Proffered Paper & Poster Discussion – Developmental Therapeutics

Abstracts No. 125O & 126O

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Disclosure slide

- Advisory:
  - Celgene, Novartis, Roche
- Research Funding:
  - MSD
- Travel Support/Grants:
  - Bayer, BMS, MSD, Novartis, Roche

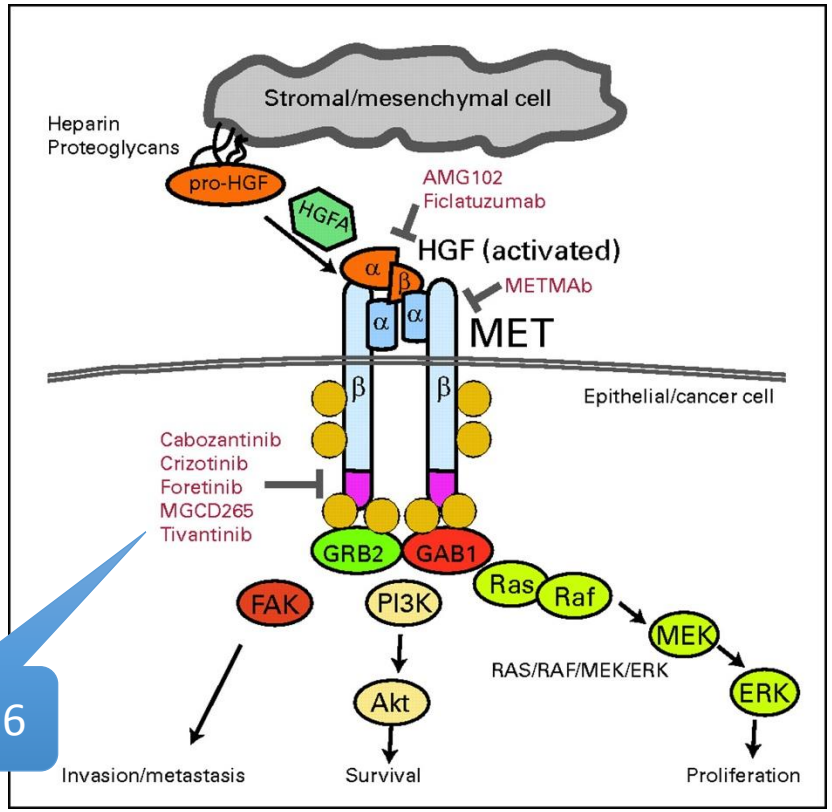
Abstracts 125O & 126O

- 125O – Hollebecque et al.
  - First-in-human study of oral S 49076, a MET/AXL/FGFR inhibitor in advanced solid tumors

- 126O – Li et al.
  - A phase 1 study evaluating the safety, efficacy, pharmacokinetics of AL3810 (lucitanib) in advanced solid tumors

Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

- S 49076 is an ATP-competitive tyrosine kinase inhibitor with specific activity on MET, AXL and FGFR 1/2/3



S 49076

IC50 values in radiometric assays on various mutant isoforms

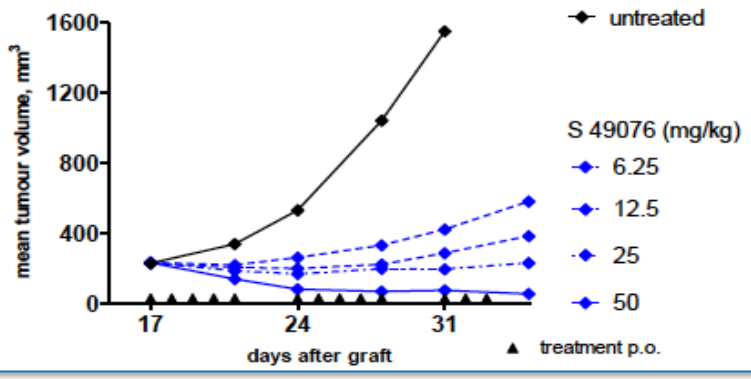
Kinase	Examples of tumors where these mutations have been detected	IC_{50} (nmol/L)
MET	–	1
MET^{D1246N}	Germline renal papillary carcinoma	8
MET^{Y1248C}		16
MET^{D1246H}	Somatic papillary renal cell carcinoma, head and neck squamous cell carcinoma, non-small-cell lung carcinoma	11
MET^{Y1248D}		17
MET^{Y1248H}		1
MET^{M1268T}		1
AXL	–	7
MER	–	2
FGFR1	–	18
$FGFR1^{V561M}$	Squamous cell lung cancer	23
FGFR2	–	17
$FGFR2^{N549H}$	Endometrial carcinoma	19
FGFR3	–	15

Appleman LJ. JCO 2011
Burbridge et al. Mol Cancer Ther 2013

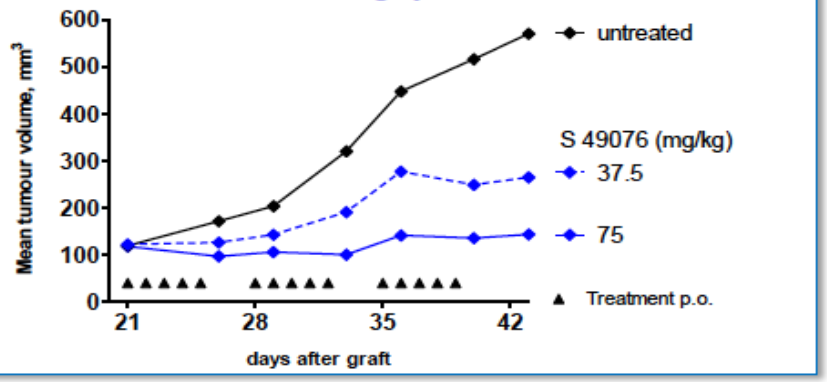
MET, AXL and FGFR TKI: S 49076

- S 49076 inhibits tumour growth in xenografts expressing activated MET, AXL or FGFR
- S 49076 is highly active in a bevacizumab-resistant model

