Where Science Becomes Hope

OPTIMAL FRONTLINE THERAPY IN METASTATIC NSCLC DRIVER NEGATIVE: WHAT'S NEXT?

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

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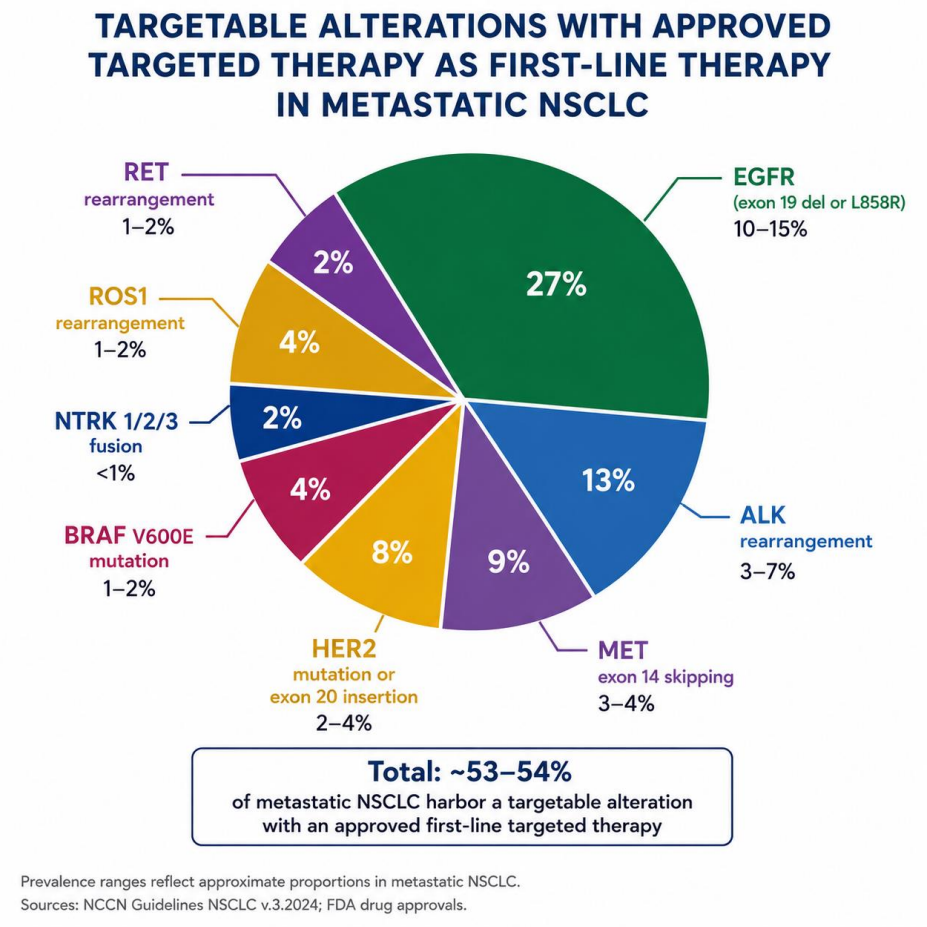
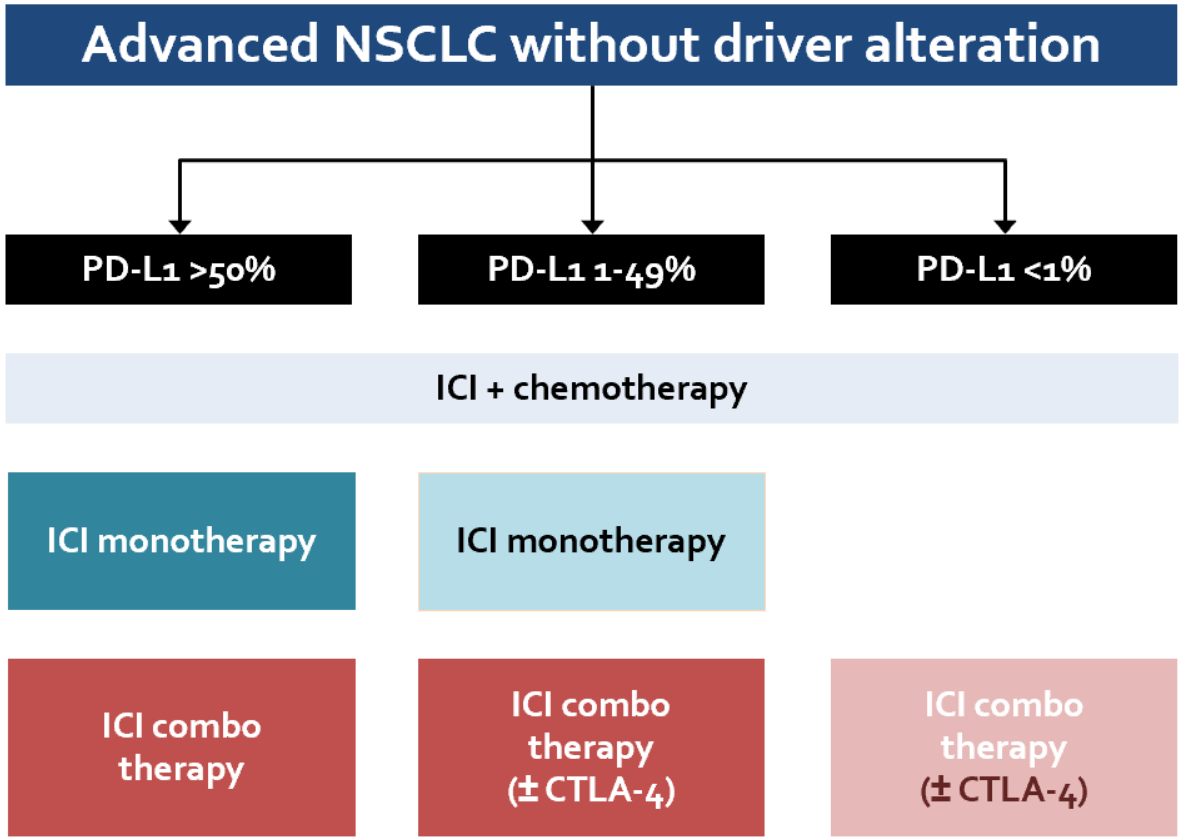
DISCLOSURES

Advisory Board- Genentech/Roche, Amgen, Astra-Zeneca, Pfizer, Boehringer-Ingelheim, Bayer, Lilly, BMS, Daichii, Gilead, Johnson and Johnson, Abbvie, Sanofi, Summit, MBrace, Erasca.

