mg/day, which is half the dose of the regular regimen. The recurrent lesion disappeared after 4 weeks (Fig. 1c).

Patient 2 was a 68-year-old man, who had undergone excision for angiosarcoma of the scalp 2 years previously (Fig. 2a). Despite administration of paclitaxel 80 mg/m^2 weekly for 3 months and recombinant interleukin-2 (at a dose of 7×10^6 U with varying administration: once weekly or once every 2 weeks) for 2 years, a purpuric lesion appeared (Fig. 2b). He had been previously treated for hypertension with nifedipine 40 mg and valsartan 80 mg, therefore we started him on oral pazopanib 400 mg/day. After 4 weeks, the recurrent lesion had almost disappeared (Fig. 2c).

The pazopanib dose was reduced because of fatigue after 5 weeks in the first patient, and because of raised serum liver enzyme levels [aspartate aminotransferase 179 IU/L (normal range 5–40 IU/L); alanine aminotransferase 285 IU/L (normal range 2–35 IU/L)] after 6 weeks in the second. Complete reduction in the first patient and partial reduction in the second patient were maintained for 6 months of follow-up, with administration of

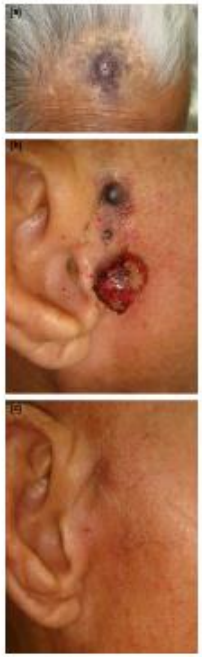


Figure 1 Patient 1: (a) nodule and purpura on the scalp; (b) nodules and purpura on the right cheek; (c) complete disappearance of both nodules and purpura after 5 weeks of pazopanib treatment.

EORTC

The future of cancer therapy

Miura et al, Clin Exp Dermatol 2015

… TRC105 (anti-endoglin) + antiangiogenic

Cancer Therapy: Clinical

Clinical Cancer Research

An Open-Label Phase Ib Dose-Escalation Study of TRC105 (Anti-Endoglin Antibody) with Bevacizumab in Patients with Advanced Cancer

Michael S. Gordon[1], Francisco Robert[2], Daniela Matei[3], David S. Mendelson[1], Jonathan W. Goldman[4], E. Gabriela Chiorean[3,5], Robert M. Strother[3], Ben K. Seon[6], William D. Figg[7], Cody J. Pearl[7], Delia Alvarez[8], Bonnie J. Adams[8], Charles P. Theuer[8], and Lee S. Rosen[4]

Abstract

Purpose: Endoglin, an endothelial cell membrane receptor expressed on angiogenic tumor vessels, is essential for angiogenesis and upregulated in the setting of VEGF inhibition. TRC105 is an anti-endoglin IgG1 monoclonal antibody that potentiates VEGF inhibitors in preclinical models. This study assessed safety, pharmacokinetics, and antitumor activity of TRC105 in combination with bevacizumab.

Experimental Design: Patients (n = 38) with advanced solid tumors, Eastern Cooperative Group performance status 0–1, and normal organ function were treated with escalating doses of TRC105 plus bevacizumab until disease progression or unacceptable toxicity using a standard 3 + 3 phase 1 design.

Results: TRC105 and bevacizumab were well tolerated at their recommended single-agent doses (10 mg/kg) when the initial dose of TRC105 was delayed by one week and divided over 2 days to limit the frequency of headache. The concurrent administration of bevacizumab and TRC105 did not otherwise potentiate known toxicities of TRC105 or bevacizumab. Hypertension and proteinuria were observed, though not at rates expected for single-agent bevacizumab. Several patients who had previously progressed on bevacizumab or VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) treatment experienced reductions in tumor volume, including two partial responses by RECIST, and 6 remained without progression for longer periods than during their prior VEGF inhibitor therapy.

Conclusions: TRC105 was well tolerated with bevacizumab and clinical activity was observed in a VEGF inhibitor–refractory population. Ongoing clinical trials are testing TRC105 in combination with bevacizumab in glioblastoma and with VEGFR TKIs in renal cell carcinoma, hepatocellular carcinoma, and soft tissue sarcoma. *Clin Cancer Res; 20(23); 5918–26. ©2014 AACR.*

Introduction

Angiogenesis is a complex process that is regulated by multiple pathways (1). Approved antiangiogenic drugs, including bevacizumab, sorafenib, sunitinib, and pazopanib, primarily target the VEGF signaling pathway and are associated with modest survival advantages in select indications (2–7). Inhibition of complementary, non-VEGF angiogenic pathways is a strategy that may improve antitumor activity and address resistance to anti-VEGF therapies.

Endoglin (CD105) is a homodimeric TGFβ coreceptor expressed on proliferating vascular endothelium in solid tumors (8, 9). Endoglin is selectively expressed at high density on proliferating endothelial cells and is upregulated by hypoxia through the induction of hypoxia-inducible factor-1-α (HIF1α; refs. 8, 10). Endoglin expression is also upregulated on tumor endothelial cells in response to inhibition of the VEGF pathway and allows continued tumor growth (11, 12). Loss of endoglin expression reverses resistance to large and small-molecule inhibitors of the VEGF pathway (13).

Endoglin is essential for normal vascular development, (14) and loss of endoglin expression is associated with the Osler–Webber–Rendu syndrome, a disease characterized by ectatic blood vessel formation that is associated with improved cancer survival, suggesting that targeting endoglin may have beneficial clinical effects (15, 16). In patients

[1]Pinnacle Oncology Hematology, Scottsdale, Arizona. [2]University of Alabama, Birmingham, Alabama. [3]Indiana University School of Medicine, Indianapolis, Indiana. [4]UCLA Department of Medicine, Los Angeles, California. [5]University of Washington, Seattle, Washington. [6]Roswell Park Cancer Institute, Buffalo, New York. [7]Clinical Pharmacology Program, National Cancer Institute, Bethesda, Maryland. [8]TRACON Pharmaceuticals, San Diego, California.

Prior presentation: Presented in part at the following conferences: 2012 ASCO Annual Meeting, Chicago, IL; The 14th International Symposium on Anti-Angiogenic Therapy, San Diego, CA; 2013 ASCO Annual Meeting, Chicago, IL; 2013 AACR–NCI–EORTC Symposium on Molecular Targets and Cancer Therapeutics, Boston, MA.

Corresponding Author: Michael S. Gordon, Pinnacle Oncology Hematology, 9055 E. Del Camino, Suite 100, Scottsdale, AZ 85258. Phone: 480-889-5000; Fax: 480-314-0033; E-mail: mgordon@azpoh.com

doi: 10.1158/1078-0432.CCR-14-1143

2015 ASCO Annual Meeting
Illumination&Innovation

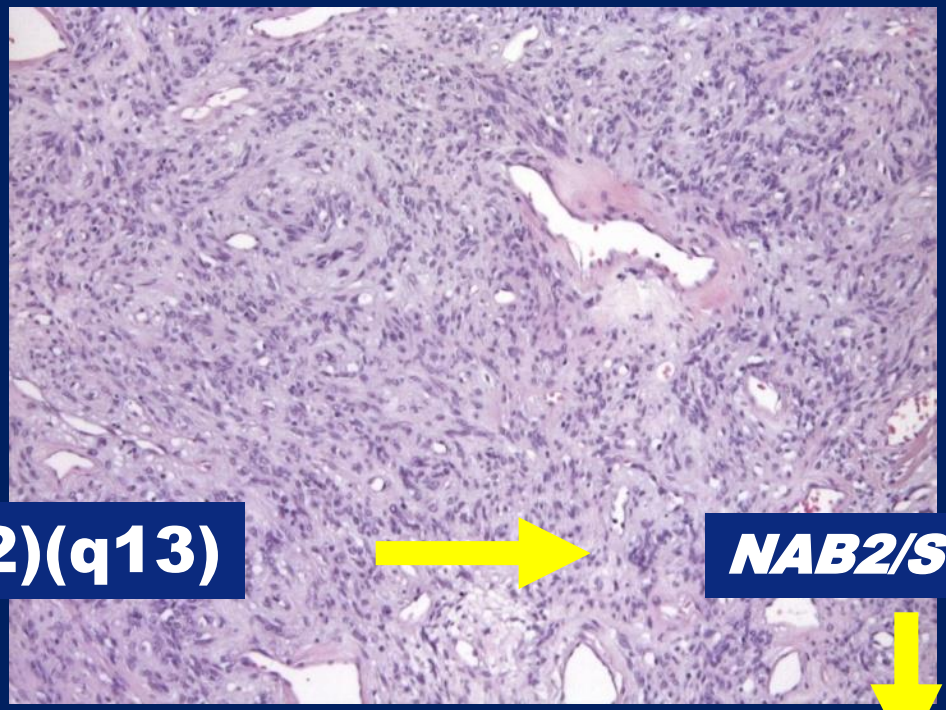
Phase Ib trial anti-endoglin antibody (TRC105) + pazopanib in STS

> 1 CR in cutaneus angioSA

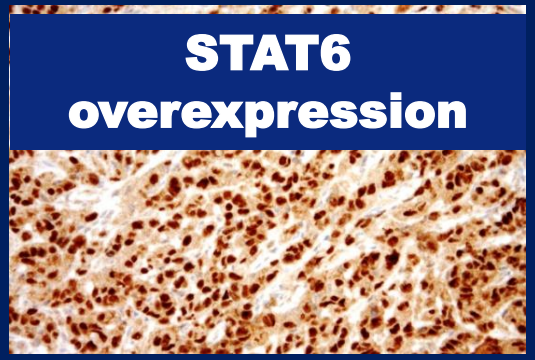
ASCO

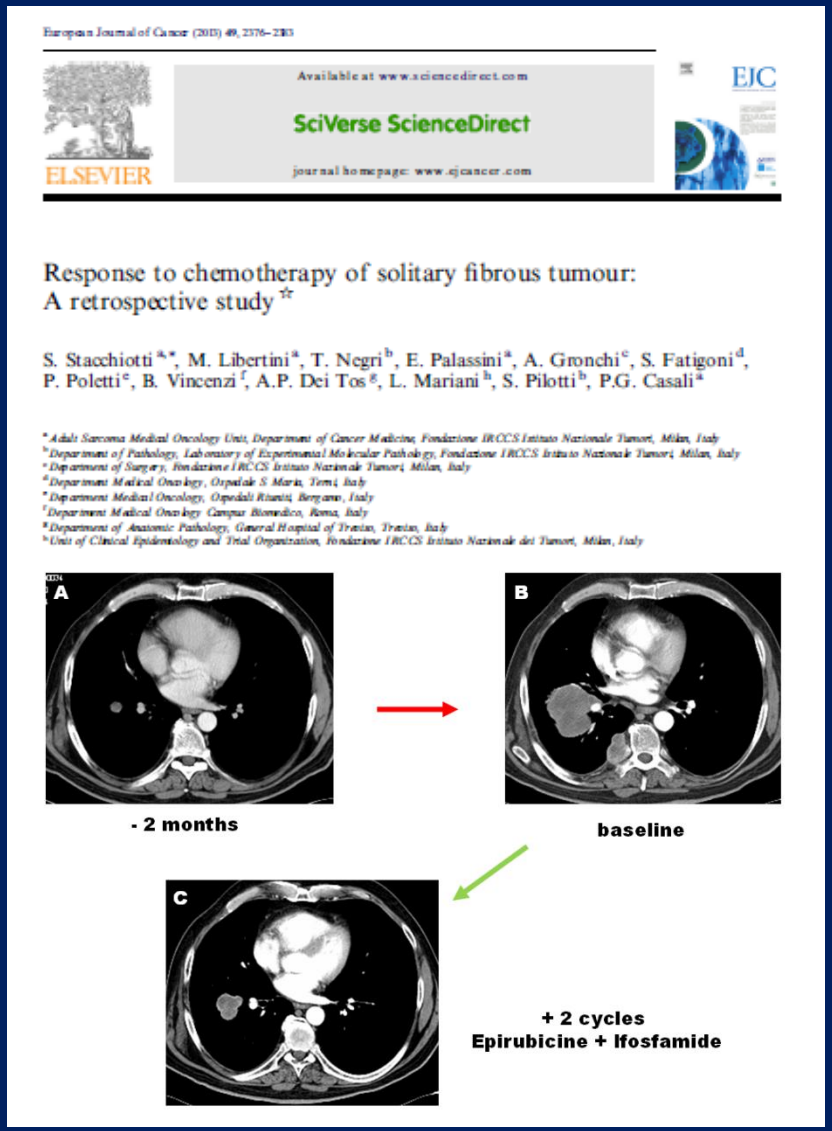
Gordon M et al, Clin Cancer Res 2014
ASCO 2015, abs 10514

Solitary Fibrous Tumor



inv(12)(q13) → *NAB2/STAT6*





European Journal of Cancer (2013) 49, 2376–2383

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Response to chemotherapy of solitary fibrous tumour: A retrospective study ☆

S. Stacchiotti [a,*], M. Libertini [a], T. Negri [b], E. Palassini [a], A. Gronchi [c], S. Fatigoni [d], P. Poletti [e], B. Vincenzi [f], A.P. Dei Tos [g], L. Mariani [h], S. Pilotti [b], P.G. Casali [a]

[a] Adult Sarcoma Medical Oncology Unit, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[b] Department of Pathology, Laboratory of Experimental Molecular Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[c] Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[d] Department Medical Oncology, Ospedale S. Maria, Terni, Italy
[e] Department Medical Oncology, Ospedali Riuniti, Bergamo, Italy
[f] Department Medical Oncology Campus Biomedico, Roma, Italy
[g] Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy
[h] Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

... adria

31 pts

Anthracyclin-based CT

RECIST: 20% PR

Median PFS 4 mos

Stacchiotti S et al, Eur J Cancer 2013

Original Article

Activity of Temozolomide and Bevacizumab in the Treatment of Locally Advanced, Recurrent, and Metastatic Hemangiopericytoma and Malignant Solitary Fibrous Tumor

Min S. Park, MD[1]; Shreyaskumar R. Patel, MD[1]; Joseph A. Ludwig, MD[1]; Jonathan C. Trent, MD, PhD[1]; Charles A. Conrad, MD[2]; Alexander J. Lazar, MD, PhD[3]; Wei-Lien Wang, MD[3]; Piyaporn Boonsirikamchai, MD[4]; Haesun Choi, MD[4]; Xuemei Wang, MS[5]; Robert S. Benjamin, MD[1]; and Dejka M. Araujo, MD[1]

BACKGROUND: Hemangiopericytomas and malignant solitary fibrous tumors (HPC/SFT) are rare, closely related sarcomas with unpredictable behavior that respond infrequently to chemotherapy. An optimal systemic treatment strategy for advanced HPC/SFT has not yet been identified. **METHODS:** We retrospectively analyzed the records of 14 patients with histopathologically confirmed HPC/SFT who were treated at The University of Texas MD Anderson Cancer Center between May 2005 and June 2007. All patients were treated with temozolomide 150 mg/m^2 orally on days 1-7 and days 15-21 and bevacizumab 5 mg/kg intravenously on days 8 and 22, repeated at 28-day intervals. Computed tomography assessment of tumor size and density (Choi criteria) was used to determine the best response to therapy. The Kaplan-Meier method was used to estimate progression-free survival. **RESULTS:** The median follow-up period was 34 months. Eleven patients (79%) achieved a Choi partial response, with a median time to response of 2.5 months. Two patients (14%) had stable disease as the best response, and 1 patient (7%) had Choi progressive disease as the best response. The estimated median progression-free survival was 9.7 months, with a 6-month progression-free rate of 78.6%. The most frequently observed toxic effect was myelosuppression. **CONCLUSION:** Combination therapy with temozolomide and bevacizumab is a generally well-tolerated and clinically beneficial regimen for HPC/SFT patients. Additional investigation in a controlled, prospective trial is warranted. *Cancer 2011;000:000–000. © 2011 American Cancer Society.*

KEYWORDS: hemangiopericytoma, solitary fibrous tumors, soft tissue sarcoma, chemotherapy, anti-angiogenesis inhibitors.