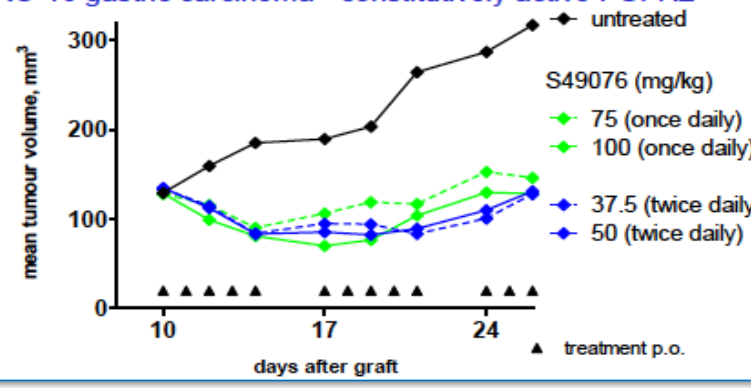
U87-MG gliobastoma - HGF-MET autocrine loop



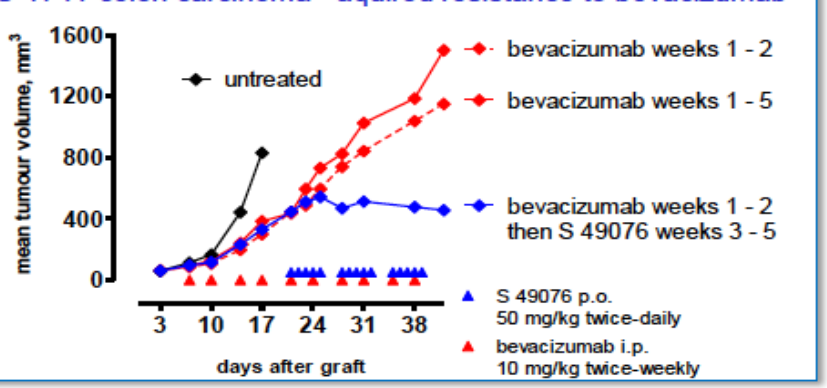
RXF 1220 renal carcinoma - highly activated MET & AXL



SNU-16 gastric carcinoma - constitutively active FGFR2



LS-174T colon carcinoma - aquired resistance to bevacizumab



Presented by Depil S. TAT 2013

Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

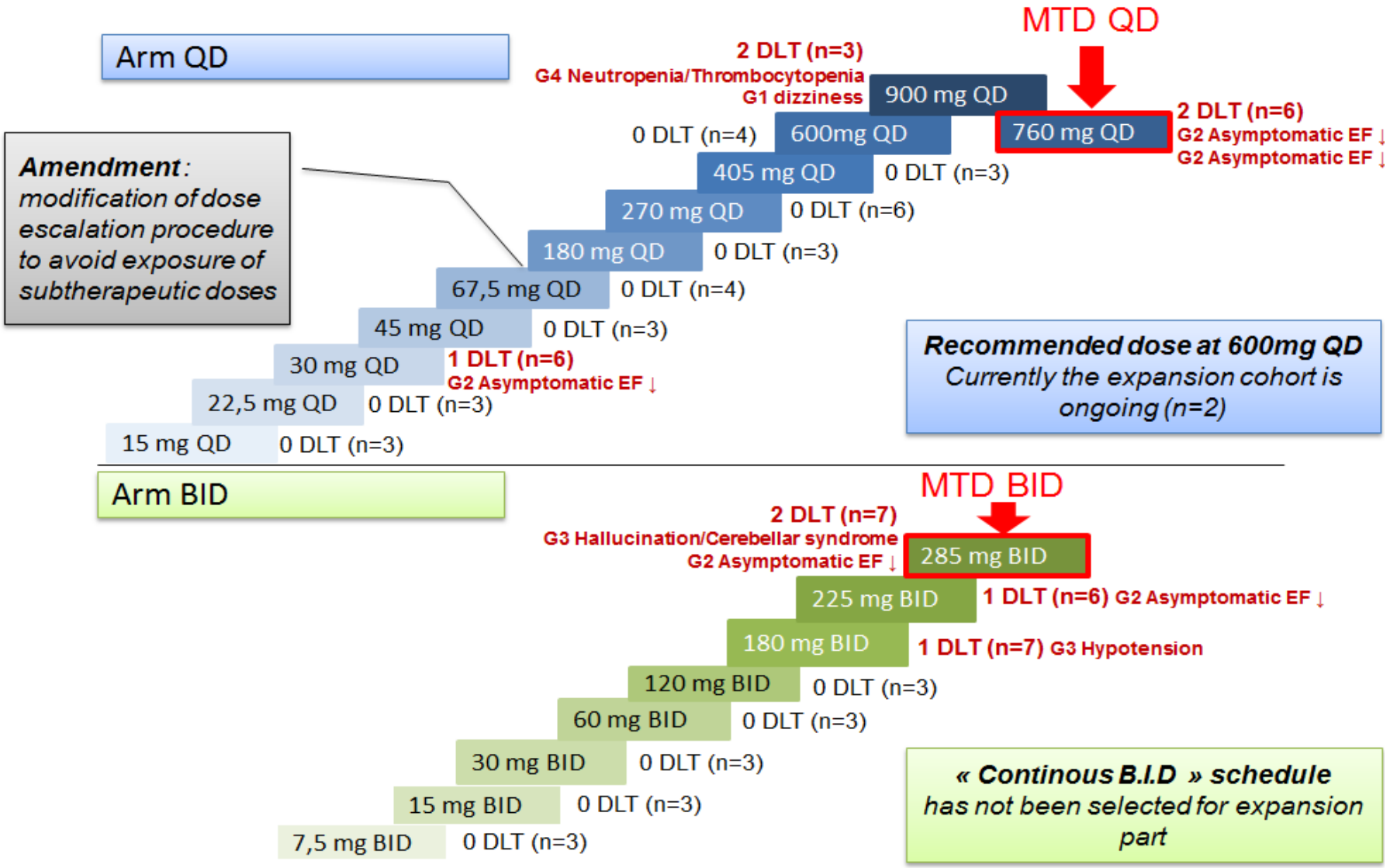
Patient Population:

- All-comers, regardless of MET amplification status
  - Majority mCRC, also lung, mesothelioma, uveal melanoma
  - 45% patients are of other primaries

Trial Design:

- Classic 3+3 design investigating 2 dosing strategies with expansion once recommended dose determined

Dose escalation – RD*



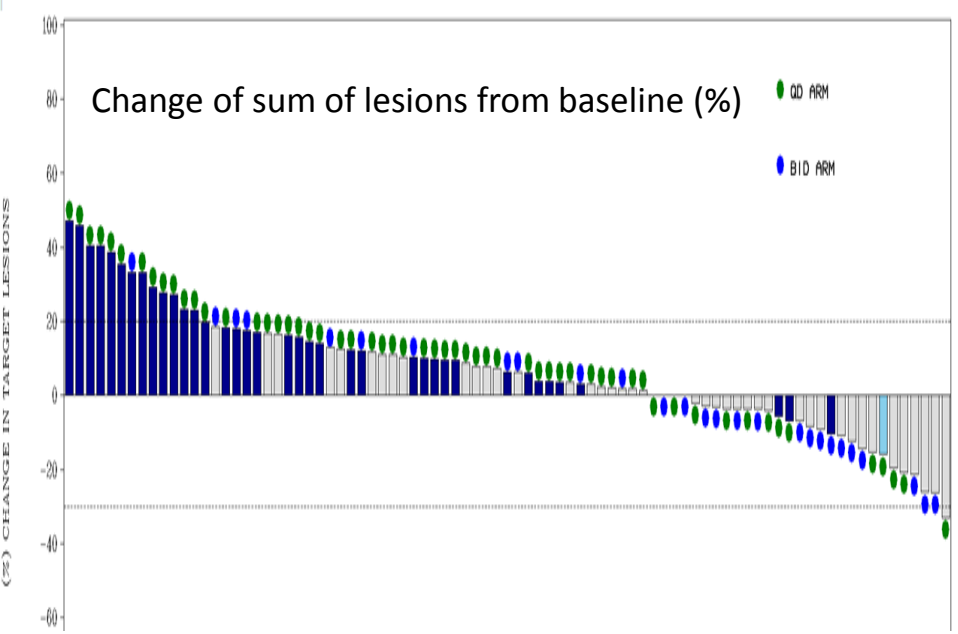
** Recommended dose*

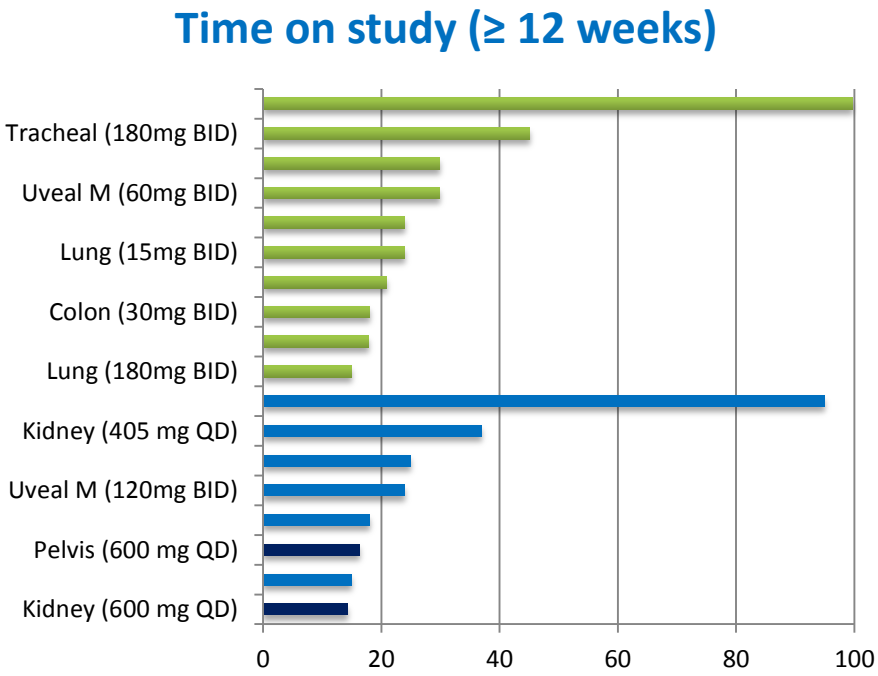
Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

- Safety and toxicity profile is what one expects from this class of agent
  - Hypoalbuminaemia }
  - Peripheral oedema } in 50% of patients at RD;
  - with only 1/28 patients >/= G3

