INFLAMMATORY MYOFIBROBLASTIC TUMORS

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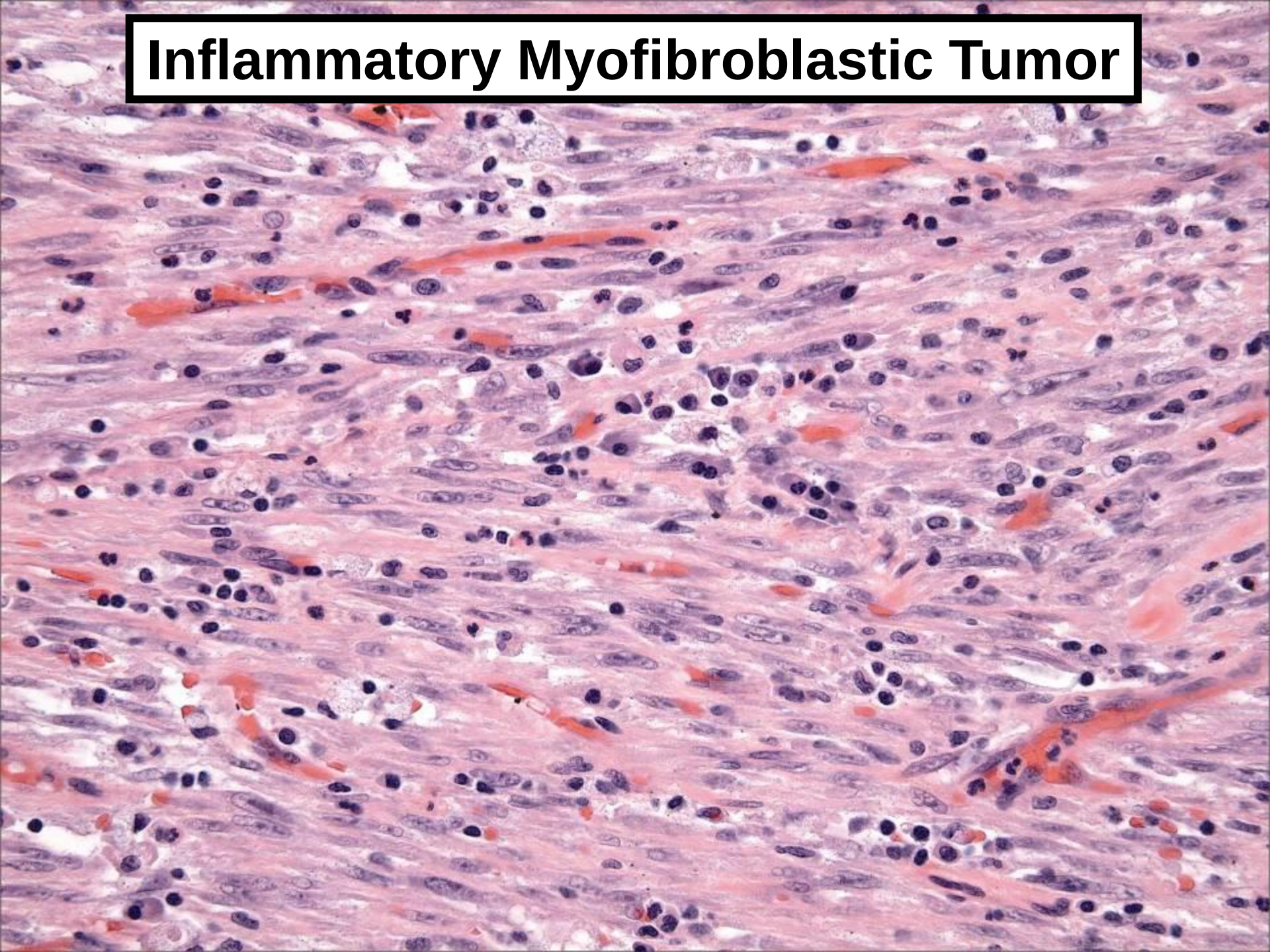
DISCLOSURE SLIDE

