Following the Research Journey in GIST

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Disclosures

- Grants from MSD Corp + GSK

- Consultant: Adaptimmune Therapeutics plc; Athenex, Inc.; Blueprint Medicines Corporation; Clinigen Group plc; Daichii Sankyo Co.; Deciphera Pharmaceuticals, Inc.; Eisai Co., Ltd.; Eli Lilly and Company; Epizyme, Inc.; Helsinn Healthcare S.A.; Immune Design Corp.; Merck & Co.; Pharmamar S.A.; Tracon Pharmaceuticals, Inc.; and UpToDate, Inc.

Plan

- Off label use
  - Nilotinib
  - Everolimus
  - Dastatinib
  - Pazopanib
  - Sorafenib
  - BRAF inhibition
  - Immunotherapy
- Larotrectinib + NTRK inhibitors in GIST
- Current + upcoming agents/ clinical trials in GIST
- Conclusion
- Questions + discussion

Current Landscape Advanced Disease

- Imatinib
- Sunitinib
- Regorafenib
- Ripretinib
- Avapritinib

Off Label use of systemic therapy

- Is the drug approved for another indication?
  - Easier to obtain access in some countries: USA + Germany
  - Challenging in other countries: UK
- Number of approved drugs
  - Toxicity management important to enable continuation of therapy
- Compassionate use/ expanded access programs
- Multidisciplinary approach
  - Solitary progression: use of local therapy (e.g. RFA) to enable continuation of therapy
- Clinical trials

Gennatas S et al. *Clin Sarcoma Res* 10; 9: 2020
Jones RL et al. *Eur J Surg Oncol* 36(5); 477-482: 2010

Off Label use of systemic therapy

- Careful discussion between patient + oncologist
  - Are trial based options available?
  - Drug availability in the future?
  - What are the pros + cons
- For this presentation: focus on clinical data + experience
  - A pragmatic approach

Nilotinib

- Tyrosine kinase inhibitor
  - BCR-ABL
  - KIT
  - PDGFR A + B
  - DDR-1 and -2

- Randomised, open-label, multicentre, phase 3 trial (ENESTg1)

- 647 patients were enrolled
  - 324 were allocated nilotinib
  - 320 were allocated imatinib

- PFS:
  - Imatinib: mPFS: 29.7 months (95%CI: 26.6 - NE)
  - Nilotinib: mPFS 25.9 months (95%CI: 19.1 - NE)
  - Hazard ratio: 1.47

Blay JY et al. *Lancet Oncol* 16(5); 550-560: 2015

Niltotinib

- KIT Exon 11
  - Imatinib: mPFS: 32.3 months (29.7 - NE)
  - Nilotinib: mPFS: NE (29.2 - NE)
    - Hazard ratio: 1.12 [95%CI, 0.683–1.836]

- KIT Exon 9
  - Imatinib: mPFS: NE (95%CI: 11.5 - NE)
  - Nilotinib: mPFS: 3 months (95%CI: 2.8 – 3.2)
    - HR 32.456 [95%CI, 7.113–148.088]

- Nilotinib adverse events:
  - Anaemia (18; 6%), elevated lipase level (15; 5%), elevated alanine aminotransferase concentration (12; 4%) + abdominal pain (11; 3%)

Blay JY et al. *Lancet Oncol* 16(5); 550-560: 2015

Everolimus

- Phase 1 – 2 trial of everolimus + imatinib

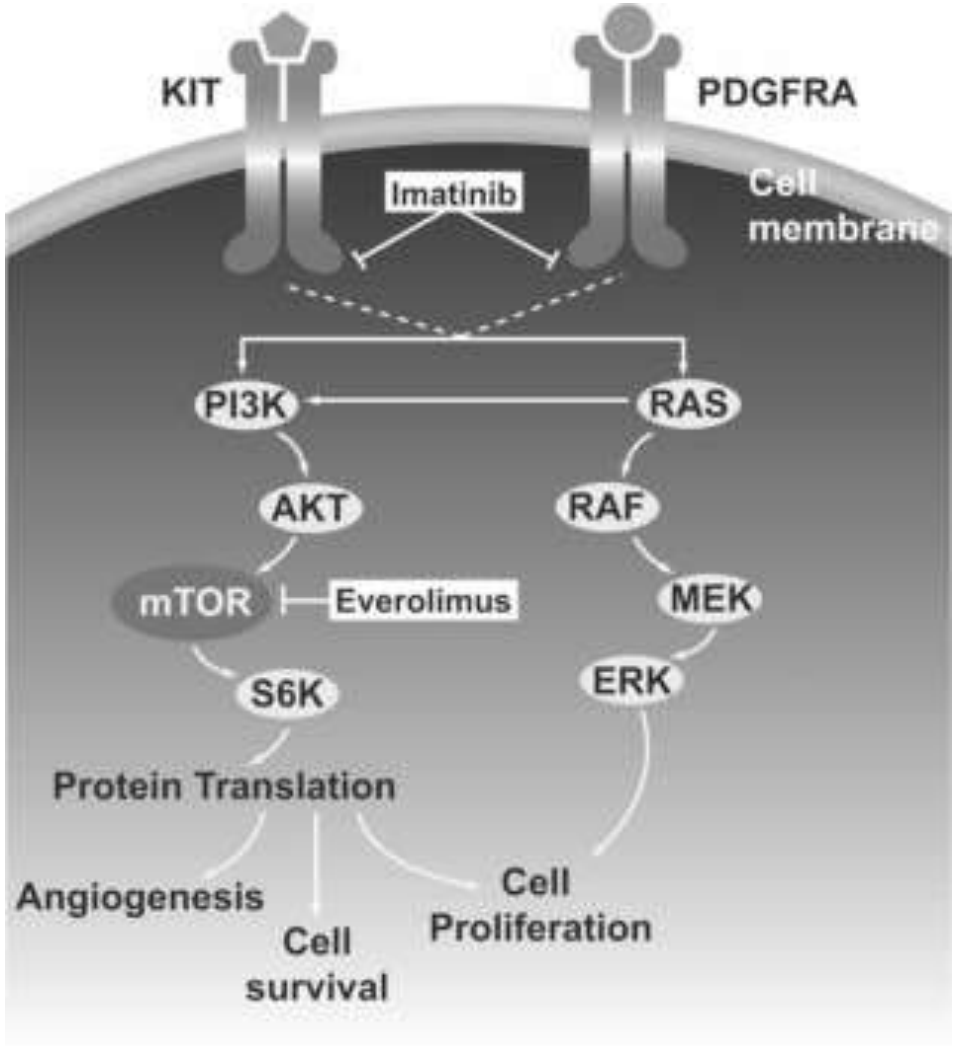
- Stratum 1: Disease progression on imatinib
  - N=28
- Stratum 2: Disease progression on imatinib + sunitinib/ other TKI
  - N=47

