2022 ASCO® ANNUAL MEETING

Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced *NRG1* fusion-positive (NRG1+) cancer

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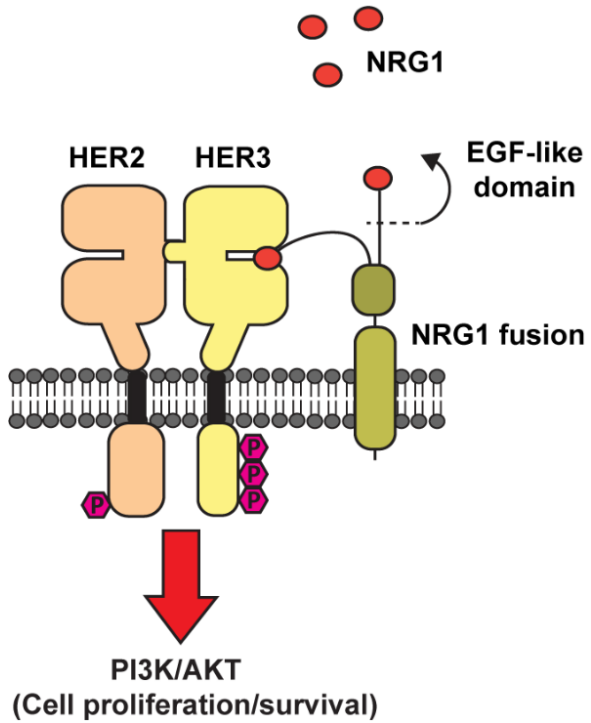
Background

NRG1 Fusions are Clinically Actionable Targets

- Neuregulin 1 (NRG1) is a ligand that binds to HER3, promotes HER2/HER3 dimerization and PI3K/AKT/mTOR signaling, and causes malignant transformation[1,2]
- Chromosomal rearrangements involving *NRG1* are rare oncogenic drivers in a broad range of solid tumors (NRG1+ cancer), including pancreatic and lung cancers[3,4]
- *NRG1* fusions are reported to be associated with poor prognosis, lower response rates to standard therapy, and shorter overall survival in lung cancer[5,6]
- NRG1+ cancer models across histologies are sensitive to HER2/HER3 directed therapy with zenocutuzumab (Zeno) *in vitro* and *in vivo*[7]

NRG1 Fusion Signaling



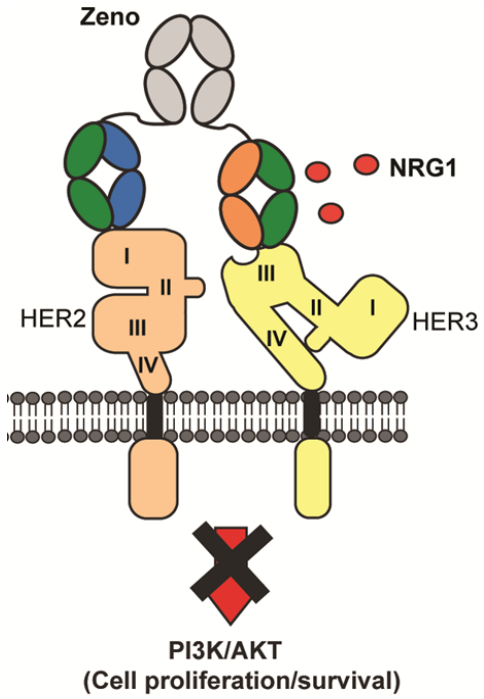
1. Fernandez-Cuesta et al. Cancer Discov, 2014; 2. Werr et al. Mol Cancer Ther, 2022; 3. Schram et al. J Clin Oncol, 2019; 4. Jonna et al. J Clin Oncol, 2020; 5. Drilon et al. J Clin Oncol, 2021; 6. Chang et al. Clin Cancer Res, 2021; 7. Schram et al. Cancer Discov, 2022

Background

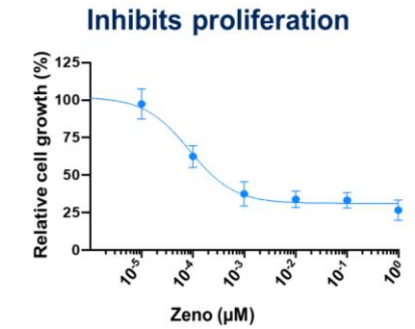
Zenocutuzumab is a Novel Therapeutic for NRG1+ Cancer

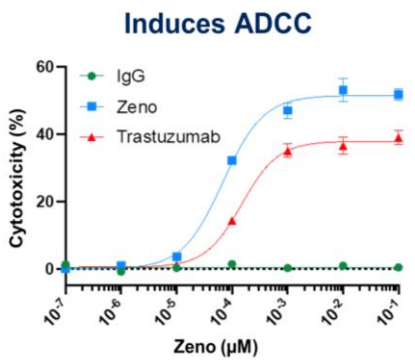
- Common light chain bispecific Biclonics® antibody with enhanced ADCC activity[1]
- Docks on HER2 and blocks NRG1 interaction with HER3, preventing HER2/HER3 heterodimerization[1]
- Potent inhibition of cell growth and molecular signaling (pHER3, pAKT) at ≤ 0.01 μM[2]
- Granted FDA Fast-Track designation for NRG1+ cancer and Orphan designation for pancreatic cancer

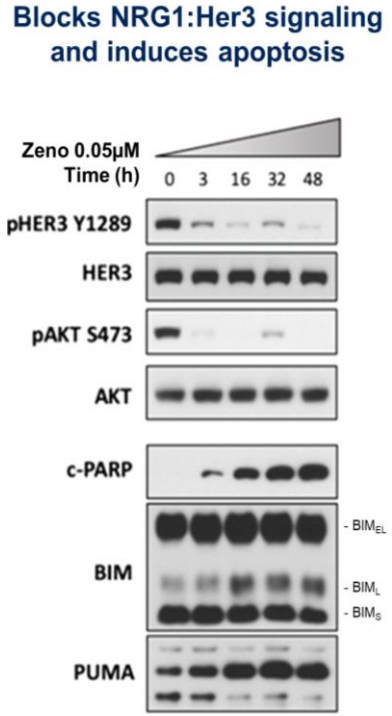
Mechanism of Action



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







1. Geuijen et al. Cancer Cell, 2018; 2. Schram et al. Cancer Discov, 2022

Schema

Global, Multicenter Zenocutuzumab 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+ cancer
- Previously treated with or unable to receive standard therapy
- ≥ 18 years-old
- ECOG PS ≤ 2