No conflicts of interest relevant to this presentation

I will discuss the off-label use of crizotinib, ceritinib, and alectinib

Inflammatory Myofibroblastic Tumor

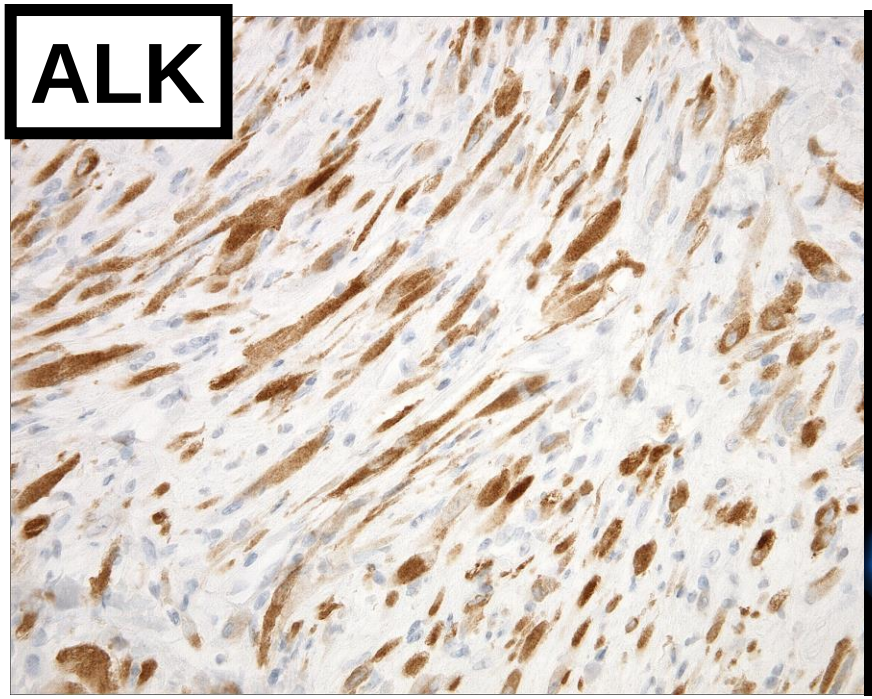


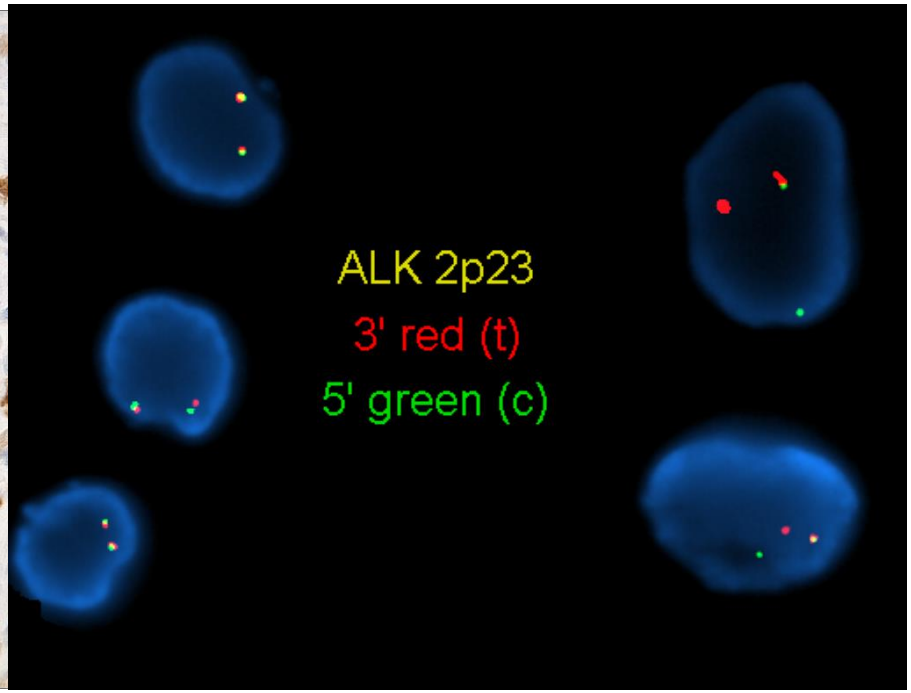
IMT – Clinical Presentation

- Previously classified as Inflammatory Pseudotumor or Inflammatory Fibrosarcoma
- Rare sarcoma of intermediate biologic potential
- Spindled cells, pale eosinophilic cytoplasm, myxoid to collagenous stroma with prominent inflammatory infiltrate, rare mitoses
- Typically in children/young adults but may also occur in older patients
- Lung/pleural, abdominopelvic, retroperitoneal sites are most common
- Symptoms of mass effect (vague abdominal pain, cough) or with an inflammatory syndrome (fever, weight loss, high ESR, microcytic anemia, hyper-gammaglobulinemia)
- Historically, treatment with steroids and non-steroidal anti-inflammatories

