Evaluation of the MET/Axl receptor tyrosine kinase (RTK) inhibitor MGCD265 in a patient with metastatic non-small cell lung cancer (NSCLC) harboring *Axl* amplification

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Lynette Sholl: no conflicts.

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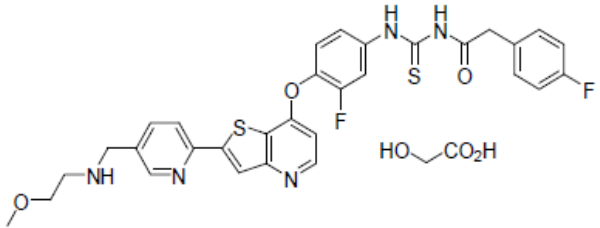
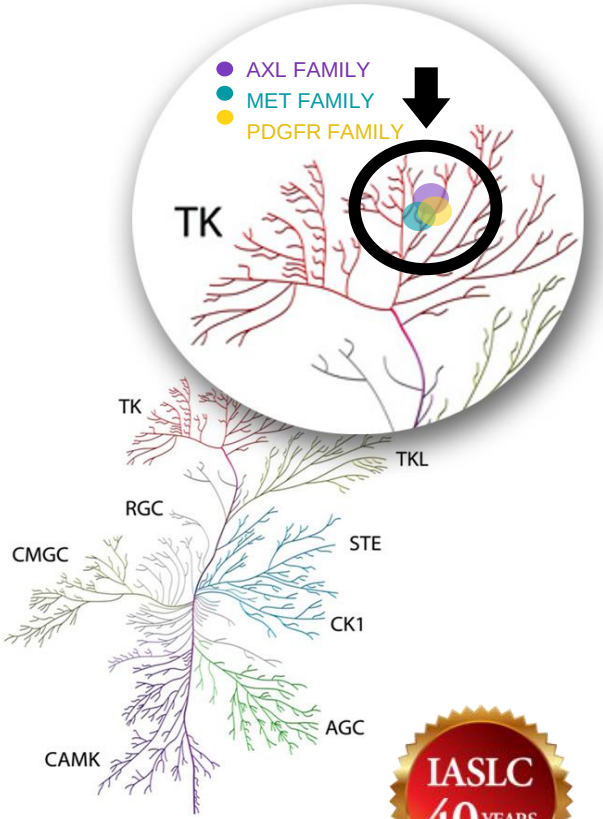
MGCD265 Target Profile

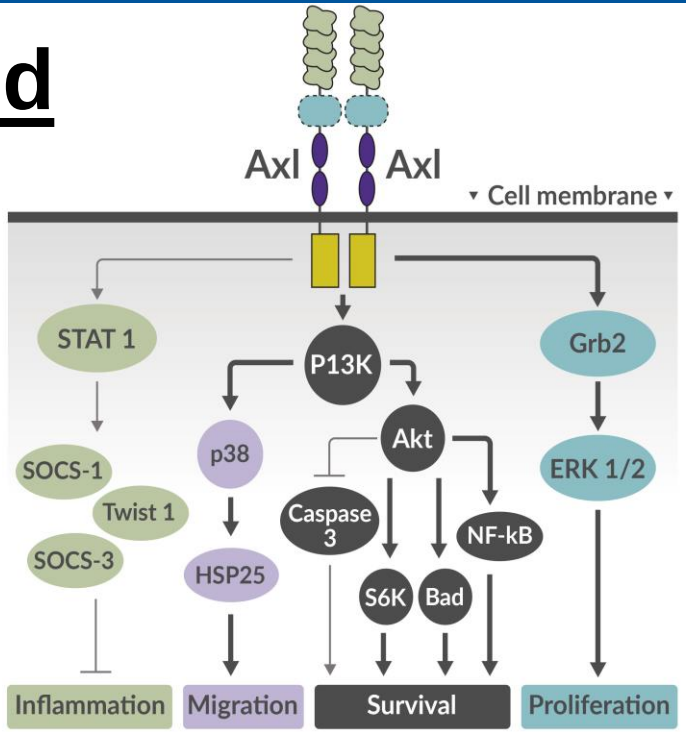
- A spectrum-selective, orally active inhibitor of the MET and Axl Family Receptor Tyrosine Kinases (RTKs)
- Demonstrated inhibition of MET and Axl pathways at current clinical dose and exposure levels
- Clinical development strategy is based on targeting patients exhibiting dysregulated MET or Axl