Treatment Plan

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

Follow-up

Survival follow-up: up to 2 years

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, pharmacokinetics, antidrug antibodies

Primary analysis population
≥ 1 dose of Zeno, opportunity for ≥ 6 months follow-up at cutoff, and met criteria for primary efficacy population

Enrollment and Analysis

Data cutoff date
12-Apr-2022

Enrollment
110 patients
64 sites
17 countries

Primary analysis population
83 patients

27 patients excluded[1]:

- 21 patients < 6 months follow-up[2]
- 2 patients baseline scan > 5 weeks before first dose
- 2 patients with other genetic drivers (*KRAS*)
- 2 patients with prior anti-HER3 inhibitor[2]
- 1 patient with ECOG PS 3

1. Per protocol/SAP
2. One patient had 2 reasons for exclusion

Patient Population

Demographics and Disease Features of NRG1+ Cancer

All Patients (N=83)	
Enrolled in eNRGy trial / EAP, n (%)	72 (87) / 11 (13)
Age in years, median (range)	59 (22 - 84)
Male / female, n (%)	34 (41) / 49 (59)
ECOG PS 0 / 1 / 2, n (%)	35 (42) / 47 (57) / 1 (1)
Race, n (%)[1]	
White	47 (57)
Asian	27 (33)
Other	3 (4)

1. Data not reported for 6 patients

All Patients (N=83)	
Metastatic disease, n (%)	82 (99)
Measurable disease, n (%)	79 (95)
Primary tumor, n (%)	
NSCLC[2]	47 (57)
PDAC	19 (23)
Breast cancer	7 (8)
Cholangiocarcinoma	3 (4)
CRC	3 (4)
Other[3]	4 (5)

2. Adenocarcinoma (N=42), IMA (N=4), mixed adeno-squamous carcinoma (N=1)

3. Endometrial soft tissue sarcoma, pancreatic neuroendocrine carcinoma, renal cell carcinoma, unknown primary

Patient Population and Disposition

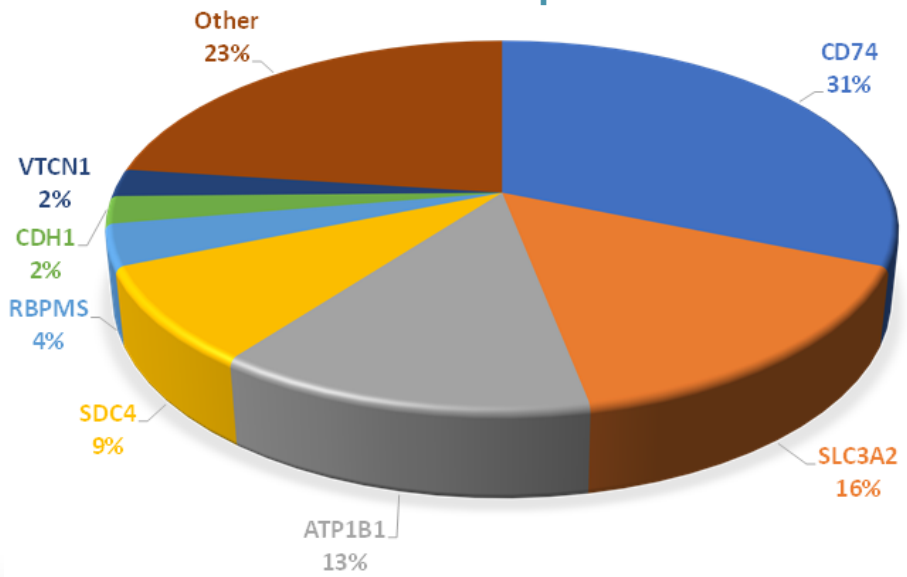
Prior Therapy, Diagnostics, and Molecular Features of NRG1+ Cancer

All Patients (N=83)	
Prior systemic therapy	
N lines, median (range)[1]	2 (0 - 8)
Prior afatinib, n (%)	9 (11)
Patient disposition	
Treatment ongoing, n (%)	20 (24)
Reason for discontinuation, n (%)	
Disease progression[2]	61 (73)
Other[3]	2 (2)
Duration of exposure, months	
Median (range)	6.3 (1 - 21)

1. 11 patients were treatment-naïve in the metastatic setting
2. Includes radiological and clinical progression
3. Unrelated AE of dyspnea due to underlying progression, pregnancy

All Patients (N=83)	
***NRG1* identification technology, n (%)**	
RNAseq	64 (77)
DNAseq	18 (22)
Nanostring	1 (1)

