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Letter from Prof Rolf Stahel

Dear Colleagues

It is my pleasure to present this ETOP slide set which has been designed to highlight and summarise key findings in thoracic cancers from the major congresses in 2024. This slide set specifically focuses on the **AACR Annual Meeting 2024** and is available in 3 languages – English, Chinese and Japanese.

The area of clinical research in oncology is a challenging and continually changing environment. Within this environment we all value access to scientific data and research which helps to educate and inspire further advancements in our roles as scientists, clinicians and educators. I hope you find this review of the latest developments in thoracic cancers of benefit to you in your practice. If you would like to share your thoughts with us, we would welcome your comments. Please send any correspondence to etop@etop.eu-org.

I would like to thank our ETOP members Drs Enriqueta Felip and Solange Peters for their roles as Editors – for prioritising abstracts and reviewing slide content. The slide set you see before you would not be possible without their commitment and hard work.

Finally, we are also very grateful to Eli Lilly, GSK, Johnson&Johnson and Roche for their financial, administrative and logistical support in the realisation of this complex yet rewarding activity.

Yours sincerely,
Rolf Stahel
President, ETOP Foundation Council

ETOP Medical Oncology Slide Deck Editors 2024

Focus: Advanced NSCLC (not radically treatable stage III and stage IV) and biomarkers (all stages)

Dr Solange Peters

Multidisciplinary Oncology Center, Lausanne Cancer Center, Lausanne, Switzerland

Focus: Early and locally advanced NSCLC (stage I–III) and other malignancies, SCLC, mesothelioma, rare tumours

Dr Enriqueta Felip

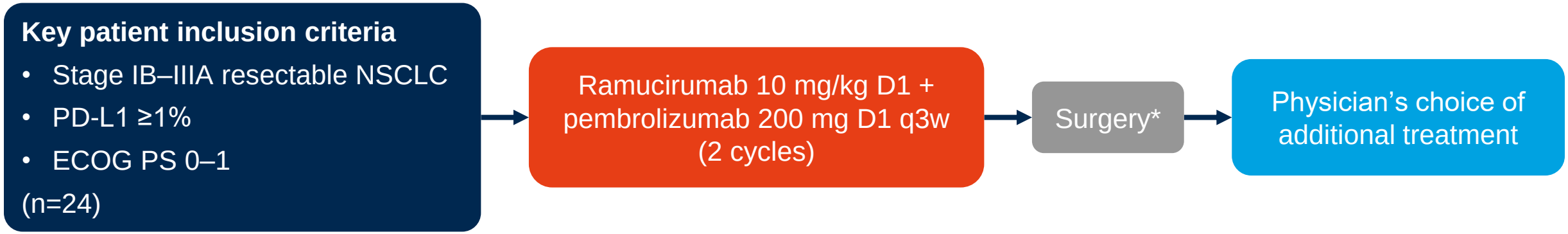
Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Contents

Early stage and locally advanced NSCLC – Stages I, II and III

1211: Biomarker analysis of pembrolizumab and ramucirumab neoadjuvant therapy for PD-L1-positive stage IB-IIIA lung cancer: EAST ENERGY trial – Nomura K, et al

- **Study objective**
  - To identify biomarkers for predicting response to neoadjuvant therapy and its impact on the tumor microenvironment (TME) in patients with PD-L1-positive stage IB–IIIA NSCLC in the phase 2 EAST ENERGY study



Analysis

- Association between TME immunological phenotype and MPR using RNA sequencing and multiplex IHC
- TME changes before (mIHC, n=20, RNA-seq, n=7) and after treatment (mIHC, n=20, RNA-seq, n=16)

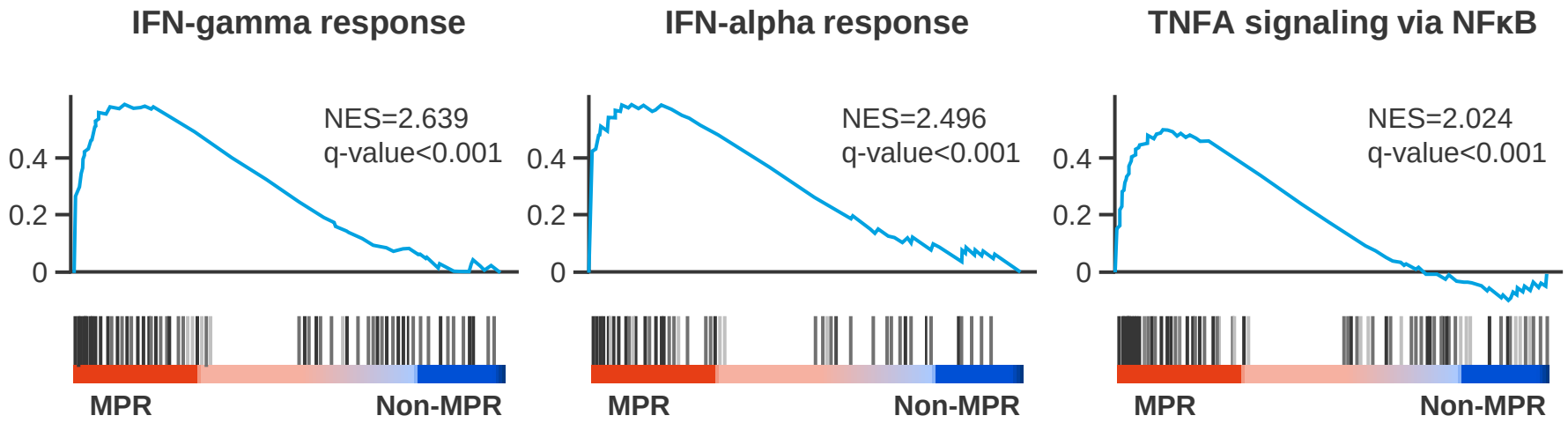
*Lobectomy, bi-lobectomy or pneumonectomy with LND

Nomura K, et al. AACR; 2024. Abstract nr 1211

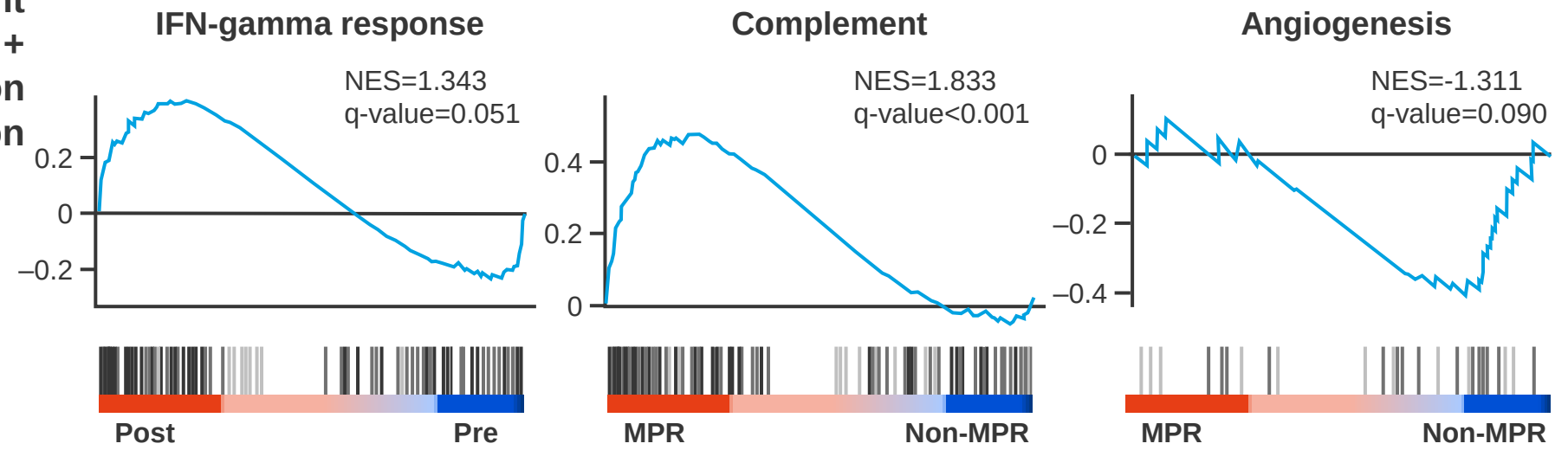
1211: Biomarker analysis of pembrolizumab and ramucirumab neoadjuvant therapy for PD-L1-positive stage IB-IIIA lung cancer: EAST ENERGY trial – Nomura K, et al

