MRO . ART
MODERN RADIATION ONCOLOGY
35° RESIDENTIAL COURSE

IMMUNOCHECKPOINT INHIBITORS

AND

TARGETED THERAPIES

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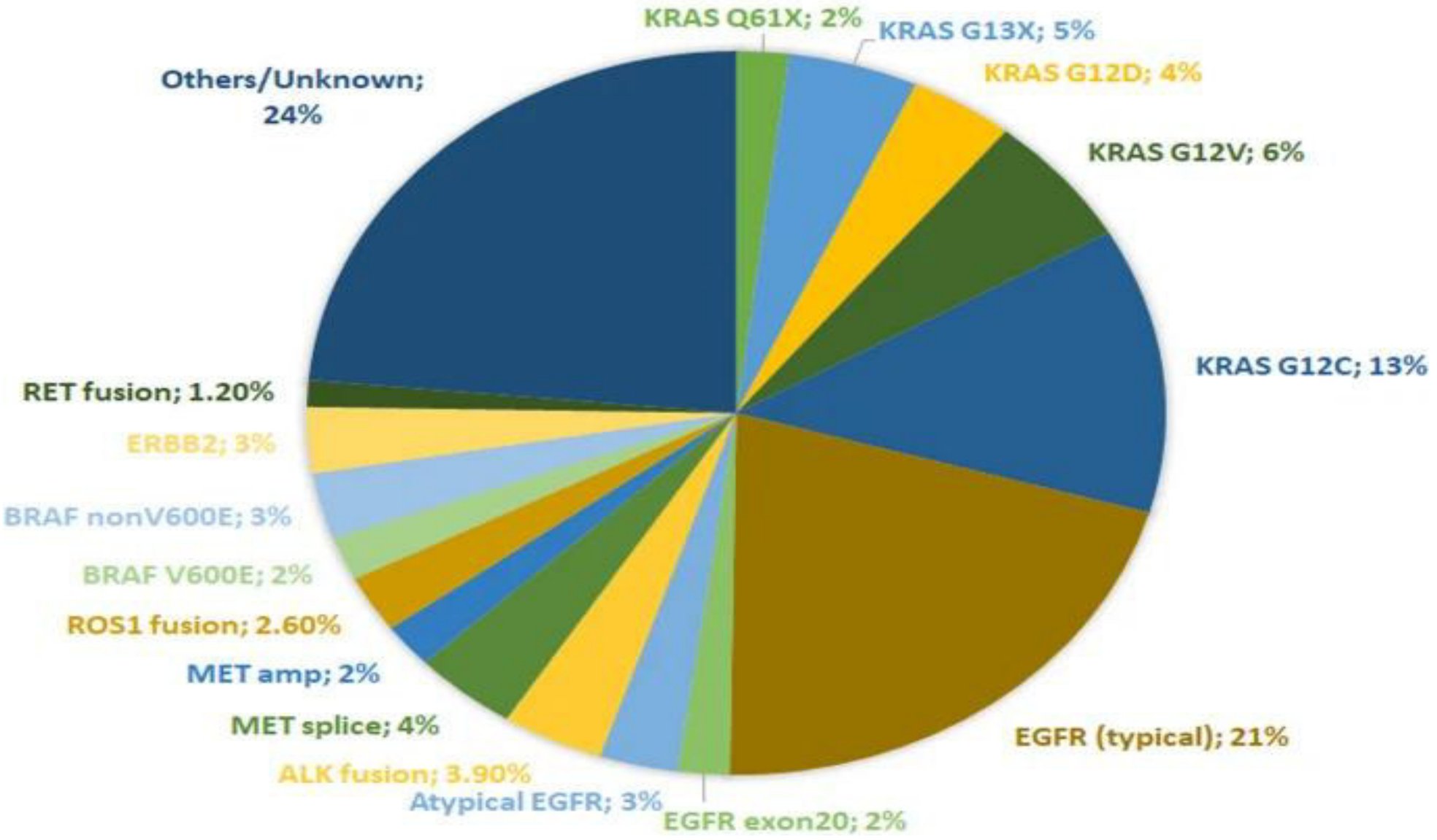
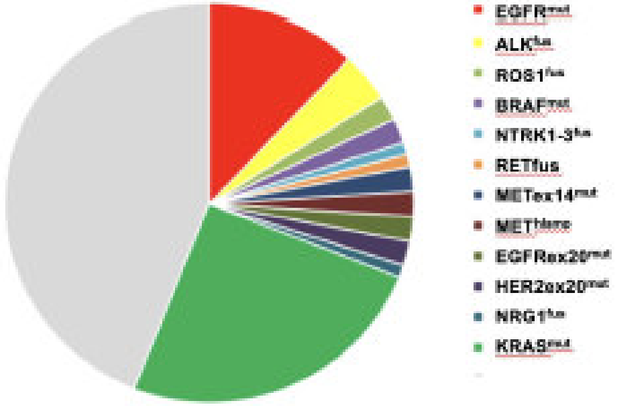
INCIDENCE OF ONCOGENIC DRIVER ALTERATIONS

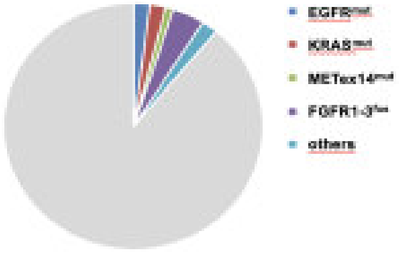


ONCOGENES PLATEAU – THERAPIES EXPAND IN NSCLC

Lung adeno-carcinoma



Lung squamous cell carcinoma



1st generation TKIs

starting with EGFR-TKIs in 2009

- Next-generation TKIs
- Antibody-drug-conjugates
- Bispecifics
- Others
- Combinations

2009 *continuous improvement of patient outcomes* 2025

EXPANDING THE ARMAMENTARIUM BEYOND TKIS

- **Next-generation TKIs**
  → deeper, more durable responses (e.g., lorlatinib, repotrectinib, zidesmatinib)

- **Antibody–drug conjugates (ADCs)**
  → *trastuzumab deruxtecan* (approved) – new agents in development targeting TROP2, MET and others

- **Bispecific antibodies**
  → *amivantamab* (EGFR/MET; approved), *ivonescimab* (PD-1/VEGF) – early promising results and others

- **Novel mechanisms**
  → MET degraders, PROTACS, SHP2 and SOS1 inhibitors, pan-KRAS inhibitors and others

- **Cell-based and immune approaches**
  → T-cell vaccines, CAR-T concepts in early testing

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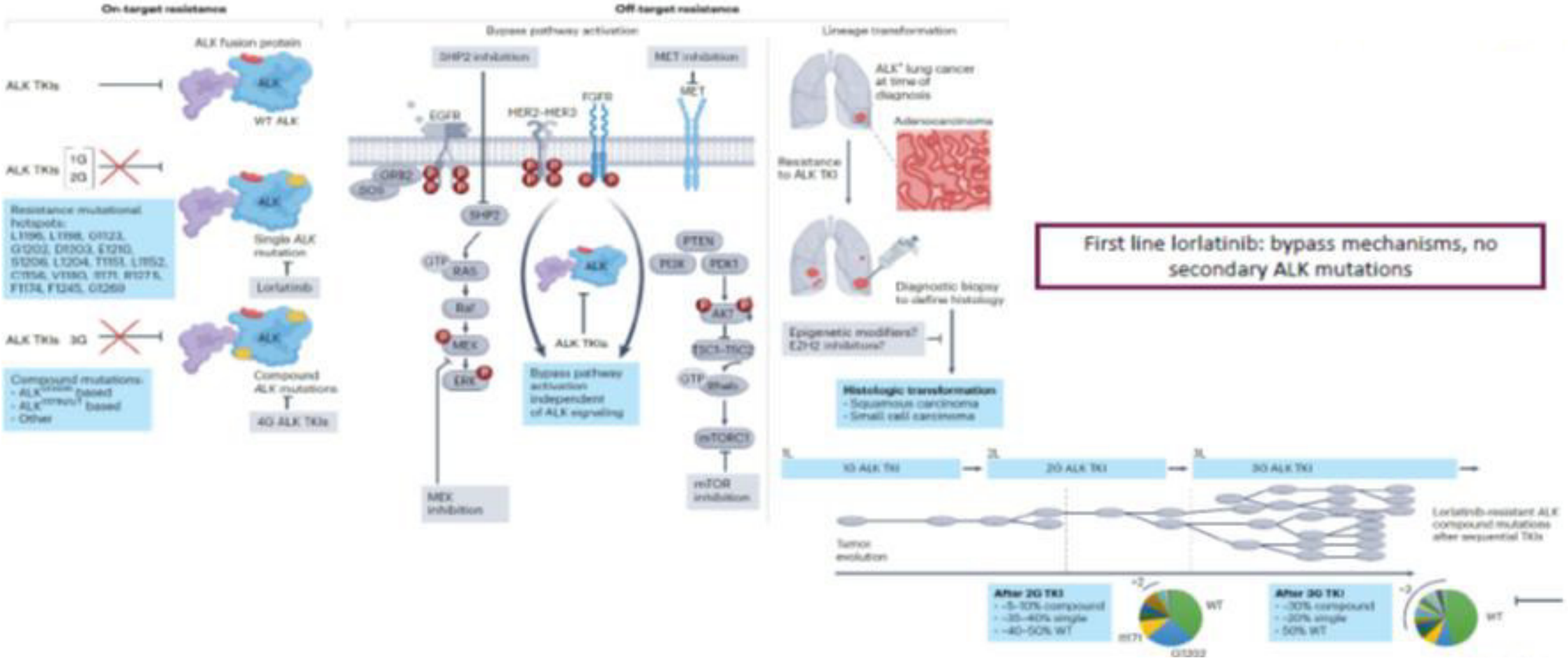
NEXT GENERATION TKIs

1. **ALK DISEASE**: 3° AND FOURTH GENERATION TKI

2. **HER-2 DISEASE**: ZONGERTINIB

3. **KRAS DISEASE:** PAN RAS INHIBITORS

RESISTANCE MECHANISMS DEPEND ON TKI AND SEQUENCE

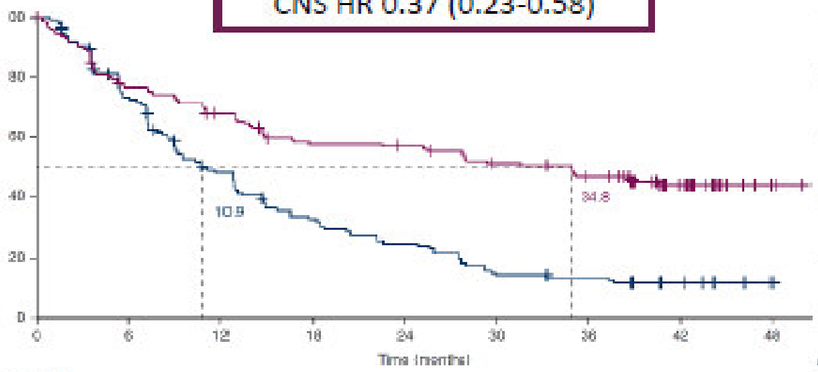


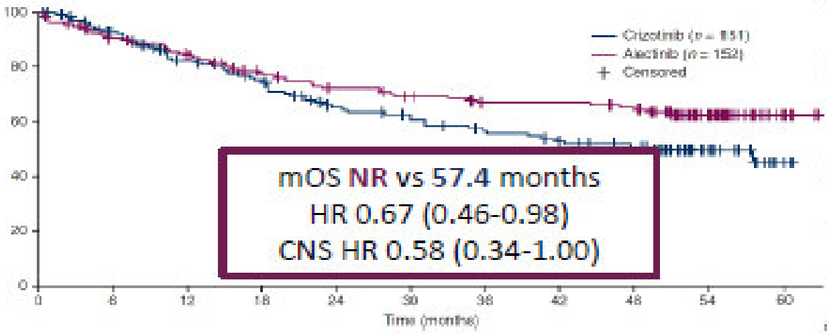
First line lorlatinib: bypass mechanisms, no secondary ALK mutations

ALECTINIB 2ND GENERATION

ALEX

mPFS 34.8 vs 10.9 months
HR 0.43 (0.32-0.58)
CNS HR 0.37 (0.23-0.58)



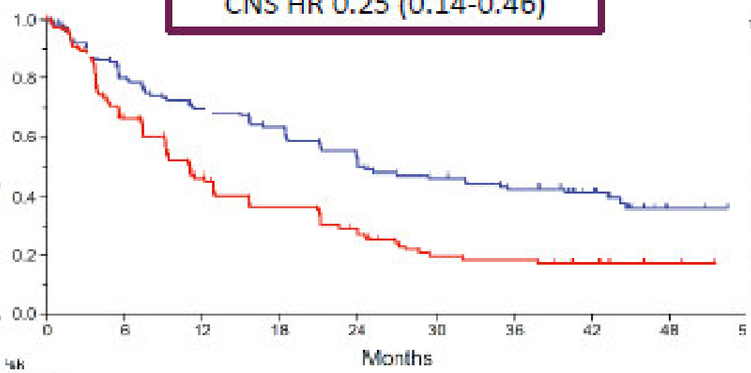


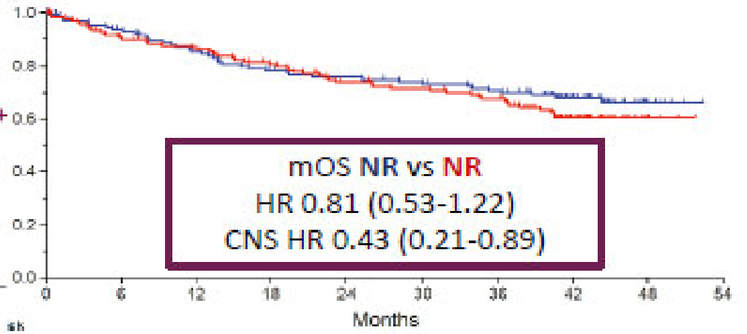
mOS NR vs 57.4 months
HR 0.67 (0.46-0.98)
CNS HR 0.58 (0.34-1.00)

BRIGATINIB 2° GENERATION

ALTA-1L

mPFS 24.0 vs 11.1 months
HR 0.48 (0.35-0.66)
CNS HR 0.25 (0.14-0.46)



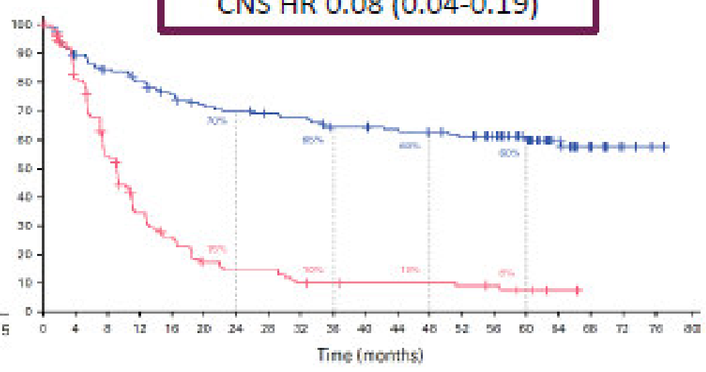


mOS NR vs NR
HR 0.81 (0.53-1.22)
CNS HR 0.43 (0.21-0.89)

LORLATINIB 3° GENERATION

CROWN

mPFS NR vs 9.1 months
HR 0.19 (0.13-0.27)
CNS HR 0.08 (0.04-0.19)



?