- 10 patients had G2 “decrease in EF” which were all asymptomatic and reversible

Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor





- Majority of clinical benefit is SD
- Apparent efficacy over a large range of doses
- ? A larger proportion of patients on BID dosing had tumour shrinkage
- ? Should we revisit the dosing schedule

Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

		MET		AXL		FGFR1		FGFR2	
		All	*RD*	*All*	*RD*	*All*	*RD*	*All*	*RD*
IHC *All n= 25* *RD n=11*	**2+**	3	1	1	0	2	1	0	0
	3+	1	0	0	0	0	0	0	0
FISH amplification *All n= 27* *RD n=11*		0	0	Not performed	Not performed	2 Confirmed by CGH	1	0	0

- About 70% of total patients had either IHC/FISH testing (close to 80% at RD)
- Small numbers of IHC/FISH +ve patients → no obvious association with response
- At present, no obvious biomarker

Abs. 125O | S 49076 – MET/AXL/FGFR inhibitor

- Possible future directions:
  - Concentrate on malignancies in which all MET, AXL and FGFR have shown resistance mechanisms
    - EGFR-resistant NSCLC
    - BRAF V600E mutated melanoma (and not uveal melanoma)
    - Chemotherapy resistant AML
  - Concentrate on malignancies where VEGF inhibitors are considered standard-of-care as MET, AXL/ and FGFRs are important in angiogenesis
  - Combination approach to standard-of-care treatments to postpone acquired resistance

Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

- Non-selective FGFR inhibitor with equipotency against FGFR1 and VEGFR1-3

Non selective FGFR inhibitors = mostly FGFR1-VEGFR inhibitors

Compound/ IC50 (nM)	FGFR-1	VEGFR-1	VEGFR-2	VEGFR-3	PDGFRα	PDGFRβ	Other
E-3810	22	7	25	10	175	525	FGFR-2 70, FGFR3 238 FGFR4 >1000; c- Kit 456
Dovitinib	8	10	13	8	unk	12	FGFR-2 40, FGFR-3 9, FLT3 2, c-Kit 1
Brivanib	148	380	25	10	unk	>6000	FGR2 202, FGFR3 503, FGFR4 2003 Flt3,Src, lyn
Sunitinib	320	9	19	4	46	41	C- Kit 104
Sorafenib	154	6	16	10	744	>1000	C-Raf 0.006 B- Raf 0.22
Pazopanib	720	10	7-47	30	unk	70-84	C-Met 6
Axitinib	218	1.2	0.25	0.29	unk	0.29	C- Kit 2
Vandetanib	3000	1800	40	110	unk	1100	EGF- R 500
BIBF 1120	69	34	21	13	59	65	FLT3 26 Src 156
Cediranib	unk	5	1	3	unk	5	C-Kit 2
Motesanib	unk	2	3	6	unk	84	C- Kit 8

