Disclosures

- Robert D. Doebele
  - Research grant from Mirati Therapeutics, Loxo Oncology, and Abbott Molecular
  - US Patent on NTRK FISH biomarker, licensed to Abbott Molecular
  - Biologic Materials licensed to Chugai, Blueprint Medicines, GVKBio, Ariad
  - Consulting/Honoraria from Pfizer, Clovis, AstraZeneca, OxOnc, Loxo Oncology

- Anh T. Le: US Patent on NTRK FISH biomarker, licensed to Abbott Molecular
- James Christensen: Employee of Mirati Therapeutics

In vitro and in vivo evaluation of the kinase inhibitor, MGCD516, in TRK and RET fusion cancer cells

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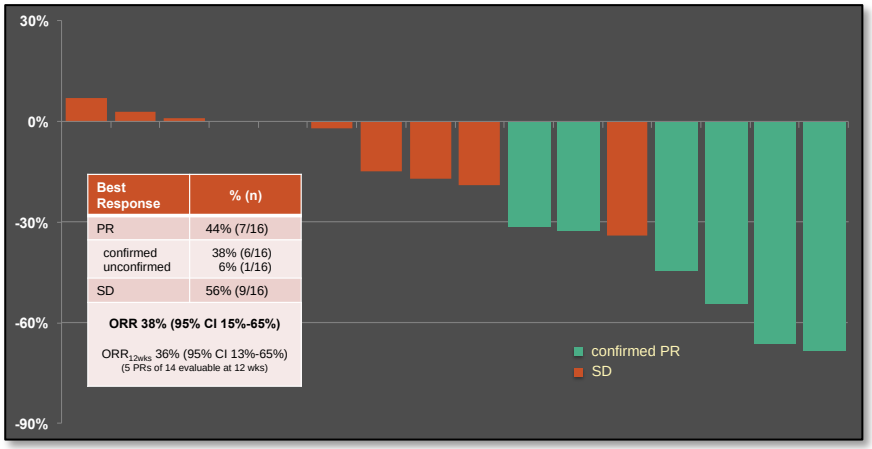
RET and *NTRK* gene fusions as oncogene targets in lung cancer

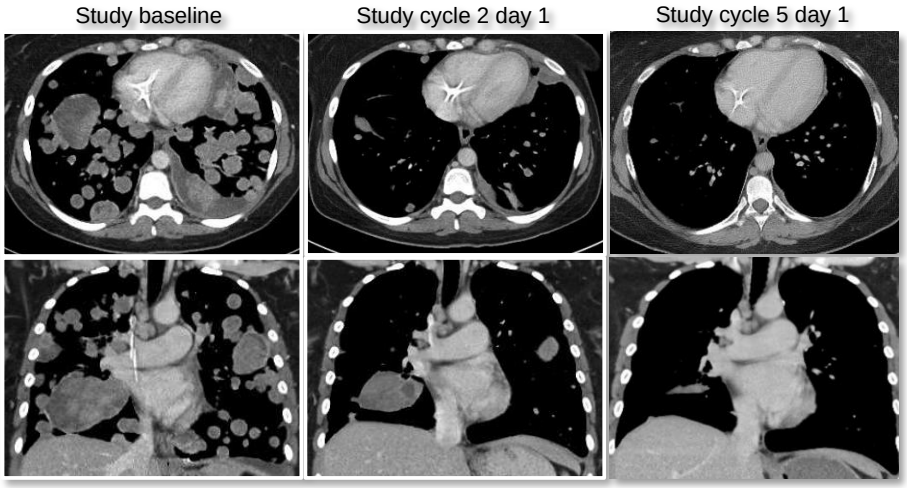
RET gene fusions

- 1-2% of NSCLC
- 38% ORR in *RET* fusion+, cabozantinib-treated NSCLC patients[1]
- No FDA approved therapies



