2021 ASCO ANNUAL MEETING

Efficacy and safety of zenocutuzumab in advanced pancreatic cancer and other solid tumors harboring NRG1 fusions

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04 June 2021

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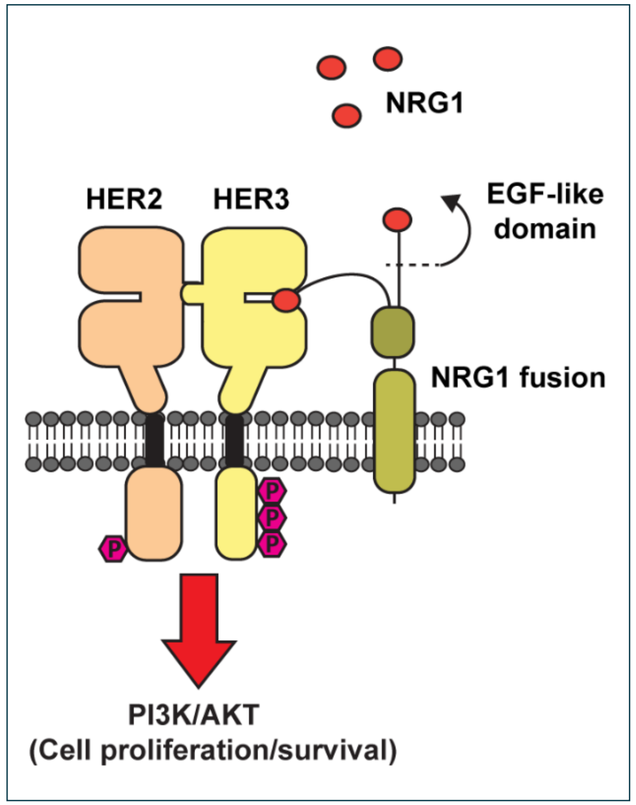
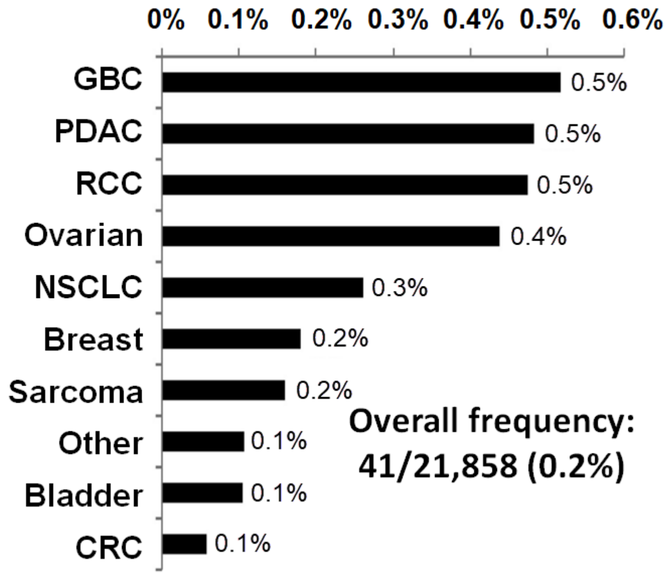
Relationships to Disclose (Research Support to Institution):

AstraZeneca, ArQule, BeiGene, Black Diamond Therapeutics, Kura, Lilly, Merus, Northern Biologics, Pfizer, Relay, Surface Oncology

NRG1 Fusions are Clinically Actionable Targets

- ***Neuregulin 1*** (**NRG1**) is a ligand that binds to HER3, promoting HER2/HER3 heterodimerization and activation of PI3K/AKT/mTOR signaling
- Chromosomal rearrangements involving NRG1 are rare oncogenic drivers in solid tumors, enriched in *KRASwt* PDAC and lung IMA
- Numerous NRG1 fusion partners identified (e.g., CD74, ATP1B1, SDC4)
- NRG1 fusion positive (NRG1+) *in vitro* and *in vivo* models are sensitive to HER2/HER3 directed therapy

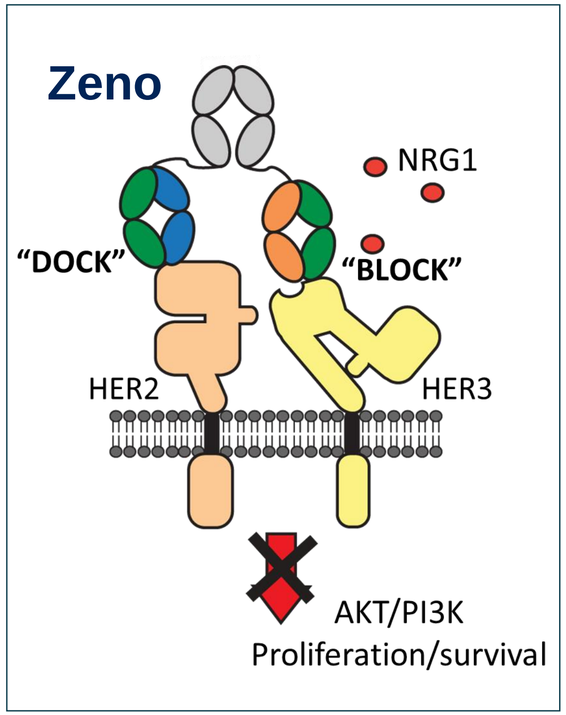




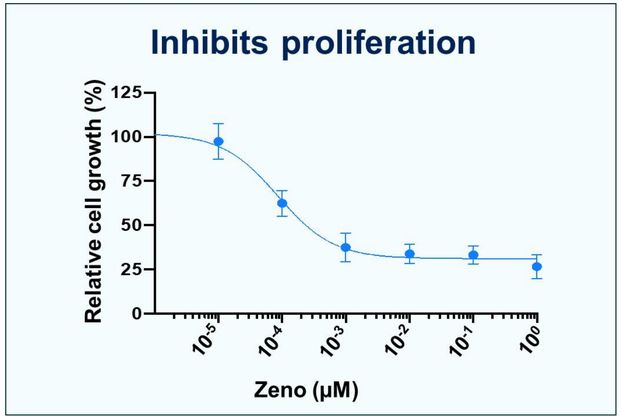
Fernandez-Cuesta et al. Cancer Discov. 2014;4:415-22; Schram et al. J Clin Oncol. 2019;37:3129
Jonna et al. J Clin Oncol. 2020;38:3113; Jonna et al. Clin Cancer Res. 2019;25:4966–7