L Hendriks

Cross-trial comparison NOT allowed

Mok Ann Oncol 2020; Camidge JTO 2021; Solomon JCO 2024

ESMO

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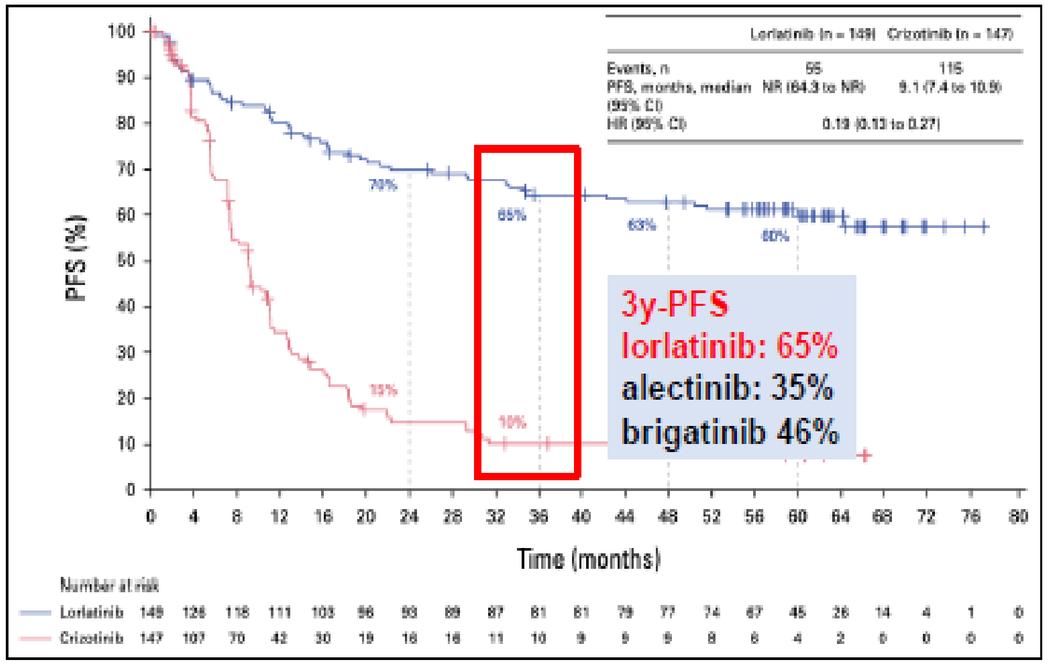
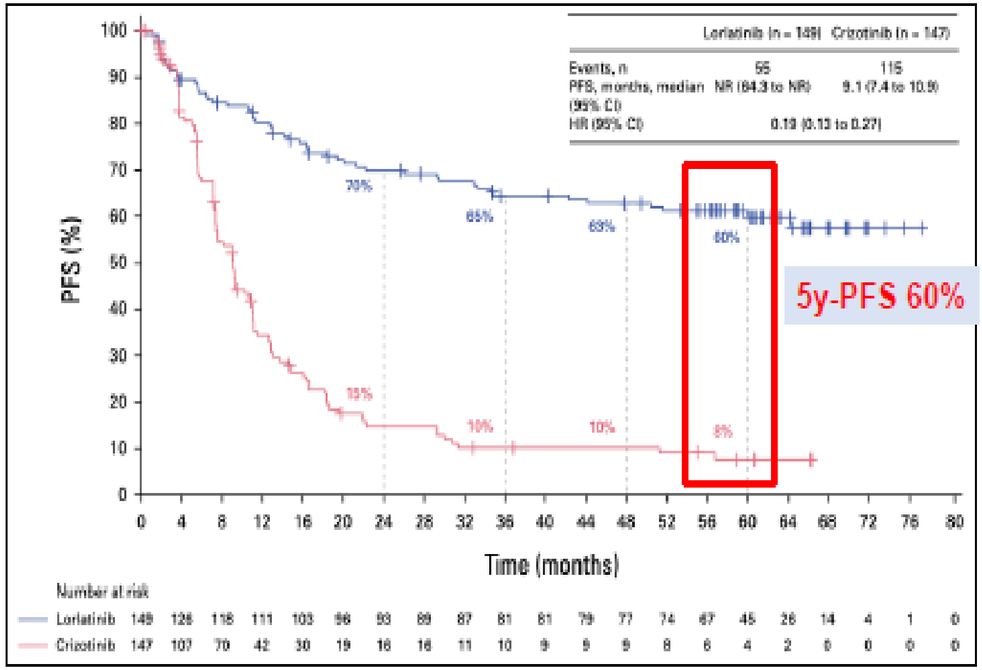
ALK FUSIONS: SETTING THE BAR 2025

CROWN phase III trial – update (1L crizotinib vs. lorlatinib)





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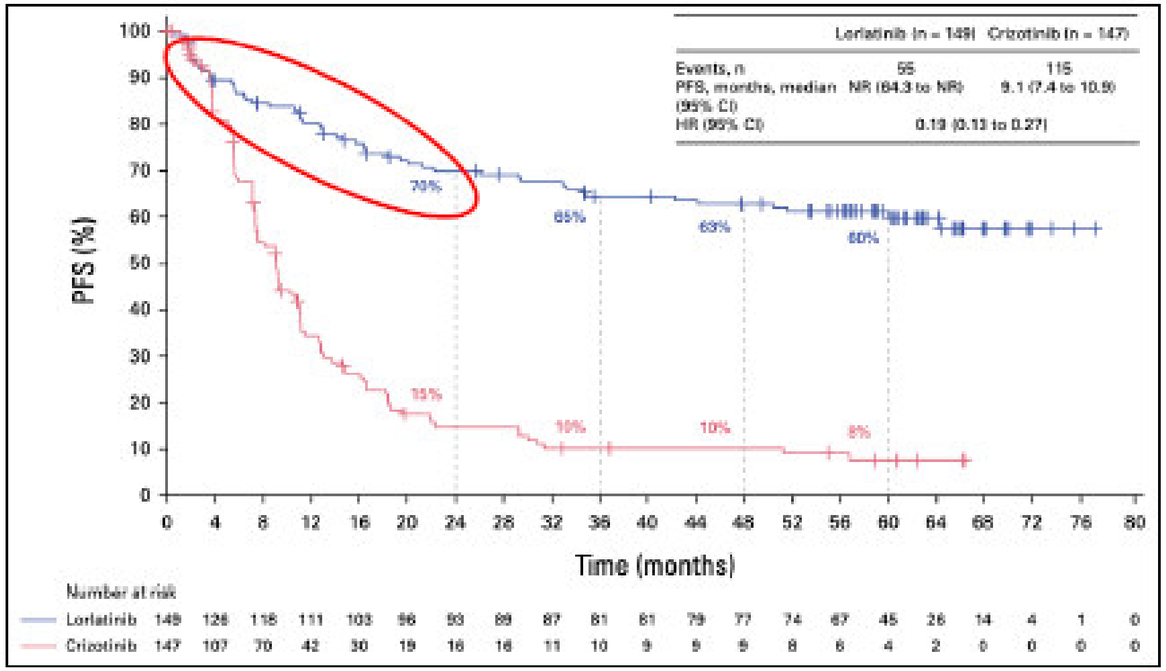


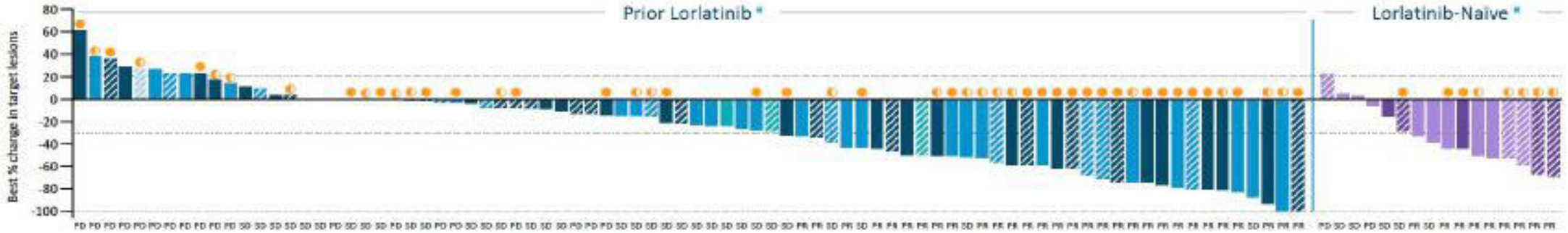
Even with remarkable PFS,

early relapses remain a relevant challenge

FOURTH GEN TKI: NVL-665 IN ALKOVE-1

ALK selective, TRK sparing

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [b]	G1202R [c]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**35%** (30/85)	**47%** (23/49)	**54%** (15/28)	**53%** (9/17)	**88%** (7/8)
RP2D	**38%** (15/39)	**55%** (12/22)	**71%** (10/14)	**35%** (11/31)	**50%** (8/16)	**64%** (7/11)	**57%** (4/7)	**80%** (4/5)



KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKIs
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

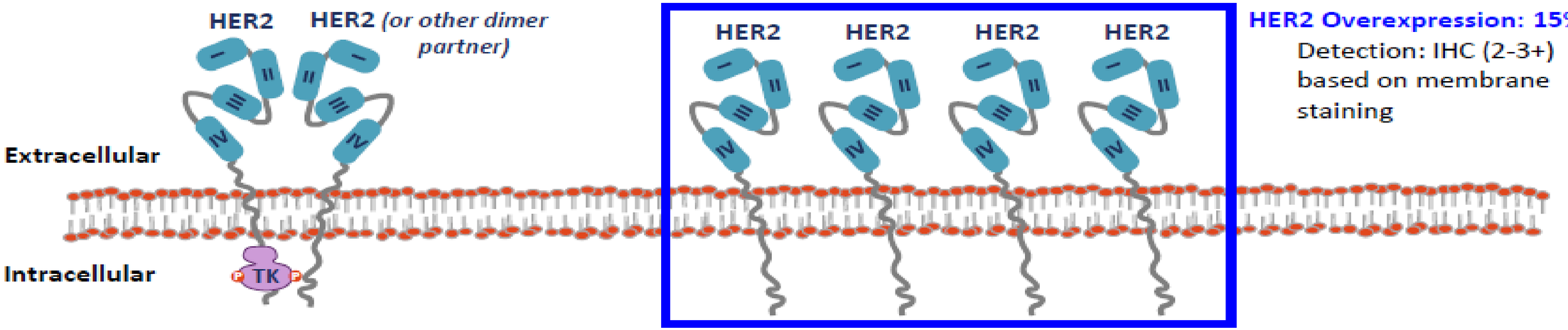
Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

- ALK single resistance mutation
- ALK compound (≥2) resistance mutation

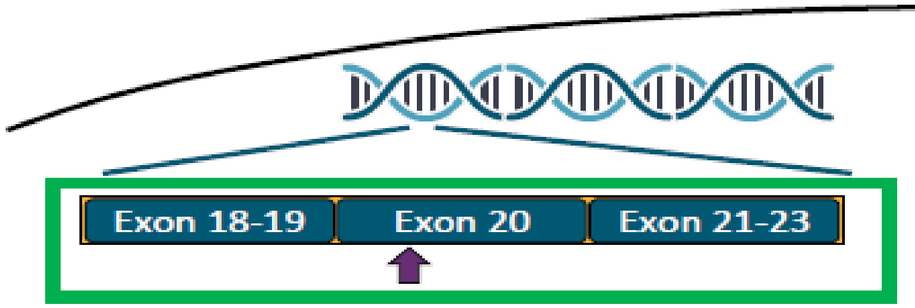
GUSTAVE ROUSSY

What is HER2-Positive NSCLC?



HER2 Overexpression: 15%-30%

Detection: IHC (2-3+) based on membrane staining



***HER2* Gene Mutation: 1%-3%**

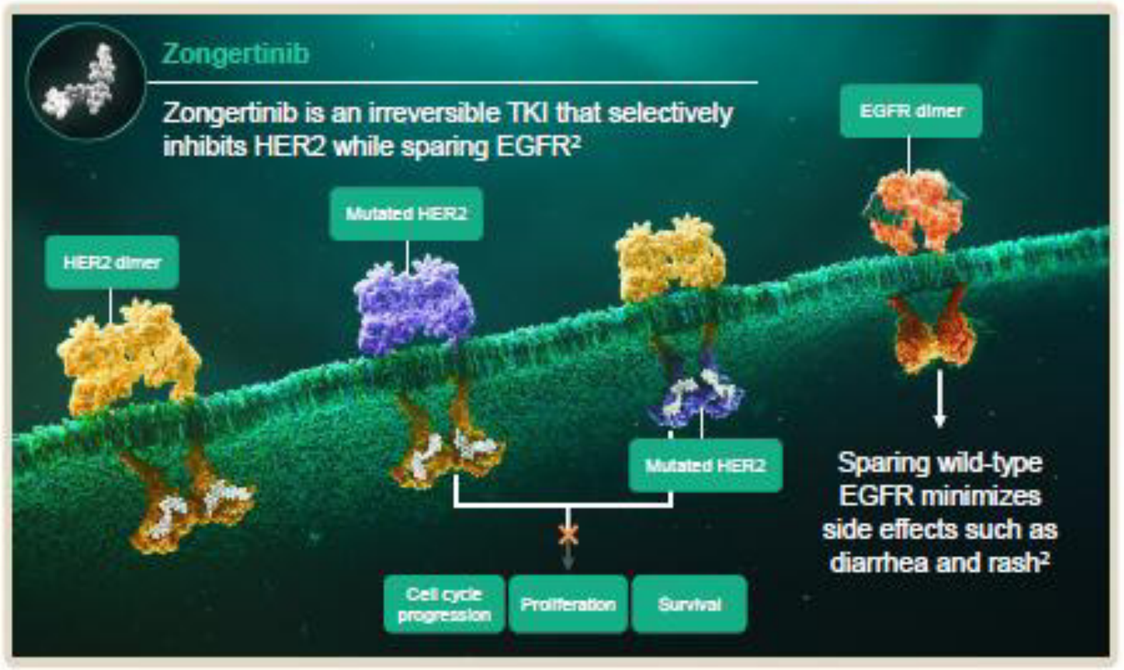
Detection: NGS (activating *HER2/ERBB2* mutation)

***HER2* Amplification: 2%-5%**

Detection: FISH (*HER2/CEP17* ratio >2 and/or HER2 copy number >6)

Zongertinib, an Oral, HER2-Specific, EGFR-Sparing TKI

- *HER2* mutations occur in approximately 2–4% of NSCLC cases, and are associated with highly aggressive disease, a poor prognosis and a high incidence of brain metastases[1]
- Zongertinib is an orally administered, irreversible TKI that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities[2]
  - In previously treated patients with *HER2*-mutant NSCLC, zongertinib provided clinically meaningful benefit and manageable safety, including in patients with brain metastases[3]
- A HER2-targeted therapy for patients with treatment-naïve *HER2*-mutant NSCLC has not yet been established; the standard of care remains chemotherapy +/- immunotherapy



A substantial unmet clinical need remains for an effective first-line HER2-targeted therapy for patients with newly diagnosed *HER2*-mutant NSCLC

Beamion LUNG-1 Study Design

Phase Ib (dose expansion): patients with advanced *HER2*-mutant NSCLC

In Phase Ia, the MTD was not reached at 360 mg QD
In Phase Ib, the selected dose after interim futility analysis was zongertinib 120 mg QD

Current analysis

Cohort 2 — **Treatment-naïve patients with TKD mutations**

Primary endpoint: Objective response by BICR (RECIST v1.1)

Secondary endpoints: DC, DoR, and PFS by BICR (RECIST v1.1)

Key inclusion criteria: aged ≥18 years, advanced/metastatic non-squamous *HER2*-mutant NSCLC (TKD mutation), ≥1 measurable non-CNS lesion (RECIST v1.1) and ECOG PS of 0/1. Patients with stable/asymptomatic brain metastases were eligible

Here we present the efficacy and safety of zongertinib 120 mg given as a first-line therapy

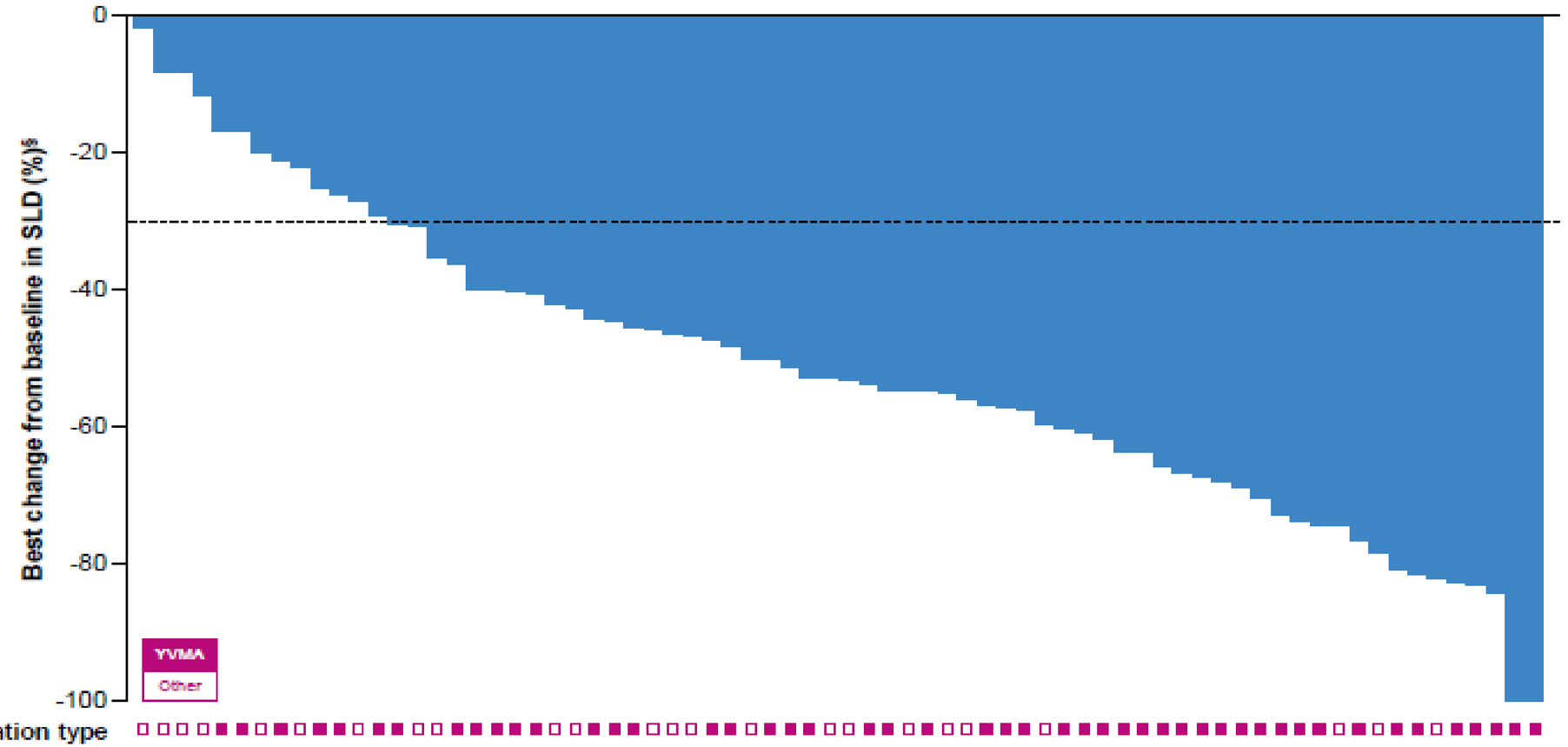
Additional cohorts not included in the current analysis

Cohort 1	Previously treated patients with TKD mutations
Cohort 3	Previously treated patients with non-TKD mutations
Cohort 4	Treatment-naïve or previously treated patients with TKD mutations and active brain metastases at baseline
Cohort 5	Patients previously treated with HER2-directed ADC and with TKD mutations