- Median PFS:
  - Stratum 1: 1.9 months
  - Stratum 2: 3.5 months

- Common adverse events
  - Diarrhea, nausea, fatigue + anemia

Schöffski P, et al. *Ann Oncol* 21(10); 1990-1998: 2010

Rationale for mTOR/ PI3 K inhibitors



Schöffski P, et al. *Ann Oncol* 21(10); 1990-1998: 2010

Dasatinib

- Phase 2 trial: 58 patients
- 3-month PFS rate: 53.4%
- Median overall survival: 14.0 months
- Neither primary nor secondary gene mutations predicted the efficacy of dasatinib
- Most common adverse events were anemia, proteinuria, fatigue, neutropenia + diarrhea

Zhou Y et al. *Cancer Med*. 2020

Dasatinib

- Phase 2 trial: 42 eligible patients
  - Median follow-up: 67.2 months

- FDG-PET/CT complete + partial response rate at 4 weeks
- 74% (95% confidence interval, 56%-85%)
  - 14 complete response
  - 17 partial response
  - 6 stable disease
  - 3 progressive disease, 2 not evaluable
- Median progression-free survival was 13.6 months

- Median overall survival: not reached

- Grade 4 toxicity in 5%
- Grade 3 in 48% of patients and was most often gastrointestinal or pulmonary

- Dose was interrupted or reduced in 25% of cycles

Montemurro M, et al. *Cancer* 124(7); 1449-1454: 2018

Dasatinib: off label experience

- Locally advanced rectal GIST 2.3cm: L576P *exon 11* mutation

- Nov 2012: Imatinib: initial response
- Oct 2013: Dasatinib 50mg twice daily
- Sep 2017: Right sided pleural effusion: secondary to dasatinib
- Treatment break

- Oct 2017: No re-accumulation effusion on Chest X-ray
- Dasatainib re-started 50 mg once daily

- Sep 2020: MRI: “At the site of previous tumour there is now just a plaque of low signal intensity in keeping with treatment related change”

Sorafenib

- Phase 2 trial: 31 patients
- Relative dose intensity of sorafenib during the first 6 months was >80%
- 4 patients: Partial response (response rate 13%, 95% CI 1-25%)
- 16 (52%): stable disease
  - DCR at 24 weeks: 36% (95% CI 19-52%)
- Median progression-free 4.9 months
- Median overall survival 9.7 months
- Well tolerated
  - Most frequent adverse events: Hand-foot skin reaction, fatigue, hypertension + abdominal pain

Park SH et al. *Invest New Drugs* 30(6); 2377-2383: 2012

Sorafenib

- Retrospective study: 60 patients

- Three (5%): objective partial responses
- 31 patients (52%): stabilization of disease > 4 months

- Median PFS: 7.7 months

- Median OS: 13.5 months

- Most common adverse events: diarrhoea, hand/ foot syndrome, fatigue, loss of weight + skin reactions
  - Grade 3-5 toxicity occurred in 35% of patients
  - 23 required sorafenib dose reductions due to adverse events

Rutkowski P, et al. *Contemp Oncol (Pozn)* 21(4); 285-289: 2017

Sorafenib

- Retrospective study, 72 patients
  - >2 lines of therapy
- Twelve (10%) patients: Tumour response

- 70 (57%) patients: Tumour stabilisation
  - Dosage was reduced in a third of patients
  - Did not have an impact on progression-free survival (PFS), p=0.15

- Median PFS: 6.4 months (95%CI, 4.6 - 8.0 months)
  - Good performance status + response significant better PFS

- Median overall survival (OS) 13.5 months (95%CI, 10.0 - 21.0 months)

- Toxicity reported in 56% of the patients
  - Rash, hand-foot-syndrome + diarrhea occurred frequently

Montemurro M, et al. *Eur J Cancer* 49(5); 1027-1031: 2013

Pazopanib

- 25 patients
- Median number of prior therapies: 3 (Range 2 - 27)
- Best response of SD: 12 (48%) patients
  - 1 patient succinate dehydrogenase (SDH)-deficient GIST continuing disease control after 17 cycles
- Non-progression rate: 17% (95%CI: 4.5 - 37)
- Median PFS: 1.9 months (95%CI: 1.6 – 5.2)
- Median OS: 10.7 months (95%CI: 3.9 - NR)
- Pazopanib was reasonably well tolerated with no unexpected toxicities

Ganjoo KN et al. *Ann Oncol* 25(1); 236-240: 2014

Pazopanib

- 81 patients, Randomly assigned to
  - Pazopanib + best supportive care (n=40) or
  - Best supportive care alone (n=41)

- Median follow-up was
  - 26·4 months (IQR 22·0-37·8) in the pazopanib + best supportive care group
  - 28·9 months (22·0-35·2) in the best supportive care group
- Median progression-free survival was
  - 3·4 months (95% CI 2·4-5·6) with pazopanib plus best supportive care
  - 2·3 months (2·1-3·3) with best supportive care alone (HR 0·59 [0·37-0·96], p=0·03)
- 36 (88%) of the patients originally assigned to the best supportive care group switched to pazopanib following disease progression
  - Median progression-free survival from pazopanib initiation of 3·5 months (95% CI 2·2-5·2)

- 55 (72%) of the 76 pazopanib-treated patients had pazopanib-related grade 3 or worse adverse events
- Most common of which hypertension
  - 15 [38%] in the pazopanib plus best supportive care group
  - 13 [36%] in the best supportive care group

- 20 (26%) patients had pazopanib-related serious adverse events (14 [35%] in the pazopanib plus best supportive care group and six [17%] in the best supportive care group)

- Including pulmonary embolism in 8 (9%)
  - 5 [13%] in the pazopanib plus best supportive care group
  - 3 [7%] in the best supportive care group).