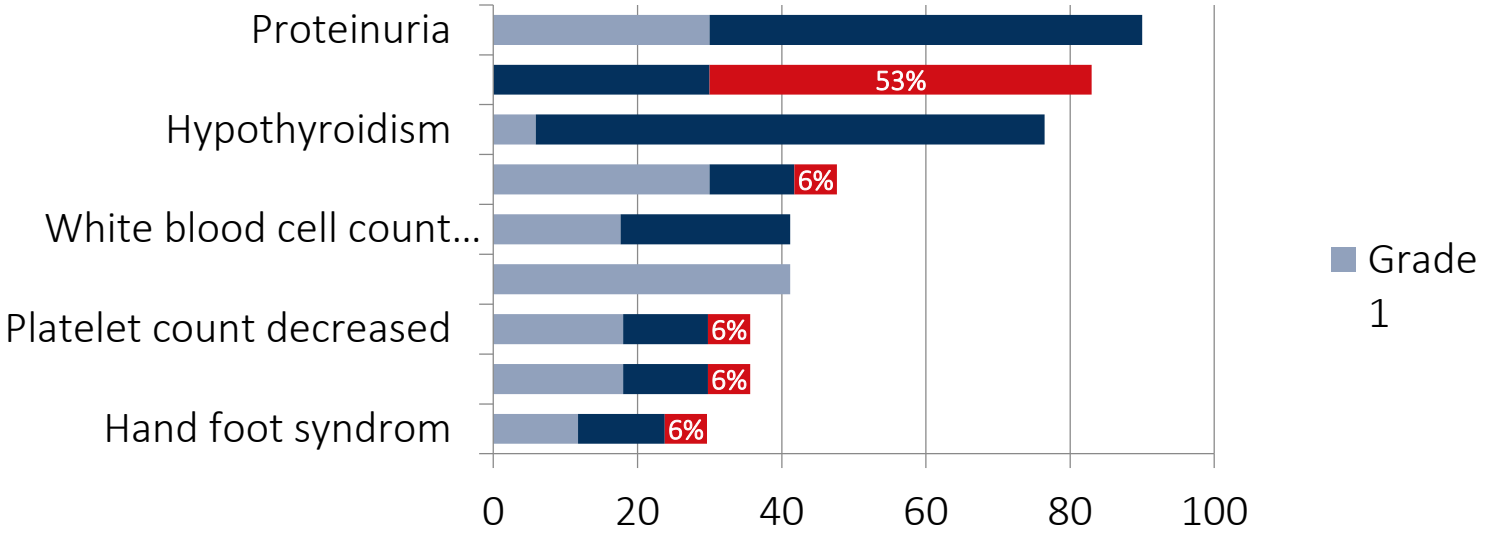
Soria JC; Presented at TAT 2014

Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

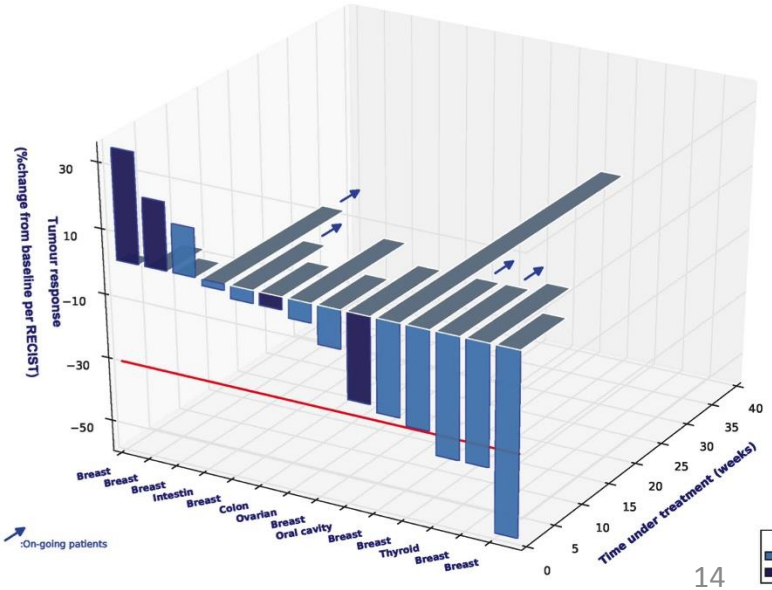
- Classical 3+3 design – extension at 10mg/d → RD
- Variety of tumour types; some heavily pre-treated with >/= 5 lines of treatment

	Dose level	Dose mg/day	Patients treated	Dose-limiting toxicity (DLT)
Escalation	1	10	3	NA
	2	15	3 + 2	G3 Fatigue G3 Blood bilirubin increase
Extension	1	10	9	G3 Cellulitis G3 Bile duct obstruction

Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor



- AEs are more reflective of anti-VEGF component
- Responses predominantly SDs
- No correlative studies on potential biomarkers



AL3810 | E3810 – Lucitanib – VEGFR, FGFR and PDGFR inhibitor

Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

J.-C. Soria[1*], F. DeBraud[2], R. Bahleda[1], B. Adamo[3], F. Andre[1], R. Dientsmann[3,4], A. Delmonte[2], R. Cereda[5,6,7], J. Isaacson[5,6,7], J. Litten[5,6,7], A. Allen[5,6,7], F. Dubois[8], C. Saba[8], R. Robert[8], M. D'Incalci[9], M. G. Camboni[5,6,7‡] & J. Tabernero[3]

[1]Department of Drug Development, Gustave-Roussy Cancer Campus, Villejuif, France; [2]European Institute of Oncology, Milan, Italy; [3]Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Sage Bionetworks, Fred Hutchinson Cancer Research Center, Seattle; [5]Clovis Oncology, Inc., San Francisco; [6]Clovis Oncology, Inc., Boulder, USA; [7]Clovis Oncology, Inc., Milan, Italy; [8]Institut de Recherche International Servier, Suresnes, France; [9]Istituto di Ricerche Farmacologiche Mario Negri, Via La Masa, Milan, Italy

- 76 patients; 42% patients had >/= 3 lines of prior chemotherapy
- Classical 3+3 design from 5mg up to 30mg/day
- **Dose expansion phase** at RD to obtain preliminary efficacy evidence on tumours which may harbour FGF-aberrant pathways or considered angiogenesis sensitive