Zongertinib was recently approved in the United States (accelerated), China (conditional), and Japan for patients with previously treated advanced *HER2*-mutant NSCLC

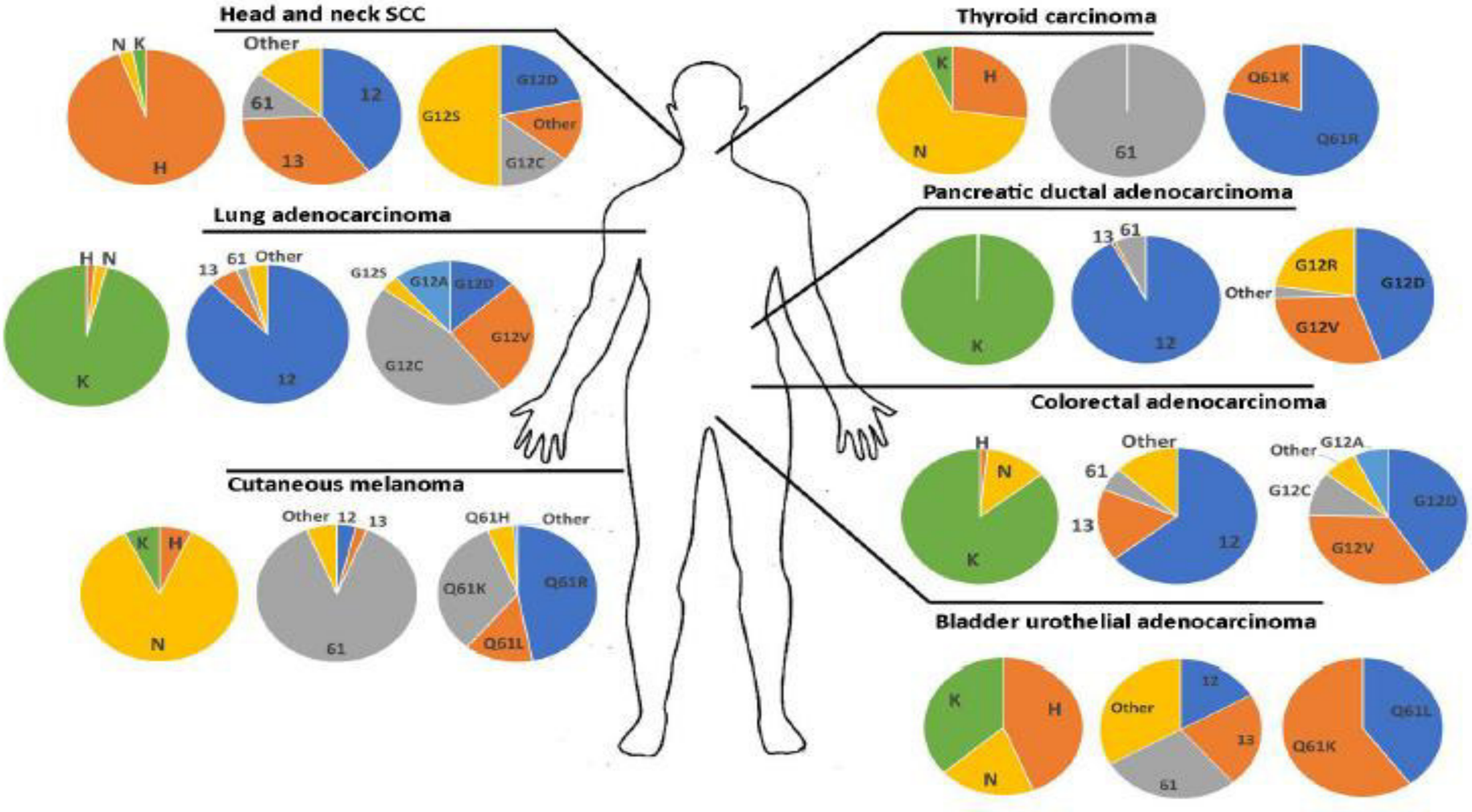
Zongertinib in Treatment-Naïve Patients: Tumor Response

Confirmed response by BICR (RECIST v1.1)	N = 74*
ORR	**77%**
95% CI	66–85
p value†	<0.0001
CR, n (%)	6 (8)
PR, n (%)	51 (69)
DCR	**96%**
95% CI	89–99
SD, n (%)	14 (19)
PD, n (%)	1 (1)‡



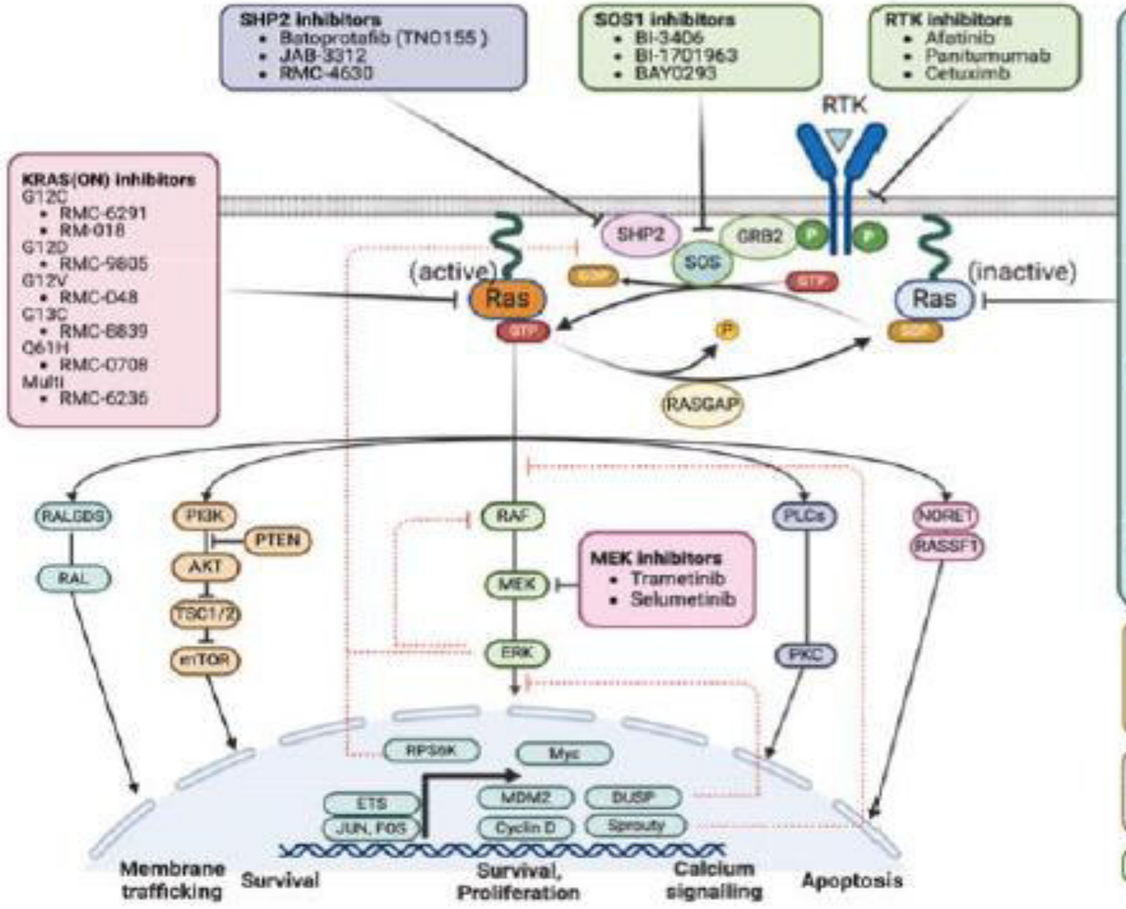
Clinical benefit was observed with zongertinib in all patients, irrespective of *HER2* mutation type

KRAS MUTATED DISEASE



Dunnett-Kane et al, Ann Oncol 2020

Newer Agents, Combinations needed to move forward…



KRAS(OFF) inhibitors
G12C
- Sotorasib
- Adagrasib
- Divarasib (GDC-6036)
- Opnurasib(JDQ443)
- Olomorasib (LY3537982)
- MK-1084
- Garsorasib(D1553)
- Glesirasib (JAB-21822)
- Fulzerasib (IBI-351)
- Bi-1823911
- JNJ-74699157
- ZG19018
- D3S-001
- GEC255
- HBI-2438
- YL-15293
- HS-10370

G12D
- MRTX1133
- HRS-4642
- JAB-22000
- KAL-21404358
- KRAS-533
- ERAS-4
- THZ-835

G12V
- JAB-23000

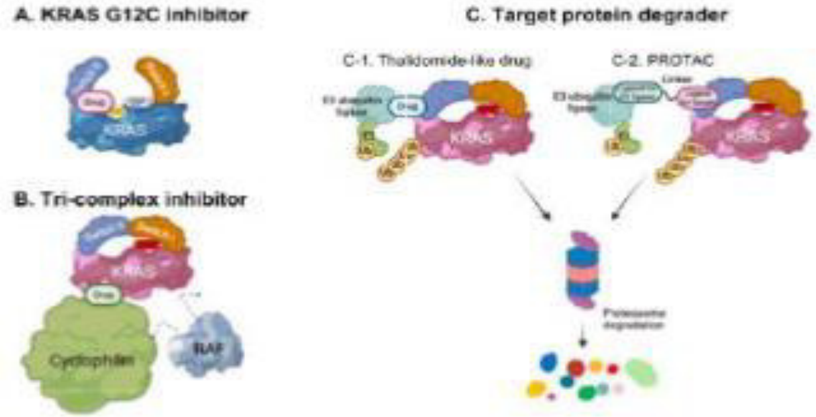
Multi
- BI-2852

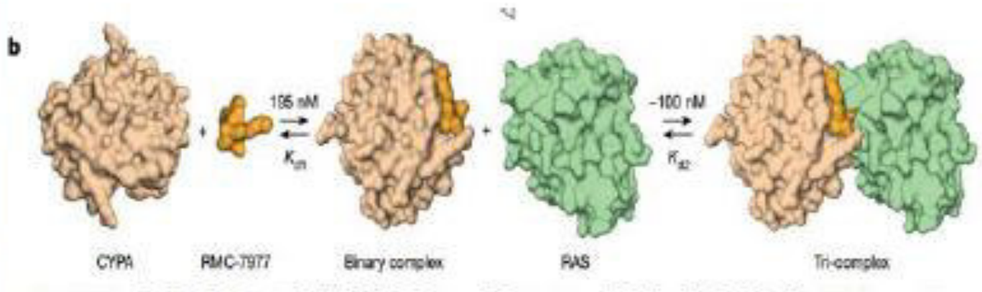
PROTAC
G12C
- LC2

G12D
- ASP3082

TCR-T
Vaccine
Hapimmune antibodies

ULK 1/2 inhibitor





RMC-7977 PanRas ON inhibitor

Oya et al Lung Cancer 2024; Holderfield et al Nature 2024

EXPANDING THE ARMAMENTARIUM BEYOND TKIS

- **Next-generation TKIs**
  → deeper, more durable responses (e.g., lorlatinib, repotrectinib, zidesmatinib)

- **Antibody–drug conjugates (ADCs)**
  → *trastuzumab deruxtecan* (approved) – new agents in development targeting TROP2, MET and others

- **Bispecific antibodies**
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- **Novel mechanisms**
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- **Cell-based and immune approaches**
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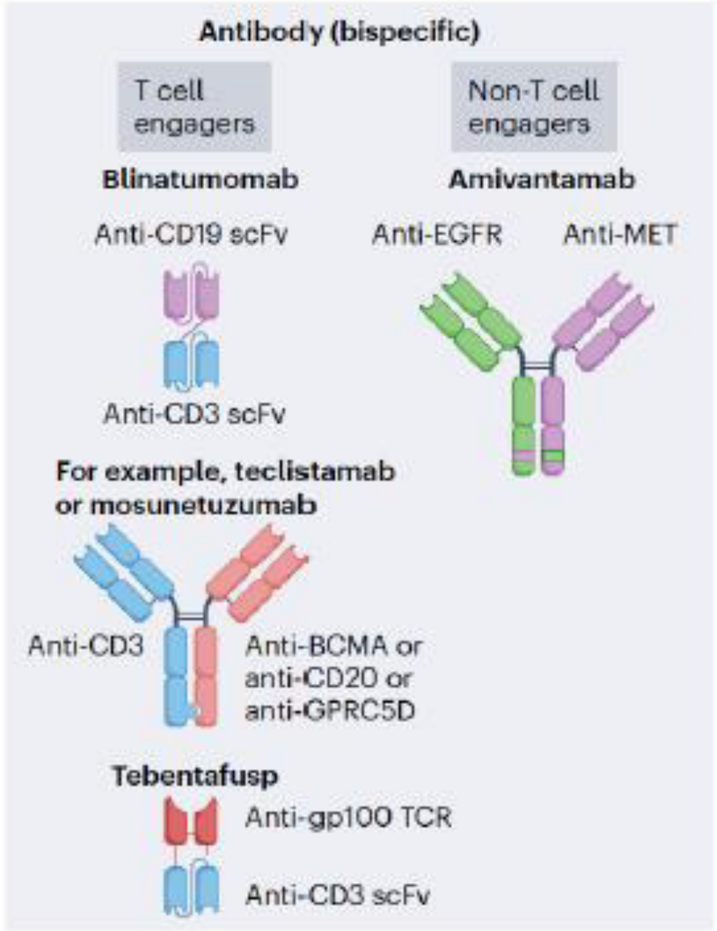
BISPECIFIC ANTIBODIES

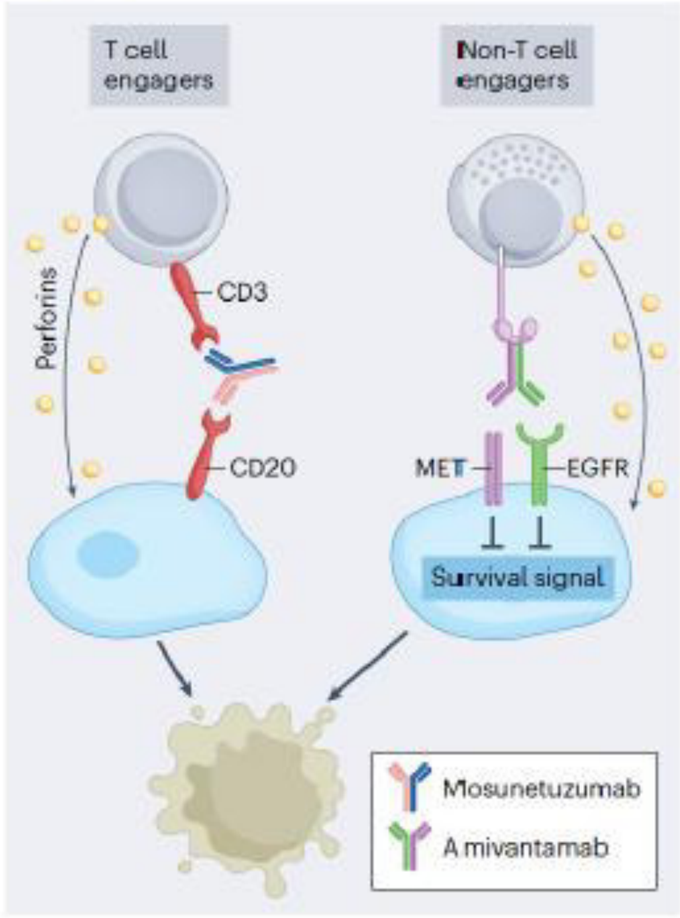
1. EGFR DISEASE: AMIVANTAMAB (MARIPOSA TRIAL)

2. SCLC DISEASE: TARLATAMAB (DELPPHI-304)

TWO MAIN CLASSES OF BISPECIFIC ANTIBODIES

Bispecific antibodies bind two different antigens or epitopes





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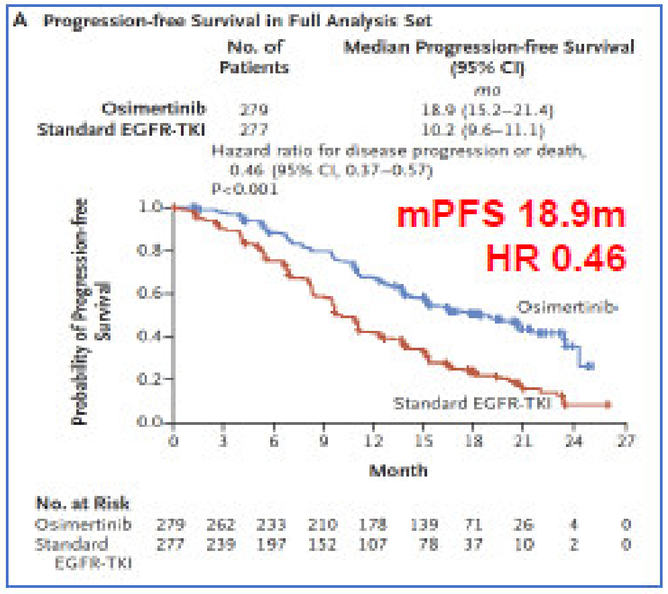
EGFR MUTATIONS (EX19DEL, L858R): BREAKING THE ESTABLISHED COMFORT ZONE

The familiar standard:

Osimertinib

vs. 1st gen. EGFR-TKI (FLAURA)