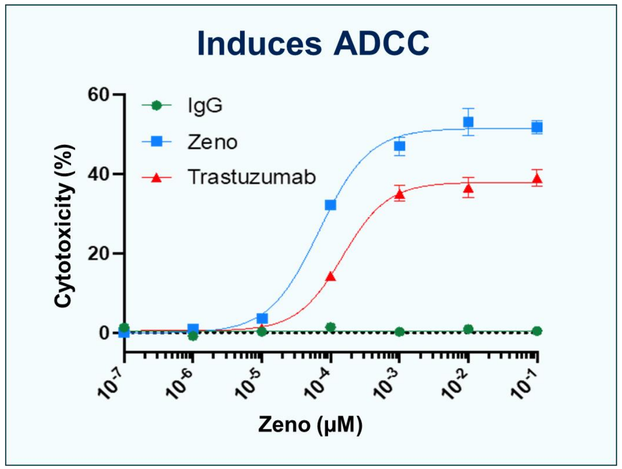
Zenocutuzumab

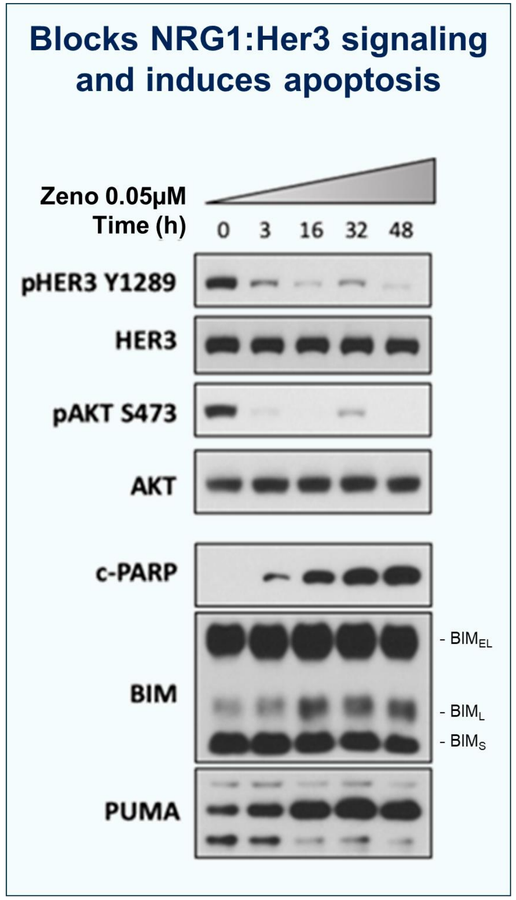
A Novel Therapeutic Paradigm for NRG1+ Cancers



- Common light chain bispecific Biclonics® antibody with enhanced ADCC activity
- Docks on HER2 and blocks NRG1 interaction with HER3
- Potent inhibition of cell growth and molecular signaling (pHER3, PI3K) at 0.01 µM
- Orphan drug and fast-track designations were granted







MDA-MB-175-VII (*DOC4-NRG1* fusion)

Geuijen et al. Cancer Cell. 2018;33:922-36
Odintsov et al. AACR. 2021; abstract 956

Zeno NRG1+ Development Program

Phase 1/2 global, open-label clinical trial (eNRGy)
+
Early Access Program (EAP)

- PDAC
- NSCLC
- Other solid tumors

Inclusion criteria

- Locally advanced, unresectable or metastatic solid tumor
- *NRG1* gene fusion
- Previously treated with or unable to receive standard therapy
- ≥ 18 years-old
- ECOG PS ≤ 2

- Zenocutuzumab 750 mg IV Q2W until PD
- Tumor assessment Q8W

Survival follow-up (up to 1 year)

Endpoints and Population

- **Primary endpoint**: Overall response rate (ORR) using RECIST v1.1 per investigator
- **Secondary endpoints**: Duration of response, ORR per central review, safety
- **Primary analysis population:** opportunity for ≥1 post-baseline tumor assessment at the cutoff

Enrollment and Analysis

- **Data cutoff date**: 13-Apr-2021
- **Enrollment:** n = 61
- **Primary analysis population:** n = 47

  Excluded:
  - *10 patients recently enrolled (first dose < 8 weeks from data cutoff date)*
  - *2 patients without baseline scan within 5 weeks of first dose*
  - *1 patient with ECOG 3 received 2 doses on non-standard treatment interval*
  - *1 patient with concomitant KRAS mutation (excluded per SAP)*

Demographics & Disease Characteristics

	PDAC (N=12)	NSCLC (N=25)	Basket (N=10)	Total (N=47)
Age, median (range)	47.5 (22 - 72)	58 (32 - 84)	63 (31 - 81)	56 (22 - 84)
Male / female, %	42 / 58	40 / 60	40 / 60	40 / 60
ECOG 0 / 1, %	58 / 42	40 / 60	50 / 50	47 / 53
Primary tumor, N (%)				
PDAC	12 (100)	0	0	12 (26)
NSCLC	0	25 (100)	0	25 (53)
Breast cancer	0	0	3 (30)	3 (6)
Unknown primary	0	0	2 (20)	2 (4)
Other*	0	0	5 (50)	5 (11)
Histology, N (%)				
Adenocarcinoma	12 (100)	21 (84)	8 (80)	41 (87)
Invasive mucinous adenocarcinoma	0	3 (12)	0	3 (6)
Other**	0	1 (4)	2 (20)	3 (6)

* Cholangiocarcinoma, colon, endometrial soft tissue sarcoma, pancreatic neuroendocrine carcinoma, renal cell
**Mixed adeno-squamous carcinoma, endometrial soft tissue sarcoma, pancreatic neuroendocrine carcinoma