- **Key results**

Immune-related gene sets in pre-treatment tumors



Effect of neoadjuvant pembrolizumab + ramucirumab on gene expression

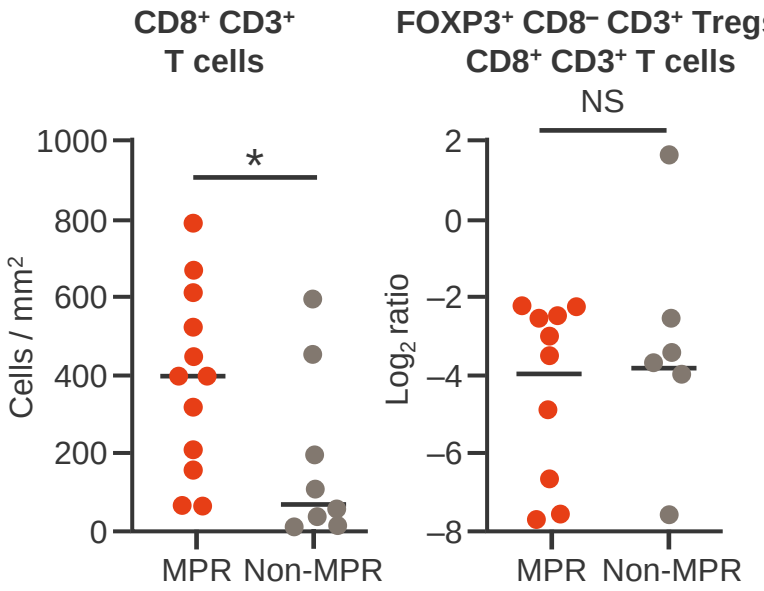


NES, normalized enrichment score

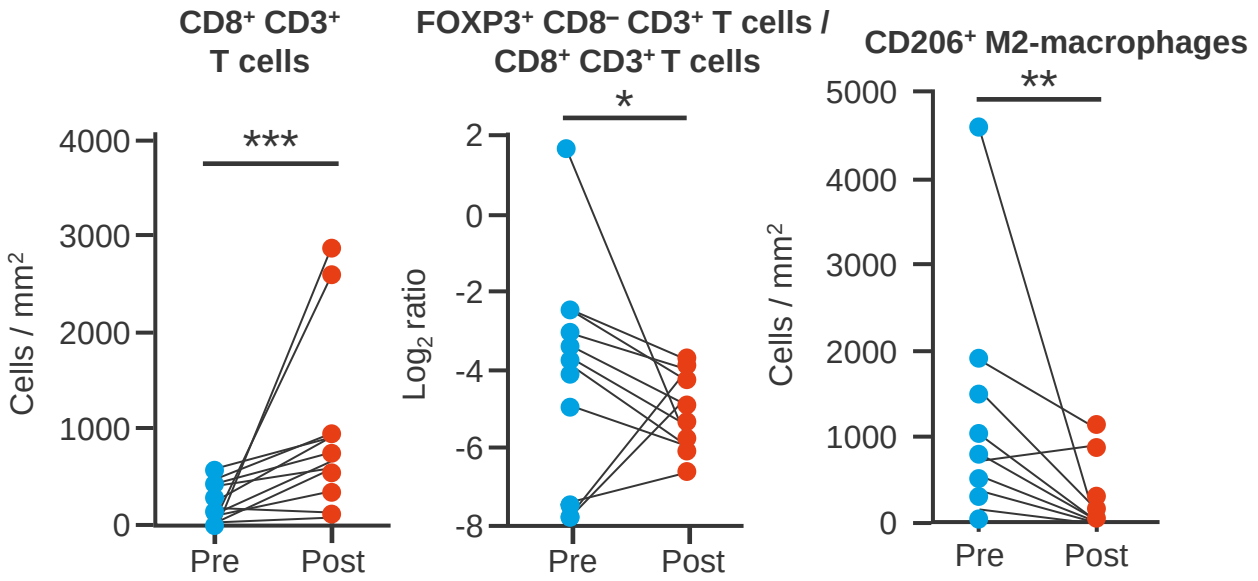
1211: Biomarker analysis of pembrolizumab and ramucirumab neoadjuvant therapy for PD-L1-positive stage IB-IIIA lung cancer: EAST ENERGY trial – Nomura K, et al

- **Key results (cont.)**

Immune cell-infiltration in pre-treatment TME



Impact on tumor immune microenvironment



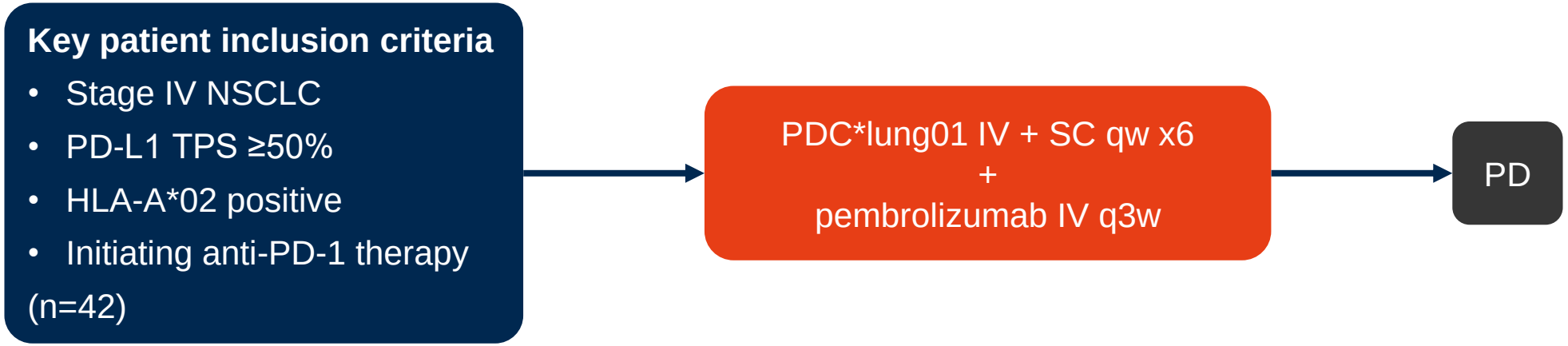
- **Conclusions**
  - In patients with PD-L1-positive stage IB–IIIA NSCLC, pre-treatment gene expression profiles and CD8+ T-cell abundance were associated with MPR, while immunosuppressive cell infiltration was not associated with treatment resistance. Neoadjuvant pembrolizumab + ramucirumab led to increases in immune-related gene expression and tumor-infiltrating CD8+ T-cells along with decreases in angiogenesis-related gene expression and immunosuppressive cells

