NRG1 AND NTRK IN NSCLC

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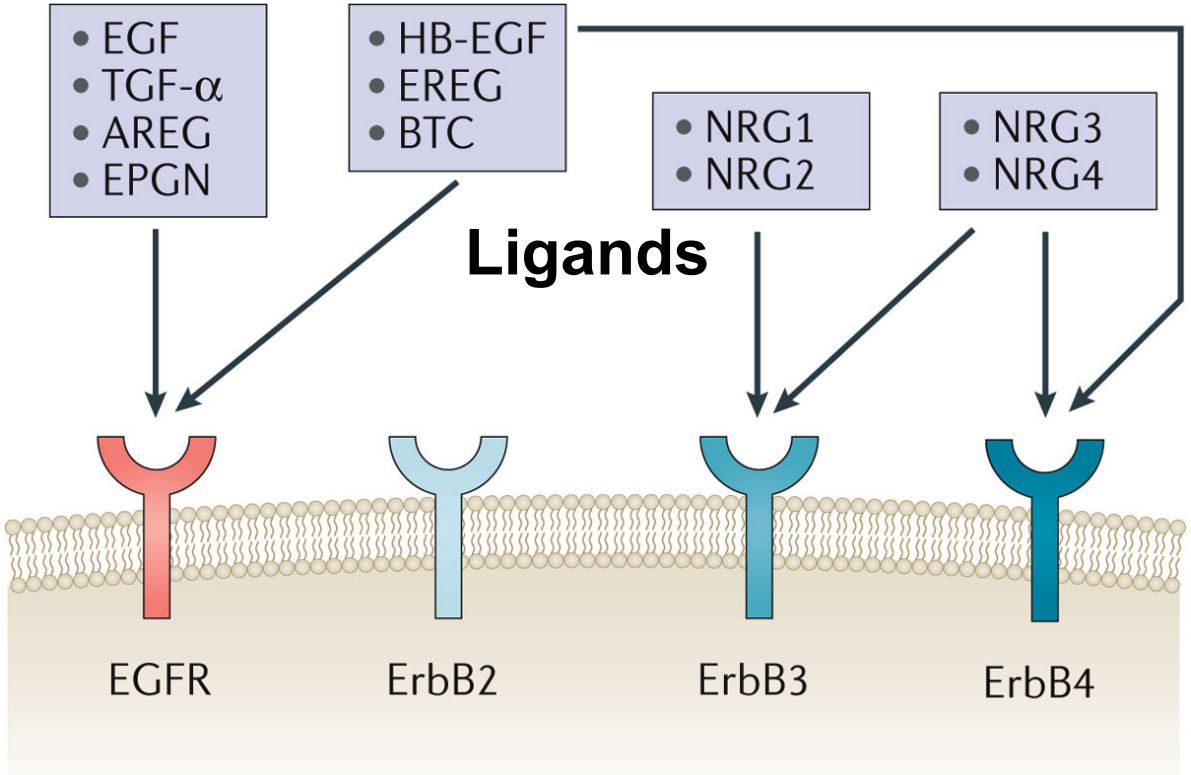
Biology of ERBB Family of Transmembrane Receptors in Cancer

Specificity of the various epidermal growth factor (EGF) receptor ligands for the four known ErbB receptors

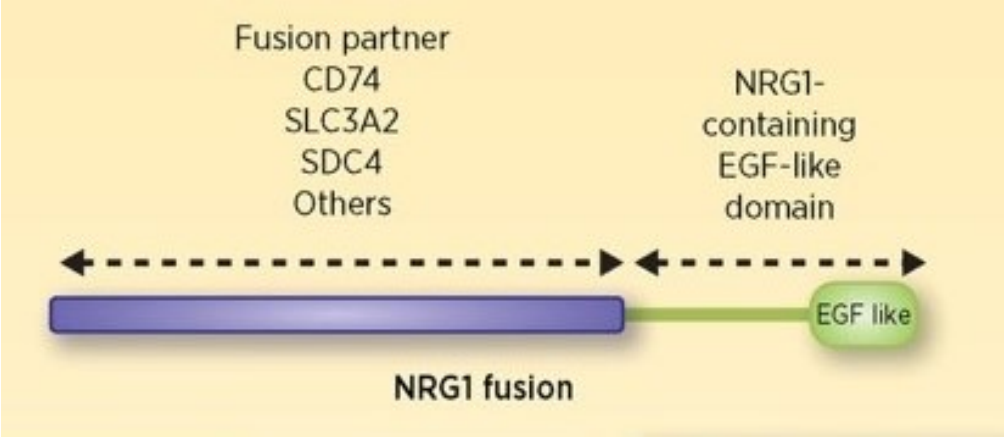


- The ERBB family are receptors for growth factors; they form homo- and heterodimers upon ligands binding.
- The dimers activate downstream pathways, especially MAPK and PI3K/AKT.
- HER2 does not have a cognate ligand and form heterodimers with HER3.
- HER3 binds to EGF-like domain of neuroregulins (NRGs).
- Upon bindings to NRGs, HER3 forms heterodimers with either EGFR and HER2.
- The HER2/HER3 heterodimers exert the strongest downstream signaling activity.

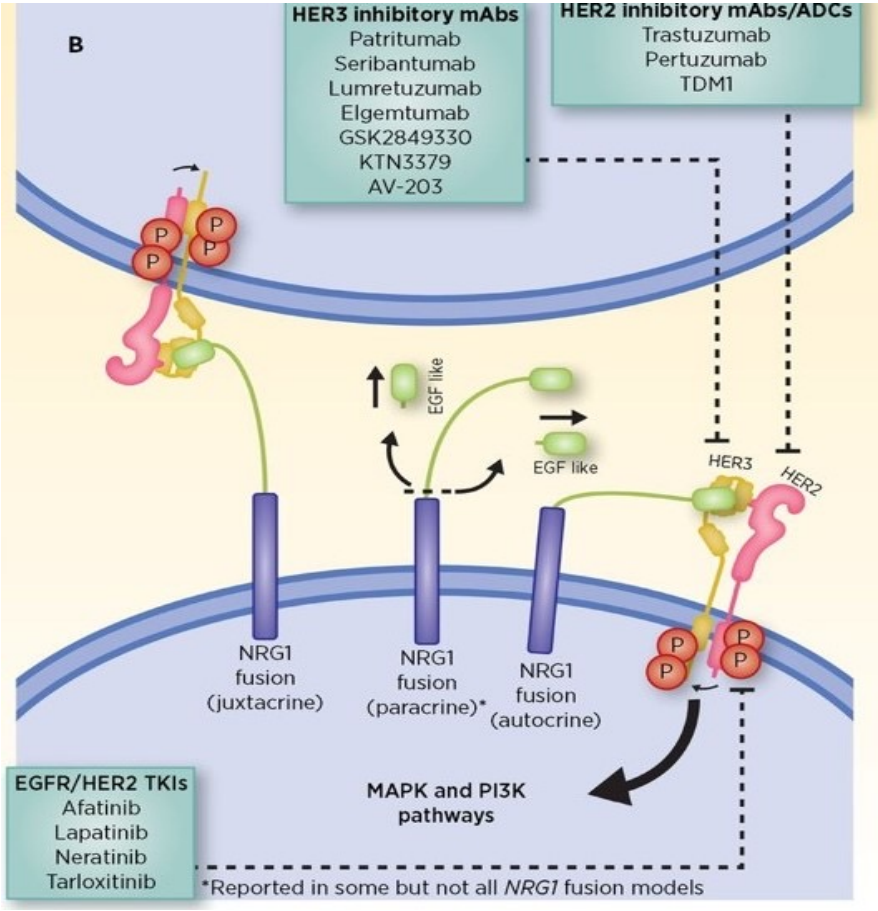
Harskamp LR et al. *Nat Rev Nephrol.* 2016;12(8):496-506.

Role of Neuroregulins in Cancer

- Of the four *NRG* genes, *NRG1* is the best characterized (over 30 isoforms).
- In cancer, gene rearrangements (fusions) have been described in *NRG1* and *NRG2* genes.
- NRG1 fusions exert pro-tumorogenic functions in several cancers, including lung.
- Several gene fusion partners have been described, like *CD74* and *SLC3A2* that fuses with *NRG1* type III-β3 isoform.