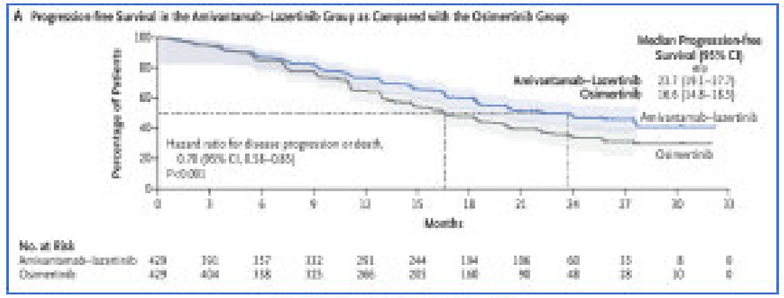


mOS: 38.6m

The challengers:

Lazertinib + amivantamab

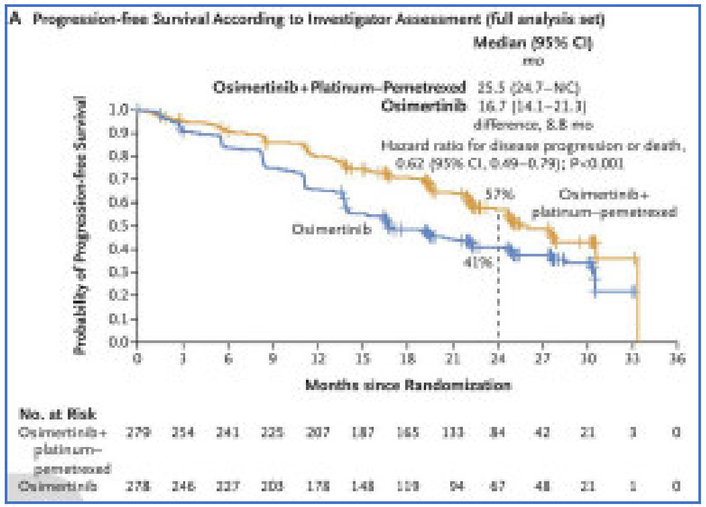
vs. osimertinib (**MARIPOSA**)



PFS: HR 0.7

Osimertinib + chemotherapy

vs. osimertinib (**FLAURA2**)

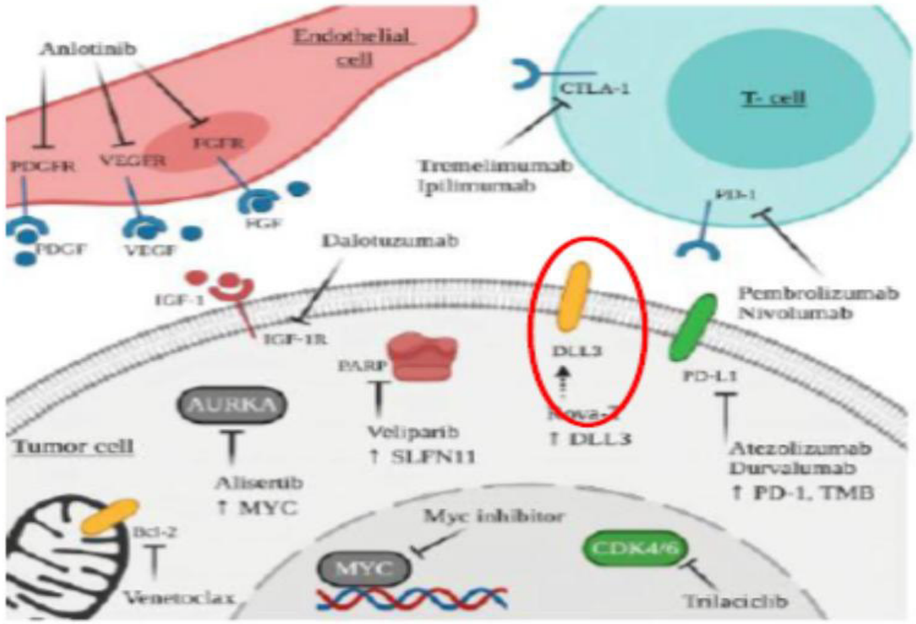


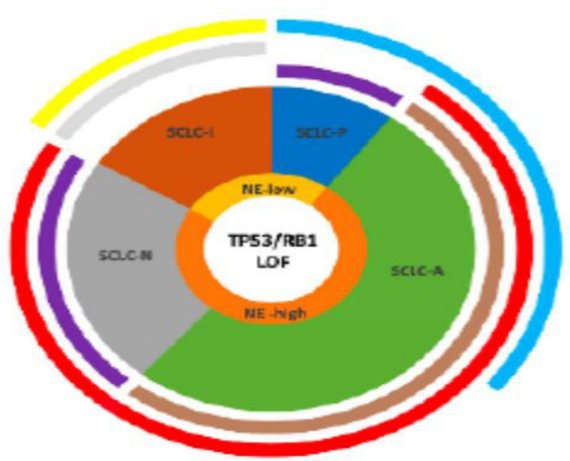
PFS: HR 0.62

> Both combinations clearly superior in PFS (primary endpoint)

DLL3: emerging target in SCLC

DLL3 is specifically expressed on the surface of SCLC tumor cells.





MYC status
- Usually MYC high
- Usually MYCL high/NOTCH low

Other markers
- DLL3
- Immune & EMT markers

Targeted therapies
- Immunotherapy
- PARPi

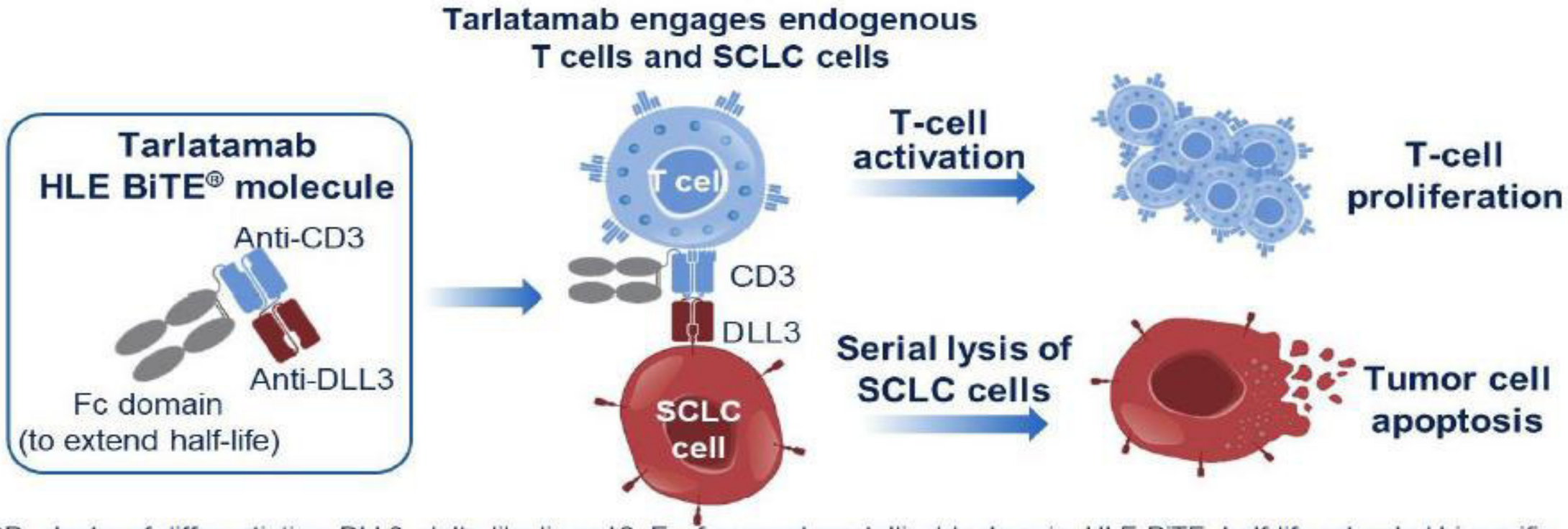
IHC Expression
- **NE-high**
  Chromogranin A^{+}, Synaptophysin^{+}, CD56^{+}, INSM1^{+}
- **NE-low**
  Chromogranin A$^{-/low}$, Synaptophysin$^{-/low}$, CD56$^{-/low}$, INSM1$^{-/low}$

Other Potential Targeted Therapies:

SCLC-A	SCLC-N	SCLC-P	SCLC-I
BCL2 inhibitors anti DLL3 targeted therapies	Aurora kinase inhibitors eSSTR2 treatment anti DLL3 targeted therapies	Anti-metabolites	BTK inhibitors

Meijer JJ, Semin Cancer Biol. 2022

Tarlatamab



CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; SCLC, small cell lung cancer.

Owonikoko et al, ASCO 2021

Randomized, controlled, phase 3 DeLLphi-304 study (NCT05740566)

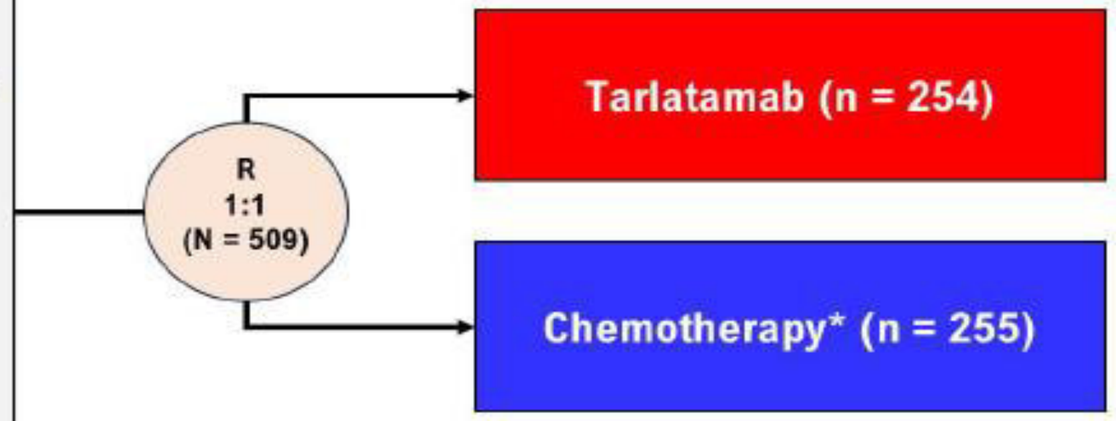
DeLLphi 304

Key inclusion criteria

- Histologically or cytologically confirmed SCLC
- Progression after 1L platinum-based chemotherapy +/- anti-PD-(L)1
- ECOG PS 0 or 1
- Asymptomatic, treated or untreated brain metastases

Randomization stratified by

- Prior anti-PD-(L)1 exposure (yes/no)
- Chemotherapy-free interval (< 90 days vs ≥ 90 to < 180 days vs ≥ 180 days)
- Presence of (previous/current) brain metastases (yes/no)
- Intended chemotherapy (topotecan/amrubicin vs lurbinectedin)



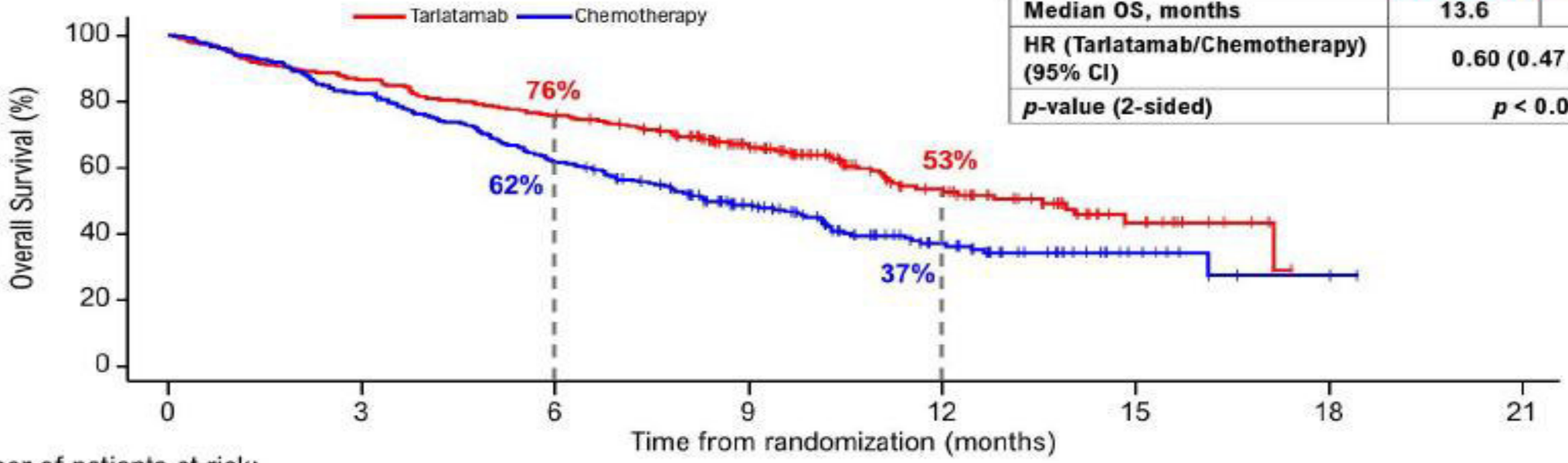
Primary Endpoint: Overall survival
Key Secondary Endpoints: Progression-free survival, patient-reported outcomes
Other Secondary Endpoints: Objective response, disease control, duration of response, safety

*Topotecan was used in all countries except Japan, lurbinectedin in Australia, Canada, Republic of Korea, Singapore and the United States, and amrubicin in Japan.
1L, first-line; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **PD-(L)1,** programmed death (ligand)-1; **R,** randomization; **SCLC,** small cell lung cancer.

Mountzious et al, NEJM 2025

DeLLphi-304 met its primary endpoint with tarlatamab demonstrating superior overall survival over chemotherapy

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Median OS, months	13.6	8.3
HR (Tarlatamab/Chemotherapy) (95% CI)	0.60 (0.47, 0.77)	
p-value (2-sided)	*p* < 0.001	



Number of patients at risk:

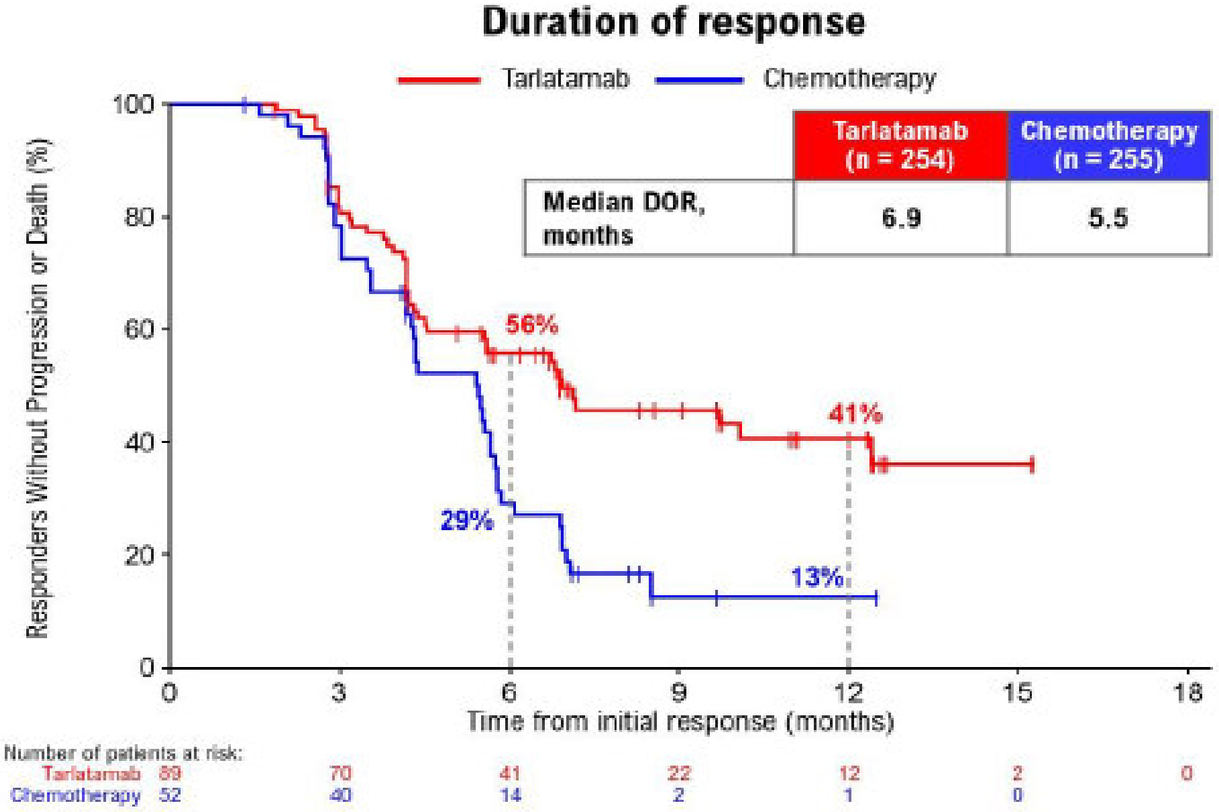
Tarlatamab	254	220	192	131	60	17	0
Chemotherapy	255	210	156	97	42	9	2	0

Median follow-up time: 11.2 months for the tarlatamab group and 11.7 months for the chemotherapy group. *p*-value was calculated using a stratified log-rank test.
HR, hazard ratio; **OS**, overall survival.

Mountzious et al, NEJM 2025

Tarlatamab was associated with more frequent and more durable responses

	Tarlatamab (n = 254)	Chemotherapy (n = 255)
Best overall response[*†], n (%)		
Complete response	3 (1)	0 (0)
Partial response	86 (34)	52 (20)
Stable disease	84 (33)	112 (44)
Progressive disease	56 (22)	50 (20)
Not evaluable/no post-baseline scan	25 (10)	41 (16)
Objective response rate[‡], % (95% CI)	35 (29–41)	20 (16–26)
Median duration of response, months	6.9	5.5
Median time to objective response, months	1.5	1.4
Ongoing response at data cutoff, n[§] (%)	42 (47)	8 (15)



*Assessment of disease response was based on RECIST 1.1 guidelines. Confirmation of complete response and partial response was required no fewer than 4 weeks after initial documentation of complete response or partial response. †Investigator-assessed response in the intention-to-treat analysis set; ‡Odds ratios and *p* value not shown as the difference in ORR between the 2 arms was not formally tested. §Percentage of total number of responders.