IMT and ALK expression/rearrangements

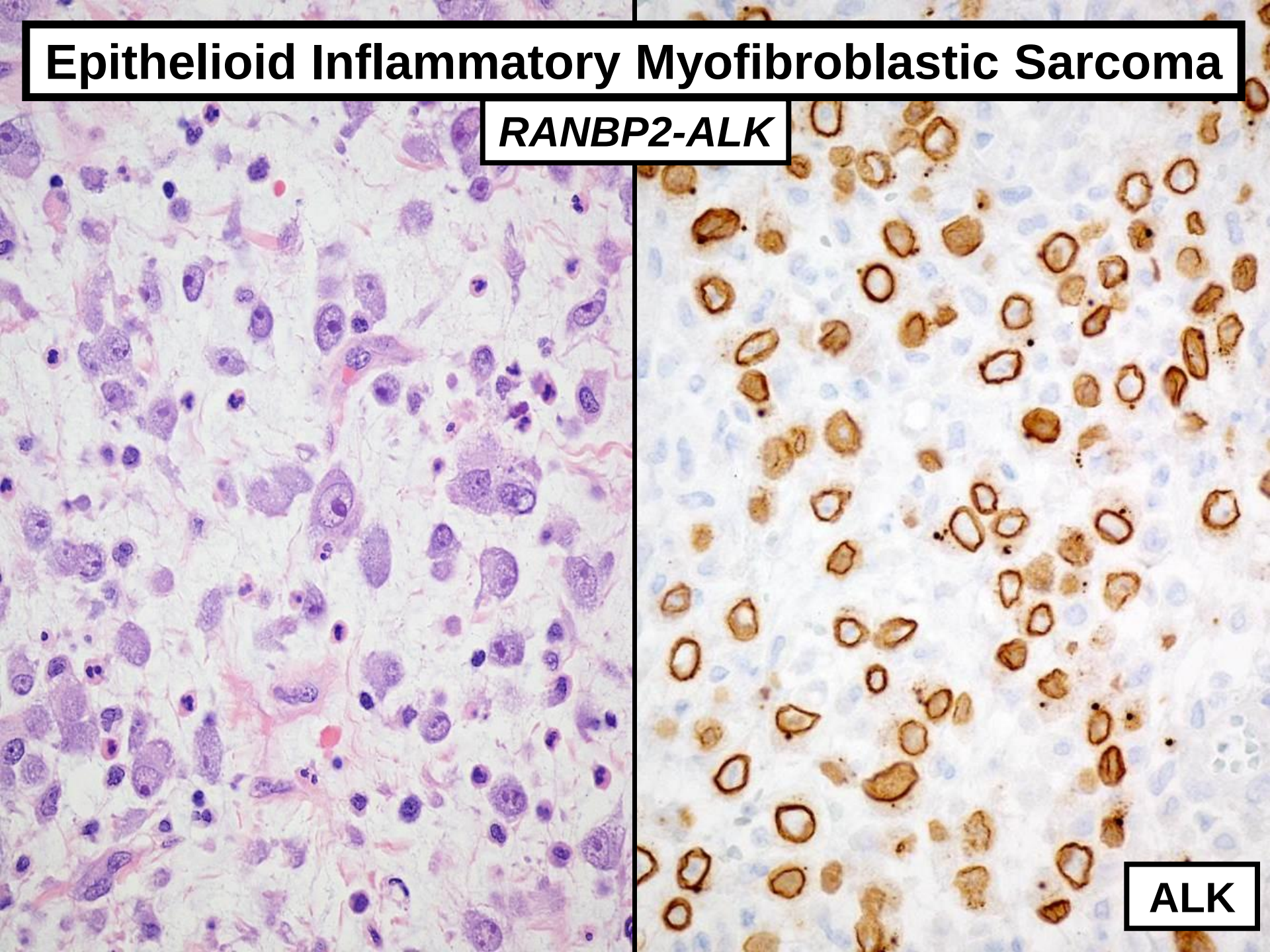
- Recurrent 2p abnormalities; *TPM3-ALK* translocations identified in 2000
- ALK expressed in 50-60% of IMT
- Translocation to 1 of at least 5 partners





Epithelioid Inflammatory Myofibroblastic Sarcoma

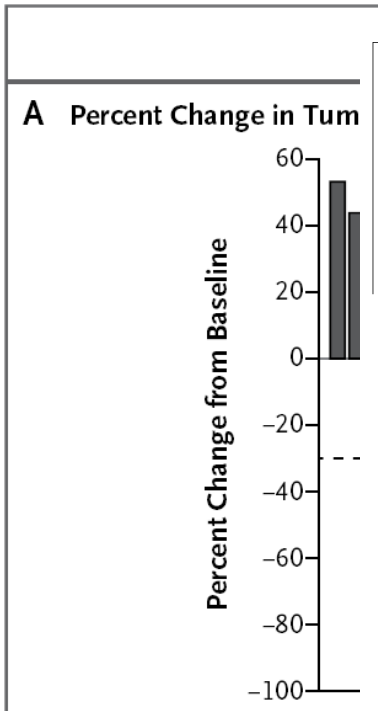
RANBP2-ALK



ALK

- "Anaplastic Lymphoma Kinase"
- Translocation identified in Anaplastic Large Cell Lymphomas in 1994
- Tyrosine kinase with limited expression in adult tissues
- Well-known now for translocations in non-small cell lung carcinoma
- Also implicated in neuroblastoma, anaplastic thyroid carcinomas, renal medullary carcinoma, and rhabdomyosarcoma