Hemangiopericytomas and solitary fibrous tumors (HPC/SFT) are closely related soft tissue sarcomas that appear to exhibit fibroblastic-type differentiation[1,2] and typically affect adults aged 20-70 years. Common sites of involvement include the lower extremities, retroperitoneum/pelvis, lung/pleura, and meninges, but these tumors may be found at virtually any body site.[3-5] Histological features that suggest aggressive behavior are not well defined in HPC/SFT. Surgery is typically the treatment of choice for localized disease, with reported 10-year overall survival rates of 54%-89% after complete surgical resection.[6-8]

For the approximately 20% of HPC/SFT patients who eventually develop local recurrences and/or distant metastases, additional resections should be considered but are not always feasible.[6,9] Options for effectively treating unresectable

Corresponding author: Min S. Park, MD, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Unit 450, P.O. Box 301402, Houston, TX 77230-1402; Fax: (713) 794-1934; mspark@mdanderson.org

[1]Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Department of Neuro-oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [3]Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [4]Department of Radiology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Department of Biostatistics and Bioinformatics, The University of Texas MD Anderson Cancer Center, Houston, Texas

Presented in part at the 44th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2008, Chicago, IL, and at the 14th Annual Meeting of the Connective Tissue Oncology Society, November 13-15, 2008, London, United Kingdom.

DOI: 10.1002/cncr.26098; Received: November 1, 2010; Revised: January 20, 2011; Accepted: January 26, 2011; Published online in Wiley Online Library (wileyonlinelibrary.com)

… temozolomide/ bevacizumab

14 pts

Tem 150 mg/day d 1-7 & 15-21 @28
Bev 5 mg/kg day 8 & 22 @28

Park H et al, Cancer 2011

… dacarbazine

Published OnlineFirst July 25, 2013; DOI: 10.1158/1078-0432.CCR-13-0776

Clinical Cancer Research

Cancer Therapy: Clinical

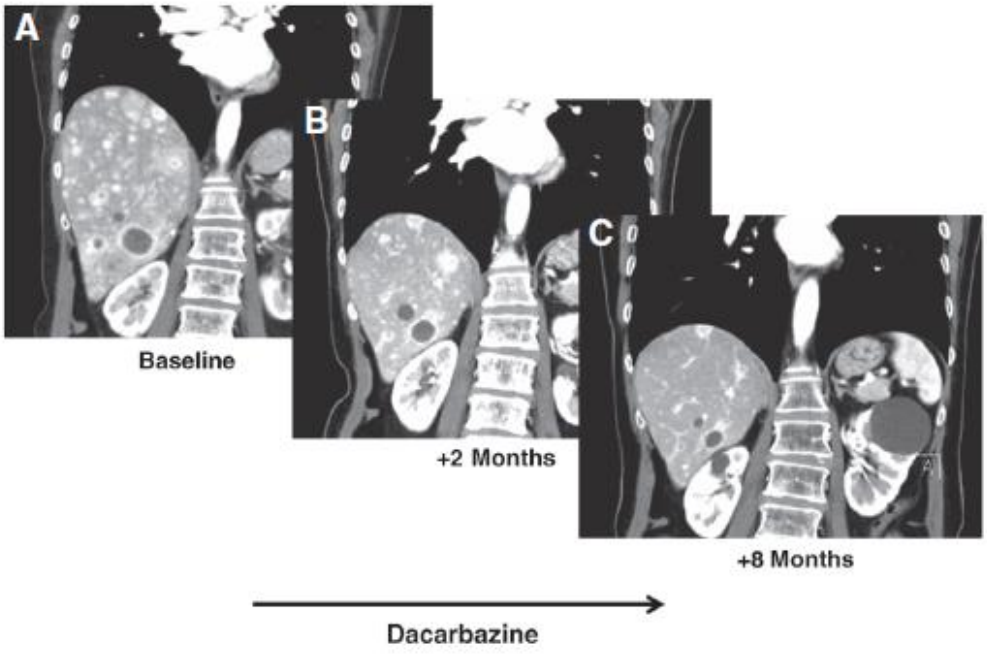
Dacarbazine in Solitary Fibrous Tumor: A Case Series Analysis and Preclinical Evidence vis-à-vis Temozolomide and Antiangiogenics

S. Stacchiotti[1], M. Tortoreto[2], F. Bozzi[3], E. Tamborini[3], C. Morosi[4], A. Messina[4], M. Libertini[1], E. Palassini[1], D. Cominetti[2], T. Negri[3], A. Gronchi[5], S. Pilotti[3], N. Zaffaroni[2], and P.G. Casali[1]

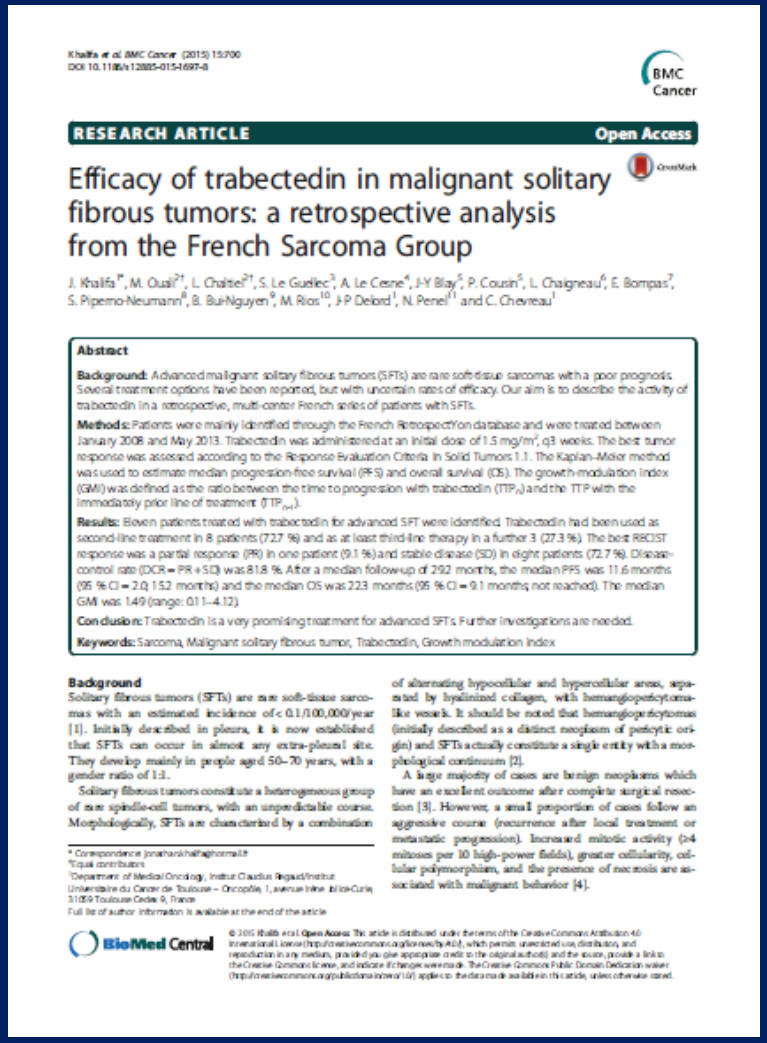
Abstract

Purpose: To explore the value of triazines in solitary fibrous tumor (SFT).

Experimental Design: We retrospectively reviewed 8 cases of patients with SFT treated with dacarbazine (1,200 mg/m^2 every 3 weeks) as from January 2012. Then, we studied a dedifferentiated-SFT subcutaneously xenotransplanted into severe combined immunodeficient (SCID) mice. Dacarbazine, temozolomide, sunitinib, bevacizumab, and pazopanib were administered at their reported optimal doses for the mouse model when mean tumor volume (TV) was about 80 mm^3; each experimental groups included 6 mice. Drug activity was assessed as tumor volume inhibition percentage (TVI%). Dacarbazine was tested according to two different schedules of administration. One hundred twenty days after treatment interruption, mouse tumor samples were analyzed.



Stacchiotti S et al, Clin Cancer Res 2013



Khalfa et al. BMC Cancer (2015) 15:700
DOI 10.1186/s12885-015-1697-8

BMC Cancer

RESEARCH ARTICLE Open Access

Efficacy of trabectedin in malignant solitary fibrous tumors: a retrospective analysis from the French Sarcoma Group

J. Khalfa[*], M. Ouali[2†], L. Chaltiel[2†], S. Le Guellec[3], A. Le Cesne[4], J-Y Blay[5], P. Cousin[5], L. Chaigneau[6], E. Bompas[7], S. Piperno-Neumann[8], B. Bui-Nguyen[9], M. Rios[10], J-P Delord[1], N. Penel[11] and C. Chevreau[1]

Abstract

Background: Advanced malignant solitary fibrous tumors (SFTs) are rare soft-tissue sarcomas with a poor prognosis. Several treatment options have been reported, but with uncertain rates of efficacy. Our aim is to describe the activity of trabectedin in a retrospective, multi-center French series of patients with SFTs.

Methods: Patients were mainly identified through the French RetrospectYon database and were treated between January 2008 and May 2013. Trabectedin was administered at an initial dose of 1.5 mg/m², q3 weeks. The best tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors 1.1. The Kaplan-Meier method was used to estimate median progression-free survival (PFS) and overall survival (OS). The growth-modulation index (GMI) was defined as the ratio between the time to progression with trabectedin (TTP_{tr}) and the TTP with the immediately prior line of treatment (TTP_{pre}).

Results: Eleven patients treated with trabectedin for advanced SFT were identified. Trabectedin had been used as second-line treatment in 8 patients (72.7 %) and as at least third-line therapy in a further 3 (27.3 %). The best RECIST response was a partial response (PR) in one patient (9.1 %) and stable disease (SD) in eight patients (72.7 %). Disease-control rate (DCR = PR + SD) was 81.8 %. After a median follow-up of 29.2 months, the median PFS was 11.6 months (95 % CI = 2.0; 15.2 months) and the median OS was 22.3 months (95 % CI = 9.1 months; not reached). The median GMI was 1.49 (range: 0.11–4.12).

Conclusion: Trabectedin is a very promising treatment for advanced SFTs. Further investigations are needed.

Keywords: Sarcoma, Malignant solitary fibrous tumor, Trabectedin, Growth modulation index

Background

Solitary fibrous tumors (SFTs) are rare soft-tissue sarcomas with an estimated incidence of < 0.1/100,000/year [1]. Initially described in pleura, it is now established that SFTs can occur in almost any extra-pleural site. They develop mainly in people aged 50–70 years, with a gender ratio of 1:1.

Solitary fibrous tumors constitute a heterogeneous group of rare spindle-cell tumors, with an unpredictable course. Morphologically, SFTs are characterized by a combination of alternating hypocellular and hypercellular areas, separated by hyalinized collagen, with hemangiopericytoma-like vessels. It should be noted that hemangiopericytomas (initially described as a distinct neoplasm of pericytic origin) and SFTs actually constitute a single entity with a morphological continuum [2].

A large majority of cases are benign neoplasms which have an excellent outcome after complete surgical resection [3]. However, a small proportion of cases follow an aggressive course (recurrence after local treatment or metastatic progression). Increased mitotic activity (≥4 mitoses per 10 high-power fields), greater cellularity, cellular polymorphism, and the presence of necrosis are associated with malignant behavior [4].

* Correspondence: jonathankhalfa@hotmail.fr
†Equal contributors
[1]Department of Medical Oncology, Institut Claudius Regaud/Institut Universitaire du Cancer de Toulouse – Oncopôle, 1, avenue Irène Joliot-Curie, 31059 Toulouse Cedex 9, France
Full list of author information is available at the end of the article

… trabectedin

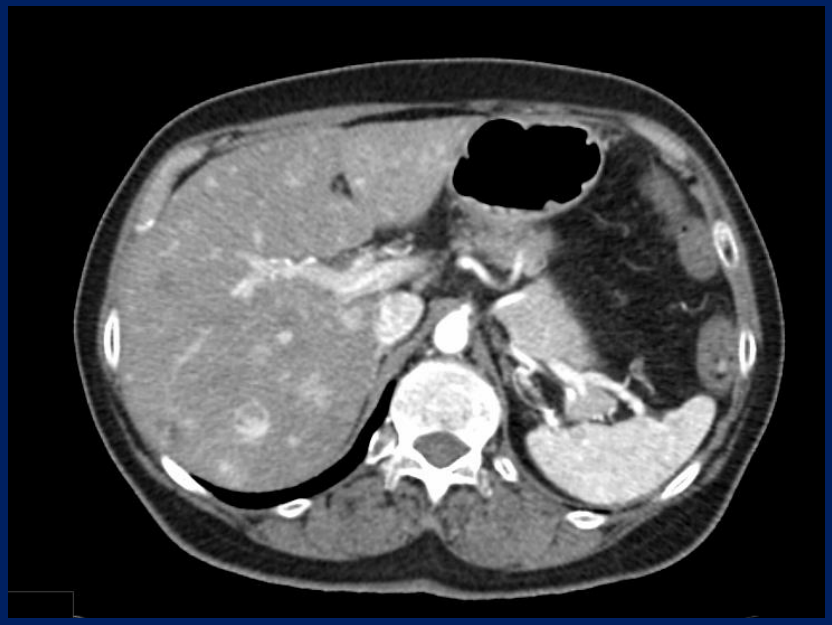
11 pts

RECIST: 1, 9% PR

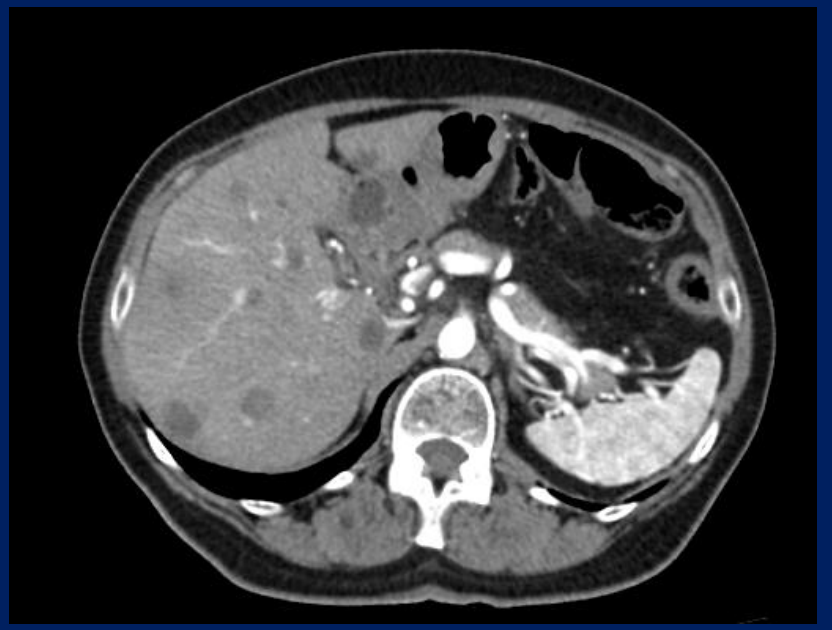
Median PFS 11 mos

Khalfa J. et al, BMC Cancer 2015

… sunitinib



0



+6 mos

… sunitinib

Annals of Oncology

original articles

Annals of Oncology 23: 3171–3179, 2012
doi:10.1093/annonc/mds143
Published online 17 June 2012

Sunitinib malate in solitary fibrous tumor (SFT)

S. Stacchiotti[1*], T. Negri[2], M. Libertini[1], E. Palassini[1], A. Marrari[1], B. De Troia[1], A. Gronchi[3], A. P. Dei Tos[5], C. Morosi[4], A. Messina[4], S. Pilotti[2] & P. G. Casali[1]

[1]Department of Cancer Medicine, Adult Sarcoma Medical Oncology Unit; [2]Department of Pathology, Experimental Molecular Pathology Unit; [3]Department of Surgery; [4]Department of Radiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [5]Department of Anatomic Pathology, General Hospital of Treviso, Treviso, Italy

Received 6 March 2012; revised 3 April 2012; accepted 10 April 2012

Background: To report on sunitinib activity in a retrospective series of 35 solitary fibrous tumor (SFT) treated at a single institution.

Patients and methods: From April 2008, 35 patients with progressive advanced SFT (male/female: 20/15; mean age: 58 years; meningeal/extrameningeal: 6/29; locally advanced/metastatic: 15/20; prior chemotherapy: 25) were treated, on an individual use basis, with continuous-dosing sunitinib 37.5 mg/day. Platelet-derived growth factor receptor beta (PDGFRB) and vascular endothelial growth factor receptor 2 (VEGFR2) status were assessed by immunohistochemistry and, in a subgroup of patients, by real time PCR.