Advanced NSCLC
Not radically treatable stage III and stage IV

Immunotherapy

CT021: Preliminary clinical results of a therapeutic cancer vaccine PDC*lung01 in combination with anti-PD-1 in patients (pts) with stage IV NSCLC – Theelan W, et al

- **Study objective**
  - To evaluate the preliminary efficacy and safety of PDC*lung01, a therapeutic cancer vaccine, combined with pembrolizumab in patients with stage IV NSCLC in Cohort B2 (high dose) of the phase 2 portion of the PDC-LUNG-101 study



Endpoints*

- Dose range, clinical activity (ORR, PFS, DCR)

*Interim analysis conducted when the 19th evaluable patient reached 9-mo PFS

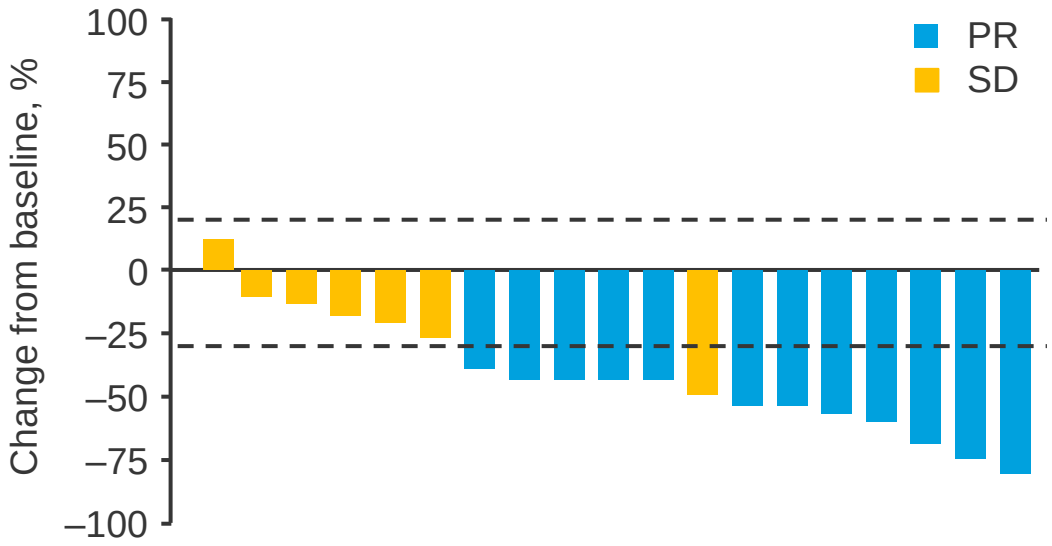
Theelan W, et al. AACR; 2024. Abstract nr CT021

CT021: Preliminary clinical results of a therapeutic cancer vaccine PDC*lung01 in combination with anti-PD-1 in patients (pts) with stage IV NSCLC – Theelan W, et al

- **Key results**

Response	PP population dosed in B2 cohort (n=19)	Total population treated in B2 cohort (n=21)
BOR, n (%) PR SD Missing	 12 (63.2) 7 (36.8) -	 12 (57.1) 8 (38.1) 1 (4.8)
ORR, n (%) [80%CI]	12 (63.2) [45.9, 78.2]	12 (57.1) [41.0, 72.2]
Median follow-up, mo (95%CI)	12.5 (9.9, 14.2)	-
mDoR, mo (95%CI)	9.5 (4.4, NR)	-
DCR, % (80%CI)	94.7 (81.0, 99.4)	-
PFS events, n (%)	11 (57.9)	13 (61.9)
9-mo PFS rate, % (80%CI)	52.1 (36.5, 65.6)	47.1 (32.7, 60.3)
mPFS, mo (95%CI)	10.9 (5.6, NR)	8.9 (5.6, NR)

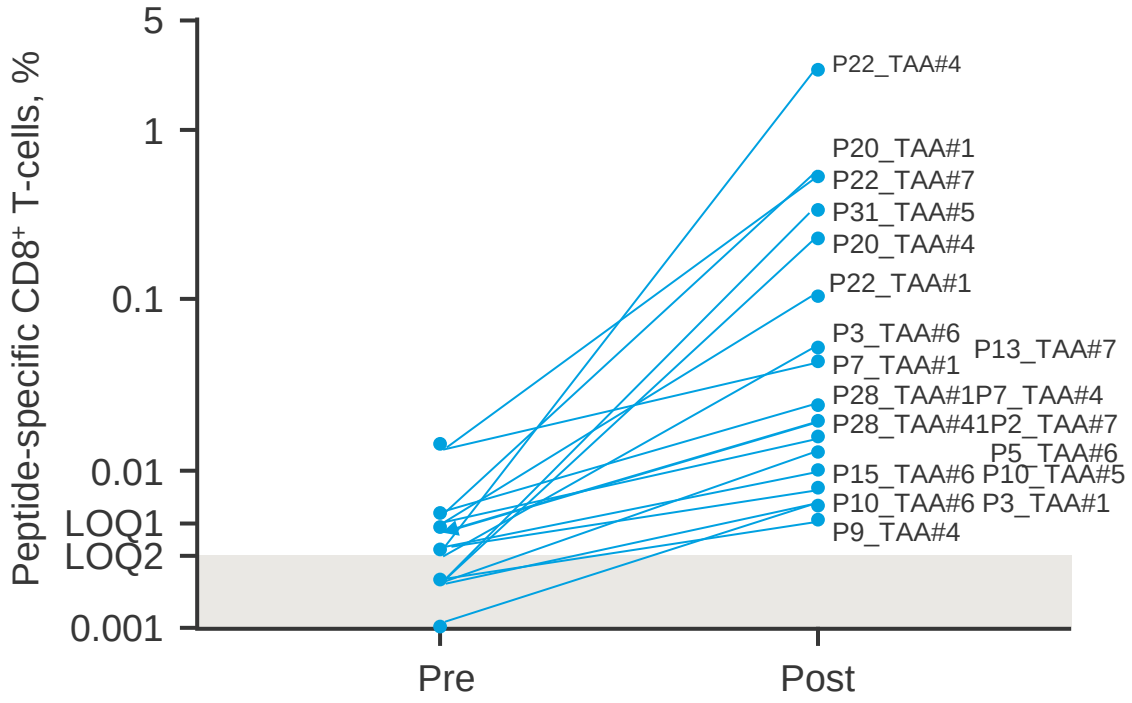
Confirmed best overall response



Tumor shrinkage reached >50% in 7 out of 12 patients presenting a PR

CT021: Preliminary clinical results of a therapeutic cancer vaccine PDC*lung01 in combination with anti-PD-1 in patients (pts) with stage IV NSCLC – Theelan W, et al