IDMC- Astra-Zeneca

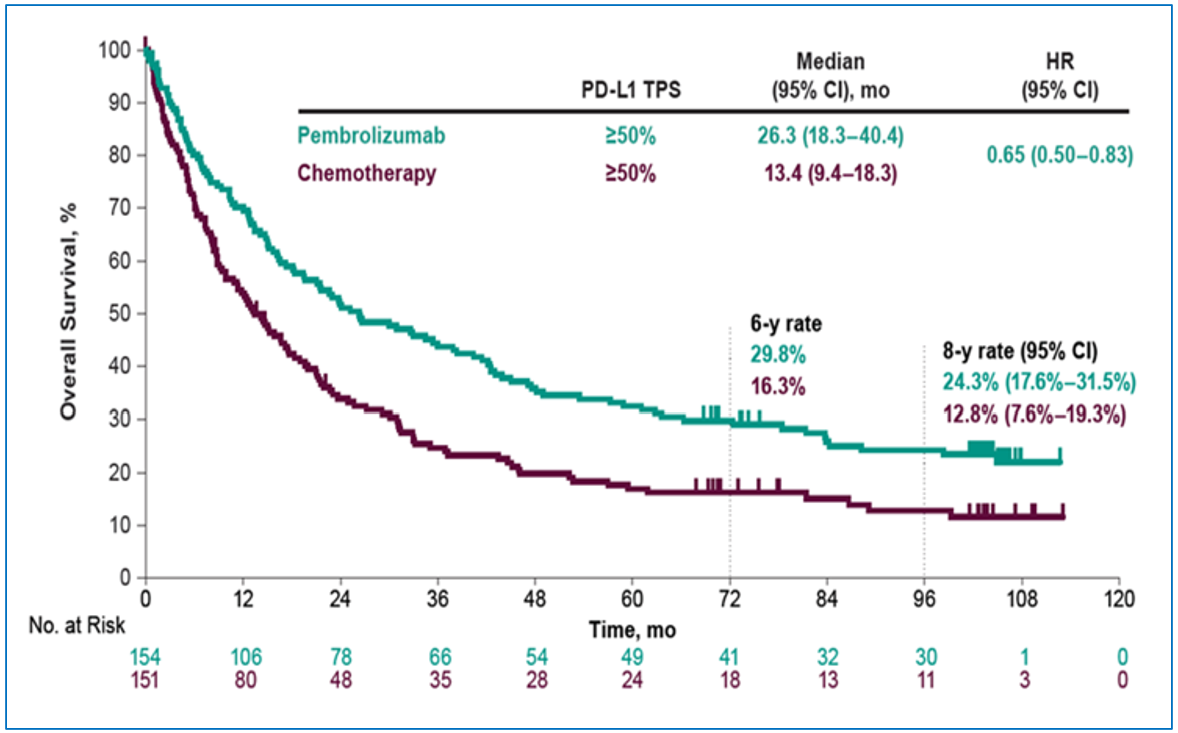
THERAPY FOR NSCLC



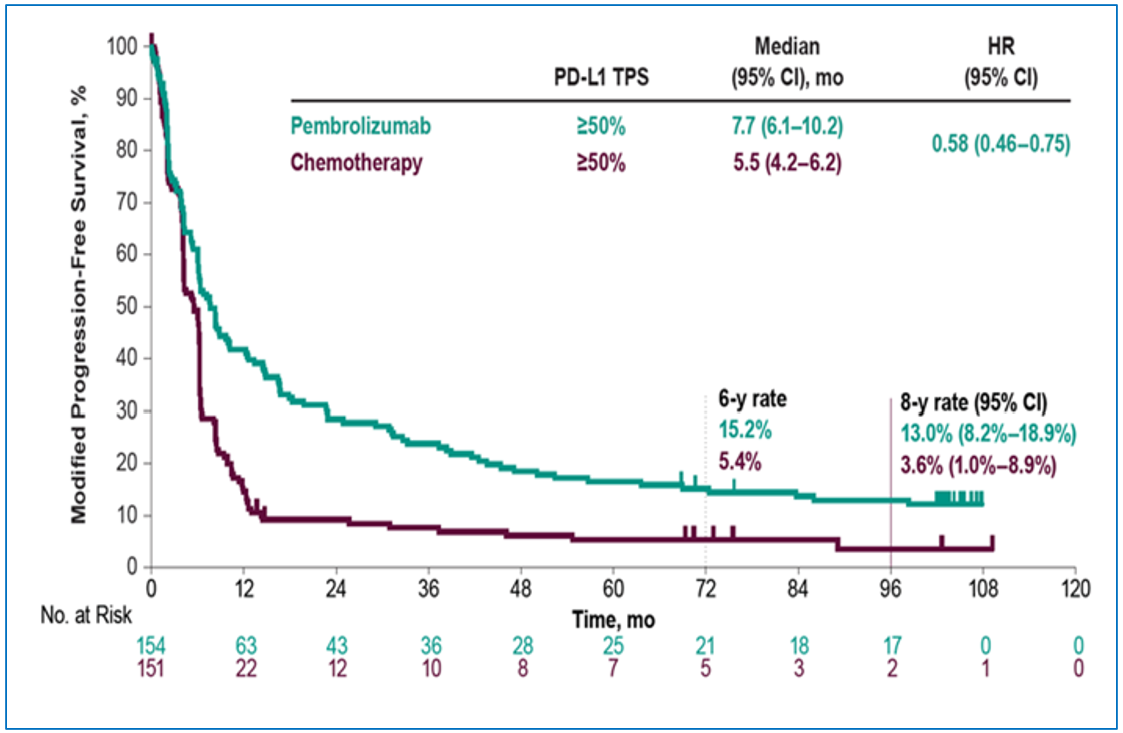


KEYNOTE-24- LONG TERM EFFICACY

OS



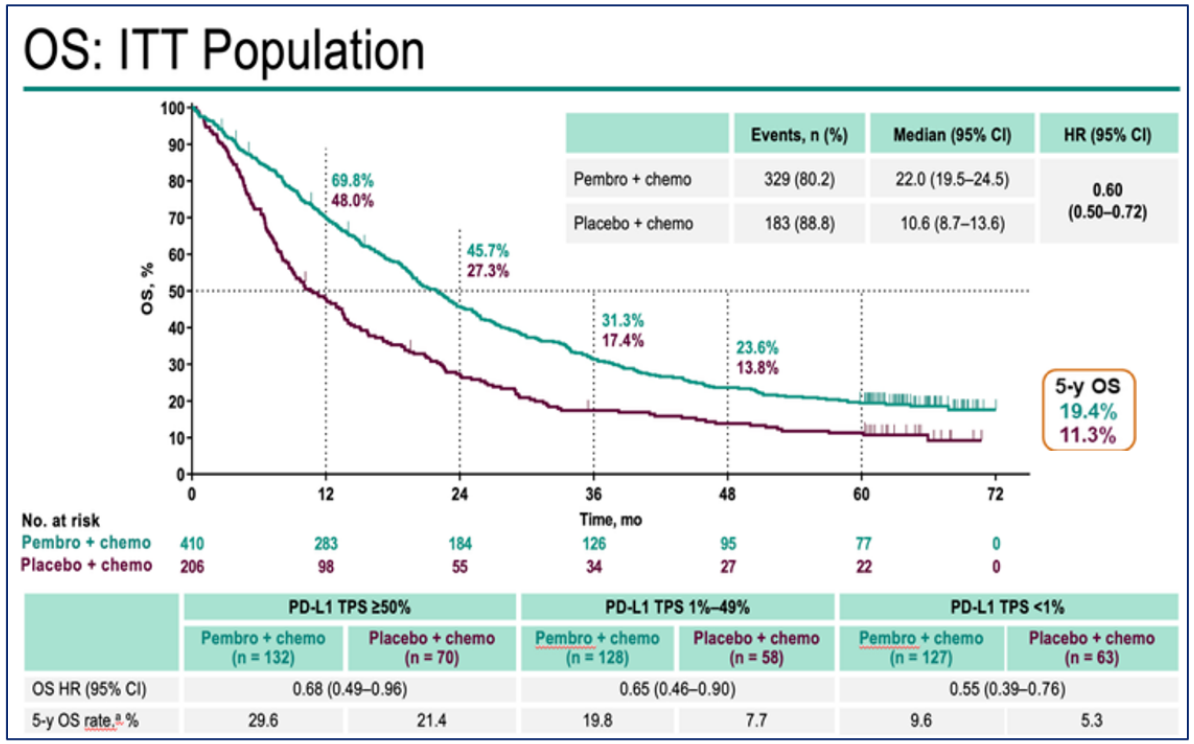
PFS

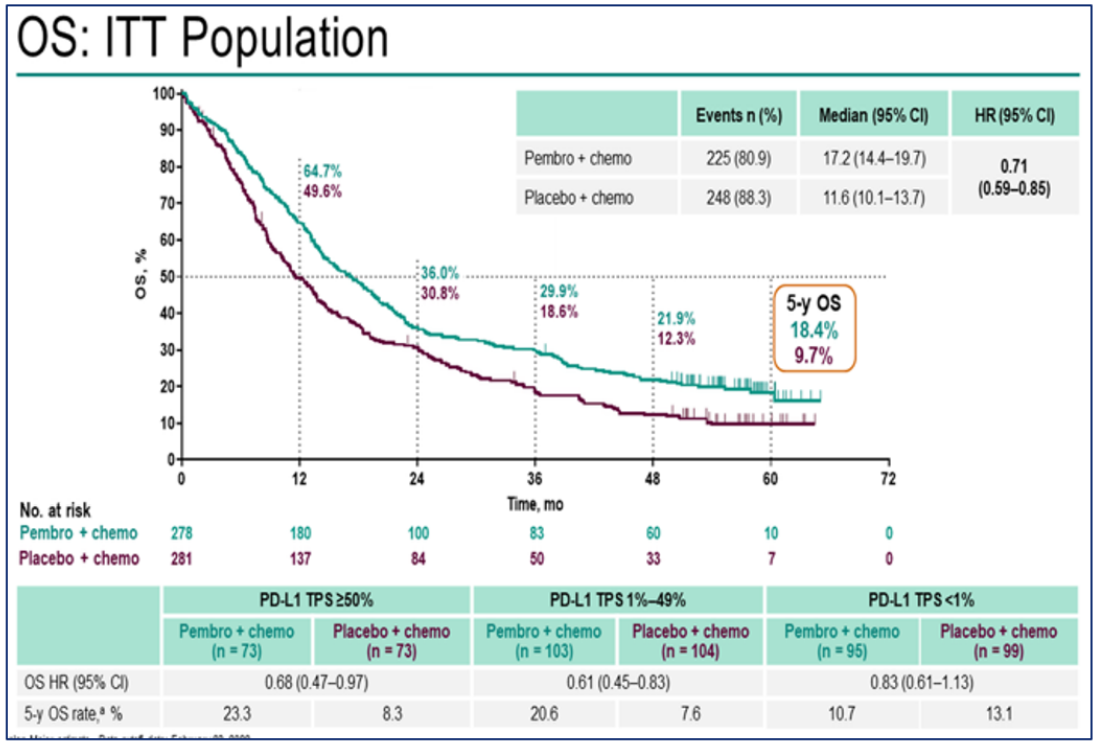


8 year OS: 24.3% vs 12.8% (HR 0.65)

Garon E et al, ESMO 2025

KN-189 AND KN-407- LONG TERM RESULTS



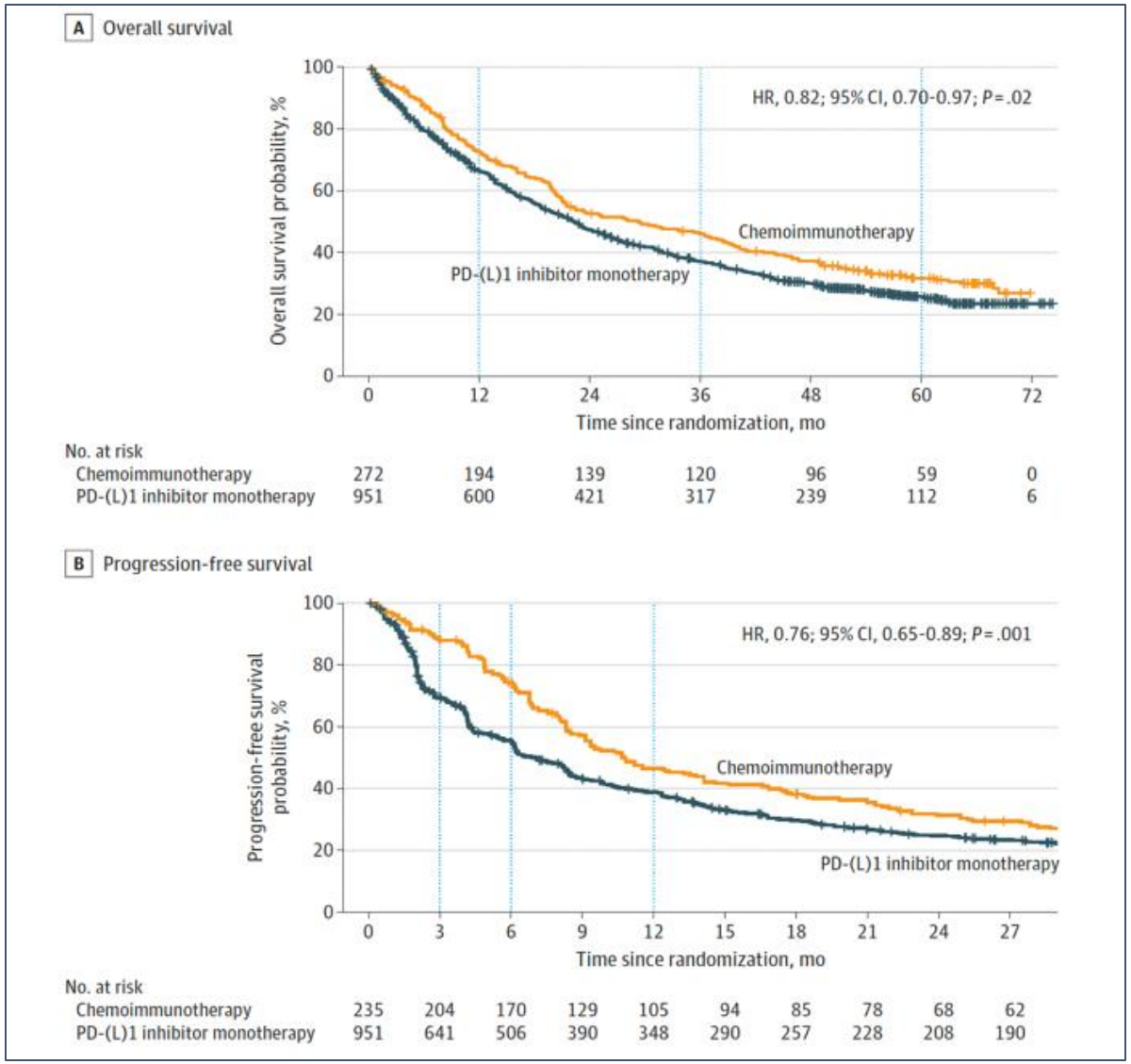


KN-189- 5 y OS 19.4% vs 11.3%, HR 0.6

KN-407- 5 y OS 18.4% vs 9.7%, HR 0.71

Garassino M, et al, ESMO 2022; J Clin Oncol 2023; Novell S, et al, ESMO 2022; J Clin Oncol 2023

META-ANALYSIS IO MONO VS IO/CT IN PD-L1 ≥50%



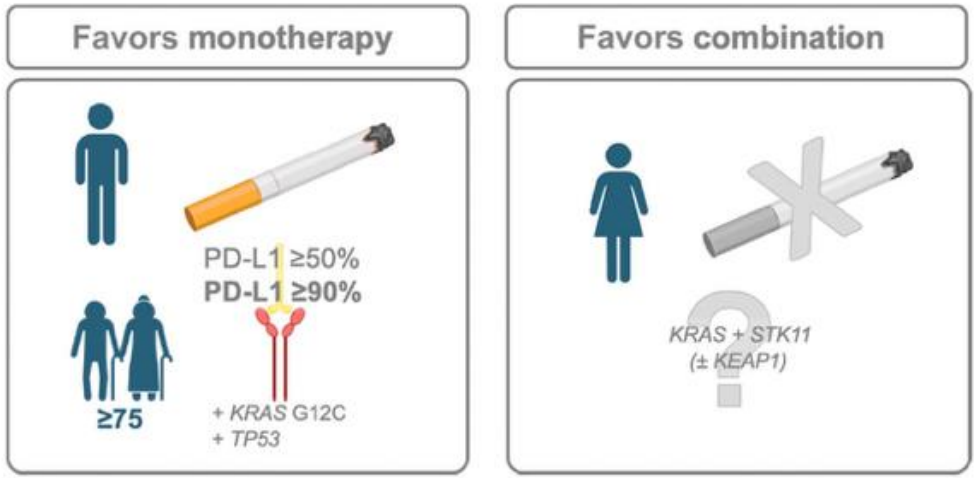
- Meta-analysis 24 randomised trials
- 5546 patients
- Including negative trials (CM 026, CM 227, Javelin Lung 100…)
- Follow up of 5 years
- Significant difference in risk of TRAEs

Di Federico A et al, JAMA Oncology 2026

IO MONOTHERAPY VS IO COMBINATION IN PATIENTS WITH PD-L1 ≥ 50% ?