Mir O et al. *Lancet Oncol* 17(5); 632-641: 2016

BRAF inhibition

www.impactjournals.com/oncotarget/ Oncotarget, February, Vol.4, No 2

BRAF Mutant Gastrointestinal Stromal Tumor: First report of regression with BRAF inhibitor dabrafenib (GSK2118436) and whole exomic sequencing for analysis of acquired resistance

G.S. Falchook[1], J.C. Trent[2], M.C. Heinrich[3], C. Beadling[3], J. Patterson[3], C.C. Bastida[1], S.C. Blackman[4], R. Kurzrock[5]

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Keywords: Gastrointestinal stromal tumor, Dabrafenib, GSK2118436, BRAF mutation, BRAF inhibition, V600E

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Immunotherapy

- Randomized, parallel group, unblinded Phase 2 trial
  - Nivolumab (240 mg Q2wks) or
  - Nivolumab (240 mg Q2wks) with ipilumab (1mg/kg Q6wks) for up to 2 years.
- Refractory to at least imatinib

- 29 patients (27 evaluable)
  - Median of 3 (1-7) lines of prior therapies

- Nivo only arm:
  - 7/15 pts had a best response of SD
  - CBR: 46.7%
  - Median PFS 8.57 weeks
- Nivo + ipi arm:
  - 1/12 patients had a PR
  - 2/12 have SD
  - CBR of 25.0% (95% exact C.I. 5.5%-57.2%)
  - Median PFS of 9.1 wks
  - 8 patients on therapy > 6 months
  - 2 patients with a KIT Exon 17 mutation had radiographic disease shrinkage

- Most AEs were grades 1-2 with fatigue (37%) being the most common
  - 4 Grade 3/4 AEs occurred in the nivo + ipi arm (hyperglycemia, weakness, diarrhea x 2)
  - 4 grade 3/4AEs occurred in the nivo arm (DKA, hyperglycemia, rash, fatigue)

Singh A et al. ASCO 2019

ONCOIMMUNOLOGY
2020, VOL. 9, NO. 1, e1710064 (6 pages)
https://doi.org/10.1080/2162402X.2019.1710064