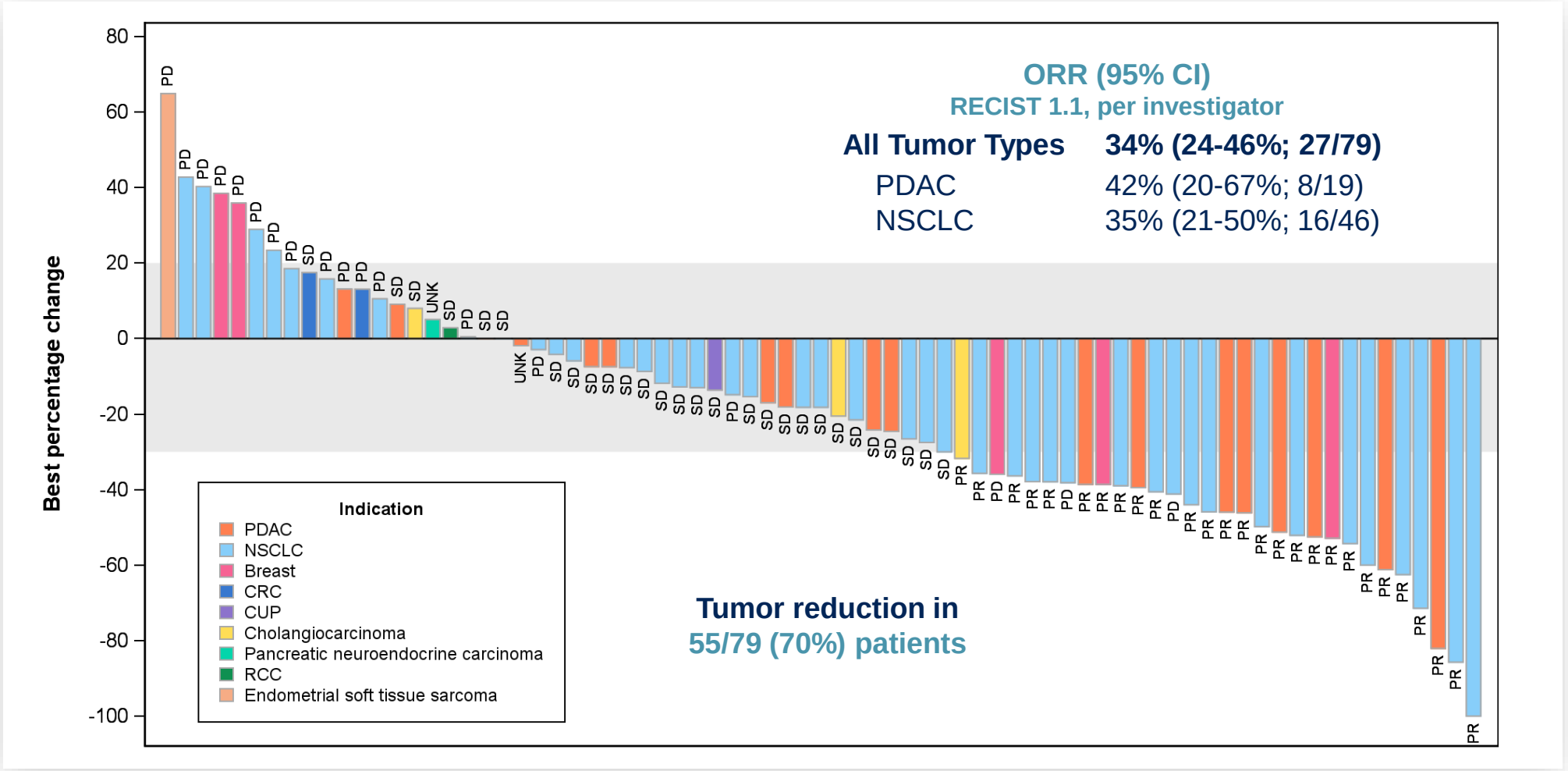
***NRG1* fusion partners**



"Other" includes 19 fusion partners with a single patient each

Zenocutuzumab Activity in NRG1+ Cancer

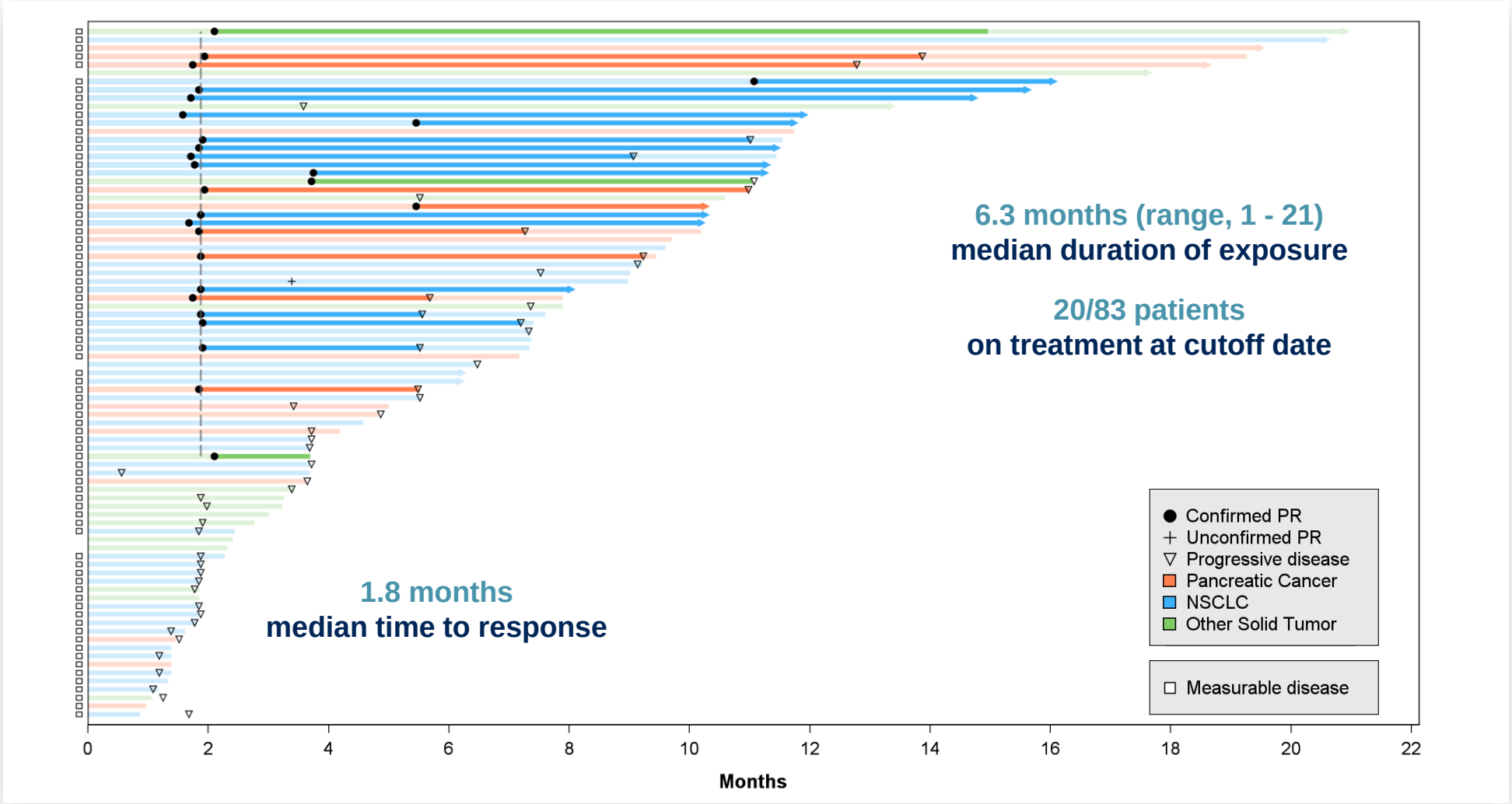
Best Percent Change in Target Lesions from Baseline



Note: 4 patients are not included in the waterfall plot, 3 due to absence of post-baseline assessment (early progression) and 1 had incomplete assessment of target lesions at first post-baseline assessment