Factors Considered

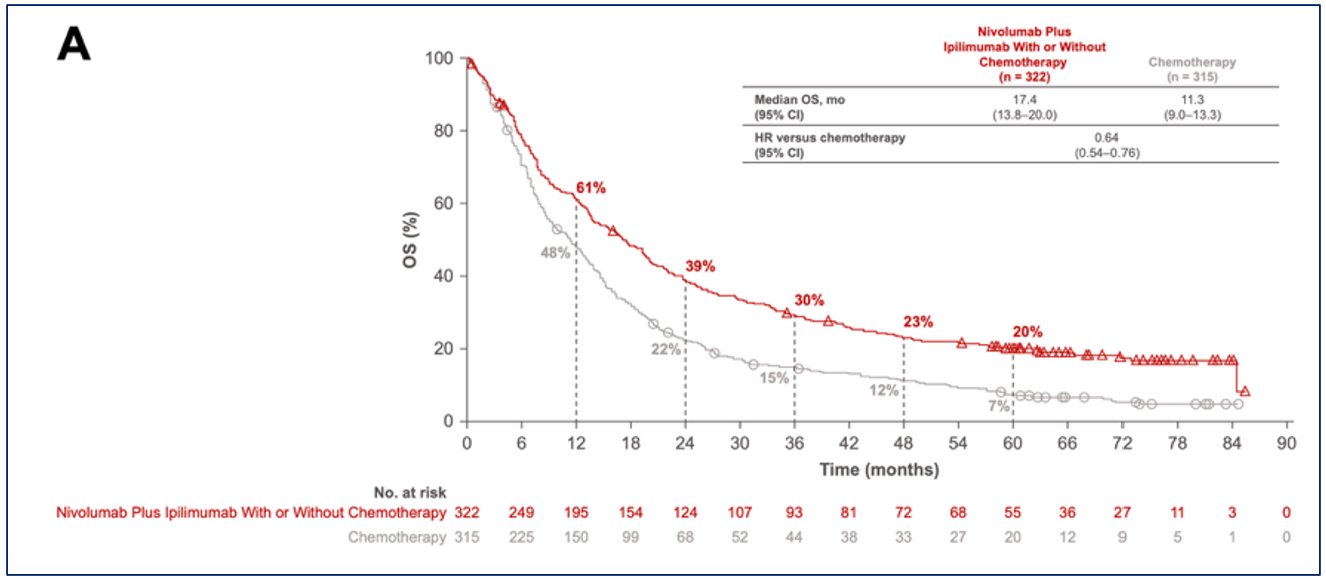
Favors Monotherapy	Favors Combination
Elderly Patients (=/> 75 y)	Tumor Burden
Smoking	Never Smoking
PD-L1 =/> 90% • Improved PFS/OS • Different Microenvironment	PD-1 < 50%
Male	Female (Enhanced efficacy by ICB-CT combination)
Molecular Profile (KRAS G12c + TP53) • Immunogenic Microenvironment	



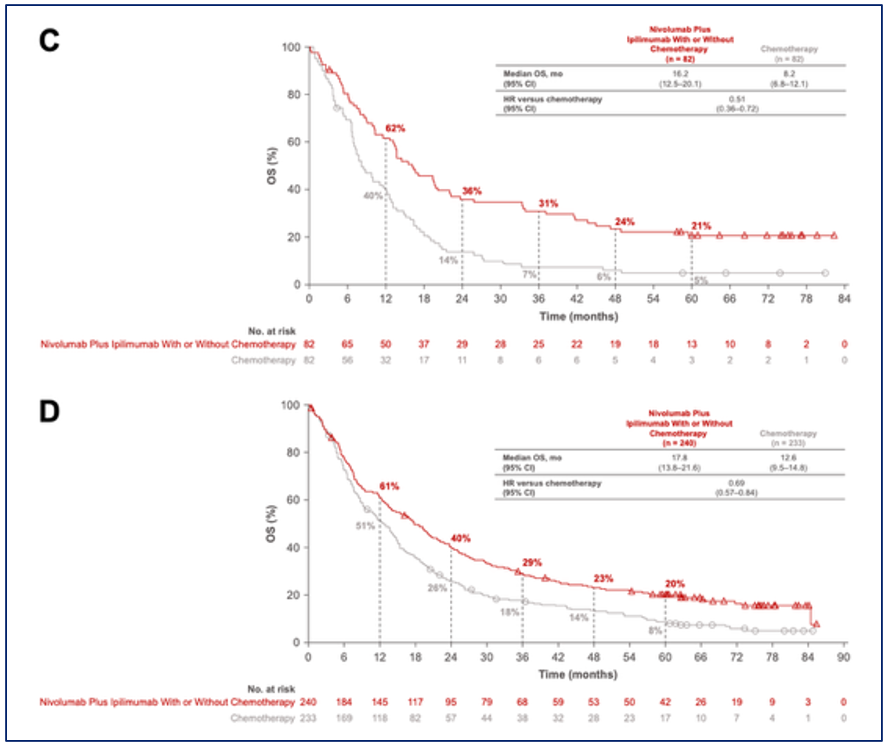
Frost N, Reck M; Am Soc Clin Oncol Educ Book 2024, 44:e432524

DOUBLE IO IN PDL1 ≤1% NSCLC- POOLED ANALYSIS

All patients, PD-L1 < 1%, 5 y OS 20%, HR 0.64



Squamous Cell NSCLC - 5 y OS 21%, HR 0.51



Non Squamous Cell NSCLC - 5 y OS 20%, HR 0.69

Peters S et al, JTO 2024

WHAT'S NEXT

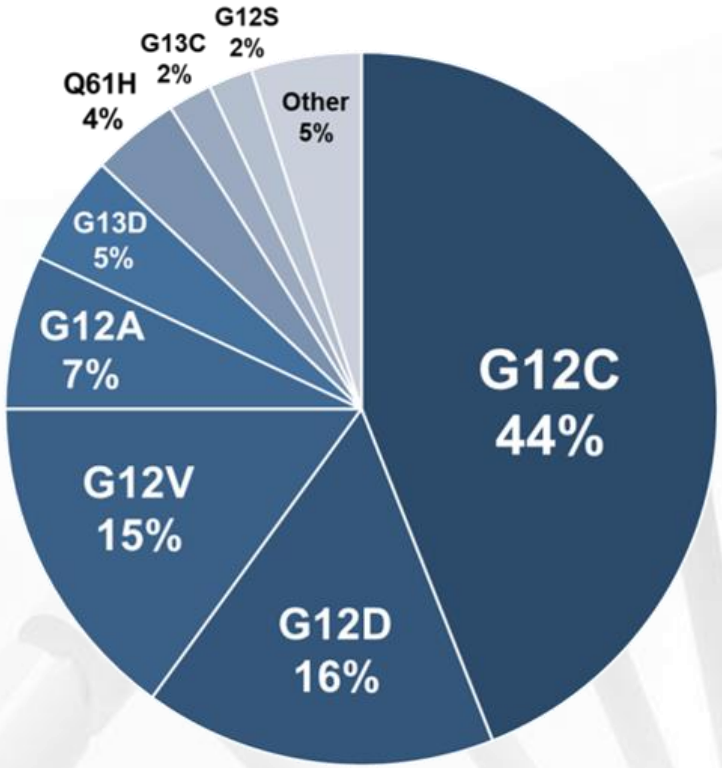
1. New Targets- Driver Mutations and Co-Mutations

2. Drugs Targeting IO Resistance

3. Novel Drugs- Antibody Drug Conjugates, Bispecific Antibodies

4. Survivorship

KRAS MUTATIONS IN NSCLC



KRAS G12C incidence across the globe

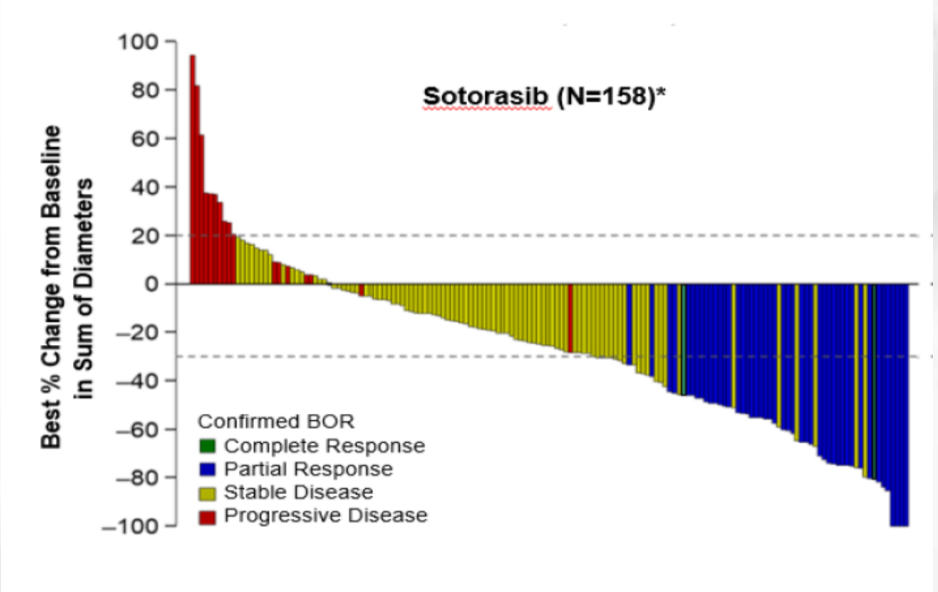
Region	KRAS G12C
North America and Europe	~ 13%
Latin America	~ 9%
Asia	~ 3%

KRAS mutations
25% of NSCLC patients
30 % of Adenocarcinomas
<5% of Squamous Cell Carcinomas

Lim TKH, et al, Lung Cancer 2023

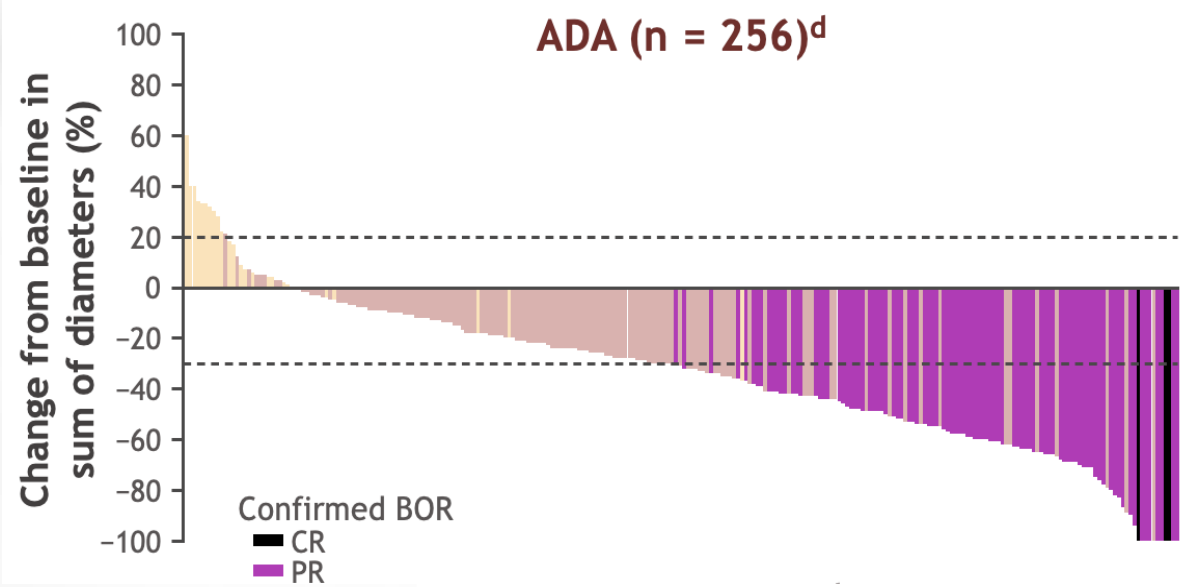
FIRST GENERATION KRAS G12C INHIBITORS

- Median PFS 5.6 mo vs. 4.5 mo, p=0.002
- 1-year PFS of 24%
- ORR 28%



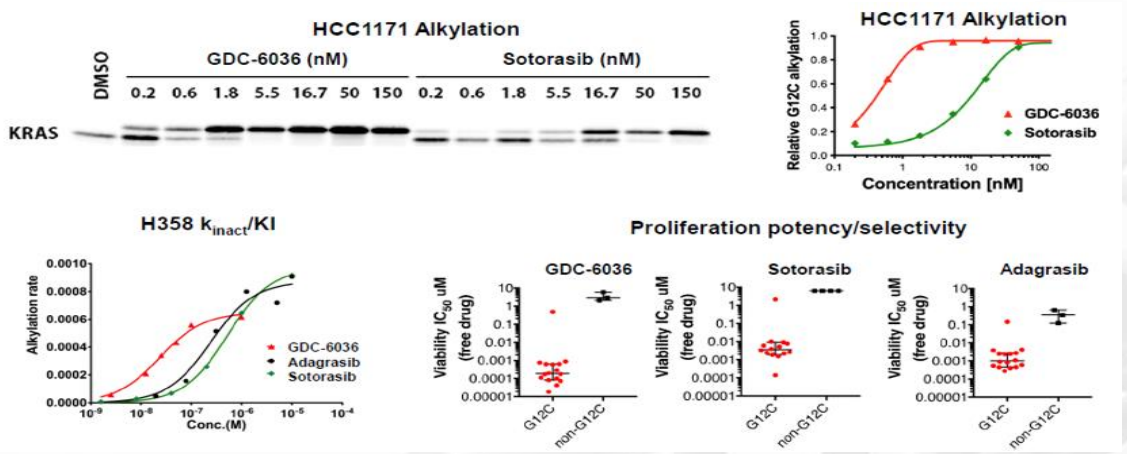
AJ de Langen, et al, Lancet 2023

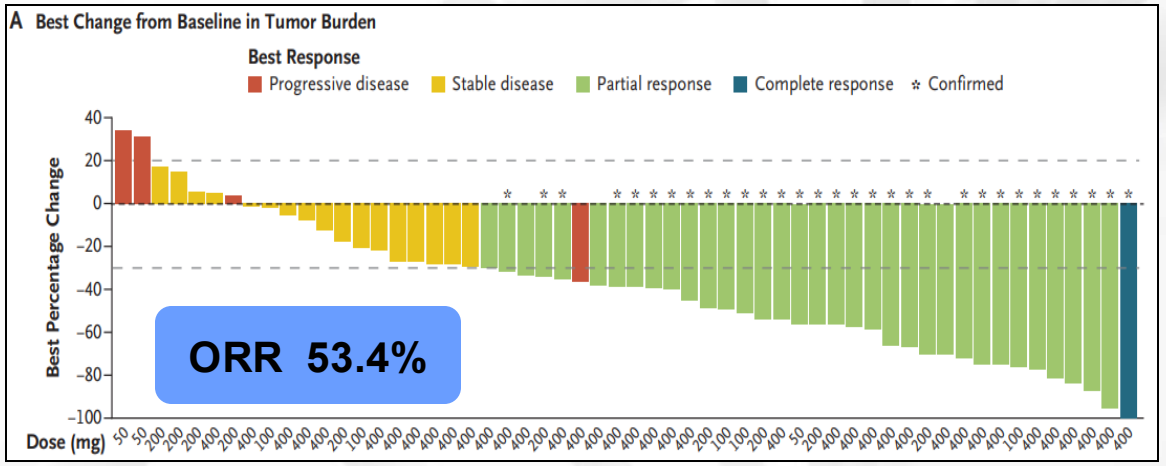
- Median PFS 5.5 mo vs. 3.8 mo, p < 0.0001
- 1-year PFS of ~27%
- ORR 32%