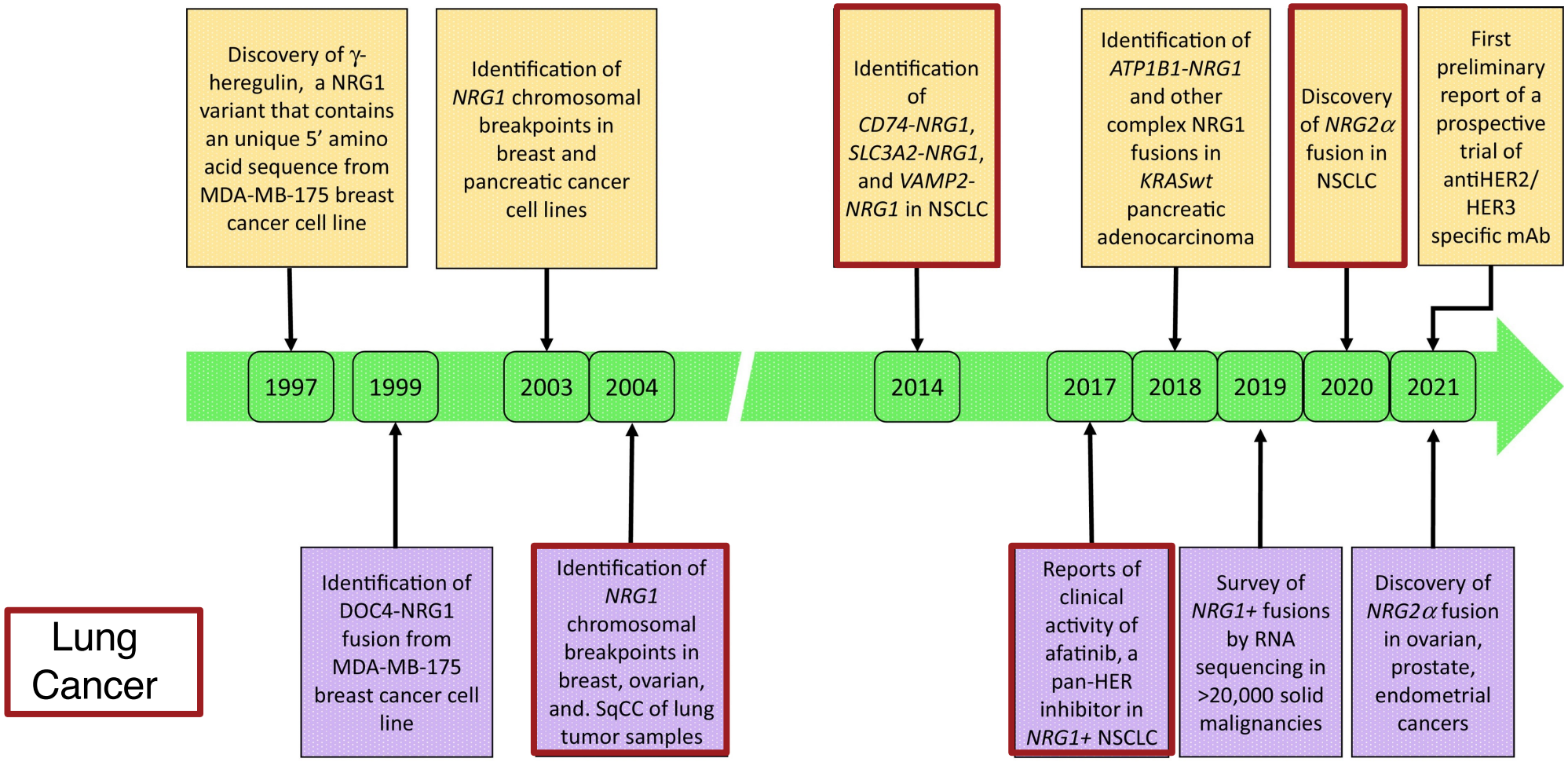


NRG1 EGF-like domain of the fused protein exerts mostly autocrine and juxtacrine activity



Dimou A, Camidge DR. *Clin Cancer Res.* 2019;25(16):4865-4867.

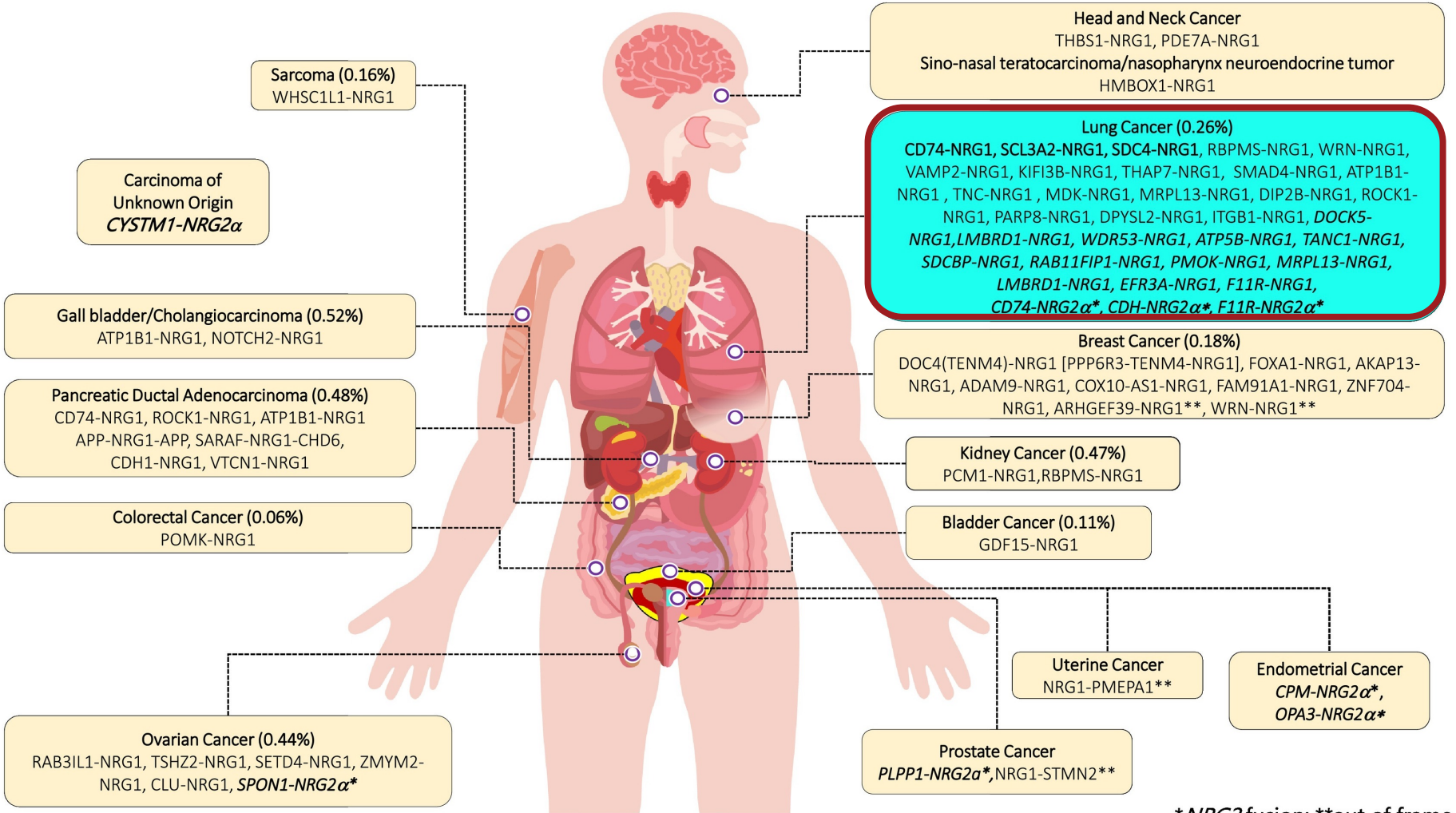
Timeline of Milestones of *NRG* Fusions in Solid Malignancies



Trends in Cancer

Nagasaka M, Ou SHI. *Trends Cancer.* 2022;8(3):242-258.

NRG Fusions in Solid Malignancies



Nagasaka M, Ou SHI. *Trends Cancer*. 2022;8(3):242-258.

Clinical Characteristics of *NRG1* Fusion Positive Lung Cancers

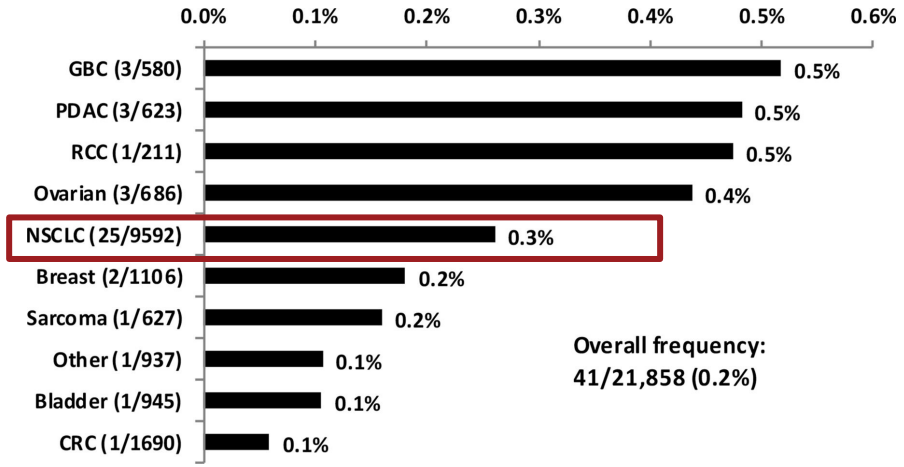
- Detected in non-small cell carcinomas (NSCLC; 0.3%), mostly adenocarcinomas.
- More frequent in invasive mucinous adenocarcinomas (IMAs 37% of *NRG1*-fusion+ NSCLCs) than other subtypes.
- More frequent in never smokers (57%) than smokers (43%).
- More frequent in females (59-68%).
- Median age 64-71 years old.