Taylor & Francis
Taylor & Francis Group

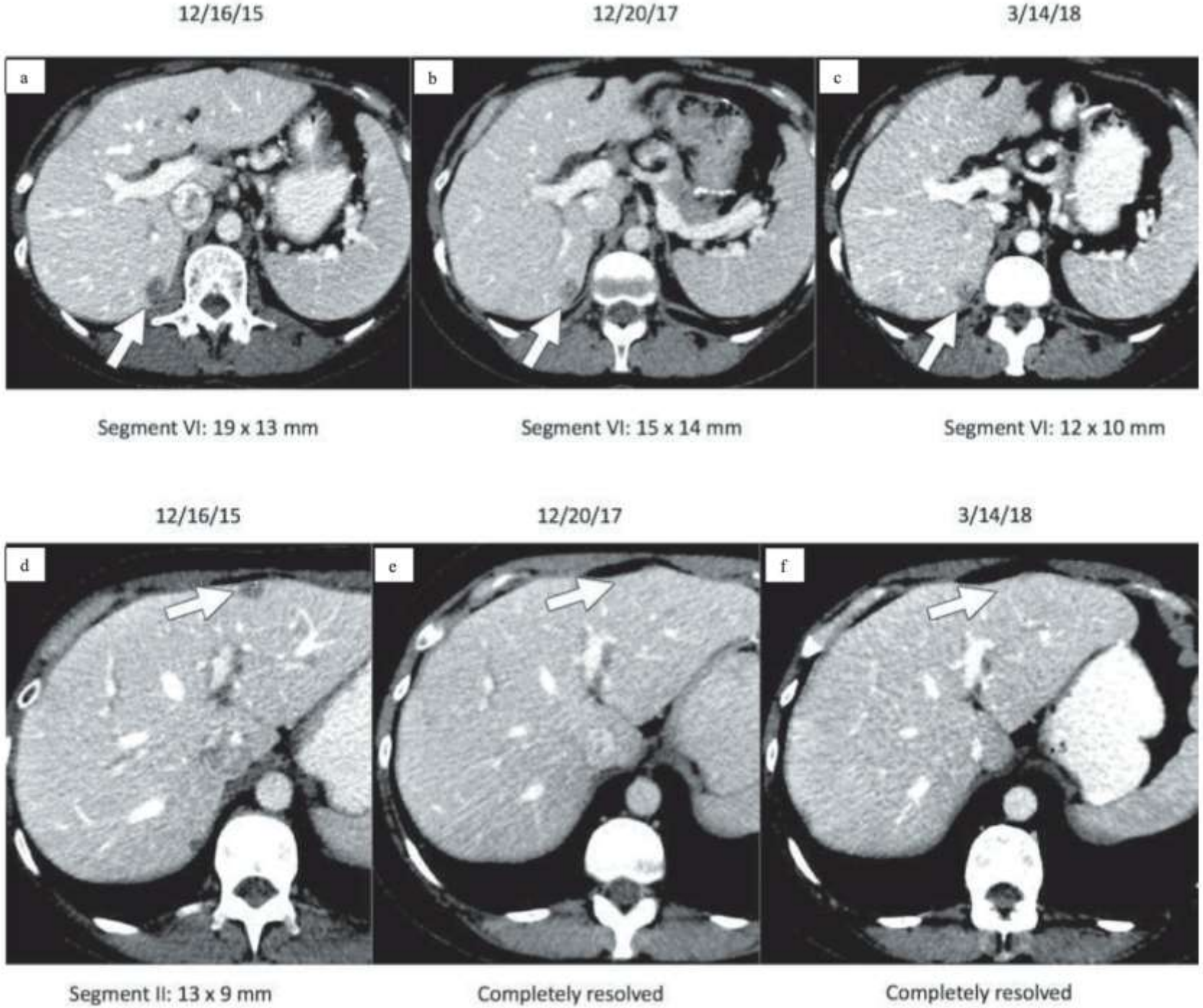
BRIEF REPORT

Durable tumor regression in highly refractory metastatic *KIT/PDGFRA* wild-type GIST following treatment with nivolumab

Brett A. Schroeder [a,b], Karan Kohli[a], Ryan B. O'Malley[c], Theresa S. Kim[a], Robin L. Jones[d], Robert H. Pierce[a], and Seth M. Pollack[a,e]

[a]Clinical Research Division, Fred Hutchison Cancer Research Center, Seattle, WA, USA; [b]Department of Medicine, Virginia Mason Medical Center, Seattle, WA, USA; [c]Department of Radiology, University of Washington, Seattle, WA, USA; [d]Sarcoma Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK; [e]Department of Medicine, University of Washington, Seattle, WA, USA

- 40-year-old woman
- June 2000 with anorexia and unintentional weight loss.
- June 2007: Imatinib side effects (fatigue, diarrhea, painful rash, and mouth sores)
- Oct 2007: Sunitinib
- January 2009: Imatinib
- Feb 2013: Regorafenib
- March 2014: Phase I trial phosphoinositide 3-kinase inhibitor, BKM-120 + imatinib
- Oct 2015: Sorafenib
- Dec 2015: Hand-foot syndrome: Reluctance to try another TKI
- Compassionate use nivolumab.



Schroeder BA, et al. *Oncoimmunology* 9(1); 2020

NTRK Inhibitors

NTRK inhibitors

- Tropomyosin Receptor Kinases (TRKs) are single-pass transmembrane receptor tyrosine kinases encoded by the
- Neurotrophic tyrosine receptor kinase 1, 2 + 3 (*NTRK1*, *NTRK2* + *NTRK3*) genes

- Function as high-affinity receptors for neurotrophins

- Role in development + normal function of nervous system

- *ETV6–NTRK3* recurrently rearranged in Infantile fibrosarcoma

- Little knowledge which sarcoma subtypes are most likely to harbour *TRK* fusions

Knezevich SR, et al. Nat Genet 18; 184–187: 1998
Wilding CP *et al.Curr Opin Oncol*. 2020

The NEW ENGLAND JOURNAL of MEDICINE

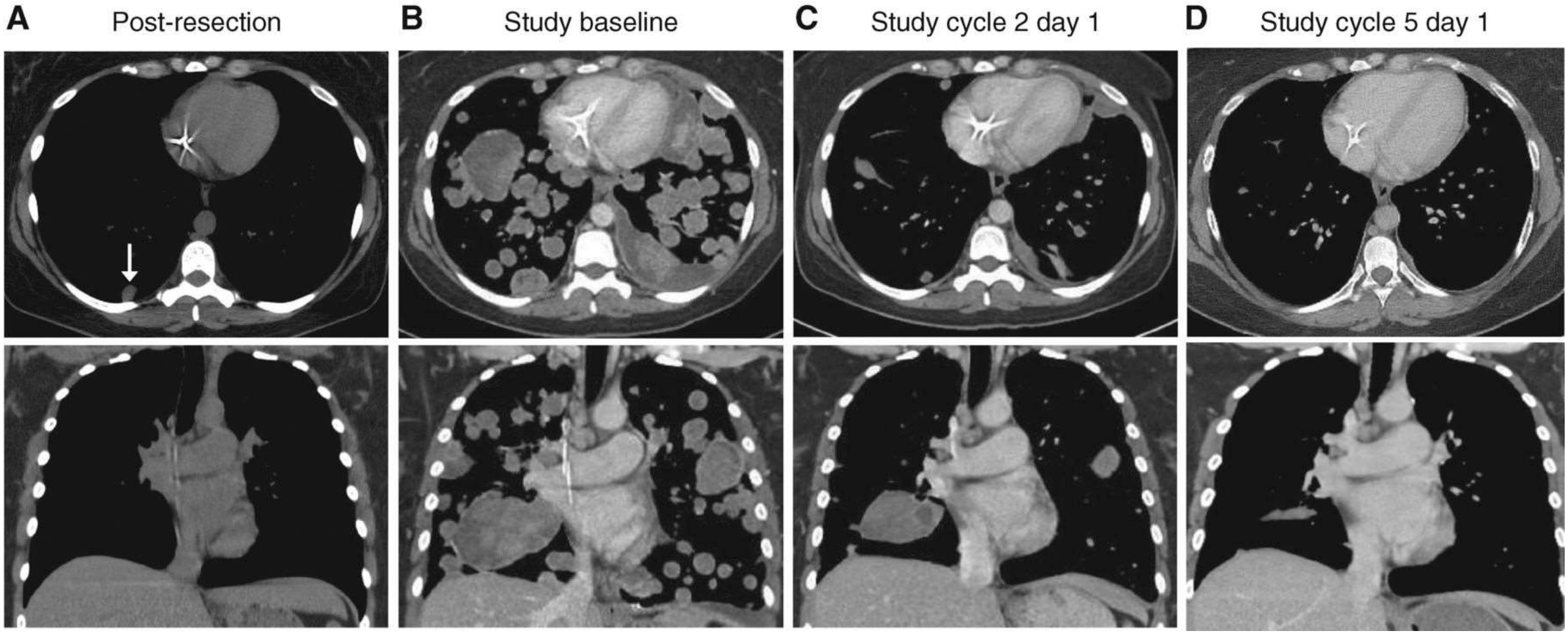
ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed, M. Ladanyi, B.B. Tuch, K. Ebata, S. Cruickshank, N.C. Ku, M.C. Cox, D.S. Hawkins, D.S. Hong, and D.M. Hyman