Barlesi F, et al, Lancet 2025

DIVARASIB- POTENT 'OFF' INHIBITORS





TRAEs OVERALL (≥10% PATIENTS) & CORRESPONDING GRADE 3-5 TRAEs	NSCLC N=65	
	All TRAEs	Grade 3-5 TRAEs
Patients with at least one AE	61 (94%)	11 (17%)
Nausea	51 (79%)	1 (2%)
Vomiting	43 (66%)	0
Diarrhea	40 (62%)	2 (3%)
Fatigue	16 (25%)	1 (2%)
Decreased appetite	15 (23%)	0
Amylase increased	11 (17%)	0
ALT increased	10 (15%)	4 (6%)
Lipase increased	10 (15%)	2 (3%)
AST increased	9 (14%)	3 (5%)

STUDY TREATMENT ACTION DUE TO TRAEs	NSCLC N=65
Patients with AEs resulting in divarasib modification (interruption/reduction/withdrawal)	25 (39%)
Patients with AEs resulting in divarasib reduction	15 (23%)
Patients with AEs resulting divarasib withdrawal	3 (5%)

Sacher A, et al, N Engl J Med 2023

KRASCENDO 1 DIVARASIB VS. ADAGRASIB/SOTORASIB

- ≥18 years of age
- 2L/3L/4L unresectable advanced or metastatic *KRAS G12C*+ NSCLC
- Prior platinum-based chemotherapy and PD-L1/PD-1
- No prior treatme pan-KRAS/RAS
- ECOG performa
- Measurable dise
- No known concomitant second oncogenic driver
- Treated, inactive CNS metastases

Divarasib
21-day cycles

Adagrasib or **sotorasib**‡
21-day cycles

atment
ntinuation

Survival follow-up§

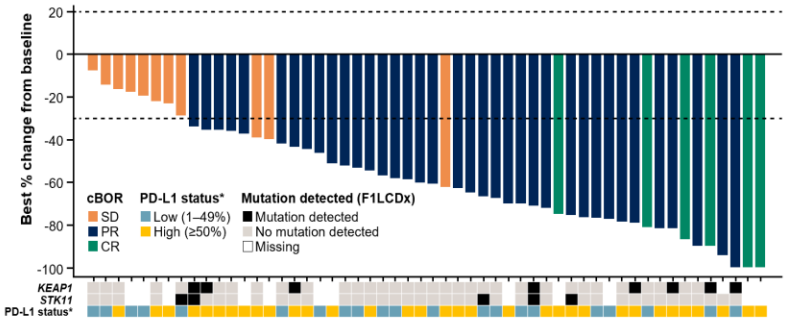
Wednesday, Jul 1, 2026

Genentech's Divarasib Shows Superiority in Head-to-Head Phase III Trial Against Approved KRAS G12C Inhibitors in Non-Small Cell Lung Cancer

EudraCT: 2024-510908-37-00; NCT06497556.*Concomitantly or sequentially; †*KEAP1* mutation status will be determined from central F1LCDx or from pre-existing results from sponsor-approved NGS tests during pre-screening or screening; ‡The control arm drug will depend on local approvals and availability. If both drugs are locally approved and readily available, the investigators will choose between them and participants will receive the same drug for the duration of the treatment period; §Patients who discontinue treatment for reasons other than disease progression per RECIST v1.1 (e.g., toxicity; symptomatic deterioration) will undergo PFS follow-up until radiographic disease progression, consent withdrawal, death, or study termination, whichever occurs first. 2L/3L/4L, second-/third-/fourth-line; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; F1LCDx, FoundationOne Liquid companion diagnostic; KRAS G12C, kirsten rat sarcoma virus oncogene homolog glycine 12 to cysteine; NGS, next-generation sequencing; PD-(L)1, programmed death-(ligand) 1; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors

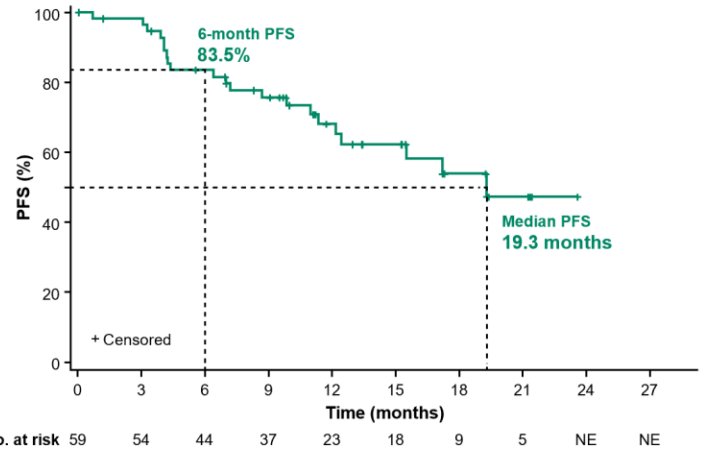
KRASCENDO-170-DIVARASIB AND PEMBROLIZUMAB

PD-L1 positive cohort: Confirmed ORR



n (%) unless specified	Divarasib + pembrolizumab (N=59)†
Confirmed ORR [95% CI]	43 (72.9) [59.7–83.6]
CR	6 (10.2)
PR	37 (62.7)
SD	11 (18.6)
PD	0
Not evaluable/missing	5 (8.5)
Median time to first response, days (range)	43 (36–164)
Median DoR, months (95% CI)	NE (14.5–NE)

- Among all enrolled patients, confirmed ORR was 72.9%
  - Confirmed ORR was 76.8% in the 56 patients who received any study treatment
  - Responses were observed regardless of PD-L1, *KEAP1*, and *STK11* status
- All patients with a post-baseline assessment had a reduction in tumor size
- Median DoR has not yet been reached and data are immature



- Median PFS was 19.3 months (95% CI: 12.4–NE); data were immature
- The 6-month PFS rate was 83.5% (95% CI: 73.6–93.3)

PD-L1 < 1%- Unconfirmed RR- 69.6%

Skoulidis F, et al, ASCO 2026

KRASCENDO-170- TOXICITIES

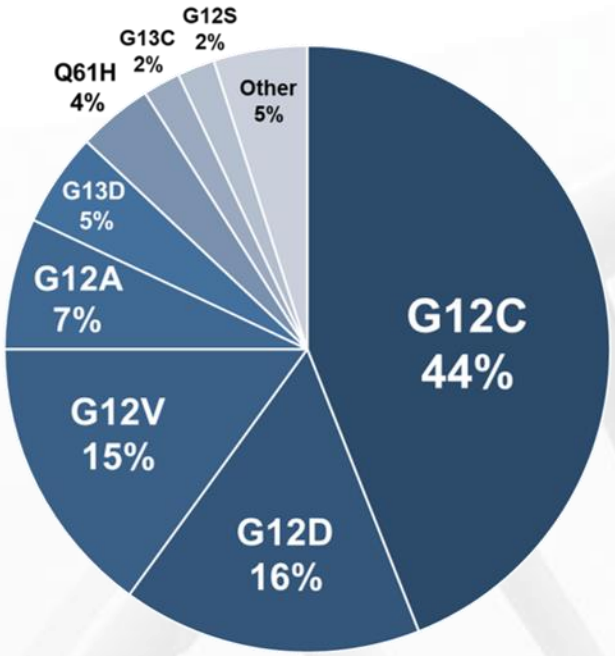
Event, n (%)	Divarasib + pembrolizumab (n=78)*
Any grade AE	78 (100)
Grade ≥3	60 (76.9)†
Serious	39 (50.0)
Any grade TRAE	77 (98.7)
Grade 3–4	51 (65.4)
Grade 5	0
Serious	22 (28.2)
TRAE leading to divarasib dose reduction	41 (52.6)
TRAE leading to dose interruption	54 (69.2)
TRAE leading to study treatment discontinuation	10 (12.8)

Primarily GI and Hepatic Toxicities

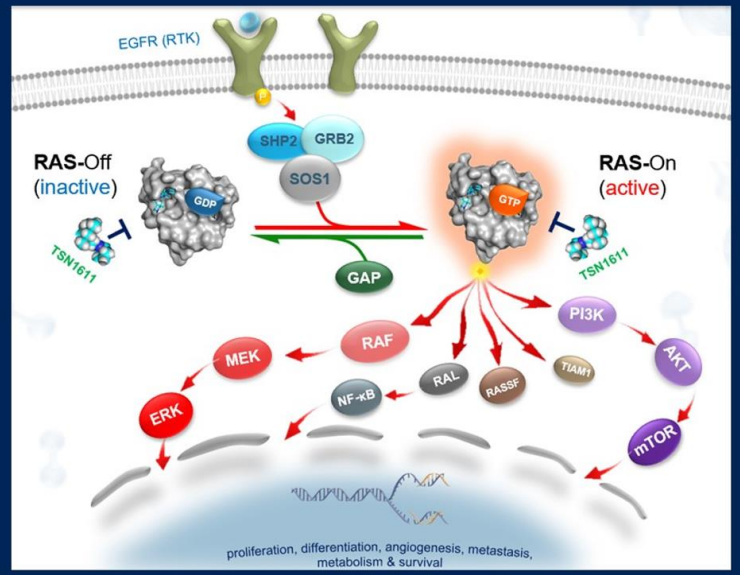
Strategies to Overcome Toxicities

Event, n (%)	Divarasib + pembrolizumab (n=78)*	
	Any grade	Grade 3–4
Diarrhea	58 (74.4)	14 (17.9)
Nausea	50 (64.1)	1 (1.3)
Vomiting	36 (46.2)	1 (1.3)
Alanine aminotransferase increase	41 (52.6)	18 (23.1)
Aspartate aminotransferase increase	38 (48.7)	14 (17.9)
Lipase increase	23 (29.5)	7 (9.0)
Decreased appetite	24 (30.8)	0
Amylase increase	16 (20.5)	3 (3.8)

‘ON’ AND ‘OFF’ KRAS INHIBITORS

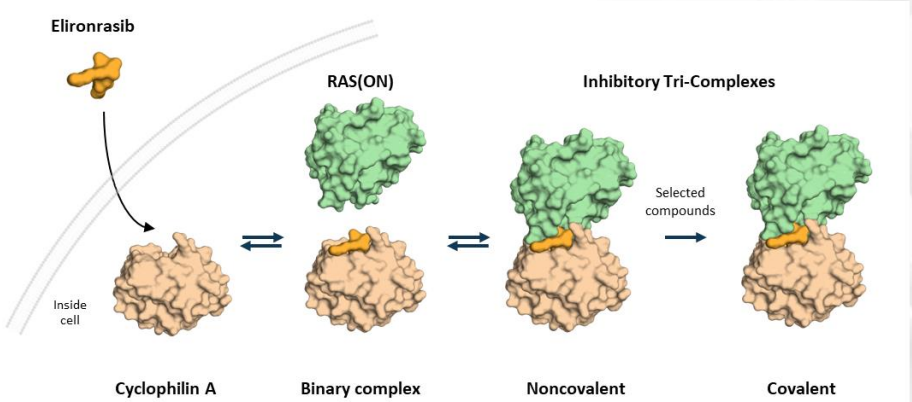


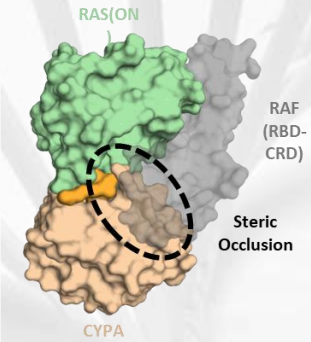
- **Significant Unmet Need:** Advanced, refractory NSCLC harboring the KRAS G12D mutation lacks effective targeted therapies.
- **Differentiated Mechanism of Action:** TSN1611 is a highly selective, novel oral small-molecule inhibitor that binds both active (GTP-bound/ON) and inactive (GDP-bound/OFF) states of KRAS G12D.
- **Promising Efficacy:** TSN1611 has demonstrated broad antitumor activity in preclinical models and promising single-agent clinical activity across multiple tumor types.