DOR, duration of response; **IRECIST**, Response Evaluation Criteria in Solid Tumors.

Mountzious et al, NEJM 2025

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Advanced Radiation Therapy

TARLATAMAB is now the standard of care for second-line therapy in ES-SCLC

EXPANDING THE ARMAMENTARIUM BEYOND TKIS

- **Next-generation TKIs**
  → deeper, more durable responses (e.g., lorlatinib, repotrectinib, zidesmatinib)

- **Antibody–drug conjugates (ADCs)**
  → *trastuzumab deruxtecan* (approved) – new agents in development targeting TROP2, MET and others

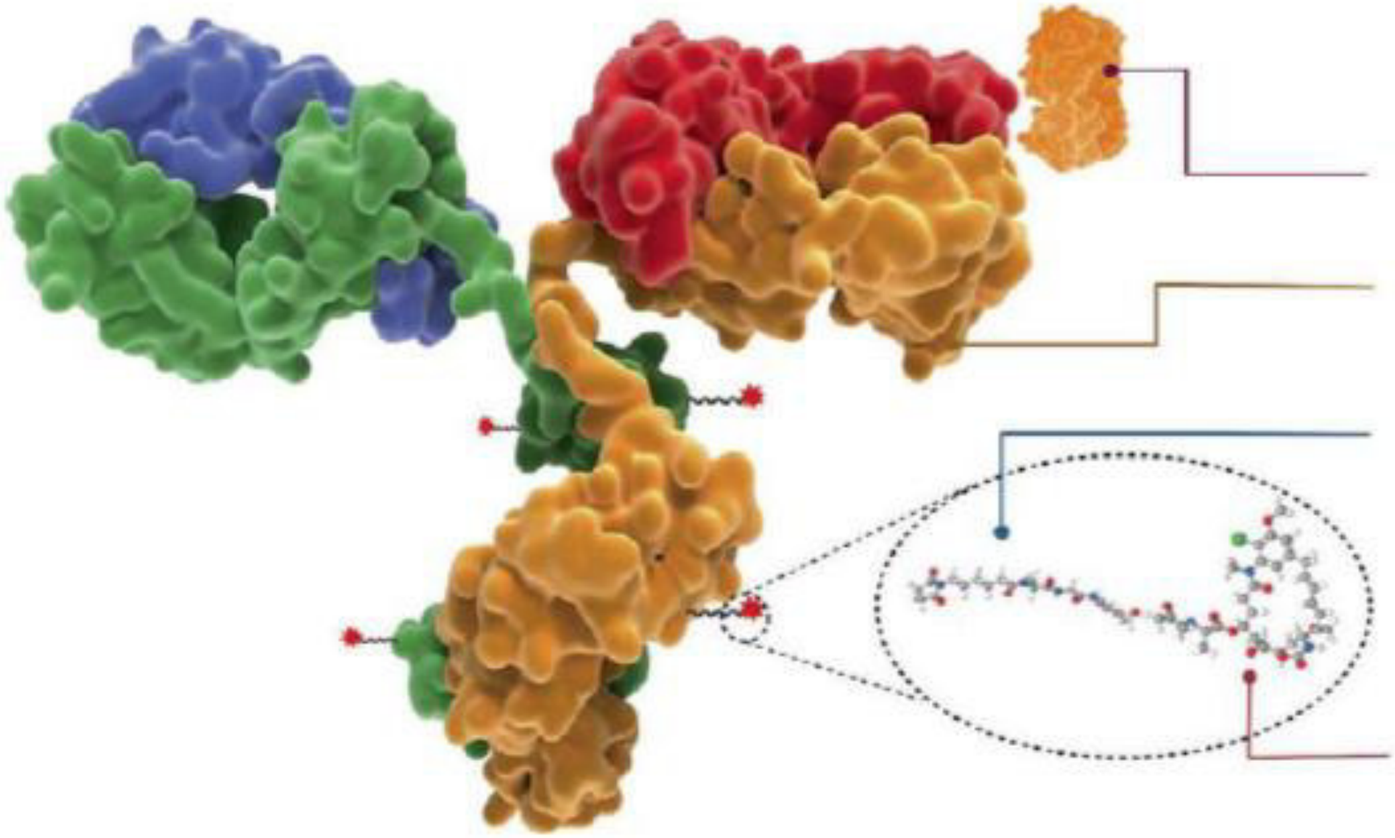
- **Bispecific antibodies**
  → *amivantamab* (EGFR/MET; approved), *ivonescimab* (PD-1/VEGF) – early promising results and others

- **Novel mechanisms**
  → MET degraders, PROTACS, SHP2 and SOS1 inhibitors, pan-KRAS inhibitors and others

- **Cell-based and immune approaches**
  → T-cell vaccines, CAR-T concepts in early testing

THE CHALLENGE

The relationship between target expression and ADC response is controversial



Key functions

Target antigen	Recognition of target cancer cells
Antibody	Guidance system for cytotoxic drugs
Linker	Bridge between antibody and drugs and to control the release of drugs inside cancer cells
Cytotoxic drug	Warhead for destroying cancer cells

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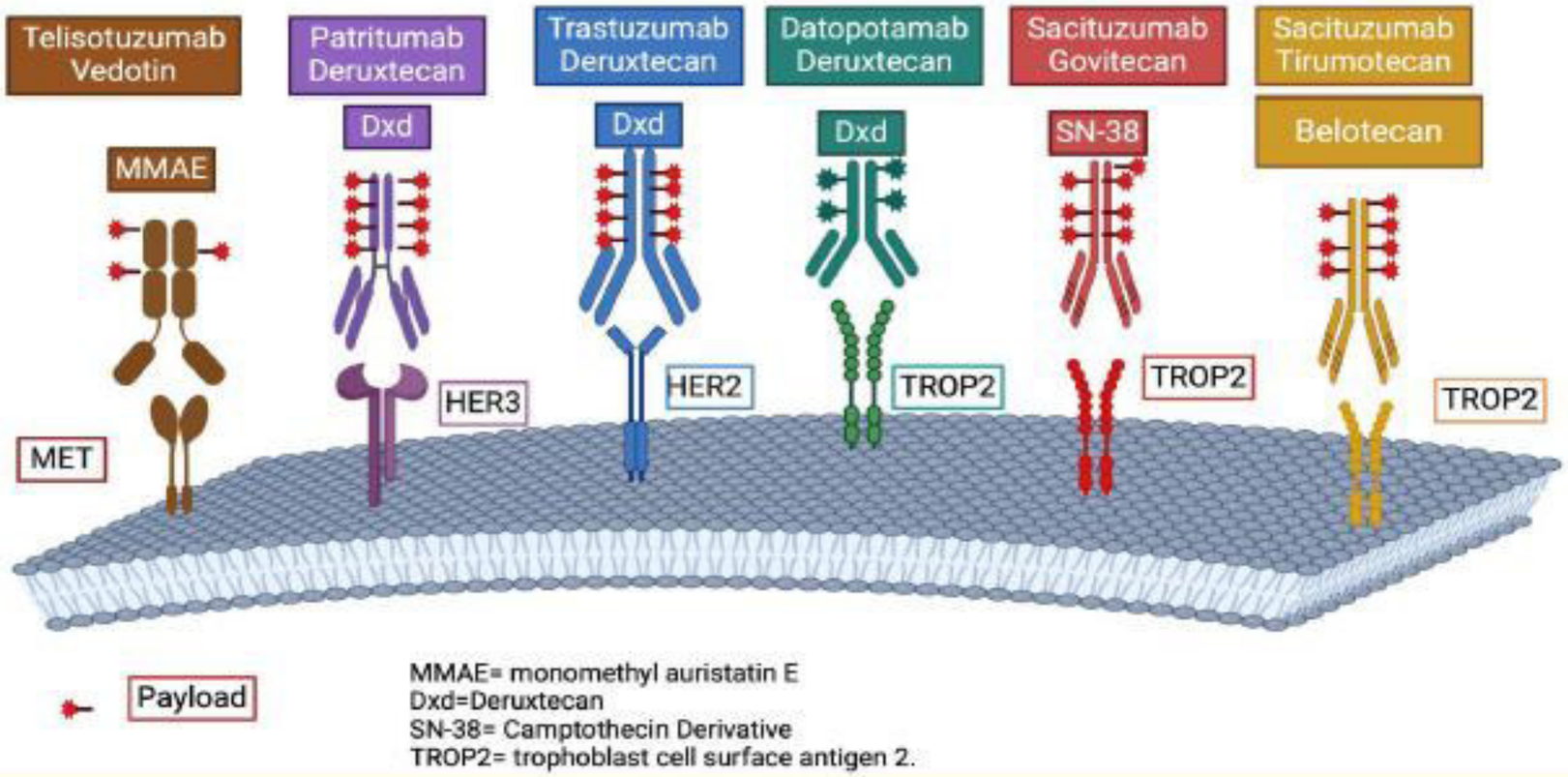
FDA-APPROVED ADC IN SOLID TUMORS …as of September 2025

Generic name	FDA approved indication	Year of approval	Molecular Target	Payload Class	MoA
Trastuzumab Emtansine	HER2+ breast cancer	2013	HER2	Maytansine	Microtubule inhibitor
Trastuzumab Deruxtecan	HER2+/low breast cancer	2019	HER2	Camptothecin	Topoisomerase I inhibitor
Sacituzumab Govitecan	Tripple-negative Breast cancer	2021	Trop-2	Camptothecin	Topoisomerase I inhibitor
Enfortumab Vedotin	Urothelial Carcinoma	2021	Nectin-4	Auristatin	Microtubule inhibitor
Trastuzumab Deruxtecan	HER2-mutant NSCLC HER2 IHC +++	2022	HER2	Camptothecin	Topoisomerase I inhibitor
Mirvetuximab Soravtansine	FRa+ ovarian cancer	2022	Folate receptor alpha	Maytansine	Microtubule inhibitor
Tisotumab Vedotin	Cervical Cancer	2022	Tissue factor	Auristatin	Microtubule inhibitor
Telisotuzumab Vedotin	MET IHC pos NSCLC	2025	c-Met	Auristatin	Microtubule inhibitor
Datopotamab Deruxtecan	ER (+), HER2(-) breast cancer	2025	Trop-2	Camptothecin	Topoisomerase I inhibitor
Datopotamab Deruxtecan	EGFR (+) NSCLC Pre-treated	2025	Trop-2	Camptothecin	Topoisomerase I inhibitor

Anatomy of an ADC: The target



Biomarker –selected ADCs: Efficacy of the ADC is related to the level of expression of the biomarker, ie c-MET, HER2

Biomarker-agnostic ADCs: Efficacy of the ADC seems to be independent of the level of expression of the biomarker, ie TROP2, HER3

ADC

1. **HER-2 DISEASE**: TRASTUZUMAB DERUXTECAN
2. **EGFR DISEASE**: DATO-DXT, SACI-TIRU, TELISO-ADI
3. **MET DISEASE:** TELISO-V, ABBV-400

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DESTINY-Lung01: study design

•Phase 2 study of T-DXd, a novel antibody-drug conjugate, in patients with HER2-overexpressing or HER2-mutated metastatic NSCLC

Key eligibility criteria
- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline
- ECOG PS of 0 or 1

Cohort 1:
HER2-overexpressing[a]
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
n = 49

Cohort 1a:
HER2-overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
n = 41

Cohort 2:
HER2-mutated
T-DXd 6.4 mg/kg q3w
n = 42

Cohort 2 expansion:
HER2-mutated
T-DXd 6.4 mg/kg q3w
n = 49

Primary end point
- Confirmed ORR by ICR

Secondary end points
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

Exploratory end point
- Biomarkers of response

ClinicalTrial.gov: NCT03505710

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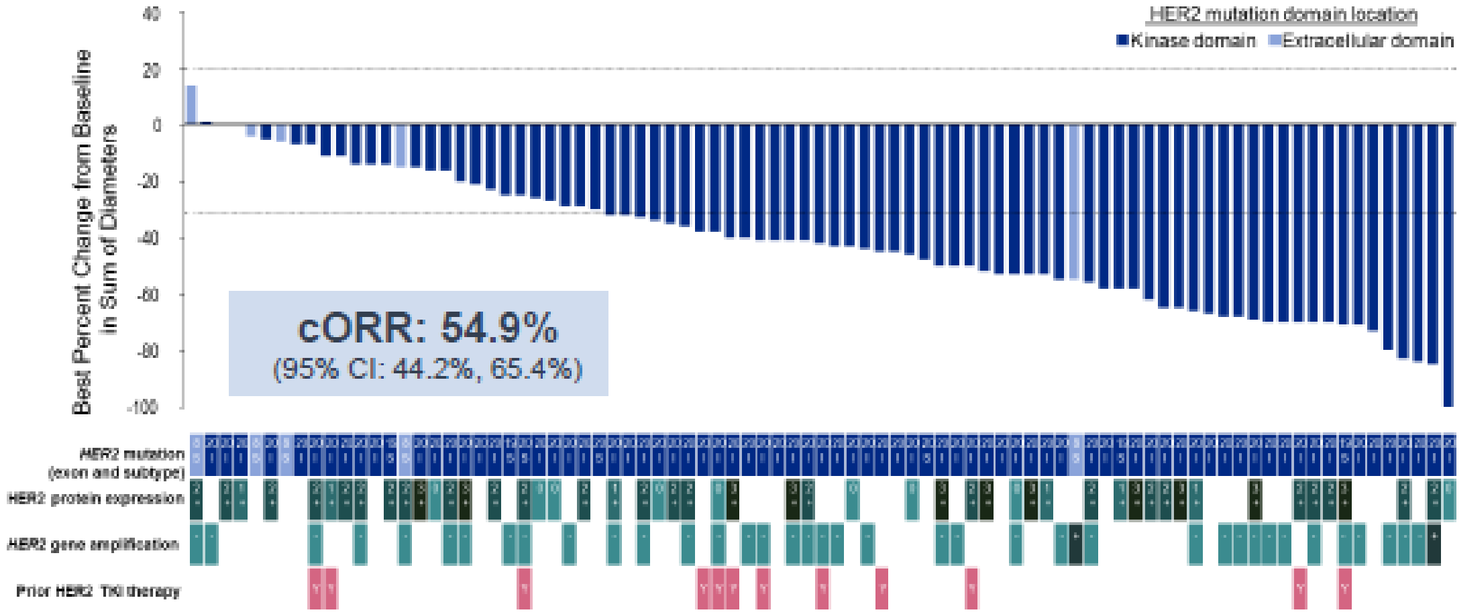
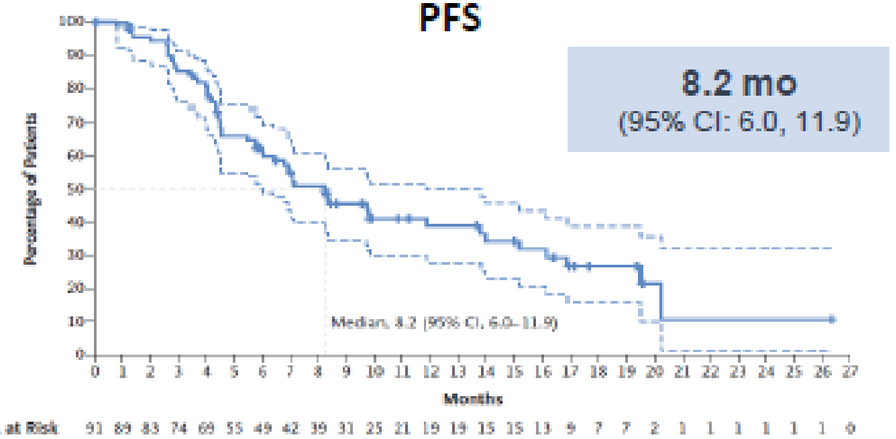
Efficacy of T-DXd in *HER2*-mutant NSCLC DESTINY-Lung01*: Cohort 2*

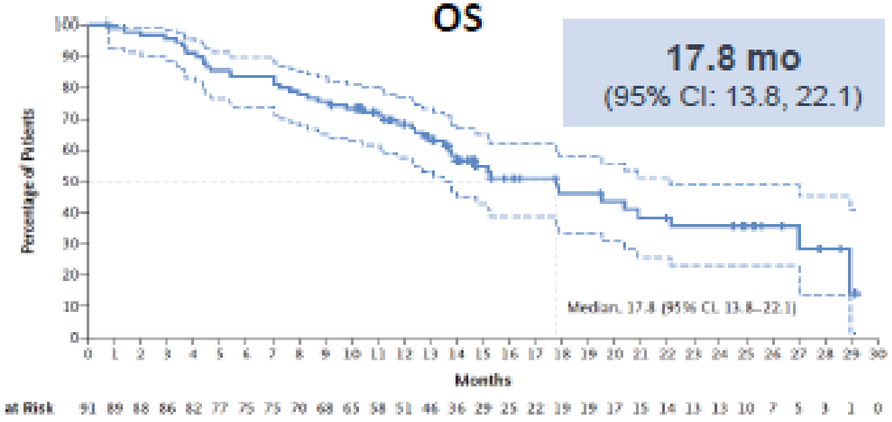
Best Percentage Change From Baseline in Sum of Diameters (n = 85)