Results: Thirty-one patients were assessable for response by RECIST (one early death; three early interruptions). Best responses were 2 partial response (PR), 16 stable disease, 13 progressive disease. A <30% decrease in size was observed in three patients. Fourteen of 29 patients assessable by Choi criteria had a PR. Median progression-free survival by RECIST was 6 months (range 1–22). In two of six patients, resistance to sunitinib was overcome by

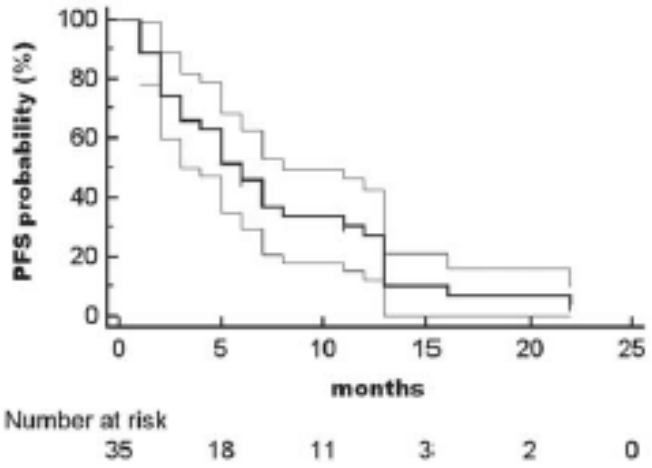


Figure 3 Progression-free survival, median 6 months.

30 pts

Sunitinib 37.5 mg/day

RECIST: **2 PR**
16 SD
13 PD

Choi: **14 (46%) PR**

Median PFS 6 months
(range 1-22)

Stacchiotti S et al, Ann Oncol 2012

Invest New Drugs
DOI 10.1007/s10637-013-0023-e

SHORT REPORT

Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group (GSF/GETO)

T. Valentin · C. Fournier · N. Penel · E. Bompas · L. Chaigneau · N. Isambert · C. Chevreau

Received: 16 July 2013 / Accepted: 30 August 2013
© Springer Science+Business Media New York 2013

Summary Malignant solitary fibrous tumors are rare soft-tissue sarcomas. They are considered as low-grade malignancies, but may display metastatic potential in 20 % of the cases. In case of metastatic or locally advanced, unresectable disease, standard treatments, like anthracycline-based regimens, are poorly effective. Previous studies suggested that antiangiogenic drugs, such as sorafenib, could be efficient to treat vascular sarcomas and solitary fibrous tumors. Five patients with progressive SFT were included in this phase 2 study, and treated with sorafenib at a dose of 800 mg daily. Two patients out of the five achieved a 9 months disease control with sorafenib, while their disease had progressed within the month preceding their inclusion. Consequently, our data suggest a potential efficacy of sorafenib in SFT. Further investigation is needed to confirm these data.

Keywords Solitary fibrous tumor · Soft tissue sarcoma · Sorafenib · Antiangiogenic treatment

Introduction

Malignant solitary fibrous tumors (SFT), or hemangiopericytomas, are rare soft tissue sarcomas. They are considered as low-grade sarcomas, but may display metastatic potential in 20 % of the cases [1]. The standard treatment of SFT consists, if possible, of a large, free-margin tumor excision. Chemotherapic agents are usually poorly effective [2].

Presented in part at the 2012 ASCO Annual Meeting, June 1–5, 2012, Chicago: abstract 10020.

T. Valentin (✉) · C. Chevreau
Medical Oncology, Claudius Regaud Institute, Toulouse, France
e-mail: thibaud.valentin@gmail.com

C. Fournier
Biostatistics Department, Oscar Lambret Center, Lille, France

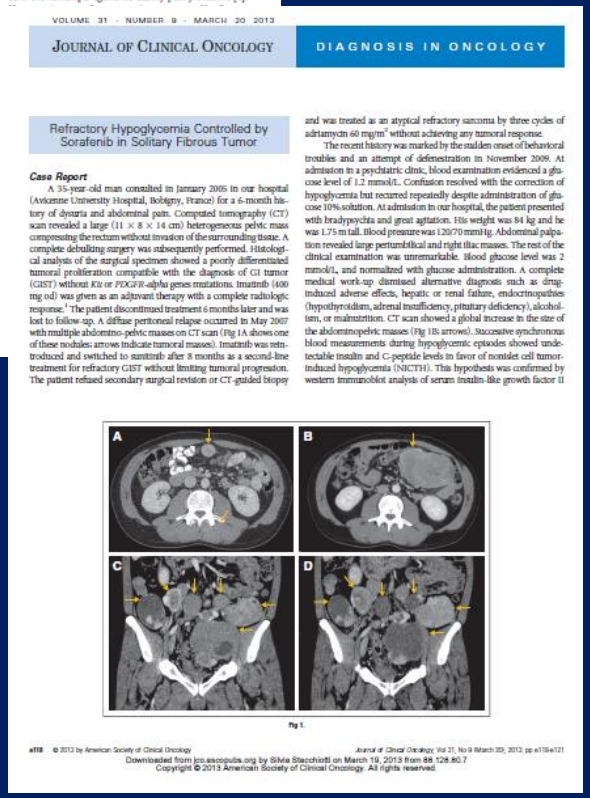
N. Penel
Medical Oncology, Oscar Lambret Center, Lille, France

E. Bompas
Medical Oncology, René Gaudducheau Center, Nantes, France

L. Chaigneau
Medical Oncology, Jean Minjoz University Hospital, Besançon, France

N. Isambert
Medical Oncology, Georges-François Leclerc Center, Dijon, France

Published online: 05 September 2013



VOLUME 31 · NUMBER 9 · MARCH 20 2013

JOURNAL OF CLINICAL ONCOLOGY | DIAGNOSIS IN ONCOLOGY

Refractory Hypoglycemia Controlled by Sorafenib in Solitary Fibrous Tumor

Case Report

A 35-year-old man consulted in January 2005 in our hospital (Avicenne University Hospital, Bobigny, France) for a 6-month history of dysuria and abdominal pain. Computed tomography (CT) scan revealed a large (11 × 8 × 14 cm) heterogeneous pelvic mass compressing the rectum without invasion of the surrounding tissue. A complete debulking surgery was subsequently performed. Histological analysis of the surgical specimen showed a poorly differentiated tumoral proliferation compatible with the diagnosis of GI tumor (GIST) without *Kit* or *PDGFR-alpha* genes mutations. Imatinib (400 mg od) was given as an adjuvant therapy with a complete radiologic response.[1] The patient discontinued treatment 6 months later and was lost to follow-up. A diffuse peritoneal relapse occurred in May 2007 with multiple abdomino-pelvic masses on CT scan (Fig 1A shows one of these nodules; arrows indicate tumoral masses). Imatinib was reintroduced and switched to sunitinib after 8 months as a second-line treatment for refractory GIST without limiting tumoral progression. The patient refused secondary surgical revision or CT-guided biopsy and was treated as an atypical refractory sarcoma by three cycles of adriamycin 60 mg/m^2 without achieving any tumoral response.

The recent history was marked by the sudden onset of behavioral troubles and an attempt of defenestration in November 2009. At admission in a psychiatric clinic, blood examination evidenced a glucose level of 1.2 mmol/L. Confusion resolved with the correction of hypoglycemia but recurred repeatedly despite administration of glucose 10% solution. At admission in our hospital, the patient presented with bradypsychia and great agitation. His weight was 84 kg and he was 1.75 m tall. Blood pressure was 120/70 mmHg. Abdominal palpation revealed large pertumbilical and right iliac masses. The rest of the clinical examination was unremarkable. Blood glucose level was 2 mmol/L, and normalized with glucose administration. A complete medical work-up dismissed alternative diagnosis such as drug-induced adverse effects, hepatic or renal failure, endocrinopathies (hypothyroidism, adrenal insufficiency, pituitary deficiency), alcoholism, or malnutrition. CT scan showed a global increase in the size of the abdominopelvic masses (Fig 1B; arrows). Successive synchronous blood measurements during hypoglycemic episodes showed undetectable insulin and C-peptide levels in favor of nonislet cell tumor-induced hypoglycemia (NICTH). This hypothesis was confirmed by western immunoblot analysis of serum insulin-like growth factor II

Fig 1.

… sorafenib

5 pts

Sorafenib 800 mg/day

2 pts PFS >9 months

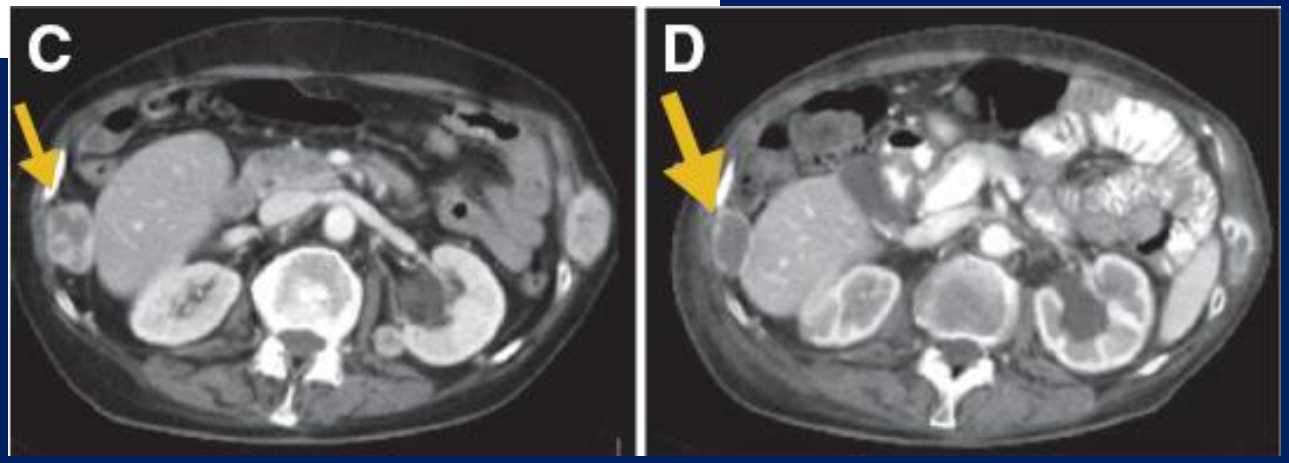
Valentin T et al, Inv New Drug 2013
JCO 2012

… pazopanib

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

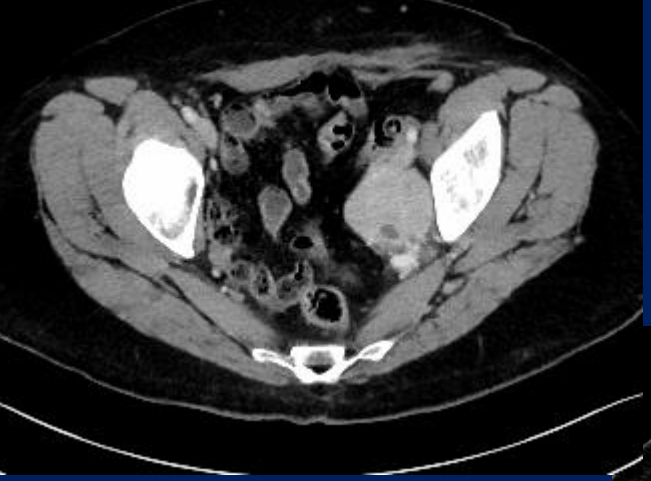
Pazopanib, a Multikinase Angiogenesis Inhibitor, in Patients With Relapsed or Refractory Advanced Soft Tissue Sarcoma: A Phase II Study From the European Organisation for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC Study 62043)

From the Department of Medical

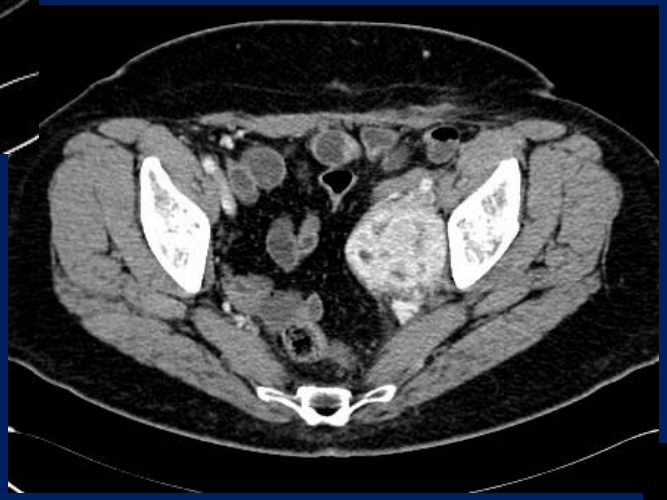


baseline **+3 mos**

Sleijfer S et al, JCO 2009

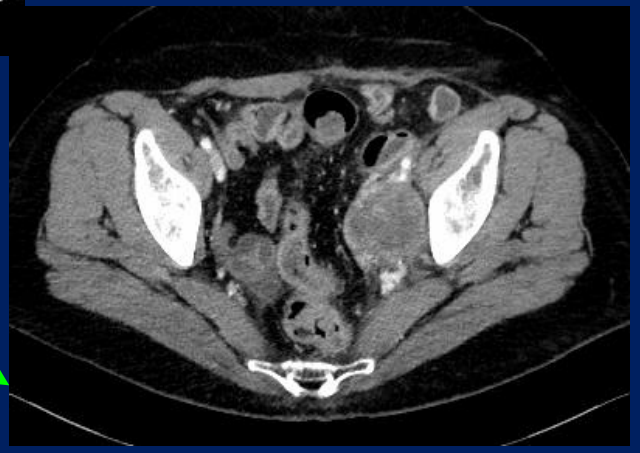


pazopanib
800 mg



+6 mos

SM 37.5 mg



+3 mos

Stacchiotti S et al, Eur J Cancer 2015

... pazopanib

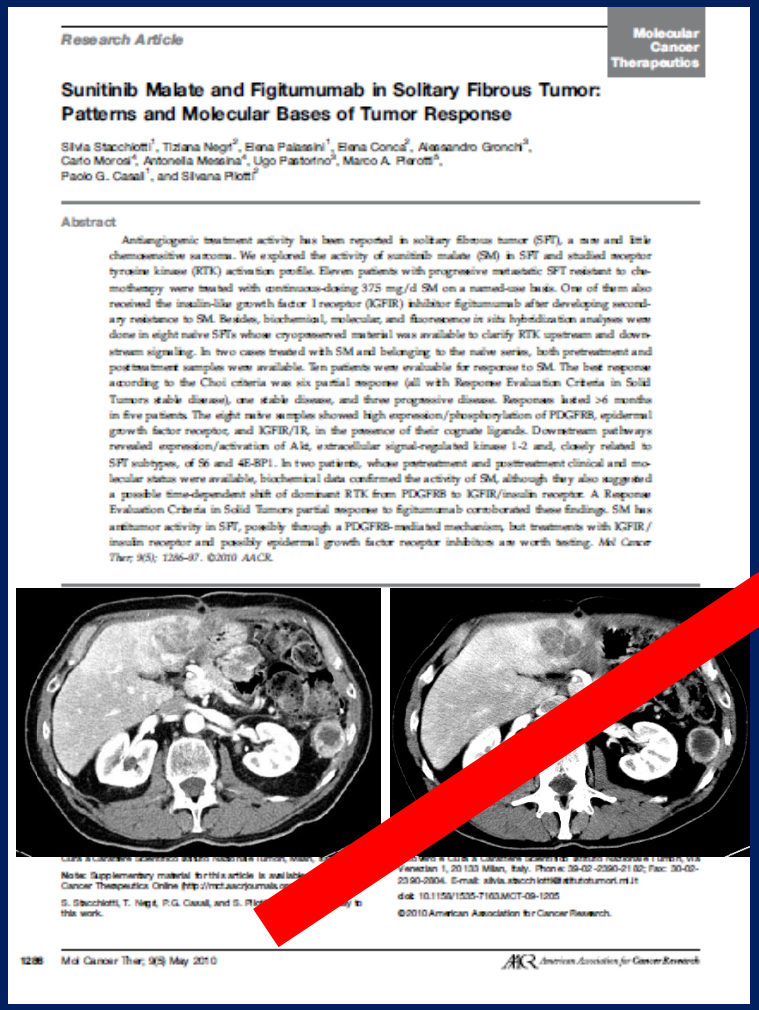
GEIS/ISG/GSF
Phase 2 study
on
pazopanib in SFT