Prior Treatment & NRG1 Fusion Partners

	PDAC (N=12)	NSCLC (N=25)	Basket (N=10)	Total (N=47)
Metastatic disease, N (%)	12 (100)	24 (96)*	10 (100)	46 (98)
N organs involved, median (range)	3 (1 - 8)	2 (0 - 7)	3 (1 - 5)	3 (0 - 8)
N lines prior systemic therapy, median (range)	2.5 (1 - 4)	2 (0 - 6)	3 (1 - 6)	2 (0 - 6)
Prior afatinib, N (%)	1 (8)	7 (28)	0	8 (17)
NRG1 testing technology, N (%)				
DNAseq	0	6 (24)	2 (20)	8 (17)
RNAseq	12 (100)	19 (76)	8 (80)	39 (83)
NRG1 fusion partners, N (%)				
ATP1B1	8 (67)	1 (4)	0	9 (19)
CD74	0	12 (48)	0	12 (26)
SLC3A2	0	7 (28)	1 (10)	8 (17)
Other**	4 (33)	5 (20)	9 (90)	18 (38)

*1 patient with locally advanced unresectable disease

**13 distinct fusion partners

Disposition & Duration of Exposure

	PDAC (N=12)	NSCLC (N=25)	Basket (N=10)	Total (N=47)
Treatment ongoing, N (%)	7 (58)	6 (24)	6 (60)	19 (40)
Reason for discontinuation, N (%)				
Disease progression	4 (33)	17 (68)	4 (40)	25 (53)
Other*	1 (8)	2 (8)	0 (0)	3 (6)
Duration of exposure, months				
Median (range)	5.7 (1 - 19)	4.6 (1 - 12)	5.0 (2 - 10)	5.5 (1 - 19)

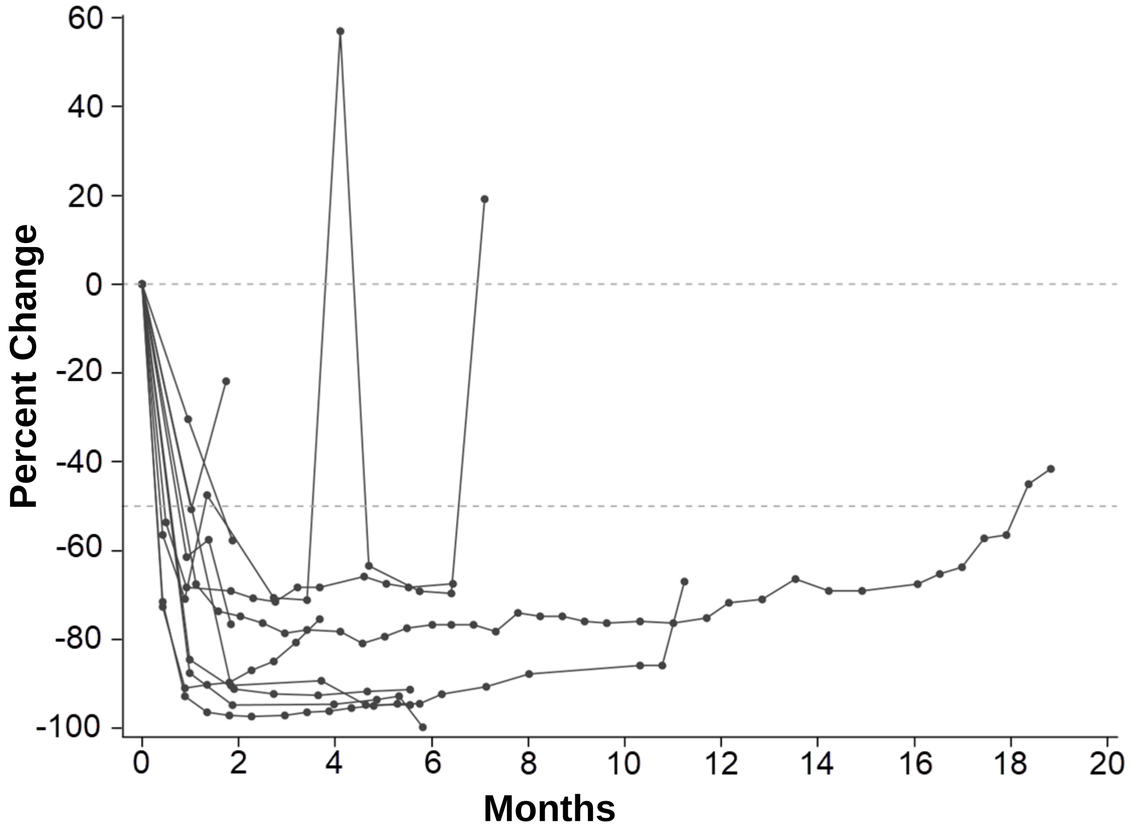
* Investigator decision (2 patients), unrelated AE (1 patient)