PFS



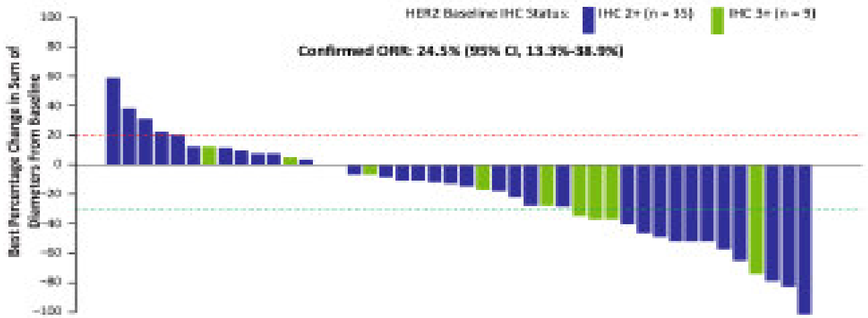
OS



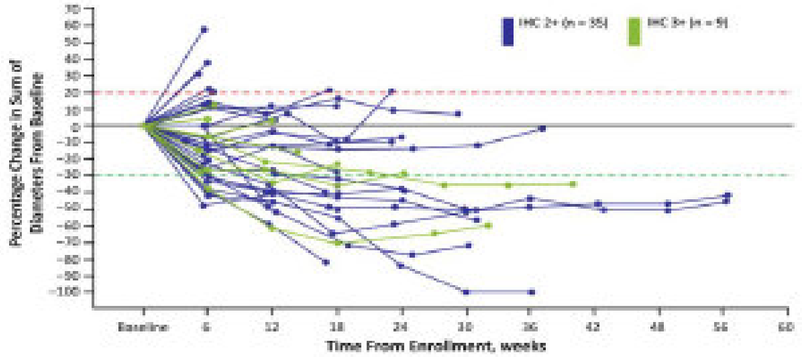
T-DXd 6.4 mg/kg showed durable anticancer activity with confirmed objective responses occurring in 55% of patients and a median DOR of 9.3 months

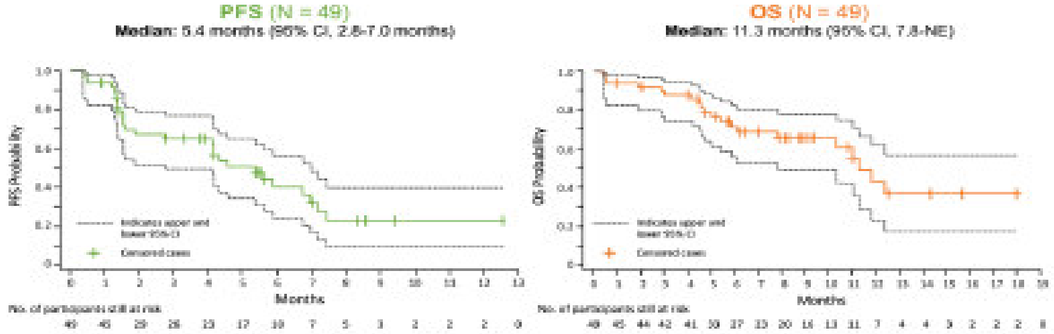
Efficacy of T-DXd in *HER2*-overexpressing NSCLC DESTINY-Lung01: *Cohort 1*

Best Percentage Change in Tumor Size With T-DXd



Change in Tumor Size Over Time With T-DXd





Key data

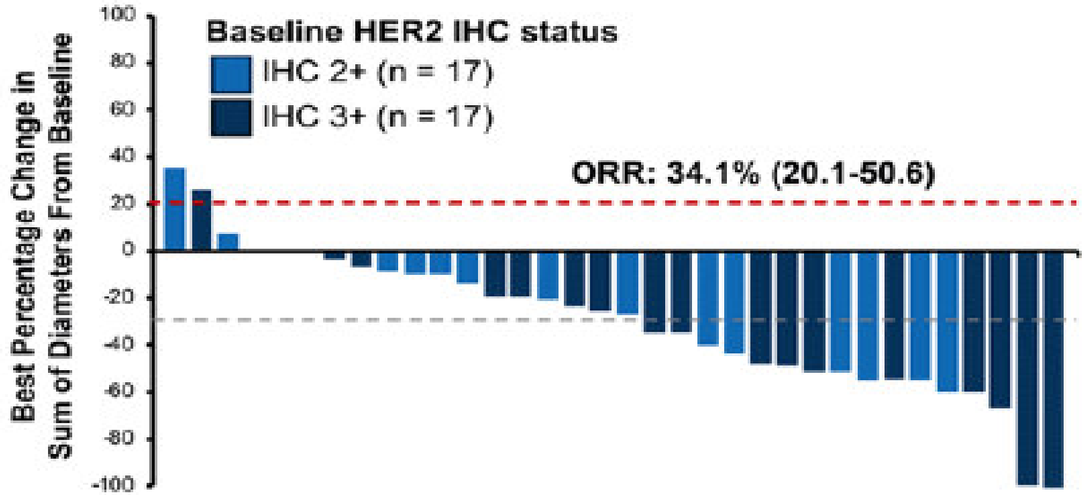
Extensively pretreated pts median of 3L of therapies (range, 1-8),

- ORR of 24.5%, with no apparent difference by HER2 expression (IHC 3+ vs 2+)
- DCR of 69.4%
- mPFS of 5.4 months
- mOS of 11.3 mohnts
- ILD occurred in 16,3%

Smit EF et al. Lancet Oncol. 2004

Efficacy of T-DXd in *HER2*-overexpressing NSCLC
DESTINY-Lung01*: Cohort 1*

Cohort 1a
Trastuzumab Deruxtecan 5.4 mg/kg
(n = 41)



mPFS: 6.7 mo
(95% CI, 4.2-8.4)

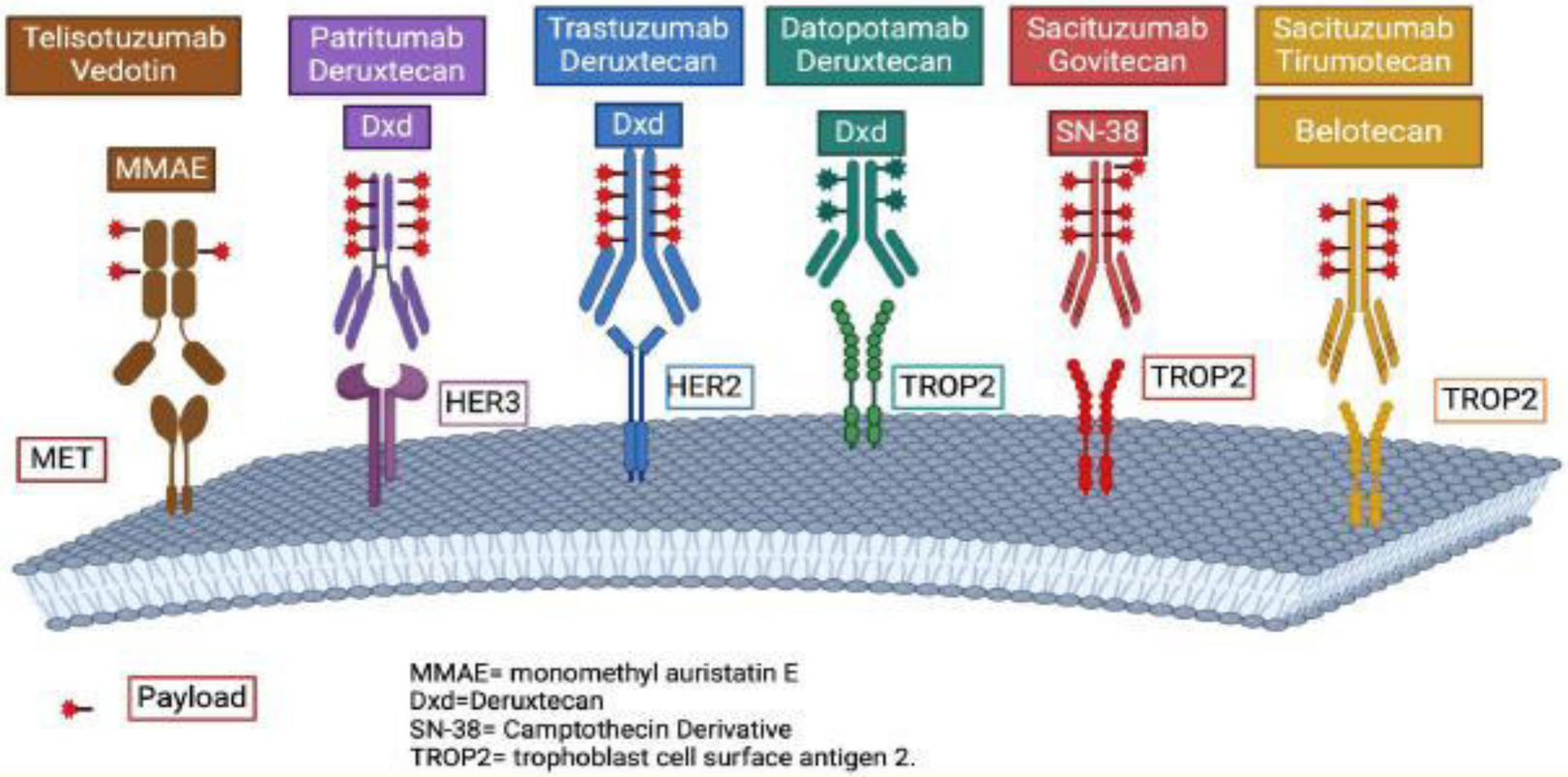
HER2-positive IHC3+ NSCLC

Efficacy Parameter	DESTINY-Lung01 (Cohort 1a) (n = 17)[2]
Confirmed ORR, % (95% CI)	52.9 (27.8-77.0)
CR	5.9
PR	47.1
mDOR, mo (range)	6.9 (4.0-11.7)

On April 5, 2024, T-DXd received accelerated approval for patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options

Smit EF et al. Lancet Oncol. 2004

Anatomy of an ADC: The target



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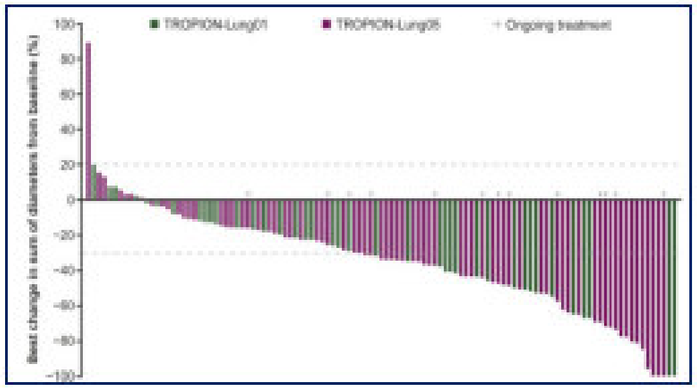
ADCS EFFECTIVE IN EGFR-MUTATED NSCLC TARGETING TROP-2 AND MET

Datopotamab-deruxtecan
Target Trop-2

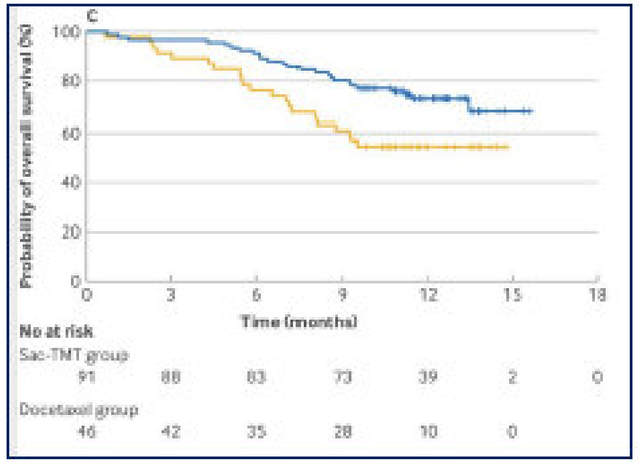
Pooled analysis from 2 phase II trials of EGFRmut pts. post EGFR-TKI



ORR: 43%
PFS: 5.8m
OS: 15.6m

Sacituzumab-tirumotecan
Target Trop-2

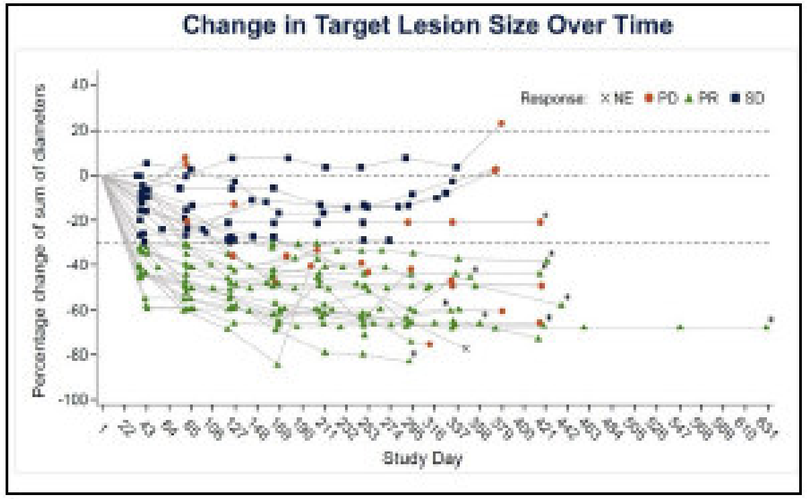
Phase III vs. docetaxel in EGFRmut pts. 3L



ORR: 45% vs. 16%
PFS: 6.9m vs. 2.8m
12m OS: 73% vs. 54%

Telisotuzumab-adizutecan
Target MET

Phase I in pretreated EGFRmut pts



ORR: 63%
PFS: 10.0m
12m OS: 69%

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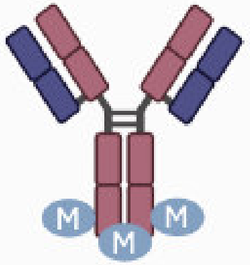
Two ADCs for MET under investigation

Teliso-V

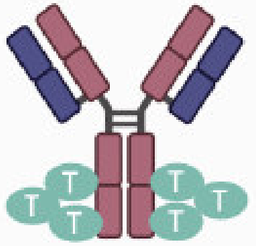
- Same base monoclonal antibody
- Payload: MMAE (Microtubulin inhibitor)
- c-MET target clinical validation



Phase 3 Clinical (FIH 2014)

ABBV-400

- Same base monoclonal antibody
- Payload: Topi (Topoisomerase 1 inhibitor (Top1i)
- Clinically validated mechanism



Phase 1 Clinical (FIH 2021)

MET targeted activity of franchise assets is not dependent on inhibition of MET signaling

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EXPANDING THE ARMAMENTARIUM BEYOND TKIS

- **Next-generation TKIs**
  → deeper, more durable responses (e.g., lorlatinib, repotrectinib, zidesmatinib)

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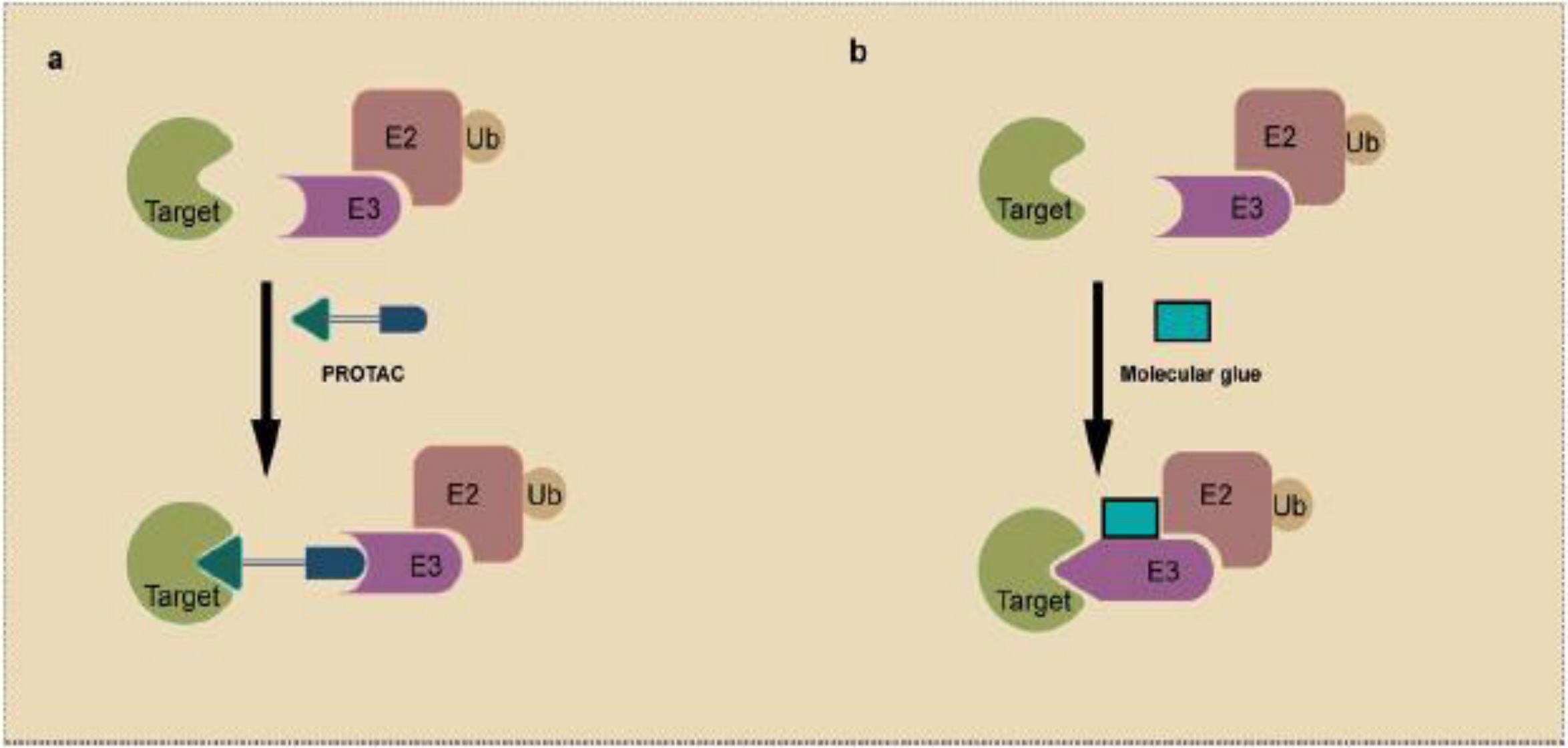
- **Cell-based and immune approaches**
  → T-cell vaccines, CAR-T concepts in early testing


a
Target
E2
Ub
E3
PROTAC
Target
E2
Ub
E3
b
Target
E2
Ub
E3
Molecular glue
Target
E2
Ub
E3