Liu SV et al. *Lung Cancer.* 2021;158:25-28.

NRG1 Fusion Positive Lung Cancer (2019)

- Assay: targeted RNA sequencing (Archer fusion assay) from FFPE tissue.
- From 21,858 solid tumor specimens: 41 (0.2%) tumors *NRG1* fusions positive.
- From 9,592 NSCLC: 25 (0.3%) *NRG1* fusion positive.
- *NRG1* fusions were mutually exclusive with oncogenic alterations in *EGFR*, *KRAS*, *ALK*, *ROS1* and *RET*.

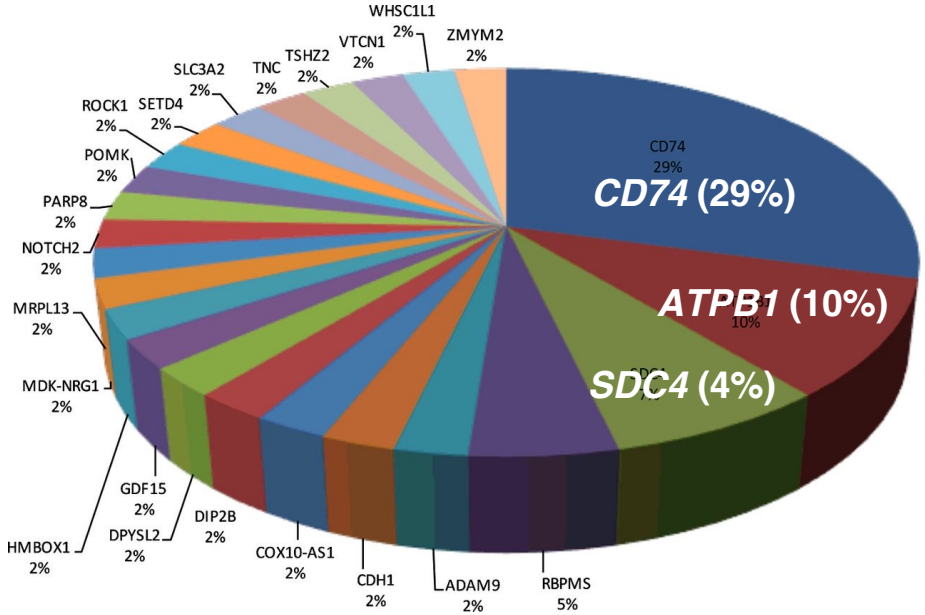
NRG1 Fusion + Tumors



NSCLC Histology (n=25)

Histology, *n*, %	
Adenocarcinoma	
Papillary	1 (4%)
Mucinous	6 (24%)
Acinar	2 (8%)
Mixed[d]	3 (12%)
Poorly differentiated	2 (8%)
NOS	8 (32%)
Squamous cell carcinoma	2 (8%)
Serous carcinoma	—
Other[e]	1 (4%)

NRG1 Gene Fusion Partners



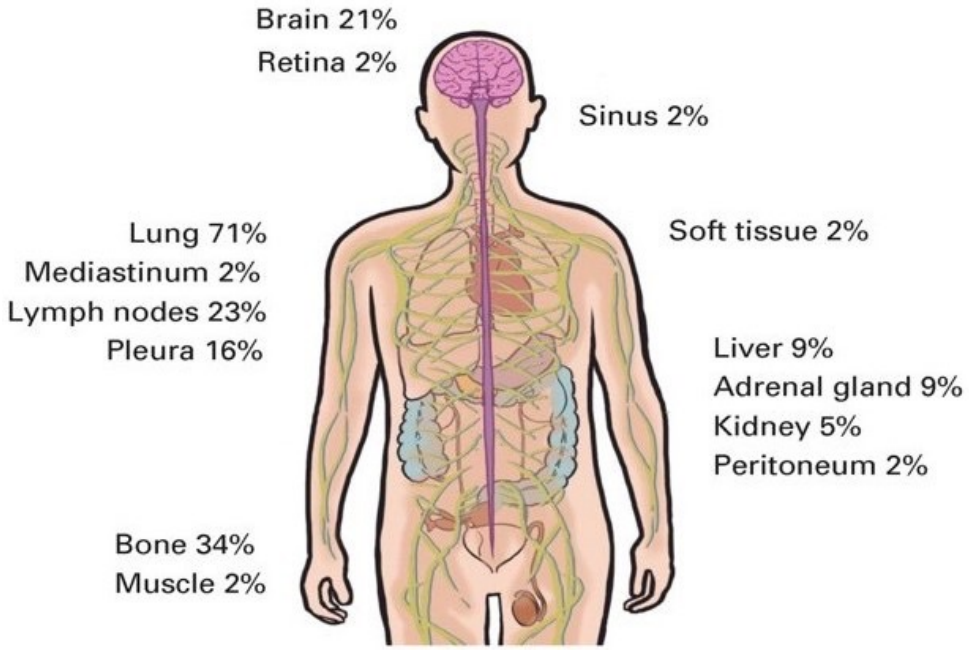
Jonna S et al. *Clin Cancer Res. 2019;*25(16):4966-4972.

NRG1 Fusion Positive Lung Cancer (2021)

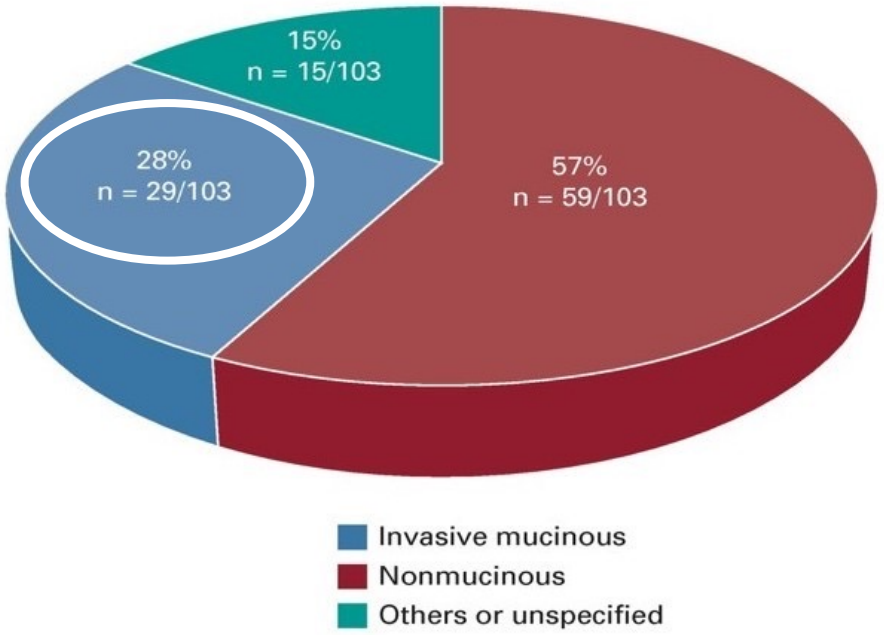
eNRGy1 Global Multicenter Registry (22 centers Europe, Asia, US): 110 tumors

Assays: DNA-based and/or RNA-based NGS and FISH.

Sites of Metastasis



Histology Types



Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802.

NRG1 Fusion Positive Lung Cancers (2021)