axitinib - regorafenib

Phase 2 study on axitinib in advanced SFT

Phase 2 study on regorafenib in advanced SFT

… IGFR inhib +/- mTOR



Research Article

Molecular Cancer Therapeutics

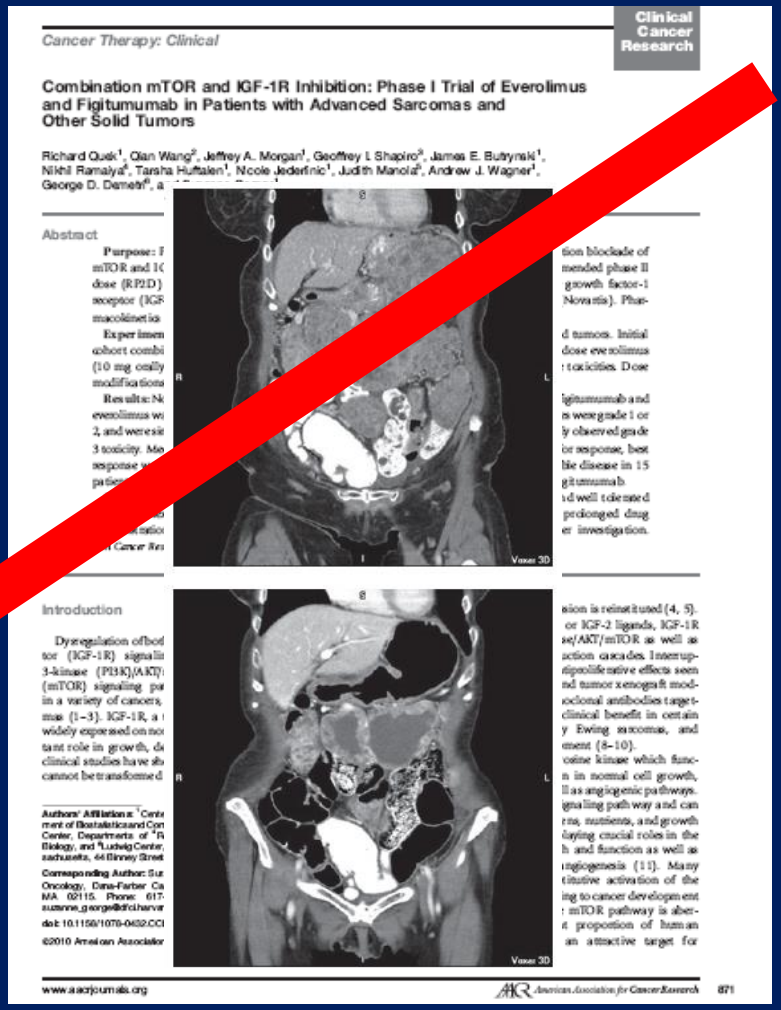
Sunitinib Malate and Figitumumab in Solitary Fibrous Tumor: Patterns and Molecular Bases of Tumor Response

Silvia Stacchiotti[1], Tiziana Negri[2], Elena Palassini[1], Elena Conca[2], Alessandro Gronchi[3], Carlo Morosi[4], Antonella Messina[4], Ugo Pastorino[3], Marco A. Pierotti[5], Paolo G. Casali[1], and Silvana Pilotti[2]

Abstract

Antiangiogenic treatment activity has been reported in solitary fibrous tumor (SFT), a rare and little chemosensitive sarcoma. We explored the activity of sunitinib malate (SM) in SFT and studied receptor tyrosine kinase (RTK) activation profile. Eleven patients with progressive metastatic SFT resistant to chemotherapy were treated with continuous-dosing 375 mg/d SM on a named-use basis. One of them also received the insulin-like growth factor 1 receptor (IGFIR) inhibitor figitumumab after developing secondary resistance to SM. Besides, biochemical, molecular, and fluorescence *in situ* hybridization analyses were done in eight naive SFTs whose cryopreserved material was available to clarify RTK upstream and downstream signaling. In two cases treated with SM and belonging to the naive series, both pretreatment and posttreatment samples were available. Ten patients were evaluable for response to SM. The best response according to the Choi criteria was six partial response (all with Response Evaluation Criteria in Solid Tumors stable disease), one stable disease, and three progressive disease. Responses lasted >6 months in five patients. The eight naive samples showed high expression/phosphorylation of PDGFRB, epidermal growth factor receptor, and IGFIR/IR, in the presence of their cognate ligands. Downstream pathways revealed expression/activation of Akt, extracellular signal-regulated kinase 1-2 and, closely related to SFT subtypes, of S6 and 4E-BP1. In two patients, whose pretreatment and posttreatment clinical and molecular status were available, biochemical data confirmed the activity of SM, although they also suggested a possible time-dependent shift of dominant RTK from PDGFRB to IGFIR/insulin receptor. A Response Evaluation Criteria in Solid Tumors partial response to figitumumab corroborated these findings. SM has antitumor activity in SFT, possibly through a PDGFRB-mediated mechanism, but treatments with IGFIR/insulin receptor and possibly epidermal growth factor receptor inhibitors are worth testing. *Mol Cancer Ther*; 9(5); 1286–97. ©2010 AACR.

Mol Cancer Ther; 9(5) May 2010



Cancer Therapy: Clinical

Clinical Cancer Research

Combination mTOR and IGF-1R Inhibition: Phase I Trial of Everolimus and Figitumumab in Patients with Advanced Sarcomas and Other Solid Tumors

Richard Quek[1], Qian Wang[2], Jeffrey A. Morgan[1], Geoffrey I. Shapiro[3], James E. Butrynski[1], Nikhil Ramaiya[4], Tarsha Huftalen[1], Nicole Jederlinic[1], Judith Manola[2], Andrew J. Wagner[1], George D. Demetri[4], a

Abstract

Purpose: I
mTOR and IG
dose (RP2D)
receptor (IGF
macolinet ics

Experimen
cohort combi
(10 mg orally
modifications

Results: Ne
everolimus wa
2; and were si
3 toxicity. Mo
response w
patien

tion blockade of
mended phase II
growth factor-1
Novartis). Phar-

d tumors. Initial
dose everolimus
: toxicities. Dose

figitumumab and
s were grade 1 or
ly observed grade
or response, best
ble disease in 15
gitumumab
d well tolerated
prolonged drug
er investigation.

Introduction

Dysregulation of bot
tor (IGF-1R) signalin
3-kinase (PI3K)/(AKT)/
(mTOR) signaling pa
in a variety of cancers,
mas (1–3). IGF-1R, a
widely expressed on no
tant role in growth, de
clinical studies have sh
cannot be transformed

sion is reinstituted (4, 5).
or IGF-2 ligands, IGF-1R
se/AKT/mTOR as well as
action cascades. Inter up-
ripolifetative effects seen
nd tumor xenograft mod-
ioclonal antibodies target-
clinical benefit in certain
y Ewing sarcomas, and
ment (8–10).
osine kinase which func-
n in normal cell growth,
ll as angiogenic pathways.
gnaling pathway and can
rs, nutrients, and growth
laying crucial roles in the
h and function as well as
ngiogenesis (11). Many
titutive activation of the
ing to cancer development
: mTOR pathway is aber-
t proposition of human
an attractive target for

Authors' Affiliations: [1]Cent
ment of Biostatistics and Cor
Center, Departments of [4]R
Biology, and [5]Ludwig Center,
sachusetts, 44 Binney Street

Corresponding Author: Su
Oncology, Dana-Farber Ca
MA 02115. Phone: 617-
suzanne_george@dfci.harvar

doi: 10.1158/1078-0432.CC

Stacchiotti S et al, Mol Cancer Ther 2010
Quek R et al, Clin Cancer Res 2011

Inflammatory Myofibroblastic Tumor (IMT)

American Journal of Pathology, Vol. 157, No. 2, August 2000
Copyright © American Society for Investigative Pathology

TPM3-ALK and *TPM4-ALK* Oncogenes in Inflammatory Myofibroblastic Tumors

Brandon Lawrence,* Antonio Perez-Atayde,† Michele K. Hibbard,* Brian P. Rubin,* Paola Dal Cin,* Jack L. Pinkus,* Geraldine S. Pinkus,* Sheng Xiao,* Eunhee S. Yi,‡ Christopher D. M. Fletcher,* and Jonathan A. Fletcher*§

From the Departments of Pathology, Brigham and Women's Hospital, Boston, Massachusetts; the Department of Pathology,† Children's Hospital Boston, Massachusetts; and the Departments of Pediatric Oncology,‡ Dana-Farber Cancer Institute, Boston, Massachusetts; and the Department of Pathology,§ University of California, San Diego Medical Center, San Diego, California*

Inflammatory myofibroblastic tumors (IMTs) are ... plasic mesenchymal proliferations featuring ... flammatory infiltrate composed primarily of ... cytes and plasma cells. The myofibroblastic ... some IMTs contain chromosomal rearrangements ... volving the *ALK* receptor tyrosine-kinase locus ... (chromosome band 2p23). ALK—which is normally restricted in its expression to neural tissues—is expressed strikingly in the IMT cells with 2p23 rearrangements. We now report a recurrent oncogenic mechanism, in IMTs, in which tropomyosin (TPM) N-terminal coiled-coil domains are fused to the ALK C-terminal kinase domain. We have cloned two *ALK* fusion genes, *TPM4-ALK* and *TPM3-ALK*, which encode ~95-kd fusion oncoproteins characterized by constitutive kinase activity and tyrosylphosphorylation. Immunohistochemical and molecular correlations, in other IMTs, implicate non-TPM ALK oncoproteins that are predominantly cytoplasmic or predominantly nuclear, presumably depending on the subcellular localization of the ALK fusion partner. Notably, a *TPM3-ALK* oncogene was reported recently in anaplastic lymphoma, and *TPM3-ALK* is thereby the first known fusion oncogene that transforms, *in vitro*, both mesenchymal and lymphoid human cell lineages. (*Am J Pathol 2000, 157:377–384*)

The inflammatory myofibroblastic tumor (IMT)[1–4] is a clinicopathologically distinctive but biologically controversial entity that was defined originally as a nonneoplastic lesion. IMTs arise usually in the soft tissues, most often in the abdomen of children and adolescents, and they are composed of myofibroblastic spindle cells admixed with a prominent inflammatory infiltrate of lymphocytes, plasma cells, and, less often, acute inflammatory cells. Notably, many patients with IMTs present with constitutional symptoms of fever and weight loss, and these same patients are often anemic and thrombocythemic. However, it is unclear whether the constitutional symptoms and inflammatory infiltrate are induced by tumor-cell factors or, alternately, whether the constitutional symptoms are secondary to the inflammatory process.

The uncertain pathogenesis of IMTs, and the ongoing question of its neoplastic versus reactive nature, is reflected in the large number of names which have been bestowed on this disorder. IMTs arising in the lung, particularly those that are well circumscribed, are generally cured by surgical excision. Until recently, these were ... sarcoma.[1,2] However, most IMTs have overlapping histological characteristics and it is difficult to distinguish those with neoplastic potential from the potentially reactive subset that belong under the umbrella category of "inflammatory pseudotumor." Another complicating feature, with respect to classification, is that differences in clinical behavior, between different IMT subcategories, do not exclude a common pathogenesis.

Cytogenetic banding studies were the first assays to demonstrate unequivocal clonal mutations—indicative of a neoplastic pathogenesis—in IMTs.[5–10] Approximately 50% of soft-tissue IMT karyotypes contain clonal rearrangements of the chromosome 2 short arm,[5–10] and each of two cytogenetically characterized IMTs arising in bone contained rearrangements of the *HMGIC* region on chromosome band 12q15.[8] Recently, Griffin et al[10] showed that IMT 2p rearrangements fall within an ~100-kb region containing the *ALK* receptor tyrosine-kinase locus, on chromosome band 2p23. These rearrangements were associated with striking ALK expression in the IMT myofibroblastic spindle cells.[10] ALK is a

Accepted for publication May 4, 2000.

The sequences reported in this paper have been deposited in the GenBank database (accession nos. AF166109 and AF166110).

Address reprint requests to Jonathan A. Fletcher, M.D., Department of Pathology, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. E-mail: jfletcher@rics.bwh.harvard.edu.

T(2;...)(2p23;...) → **.... -ALK**

↓

ALK overexpression

Lawrence et al., J Surg Path 2000

… crizotinib

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Paul A. Janne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

SUMMARY

Inflammatory myofibroblastic tumor (IMT) is a distinctive mesenchymal neoplasm characterized by a spindle-cell proliferation with an inflammatory infiltrate. Approximately half of IMTs carry rearrangements of the anaplastic lymphoma kinase (*ALK*) locus on chromosome 2p23, causing aberrant ALK expression. We report a sustained partial response to the ALK inhibitor crizotinib (PF-02341066, Pfizer) in a patient with *ALK*-translocated IMT, as compared with no observed activity in another patient without the *ALK* translocation. These results support the dependence of *ALK*-rearranged tumors on ALK-mediated signaling and suggest a therapeutic strategy for genomically identified patients with the aggressive form of this soft-tissue tumor. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

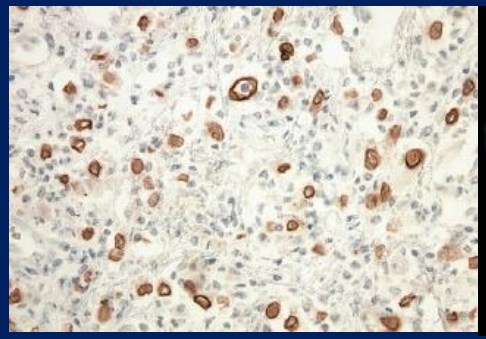
From the Dana–Farber Cancer Institute (J.E.B., M.C., N.R., P.A.J., G.D.D., G.I.S.); the Ludwig Center at Dana–Farber/Harvard Cancer Center (J.E.B., G.D.D.); Harvard Medical School (J.E.B., J.L.H., M.C., S.J.R., E.L.K., J.W.C., P.A.J., G.D.D., G.I.S.); Brigham and Women's Hospital (J.L.H., R.D.C., S.J.R.); and Massachusetts General Hospital (E.L.K., J.W.C.) — all in Boston; Memorial Sloan-Kettering Cancer Center, New York (C.R.A., S.C.J., M.L., R.G.M.); and Pfizer Global Research and Development, La Jolla, CA (K.D.W., J.G.C.). Address reprint requests to Dr. Demetri at the Ludwig Center at Dana–Farber/Harvard Cancer Center and Center for Sarcoma and Bone Oncology, Dana–Farber Cancer Institute, Dana 1221, 44 Binney St, Boston, MA 02115, or at gdemetri@partners.org; or to Dr. Shapiro at the Early Drug Development Center, Dana–Farber Cancer Institute, Dana 930A, 44 Binney St, Boston, MA 02115, or at gfshapiro@lds.harvard.edu.

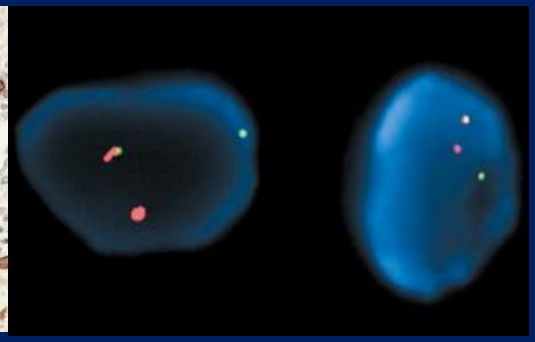
N Engl J Med 2010;363:1727-33.