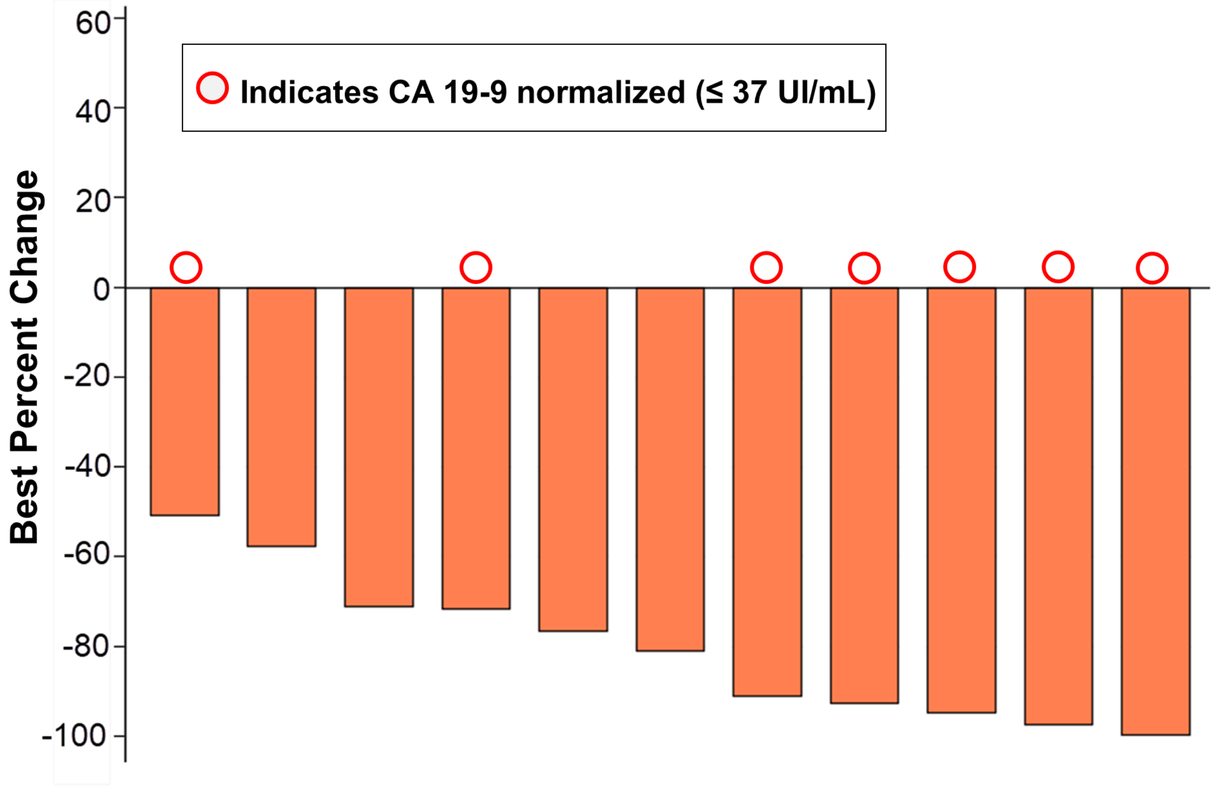
Efficacy in NRG1+ PDAC

Best Percent Change in Target Lesions from Baseline

Percent Change in CA 19-9 from Baseline

Patients with NRG1+ PDAC

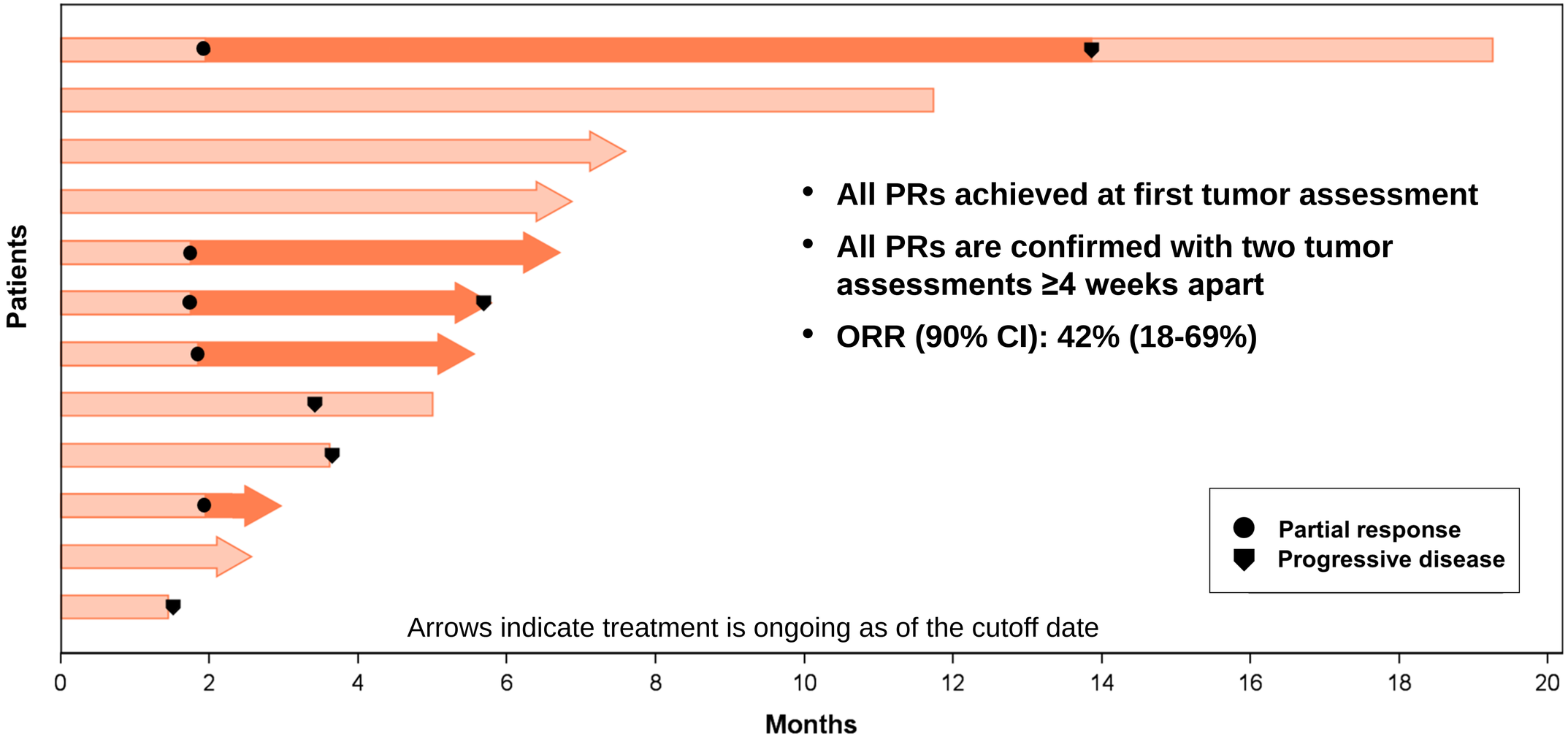