NTRK1/2/3 fusions

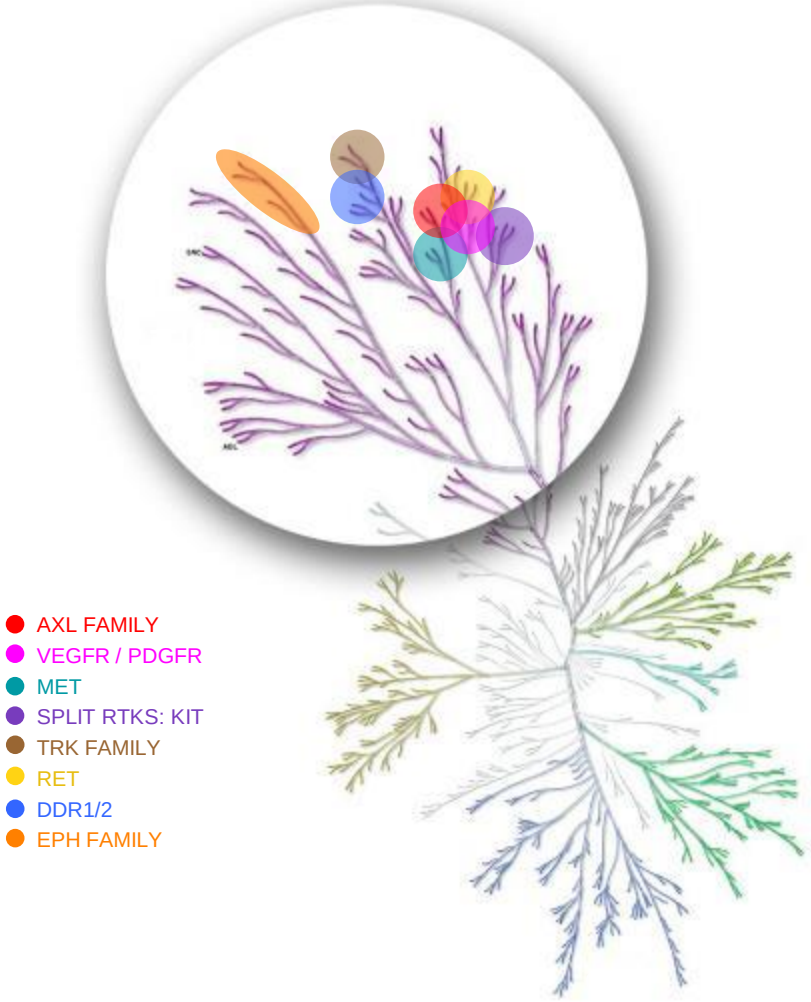
- ~1-2% of NSCLC (combined frequency)
- Clinical activity observed in *NTRK1* or *NTRK3* fusion positive patients[2,3]
- No FDA approved therapies



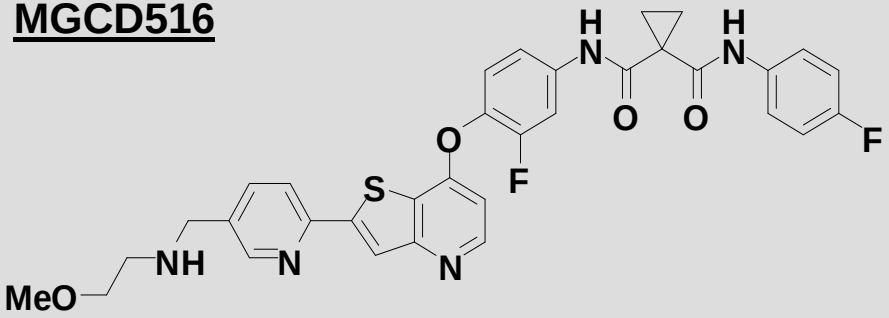
[1]Drilon et al., ASCO 2015 #8007
[2]Doebele et al., Cancer Discovery 2015
[3]Patel et al., ASCO 2015 #2596