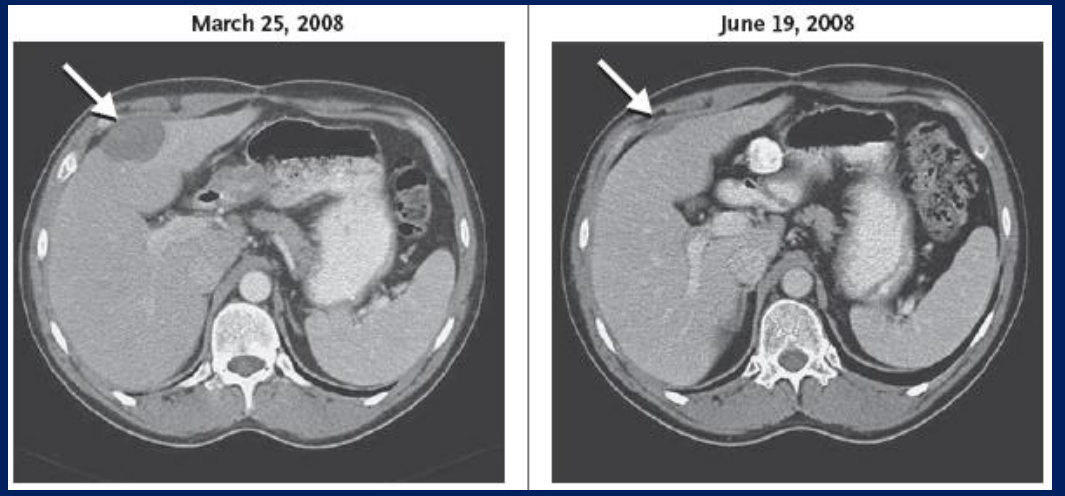
INFLAMMATORY MYOFIBROBLASTIC TUMORS (IMTs) OCCUR PRIMARILY DURING the first two decades of life and typically arise in the lung, retroperitoneum, or abdominopelvic region.[1,2] Abdominal tumors may be multifocal. Lesional cells are predominantly myofibroblasts in a myxoid to collagenous stroma admixed with inflammatory cells.[3,4] Local recurrence may occur after initial surgery, with a low risk of distant metastases,[1,2] so that IMTs are considered to be soft-tissue tumors of intermediate biologic potential, with a small fraction behaving aggressively.[5]

Rearrangements involving the *ALK* locus on chromosome 2p23 have been documented in approximately 50% of IMTs.[3,4] *ALK* aneuploidy has also been described, with a gain in copy number without rearrangement.[6] Among cancers with rearrangement, several fusion partners have been identified that serve to constitutively activate ALK.[7-10] ALK expression reliably correlates with *ALK* rearrangement.[3,4] Distant metastases occur primarily in ALK-negative IMTs, but local recurrence occurs regardless of ALK expression.[3,4,6]

Several ALK fusion proteins, including TPM3-ALK found in IMT, induce transformation in cell lines and animal models,[8,9] a finding that suggests that *ALK* rearrangement may define a subgroup of IMTs that is sensitive to targeted kinase inhibition. We therefore enrolled two patients with IMT in a dose-escalation phase 1 trial of crizotinib, an orally bioavailable ATP-competitive inhibitor of the ALK and MET tyrosine kinases.[11,12]







Butrynski J et al, JCO 2010

… crizotinib

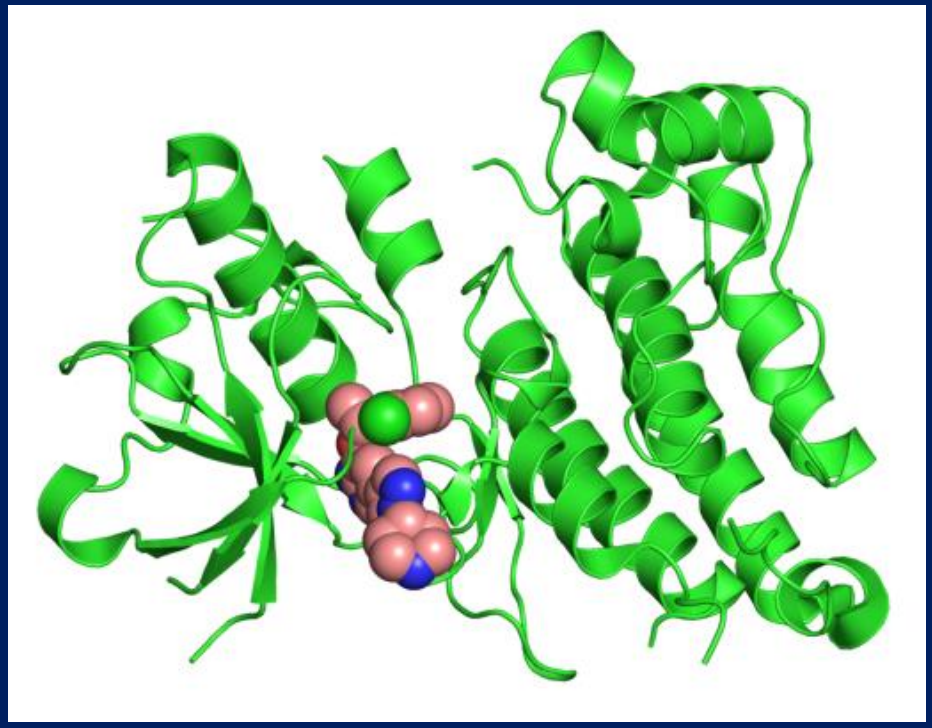
EORTC
European Organisation for Research and Treatment of Cancer

EORTC
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

CREATE
Phase II study

IMT

Crizotinib, ALK inhibitor



... and MET inhibitor

… crizotinib

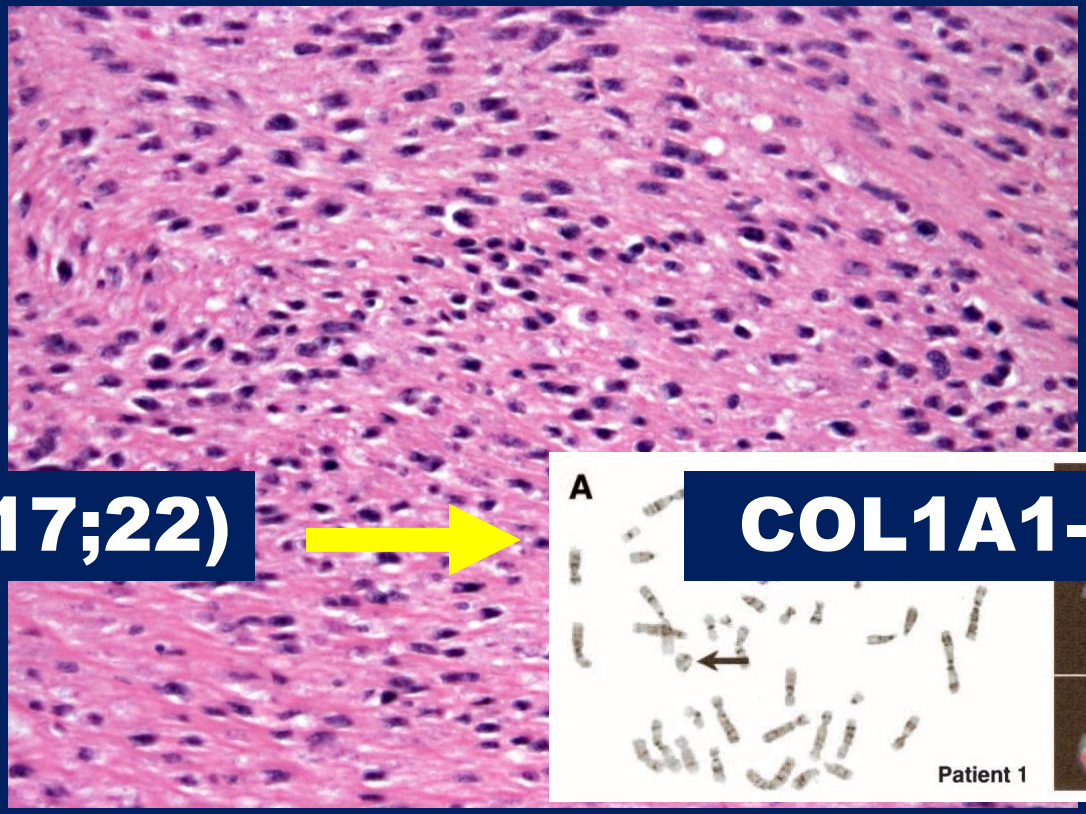
EORTC
Avenue E. Mounierlaan 83 / 11
Brussel 1200 Bruxelles
België - Belgique
Tel : +32 2 774 16 11
Fax : +32 2 772 35 45
E-mail : eortc@eortc.be
Web : http://www.eortc.be

CREATE
Phase II study

IMT
Alveolar soft part sarcoma,
Clear cell sarcoma, Alveolar rhabdo

Wagner A et al, Cancer 2012

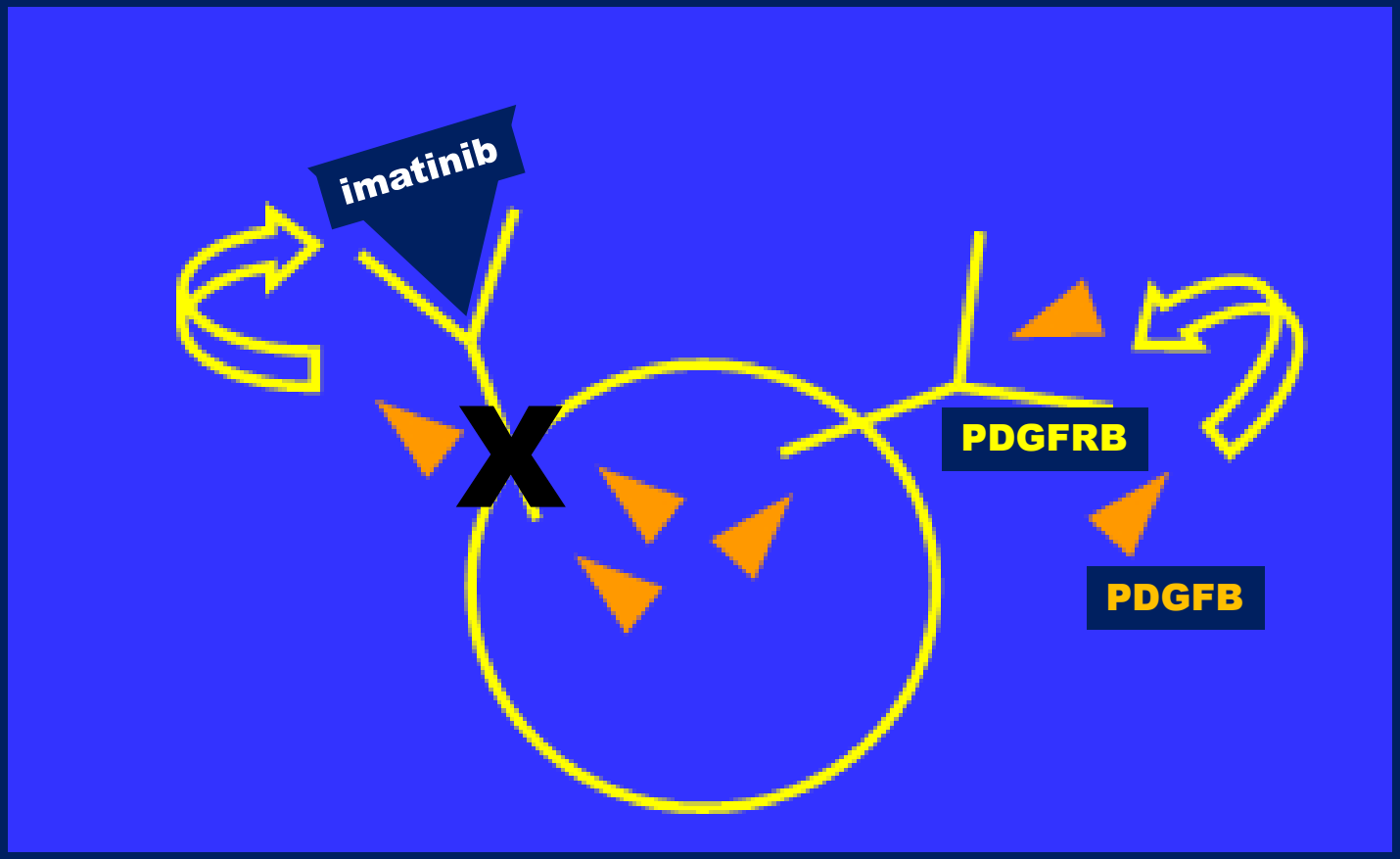
Dermatofibrosarcoma Protuberans (DFSP)



t(17;22)

COL1A1-PDGFB

PDGFB


imatinib
X
PDGFRB
PDGFB

… imatinib

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Imatinib Mesylate in Advanced Dermatofibrosarcoma Protuberans: Pooled Analysis of Two Phase II Clinical Trials

Piotr Rutkowski, Martine Van Glabbeke, Cathryn J. Rankin, Włodzimierz Ruka, Brian P. Rubin, Maria Debiec-Rychter, Alexander Lazar, Hans Gelderblom, Raf Sciot, Dolores Lopez-Terrada, Peter Hohenberger, Allan T. van Oosterom, and Scott M. Schuetze

ABSTRACT

Purpose
Dermatofibrosarcoma protuberans (DFSP) is a dermal sarcoma typically carrying a translocation between chromosomes 17 and 22 that generates functional platelet-derived growth factor B (PDGFB).

Patients and Methods
Two distinct phase II trials of imatinib (400 to 800 mg daily) in patients with locally advanced or metastatic DFSP were conducted and closed prematurely, one in Europe (European Organisation for Research and Treatment of Cancer [EORTC]) with 14-week progression-free rate as the primary end point and the other in North America (Southwest Oncology Group [SWOG]) with confirmed objective response rate as the primary end point. In the EORTC trial, confirmation of *PDGFB* rearrangement was required, and surgery was undertaken after 14 weeks if feasible. The SWOG study confirmed t(17;22) after enrollment.

Results
Sixteen and eight patients were enrolled onto the EORTC and SWOG trials, respectively. Tumor size ranged from 1.2 to 49 cm. DFSP was located on head/neck, trunk, and limb in seven, 11, and six patients, respectively, and was classic, pigmented, and fibrosarcomatous DFSP in 13, one, and nine patients, respectively. Metastases were present in seven patients (lung involvement was present six patients). Eleven patients (46%) had partial response as best response, and four patients had progressive disease as best response. Median time to progression (TTP) was 1.7 years. Imatinib was stopped in 11 patients because of progression, one patient because of toxicity, and two patients after complete resection of disease. Median overall survival (OS) time has not been reached; 1-year OS rate was 87.5%.

Conclusion
Imatinib is active in DFSP harboring t(17;22) including fibrosarcomatous DFSP, with objective response rate approaching 50%. Response rates and TTP did not differ between patients taking 400 mg daily versus 400 mg twice a day.

J Clin Oncol 28. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor (comprising approximately 1% of sarcomas) with typically indolent growth and a less than 5% probability of metastasis.[1,2] It is believed that metastases develop more commonly in DFSP harboring areas of fibrosarcoma, known as fibrosarcomatous DFSP (DFSP-FS).[3-6] If metastases occur, they often are localized in the lungs and are less commonly localized in lymph nodes.

The standard treatment of this cutaneous sarcoma is wide local excision. A surgical margin of at least 3 cm has been recommended, and often, reconstructive techniques are needed, which may result in disfigurement or functional impairment.[3,7] However, locoregional recurrence rates ranging from 24% to 99% after complete excision have been reported, and many recurrences can occur late.[3,4,8-12] The majority of authors reported a median time to disease recurrence between 2 and 3 years.[3,4,11] A limited experience with Mohs surgery exists.[13-15]

Radiotherapy is a treatment option for unresectable lesions or in case of margin involvement[10-12] but has limited value as primary therapy of patients who can be cured by surgery. In patients with locally advanced disease, effective use of cytotoxic chemotherapy is anecdotal.[11]

DFSP is characterized by a specific rearrangement of chromosomes 17 and 22, which can be

From the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; European Organisation for Research and Treatment of Cancer Headquarters, Brussels; Catholic University of Leuven, Leuven, Belgium; Leiden University Medical Centre, Leiden, the Netherlands; Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Centre, University of Heidelberg, Heidelberg, Germany; Southwest Oncology Group Statistical Center, Seattle, WA; Cleveland Clinic Foundation, Cleveland, OH; The University of Texas M. D. Anderson Cancer Center, Texas Children's Hospital and Baylor College of Medicine, Houston, TX; and University of Michigan, Ann Arbor, MI.