Soria JC et al. 2014

AL3810 | E3810 – Lucitanib – VEGFR, FGFR and PDGFR inhibitor

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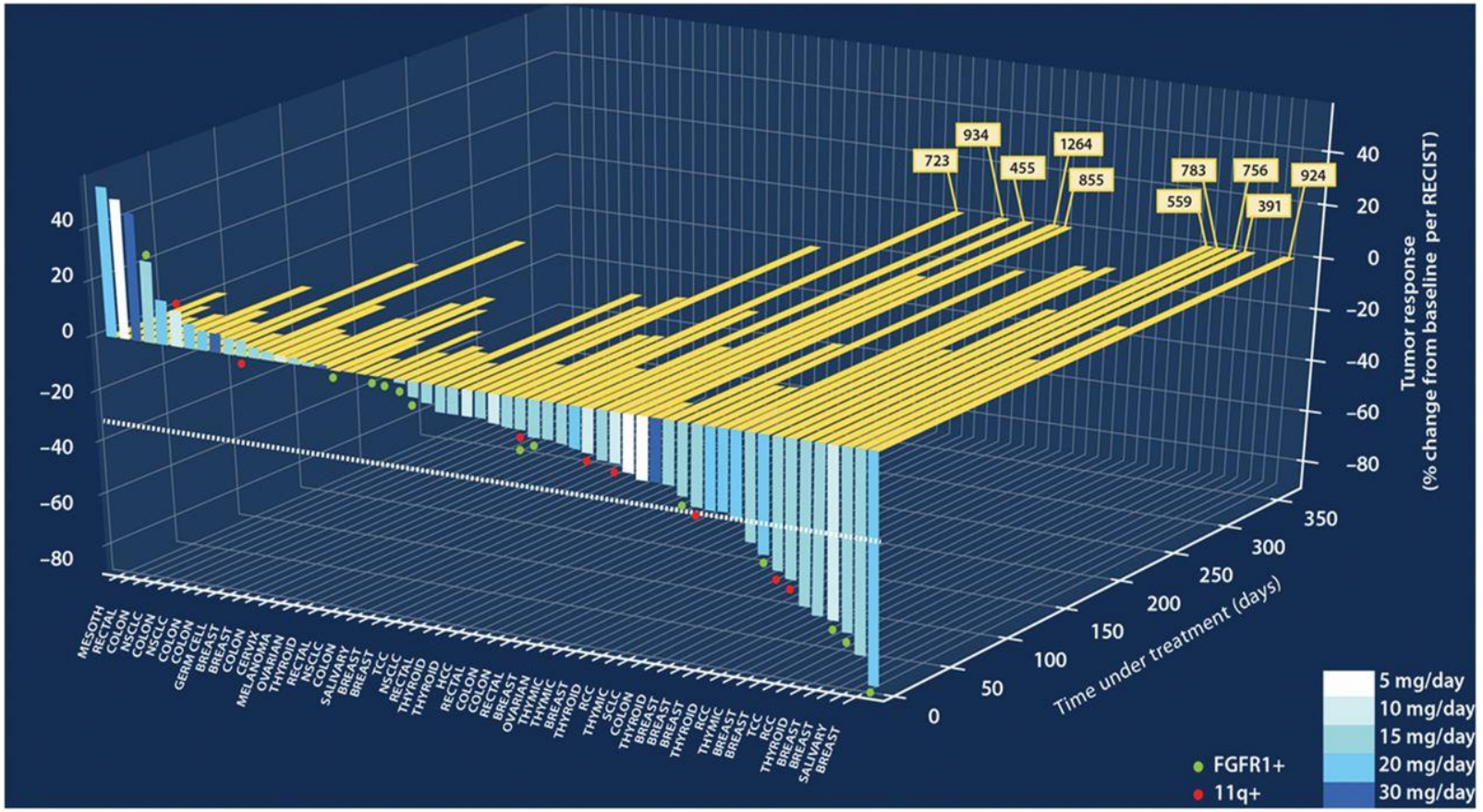
- MTD 30mg/d, Initial RD 20mg/d; then adjust to 15mg/d as pts cannot be sustained on multiple cycles
- Presumably East Asians/Chinese population is a minority or absent.

Soria JC et al. 2014

Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors

Tumor response to treatment (RECIST) in 58 assessable patients with measurable lesions and time on treatment (days).



- All 12 FGFR aberrant breast patients had treatment benefit (50% SD, 50% PR)

J.-C. Soria et al. Ann Oncol 2014;25:2244-2251

A Phase 2, Randomized, Open-Label Study of Lucitanib in Patients with FGF Aberrant Metastatic Breast Cancer

Maysa M. Abu-Khalaf[1], Ingrid A. Mayer[2], Chris Tankersley[3], Jadine Moy[3], Andrew Allen[3], Charles Vogel[4], Frankie Holmes[5], Rita Nanda[6], Kathy Miller[7], Ravindranath Patel[8], Lajos Pusztai[1], Carlos L. Arteaga[2]

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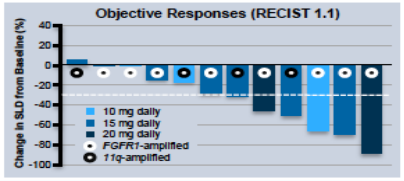
TPS628

BACKGROUND

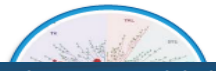
- Metastatic breast cancer (MBC) remains an incurable disease, with approximately 41,000 disease-associated deaths in the United States (US) annually.[1]
- FGF-pathway aberrancy, defined as amplification of *FGFR1* or *11q* (which includes *FGF3,4,19* ligands and *CCD1*), is observed in about 25% of patients with MBC, and portends a poor prognosis and is thought to be a targetable biologic driver in these patients.[2, 3]
- In the FIH study, patients with *FGF*-aberrant breast cancer experienced an objective response rate (ORR) of 50% (figure below) and progression-free survival (PFS) of 9.6 months.[2]



POTENT & SPECIFIC ACTIVITY

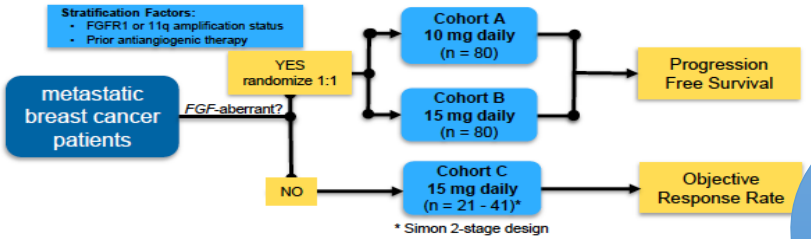
- Lucitanib is an orally available, potent inhibitor of the tyrosine kinases FGFR1–3, VEGFR1–3, and PDGFRα/β.
- Lucitanib has demonstrated meaningful activity in FGF-driven cancer models.[4]

Lucitanib KINOMEscan



Inhibition Profile	
Kinase	Kd (nM)
FGFR1	21
FGFR2	41
FGFR3	51

STUDY SCHEMA



* Simon 2-stage design

OBJECTIVES

PRIMARY:
- COHORTS A and B: PFS of lucitanib at a starting dose of 10 mg daily versus 15 mg daily
- COHORT C: ORR

SECONDARY:
- COHORTS A and B: ORR, duration of response (DR), disease control rate (DCR), overall survival (OS), patient reported outcomes (PRO)
- COHORT C: DR, DCR, PFS, OS, comparative PK, PRO

EXPLORATORY:
- Explore biomarkers that may be predictive of response or primary resistance to treatment with lucitanib

PATIENTS CHARACTERISTICS

SUMMARY

- The gene regions coding for *FGFR1* on 8p, *FGF3*, *FGF4*, and *FGF19* on *11q* are freq amplified in breast cancers, with amplifie associated with a poor prognosis.
- Breast cancer patients with amplification o regions treated with lucitanib monotherapy study of lucitanib experienced 100% clinical b rate.
- This promising clinical activity led to this Ph in *FGF*-aberrant MBC at 30 medical centers US (NCT022202746).
- Toxicities in the FIH study are consistent wit lucitanib as a potent antiangiogenic drug and hypertension, proteinuria, and hypothyroidism.
- The study is ongoing with 60 patients en Cohorts A and B.