MGCD265 Target Background

- MET and Axl may be activated in NSCLC by gene mutation, amplification or rearrangement, resulting in oncogene addiction
- MET and Axl are both implicated in progression of NSCLC and in acquired resistance to EGFR TKIs and chemotherapy
- *Axl* genomic abnormalities have been reported in NSCLC, but therapeutic targeting of such alterations with Axl inhibitors has not been clinically validated



Adapted from Korschunov, VA. "Axl-dependent signaling: A clinical update." Clinical Science 122, 361-368.

Phase 1/1b open-label study of MGCD265 in subjects with solid tumors

Dose Escalation Cohort
(Patients with solid tumors)

- **Patients treated with 600, 1200, or 1050 mg BID:**
  - **— 1200 mg DLTs:**
    - **Grade 3 diarrhea (n=1)**
    - **Grade 3 fatigue (n=1)**
  - **— 1050 mg DLTs: None**
- **Full inhibition of MET and Axl observed in patients using plasma surrogate PD marker assays**

Dose Expansion Cohort
(Patients selected for gene alterations in *MET* or *Axl*)

1050mg BID MTD / RP2D

- **NSCLC**
  n=10-20
  7 patients currently enrolled
- **Basket cohort: other tumors**
  n=10-20
  2 patients currently enrolled

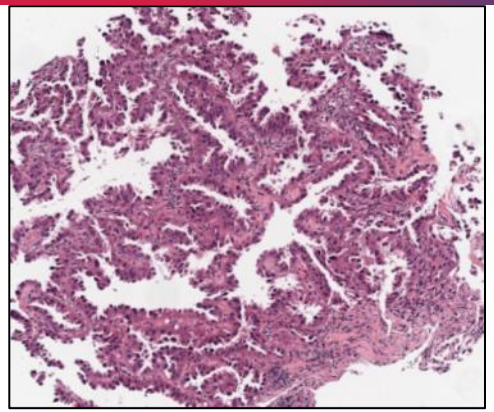
Case History

Patient Background

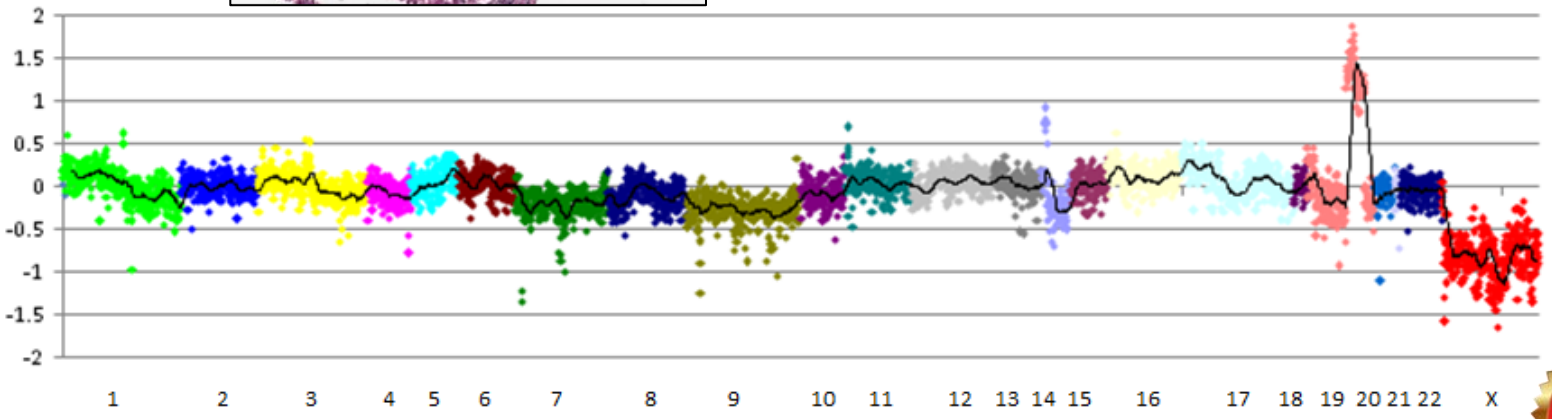
- 56 year-old male, never smoker, metastatic adenocarcinoma of the lung
- At diagnosis: Bilateral mediastinal lymphadenopathy and pleural carcinomatosis
- Tumor: wild-type for *EGFR*, *ALK*, *ROS1*, *RAS*, *MET*