Submitted August 20, 2009; accepted November 2, 2009; published online ahead of print at www.jco.org on March 1, 2010.

Written on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue/Bone Sarcoma Group and the Southwest Oncology Group.

Supported in part by Public Health Service Cooperative Agreement Grants No. CA32102, CA38926, CA27057, CA20319, and CA42777 awarded by the National Cancer Institute, Department of Health and Human Services.

P.R., A.T.v.O., and S.M.S. contributed equally to this work.

Presented in part at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29-June 2, 2009, Orlando, FL.

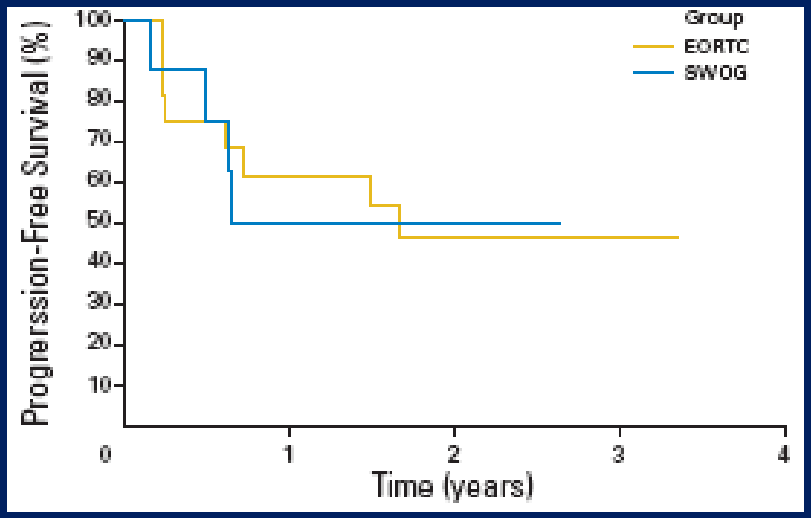
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Piotr Rutkowski, MD, PhD, Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Roentgena 5, 02-781 Warsaw, Poland; e-mail: rutkowskip@coi.waw.pl.

0732-183X/10/2899-1/$20.00

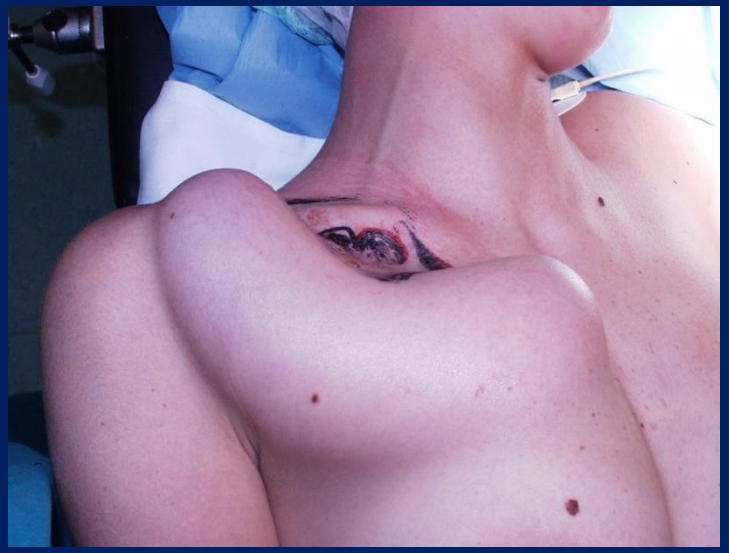
DOI: 10.1200/JCO.2009.25.7999

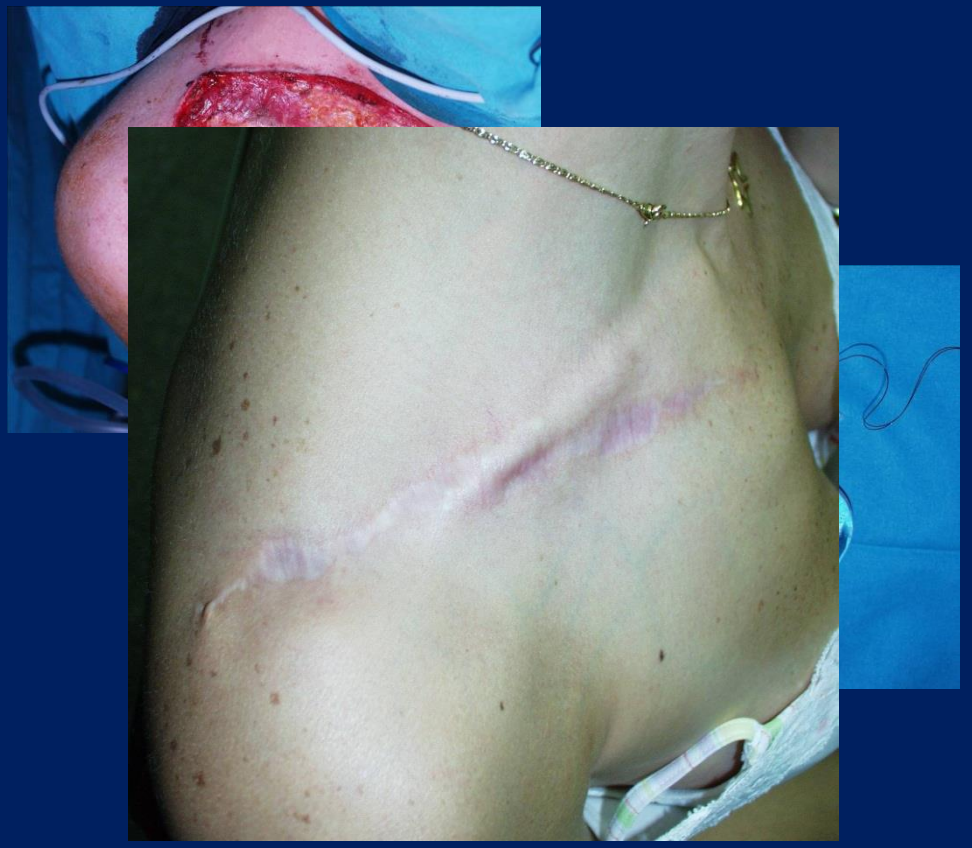


- **RECIST RR 46%**
- **Median PFS 1.7 years**

Rutkowskiet al, JCO 2010
Rubin et al, JCO 2002

… locally advanced pts





Cancer Therapy: Clinical

Clinical Cancer Research

Neoadjuvant Imatinib in Advanced Primary or Locally Recurrent Dermatofibrosarcoma Protuberans: A Multicenter Phase II DeCOG Trial with Long-term Follow-up

Selma Ugurel[1], Thomas Mentzel[2], Jochen Utikal[3,4], Peter Helmbold[5,6], Peter Mohr[7], Claudia Pföhler[8], Meinhard Schiller[9], Axel Hauschild[10], Rüdiger Hein[11], Eckhardt Klempnauer[12], Ivonne Kellner[13], Martin Leverkus[5], Jürgen C. Becker[14], Philip Ströbel[14], and Dirk Schadendorf[6]

Abstract

Purpose: Dermatofibrosarcoma protuberans (DFSP) is a rare cutaneous tumor. *COL1A1–PDGFB* gene fusion is frequent in DFSP, rendering tumor cell proliferation and survival dependent on PDGFRβ (platelet-derived growth factor receptor β) signaling. This trial investigated imatinib as neoadjuvant treatment of DFSP, including long-term follow-up.

Experimental Design: The primary endpoint of this multicenter phase II trial was response; secondary endpoints were safety, tumor relapse, and response biomarkers. Patients with advanced primary or locally recurrent DFSP and measurable disease by RECIST (response evaluation criteria in solid tumors) were eligible and received imatinib 600 mg/d until definitive surgery with histopathologic proof of tumor-free margins.

Results: Sixteen patients received imatinib, and 14 patients were evaluable for all endpoints. Median treatment duration was 9.1 months; median tumor shrinkage was 31.5%. Best overall response was 7.1% complete response (CR), 50.0% partial response (PR), 35.7% stable disease, and 7.1% progressive disease (PD). Toxicity was moderate with 25.0% grade 3 and 4 events. During a median follow-up of 6.4 years, one patient developed secondary resistance to imatinib but responded to second-line sunitinib. This patient also presented local recurrence, distant metastasis, and death from DFSP. Exploratory analysis showed that response to imatinib was associated with decreased tumor cellularity and formation of strong hyalinic fibrosis. Weak PDGFRB phosphorylation and pigmented-type DFSP were associated with non-response. Additional to PDGFRB, the kinases EGFR and insulin receptor were found activated in a high percentage of DFSPs.

Conclusion: The neoadjuvant use of imatinib 600 mg/d in DFSP is efficacious and well tolerated. Long-term follow-up results do not definitely support smaller surgical margins after successful imatinib pretreatment, and presume that secondary resistance to imatinib might promote accelerated disease progression. *Clin Cancer Res; 20(2); 499–510. ©2013 AACR.*

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a malignant tumor of the dermis assumed to be of fibroblastic origin (1–3). DFSP is remarkable for its slow but infiltrative growth, and frequently enforces multiple surgical procedures to ensure complete resection (2, 4). Under the premise of tumor-free surgical margins, the rates of local recurrence and metastasis are low (5, 6), rendering the main therapeutic efforts focused on the primary tumor. This situation is different in fibrosarcomatous DFSP (DFSP-FS),

Authors' Affiliations: [1]Department of Dermatology, University of Würzburg, Würzburg; [2]Dermatopathology Bodensee, Friedrichshafen; [3]Skin Cancer Unit, German Cancer Research Center, Heidelberg; [4]Department of Dermatology, University Hospital Heidelberg, Heidelberg; [5]Department of Dermatology, University Medical Center Mannheim, University of Heidelberg, Mannheim; [6]Department of Dermatology, Martin Luther University, Halle/Saale; [7]Department of Dermatology, Elbe Klinikum Buxtehude, Buxtehude; [8]Department of Dermatology, Saarland University Hospital, Homburg, Saarland; [9]Department of Dermatology, University Hospital of Münster, Münster; [10]Department of Dermatology, University of Kiel, Kiel; [11]Department of Dermatology, Technical University Munich, Munich; [12]Department of Dermatology, University Hospital Erlangen, Erlangen; [13]Department of Dermatology, Helios Klinikum Erfurt, Erfurt; [14]Department of Pathology, University of Göttingen, Göttingen; [15]Department of Dermatology, University of Essen, Essen, Germany; and [16]Department of Dermatology, Medical University Graz, Graz, Austria

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Selma Ugurel, Department of Dermatology, Julius-Maximilians University, Josef-Schneider-Straße 2, 97080 Würzburg, Germany. Phone: 00-49-931-201-26931; Fax: 00-49-931-201-26930; E-mail: ugurel_s@klinik.uni-wuerzburg.de

doi: 10.1158/1078-0432.CCR-13-1411

...neoadj imatinib

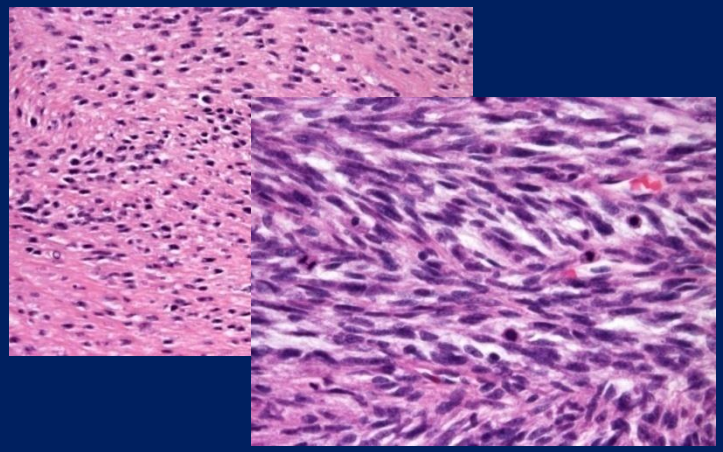
- 16 pts, neoadj Tx
- imatinib 600 mg/day
- RR 50%

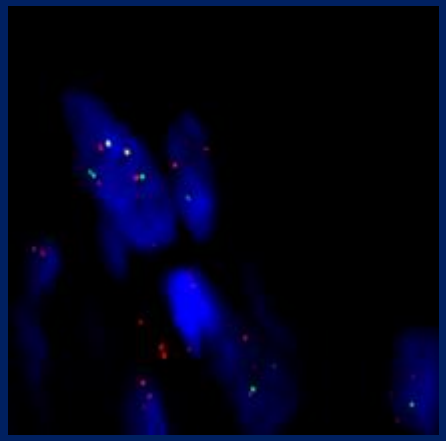
- no smaller surgical margins

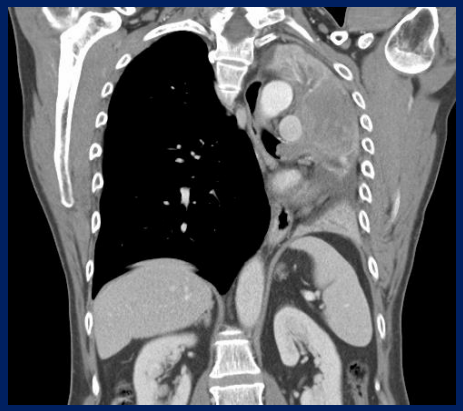
Ugurel S et al, Clin Cancer Res 2014

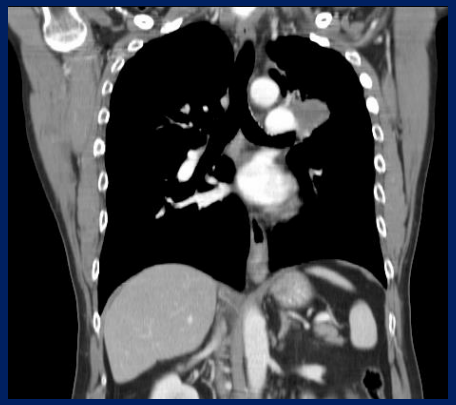
… metastatic pts

<5% (10-15% FS-DFSP)









Stacchiotti S et al, Int J Cancer 2010
Stacchiotti S et al, Clin Cancer Res 2015

...sorafenib, sunitinib

Kamar et al. Clinical Sarcoma Research 2013, 3:5
http://www.clinicalsarcomaresearch.com/content/3/1/5

CLINICAL SARCOMA RESEARCH

CASE REPORT Open Access

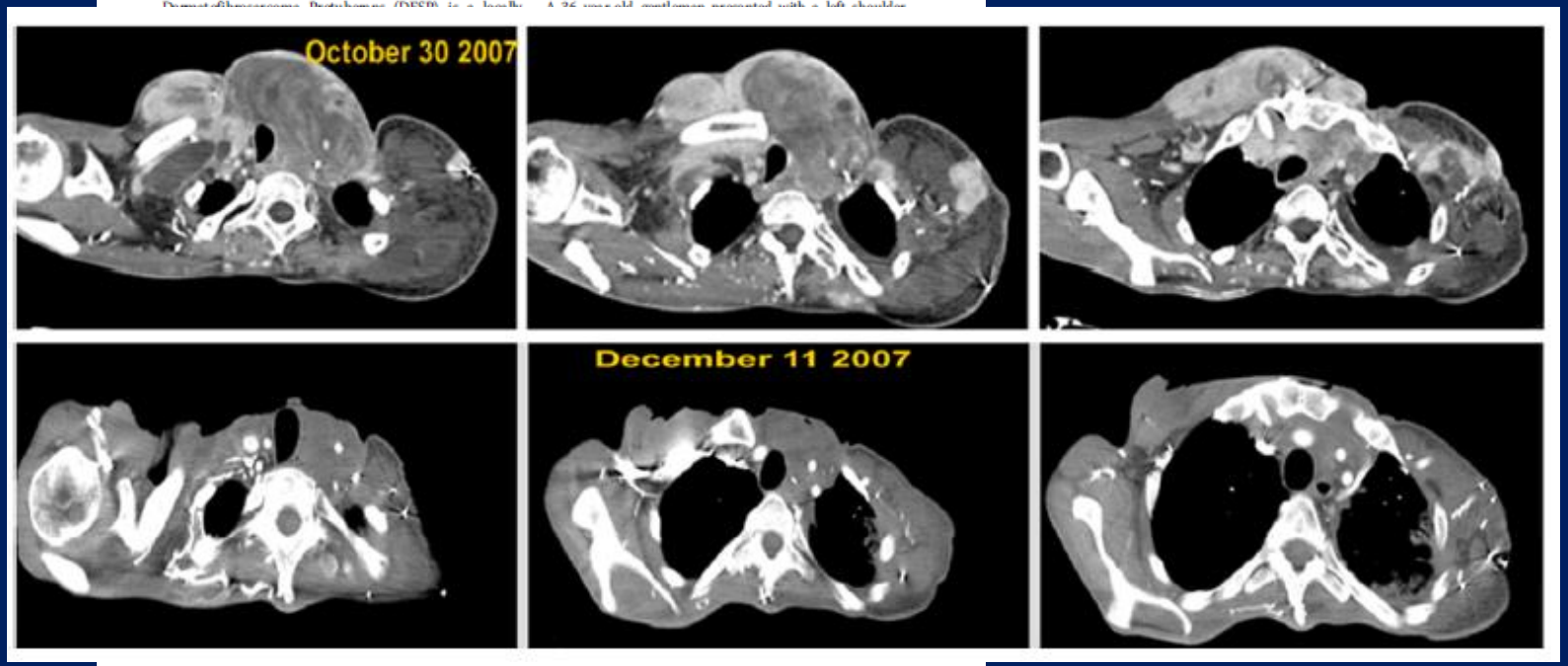
Dermatofibrosarcoma protuberans (DFSP) successfully treated with sorafenib: case report