ALK Translocations in NSCLC: Dramatic Response to MET/ALK Inhibitor Crizotinib



The NEW ENGLAND JOURNAL of MEDICINE

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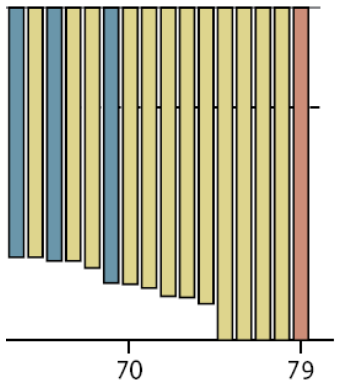
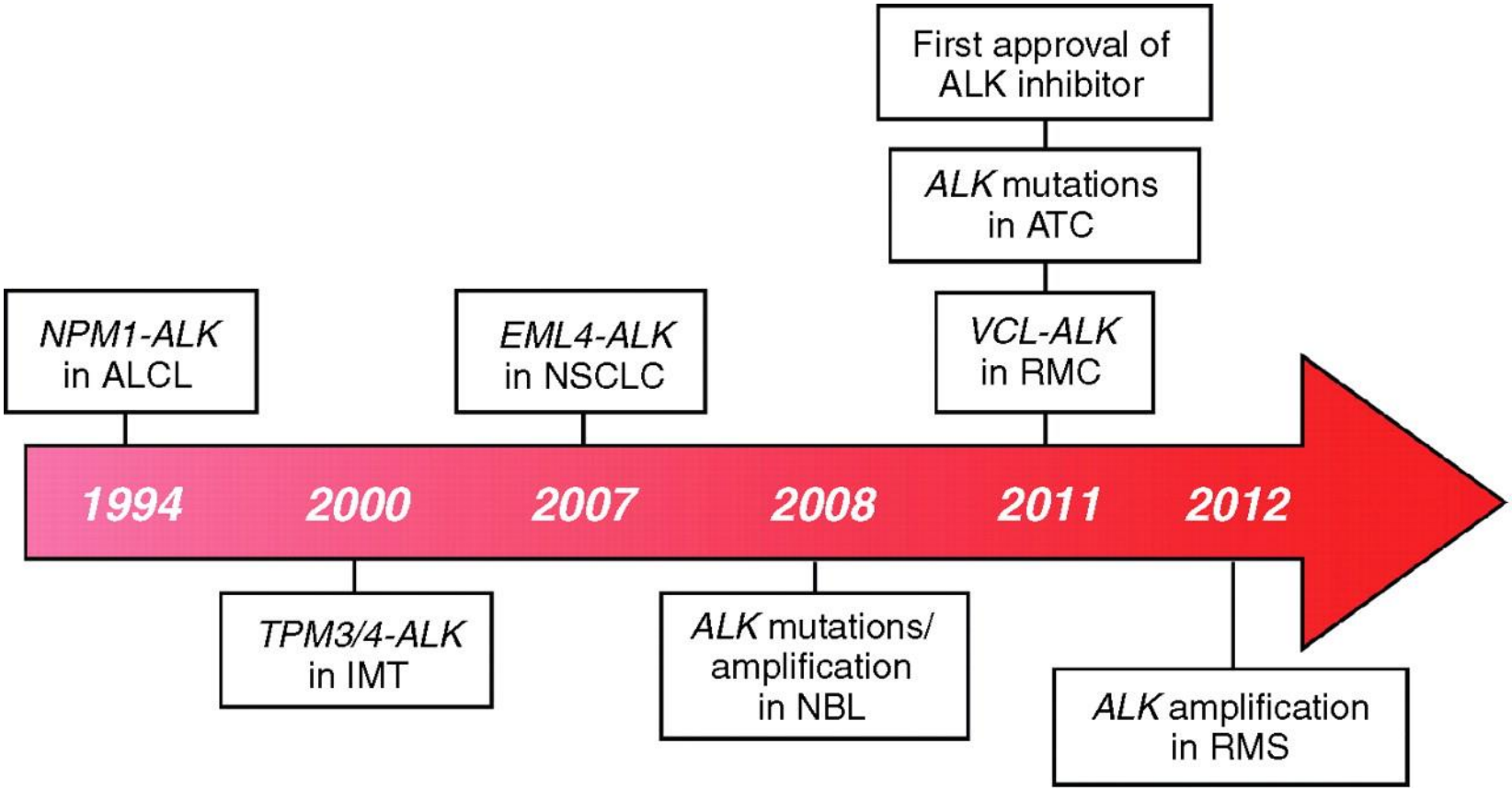
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.



