Memorial Sloan Kettering Cancer Center

Clinical proof-of-concept for MCLA-128, a bispecific HER2/3 antibody therapy, in NRG1 fusion-positive cancers

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Disclosures: Alison Schram
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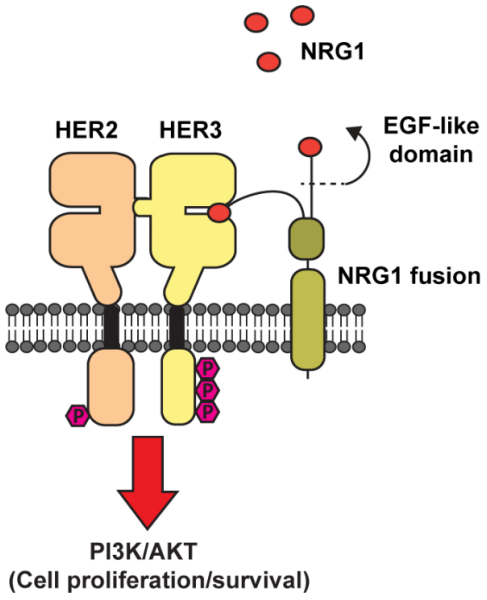
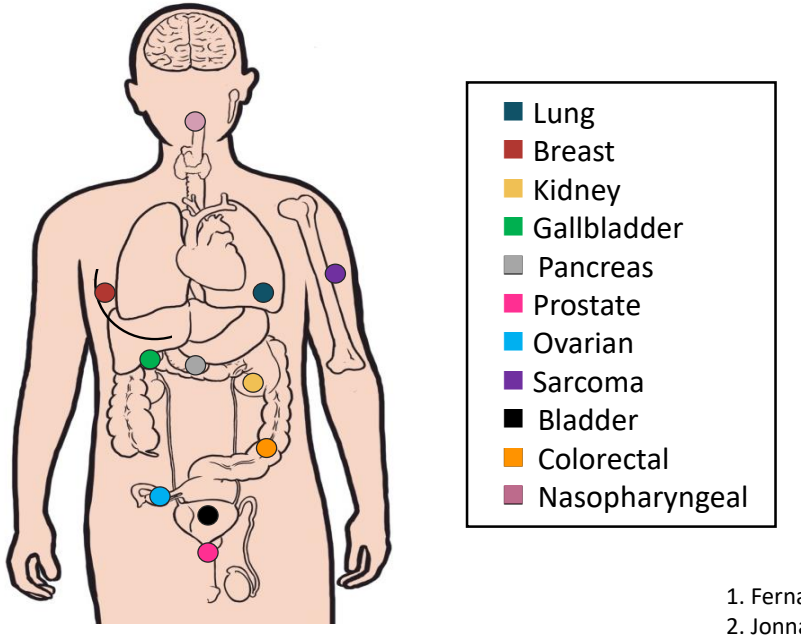
- I have no financial relationships to disclose
- I will discuss the following investigational agent in my presentation: MCLA-128

NRG1 fusions: clinically actionable targets

- Neuregulin 1 (NRG1) is a ligand that binds HER3, promoting HER2/HER3 heterodimerization and activation of PI3K/AKT/mTOR signalling[1]
- *NRG1* fusions are oncogenic drivers found across numerous solid tumor types[2,3]
  - Low overall incidence <1%
  - Enriched in *RASwt* pancreas and lung invasive mucinous adenocarcinoma (IMA)