Zenocutuzumab Activity in NRG1+ Cancer

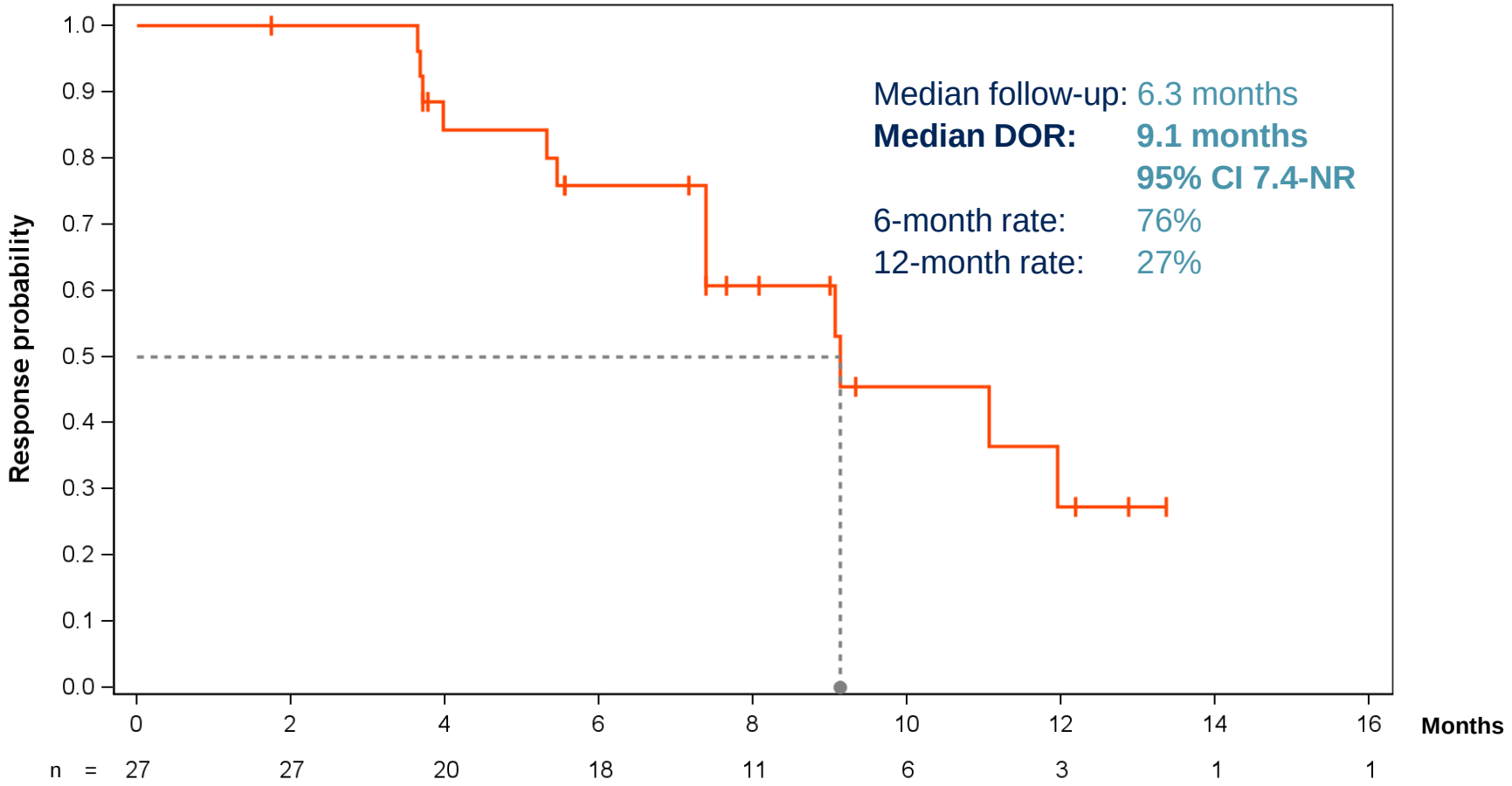
Time to Response and Time on Therapy



Arrows indicate treatment is ongoing at the cutoff date

Zenocutuzumab Activity in NRG1+ Cancer

Duration of Response



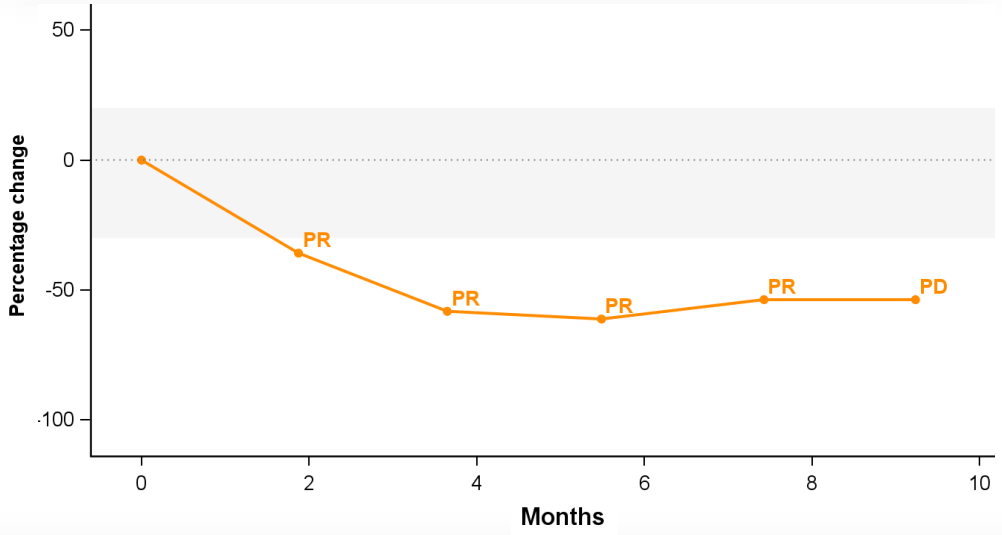
Note: 20/83 patients were on treatment at cutoff date

Zenocutuzumab Activity in NRG1+ Cancer

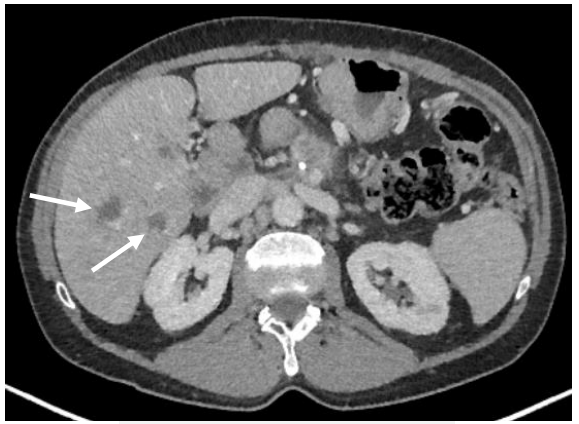
51-year-old man with an *ATP1B1-NRG1* pancreatic adenocarcinoma