Prior Treatments

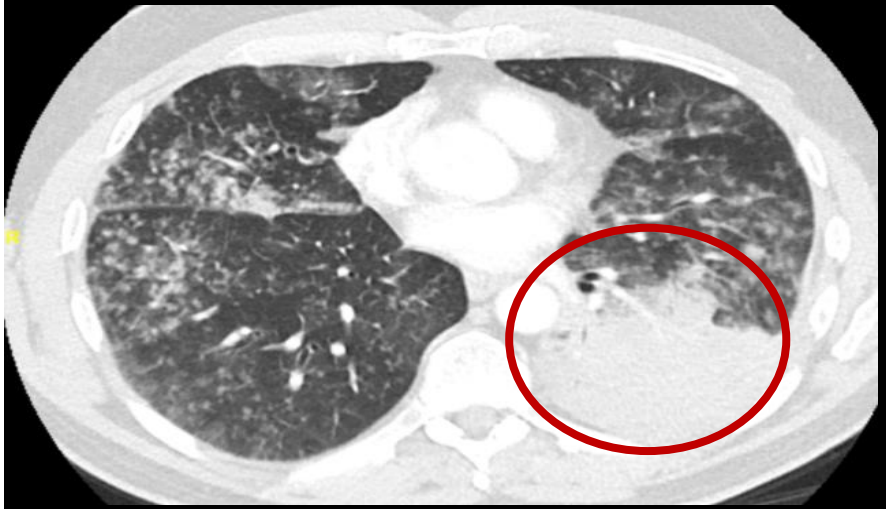
- Carboplatin/pemetrexed + bevacizumab
  → progressive disease after 2 months
- Docetaxel
  → complicated by hospitalization for empyema hydropneumothorax
- Clinical trial of ATR inhibitor + cisplatin
  → complicated by hospitalization for pneumonia



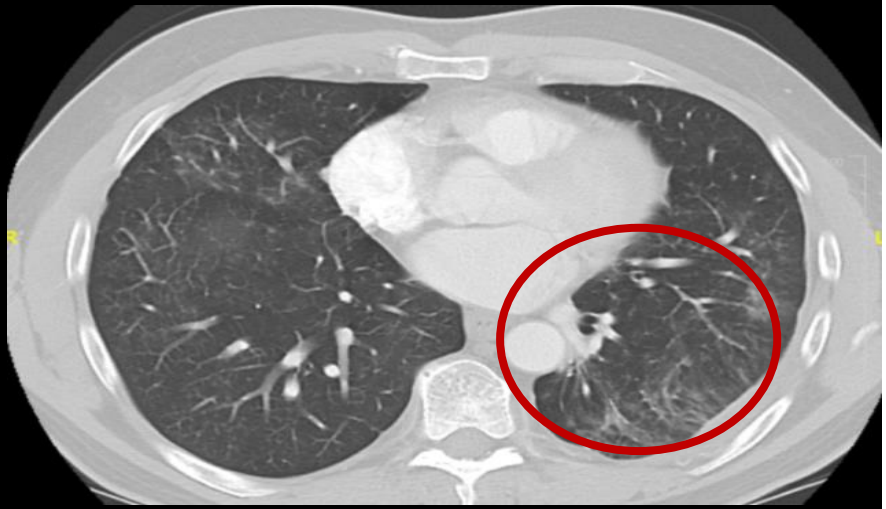
19q12-13.11 focal gain:
CCNE1
RHPN2
CEBPA
AKT2
AXL