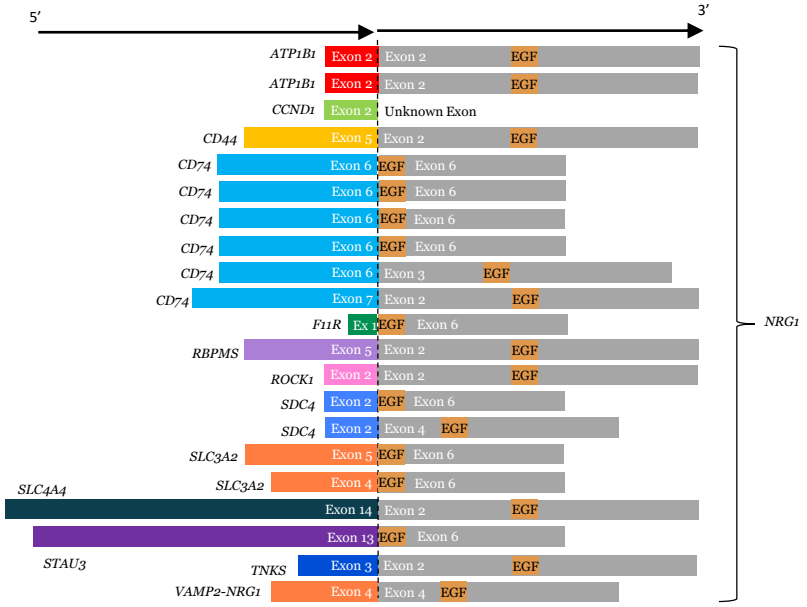


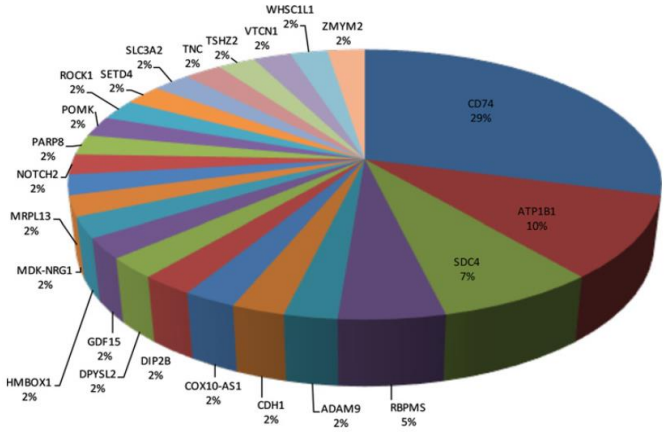


1. Fernandez-Cuesta et al. Cancer Discov. 2014,4(4):415-22
2. Jonna et al. Clin Cancer Res. 2019;25(16):4966-72
3. Schram et al. ASCO Annual Meeting. 2019

NRG1 fusions: clinically actionable targets

- Numerous fusion partners have been identified[1,2]
  - Some recurrent, others unique
  - Detected by DNA/RNA-based NGS or FISH
- Functional fusions include the EGF-like domain
- *NRG1* fusion-positive models are sensitive to HER2/HER3 directed therapy *in vitro/in vivo*, and are emerging as clinically actionable targets[3,4]



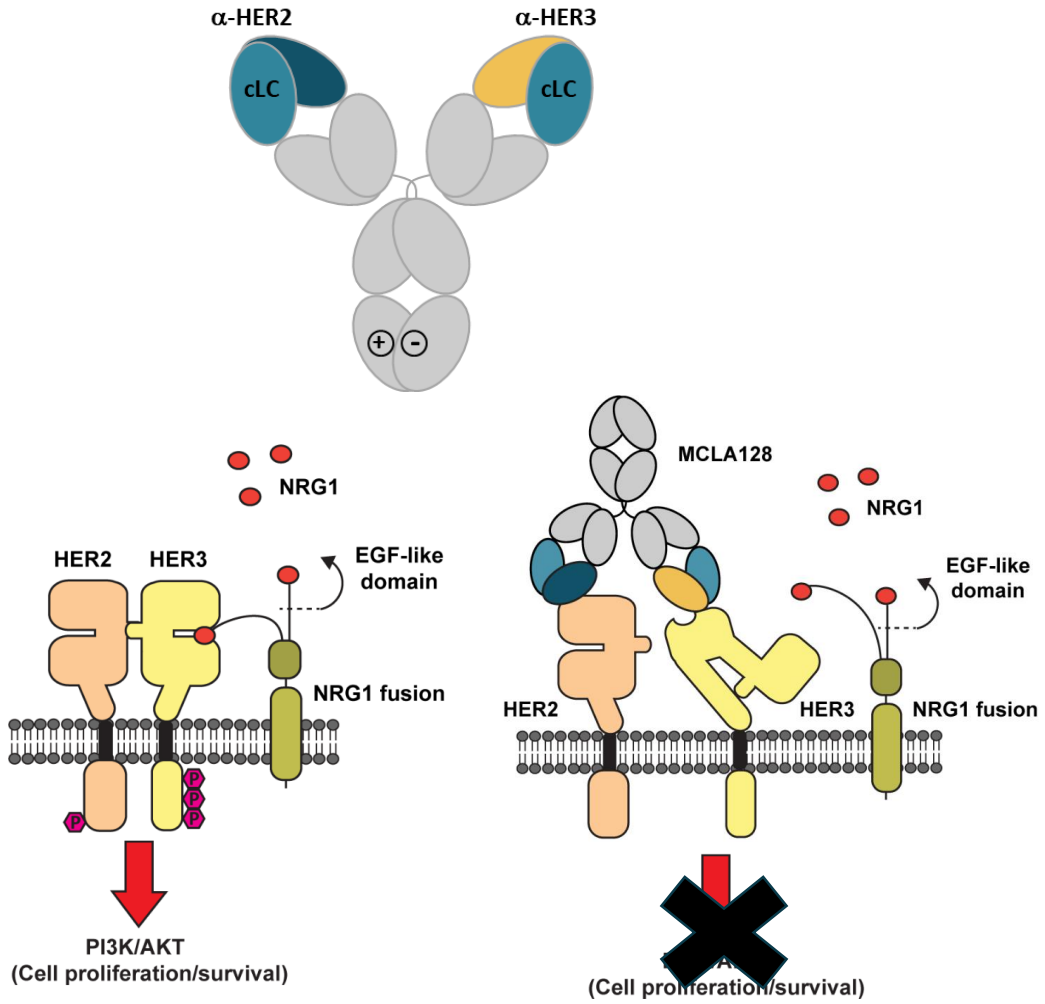


1. Jonna et al. Clin Cancer Res. 2019;25(16):4966-72
2. Schram et al. ASCO Annual Meeting. 2019
3. Drilon et al. Cancer Discov. 2018;8(6):686-95
4. Jones et al Clin Cancer Res. 2019;25(15):4674-81