Lim TKH, et al, Lung Cancer 2023

KRAS ON INHIBITORS- ELIRONRASIB

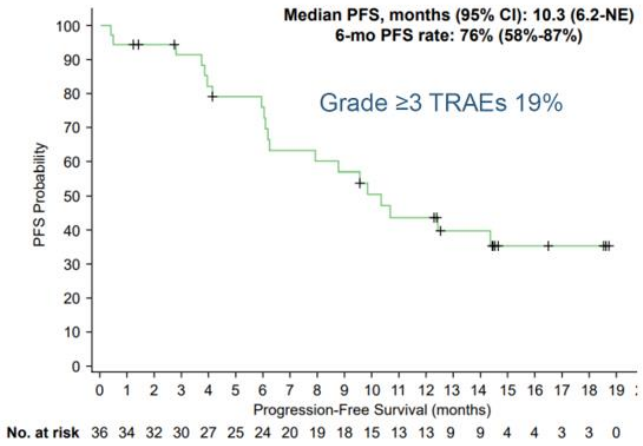




KRAS G12C on inhibitors – Elironrasib

Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	**KRAS G12C inhibitor-Naïve (N = 36)**
Complete response	2 (6)
Partial response	18 (50)
Stable disease	14 (39)
Progressive disease	1 (3)
Not evaluable	1 (3)
Confirmed ORR, n (%)	20 (56)
DCR (CR+PR+SD), n (%)	34 (94)
DoR, median (95% CI)	9.8 mo (5.4-NE)
TTR, median (Q1-Q3)	1.4 mo (1.3-2.6)

Data Cutoff 04 August 2025

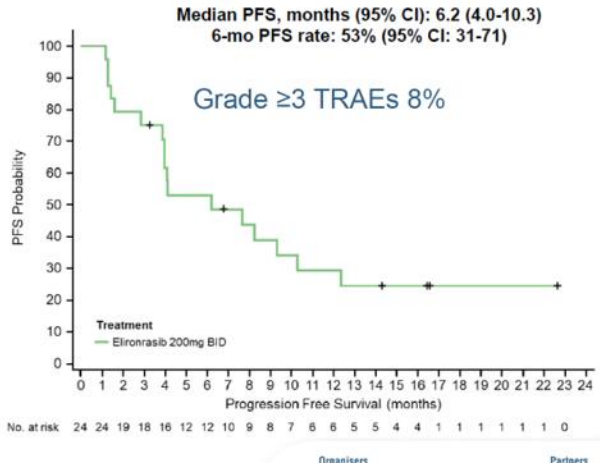


Sequential treatment with KRAS G12C on inhibitors

Elironrasib

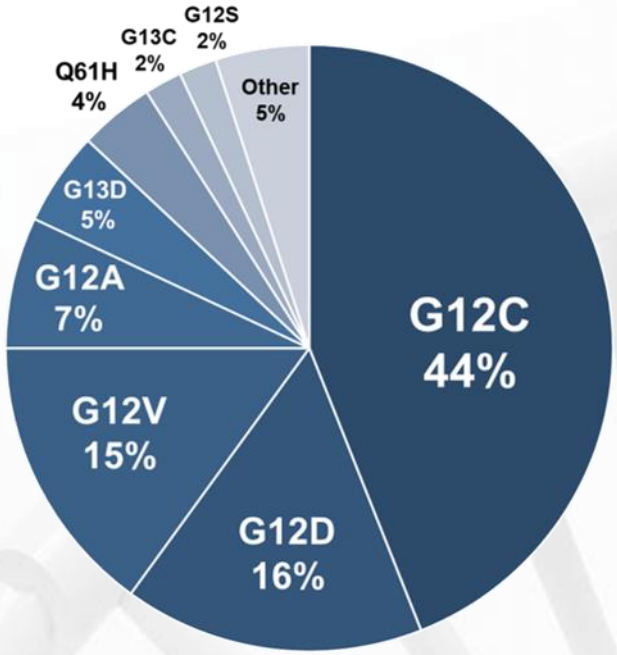
Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	**200 mg BID (n=24)**
Partial response	10 (42)
Stable disease	9 (38)
Progressive disease	4 (17)
Not evaluable*	1 (4)
Confirmed ORR, n (%)	10 (42)
DCR (CR+PR+SD), n (%)	19 (79)
DoR, median (95% CI)	11.2 mo (5.9-NE)
TTR, median (Q1-Q3)	1.4 mo (1.3-2.6)

*Patient passed away prior to the first post-baseline scan
^Median follow up was 17.6 months

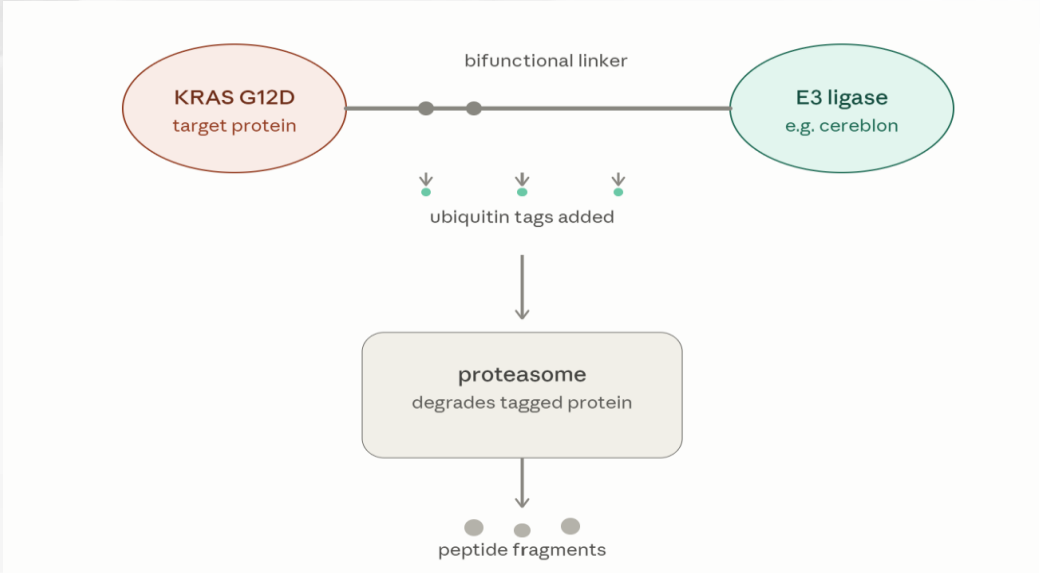


Pellini et al.., AACR-NCI-EORTC, 2025

KRAS INHIBITORS IN NSCLC

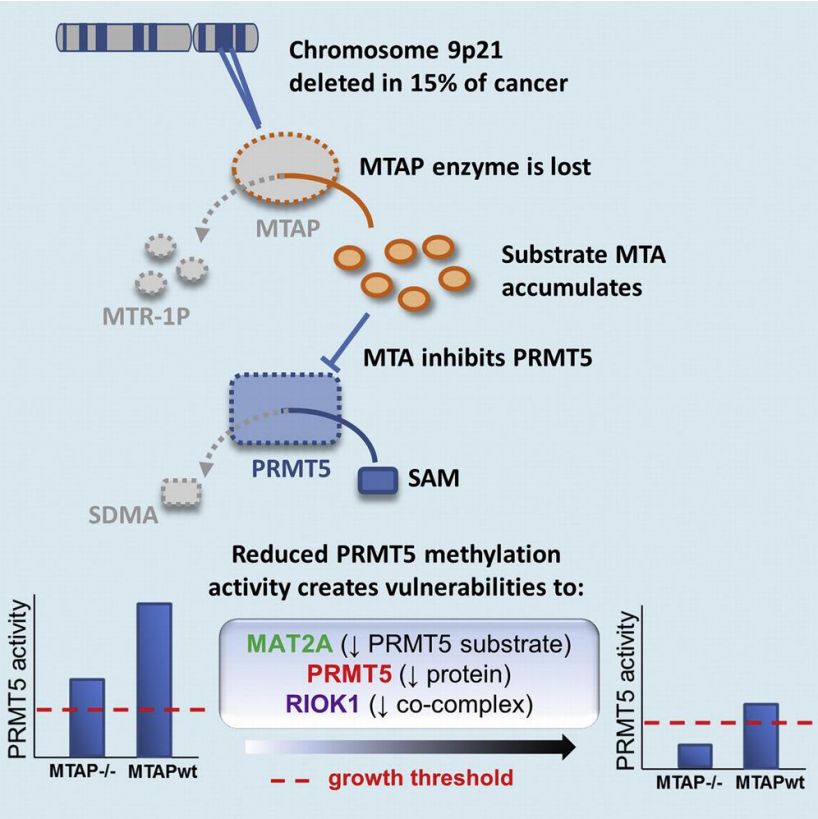


Allele Specific Inhibitors and Degraders
KRAS G12D, G12V
PAN- RAS Inhibitors and Degraders



Lim TKH, et al, Lung Cancer 2023

CO-MUTATIONS- MTAP DELETION

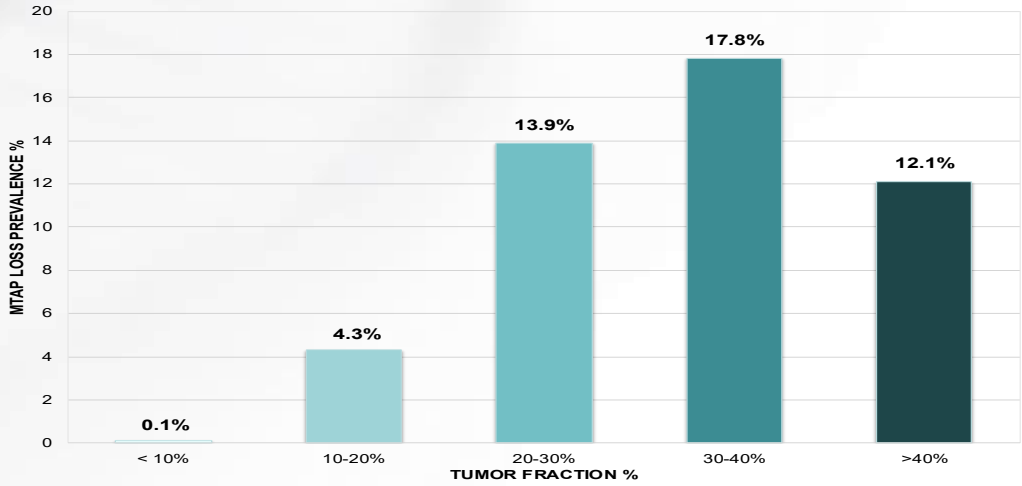


MTAP is involved in methionine salvage pathway

Loss of MTAP leads to accumulation of MTA

MTA inhibits PRMT5 which regulates gene expression and cell cycle.