- **Key results (cont.)**



AEs, n (%)	Dosed in B2 cohort (n=38)
DLT	1 (3)
Any TEAE	36 (95)
Any TRAE	28 (74)
Grade ≥3 TRAEs	2 (5)
SAEs	13 (34)
Led to death	3 (8)
TEAE led to IMP delay	7 (18)
TEAE led IMP discontinuation	2 (5)

- **Conclusions**
  - In patients with stage IV NSCLC, PDC*lung01 + pembrolizumab demonstrated promising clinical activity with a mild safety profile

Theelan W, et al. AACR; 2024. Abstract nr CT021

CT032: Promotive clinical effects of pembrolizumab with necitumumab in patients having advanced non-small cell lung cancer with PD-L1 expression of 50% or higher in a phase II study (K-TAIL-202) – Horiike A, et al

- **Study objective**
  - To evaluate the efficacy and safety of 1L pembrolizumab + necitumumab in patients with PD-L1-positive advanced NSCLC in the phase 2 K-TAIL-202 study

Key patient inclusion criteria

- Advanced NSCLC
- PD-L1 expression ≥50% (IHC)
- No EGFR or ALK alterations
- No prior systemic therapy for advanced disease
- ECOG PS 0–1

(n=50)

→ Necitumumab 800 mg D1, 8 + pembrolizumab 200 mg D1 IV q3w (up to 2 years/35 cycles)

Primary endpoint

- ORR

Secondary endpoints

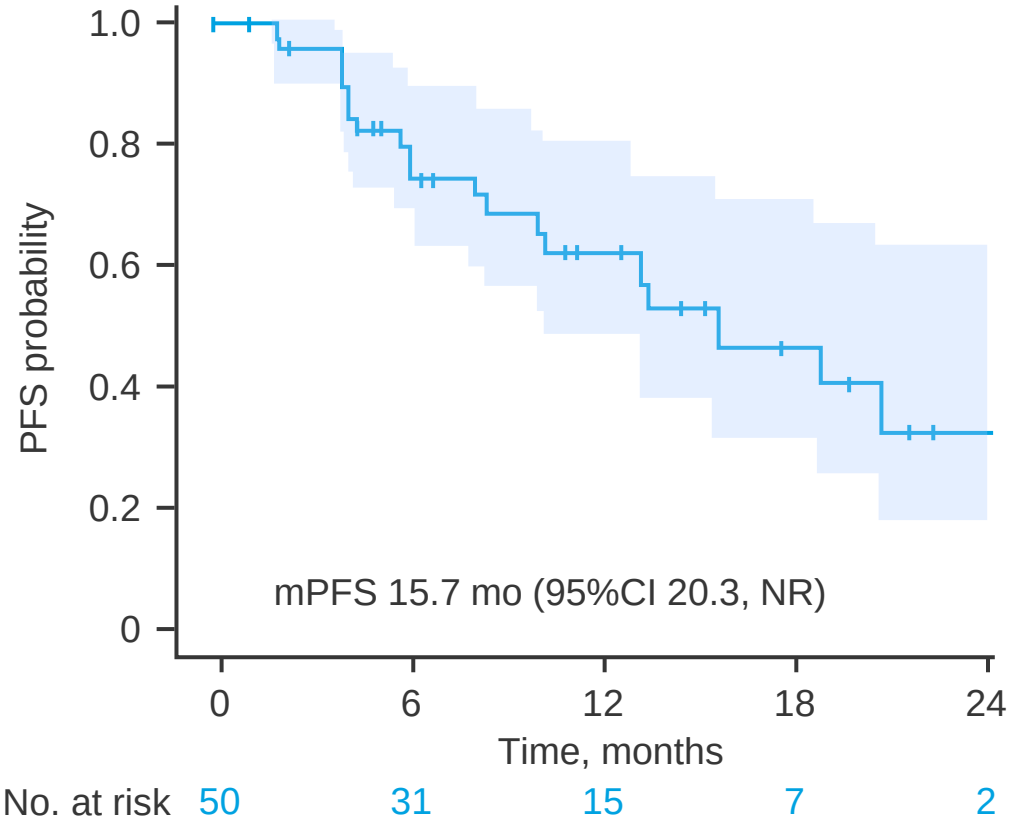
- PFS, OS, safety

Horiike A, et al. AACR; 2024. Abstract nr CT032

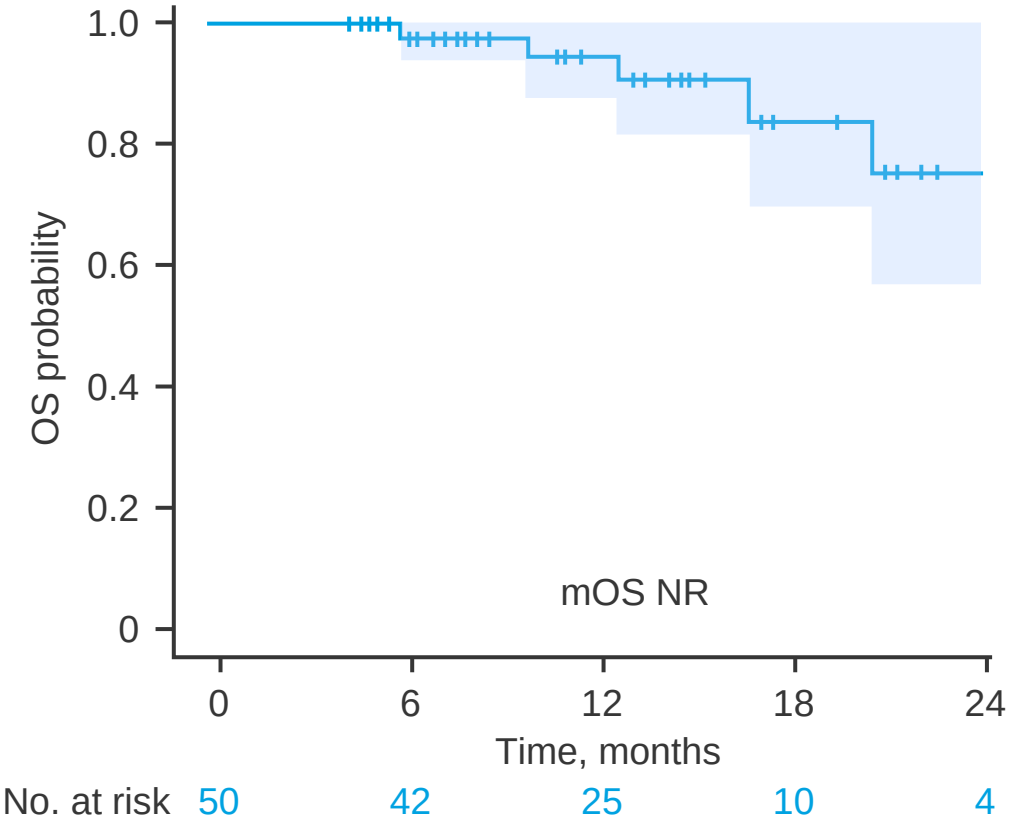
CT032: Promotive clinical effects of pembrolizumab with necitumumab in patients having advanced non-small cell lung cancer with PD-L1 expression of 50% or higher in a phase II study (K-TAIL-202) – Horiike A, et al