MCLA 128: a HER2/HER3 bispecific antibody

- MCLA-128 is a bispecific antibody with enhanced ADCC activity
- One arm binds the HER2 receptor, optimally positioning the anti-HER3 arm to block the HER3/ligand interaction
- MCLA-128 blocks NRG1 from binding to HER3, even in the presence of very high ligand expression
- This prevents HER2/HER3 dimerization and downstream PI3K/AKT/mTOR signaling

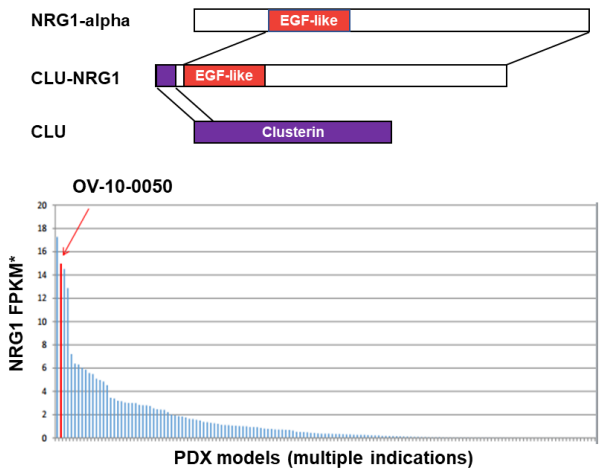
→ MCLA-128 offers a novel therapeutic paradigm for *NRG1* fusion-positive cancers

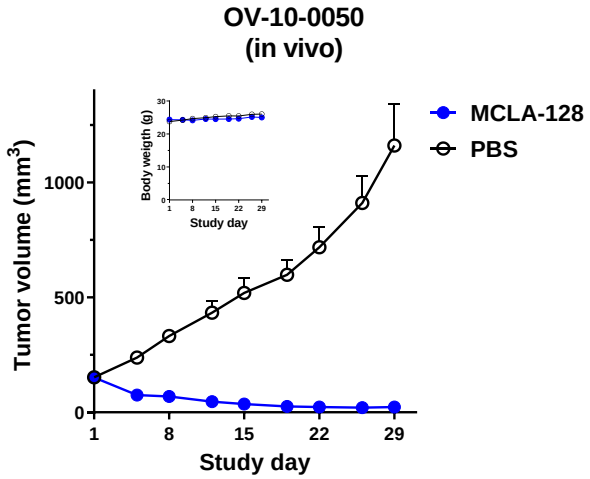


Geuijen et al. *Cancer Cell.* 2018;33(5):922-36

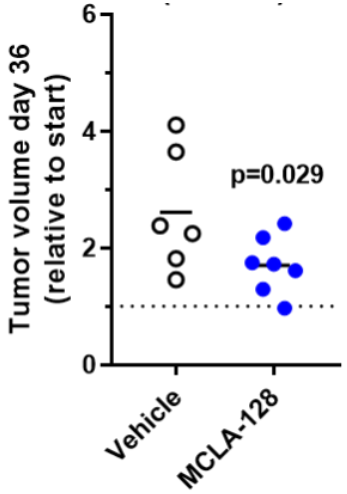
MCLA-128 inhibits tumor growth in *NRG1* fusion-positive models