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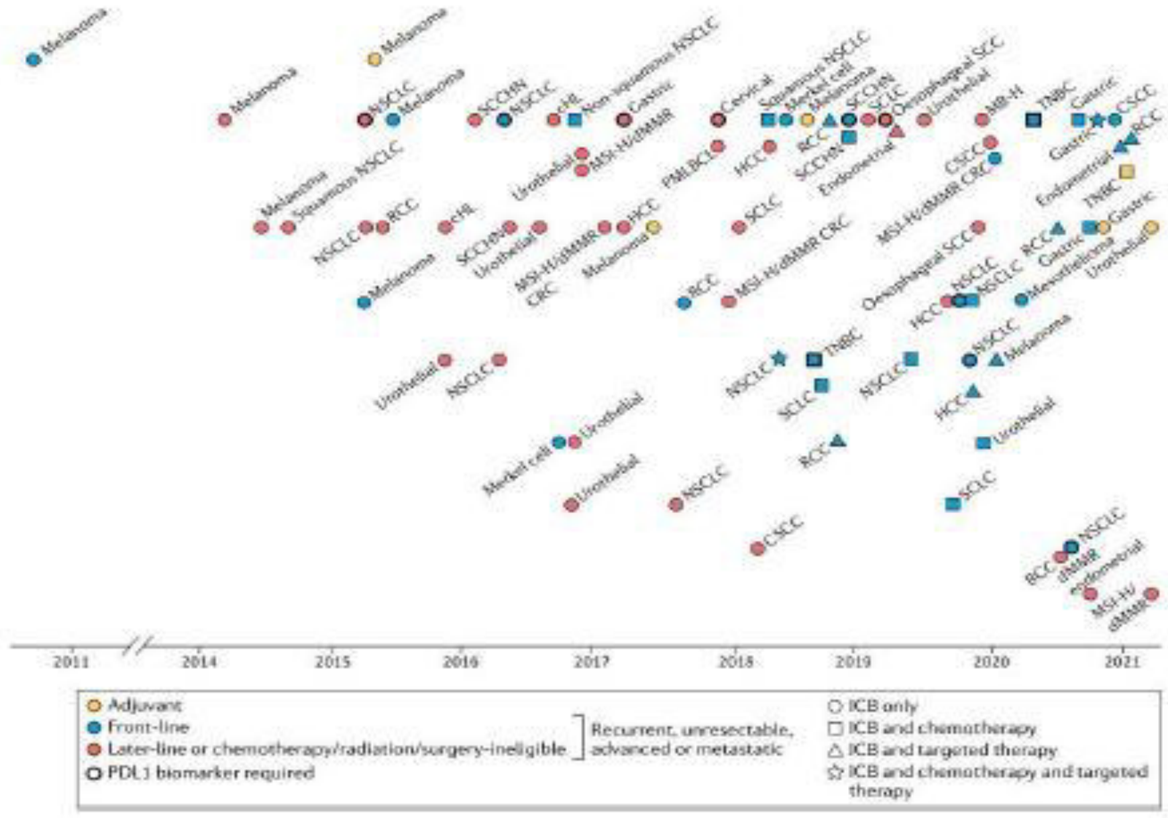
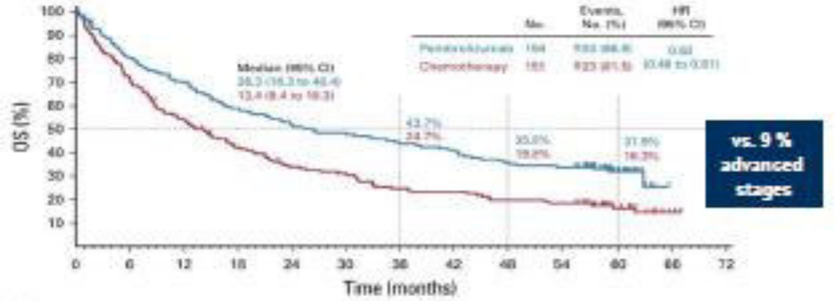
Systemic therapy: Immunotherapy

Immune Checkpoint Inhibitors, Clinical development

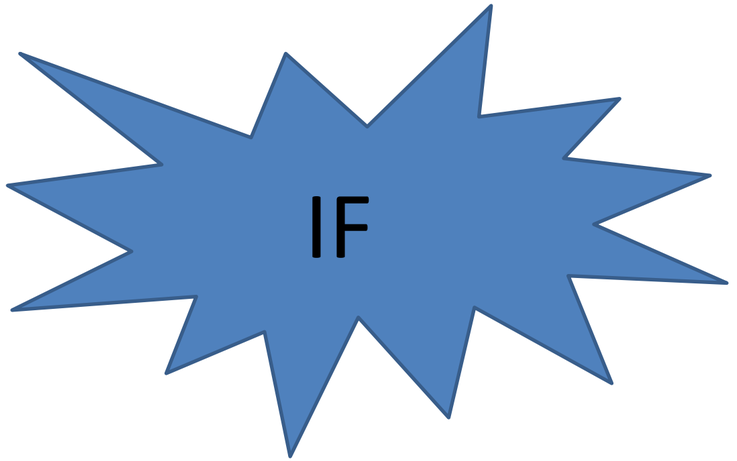


KEYNOTE 024, NSCLC, 5 years OS

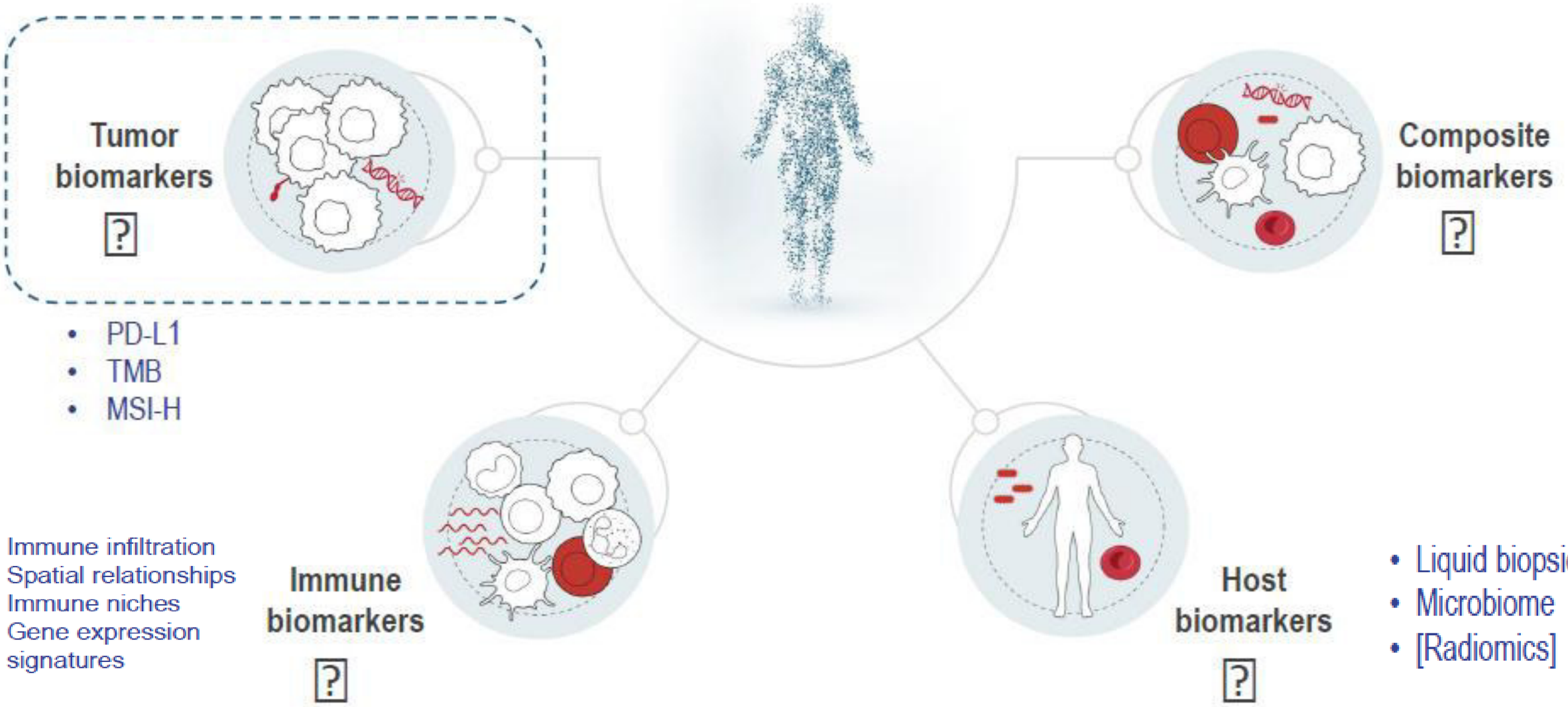


Korman, Garret-Thomson, Nat Rev Drug Discov 2022;
https://www.cancerresearch.org/pd-1-pd-l1-landscape,
Reck, M. et al, J Clin Oncol 2021

RESPONCE TO IMMUNOTHERAPY



Overview of biomarker classes to predict CPI response



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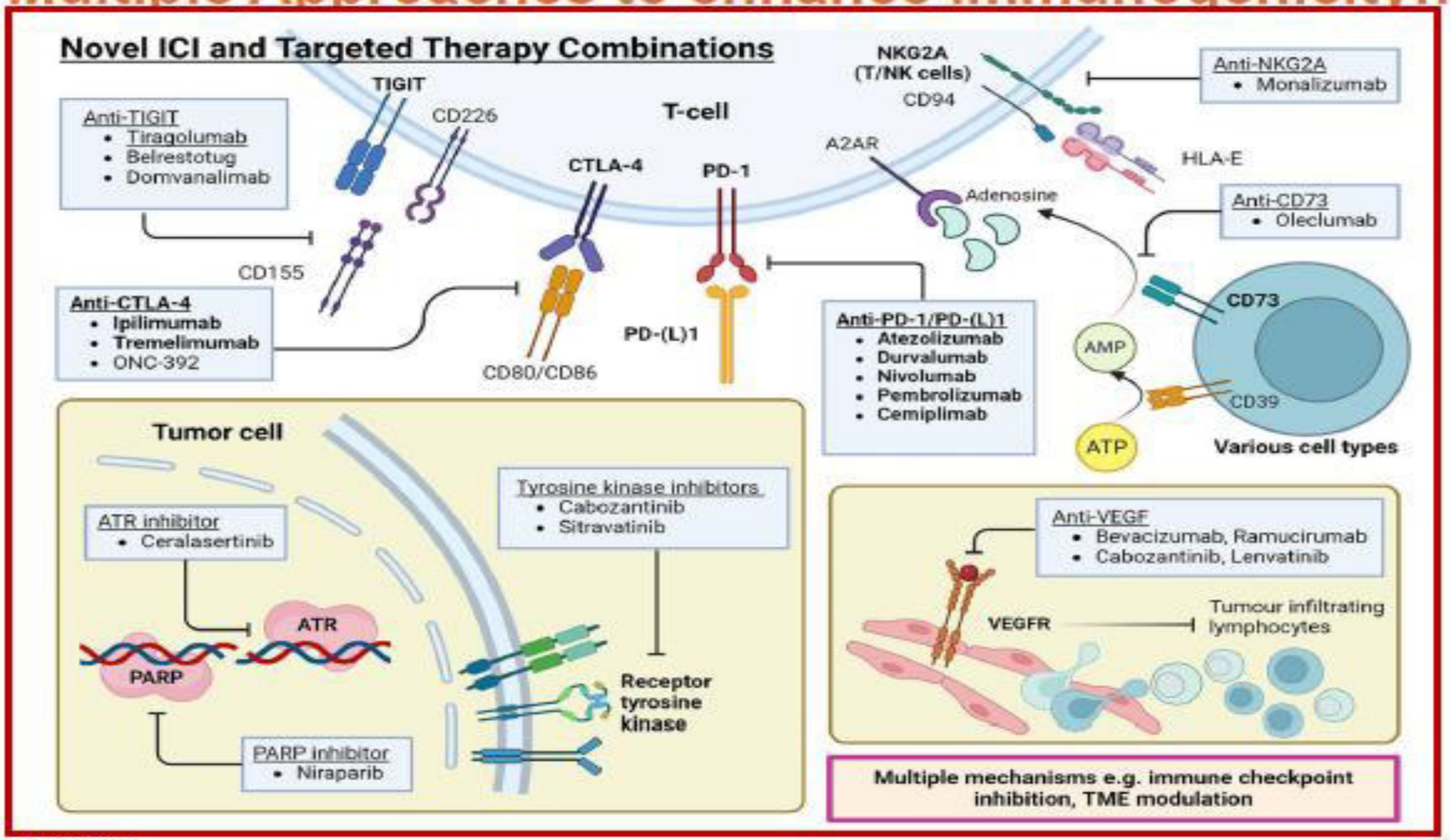
Multiple Approaches to enhance immunogenicity…



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Ivonescimab in NSCLC: *Phase III trials*

Ivonescimab

EGFR pop after TKI (2L)

HARMONi

2L+ NSQ NSCLC EGFRm+ after a 3rd Gen TKI

Ivonescimab + chemo
vs. placebo + chemo

Summit Therapeutics

HARMONi-A

2L+ NSQ NSCLC EGFRm+ after a TKI

Ivonescimab + chemo
vs. placebo + chemo

Akesobio

Asian pop

Combo + Chemo

No driver NSCLC (1L)

HARMONi-2

1L SQ + NSQ NSCLC PD-L1 TPS ≥ 1%

Ivonescimab
vs. pembrolizumab

Akesobio

Asian pop

HARMONi-3

1L NSCLC Squamous

Ivonescimab + chemo
vs. pembrolizumab + chemo

Summit Therapeutics

Mono therapy

Combo + Chemo

https://www.smmtx.com/digital-library/
Zhang L et al. ASCO 2024,
Zhao YY et al. eClinicalMedicine 2023,
Goldman J, WCLC 2025

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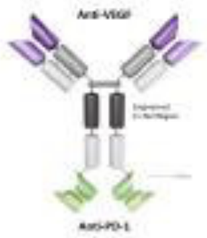
Ivonescimab in NSCLC: *Phase III trials*



Ivonescimab

EGFR pop after TKI (2L)

HARMONi

2L+ NSQ NSCLC EGFRm+ after a 3rd Gen TKI

Ivonescimab + chemo
vs. placebo + chemo

Summit therapeutics

HARMONi-A

Approved in China

2L+ NSQ NSCLC EGFRm+ after a TKI

Ivonescimab + chemo
vs. placebo + chemo

Akesobio

Asian pop

Combo + Chemo

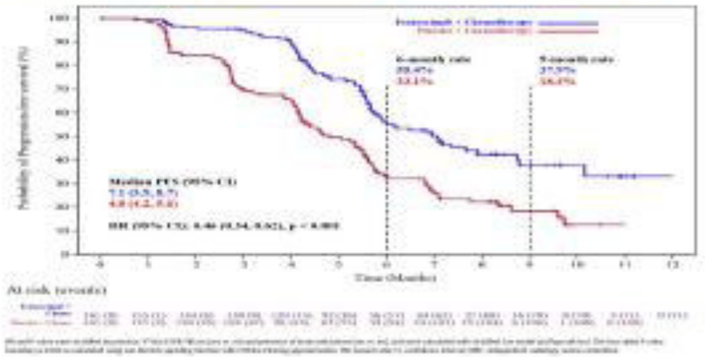
Primary Endpoint: Overall Survival

HARMONi

Favorable Trend Observed; NA & EU Follow-up Not Yet Mature

No detrimental impact on any predefined subgroups

HARMONi-A: Study Met Primary Endpoint of PFS per IRRC



https://www.ommtx.com/digital-library/
Zhang L et al. ASCO 2024,
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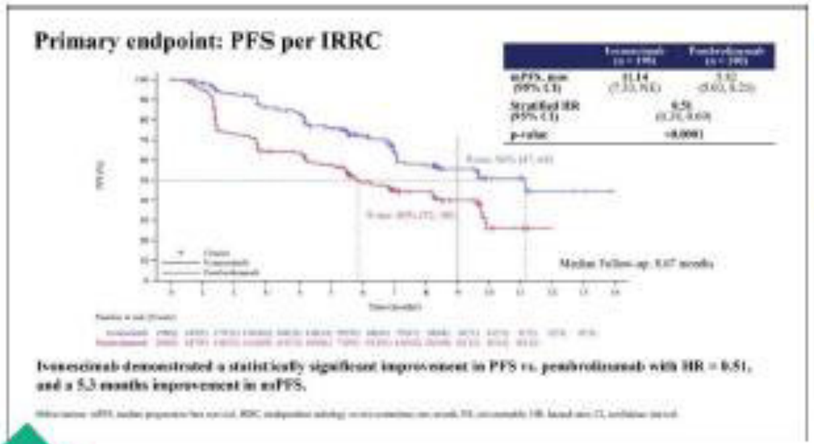
Ivonescimab in NSCLC: *Phase III trials*