Francois G Kamar[1*], Victor F Kairouz[2] and Alain N Sabri[3]

Abstract

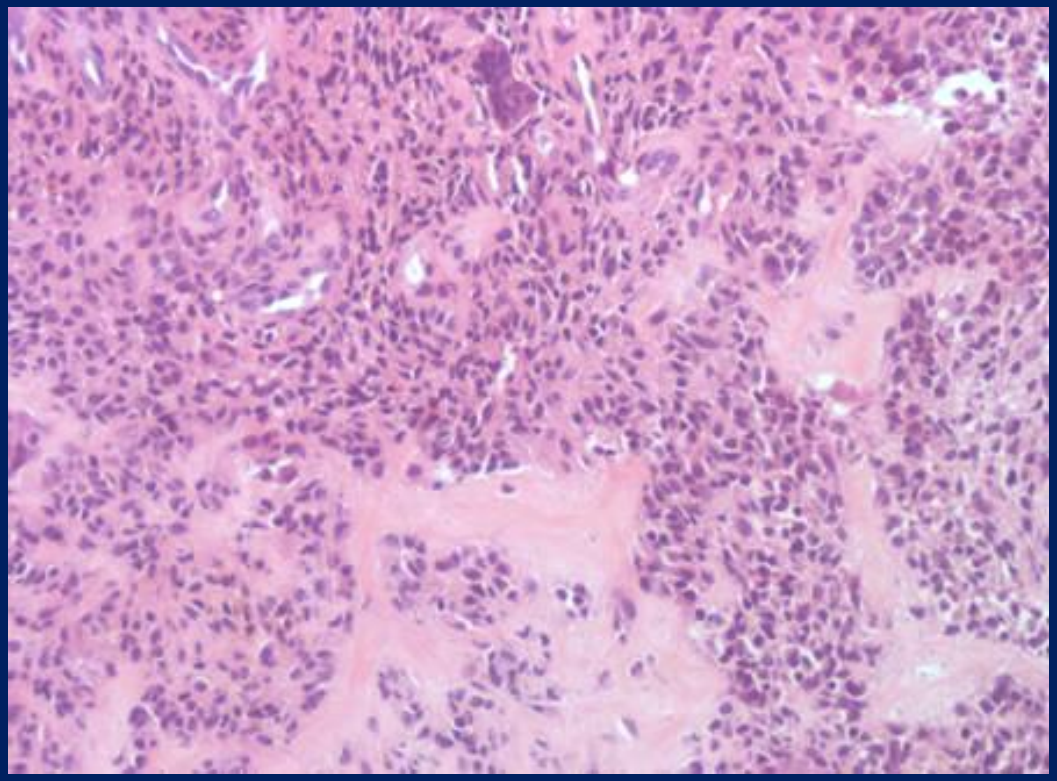
DFSP is a locally invasive, slow-growing tumor of the subcutaneous tissue that rarely metastasizes but recurs frequently after surgical excision. We report herein a case of highly recurrent, locally invasive DFSP that failed both postoperative radiation therapy and complete trial of imatinib, but was successfully treated with Sorafenib, which showed unprecedented response.

Background **Case report**

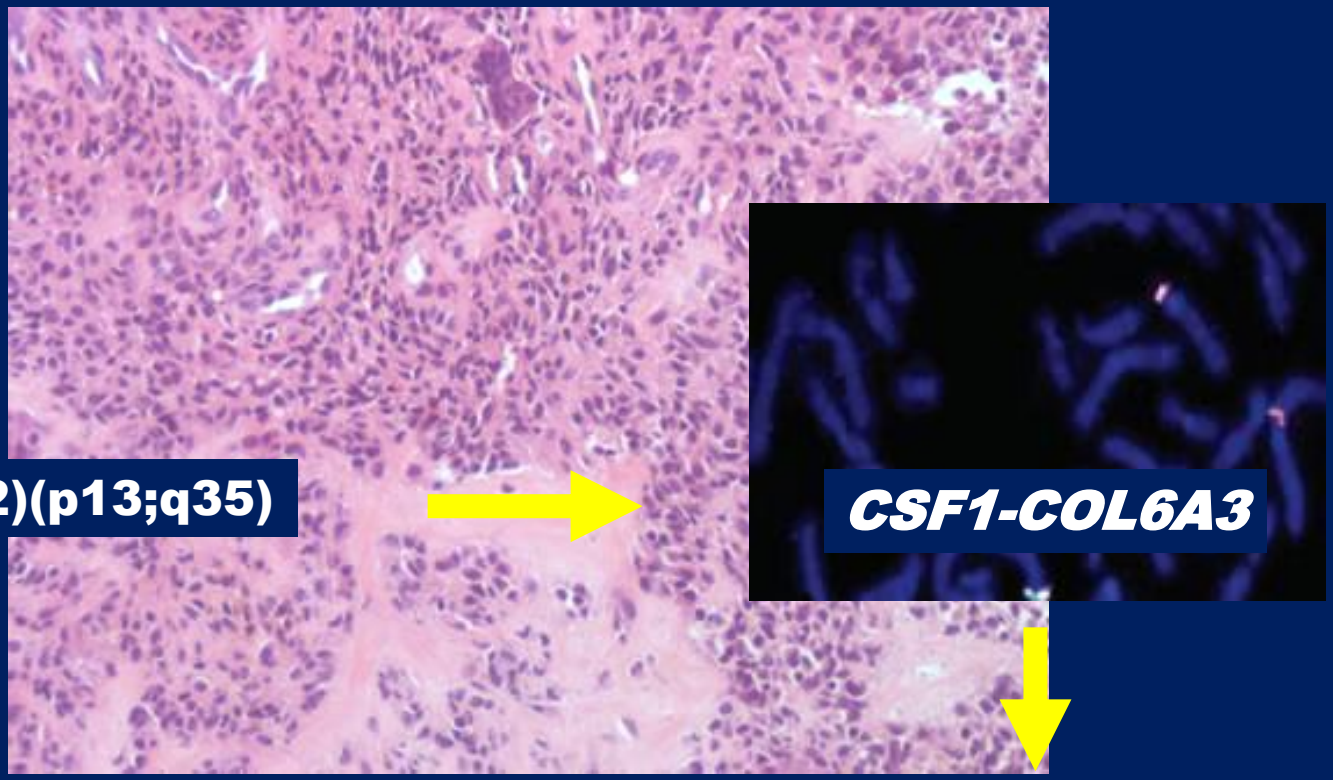


Kamar FG et al, Clin Sarc Res 2015
Ugurel S et al, Clin Cancer Res 2014

Pigmented Villonodular Tenosynovitis (PVNS)

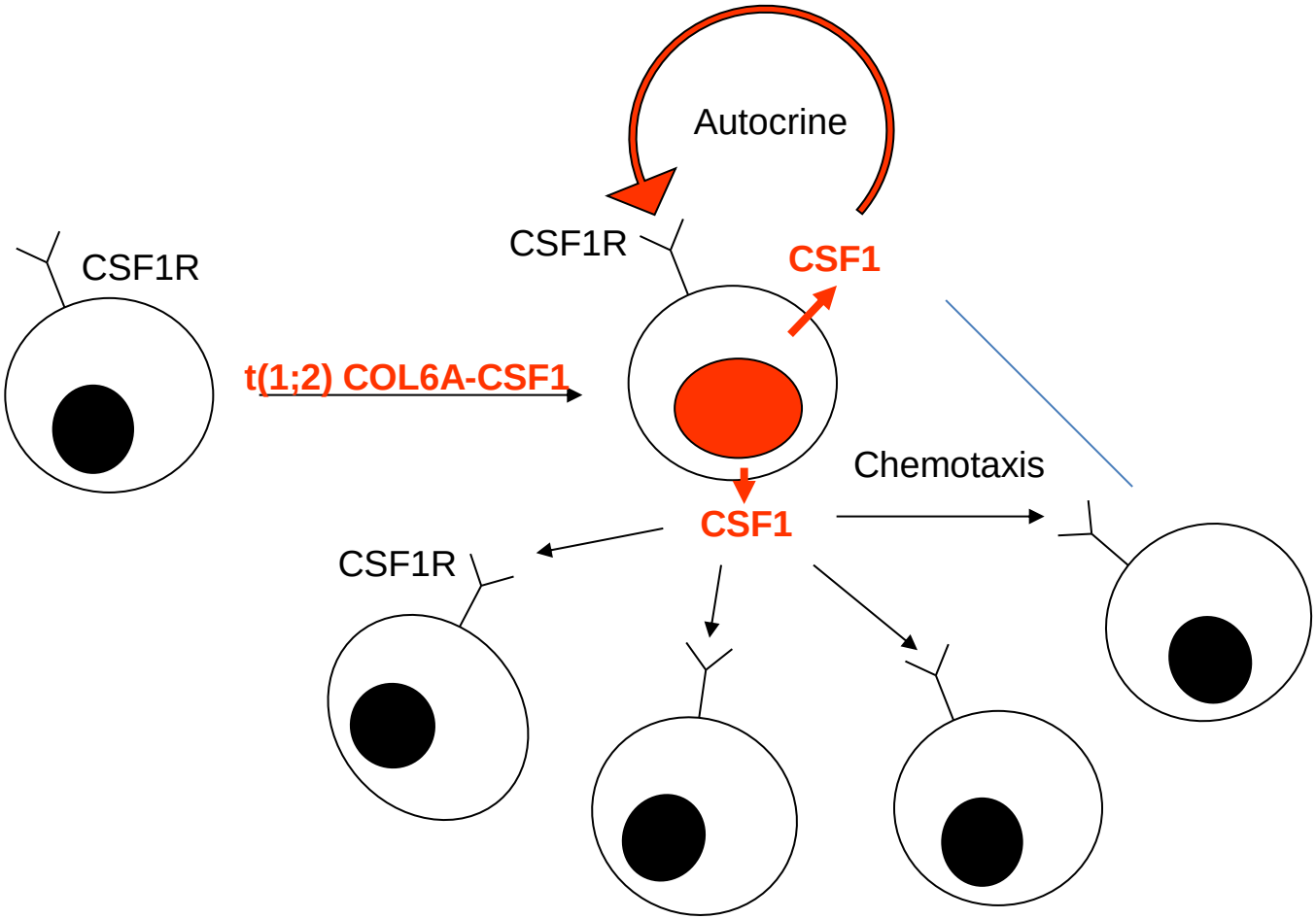


Pigmented Villonodular Tenosynovitis (PVNS)



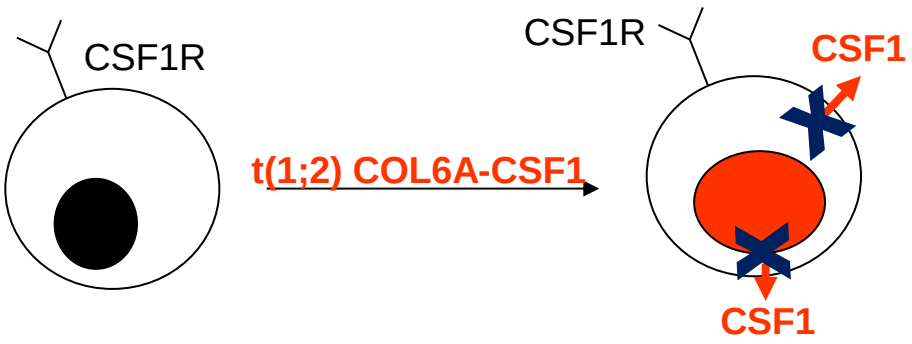
CSF1 (M-FCS1) overexpression

Dal Cin P et al, Cancer Res 1994



West et al, PNAS 2005

… CSF1R inhibitors



...imatinib

Annals of Oncology 19: 821–826, 2008

Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT)

Pigmented villonodular synovitis (PVNS), also known as tenosynovial giant cell tumor (TGCT), is a rare pathological entity affecting the synovium in young adults [1, 2]. Initially considered as an inflammatory reactive process, recent observations have shown that this disease may actually be a benign neoplastic process with specific genetic alterations [3, 4]. Indeed, a specific t(1;2) translocation, involving the collagen 6A3 gene (on 2q35) and the macrophage colony-stimulating factor (M-CSF) (also known as CSF1) gene (on 1p13), is present in a fraction of tumor cells in PVNS/TGCT. This fusion gene expressed by a fraction of the cells encodes for a fusion protein which attracts non-neoplastic cells expressing Macrophage colony stimulating factor (M-CSFR), through a paracrine—'landscape'—effect [3, 4].

PVNS/TGCT is generally treated by surgery alone. However, relapses may occur, and re-excision may be needed, with possible important functional impairment [1, 2]. In addition to its inhibitory activity on BCR-ABL, KIT, and platelet derived growth factor receptor alpha, imatinib has recently been reported to block M-CSFR activation at therapeutic concentration [5]. These observations prompted us to evaluate imatinib in a patient with recurrent and symptomatic PVNS/TGCT following surgery, in whom surgical re-excision would have had important functional consequences.

A 54-year-old right-handed female was referred to us for a rapid painful relapse of PVNS/TGCT of the right elbow 5 months after surgical removal of the lesion. Imatinib was initiated at a dose of 400 mg/day on 18 September 2006 (Figure 1). A partial response was observed at month 2 (08 November 2006) and complete remission was observed at month 5 (28 February 2007). Treatment was interrupted at month 7. In June 2007 (month 9), a symptomatic painful relapse of the tumor was diagnosed both clinically and on magnetic resonance imaging. Imatinib was reintroduced at the same dose and a second complete remission was observed in September 2007 and confirmed in December 2007 at month 14.

The rationale for imatinib treatment in this observation came out from the hypothesis that imatinib may disrupt the paracrine loop found responsible for PVNS/TGCT growth [3, 4, 6]. In this patient, the rapid response observed with imatinib,

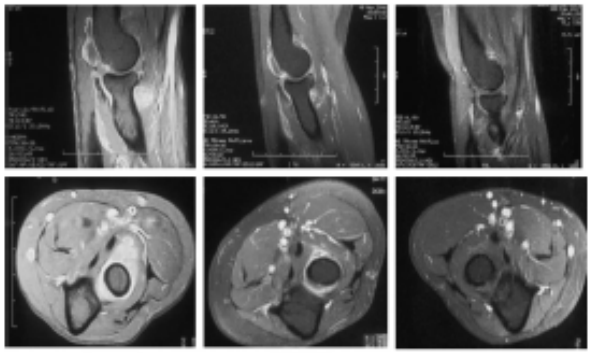


Figure 1. Response to imatinib in PVNS.