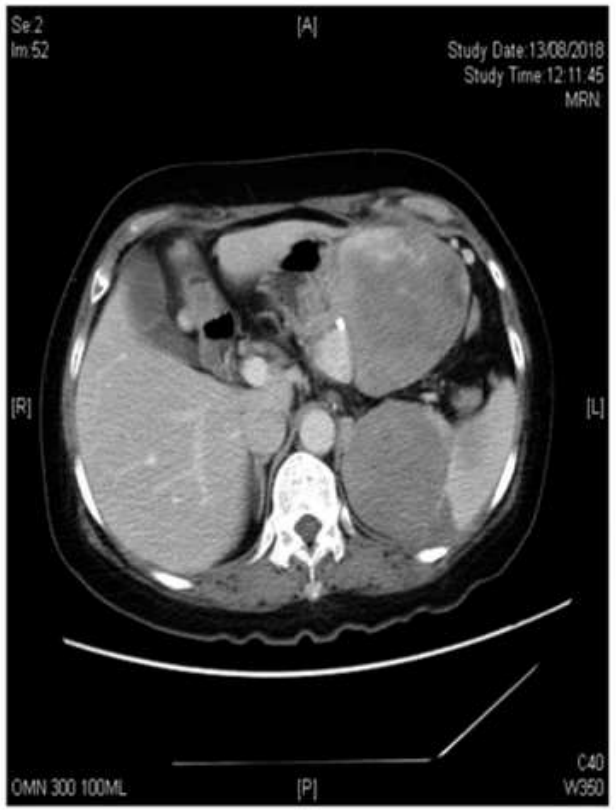
- Histology agnostic approval

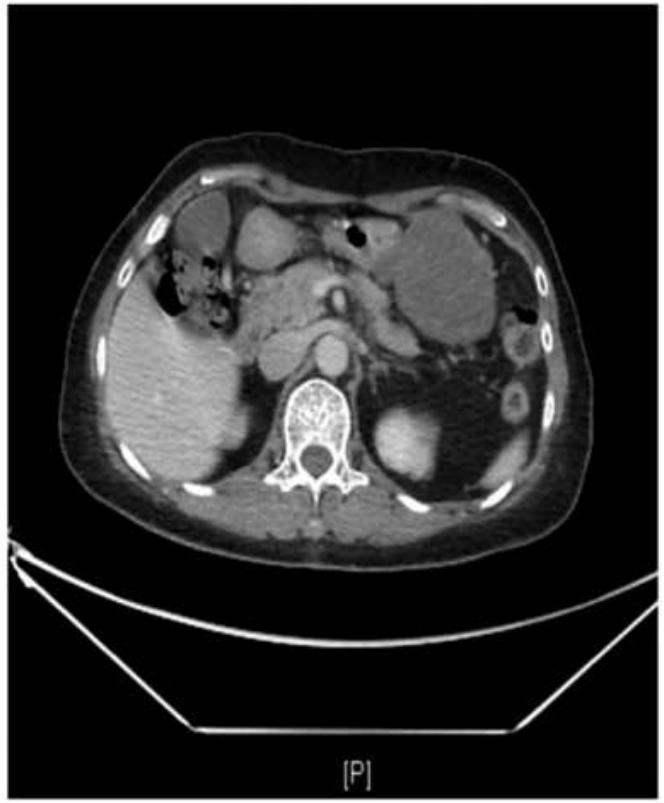
Response in an undifferentiated sarcoma

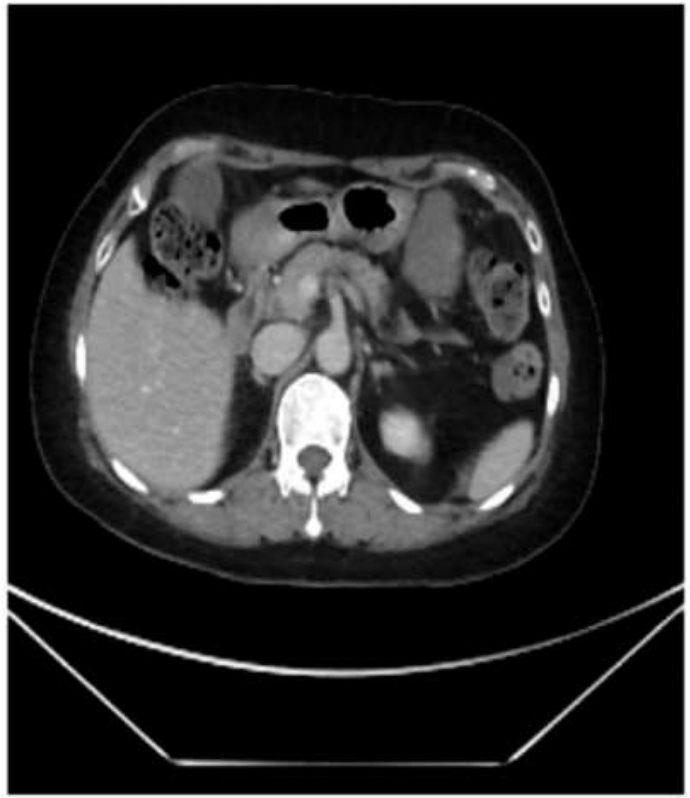


Doebele RC, et al. *Cancer Discov* 5(10); 1049-1057: 2015

Entrectinib: Radiological response in a high grade sarcoma with histiocytic differentiation (ETV6:NTRK3 exon 14)