Confirmed PR with ~49% reduction in index lesion

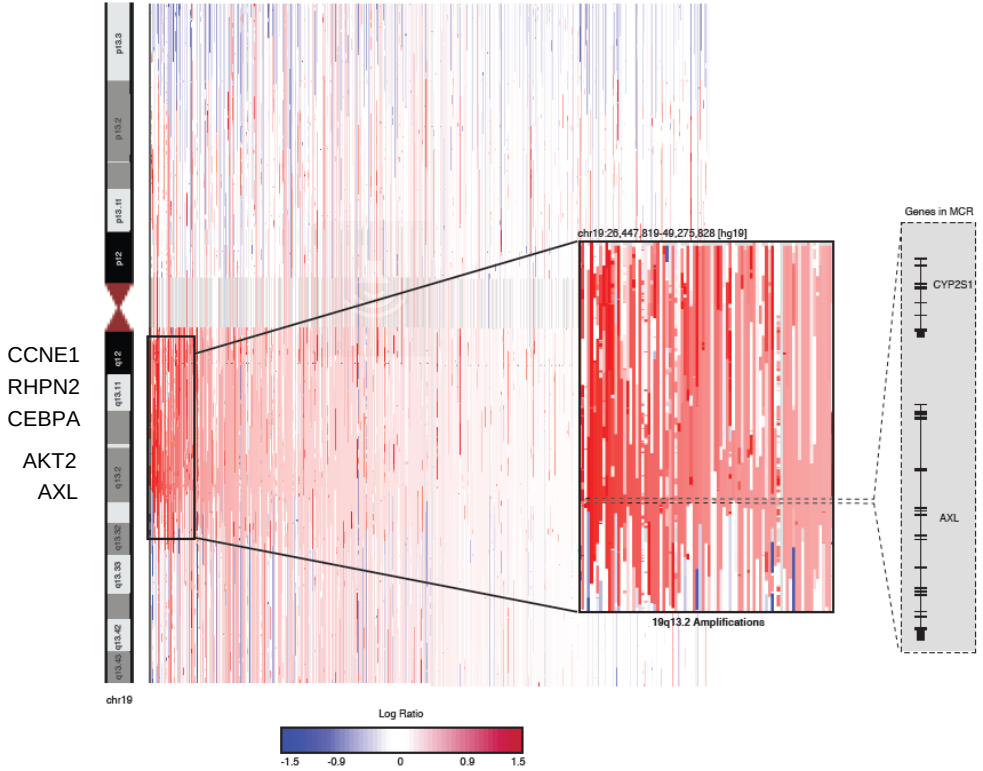


LLL mass prior to MGCD265



LLL mass after 4 cycles of MGCD265

- After 5 days of treatment patient experienced resolution of baseline dyspnea, pleuritic chest pain and cough. After 3 weeks, supplemental oxygen not required, significant increase in exercise tolerance of up to 7 miles biking p/day
- Well tolerated with only grade 1 adverse events (diarrhea, transaminase increase, xerostomia and dyspepsia)
- Patient remains on treatment in Cycle 7



Axl amplification frequency

Tumor Type	TCGA	FMI	Broad
NSCLC	**0.9%**	**0.6%**	**0.9%**
Ovarian	1.6%	0.5%	1.9%
Gastric	1.4%	0.3%	NA
Bladder	1.0%	0.9%	NA
Pancreas	1.0%	0.4%	NA
Breast	0.8%	0.5%	0.8%
Melanoma	0.7%	0.0%	0.8%

TCGA = The Cancer Genome Atlas
FMI = Foundation Medicine
Broad = Tumorscape database

Conclusions:

- To our knowledge, this is the first report of an objective response in a NSCLC patient with *Axl* gene amplification treated with a small molecule inhibitor of Axl. This suggests that *Axl* alterations are clinically relevant oncogenic drivers.
- MGCD265 is well-tolerated at the recommended Phase 2 dose.
- The dose expansion phase of the MGCD265 Phase 1/1b trial in patients with *MET* (gene amplification or mutations) or *Axl* (gene amplification or gene fusions) is ongoing (NCT00697632).
- Further study of MGCD265 in tumors with *Axl* genetic alterations is warranted and ongoing.