A single arm, open-label, phase 2 study to assess the efficacy and safety of lucitanib given orally as a single agent to patients with advanced/metastatic lung cancer and FGF, VEGF, or PDGF-related genetic alterations

David R. Spigel[1], Enriqueta Felip[2], Silvia Novello[3], Marina Garassino[4], Melanie Collins[5], Jason Litten[5], Andrew Allen[5], Roberta Cereda[6], Taofeek Owonikoko[7], Mark A. Socinski[8], D. Ross Camidge[9], Benjamin Besse[10]

1. Sarah Canon Research Institute, Nashville, TN
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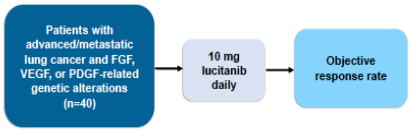
3. AOU San Luigi Gonzaga, Orbassano, IT
4. Fondazione IRCCS Istituto Nazionale Tumori, Milano, IT
5. Clovis Oncology, Inc., San Francisco, CA
6. Clovis Oncology Italy S.r.l., Milano, IT
7. Emory University Winship Cancer Institute,
8. University of Pittsburgh Medical
9. University of Colorado, Denv
10. Institut Gustave-Roussy, Vil

P2.01-090

BACKGROUND

- Lung cancer is the leading cause of cancer-related mortality, accounting for approximately 10% of cancer-related deaths worldwide annually[1]
- The recent discovery of genetic changes that drive tumor growth has accelerated the development of novel targeted therapies
- Genetic changes associated with tumor growth and metastases include abnormalities related to fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) signaling
- Abnormalities in the FGF, VEGF, and PDGF-related genes have been described across lung cancer histologies at incidences varying between 1–25%, depending on that abnormality[2]
- Lucitanib is a potent selective tyrosine kinase inhibitor of FGFR1–3, VEGFR1–3, and PDGFRα/β
- In biomarker unselected patients enrolled into the first-in-human study of lucitanib, a disease control rate (defined as complete response + partial response + stable disease) was observed in >80% of patients, and an objective response rate ([ORR], defined as complete response + partial response) was observed in >25% of patients[3]
- This study is enrolling lung cancer patients with a variety of histologic subtypes and biomarkers with the aim of identifying biomarkers predictive of exceptional responses to lucitanib in lung cancer

STUDY SCHEMA



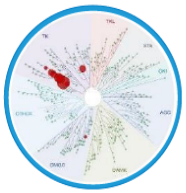
ORR: Proportion of patients with a confirmed complete response (CR) or a confirmed partial response (PR), as best overall response according to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 criteria

- Enrollment into the study is currently ongoing at 19 study centers specializing in genetic screening, in 5 countries across the United States and Europe (France, Germany, Italy, and Spain)

POTENT & SPECIFIC ACTIVITY

- Lucitanib is an orally available, potent inhibitor of the tyrosine kinases FGFR1–3, VEGFR1–3, and PDGFRα/β
- Lucitanib has shown potent anti-tumor and anti-angiogenic activity *in vitro* proliferation assays and *in vivo* using human tumor xenograft models, with a trend for stronger efficacy in those with genomic aberrancies in the *FGF* and *PDGF* signaling pathway

Lucitanib KINOMEscan



Inhibition Profile	
Kinase	Kd (nM)
FGFR1	21
FGFR2	41
FGFR3	51
VEGFR1	1
VEGFR2	1.1
VEGFR3	7.1
PDGFRα	0.43
PDGFRβ	0.26

PRIMARY OBJECTIVE

- Evaluate the ORR of lucitanib in patients with advanced/metastatic lung cancer and FGF, VEGF, or PDGF-related genetic alterations

SECONDARY & EXPLORATORY OBJECTIVES

- Evaluate the clinical benefit rate (CBR), progression-free survival (PFS), duration of the response (DR), and overall survival (OS)
- Evaluate the kinetics of tumor size change prior to and after lucitanib exposure
- Evaluate the safety profile of lucitanib
- Collect additional information on the pharmacokinetic (PK) profile of lucitanib
- Perform a pharmacogenomic analysis of inter-patient variation in genes encoding for proteins involved in absorption/distribution/metabolism/excretion (ADME)
- Evaluate the pharmacodynamic (PD) profile of lucitanib by characterizing its biological activity and by exploring biomarkers potentially predictive for benefit from lucitanib

KEY INCLUSION CRITERIA

- Patients with advanced/metastatic small cell lung cancer and non-small cell lung cancer and FGF, VEGF, or PDGF-related genetic alterations. Qualifying tumor-tissue based genetic alterations include:
  - FGFR1, FGFR2, FGFR3, VEGFA, or PDGFRα amplification
  - Any FGFR1, FGFR2, or FGFR3 gene fusion
  - FGFR1, FGFR2, or FGFR3 activating mutation
- Documented radiographic disease progression following at least one line of therapy in the advanced/metastatic setting
- Availability of formalin-fixed paraffin embedded tumor tissue sufficient for central confirmation genetic aberration and biomarker analyses
- ECOG performance status grade 0 or 1