Baseline

~ 3 months after treatment

Nadir achieved at ~6 months after treatment

Wilding CP *et al.Curr Opin Oncol*. 2020

NTRK inhibition in GIST

- 24 GIST lacking alterations in canonical KIT/PDGFRA/RAS pathways
  - Including 12 without SDHx alterations

- 24 GIST were more commonly mutated at 7 genes:
  - *ARID1B, ATR, FGFR1, LTK, SUFU, PARK2* and *ZNF217*
  - 2 tumors harbored *FGFR1* gene fusions (*FGFR1-HOOK3, FGFR1-TACC1*)
  - 1 harbored an *ETV6-NTRK3* fusion that responded to TRK inhibition

- Independent sample set:
  - 5 GIST cases lacking alterations in the KIT/PDGFRA/SDHx/RAS pathways

- Including two additional cases with
  - *FGFR1-TACC1*
  - *ETV6-NTRK3* fusions

Shi E et al. *J Transl Med* 14(1); 339: 2016

NTRK inhibition in GIST

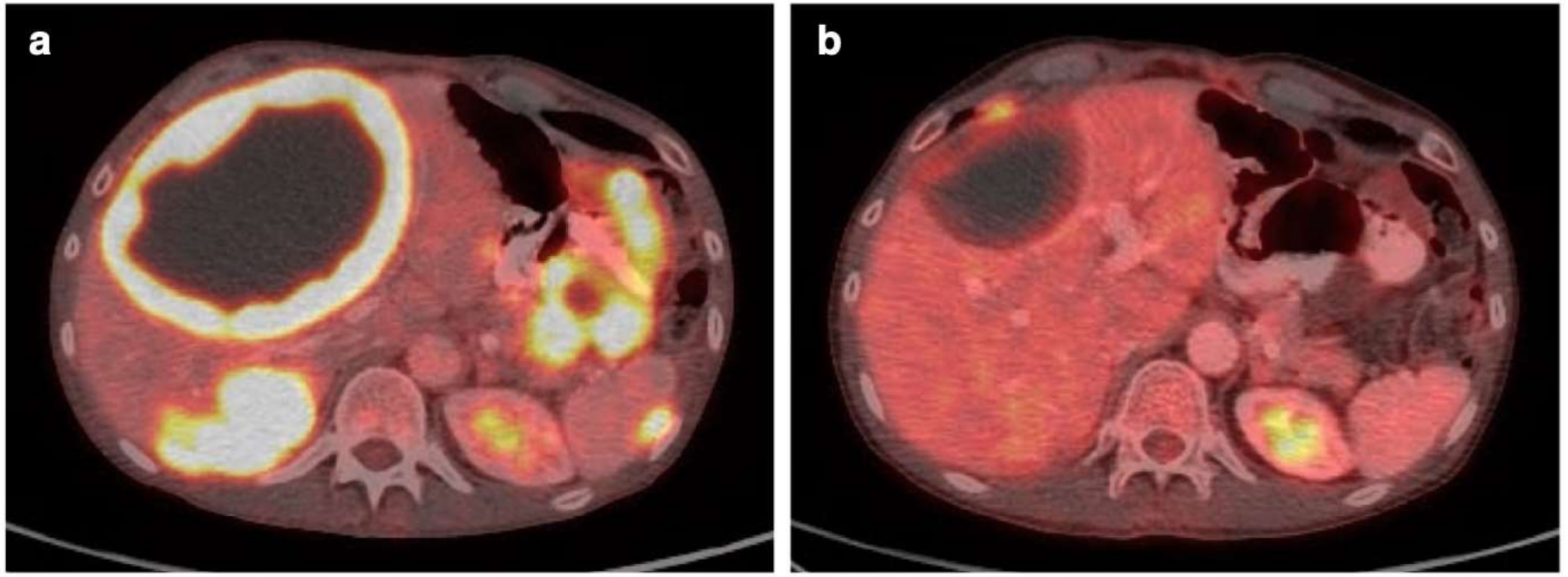


Fig. 4 Radiological response of a GIST possessing an ETV6–NTRK3 fusion following treatment with LOXO-101, a selective TRK inhibitor. A 55-year old male with a T3N0M1 small intestine GIST had progression of disease on five lines of tyrosine kinase inhibitors targeting KIT prior to identification of an ETV6–NTRK3 fusion in the tumor. He was enrolled on a Phase I clinical trial of oral LOXO-101 (Loxo Oncology, Stamford, CT), a selective TRK inhibitor. As compared to baseline PET/CT images (**a**), the tumors had decreased size and FDG-uptake at week 8 (**b**). At 4 months, the patient had ongoing partial response (44%) according to RECIST 1.1 criteria

Journal Pre-proof

Diagnosis and management of tropomyosin receptor kinase (TRK) fusion sarcomas: expert recommendations from the World Sarcoma Network

G.D. Demetri, C.R. Antonescu, B. Bjerkehagen, J.V.M.G. Bovée, K. Boye, M. Chacón, A.P. Dei Tos, J. Desai, J.A. Fletcher, H. Gelderblom, S. George, A. Gronchi, R.L. Haas, N. Hindi, P. Hohenberger, H. Joensuu, R.L. Jones, I. Judson, Y.-K. Kang, A. Kawai, A.J. Lazar, A. Le Cesne, R. Maestro, R.G. Maki, J. Martín, S. Patel, F. Penault-Llorca, C. Premanand Raut, P. Rutkowski, A. Safwat, M. Sbaraglia, I.-M. Schaefer, L. Shen, C. Serrano, P. Schöffski, S. Stacchiotti, K. Sundby Hall, W.D. Tap, D.M. Thomas, J. Trent, C. Valverde, W.T.A. van der Graaf, M. von Mehren, A. Wagner, E. Wardelmann, Y. Naito, J. Zalcberg, J.-Y. Blay

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Reference: ANNONC 322

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NTRK testing in sarcomas:

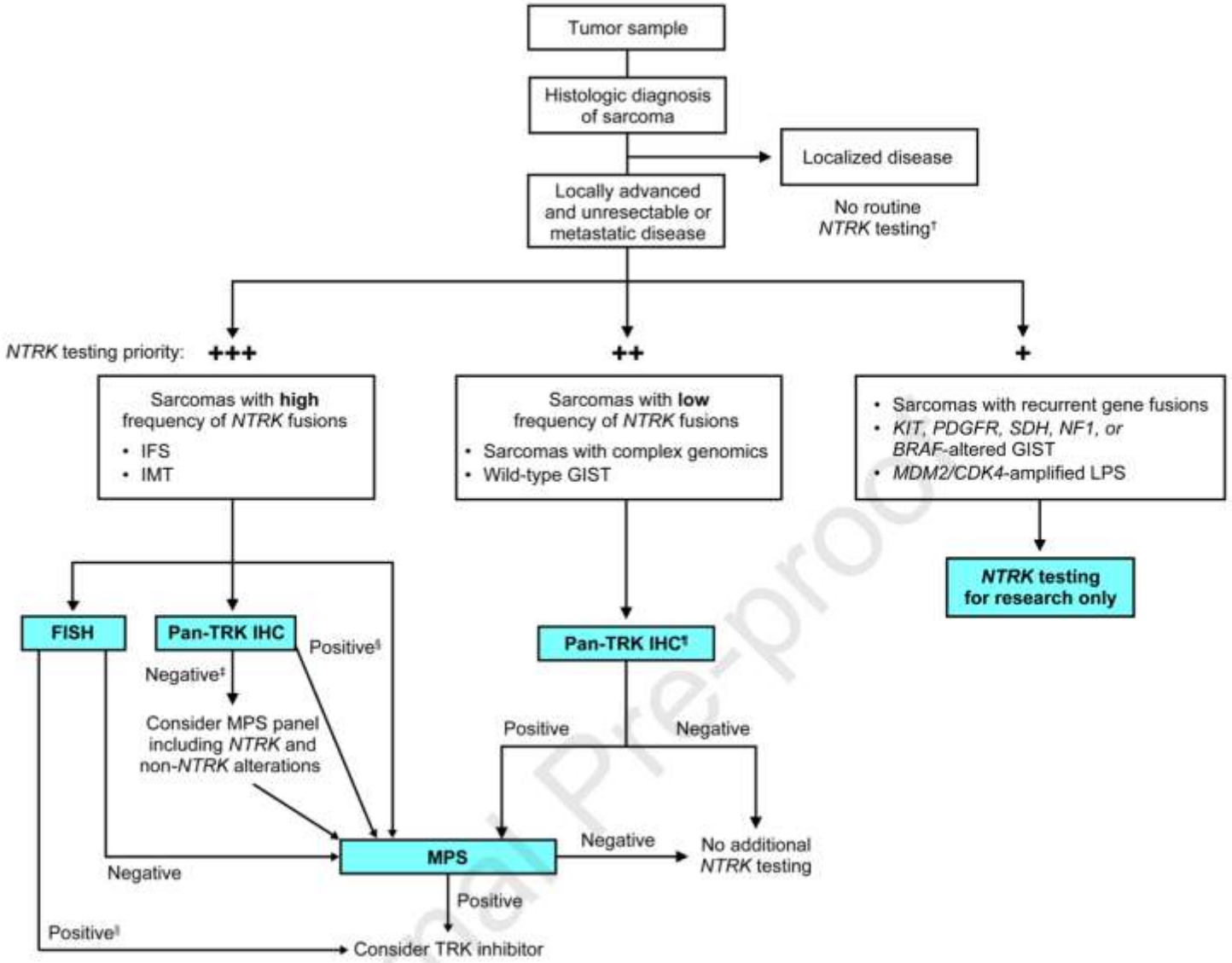

Figure 2

Clinical Trials

Ripretinib

- INTRIGUE
- 2nd line: ripretinib vs sunitinib

- INVICTUS
- Median progression-free survival:
- Ripretinib: 6·3 months (95% CI 4·6-6·9) compared
- Placebo: 1·0 months (0·9-1·7)
  - Hazard ratio 0·15, 95%CI: 0·09-0·25
  - p<0·0001

- Alopecia, laboratory abnormalities

Blay JY et al. *Lancet Oncol* 21(7); 923-934: 2020

Avapritinib

- NAVIGATOR:
  - PDGFRA D842V: 91% response rate (n=38)
  - Adverse events (safety population, n=250):
    - Intracranial bleed: 7 (3%)
    - Neuro cognitive: 115 (46%)
- VOYAGER (3rd/ 4th line):
- Avapritinib (N=240) vs Regorafenib (N=236)
- Median PFS:
  - Avapritinib: 4.2 months
  - Regorafenib: 5.6 months
- Response rate:
  - Avapritinib: 17%
  - Regorefnib: 7%

Cabozantinib in GIST: Phase 2 trial

- 50 eligible patients, 4 (8%) still continuing cabozantinib at clinical cut-off
- 41 eligible + evaluable patients
  - 24 were progression-free at week 12 (58·5%, 95% confidence interval [CI] 42·0-74·0%)

- All 50 patients, 30 were progression-free at week 12 (60%, 95% CI 45-74%)
  - 7 partial response (14%, 95% CI 6-27%)
  - 34 stable disease (68%, 95% CI 53-80%)
  - 8 progressive disease (16%, 95% CI 7-29%) + one not evaluable

- Disease control: 41 patients (82%, 95% CI 69-91%)

- Median progression-free survival: 5·5 months (95% CI 3·6-6·9)

- Most common adverse events:
  - Diarrhoea (76%), palmar-plantar erythrodysesthesia syndrome (60%), fatigue (50%), hypertension (42%), weight loss (40%) + oral mucositis (30%)
  - 32 (64%) patients requiring dose reductions
  - 27 (54%) having treatment interruptions