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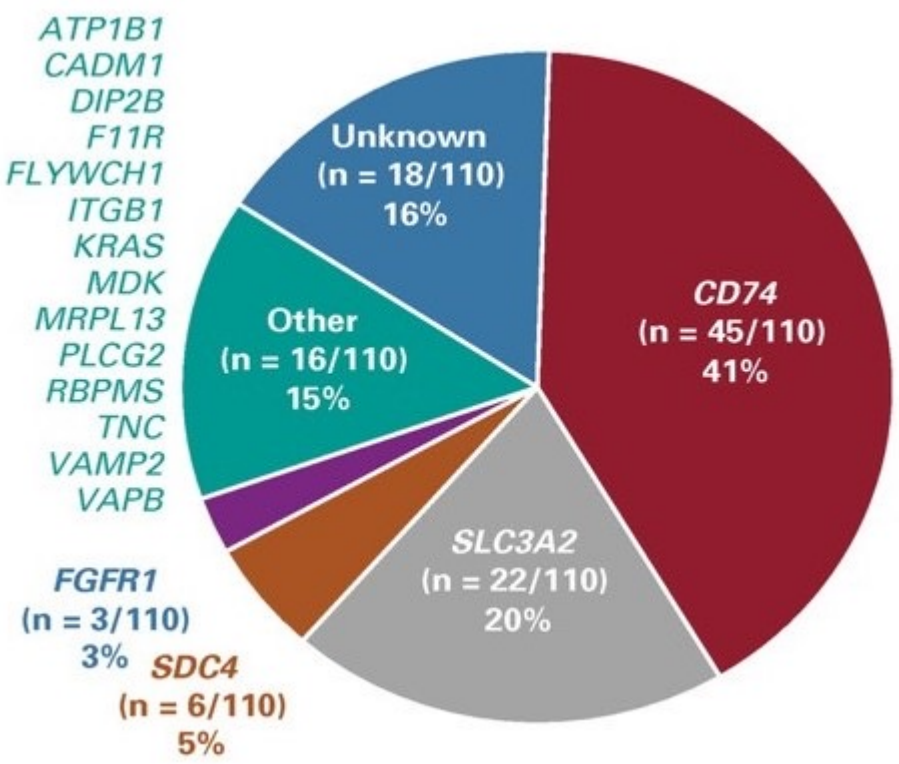
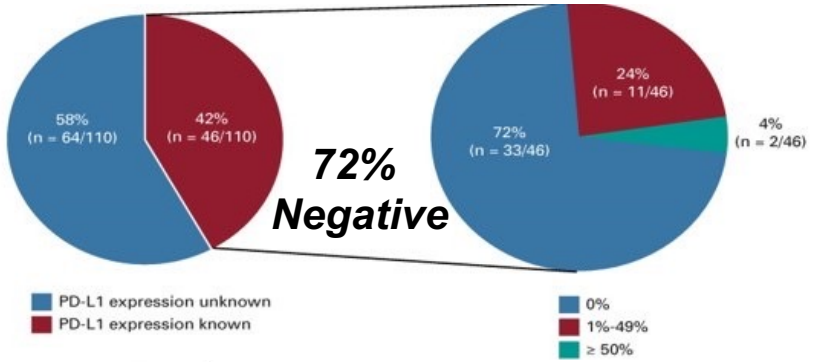
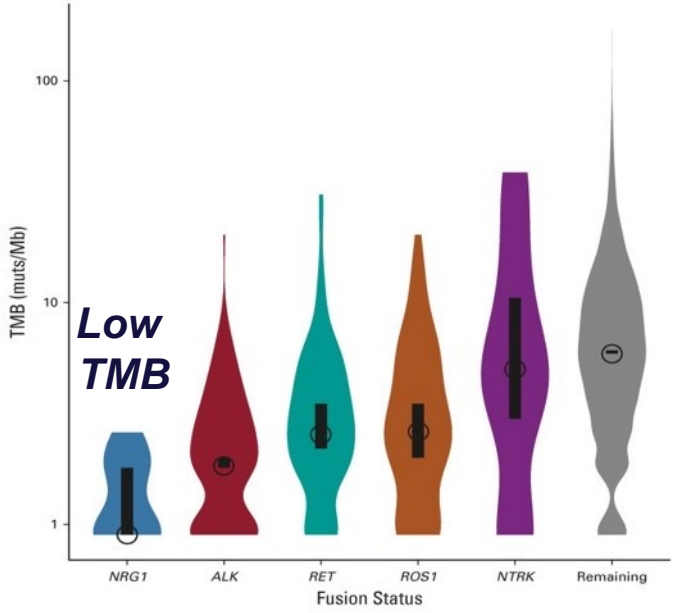
NRG1 Gene Fusion Partners



PD-L1 IHC Expression



Tumor Mutation Burden (TMB)



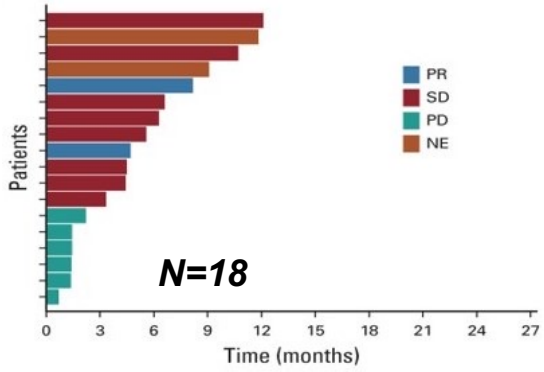
Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802.

NRG1 Fusion Positive Lung Cancers (2021)

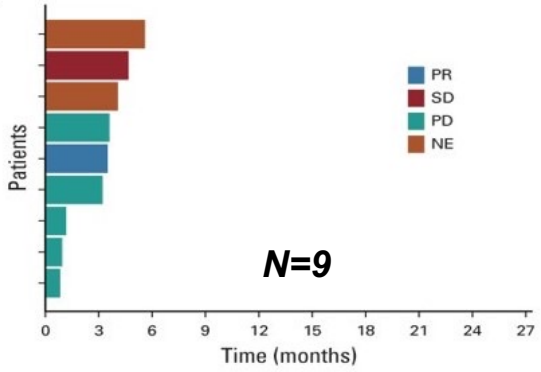
eNRGy1 Global Multicenter Registry (22 centers Europe, Asia, US): 110 tumors

Response to Systemic Therapy

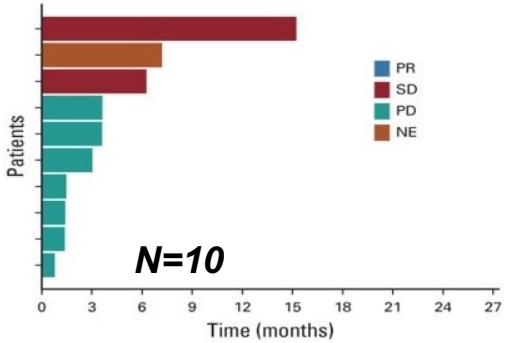
Platinum-doublet



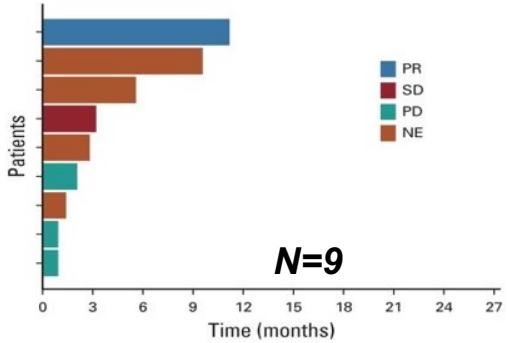
Taxane-based (after platinum)



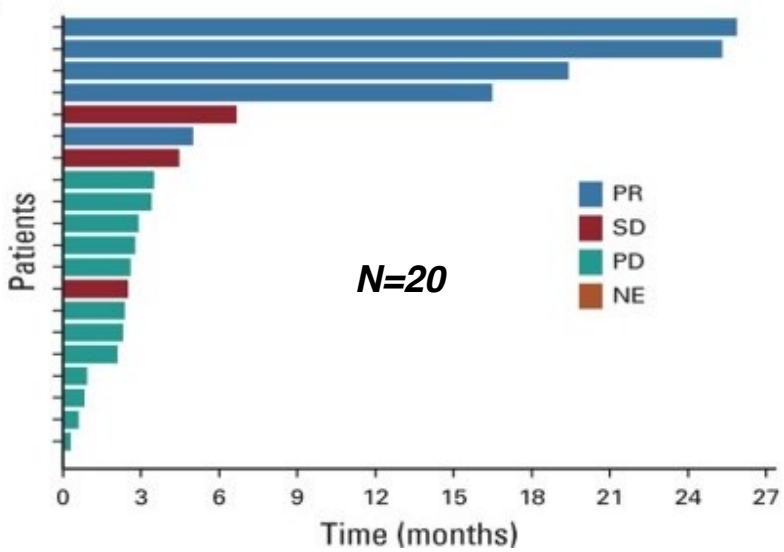
Immune Checkpoint + Chemotherapy



Single-agent Immune Checkpoint



Afatinib



Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802.

NRG1 Fusion Positive Lung Cancers (2021)