CLU-NRG1

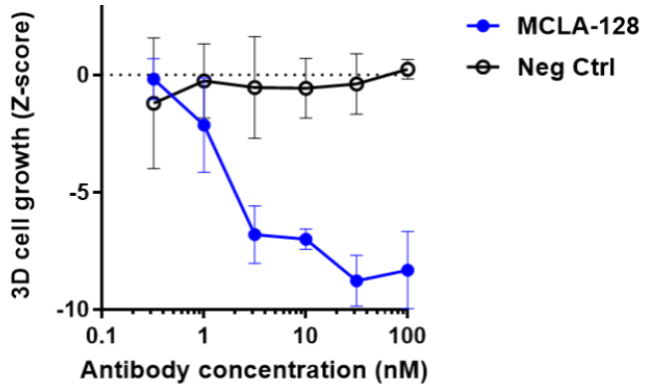


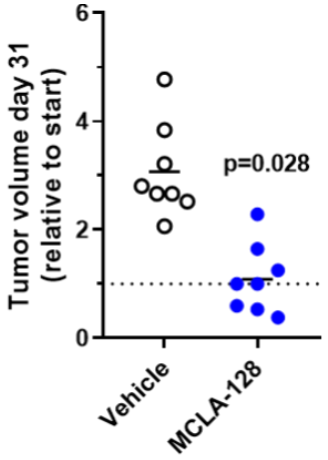


TNFRSF10B-NRG1



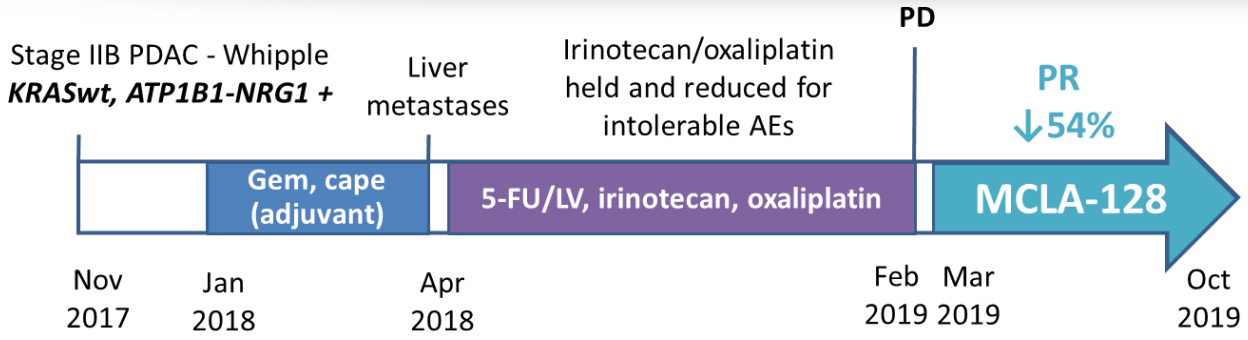
DOC4-NRG1



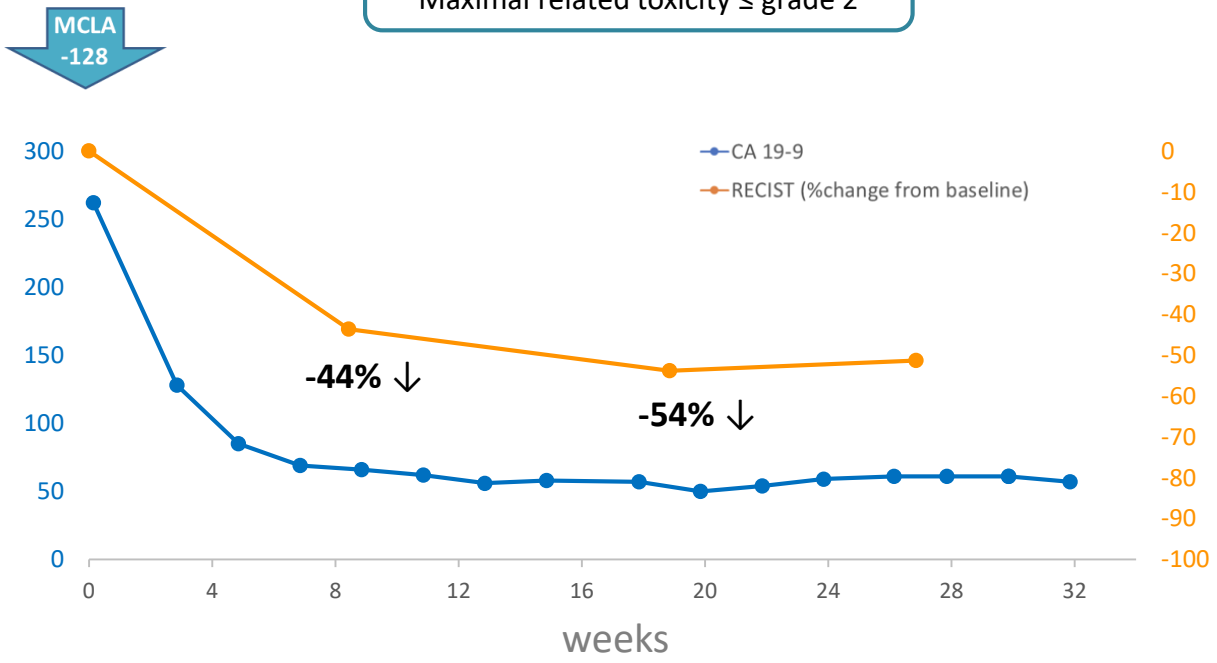