- **Key results**

Progression-free survival



Overall survival



Horiike A, et al. AACR; 2024. Abstract nr CT032

CT032: Promotive clinical effects of pembrolizumab with necitumumab in patients having advanced non-small cell lung cancer with PD-L1 expression of 50% or higher in a phase II study (K-TAIL-202) – Horiike A, et al

- **Key results (cont.)**

Response	Pembrolizumab + necitumumab (n=50)
ORR, % (95%CI)	76.0 (61.9, 86.9)
BOR, %	
CR	2
PR	74
SD	10
PD	8
DCR, % (95%CI)	86.0 (73.3, 94.2)

AEs, n (%)	Pembrolizumab + necitumumab (n=50)
Any TEAEs	50 (100)
Grade ≥3	24 (48)
Led to discontinuation	13 (26)
Led to death	1 (2)
Any TRAEs due to necitumumab	49 (98)
Grade ≥3	20 (40)

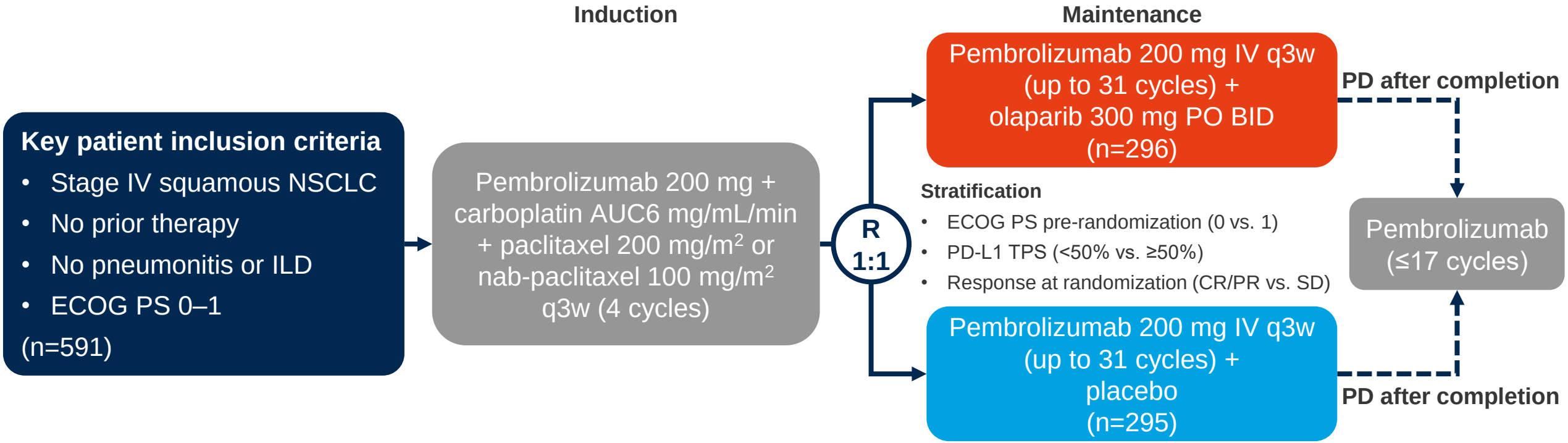
	Pembrolizumab + necitumumab (n=50)	
TEAEs, n (%)	Grade 3	Grade 4
Acneiform rash	5 (10)	0
Interstitial lung disease	5 (10)	0
Hypokalemia	4 (8)	0
Lung infection	3 (6)	1 (2)
Hypomagnesemia	2 (4)	2 (4)
Dry skin	1 (2)	0
Oral mucositis	1 (2)	0
Anorexia	1 (2)	0
Eczema	1 (2)	0
Maculopapular rash	1 (2)	0
Pruritus	1 (2)	0

- **Conclusions**
  - In patients with advanced PD-L1-positive (≥50%) NSCLC, 1L pembrolizumab + necitumumab demonstrated preliminary encouraging clinical activity with no unexpected safety findings

Horiike A, et al. AACR; 2024. Abstract nr CT032

CT034: Results from phase 3 KEYLYNK-008: Pembrolizumab (pembro) with and without maintenance olaparib (ola) after first-line (1L) pembro plus chemotherapy (chemo) for metastatic squamous non-small-cell lung cancer (sqNSCLC) – Hochmair M, et al

- **Study objective**
  - To evaluate the efficacy and safety of pembrolizumab ± olaparib after 1L pembrolizumab + chemotherapy in patients with metastatic squamous NSCLC in the phase 3 KEYLYNK study



Primary endpoints

- PFS (RECIST v1.1, BICR), OS

Secondary endpoints

- ORR, DoR, safety

Presented by Ernest Nadal

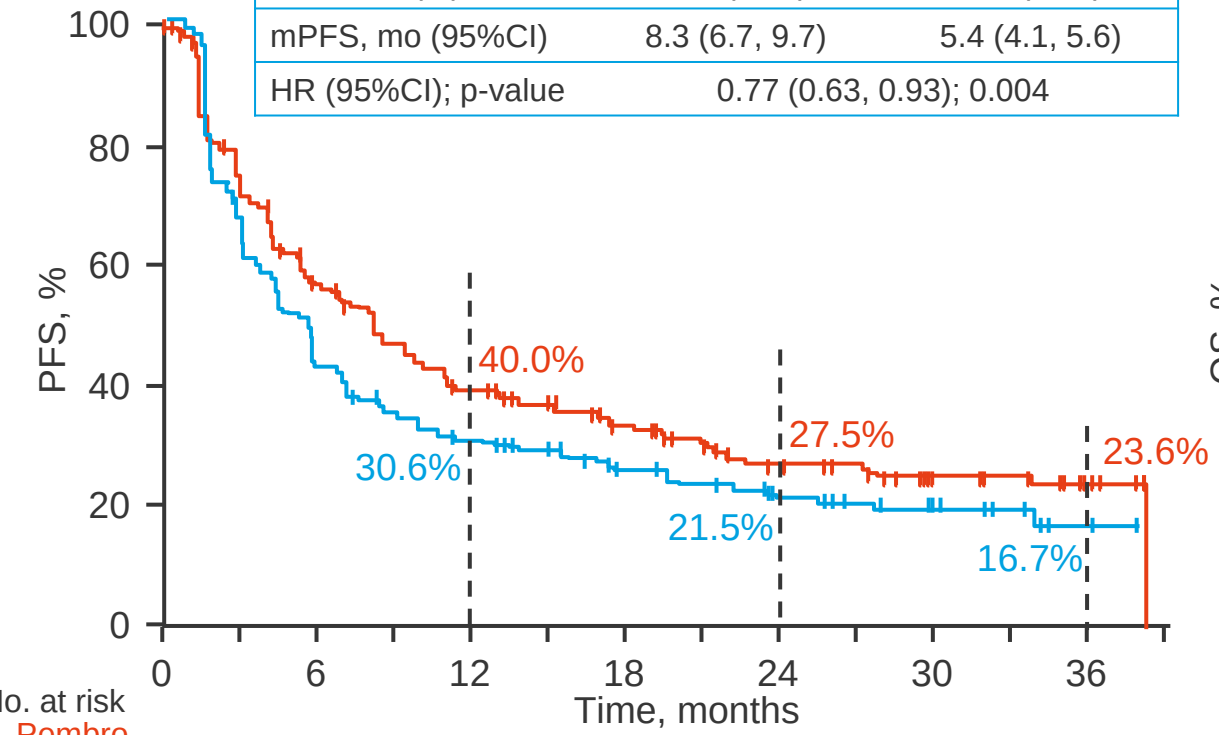
Hochmair M, et al. AACR; 2024. Abstract nr CT034