MGCD516

Spectrum-Selective RTK Inhibitor Profile

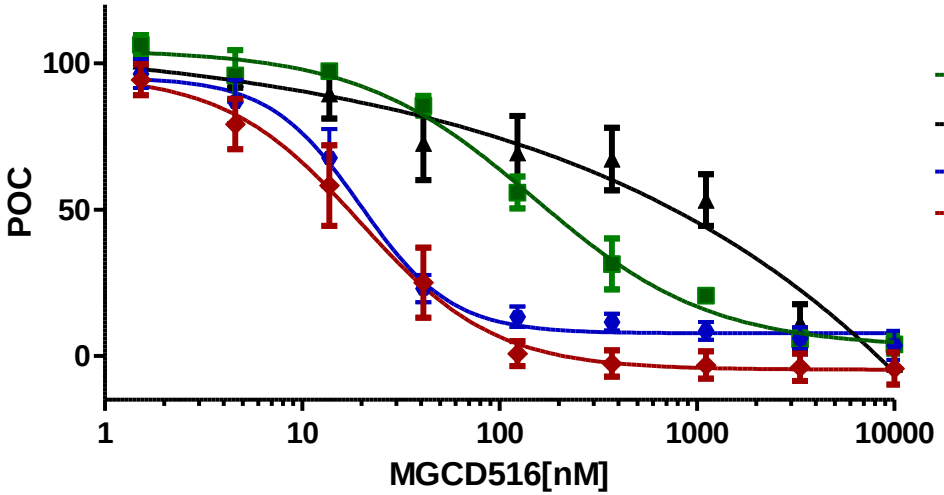


MGCD516

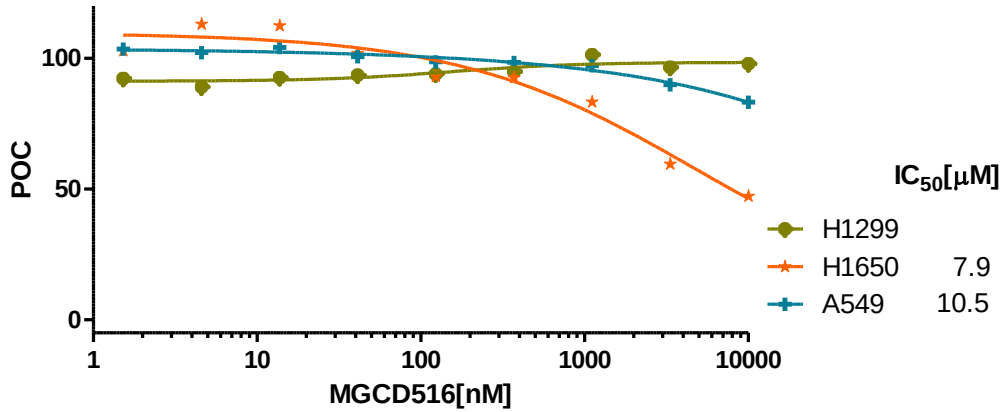


No inhibition of >150 serine threonine kinases noted at concentrations <1000 nM or within 250X of Target IC_{50} value