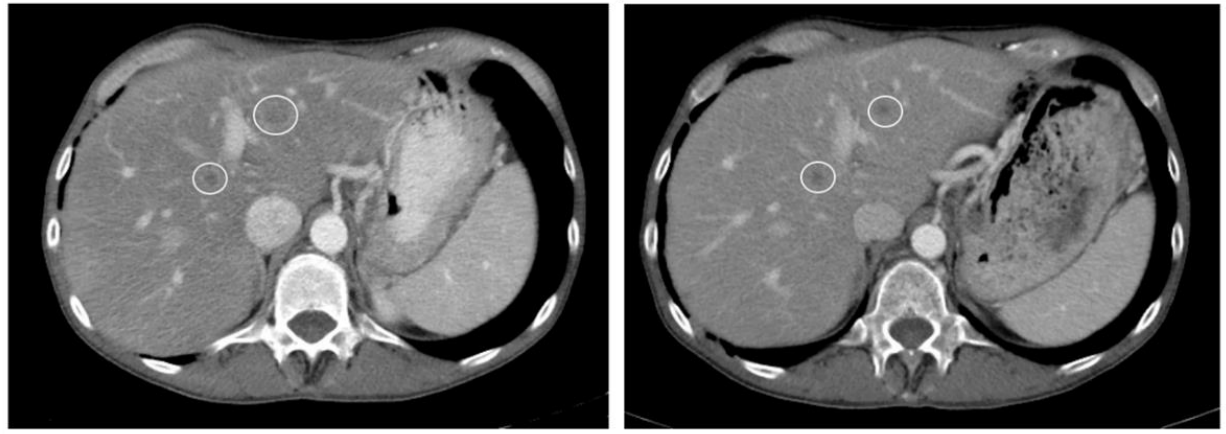
Geuijen et al.
Cancer Cell. 2018;33(5):922-36

52-year-old male with *ATP1B1-NRG1* pancreatic CA



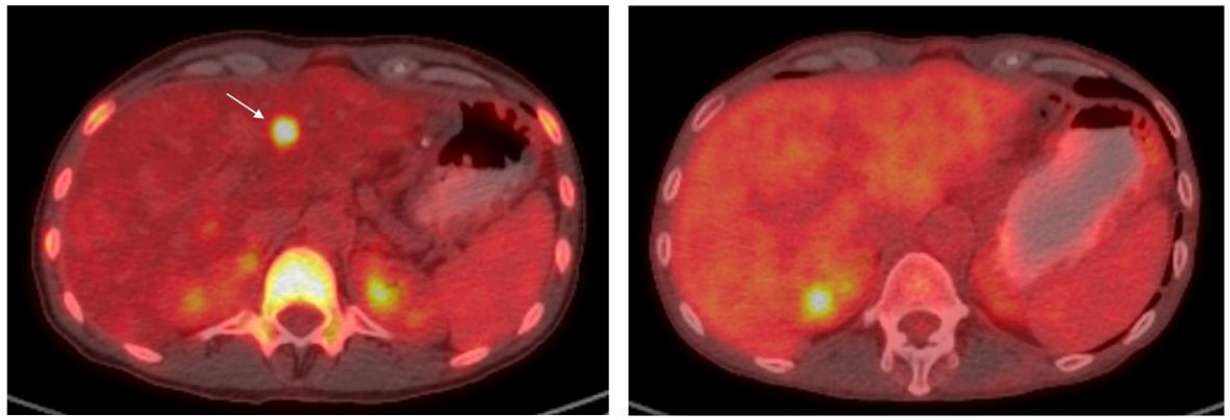
7+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 2