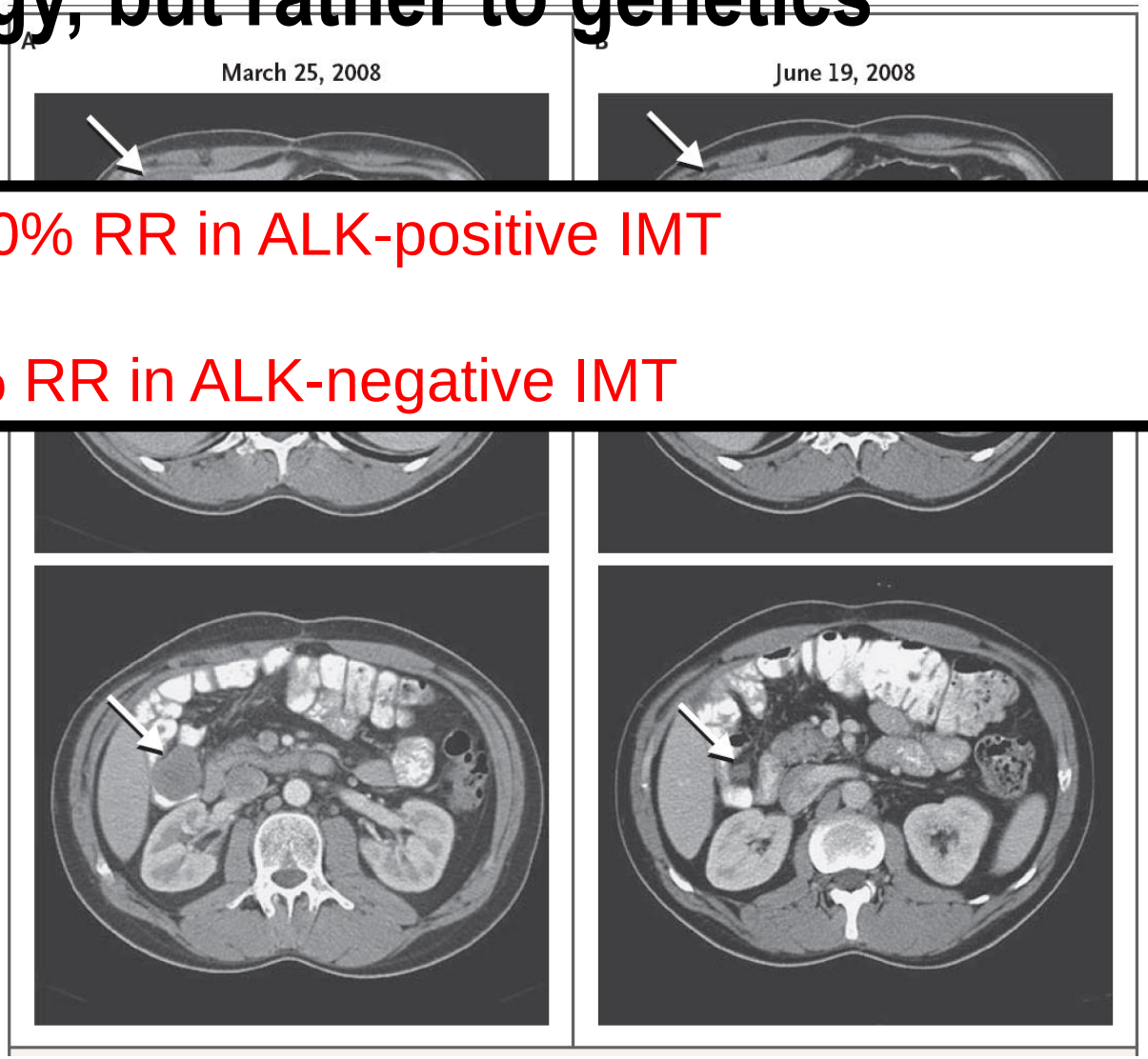
History of ALK in oncology



Hiroyuki Mano Cancer Discovery 2012;2:495-502

AACR American Association for Cancer Research
CANCER DISCOVERY

Sarcoma led the way: Efficacy of crizotinib is not limited to histology, but rather to genetics