eNRGy1 Global Multicenter Registry (22 centers Europe, Asia, US): 110 tumors

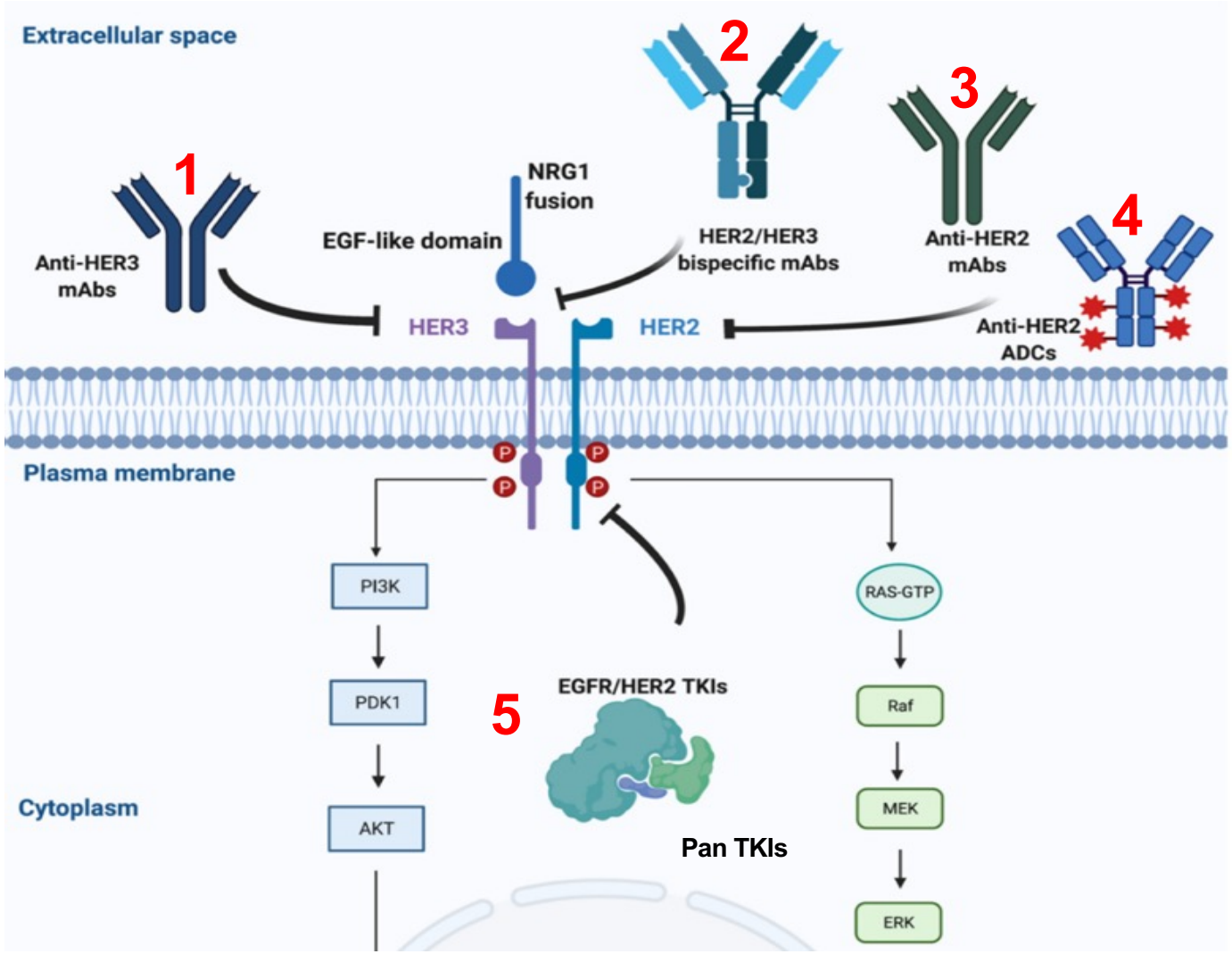
Response to Systemic Therapy

Response	Platinum-Doublet–Based Chemotherapy	Taxane-Based Chemotherapy	Combined Chemotherapy and Immune Therapy	Single-Agent Immunotherapy	Targeted Therapy With Afatinib
Response rate, %	13	14	0	20	25
CR, % (n/N)	0 (0/15)	0 (0/7)	0 (0/9)	0 (0/5)	0 (0/20)
PR, % (n/N)	13 (2/15)	14 (1/7)	0 (0/9)	20 (1/5)	25 (5/20)
SD, % (n/N)	47 (7/15)	14 (1/7)	44 (4/9)	20 (1/5)	15 (3/20)
PD, % (n/N)	40 (6/15)	71 (5/7)	56 (5/9)	60 (3/5)	60 (12/20)
Median PFS (95% CI), range	5.8 months (2.2 to 9.8), 0.7-12.1	4.0 months (0.8 to 5.3), 0.8-5.5	3.3 months (1.4 to 6.3), 1.4-15.2	3.6 months (0.9 to undefined), 0.9-11.2	2.8 months (1.9 to 4.3), 0.3-25.3

Abbreviations: CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Drilon A et al. *J Clin Oncol*. 2021;39(25):2791-2802.

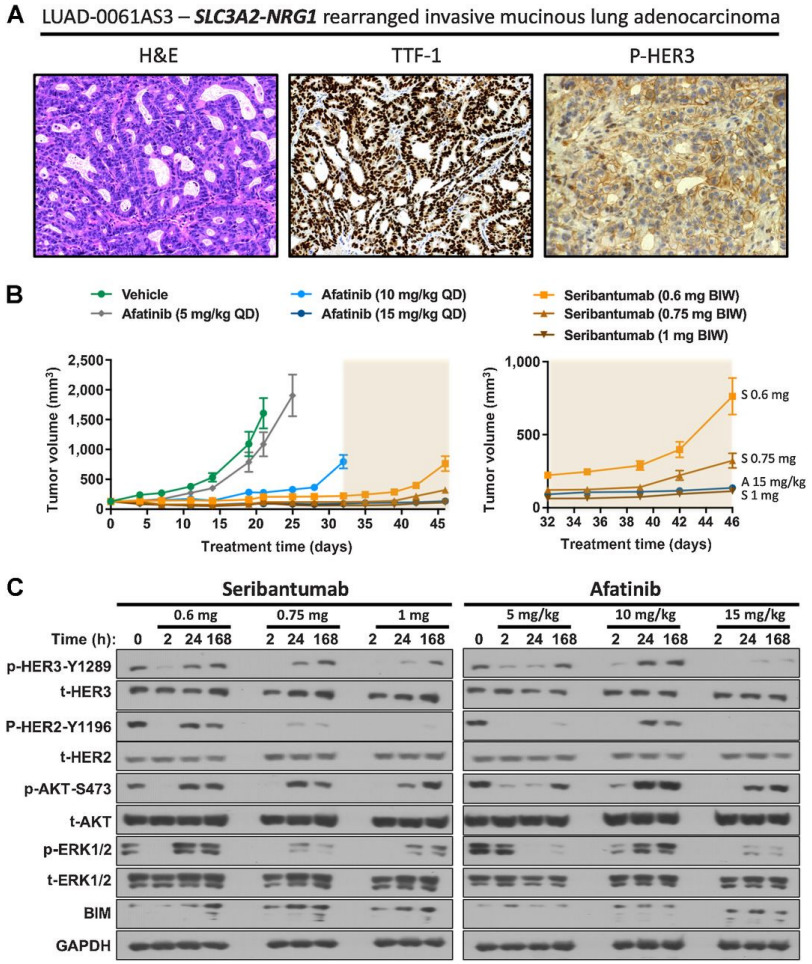
Therapeutic Approaches *NRG1* Fusion Positive



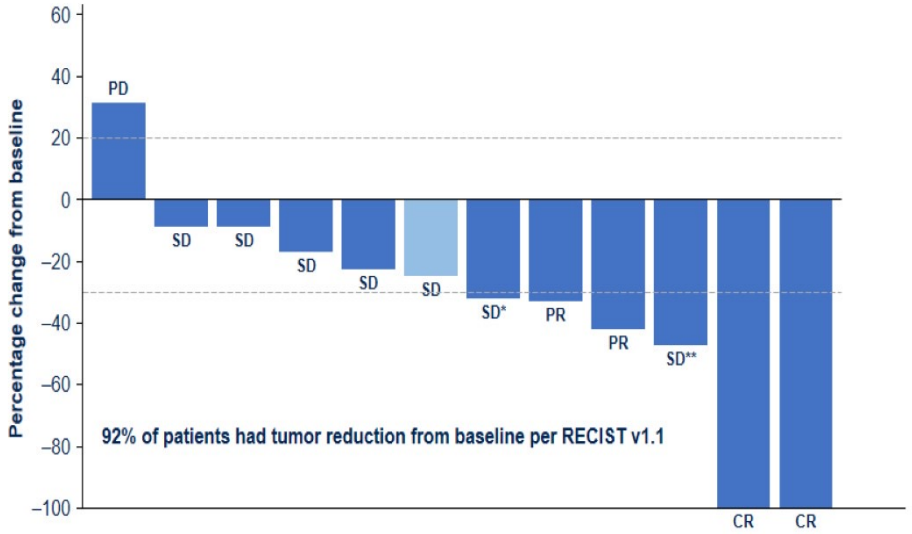
Rosas D et al. *Cancers.* 2021;13(20):5038.

Seribantumab-Anti-HER3 monoclonal antibody

NSCLC PDXs - Response



Seribantumab (CRESTONE Trial)



Confirmed INV-ORR	
Overall	33% (4/12)
NSCLC	36% (4/11)

Primary tumor type:
- Lung/NSCLC
- Pancreas

*Unconfirmed partial response (PR), unable to be confirmed as subsequent scans showed patient in stable disease (SD);
**Unconfirmed PR, patient died due to lung infection (history of COVID-19 infection) before confirmatory scan was able to be completed, no evidence of clinical disease progression at time of death.
Visit cut-off: 18 April 2022.