Baseline CT

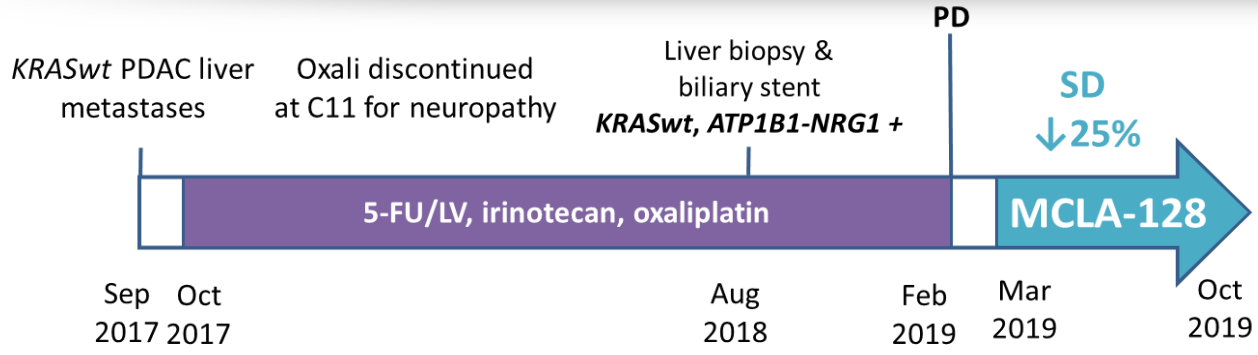
8 week CT



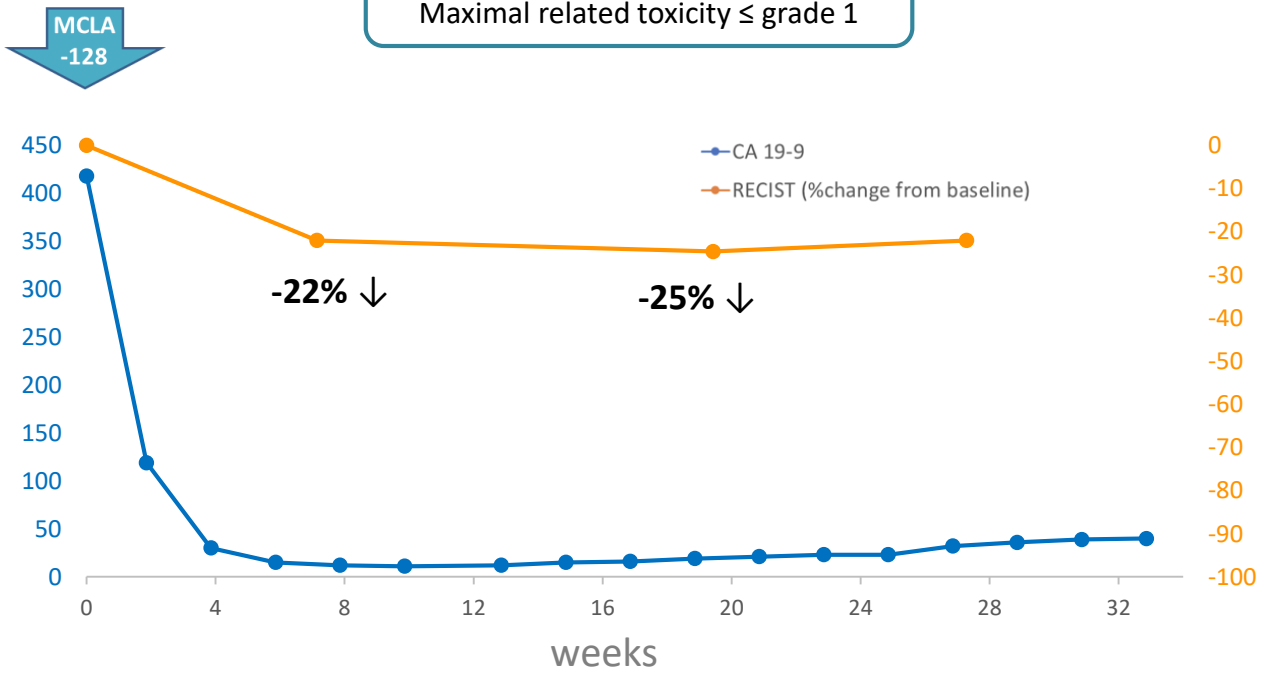
Baseline PET

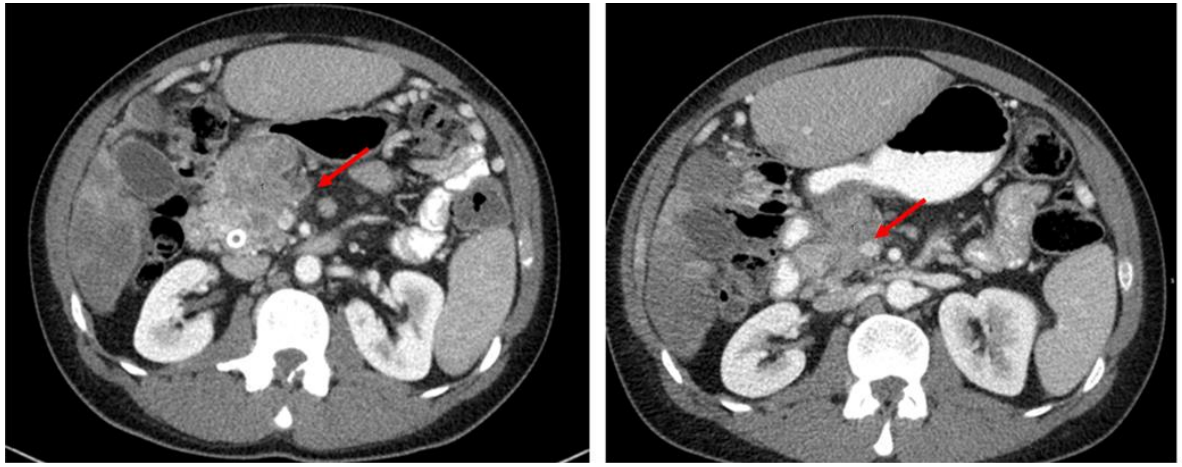
8 week PET

34-year-old male with *ATP1B1-NRG1* pancreatic CA

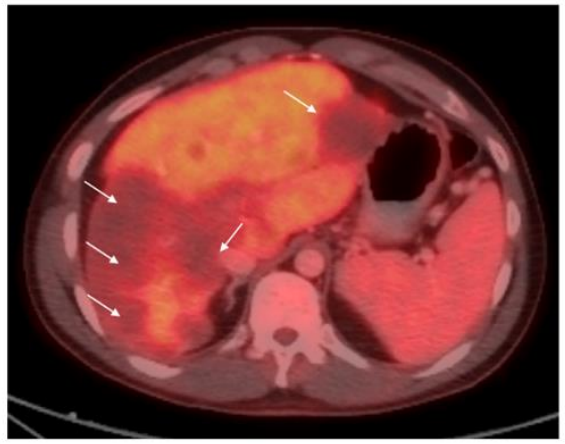


7+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 1



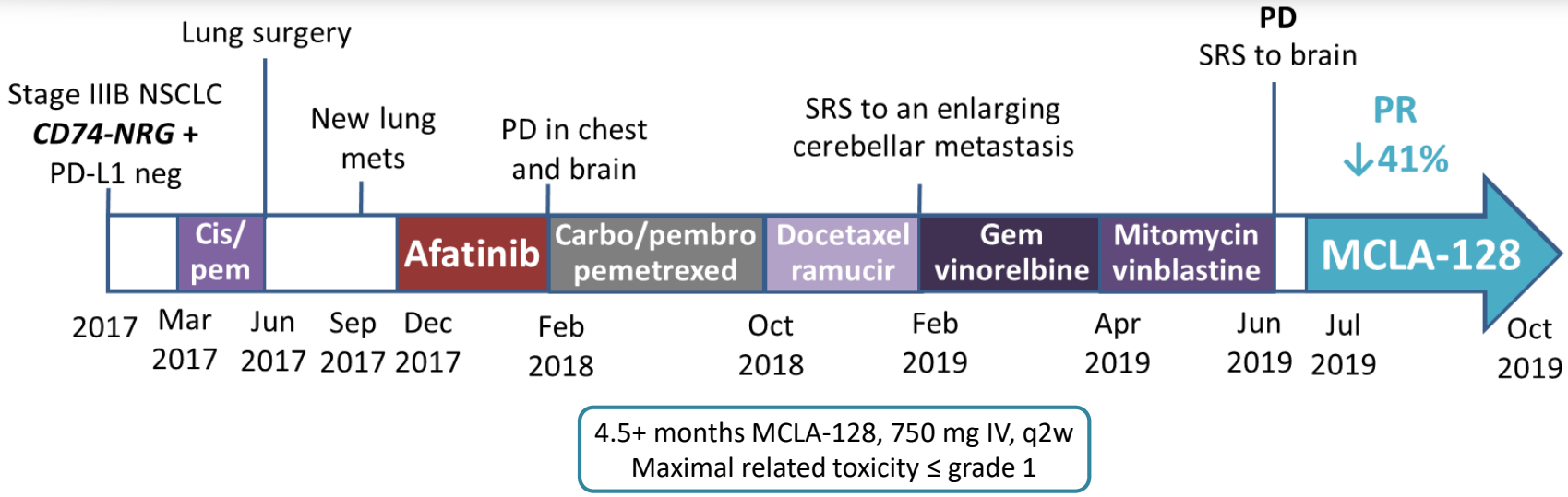


Baseline CT **7 week CT**

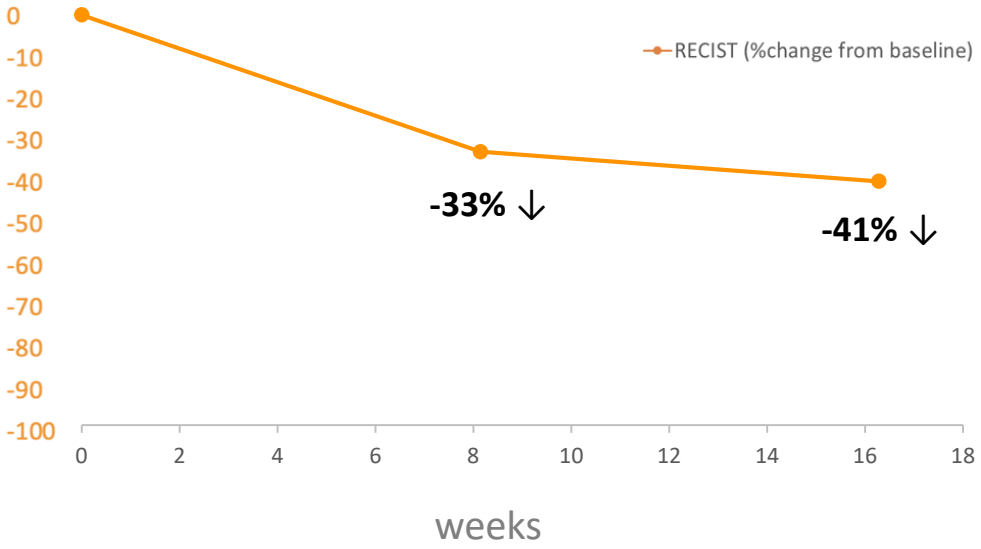


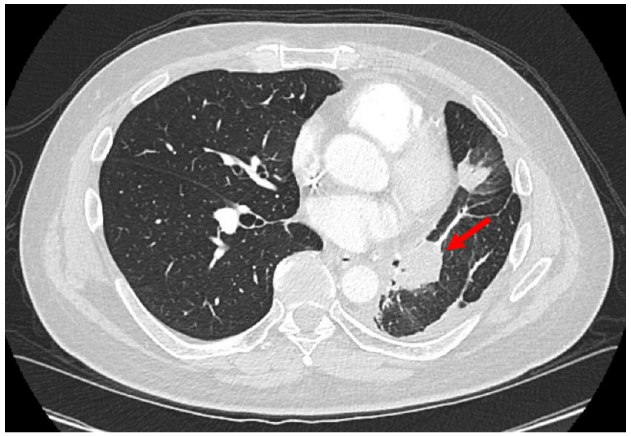
10 week PET

54-year-old male with *CD74-NRG1* NSCLC

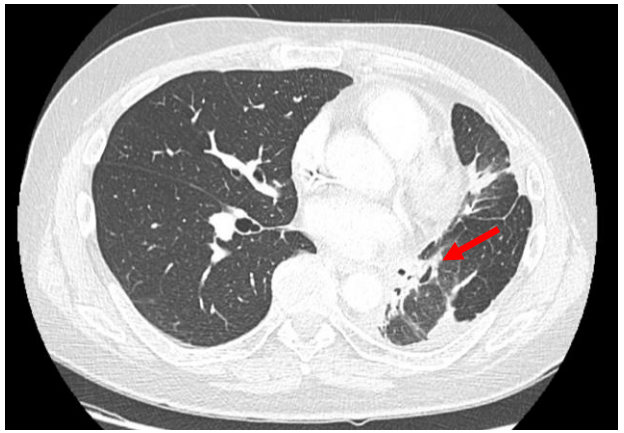


4.5+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 1





Baseline



Week 16

MCLA-128: well tolerated safety profile

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AEs at RP2D (N=117)

	AEs irrespective (>7.5% patients)		AEs related (>2% + >G3)	
	All grades	G3*	All grades	G3*
≥1 adverse event	109 (93.2)	43 (36.8)	67 (57.3)	5 (4.3)
Diarrhea	35 (29.9)	1 (0.9)	22 (18.8)	0