MGCD516 inhibits growth of TRK+ and RET+ cancer cells *in vitro*

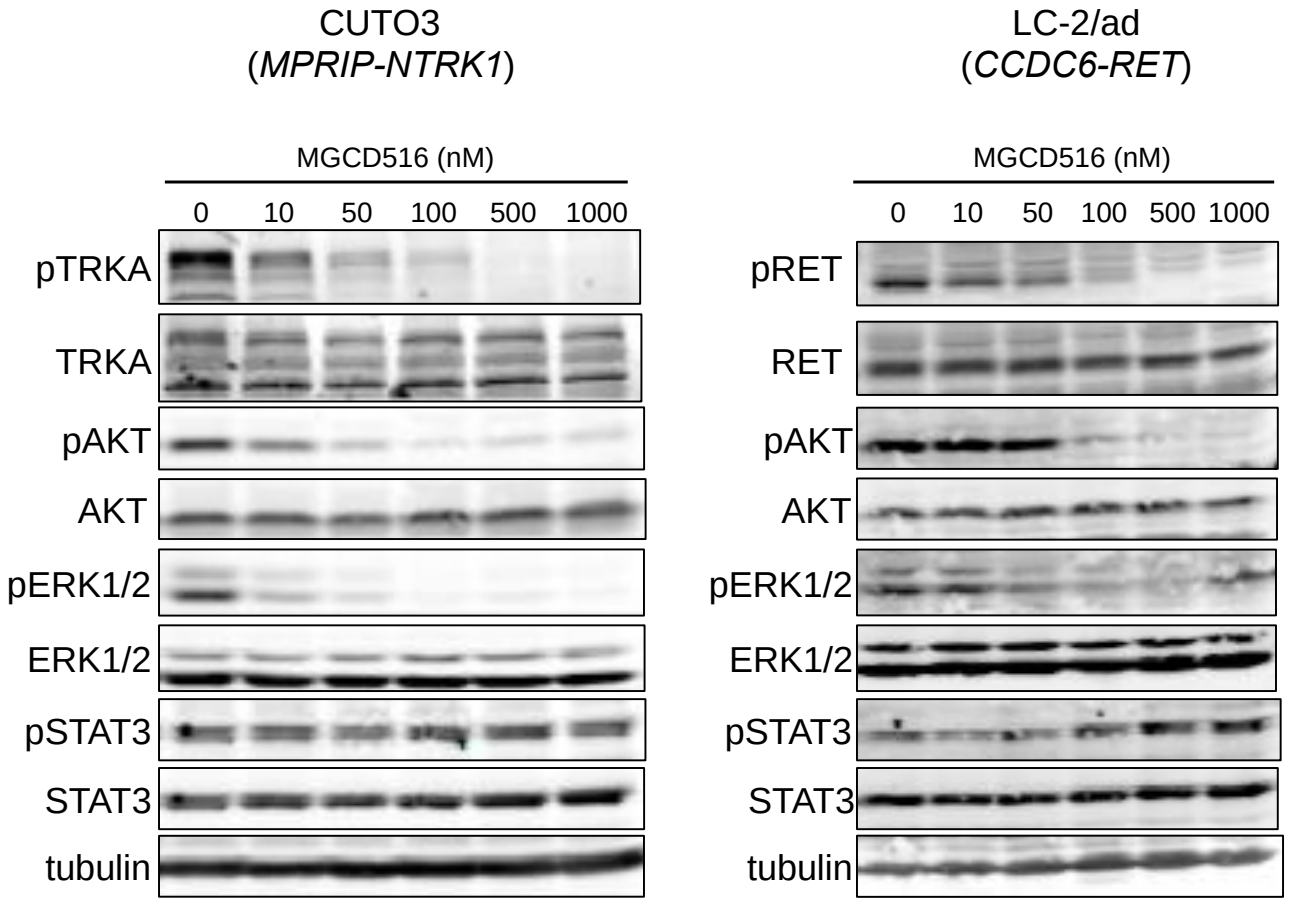


	IC_{50}[nM]	
LC-2/AD	150.1	*CCDC6-RET*, LuAd[1]
CUTO3	763.8	*MPRIP-NTRK1*, LuAd[2]
KM12	19.7	*TPM3-NTRK1*, CRC[2]
MO91	19.6	*ETV6-NTRK3*, AML[3]