CT034: Results from phase 3 KEYLYNK-008: Pembrolizumab (pembro) with and without maintenance olaparib (ola) after first-line (1L) pembro plus chemotherapy (chemo) for metastatic squamous non-small-cell lung cancer (sqNSCLC) – Hochmair M, et al

- **Key results**

Progression-free survival at IA2

	Pembrolizumab + olaparib	Pembrolizumab + placebo
Events, n (%)	197 (66.6)	217 (73.6)
mPFS, mo (95%CI)	8.3 (6.7, 9.7)	5.4 (4.1, 5.6)
HR (95%CI); p-value	0.77 (0.63, 0.93); 0.004	

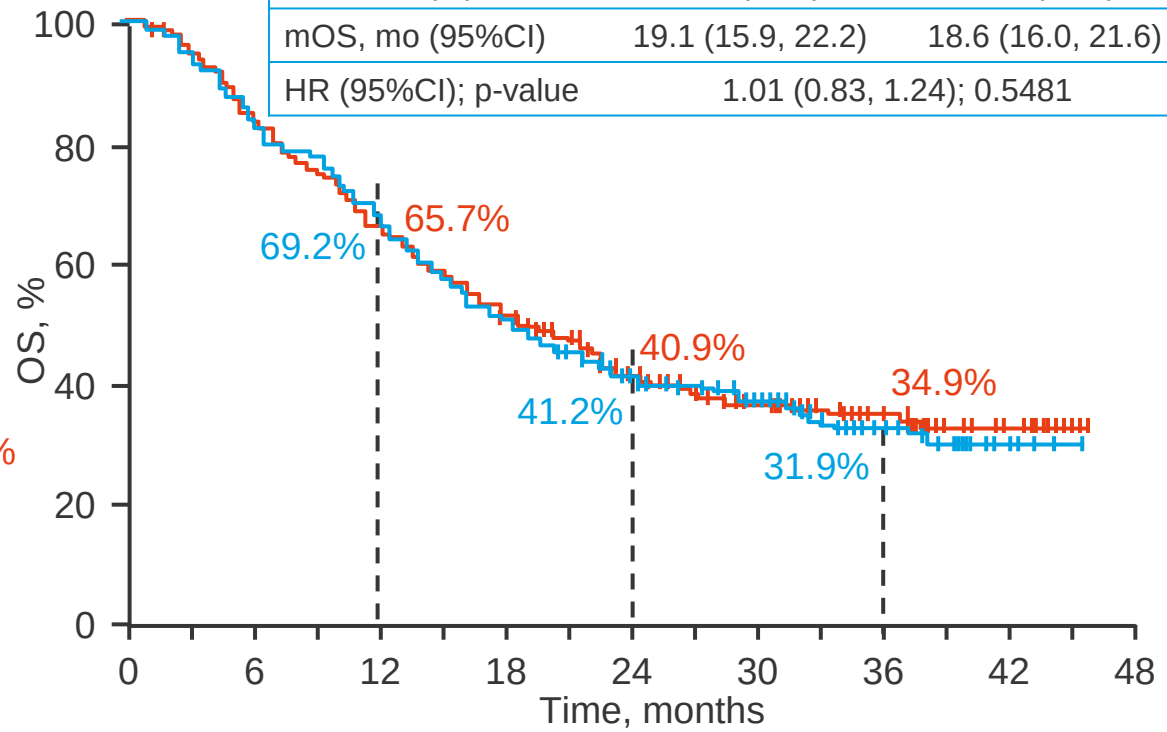


No. at risk

Pembro + olaparib	296	205	153	124	102	88	67	55	41	38	22	16	5	0
Pembro + placebo	295	170	115	91	79	68	49	40	29	23	14	8	1	0

Overall survival at IA3

	Pembrolizumab + olaparib	Pembrolizumab + placebo
Events, n (%)	188 (63.5)	191 (64.7)
mOS, mo (95%CI)	19.1 (15.9, 22.2)	18.6 (16.0, 21.6)
HR (95%CI); p-value	1.01 (0.83, 1.24); 0.5481	



Pembro + olaparib	296	281	248	220	193	170	154	127	104	82	67	54	41	27	19	5	0	
Pembro + placebo	295	281	252	230	204	174	150	123	102	81	68	56	39	22	9	1	0	

Hochmair M, et al. AACR; 2024. Abstract nr CT034

CT034: Results from phase 3 KEYLYNK-008: Pembrolizumab (pembro) with and without maintenance olaparib (ola) after first-line (1L) pembro plus chemotherapy (chemo) for metastatic squamous non-small-cell lung cancer (sqNSCLC) – Hochmair M, et al

- **Key results (cont.)**

Response in patients with CR/PR/SD after induction at IA3	Pembrolizumab + olaparib	Pembrolizumab + placebo
ORR, % (95%CI)	25.0 (20.2, 30.3)	15.3 (11.3, 19.9)
BOR, %		
CR	3.7	1.7
PR	21.3	13.6
SD	51.7	52.9
PD	20.3	28.8
NE	0.7	1.7
NA	2.4	1.4
mDoR, mo (range)	21.0 (2.1, 42.8+)	26.0 (1.2+, 39.6+)

AEs, n (%)	Pembrolizumab + olaparib (n=294)	Pembrolizumab + placebo (n=292)
Any TEAE	281 (95.6)	269 (92.1)
Grade 3–5	160 (54.4)	112 (38.4)
Led to death	30 (10.2)	18 (6.2)
Any TRAE	225 (76.5)	190 (65.1)
Grade 3–5	87 (29.6)	37 (12.7)
Led to discontinuation		
Any drug	38 (12.9)	19 (6.5)
Pembrolizumab	20 (6.8)	16 (5.5)
Olaparib or placebo	34 (11.6)	15 (5.1)
Led to death	2 (0.7)	1 (0.3)