Patient Data

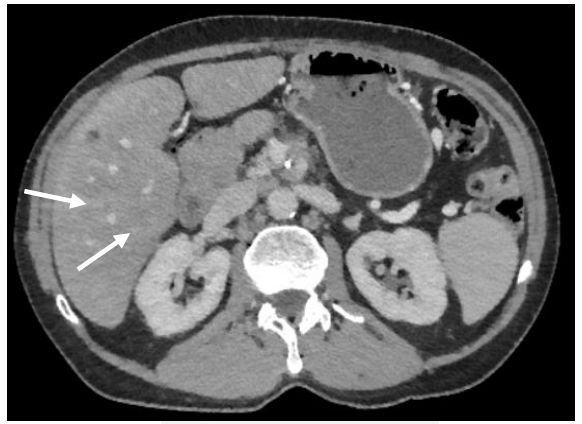
Metastases	Liver, lymph nodes
Prior Lines	Neoadjuvant FOLFIRINOX
Zeno Treatment	10 cycles
RECIST 1.1	Partial Response (61% reduction)



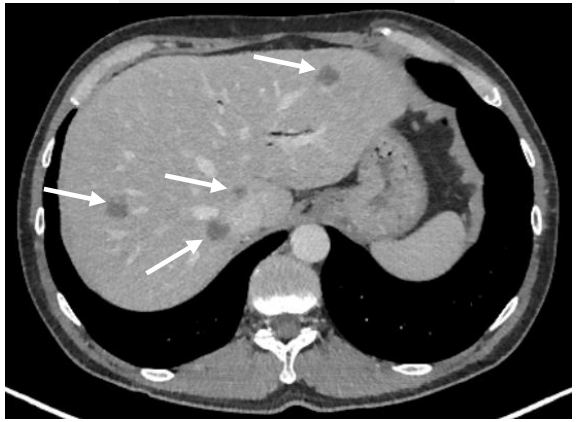
Clinical Results

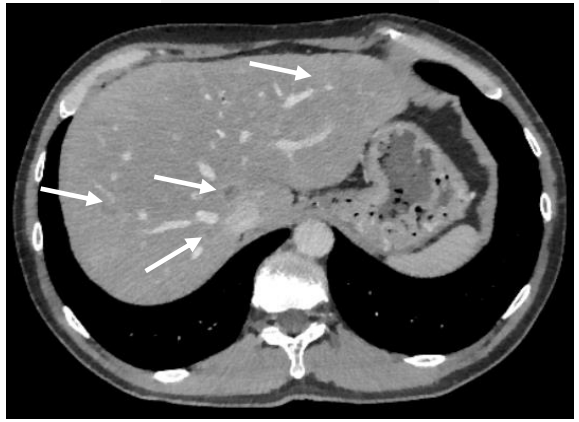


Baseline



Cycle 10





Zenocutuzumab Activity in NRG1+ Cancer

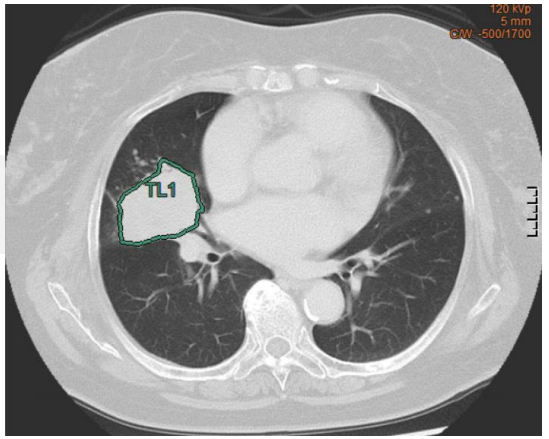
84-year-old woman with an *SLC3A2-NRG1* lung cancer

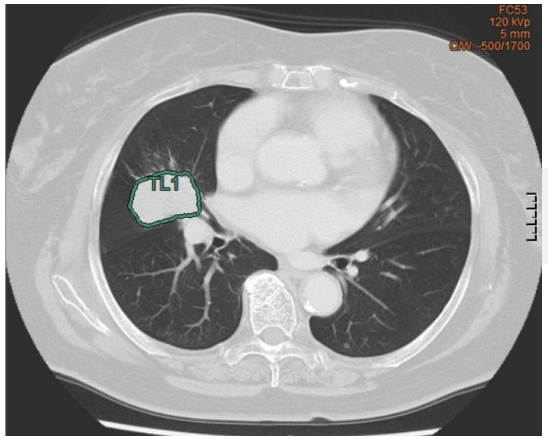
Patient Data

Metastases	Lung, lymph nodes
Prior Lines	First line
Zeno Treatment	17 cycles (ongoing)
RECIST 1.1	Partial Response (38% reduction)

Clinical Results - Update

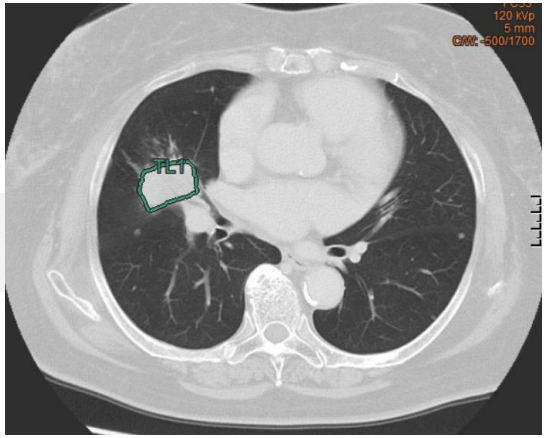
Baseline





Cycle 16

Cycle 4 (ASCO 2021)