Asthenia	27 (23.1)	3 (2.6)	10 (8.5)	1 (0.9)
Anemia	22 (18.8)	4 (3.4)	1 (0.9)	0
Nausea	20 (17.1)	0	10 (8.5)	0
Fatigue	18 (15.4)	2 (1.7)	8 (6.8)	0
Vomiting	17 (14.5)	0	3 (2.6)	0
Decreased appetite	15 (12.8)	1 (0.9)	6 (5.1)	0
Dyspnea	15 (12.8)	7 (6.0)	2 (1.7)	1 (0.9)
Hypomagnesaemia	14 (12.0)	1 (0.9)	0	0
Constipation	12 (10.3)	0	1 (0.9)	0
Cough	12 (10.3)	1 (0.9)	2 (1.7)	1 (0.9)
Abdominal pain	11 (9.4)	0	2 (1.7)	0
ALT increased	10 (8.5)	4 (3.4)	0	0
AST increased	10 (8.5)	4 (3.4)	0	0
Abdominal pain upper	9 (7.7)	0	0	0
IRR	9 (7.7)	2 (1.7)	9 (7.7)	2 (1.7)
Pyrexia	6 (5.1)	0	3 (2.6)	0
Myalgia	5 (4.3)	1 (0.9)	3 (2.6)	1 (0.9)
Mucosal inflammation	5 (4.3)	0	4 (3.4)	0
Chills	4 (3.4)	0	4 (3.4)	0
Hypersensitivity**	4 (3.4)	0	4 (3.4)	0
Stomatitis	3 (2.6)	0	3 (2.6)	0

- 117 patients treated with single-agent MCLA-128 at the RP2Ds in the ongoing phase 2 study (750 mg q3w; 800+400 mg weekly)
- Most suspected related AEs were grade 1-2, with grade 3 in <5% of patients and no grade 4 related events
- No severe related gastrointestinal or skin toxicity, nor clinically significant LVEF decreases or cardiac AEs

Data cut off: 12-Jan-2019.
* 3 patients (2.6%) each had 1 grade 4 unrelated AE; no patients had grade 4 related AEs.
**A 71-year-old patient had a grade 5 hypersensitivity reaction followed by cardiorespiratory arrest (*Alsina et al. ESMO. 2018 #664P*). The patient's baseline cardiac condition (severe aortic stenosis) contributed to the fatal outcome.

Conclusions

- ✓ MCLA-128 potently inhibits NRG1 fusion-positive tumors *in vitro* and *in vivo*
- ✓ We provide a clinical proof-of-concept of MCLA-128 in *NRG1* fusion-positive pancreatic and lung cancers
- ✓ Very well tolerated safety profile, with a notable lack of cardiotoxicity and severe gastrointestinal or skin toxicity

Open-label worldwide phase 2 study with single-agent MCLA-128 in *NRG1* fusion-positive cancers