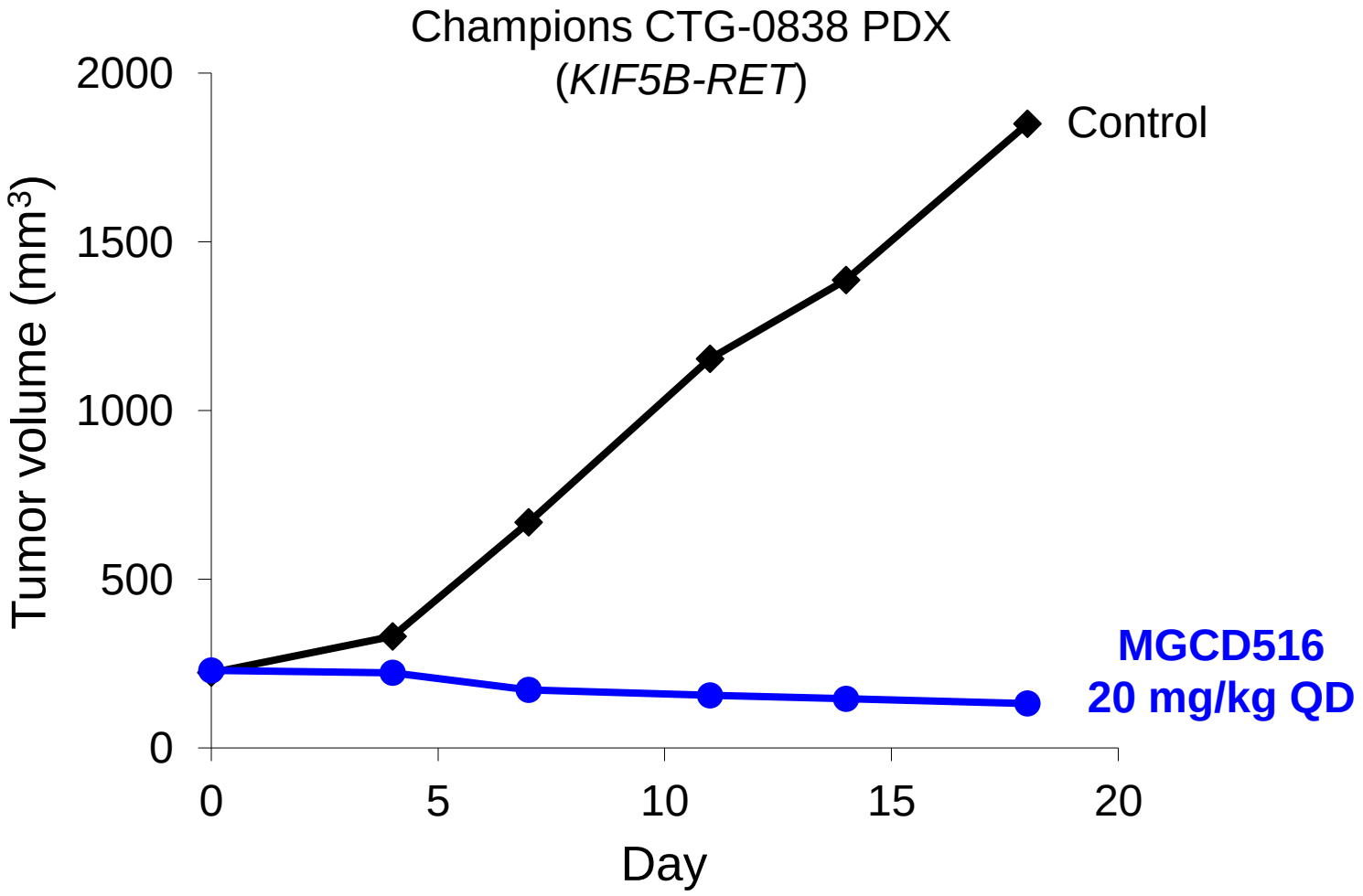


[1]Matsubara et al. JTO 2012
[2]Vaishnavi et al., Nat Med 2013
[3]Gu et al., Leukemia 2007