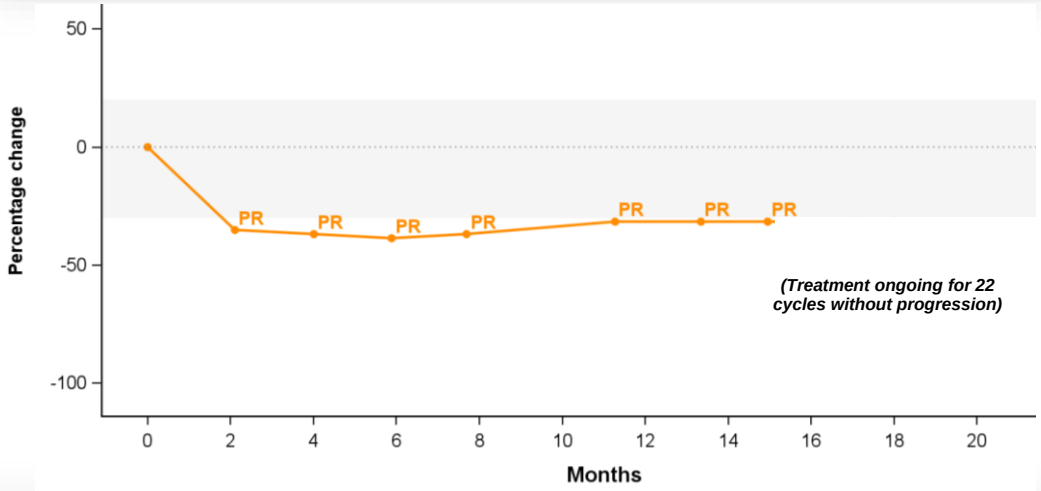


Zenocutuzumab Activity in NRG1+ Cancer

64-year-old woman with an *SLC3A2-NRG1* ER-positive breast cancer

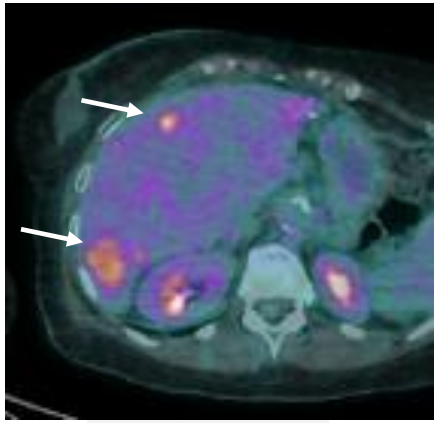
Patient Data

Metastases	Liver, bone
Prior Lines	1) Paclitaxel + bevacizumab / letrozole 2) Palbociclib + fulvestrant 3) Capecitabine
Zeno Treatment	22 cycles (ongoing)
RECIST 1.1	Partial Response[1] (39% reduction)
PERCIST	Complete Response