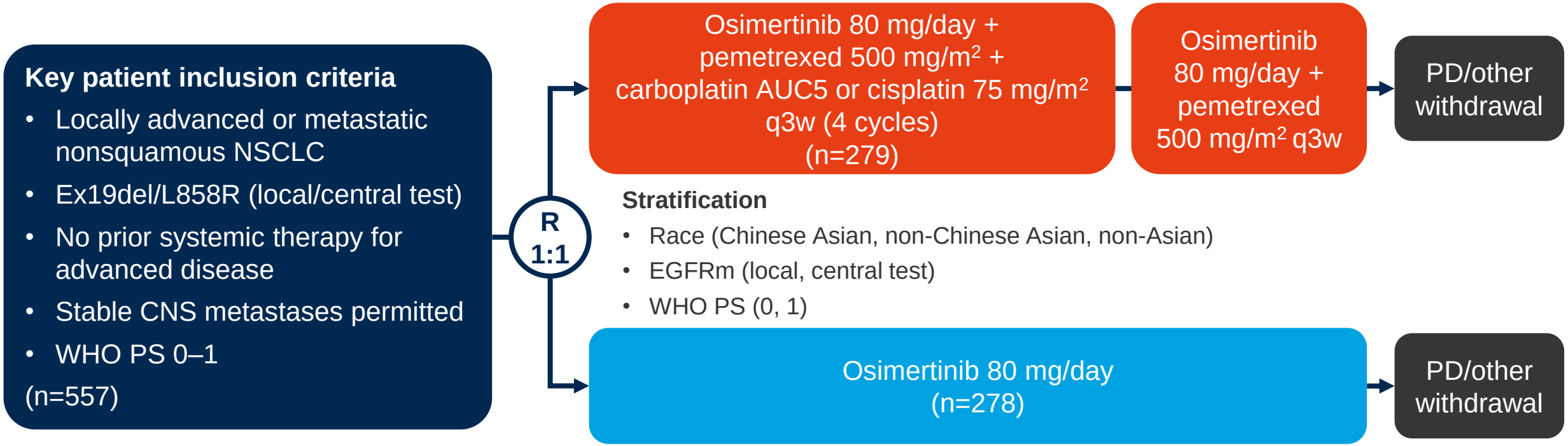
- **Conclusions**
  - In patients with stage IV squamous NSCLC, pembrolizumab + olaparib maintenance therapy after 1L pembrolizumab + chemotherapy induction did not significantly improve PFS or OS compared with pembrolizumab alone. There were no unexpected safety findings with the combination therapy

Advanced NSCLC
Not radically treatable stage III and stage IV

Targeted therapies

CT017: FLAURA2: Exploratory analysis of baseline (BL) and on-treatment plasma EGFRm dynamics in patients (pts) with EGFRm advanced NSCLC treated with first-line (1L) osimertinib (osi) ± platinum-pemetrexed – Jänne PA, et al

- **Study objective**
  - To evaluate the plasma EGFRm dynamics in patients with EGFRm advanced NSCLC treated with 1L osimertinib ± platinum-pemetrexed in an exploratory analysis of the phase 3 FLAURA2 study



Primary endpoint
- PFS

Secondary endpoints
- OS, ORR, DoR, DCR, PFS2, safety

Exploratory endpoints
- Correlation of baseline-detected plasma EGFRm and its clearance with PFS

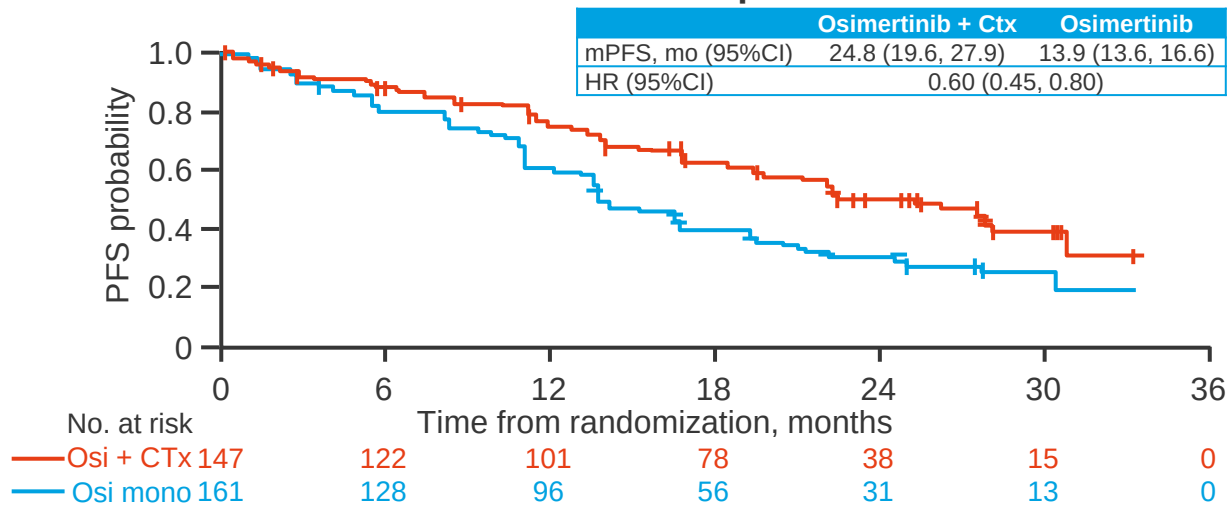
Jänne PA, et al. AACR; 2024. Abstract nr CT017

CT017: FLAURA2: Exploratory analysis of baseline (BL) and on-treatment plasma EGFRm dynamics in patients (pts) with EGFRm advanced NSCLC treated with first-line (1L) osimertinib (osi) ± platinum-pemetrexed – Jänne PA, et al