100% RR in ALK-positive IMT

0% RR in ALK-negative IMT

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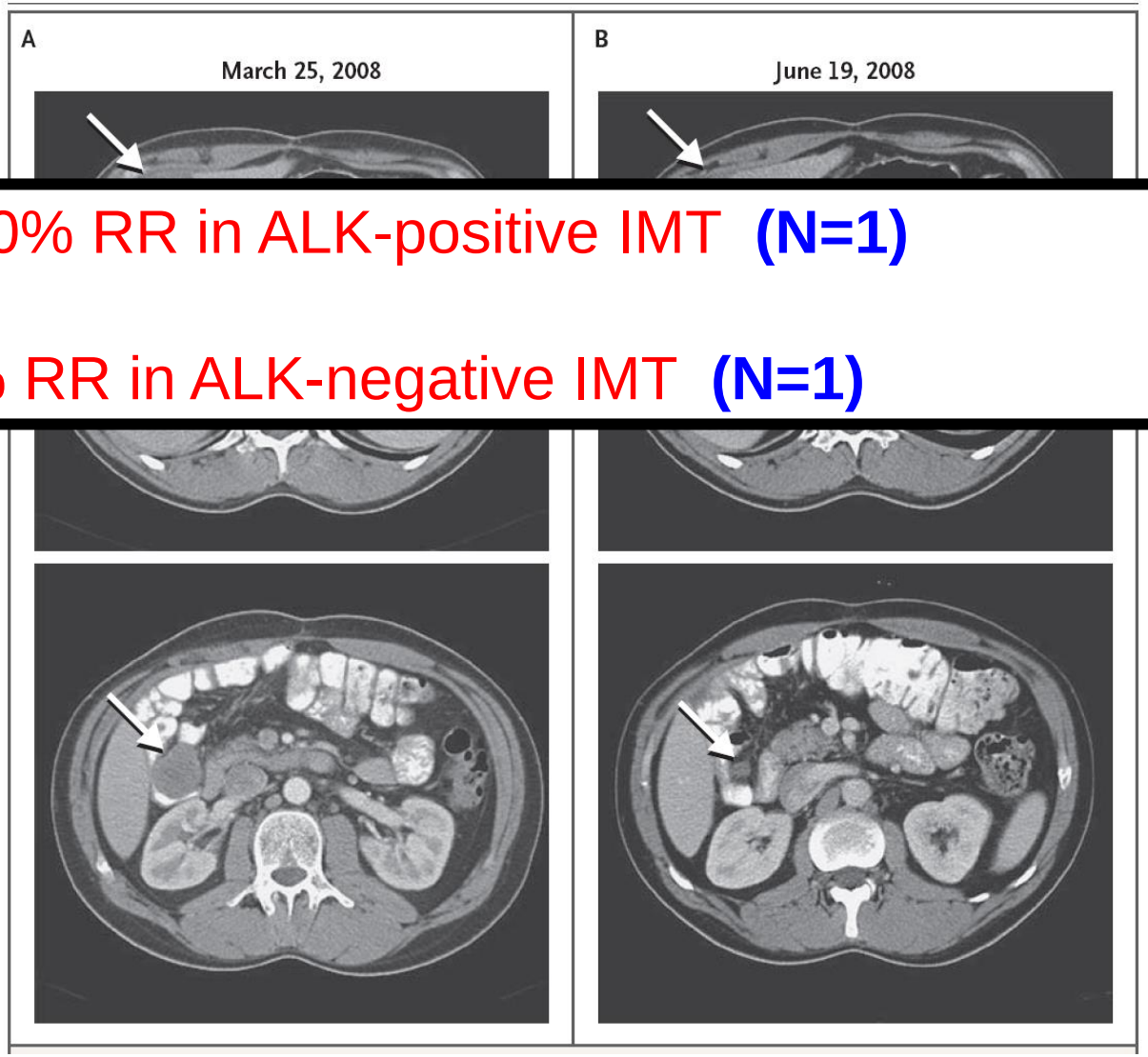
Efficacy of crizotinib is not limited to histology, but rather to genetics



100% RR in ALK-positive IMT **(N=1)**

0% RR in ALK-negative IMT **(N=1)**

Crizotinib in IMT

A few case reports describing responses

Phase I study in children; 3/6 had PR, others SD

Lancet Oncol. Author manuscript; available in PMC 2013 Aug 1.
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Lancet Oncol. 2013 May; 14(6): 472–480.
Published online 2013 Apr 16. doi: 10.1016/S1470-2045(13)70095-0