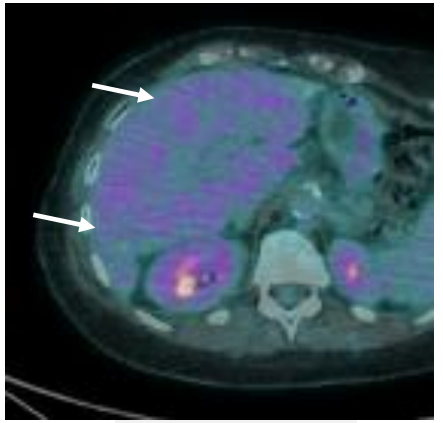


1. Modality assessment changed post cycle 16; subsequent measurements not considered

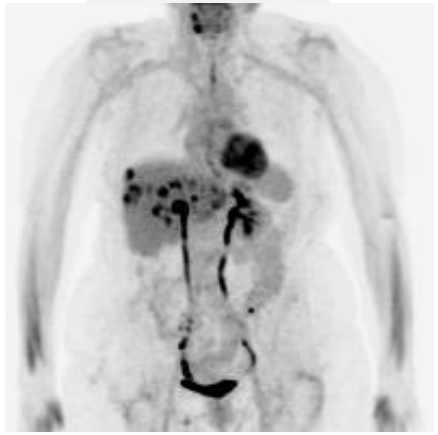
Clinical Results

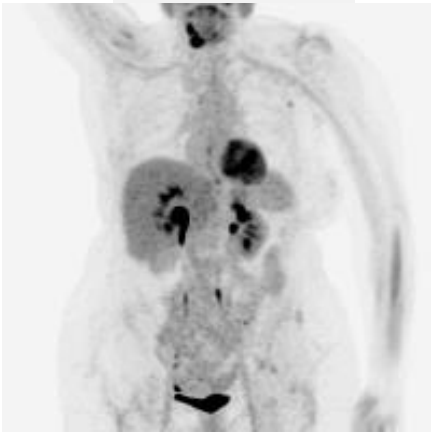


Baseline



Cycle 2





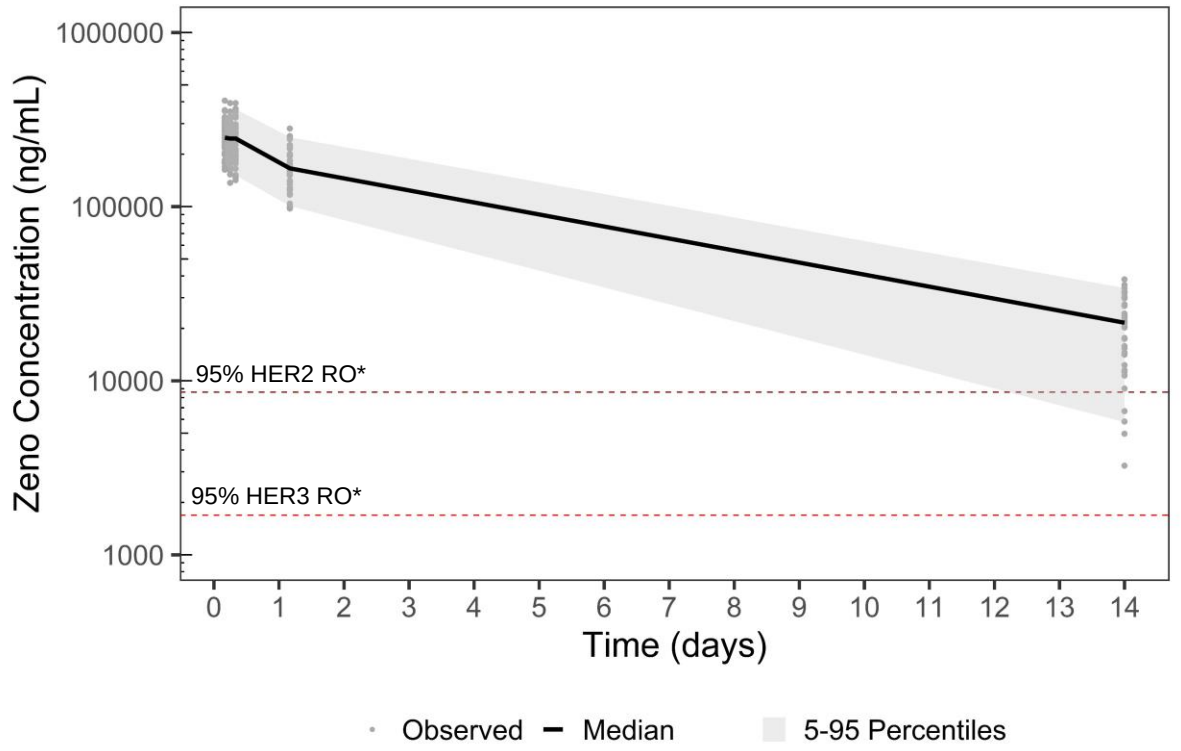
Pharmacokinetics and Immunogenicity

Zenocutuzumab achieved substantial receptor occupancy and was not immunogenic

- Mean terminal half-life is approx. 4 days
- >95% receptor occupancy (RO) for HER3 and HER2 predicted for the entire dosing interval in the majority of patients, after the first 750 mg Q2W dose
- No treatment-emergent positive anti-Zeno antibodies observed up to 12 weeks with 750 mg Q2W (based on available data from N=31)

Zeno Serum Concentration vs Time Profile

Patients treated with the first dose of 750 mg (N=45)



** RO based on average of KD values for binding affinities. Geuijen et al. Cancer Cell, 2018.*

Safety Profile

Zenocutuzumab is well tolerated

- Safety profile of 208 patients treated with Zeno at the RP2D[1] in the single agent program
- Low incidence of Grade ≥3 treatment-related AEs
- Low incidence of severe gastrointestinal and skin toxicity, and no clinical cardiotoxicity
- <1% of patients discontinued due to AEs

	AEs Irrespective of Causality (>10%)			Treatment-Related AEs (>10% and all Grade 3-5)		
	ALL GRADES	GRADE 3-4	GRADE 5	ALL GRADES	GRADE 3-4[2]	GRADE 5
Patients with ≥1 AE	**92%**	**36%**	**3%**	**61%**	**5%**	**0.5%**
Diarrhea	32%	2%	-	21%	0.5%	-
Asthenia/fatigue	30%	4%	-	12%	0.5%	-
Nausea	20%	1%	-	10%	0.5%	-
Anemia	19%	3%	-	1%	-	-
Infusion-related reaction[3,4]	15%	1%	0.5%	15%	1%	0.5%[3]
Dyspnea	14%	4%	-	2%	0.5%	-
Vomiting	13%	0.5%	-	4%	-	-
Abdominal pain	12%	1%	-	2%	0.5%	-
Constipation	11%	-	-	2%	-	-
Decreased appetite	10%	0.5%	-	4%	-	-
AST increase	9%	3%	-	2%	0.5%	-
Cough	8%	0.5%	-	1%	0.5%	-
ALT increase	7%	3%	-	1%	0.5%	-
Myalgia	4%	0.5%	-	2%	0.5%	-
Neutropenia	3%	1%	-	2%	0.5%	-
Hypertension	1%	1%	-	0.5%	0.5%	-
Platelet count decrease	1%	0.5%		0.5%	0.5%	-
Hyperuricemia	0.5%	0.5%	-	0.5%	0.5%	-
Lymphadenitis	0.5%	0.5%	-	0.5%	0.5%	-
Hypoxia	0.5%	0.5%	-	0.5%	0.5%	-
Bacteremia	0.5%	0.5%	-	0.5%	0.5%	-

Safety data cut off:12-Jan-2022
1. 101 patients with 750 mg Q3W; 26 patients with QW; 81 patients with 750 mg Q2W

2. No Grade 4 treatment-related AEs reported
3. One Grade 5 hypersensitivity (previously reported; Alsina et al. ASCO, 2017)
4. Composite term covering preferred terms considered by the investigator to be IRRs occurring within 24 hours of infusion start

Zenocutuzumab Conclusions

- **Durable responses in previously treated advanced NRG1+ cancer**
  - ORR 34% (95% CI: 24-46%; n=79)
  - Median DOR 9.1 months (95% CI: 7.4-NR)
  - Antitumor activity across multiple tumor types
- **Extremely well tolerated safety profile**
  - Most adverse events were low grade
  - Very low rate of discontinuations due to toxicity
- **Offers potential new standard of care for patients with NRG1+ cancer**
  - Currently no approved targeted therapy for NRG1+ cancer
  - Great unmet medical need