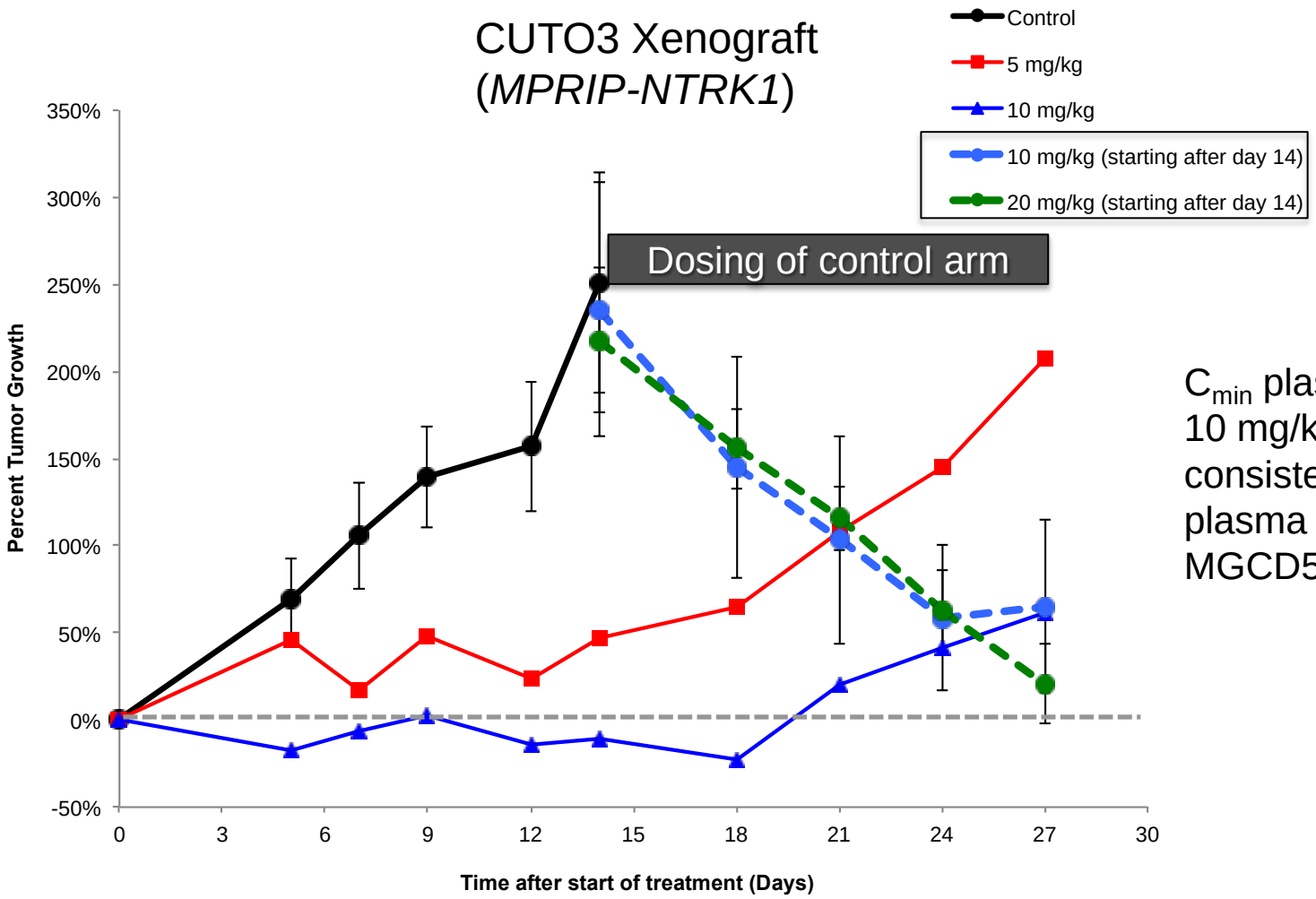
MGCD516 causes dose-dependent inhibition of TRK and RET signaling



Potent Cytoreductive Activity of MGCD516 in a *RET* Fusion-Positive Lung Cancer Model



MGCD516 induces tumor regression in *NTRK1* fusion positive lung cancer model



C_{min} plasma levels at 10 mg/kg in mice are consistent with C_{min} plasma levels in MGCD516 Phase 1 trial

Summary

MGCD516:

- Shows dose-dependent target inhibition in both RET and TRK fusion proteins
- Shows *in vitro* and *in vivo* growth inhibition of RET and TRK fusion cancer models
- Is currently in Phase 1 dose escalation (NCT02219711) with planned dose expansion cohort in NSCLC that will include *RET* and *TRK* fusion positive patients

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