11/11 (100%) patients with CA 19-9 measurements had >50% decline

Time to Response & Duration of Exposure

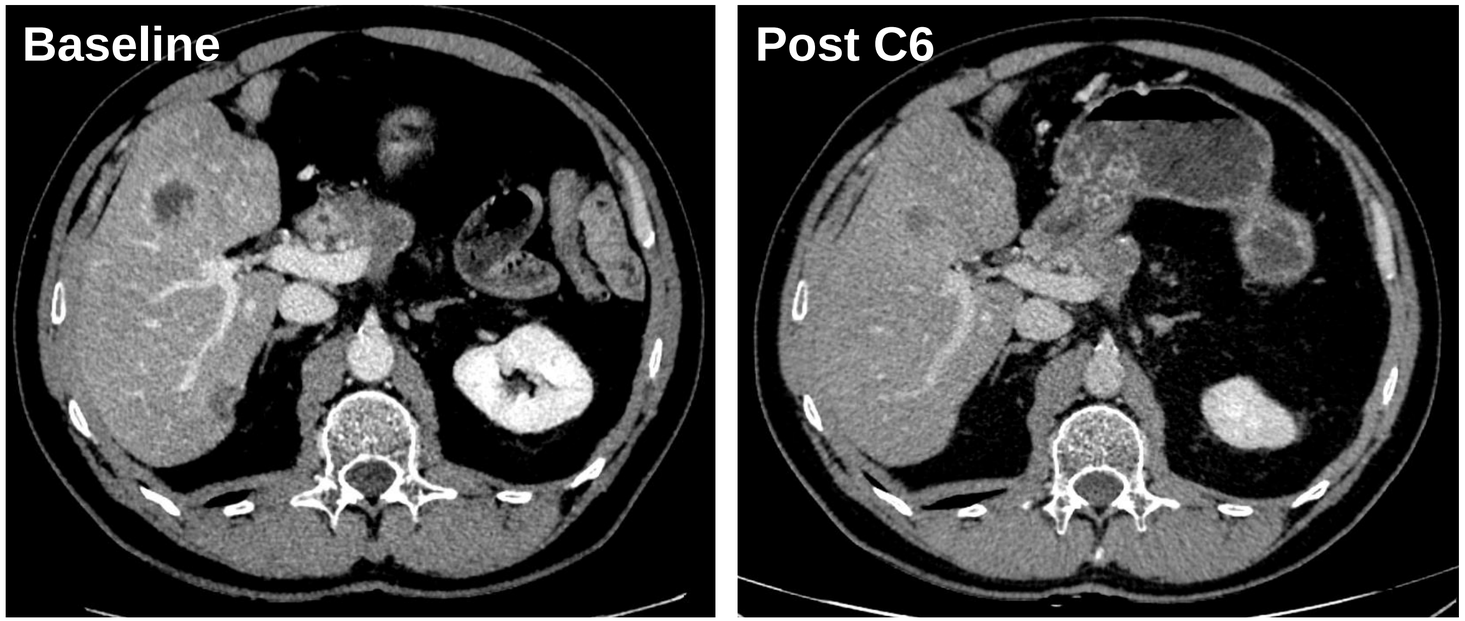
Patients with NRG1+ PDAC

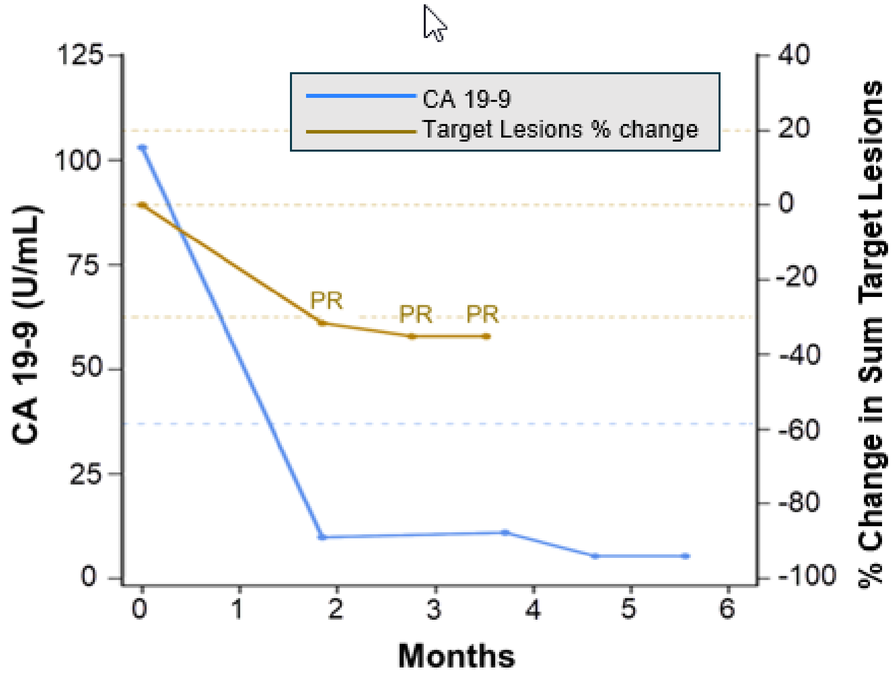


Clinical Response in NRG1+ PDAC (ATP1B1-NRG1)