Median DOR 6.3+ months

(range 1.4+ - 11.5+ months)

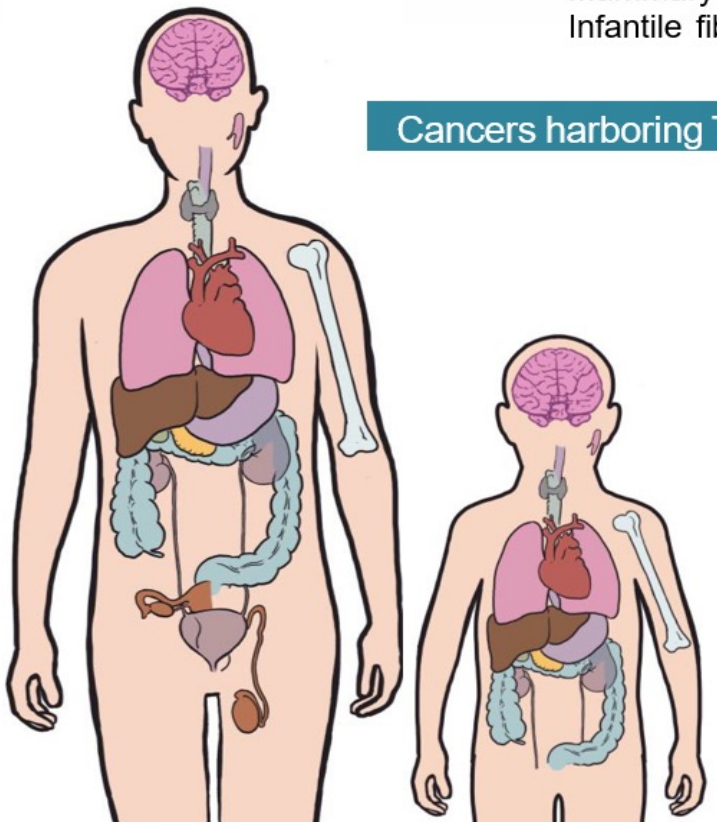
Odinstov I et al. *Clin Cancer Res.* 2021;27(11):3154-3166; Carrizosa DR et al. *J Clin Oncol. 2020;*40(16_suppl):3006-6.

NRG1 Fusion Positive Clinical Trials

Clinical Trial (*ClinicalTrials.gov (March 8th, 2023)*	Disease	Drug
To Evaluate the Efficacy of Afatinib in the Treatment of Locally Advanced/Metastatic Non-Small Cell Lung Cancer With NRG1 Fusion (NCT04814056; Not yet recruiting; China)	NRG1-fused **NSCLC**	Afatinib Dimaleate (pan-inhibitor of ERBB family of tyrosine kinases)
Real-World Effectiveness of Afatinib (Gilotrif) Following Immunotherapy in the Treatment of Metastatic, Squamous Cell Carcinoma of the Lung: A Multi-Site Retrospective Chart Review Study in the U.S. (NCT04750824; completed; US)	Non-squamous, **NSCLC**	Afatinib (pan-inhibitor of ERBB family of tyrosine kinases) + other systemic therapy
Early Access Program Providing HER2/HER3 Bispecific Antibody, MCLA-128, for a Patient With Advanced NRG1-Fusion Positive Solid Tumor (NCT04100694; available)	NRG1; NRG1 Fusion; Pancreatic Cancer; **NSCLC** (and 9 more...)	Zenocutuzumab (MCLA-128; HER2-HER3 Bispecific Antibody)
A Study of Zenocutuzumab (MCLA-128) in Patients With Solid Tumors Harboring an NRG1 Fusion (eNRGy) (NCT02912949; recruiting; US)	Solid Tumors, **NSCLC, Pancreatic Cancer, Harboring NRG1** Fusion; and NRG1 Fusion	Zenocutuzumab (MCLA-128; HER2-HER3 Bispecific Antibody)
Study of Seribantumab in Adult Patients With NRG1 Gene Fusion Positive Advanced Solid Tumors (NCT04383210; active, not recruiting; US)	Locally Advanced Solid Tumor; Metastatic Solid Tumor; Pancreatic Cancer; **Lung Cancer; (**and 14 more...)	Seribantumab (anti-HER3 monoclonal)
Study of Tarloxotinib in Pts With NSCLC (EGFR Exon 20 Insertion, HER2-activating Mutations) & Other Solid Tumors With NRG1/ERBB Gene Fusions (NCT03805841; terminated; US)	**NSCLC**, Stages IV, IIB, IIIC (and 5 more...) (EGFR Exon 20 Insertion Mutation; HER2-activating Mutation; ERBB Fusion)	Tarloxotinib bromide (HER tyrosine kinase inhibitor)
HMBD-001 in Advanced HER3 Positive Solid Tumors (NCT05057013; recruiting; UK)	Bladder Cancer; Triple Negative Breast Cancer; Castration-resistant Prostate Cancer; **NSCLC**; (and 11 more...)	HMBD-001 (anti-HER3 monoclonal antibody)

NTRK Fusions in Solid Tumors

Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually



Cancers enriched for TRK fusions

Secretory breast carcinoma
Mammary analogue secretory carcinoma
Infantile fibrosarcoma

Frequency
75% to >90%

Cancers harboring TRK fusions at lower frequencies

Congenital mesoblasticnephroma
Pontine glioma
Spitzoid melanoma
Thyroid Cancer
GIST ("pan-negative")

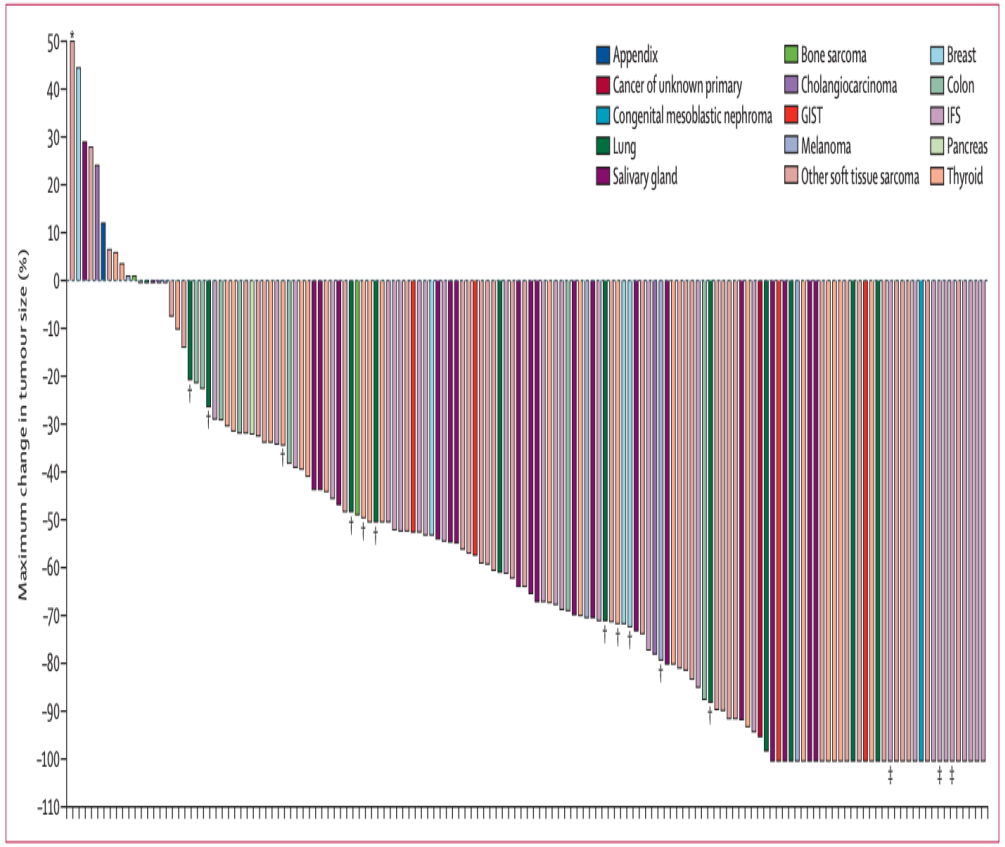
Frequency
5% to 25%

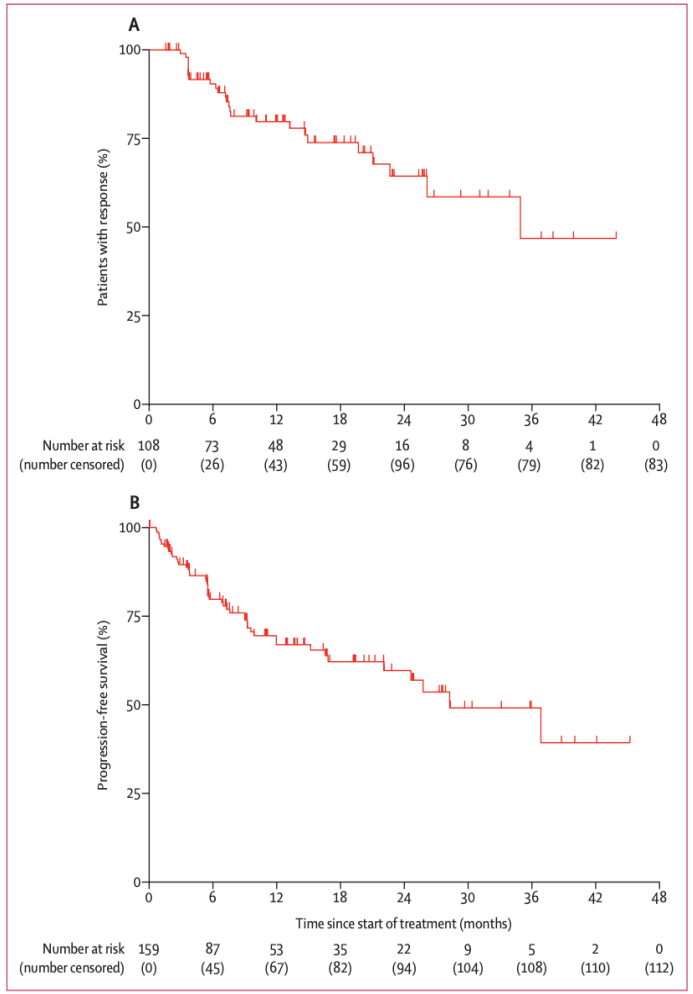
Lung cancer
Other sarcomas
Astrocytoma/Glioblastoma
Colorectal cancer
Cholangiocarcinoma
Pancreatic cancer
Head and neck squamous cancer
Breast cancer
Melanoma