Acknowledgements

Thanks To

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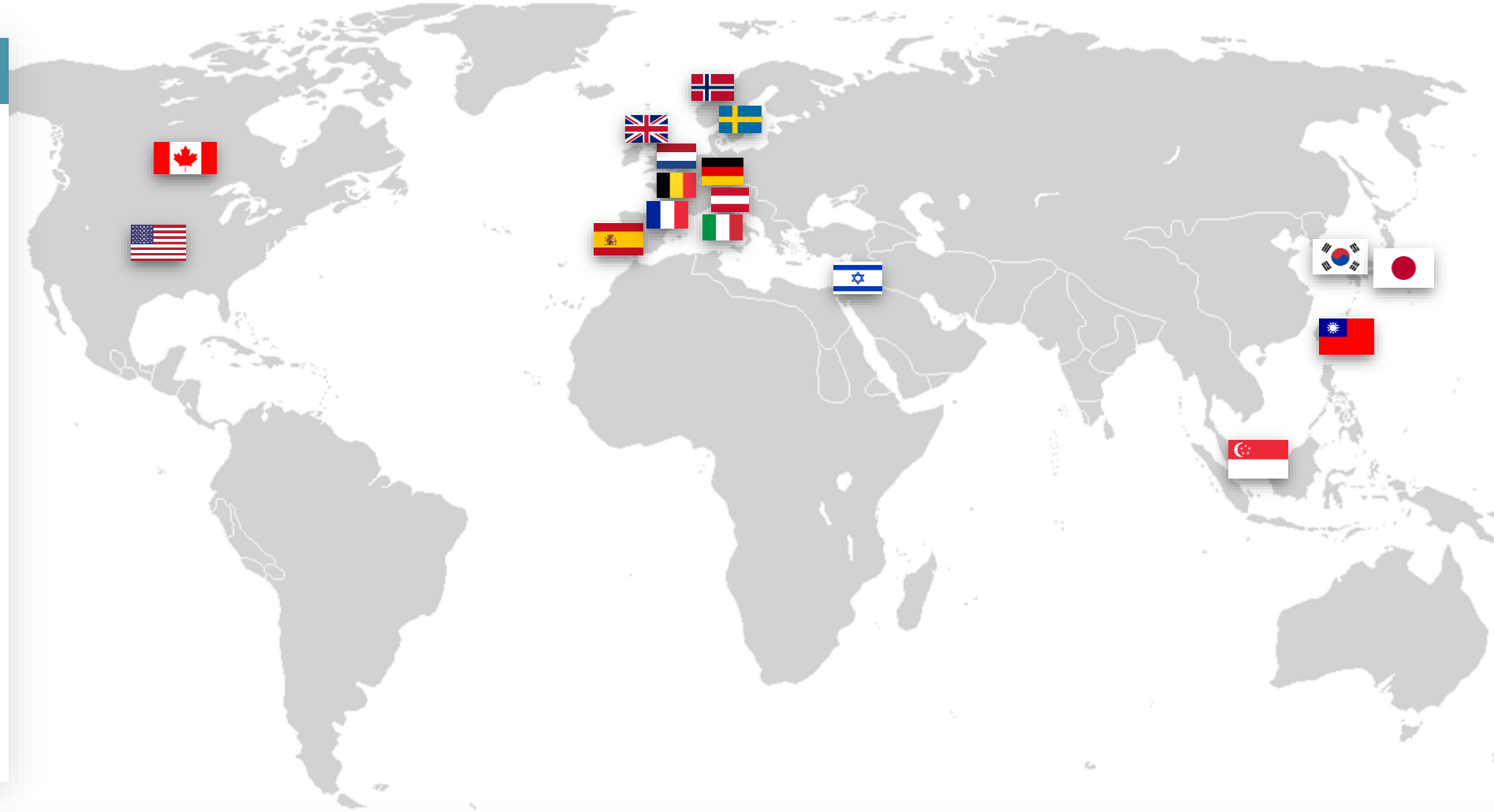
- CROs & diagnostic companies
  - *Labcorp Drug Development Inc*
  - *Caris Life Sciences*
  - *Foundation Medicine Inc.*
  - *Tempus Labs Inc.*
  - *Sema4*



Additional Acknowledgements

Europe & Israel

Country	PI	Institute
Austria	Greil	Salzburger Universitatsklinikum
Belgium	Van Cutsem	UZ Leuven
France	Martin-Romano/Hollebecque	Gustave Roussy
France	Duruisseaux	CHU de Lyon - Louis Pradel Hospital
France	Wislez	Hôpital Cochin
France	Neuzillet	Institut Curie
France	De La Fouchardiere	Centre Léon Bérard
Germany	Springfeld	Deutsches Krebsforschungszentrum
Germany	Arnold	Asklepios Klinik Altona
Germany	Wesseler	Asklepios Kliniken Hamburg GmbH
Germany	Hoffknecht	Niels-Stensen Kliniken, Osnabruck
Israel	Golan	The Chaim Sheba Medical Center
Israel	Peled	Shaare Zedek Medical Center
Italy	Siena	A.O. Niguarda Cà Granda Farmacia Ospedaliera
Italy	Reni	Ospedale San Raffaele
Italy	Cappuzzo	Istituti Fisioterapici Ospitalieri
Netherlands	Opdam	Netherlands Cancer Institute
Netherlands	Gort	Universitair Medisch Centrum Utrecht
Netherlands	Wilmink	VU University Medical Center
Netherlands	Verheul	Radboud UMC
Norway	Guren	Oslo universitetssykehus HF Radiumhospitalet
Spain	Moreno	Centro Integral Oncológico Clara Campal
Spain	Macarulla	Hospital Universitario Vall d'Hebron, Barcelona
Spain	Moreno Garcia	Hospital Universitario Fundacion Jimenez Diaz
Spain	Paz-Ares Rodriguez	Hospital Universitario 12 de Octubre
Spain	Roda Perez	Hospital Clinico Universitario de Valencia
Spain	Gil-Bazo	Clínica Universidad de Navarra
Spain	Guerrero	Hospital Quirónsalud Valencia
Sweden	Yachnin	Karolinska Universitetssjukhuset - Solna
UK	Arkenau	Sarah Cannon Research Institute

Asia Pacific

Country	PI	Institute
Japan	Goto	National Cancer Center Hospital (NCCH) East
Japan	Umemoto	St. Marianna University Hospital
Japan	Morizane	National Cancer Center Hospital (NCCH)
Japan	Nishino	Osaka International Cancer Institute
South Korea	Kim	Seoul National University Hospital
South Korea	Park	Samsung Medical Center
South Korea	Rha	Severance Hospital - Yonsei Cancer Center
Singapore	Lam	National Cancer Centre of Singapore Pte Ltd.
Taiwan	Yang	National Taiwan University Hospital

Americas

Country	PI	Institute
Canada	Moore	Princess Margaret Cancer Centre
US	Schram / Drilon	Memorial Sloan-Kettering Cancer Center
US	Rodon Ahnert	MD Anderson Cancer Center
US	Cleary	Dana-Farber Cancer Institute
US	Liu	Georgetown University Department of Medicine
US	Nagasaka	University of California Irvine Medical Center
US	Ford	Stanford University School of Medicine
US	Bekaii-Saab	Mayo Clinic Hospital - Phoenix
US	Ma	Mayo Clinic Cancer Center - Rochester
US	Starr	21st Century Oncology of Jacksonville
US	Al Hallak	Karmanos Cancer Institute
US	Senecal	Northwest Medical Specialties
US	Puri	Huntsman Cancer Institute
US	Chaudhry	Medical Oncology Associates
US	Gbolahan	Emory Clinic
US	Picozzi	Virginia Mason Hospital & Seattle Medical Center
US	Reiss Binder	University of Pennsylvania - Penn Memory Center
US	Massouh	St. James Healthcare
US	Huber	Avera Medical Group - Gynecologic Oncology Sioux Falls
US	Whitehurst	Hematology-Oncology Associates of Fredericksburg
US	Raez	Memorial Cancer Institute
US	Trikha	Cancer Specialists of North Florida
US	Kendall	Utah Cancer Specialists
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US	Jain	Texas Oncology, Denton