59-Year-Old Male Patient

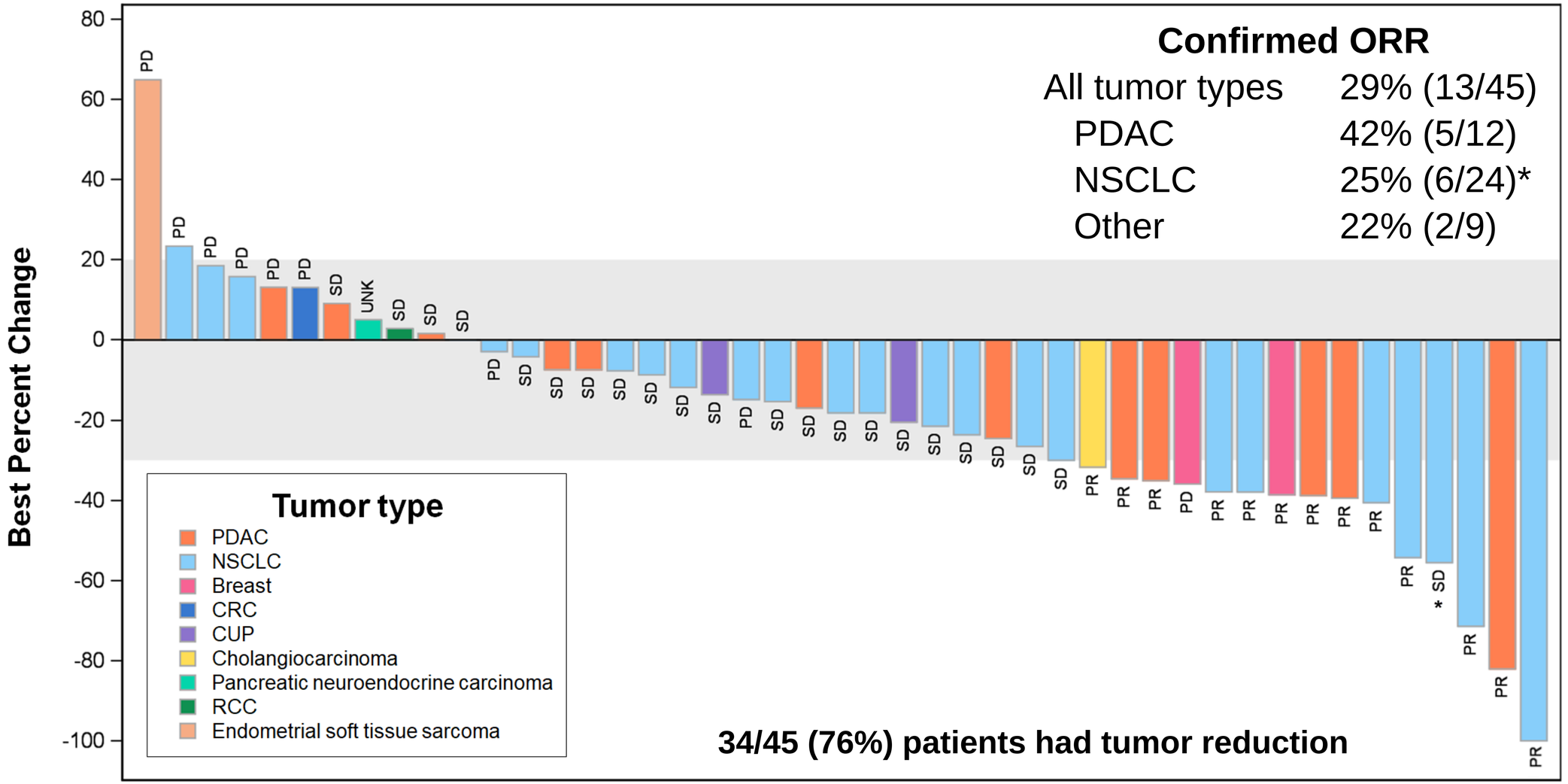
Metastases:	Liver
Prior lines:	(1) FOLFIRINOX; (2) nab-pac/gemcitabine
Zeno treatment:	7 cycles (ongoing)
CA 19-9:	Drop from 103 to 5.4 U/mL (95% reduction)
RECIST 1.1:	Partial response (35% reduction)





Efficacy Across Multiple NRG1+ Tumor Types

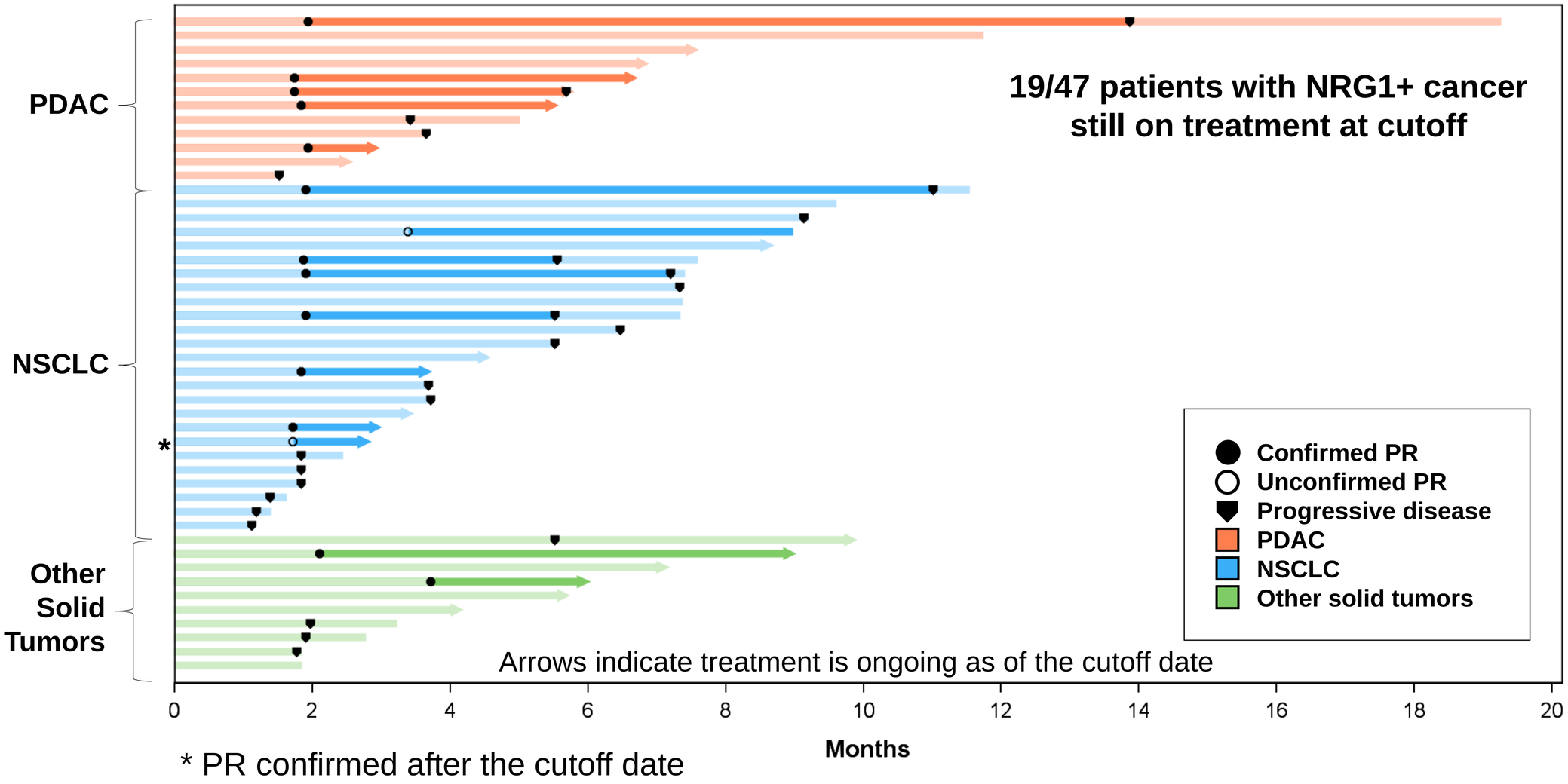
Best Percent Change in Target Lesions from Baseline