Frequency
<1% to <5%

Cocco, Nat Rev Clin Oncol, 2018

Larotrectinib in NTRK fusion positive tumors

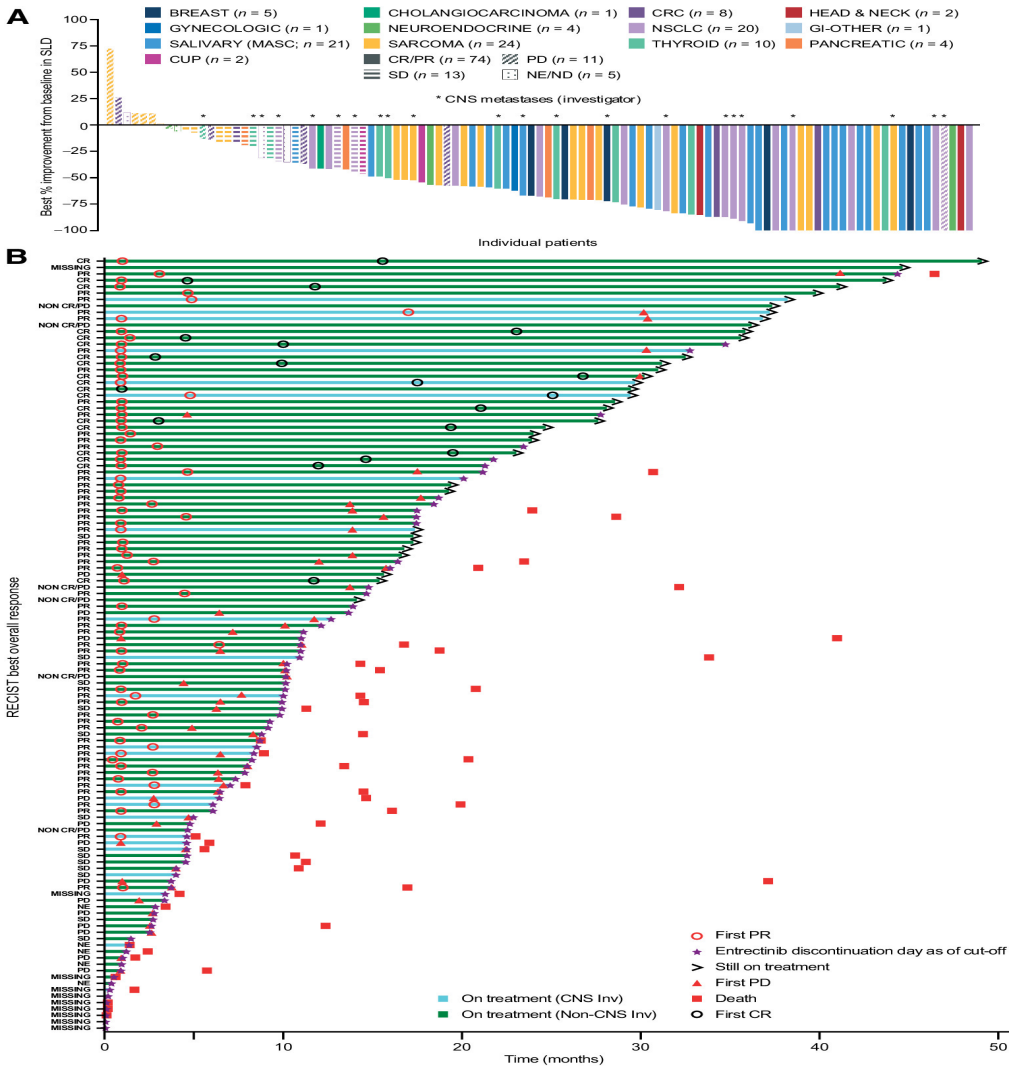




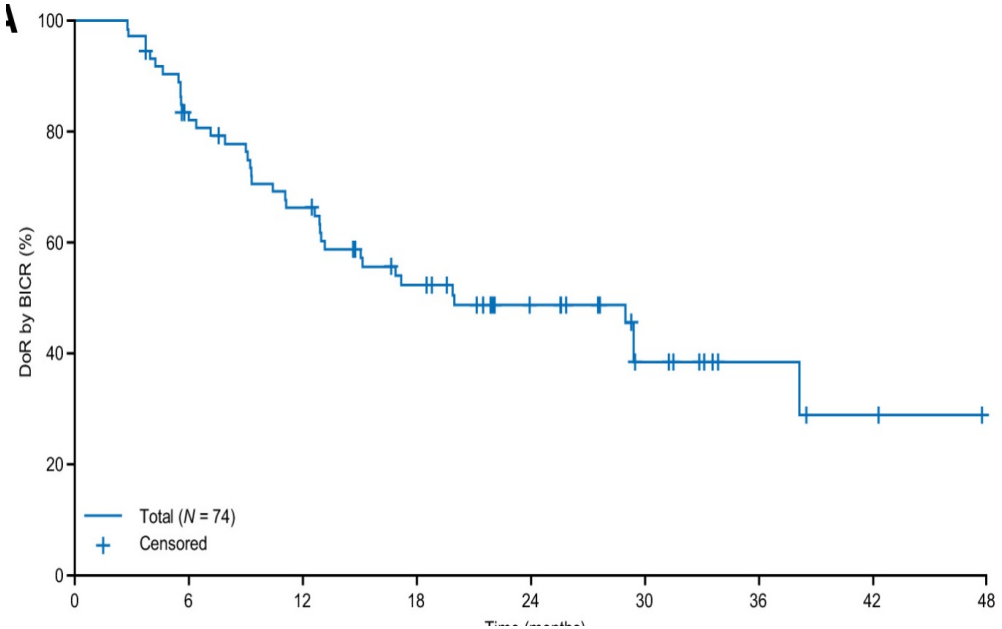
- ORR 79%
- mDOR 35.2
- mPFS 25.8

Hong, Lancet Oncology 2020

Entrectinib in NTRK fusion positive tumors

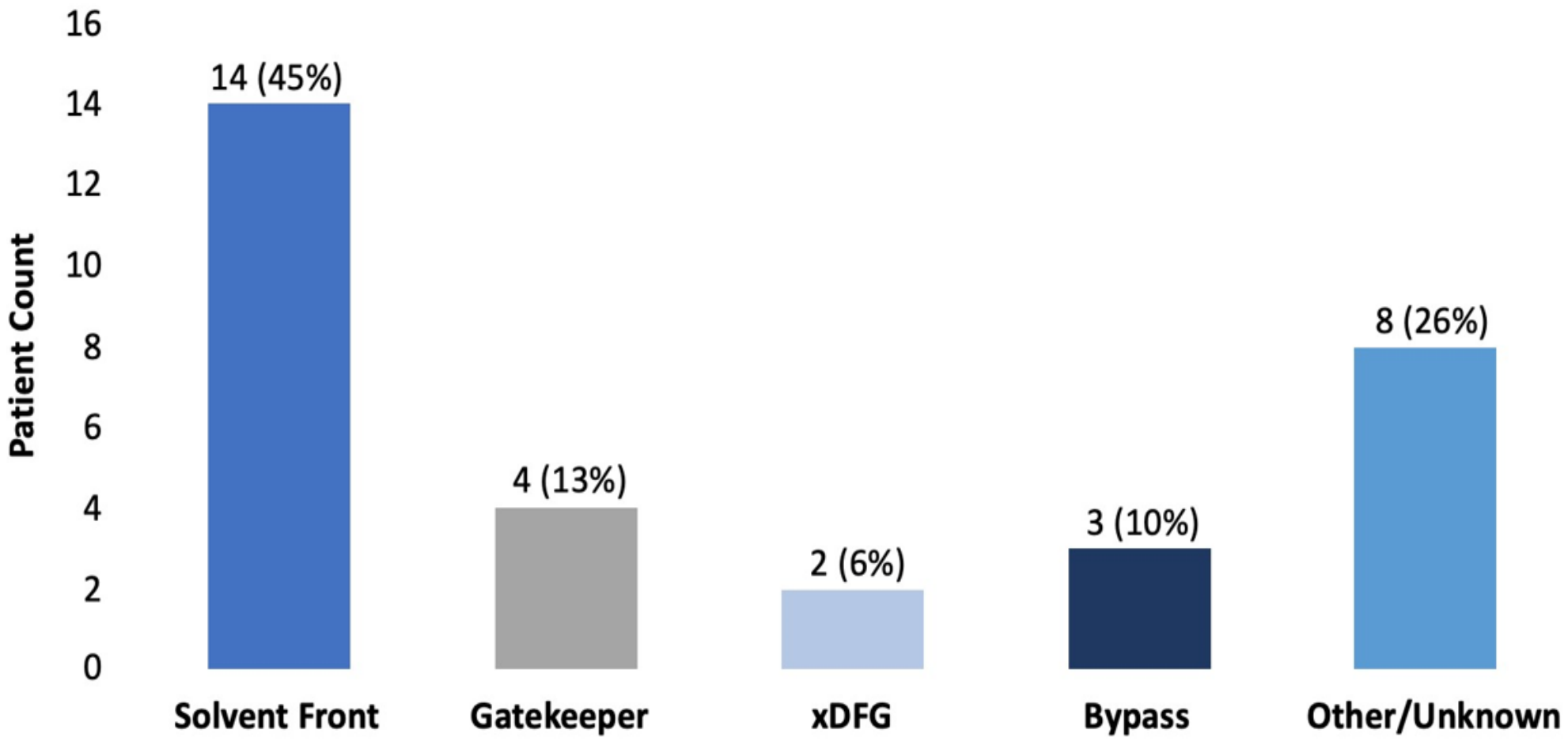


Demetri et al. CCR 2022



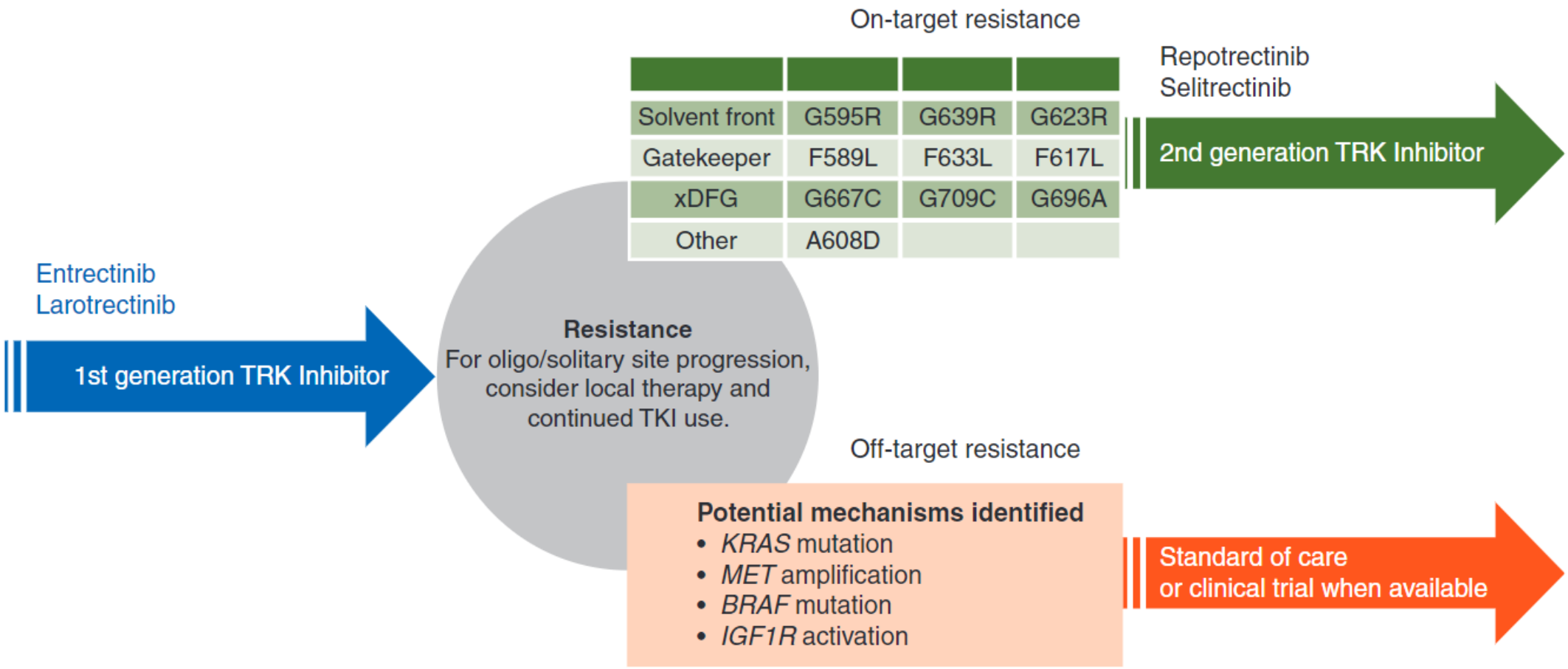
- ORR 61.2%
- mDOR 20.0
- mPFS 11

On-Target Resistance Mechanisms After TRK inhibition



Hyman. AACT. 2019. #CT127

Sequential Therapy



Drilon. Ann Oncol. 2019;30

TRIDENT-2: Repotrectinib

NTRK+ Advanced Solid Tumors	
EXP-5 TRK TKI-naïve (N=55)	**EXP-6** TRK TKI-pretreated (N=40)
Treated **(N=20)**	**Treated** **(N=24)**
Efficacy Evaluable **(N=15)**	**Efficacy Evaluable** **(N=22)**

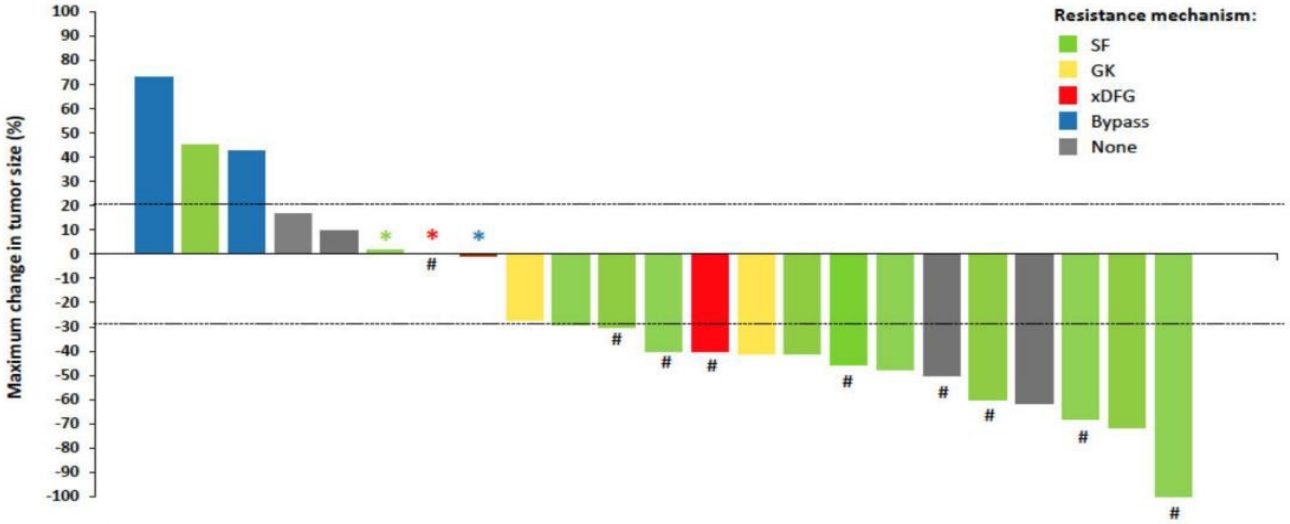
- Initial preliminary data in NTRK+ TKI-naïve advanced solid tumor patients (N=17):
  - cORR 41% (95% CI: 18 - 67)
- Preliminary data in NTRK+ TKI-pretreated advanced solid tumor patients (N=23) with limited treatment options:
  - cORR 43% (95% CI: 23 – 66)
  - In the 56% of patients with SFM (N=13): cORR 54% (95% CI: 25 – 81)
- Repotrectinib was generally well-tolerated in a total of 301 patients
- Enrollment is ongoing in the registrational Phase 2 TRIDENT-1 study evaluating repotrectinib for the treatment of TKI-naive and TKI-pretreated patients with *ROS1*+ advanced NSCLC and *NTRK*+ advanced solid tumors

Besse, Proc AACr-NCI-EORTC 2021

Selitrectinib

LOXO-195 (BAY2731954)
Phase I and Expanded Access Experience

Best tumor change by resistance mechanism



7 patients were non-evaluable.
*Patients with responses at or close to 0%. # SPP population.
1 SPP patient with an SF kinase mutation had PD is not included

Hyman, 2019

Conclusions

- NRG1 and NTRK fusions are rare but actionable alterations with overall frequency of 0.3% across tumor types
- Ongoing trials are enrolling patients with NRG1 fusion–positive solid tumors
- NTRK first generation TKIs lead to deep and durable responses
- NTRK second generation TKIs in clinical development and are promising