Blay JY et al, Ann Oncol 2008

Articles

CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study

Philippe A Cassier*, Antoine Italiano*, Carlos A Gomez-Roca, Christophe Le Tourneau, Maud Toulmonde, Michael A Cannarile, Camilla Ries, Anne Brillouet, Claudia Müller, Anna-Maria Jegg, Ann-Marie Bruhns, Markus Dembowski, Katharine Bray-French, Christine Fruehinger, Georgina Menezes-Loureiro, Monika Boehnke, Ross Harding, Jayantha Ratnayake, Kashan Abiraj, Nathalie Gass, Karen Noh, Randolph D Christen, Lidia Ulianova, Emmanuelle Bompas, Jean-Yves Blay†, Dominik Rüttinger†

Summary

Background Diffuse-type tenosynovial giant cell tumour (ds-GCT) of the soft tissue (alternatively known as pigmented villonodular synovitis), an orphan disease with unmet medical need, is characterised by an overexpression of colony-stimulating factor 1 (CSF1), and is usually caused by a chromosomal translocation involving CSF1. CSF1 receptor (CSF1R) activation leads to the recruitment of CSF1R-expressing cells of the mononuclear phagocyte lineage that constitute the tumor mass in ds-GCT. Emactuzumab (RG7155) is a novel monoclonal antibody that inhibits CSF1R activation. We have assessed the safety, tolerability and activity of emactuzumab in patients with ds-GCT of the soft tissue.

Methods In this phase 1, first-in-human dose-escalation and dose-expansion study, eligible patients were aged 18 years or older with ds-GCT of the soft tissue with locally advanced disease or resectable tumours requiring extensive surgery, an Eastern Cooperative Oncology Group performance status of 1 or less, measurable disease according to Response Evaluation Criteria In Solid Tumors version 1.1, and adequate end-organ function. Patients with GCT of the bone were not eligible. Patients received intravenous emactuzumab at 900 mg, 1350 mg, or 2000 mg every 2 weeks in the dose-escalation phase and at the optimal biological dose in a dose-expansion phase. The primary objective was to evaluate the safety and tolerability of emactuzumab, and to determine the maximum tolerated dose or optimal biological dose. All treated patients were included in the analyses. Expansion cohorts are currently ongoing. This study is registered with ClinicalTrials.gov, number NCT01494688.

Findings Between July 26, 2012, and Oct 21, 2013, 12 patients were enrolled in the dose-escalation phase. No dose-limiting toxicities were noted in the dose-escalation cohort; on the basis of pharmacokinetic, pharmacodynamic, and safety information, we chose a dose of 1000 mg every 2 week for the dose-expansion cohort, into which 17 patients were enrolled. Owing to different cutoff dates for safety and efficacy readouts, the safety population comprised 25 patients. Common adverse events after emactuzumab treatment were facial oedema (16 [64%] of 25 patients), asthenia (14 [56%]), and pruritus (14 [56%]). Five serious adverse events (periorbital oedema, lupus erythematosus [occurring twice], erythema, and dermatopolymyositis all experienced by one [4%] patient each) were reported in five patients. Three of the five serious adverse events—periorbital oedema (one [4%]), lupus erythematosus (one [4%]), and dermatopolymyositis (one [4%])—were assessed as grade 3. Two other grade 3 events were reported: mucositis (one [4%]) and fatigue (one [4%]). 24 (86%) of 28 patients achieved an objective response; two (7%) patients achieved a complete response.

Interpretation Further study of ds-GCT is warranted and different possibilities, such as an international collaboration with cooperative groups to assure appropriate recruitment in this rare disease, are currently being assessed.

Funding F Hoffmann-La Roche.

Lancet Oncol 2015; 16: 949–56
Published Online July 13, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00132-1
See Comment page 875
*Contributed equally
†Contributed equally

Department of Medicine, Centre Léon Bérard, Lyon, France (P A Cassier MD, Prof J-Y Blay MD); Department of Medical Oncology, Institut Bergonié, Bordeaux, France (A Italiano MD, M Toulmonde MD); Department of Medicine, Institut Claudius Regaud, Toulouse, France (C A Gomez-Roca MD, Prof J Delord MD); Department of Medical Oncology, Institut Curie, Paris a Saint-Cloud, France (C Le Tourneau MD, Prof J-P Delord MD); Roche Innovation Center Penzberg, Roche Pharmaceutical Research and Early Development, Penzberg, Germany (M A Cannarile PhD, C Ries PhD, C Müller PhD, A-M Jegg PhD, A-M Bruhns PhD, M Boehnke PhD, D Rüttinger MD); Roche Innovation Center Basel, Roche Pharmaceutical Research and Early Development, Basel, Switzerland (A Brillouet BSc, M Dembowski PhD, K Bray-French PhD, C Fruehinger PhD, K Abiraj PhD, N Gass PhD, K D Christen MD, L Ulianova MD); Roche Innovation Center Welwyn, Roche Pharmaceutical Research and Early Development, Welwyn, UK (G Menezes-Loureiro PhD, R Harding PhD, J Ratnayake PhD); Roche Innovation Center New York, Roche Pharmaceutical Research and Early Development, New York, NY,

Introduction

The molecular features of mesenchymal tumours have many similarities to those of haematological malignancies, including genetic aberrations creating deregulated kinases, overexpressed oncogenes, or fusion transcription factors. Such biologically disparate entities need subtype-specific treatments. Even when individual cases are rare, every effort should be made to validate the efficacy of new therapies with a treatment approach tailored to the underlying subtype-specific biology.[1]

Diffuse-type giant cell tumour (ds-GCT) of the soft tissue, alternatively known as pigmented villonodular synovitis, is a rare and destructive proliferation of synovial-like mononuclear cells, admixed with multinucleate giant cells, foam cells, siderophages, and inflammatory cells.[2] GCT can be localised or diffuse, and occurs more frequently in young adults, with no sex predilection in intra-articular disease, and a slight female predominance in extra-articular disease.[3] The knee is the most frequent (66–80%) intra-articular location for the development of these lesions, followed by the hip, ankle, elbow, and shoulder.[4] Total synovectomy is the standard of care for ds-GCT. However, recurrence is frequent (up to 55% of patients recur, depending on disease localisation) and

...Emactuzumab

Phase 1-2 study

28 patients

2/28 CR
24/28 PR

Cassier P et al, Lancet Oncol 2015

...PLX3397

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor

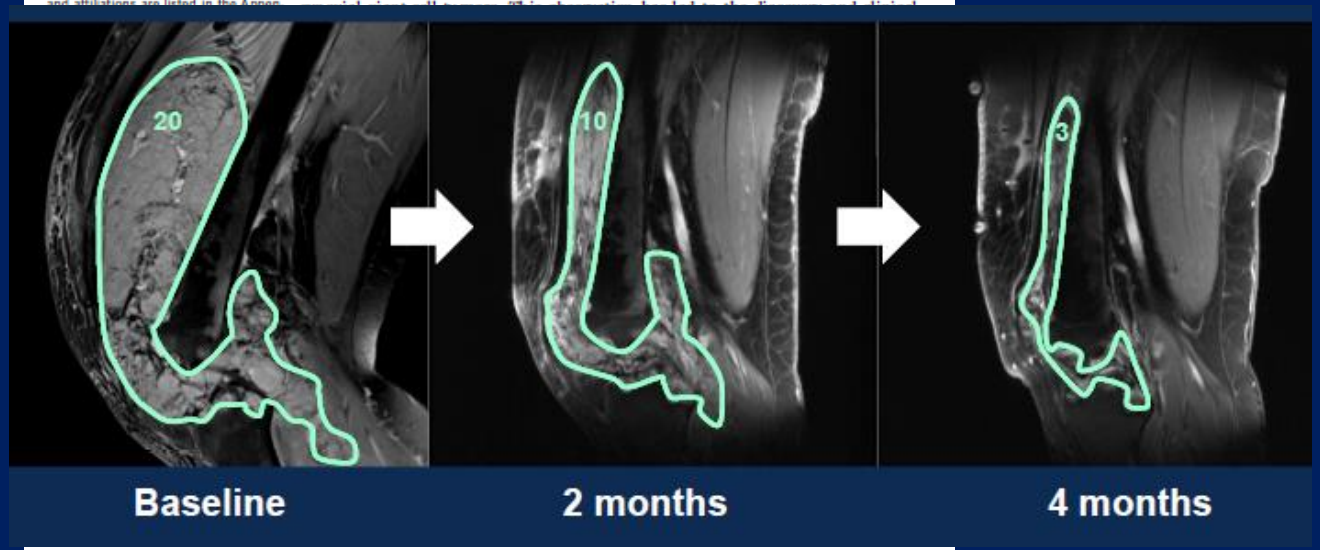
W.D. Tap, Z.A. Wainberg, S.P. Anthony, P.N. Ibrahim, C. Zhang, J.H. Healey, B. Chmielowski, A.P. Staddon, A.L. Cohn, G.I. Shapiro, V.L. Keedy, A.S. Singh, I. Puzanov, E.L. Kwak, A.J. Wagner, D.D. Von Hoff, G.J. Weiss, R.K. Ramanathan, J. Zhang, G. Habets, Y. Zhang, E.A. Burton, G. Visor, L. Sanftner, P. Severson, H. Nguyen, M.J. Kim, A. Marimuthu, G. Tsang, R. Shellooe, C. Gee, B.L. West, P. Hirth, K. Nolop, M. van de Rijn, H.H. Hsu, C. Peterfy, P.S. Lin, S. Tong-Starksen, and G. Bollag

ABSTRACT

BACKGROUND

Expression of the colony-stimulating factor 1 (CSF1) gene is elevated in most teno-

The authors' full names, academic degrees, and affiliations are listed in the Appen



Phase 1-2 study

23 patients
12/23 PR
7/23 SD

Tap W et al, NEJM 2015

...PLX3397

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor

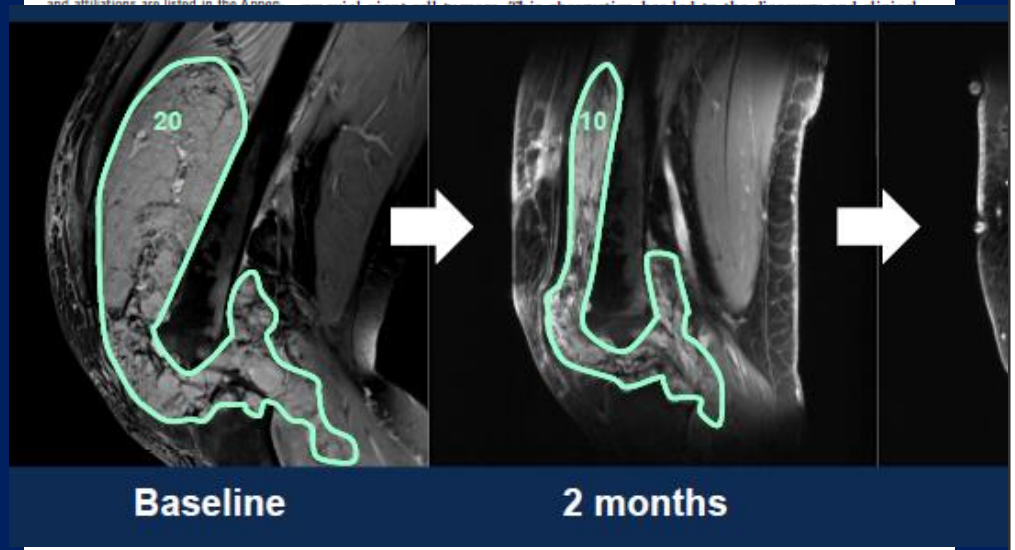
W.D. Tap, Z.A. Wainberg, S.P. Anthony, P.N. Ibrahim, C. Zhang, J.H. Healey, B. Chmielowski, A.P. Staddon, A.L. Cohn, G.I. Shapiro, V.L. Keedy, A.S. Singh, I. Puzanov, E.L. Kwak, A.J. Wagner, D.D. Von Hoff, G.J. Weiss, R.K. Ramanathan, J. Zhang, G. Habets, Y. Zhang, E.A. Burton, G. Visor, L. Sanftner, P. Severson, H. Nguyen, M.J. Kim, A. Marimuthu, G. Tsang, R. Shellooe, C. Gee, B.L. West, P. Hirth, K. Nolop, M. van de Rijn, H.H. Hsu, C. Peterfy, P.S. Lin, S. Tong-Starksen, and G. Bollag

ABSTRACT

BACKGROUND

Expression of the colony-stimulating factor 1 (CSF1) gene is elevated in most teno-

The authors' full names, academic degrees, and affiliations are listed in the Appen



CLINICAL STUDY PROTOCOL

Protocol Number:	PLX108-10
Title:	A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath
Indication:	Pigmented villonodular synovitis (PVNS) / giant cell tumor of tendon sheath (GCT-TS)
Phase:	3
Sponsor: (all regions except Europe)	Daiichi Sankyo Pharma Development 399 Thornall Street Edison, NJ 08837, USA
Sponsor: (Europe)	Daiichi Sankyo Development Limited Chiltern Place, Chalfont Park Gerrards Cross, Buckinghamshire SL9 0BG United Kingdom
EudraCT Number:	2014-000148-14
Therapeutic Area:	Antineoplastic agent
IND Number:	117,332
Version:	3.0, 11 Feb 2015
Superceded Versions:	2.0, 05 Dec 2014
Original Protocol:	1.0, 18 Sep 2014

CONFIDENTIALITY STATEMENT

Tap W et al, NEJM 2015

Adipocytic tumours
- Well deifferentiated / dedifferentiated liposarcoma
- Myxoid / round cell liposarcoma
- Pleomorphic liposarcoma
- …..

Fibroblastic / myofibroblastic tumours
- Fibromatosis (desmoid)
- Solitary fibrous tumour / haemangiopericytoma
- Low grade myofibroblastic tumour
- Infantile fibrosarcoma
- Adult fibrosarcoma
- Mixofibrosarcoma
- …..

So-called fibrohistiocytic tumours
- Pleomorphic MFH / Undifferentiated pleomorphic sarcoma
- …..

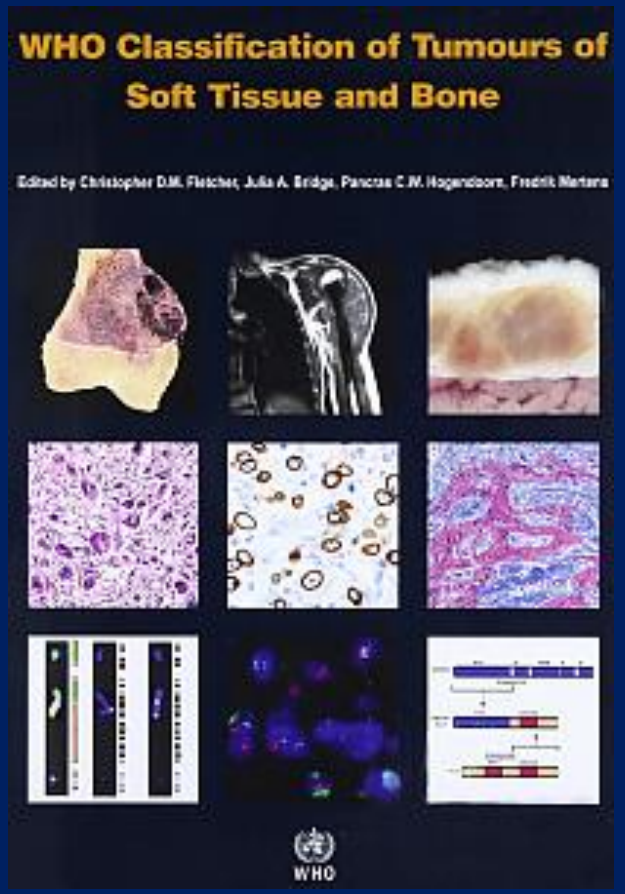
Smooth muscle tumours
- Leiomyosarcoma
- …..

Skeletal muscle tumours
- Embryonal rhabdomyosarcoma
- Alveolar rhabdomyosarcoma
- Pleomorphic rhabdomyosarcoma

Vascular tumours
- Epithelioid haemangioendothelioma
- Angiosarcoma of soft tissue
- …..

Chondro-osseous tumours
- Mesenchymal chondrosarcoma
- Extraskeletal osteosarcoma

Tumours of uncertain differentiation
- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing tumour
- Desmoplastic small round cell tumour
- Extra-renal rhabdoid tumour
- Malignant mesenchymoma
- Neoplasms with perivascular epithelioid cell differentiation (PEComa)
- Intimal sarcoma



Silvia Stacchiotti
silvia.stacchiotti@istitutotumori.mi.it