Cancer cells with MTAP deletion makes them sensitive to further PRMT5 inhibition



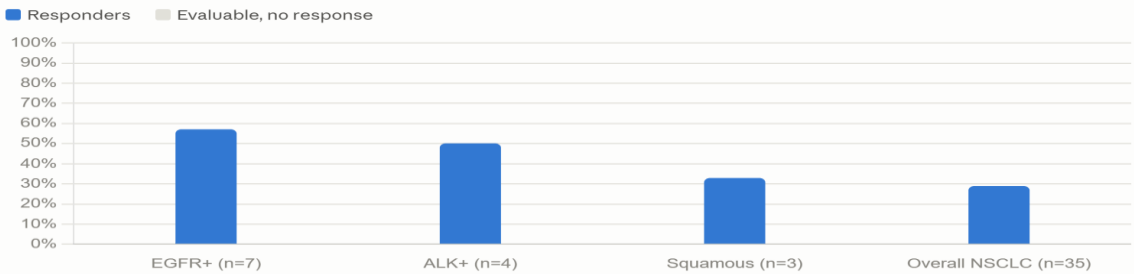
Rate of MTAP deletion is about 25% in NSCLC

Marjon K, Cell Reports 2016; Ikushima, H ESMO Open 2025; Gadgeel AACR 2026

NAVLIMETOSTAT (BMS-986504)

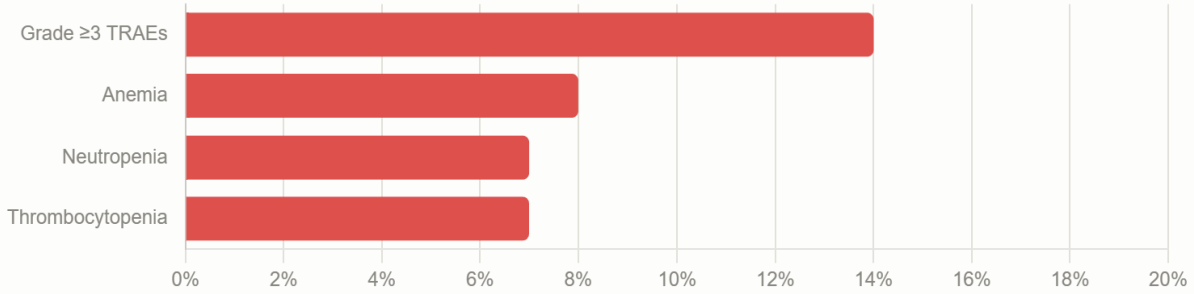
Efficacy

NSCLC patients	ORR	Disease control rate	Median DOR
35	29%	80%	10.5 mo



Time to response	Median follow-up
4.3 months	11.7 months

Toxicity



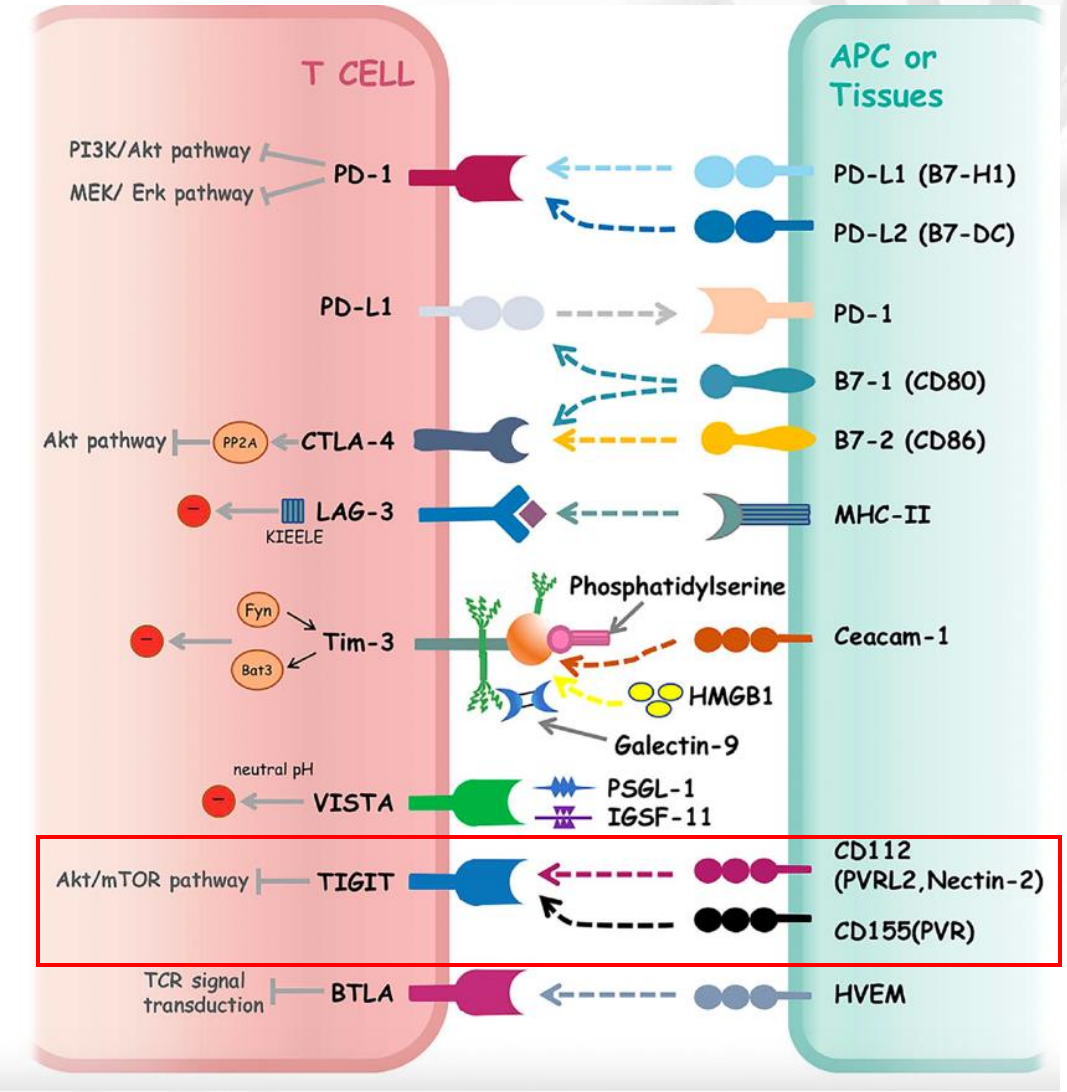
Janne, et al, WCLC 2025

THERAPIES TO ENHANCE IO ACTIVITY

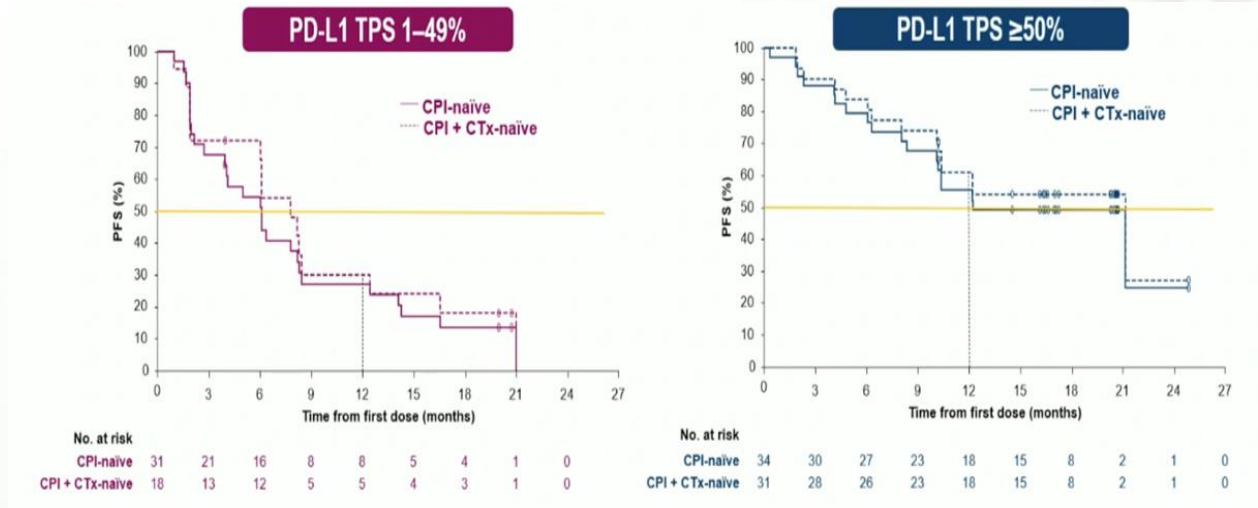
ENHANCE TUMOR IMMUNOGENICITY	ENHANCE T-CELL FUNCTION AND INFILTRATION	TARGET IMMUNE SUPPRESSIVE TME
Combination with chemo / ADC/ RT	Combination with other CPIs, e.g. LAG3 or TIGIT	Combination with anti-angiogenics
Vaccines oncolytic viruses	Cellular therapies, e.g. CAR-T cells, TILs	Combination with TAM receptor inhibitors
Other targeted therapies	TLR9 / STING agonists HDAC inhibitors T/NK cell engagers	Adenosine pathway inhibitors
Combination with DNA damage repair inhibitors	Co-stimulatory signals (e.g. OX40, cytokines e.g. IL-2)	Targeting Tregs & MDSCs, e.g. new CTLA-4 and CCR8

Courtesy- Dr. Solange Peters

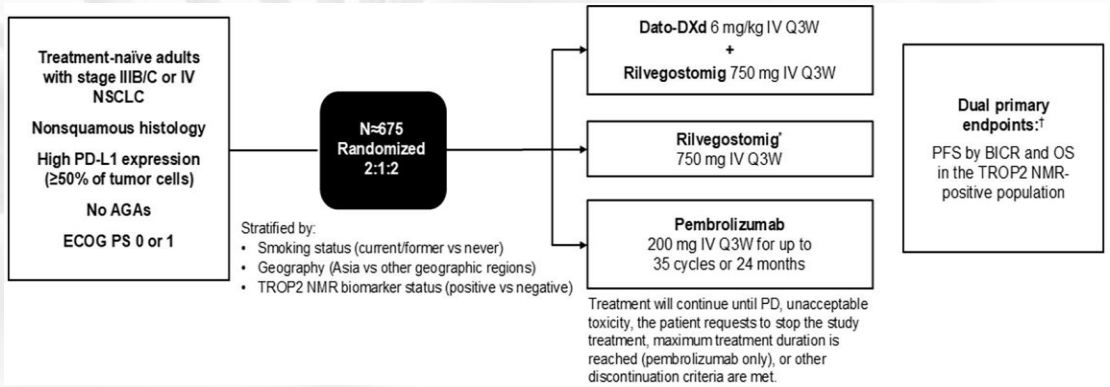
CHECKPOINTS BEYOND PD-1



RILVEGOSTOMIG- ANTI-PD-1/TIGIT BISPECIFIC



	PD-L1 TPS 1–49%		PD-L1 TPS ≥50%	
	CPI-naïve (n=31)	CPI + CTx-naïve (n=18)	CPI-naïve (n=34)	CPI + CTx-naïve (n=31)
Median PFS, months (95% CI)	6.1 (2.7–8.3)	7.8 (1.9–12.5)	12.3 (8.4–NC)	21.2 (10.2–NC)
12-month PFS, % (95% CI)	27.2 (12.9–43.6)	30.1 (11.1–52.0)	55.5 (37.3–70.3)	60.8 (41.4–75.6)



Tropion Lung 10 Trial

Cho BC, et al, ESMO 2025

2026 ASCO® ANNUAL MEETING

IVONESCIMAB PLUS CHEMOTHERAPY VERSUS TISLELIZUMAB PLUS CHEMOTHERAPY IN PREVIOUSLY UNTREATED ADVANCED SQUAMOUS NON-SMALL CELL LUNG CANCER: OVERALL SURVIVAL RESULTS OF THE PHASE 3 HARMONI-6