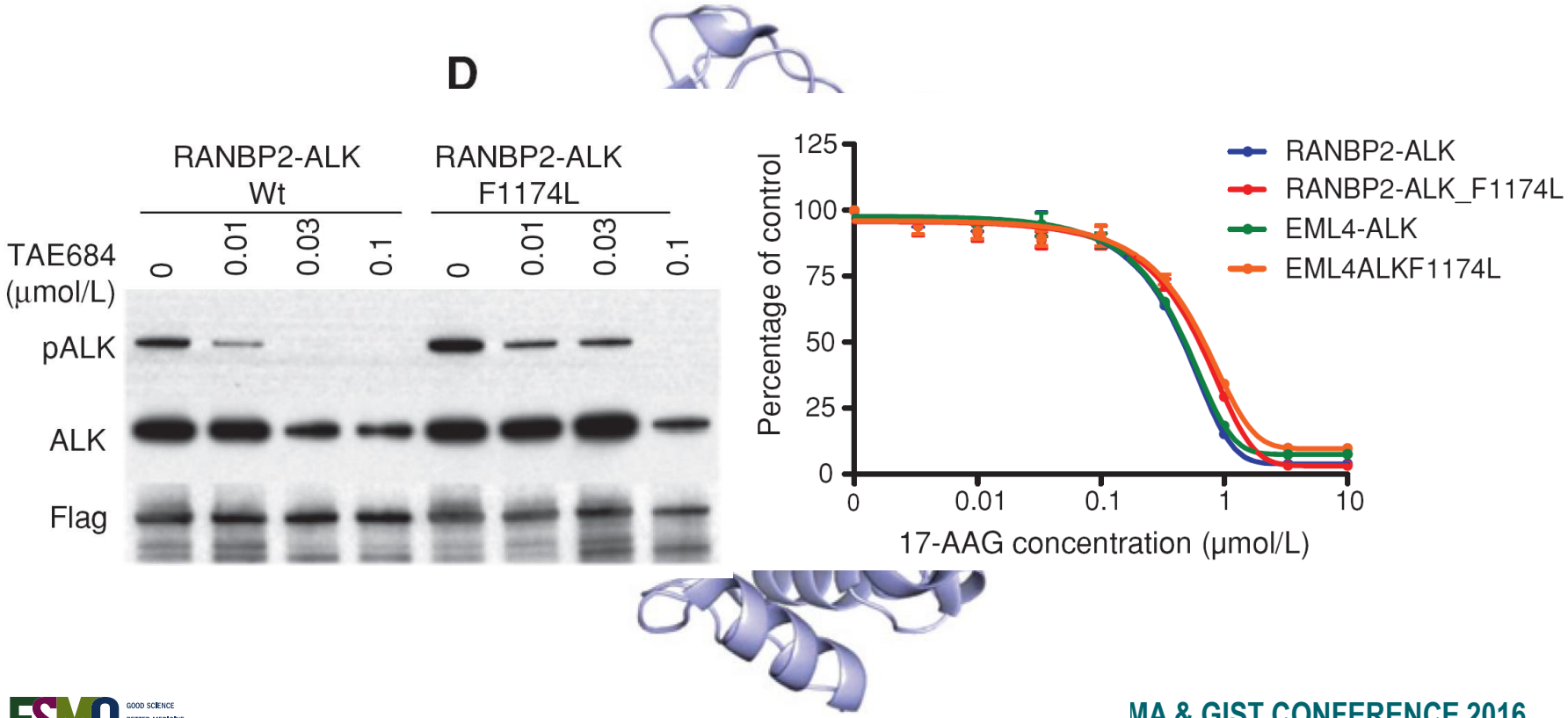
PMCID: PMC3730818
NIHMSID: NIHMS476957

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study

Yael P Mossé, MD, Megan S Lim, MD, Stephan D Voss, MD, Keith Wilner, PhD, Katherine Ruffner, MD, Julie Laliberte, Delphine Rolland, Prof. Frank M Balis, MD, Prof. John M Maris, MD, Brenda J Weigel, MD, Ashish M Ingle, MS, Charlotte Ahern, PhD, Prof. Peter C Adamson, MD, and Prof. Susan M Blaney, MD

The Neuroblastoma-Associated F1174L ALK Mutation Causes Resistance to an ALK Kinase Inhibitor in ALK-Translocated Cancers

Takaaki Sasaki[1,2], Katsuhiro Okuda[1,2], Wei Zheng[3,4], James Butrynski[2,5], Marzia Capelletti[1,2], Liping Wang[1,2], Nathanael S. Gray[3,4], Keith Wilner[6], James G. Christensen[6], George Demetri[2,5], Geoffrey I. Shapiro[1,2,7,9], Scott J. Rodig[8], Michael J. Eck[3,4], and Pasi A. Jänne[1,2,9]



What to do with crizotinib-resistant ALK+ disease?

- Ceritinib and alectinib are now approved for treatment of crizotinib-resistant ALK+ NSCLC

- 1 patient with IMT reported to have PR on ceritinib

J Thorac Oncol. 2015 Jul; 10(7): 1058–1066.
Published online 2015 Jun 24. doi: 10.1097/JTO.0000000000000566
PMCID: PMC4467585

Phase I Study of Ceritinib (LDK378) in Japanese Patients with Advanced, Anaplastic Lymphoma Kinase-Rearranged Non–Small-Cell Lung Cancer or Other Tumors

Makoto Nishio, MD,[✉*] Haruyasu Murakami, MD, PhD,[†] Atsushi Horiike, MD,[*] Toshiaki Takahashi, MD,[†] Fumihiko Hirai, MD,[‡] Naoko Suenaga, PhD,[§] Takeshi Tajima, PhD,[§] Kota Tokushige, MEng,[§] Masami Ishii, MD, PhD,[§] Anthony Boral, MD, PhD,[‖] Matthew Robson, MD,[¶] and Takashi Seto, MD[‡]