Ivonescimab



HARMONI- 6

Asian pop

Presidential Symposium II

LBA4 - Phase III study of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small cell lung cancer (HARMONI-6)

No driver NSCLC (1L)

HARMONI-2

1L SQ + NSQ NSCLC PD-L1 TPS ≥ 1%

Ivonescimab
vs. pembrolizumab

Akesobio

Asian pop

HARMONI-3

1L NSCLC Squamous

Ivonescimab + chemo
vs. pembrolizumab + chemo

Summit Therapeutics

Mono therapy

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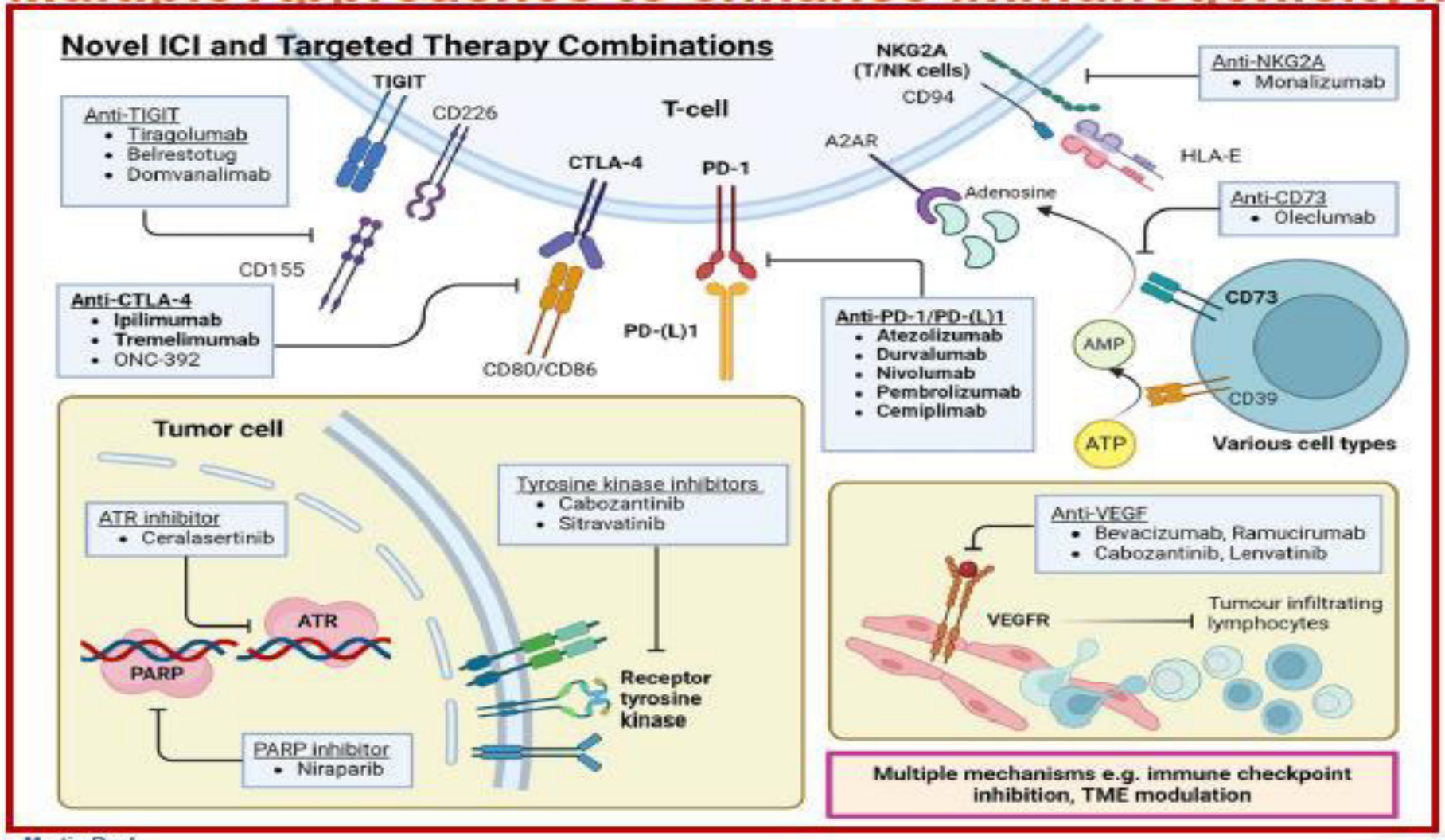
Multiple Approaches to enhance immunogenicity…



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NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Tina Cascone,[1] Florian Guisier,[2] Laura Bonanno,[3,4] Moishe Liberman,[5,6] Olivier Bylicki,[7] Amelia Insa,[8] Lorenzo Livi,[9] Romain Corre,[10] Thomas Egenod,[11] Agata Bielska,[12] Alula Yohannes,[13] Ray Mager,[13] Yun He,[12] Adam Dowson,[14] Lara McGrath,[12] Rakesh Kumar,[13] Italia Grenga,[12] Jonathan Spicer,[15] Patrick Forde[16]

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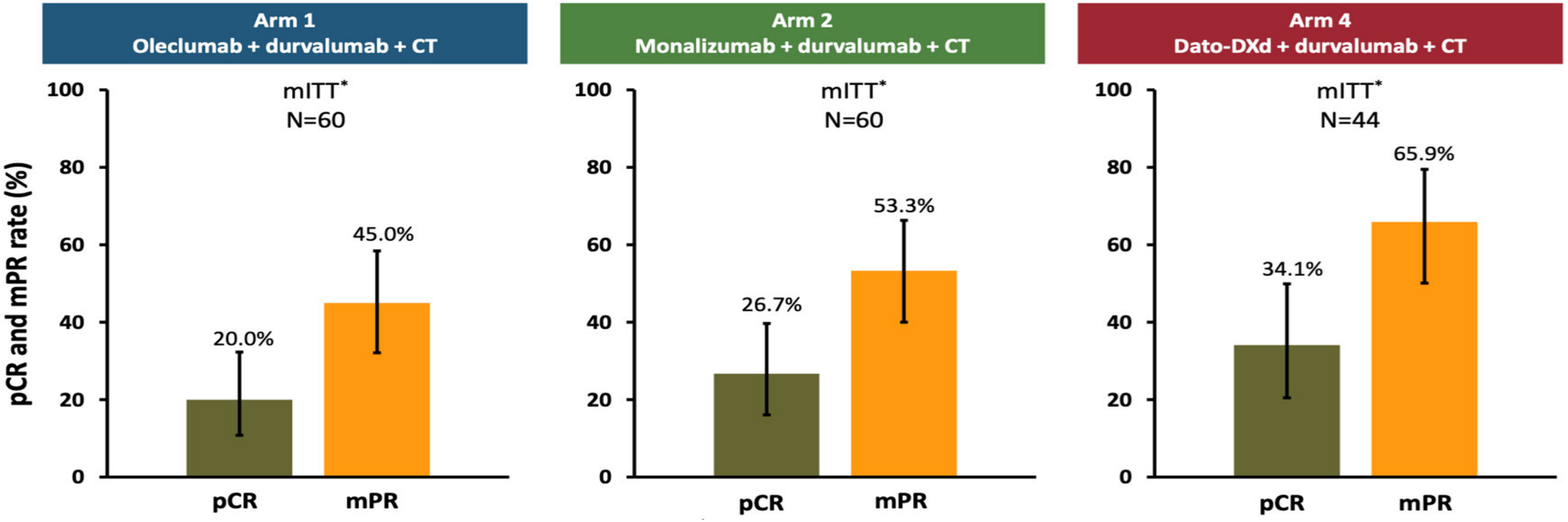
NeoCOAST-2: pCR and mPR rates across treatment arms



EXPANDING THE ARMAMENTARIUM BEYOND TKIS

- **Next-generation TKIs**
  → deeper, more durable responses (e.g., lorlatinib, repotrectinib, zidesmatinib)

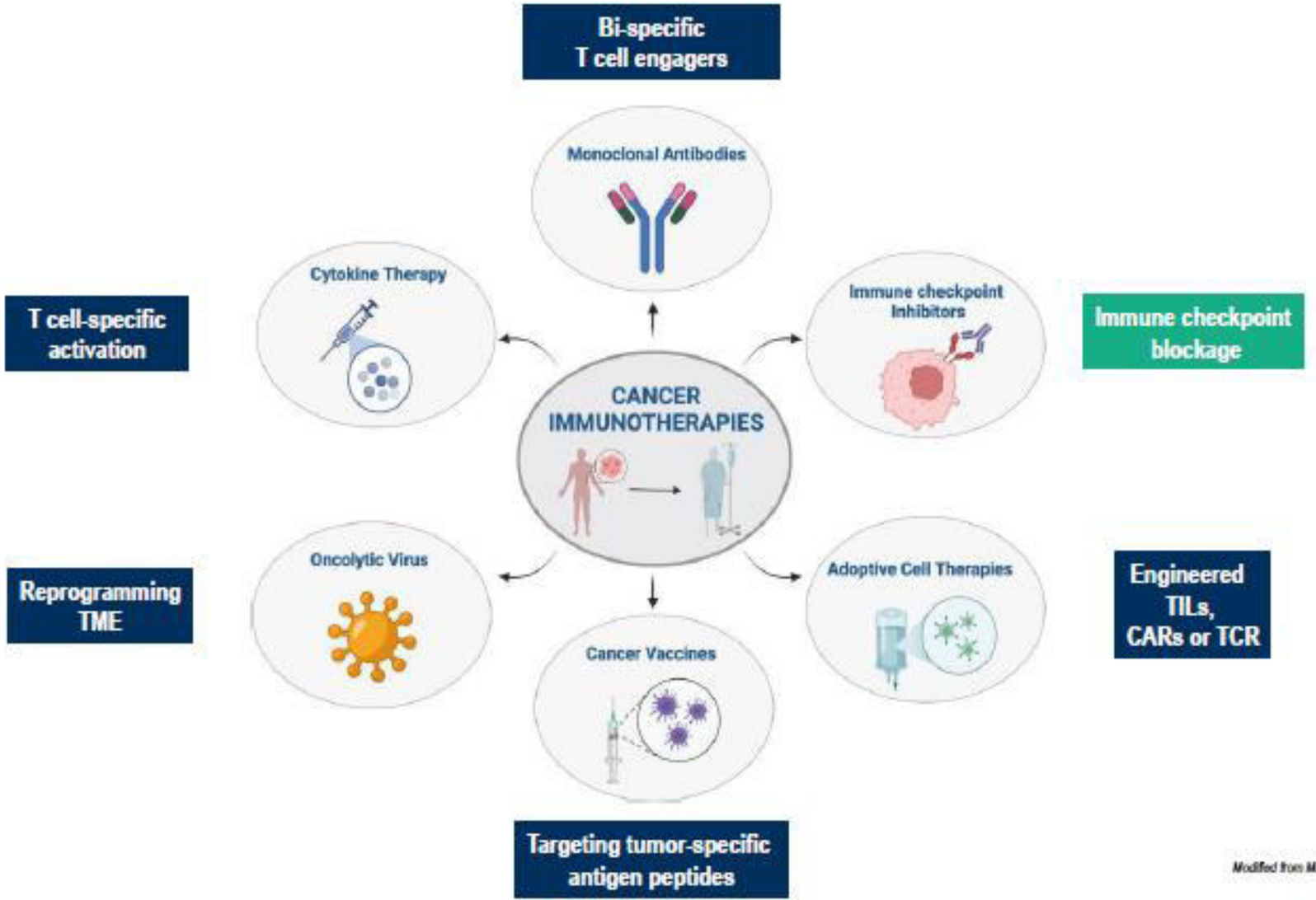
- **Antibody–drug conjugates (ADCs)**
  → *trastuzumab deruxtecan* (approved) – new agents in development targeting TROP2, MET and others

- **Bispecific antibodies**
  → *amivantamab* (EGFR/MET; approved), *ivonescimab* (PD-1/VEGF) – early promising results and others

- **Novel mechanisms**
  → MET degraders, PROTACS, SHP2 and SOS1 inhibitors, pan-KRAS inhibitors and others

- **Cell-based and immune approaches**
  → T-cell vaccines, CAR-T concepts in early testing

Immuno-oncology 2.0: redefining targets & mechanisms



Modified from Mishra AK, Malonis SK, Cell-based Immunotherapies for Cancer 2025

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I have a Dream

M.L.K

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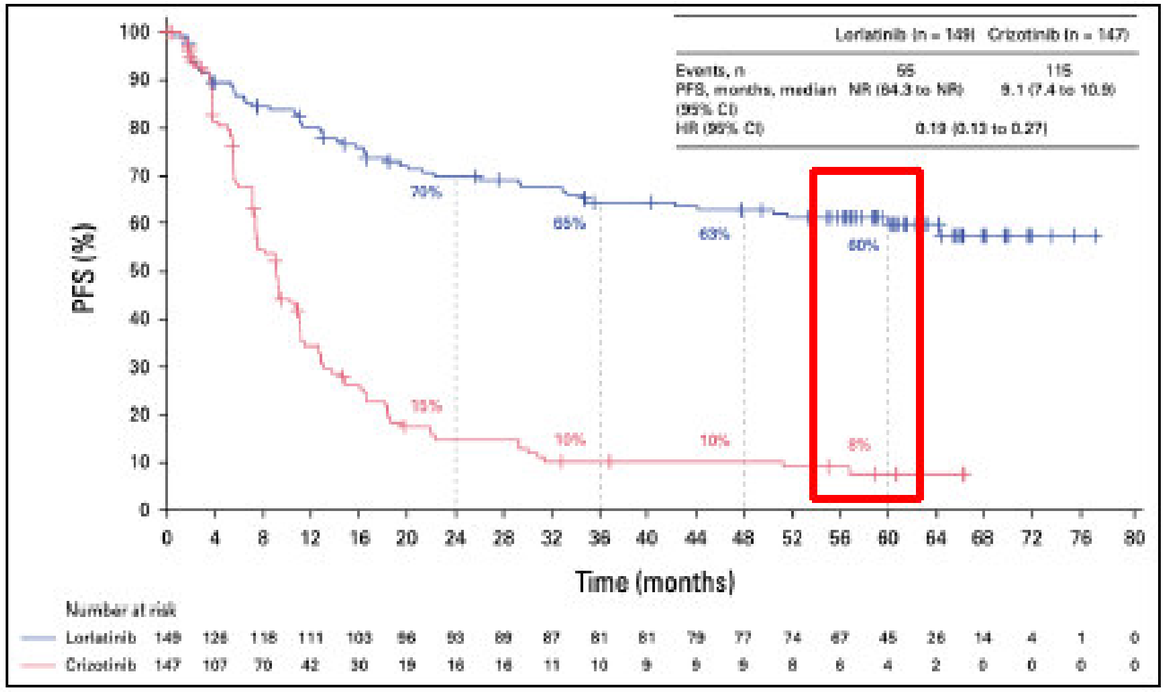
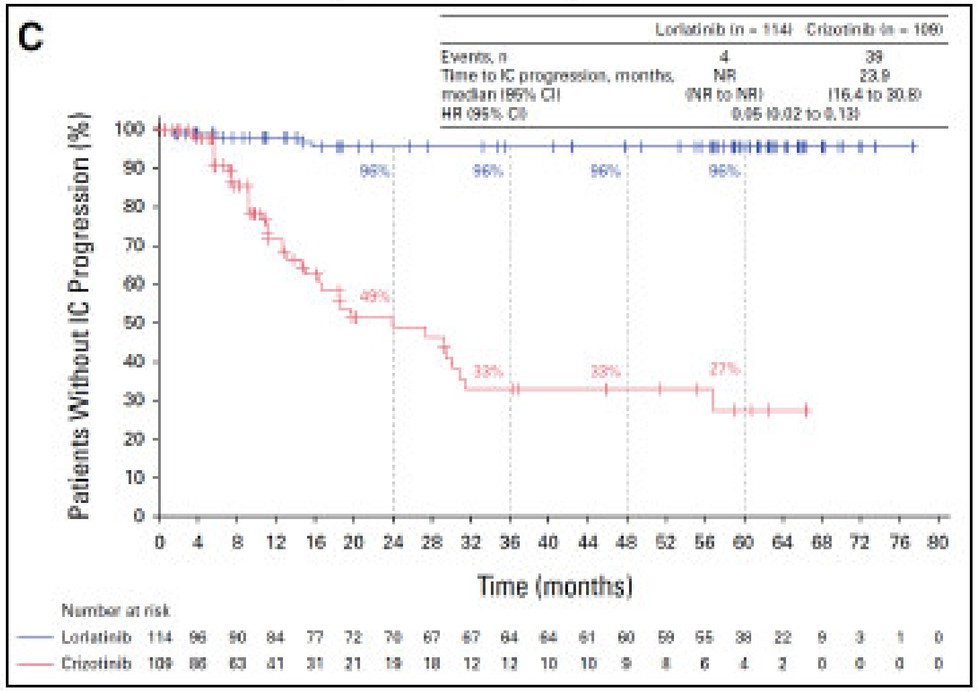
ALK FUSIONS: SETTING THE BAR 2025

CROWN phase III trial – update (1l crizotinib vs. lorlatinib)



Time to CNS-progression in pts. w/o initial brain mets



- **excellent CNS-efficacy**

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