KEY EXCLUSION CRITERIA

- Ongoing adverse events from prior anticancer therapies without resolution of any grade 2 or greater side effects to grade ≤1
- Known symptomatic central nervous system (CNS) metastases not controlled by prior surgery or radiotherapy and/or low-dose steroids
- Uncontrolled hypertension at time of enrollment
- Tumors that are invading a major vessel

SUMMARY

- Based on lucitanib's potent and unique spectrum of activity, this study will enroll advanced lung cancer patients with evidence of tumor genetic alterations that may confer sensitivity to lucitanib treatment
- The study is designed to explore the anti-tumor activity of lucitanib in lung cancer patients with FGF, VEGF, and PDGF genetic alterations
- Although these alterations occur at relatively low frequencies, this study is expected to identify patients who are exceptional responders to lucitanib and evaluate potential biomarkers for future development of lucitanib in lung cancer
- In addition to this clinical trial, a global development program for lucitanib in breast cancer and other solid tumors is ongoing

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008, Cancer Incidence and mortality worldwide: IARC CancerBase No. 10 [Internet].
2. Schuthels et al, 2014; Capelletti et al, 2014; Tran TN et al, 2013; Majewski et al, 2013; Heist et al, 2012; Weiss et al, 2010; Clovis (data on file).
3. Soria JC et al. *Annals of Oncology*. 2014;00:1-8.

Abu-Kalaf et al.
ASCO 2015 – TIP

Phase II trials in molecularly enriched populations of mBC and mNSCLC already underway

Spigel et al.
WCLC 2015 - TIP

Abs. 126O | AL3810 (Lucitanib) –VEGFR, FGFR, PDGFR inhibitor

Direction:

- Future trials need to be biomarker driven

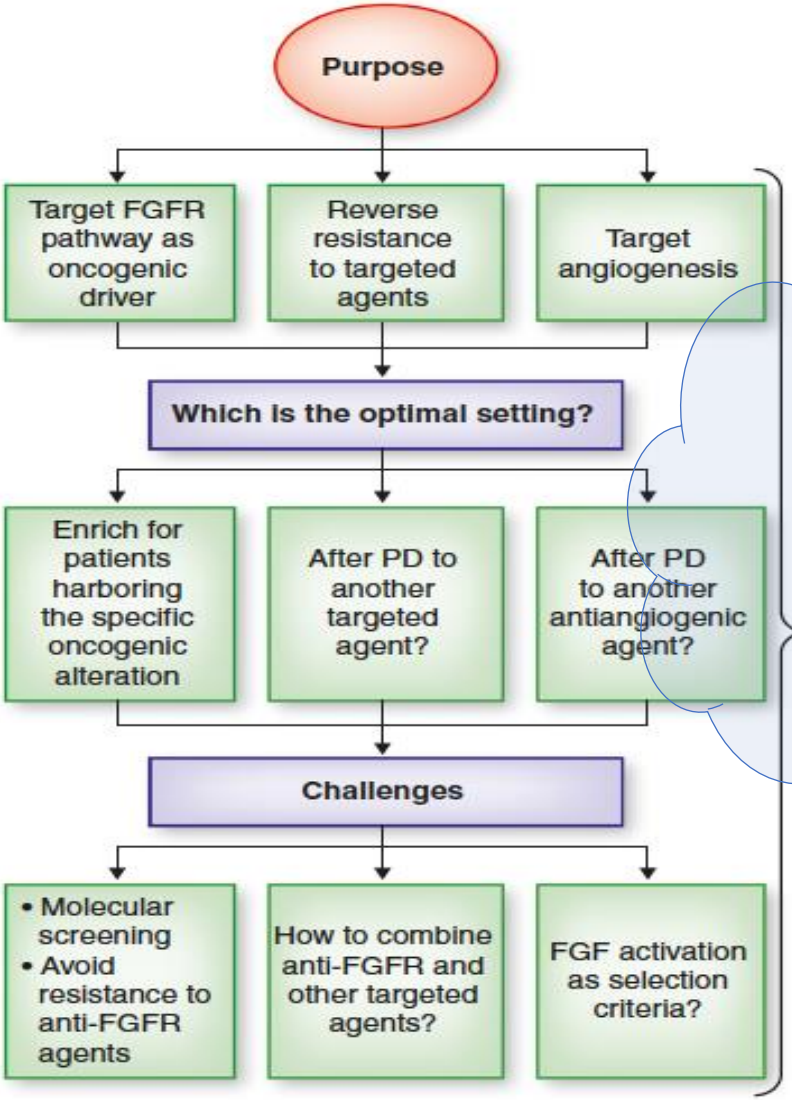
Challenge:

- Identify a robust biomarker
  - Definition of FGFR pathway amplification varies between trials in methods used and threshold copy number
  - No consensus → difficulties for cross trial comparison

Future Directions:

- Correlate PK/PD differences between ethnicities of patients across trials
- Asian to take leadership roles in niche Asian FGFR related tumours
  - e.g. Hepatocellular Ca, Gastric Ca

Challenges of Targeting FGFR as a whole



Unsolved questions

- Selective vs. nonselective anti-FGFR
- Feasibility of combinations
- Long-term safety of FGFR inhibition

Dieci MV, Arenedos M, Andre F, Soria JC; Cancer Discovery 2013

https://upload.wikimedia.org/wikipedia/commons/1/18/Hong_Kong_Night_Skyline.jpg