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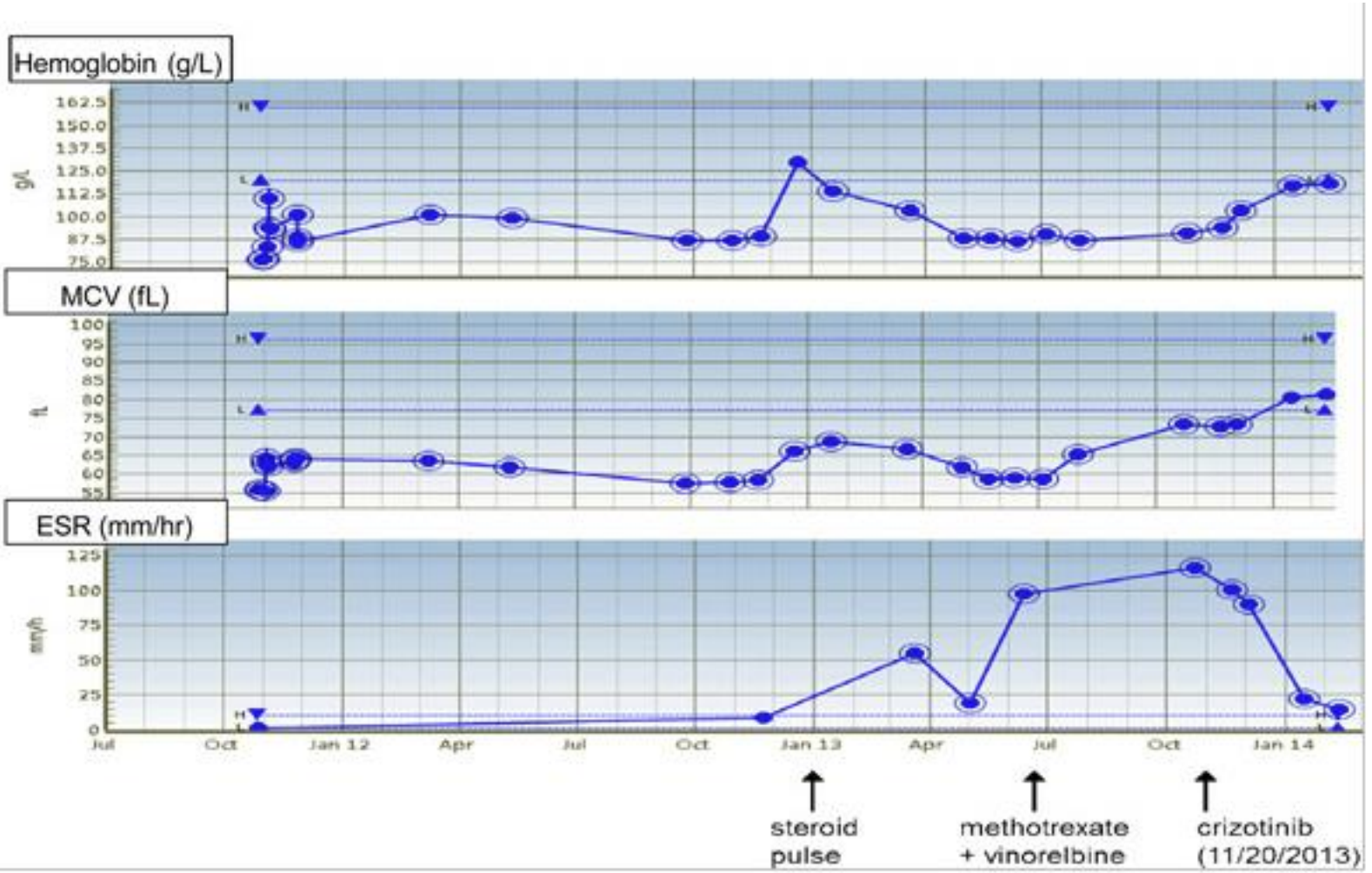

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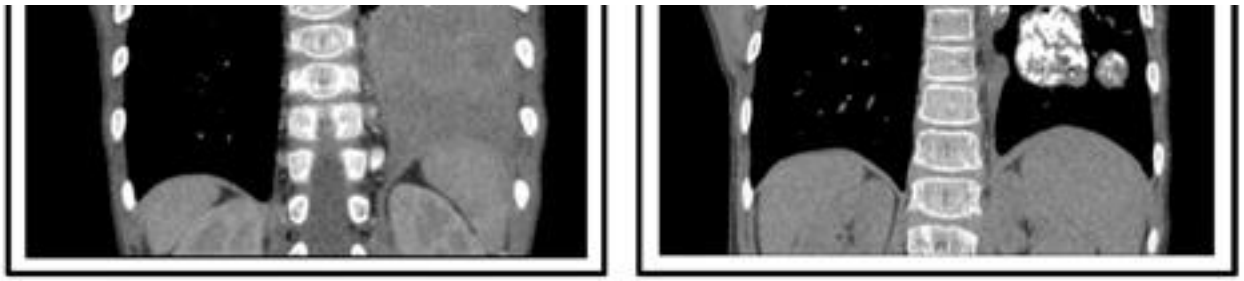
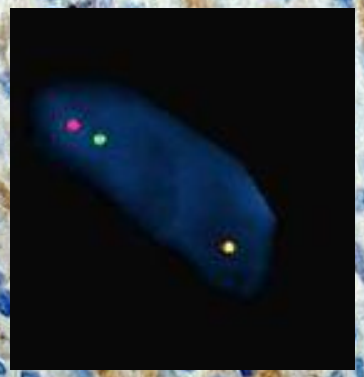


Inflammatory Myofibroblastic Tumor

TFG-ROS1

Courtesy of Jason Hornick



Courtesy of Paola Dal Cin

ROS1

Hornick et al. *Mod Pathol* 2015

SUMMARY

- IMT is a rare, locally aggressive, rarely metastasizing sarcoma
- Can present with systemic inflammatory symptoms
- Approximately 70% are driven by translocations involving ALK, ROS, or other TK
- Immunohistochemistry correlates with translocation
- Inhibitors of ALK and ROS are commercially available although not approved for treatment of IMT
- For non-translocated disease, consider steroids or NSAIDs

- What about other treatments for refractory disease? Is there a role for immune checkpoint inhibitors?