*** One additional PR confirmed after the cutoff date; NSCLC ORR 29% (7/24)**

Time to Response & Duration of Exposure

All Patients with NRG1+ Cancer

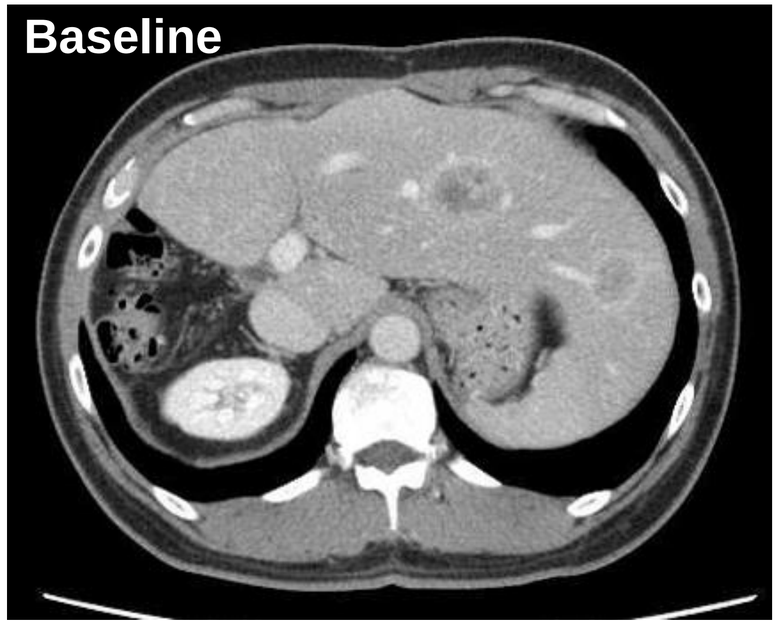


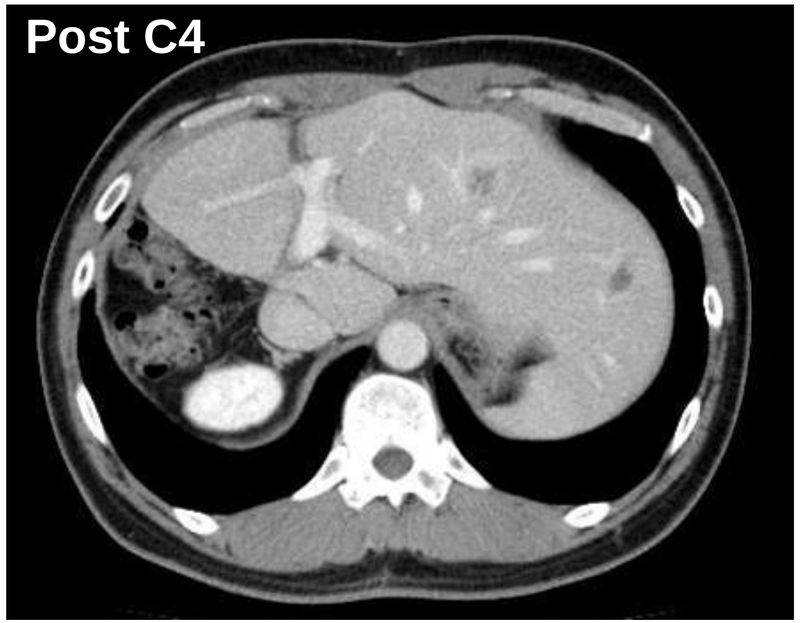
* PR confirmed after the cutoff date

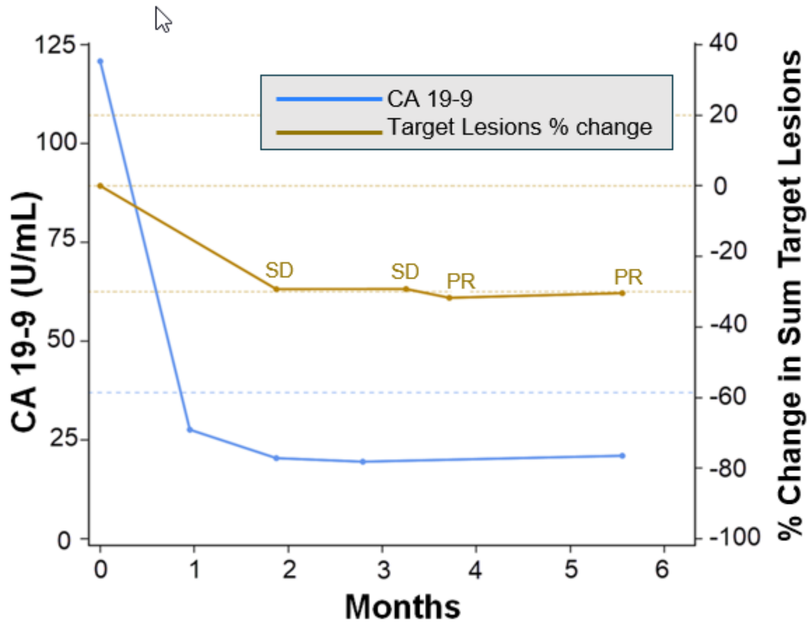
Clinical Response in NRG1+ Cholangiocarcinoma (SDC4-NRG1)

48-Year-Old Male Patient

Metastases:	Liver, lymph nodes, lung
Prior lines:	(1) gemcitabine/cisplatin; (2) S-1
Zeno treatment:	7 cycles (ongoing)
CA 19-9:	Drop from 121 to 20 U/mL (84% reduction)
RECIST 1.1:	Partial response (32% reduction)