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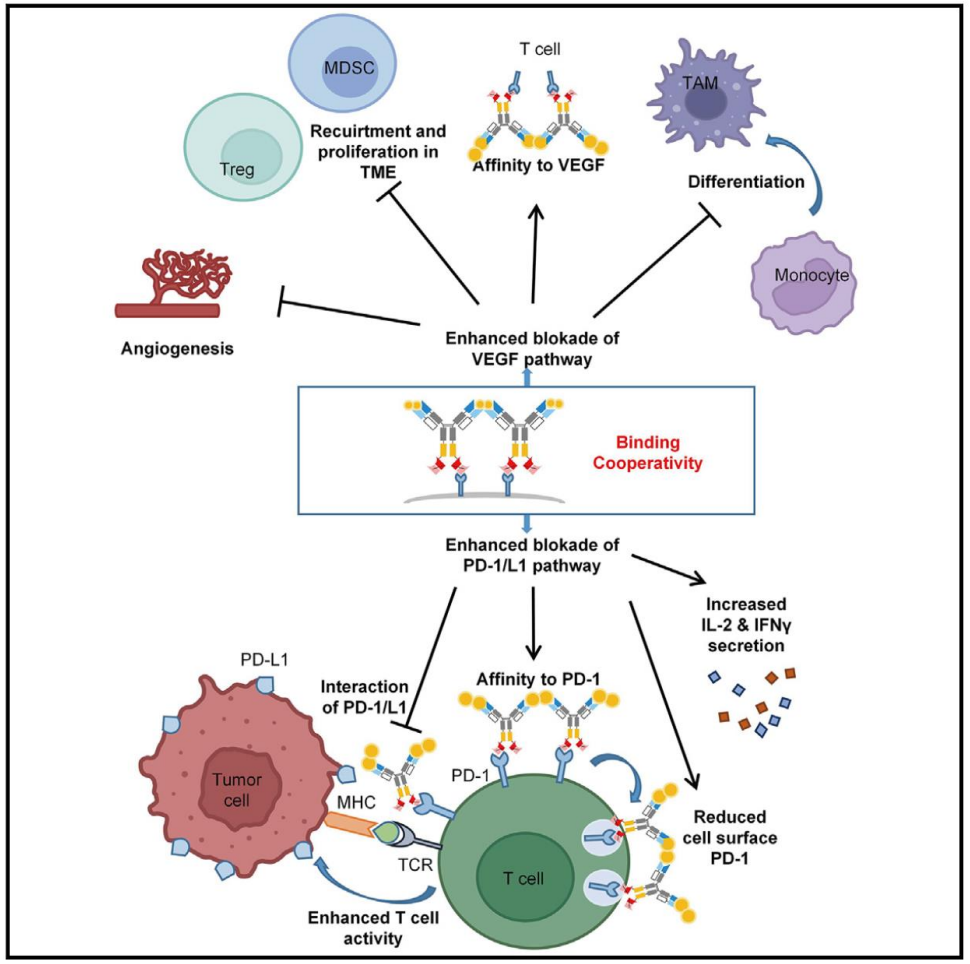
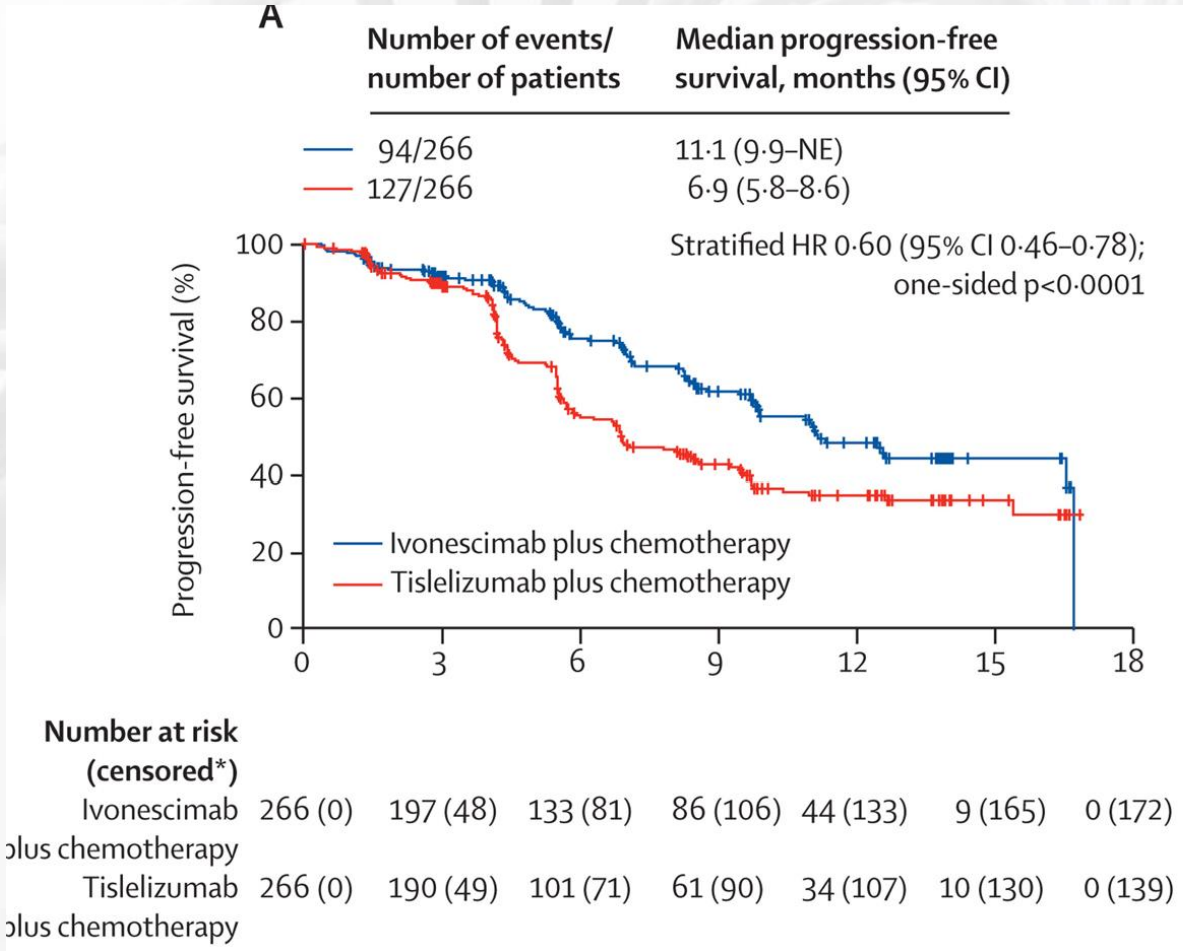
Shun Lu, MD, PhD

BACKGROUND



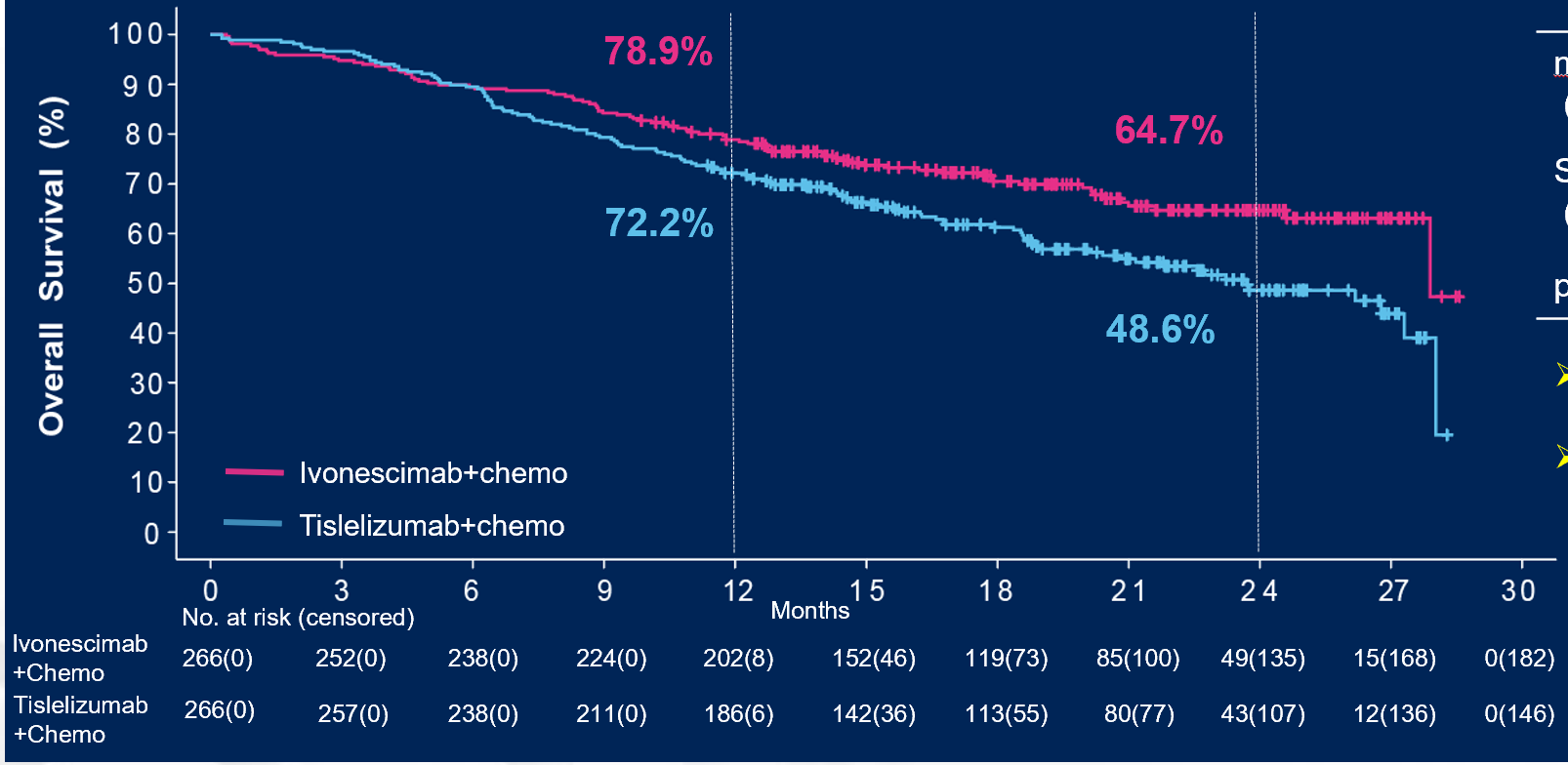


Inhibiting VEGF makes the TME less immunosuppressive
Co-operative binding enhance both PD-1 and VEGF inhibition and limits to TME

Zhong T, et al, iScience 2024; Chen Z, et al, Lancet 2025

OVERALL SURVIVAL

✓ Ivonescimab with chemotherapy significantly improved OS



	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
mOS, months (95% CI)	27.89 (27.89, NE)	23.69 (20.11, NE)
Stratified HR (95% CI)	**0.66** (0.50, 0.87)	
p-value	**0.0017**	

- OS significance boundary: 0.0049
- The median OS in the ivonescimab group would have not been reached without the last single event

- Data cutoff date: Feb 27, 2026
- Median Follow-up: 21.36 months

TOXICITIES

- **Possibly VEGF-related AEs occurred more frequently in the ivonescimab arm, most of which were grade 1-2**

Possibly VEGF-Related AEs#	Ivonescimab + chemo (N=266)				Tislelizumab + chemo (N=265)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
Proteinuria	113 (42.5)	35 (13.2)	60 (22.6)	**18 (6.8)**	34 (12.8)	26 (9.8)	8 (3.0)	**0**
Haemorrhage	**66 (24.8)**	**39 (14.7)**	**20 (7.5)**	**7 (2.6)**	**32 (12.1)**	**24 (9.1)**	**6 (2.3)**	**2 (0.8)**
Hypertension	39 (14.7)	7 (2.6)	22 (8.3)	**10 (3.8)**	15 (5.7)	3 (1.1)	7 (2.6)	**5 (1.9)**
Arterial thromboembolism	4 (1.5)	1 (0.4)	0	**3 (1.1)**	0	0	0	**0**
Venous thromboembolism	2 (0.8)	0	2 (0.8)	**0**	3 (1.1)	0	2 (0.8)	**1 (0.4)**
Fistula	1 (0.4)	0	1 (0.4)	**0**	0	0	0	**0**

- # AE terms were grouped terms
- Data are n (%)

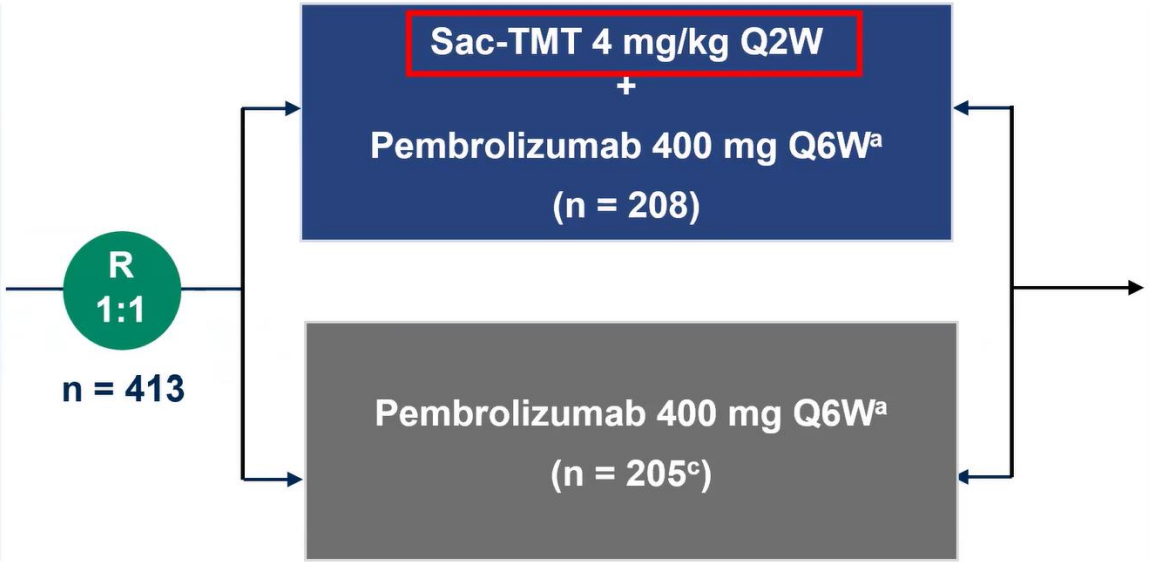
Grade 3 TRAEs was higher (69% vs. 59%)