Schöffski P, et al. *Eur J Cancer* 134; 62-74: 2020

PLX9486

- Potent + selective inhibitor of KIT D816V

- Phase 1/ 2 trial
- PLX9486 + sunitinib

- Median PFS: 11 months

- Future clinical trial

Ilixadencel

- Ilixadencel (allogeneic inflammatory dendritic cells)
  - Cell-based immune primer injected intratumorally
  - Investigated in metastatic renal cell + hepatocellular carcinoma

- Single arm phase I trial ilixadencel in advanced GIST
  - Ongoing treatment >2nd line tyrosine kinase inhibitors
  - 4 continued tumor progression at 3 months
  - 1 patient (on 3rd line regorafenib): stable disease for 9 months
  - 1 patient (on 2nd line sunitinib) stable disease at end of study (12 months)
    - These two patients: CHOI partial response: duration of 3 + 6 months

- Median progression-free survival: 4.0 months

- No severe adverse events due ilixadencel

Fröbom R, et al. *Cancer Immunol Immunother* 2020

Crenolanib

- Randomized phase III trial
- Advanced or metastatic GIST with a *PDGFRA D842V* mutation
- Prior treatment with TKI allowed
- Approximately 120 patients
- Randomized in a 2:1 ratio to receive either
  - Crenolanib 100 mg or
  - Matching placebo orally 3 times daily

Conclusion

- Off label use:
  - Good option in select situations
  - Careful discussion patient + oncologist

- NTRK inhibitors
  - Little knowledge currently
  - Impressive responses

- Clinical trials
  - Important + essential for improving treatment + outcome

Thank you patients staff Royal Marsden + ICR

- Surgical Oncology:
  - Andrew Hayes
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  - Simon Jordan
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  - Shane Zaidi
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  - Angela Teague
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  - Lucy Dean
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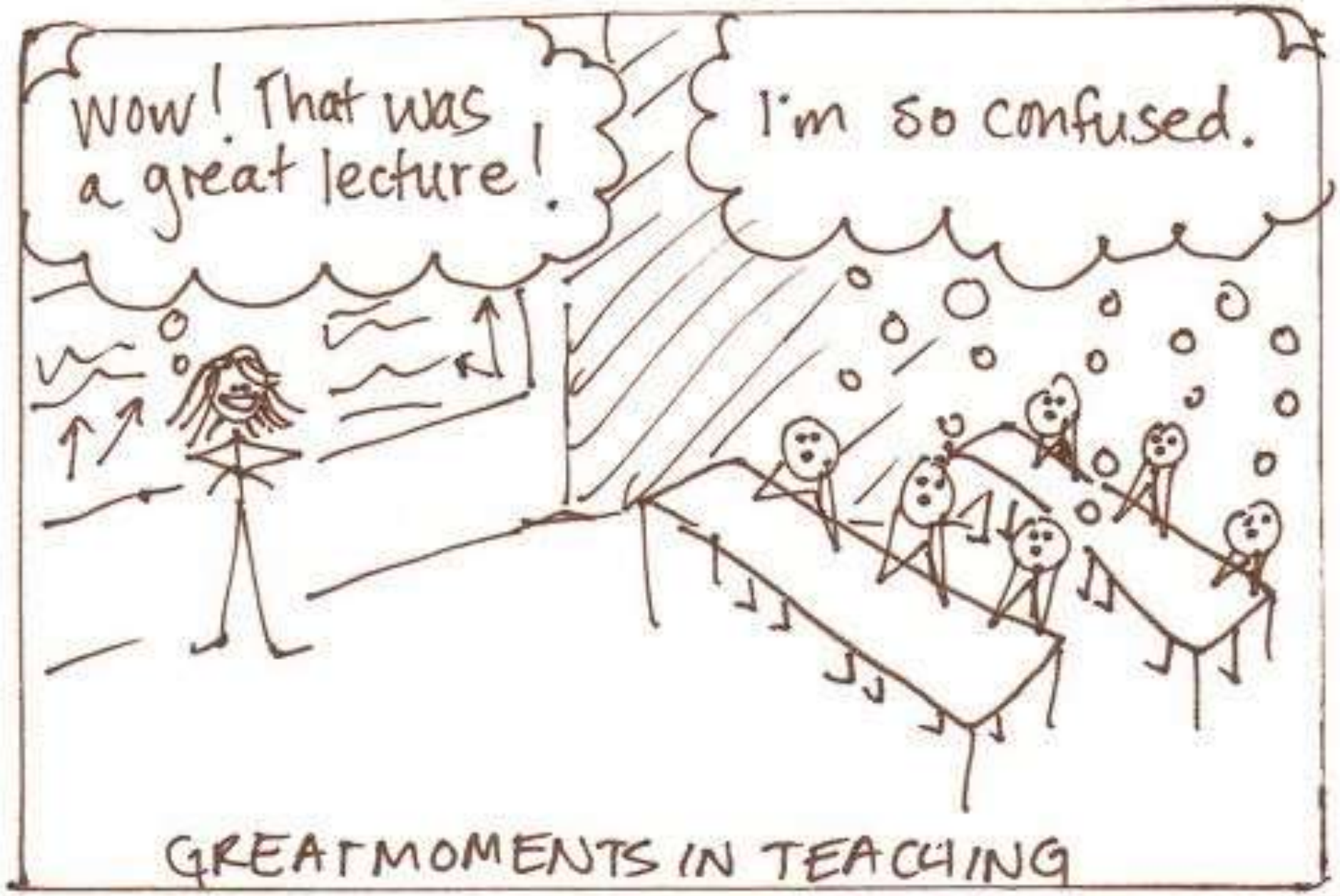
  - Alannah Smrke
  - Alex Ostler
  - Yolanda Augustin
  - Eniola Ayeni
- Paul Huang + Lab
- Janet Shipley + Lab


Wow! That was a great lecture!
I'm so confused.
GREAT MOMENTS IN TEACHING
2008©