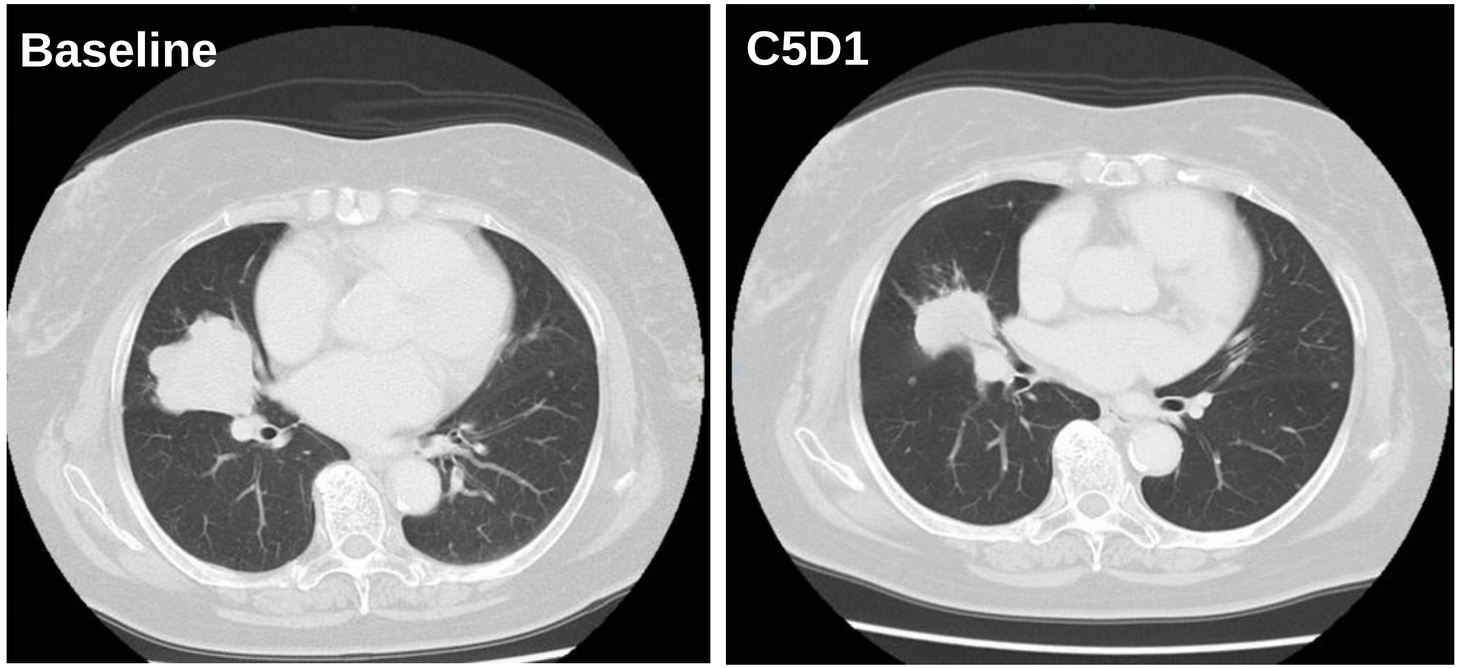




Clinical Response in NRG1+ NSCLC (SLC3A2-NRG1)

84-Year-Old Female Patient

Metastases:	Lung, lymph nodes
Prior lines:	First-line
Zeno treatment:	5 cycles (ongoing)
RECIST 1.1:	Partial response (38% reduction)



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Zenocutuzumab is Well Tolerated

PREFERRED TERM	AEs Irrespective of Causality >10%			Treatment-related AEs >10% and all ≥ Grade 3		
	ALL GRADES	GRADE 3-4	GRADE 5	ALL GRADES	GRADE 3-4*	GRADE 5
Patients with ≥1 AE	**94%**	**34%**	**4%**	**59%**	**3%**	**<1%**
Asthenia/fatigue	35%	4%	-	13%	<1%	-
Diarrhea	30%	1%	-	20%	-	-
Anemia	20%	4%	-	<1%	-	-
Nausea	18%	-	-	10%	-	-
Dyspnea	13%	5%	-	1%	<1%	-
Vomiting	13%	<1%	-	3%	-	-
Abdominal pain	11%	<1%	-	2%	-	-
Decreased appetite	11%	<1%	-	4%	-	-
Constipation	10%	-	-	1%	-	-
Hypomagnesaemia	10%	<1%	-	<1%	-	-
Infusion-related reaction	7%	1%	-	7%	1%	-
Myalgia	4%	<1%	-	3%	<1%	-
Hypersensitivity**	3%	-	-	3%	-	<1%
Cough	8%	<1%	-	1%	<1%	-
Hypertension	<1%	<1%	-	<1%	<1%	-
Hypoxia	<1%	<1%	-	<1%	<1%	-
Neutropenia	<1%	<1%	-	<1%	<1%	-

* No Grade 4 treatment-related AEs reported
** One event of Grade 5 hypersensitivity (previously reported)
Data cutoff date 12-Jan-2021

- Safety profile of 157 patients across multiple indications treated with Zenocutuzumab at RP2D in the single agent program
  - The majority of AE were grade 1-2
  - Absence of severe gastrointestinal toxicity, skin toxicities and clinical cardiotoxicity

Conclusions

- Zenocutuzumab is highly effective in pretreated NRG1+ PDAC with rapid and durable responses
- Activity across multiple NRG1+ cancer types and fusion partners
- Extremely well tolerated safety profile
- First prospective clinical validation of NRG1 fusions as actionable oncogenic drivers
- First demonstration of effective targeting of mutant ligand
- Zenocutuzumab is the first genome-directed therapy studied in NRG1+ cancer, offering a potential new standard of care

Acknowledgements

- Patients and families, particularly in the context of COVID-19 challenges
- Investigators and their teams
- Clinical and translational teams

  Kees-Jan Koeman, Anastasia Murat, Bryan Dumont, Marina Magin, Ron Schackmann
- MyTomorrows
- CROs and collaborators

  Covance Inc., Caris Life Sciences, Foundation Medicine Inc., Tempus Labs Inc., Sema4

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South Korea	Seoul	Seoul National University Hospital	D-W. Kim / DY. Oh
Taiwan	Taipei	National Taiwan Cancer Centre	J. Chih-Hsin Yang