OptiTROP-Lung05 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT06448312)

Key Eligibility

- Locally advanced (stage IIIB/IIIC) or metastatic (stage IV) NSCLC
- No prior systemic antitumor therapy
- No sensitizing *EGFR* or *ALK* alteration
- PD-L1 TPS≥ 1% (IHC 22C3, central lab)
- ECOG score 0 or 1



Endpoints [b]

Primary

- PFS assessed by BICR

Secondary

- OS (key secondary endpoint)
- PFS assessed by investigator
- ORR, DCR, DOR, etc.
- Safety

Stratification factors

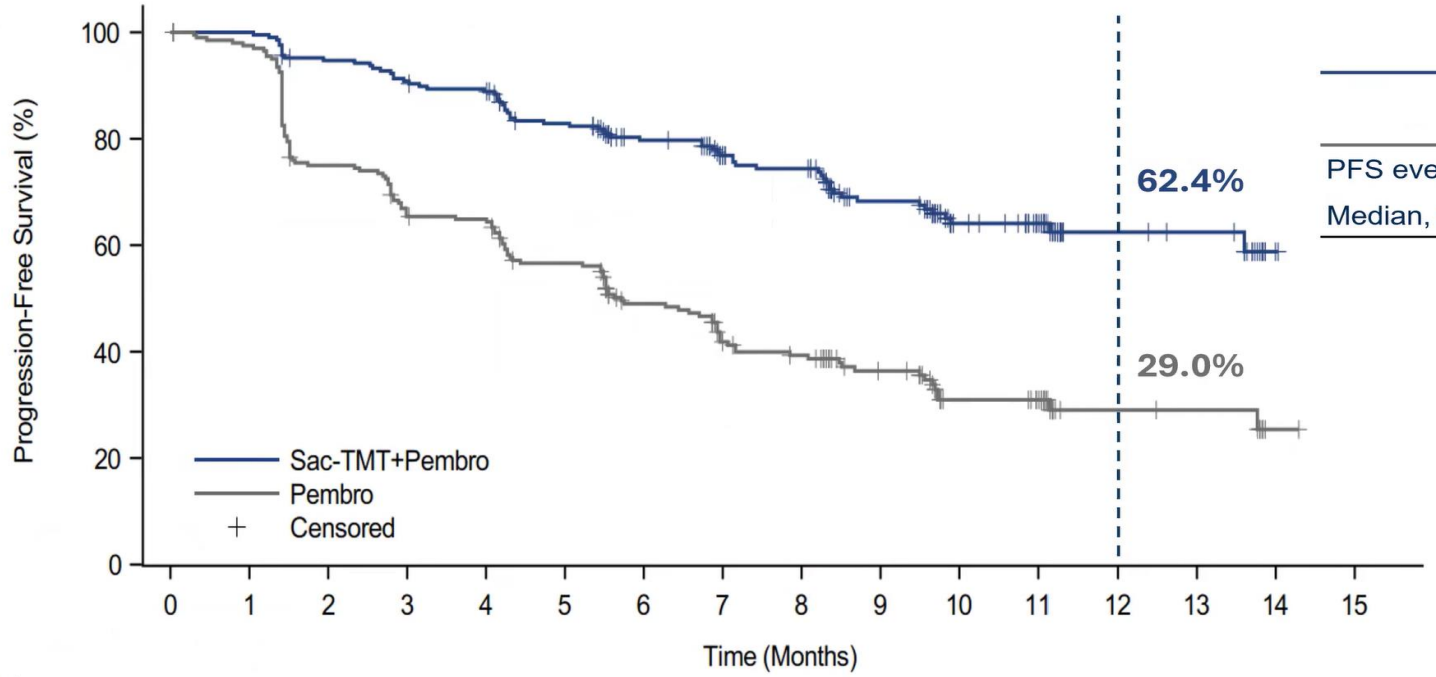
- Histology (squamous vs. non-squamous)
- PD-L1 TPS (1-49% vs. ≥ 50%)
- ECOG score (0 vs. 1)

Patients received sac-TMT + pembro or pembro monotherapy until disease progression or unacceptable toxicity

Zhou C, et al, ASCO 2026

EFFICACY

Sac-TMT + pembro significantly improved PFS vs. pembro, with a 65% reduction in risk of disease progression or death



No.at risk

Sac-TMT+Pembro	208	208	195	187	182	164	144	126	120	90	62	47	20	18	1	0
Pembro	205	195	149	129	127	108	84	67	61	46	28	24	9	8	1	0

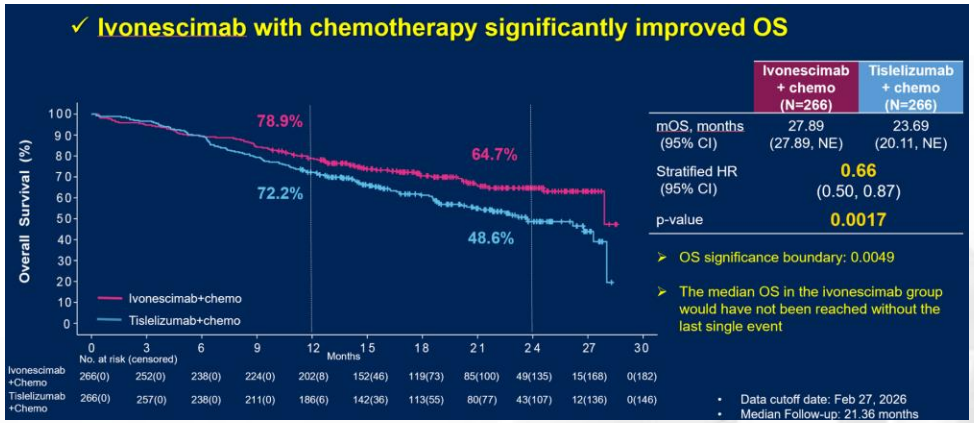
	Sac-TMT + Pembro (n = 208)	Pembro (n = 205)
PFS events, n (%)	66 (31.7)	128 (62.4)
Median, mo (95%CI)	NR (13.6, NE)	5.7 (4.3, 7.0)

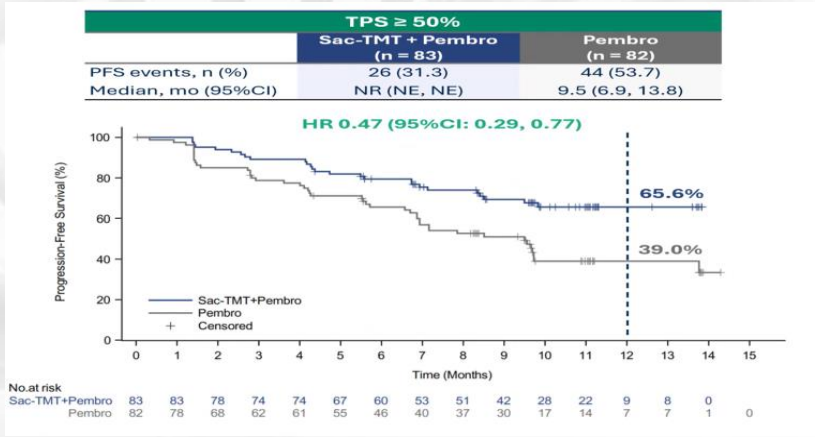
HR 0.35 (95%CI: 0.26, 0.47)

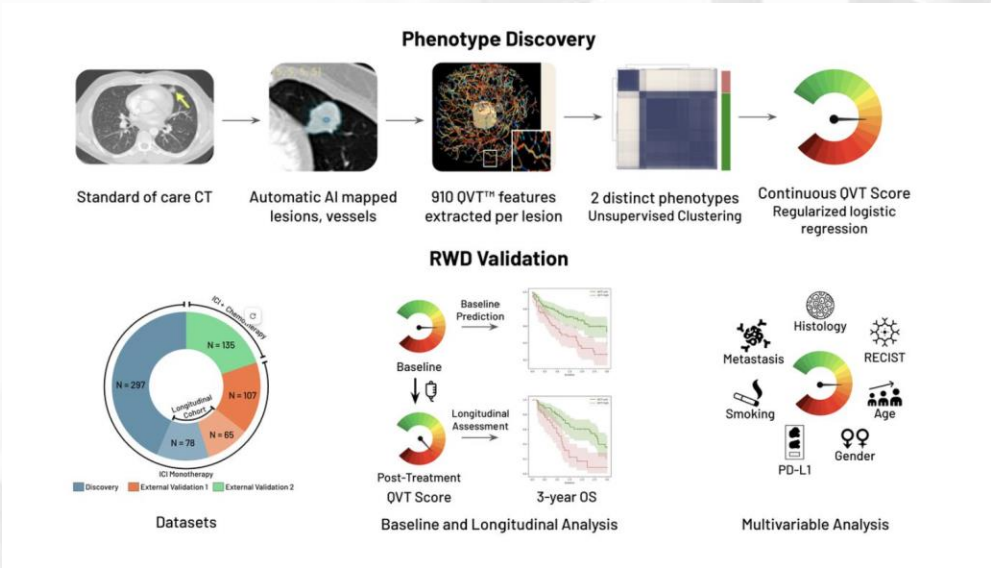
***p* < 0.0001[a]**

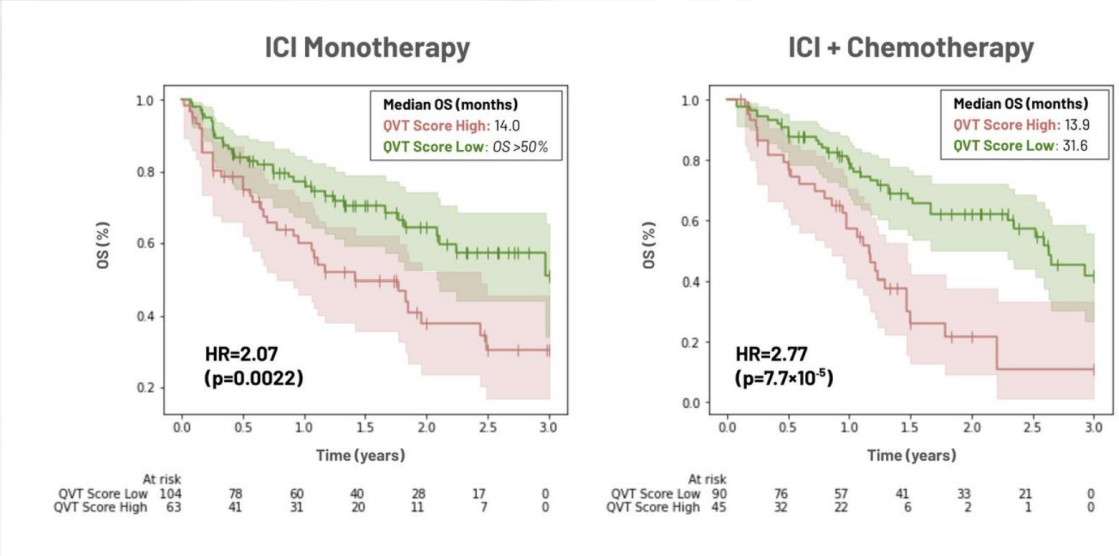
[a] Updated efficacy boundary (corresponding to actual PFS events of 194): 0.0174 (2-sided).
NE, not estimable; NR, not reached.

PERSONALIZED THERAPY









Chae, Y, **Madabhushi A**, Braman N, et al JTC 2026

ADVANCED LUNG CANCER SURVIVORSHIP

Advanced lung cancer survivorship

Physical symptoms
Dyspnea, fatigue, pain

Psychological
Anxiety and distress

Financial toxicity
Costs and income loss

Social & role changes
Relationship and caregiver strain

Ongoing surveillance
Scans, specialists, monitoring

CONCLUSIONS

1. **Comprehensive assessment of patient and tumor is critical in making the most appropriate treatment decision**

2. Drugs targeting driver mutations and co-mutations are in development

3. Drugs to enhance IO efficacy and Antibody Drug Conjugates are being evaluated

4. Biomarkers to identify the most appropriate drugs for each patient are needed.

5. Addressing Survivorship is critical in the management of lung cancer patients.

6. **Providing access to clinical trials is of paramount importance.**

THANK YOU

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