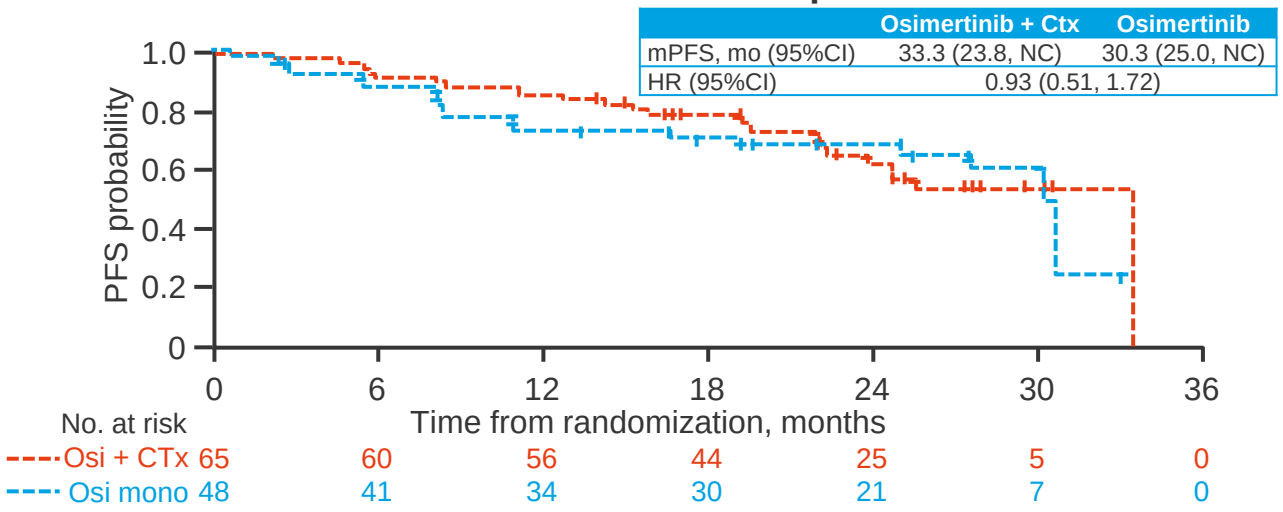
- **Key results**

Progression-free survival

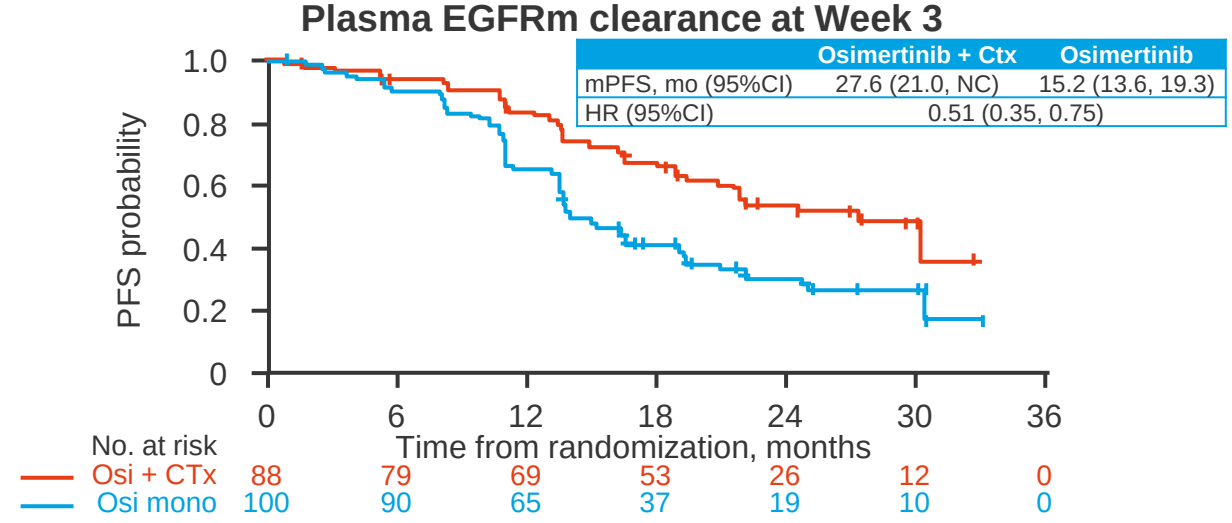
Baseline-detected plasma EGFRm



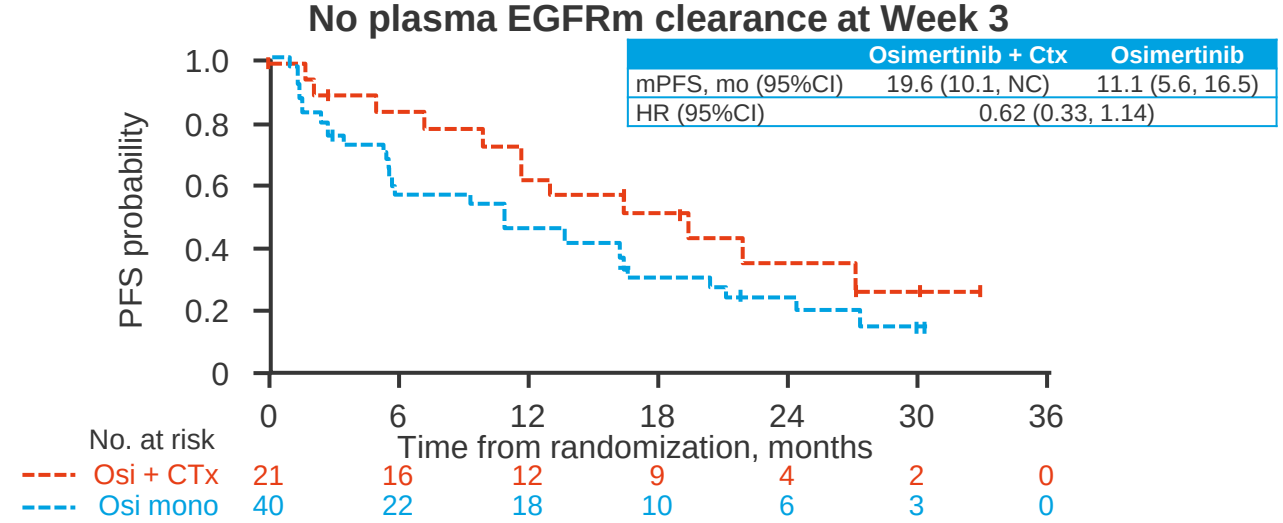
No baseline-detected plasma EGFRm



Plasma EGFRm clearance at Week 3



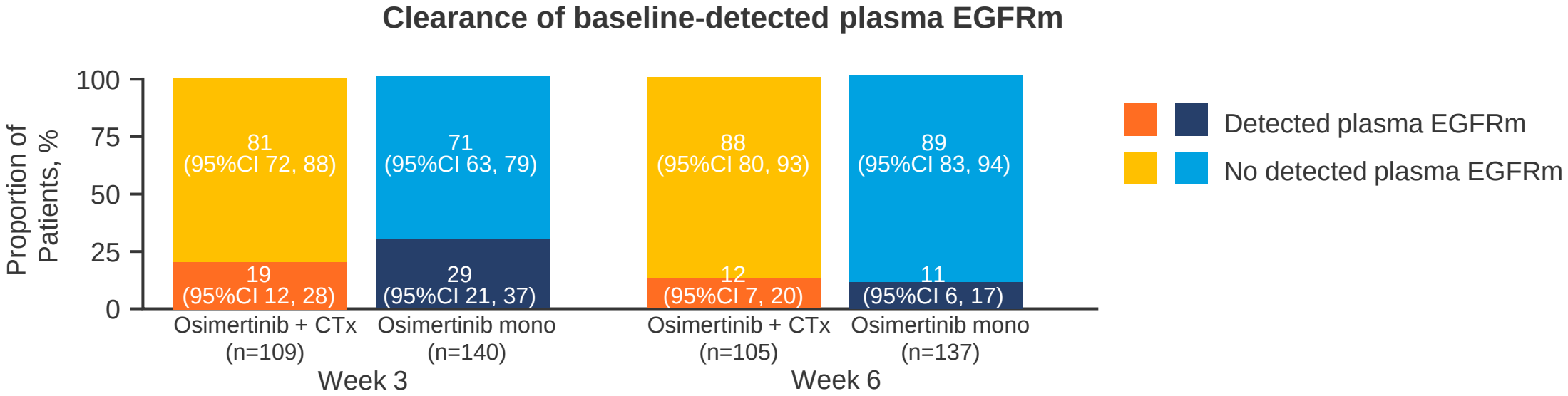
No plasma EGFRm clearance at Week 3



Jänne PA, et al. AACR; 2024. Abstract nr CT017

CT017: FLAURA2: Exploratory analysis of baseline (BL) and on-treatment plasma EGFRm dynamics in patients (pts) with EGFRm advanced NSCLC treated with first-line (1L) osimertinib (osi) ± platinum-pemetrexed – Jänne PA, et al

- **Key results**



- **Conclusions**
  - In patients with advanced EGFRm NSCLC, baseline detection of plasma EGFRm may help to identify those patients who will derive the most benefit from 1L osimertinib + platinum-pemetrexed chemotherapy over osimertinib alone, although this hypothesis requires further formal prospective validation

Jänne PA, et al. AACR; 2024. Abstract nr CT017

1229: BDTX-1535: A MasterKey EGFR inhibitor targeting classical and non-classical oncogenic driver mutations and the C797S acquired resistance mutation to address the evolving molecular landscape of EGFR mutant NSCLC – Dardenne E, et al

- **Study objective**
  - To evaluate BDTX-1535, a fourth generation EGFR TKI targeting classical and non-classical driver mutations including C797S acquired resistance, in patients with EGFRm NSCLC in a phase 1 study

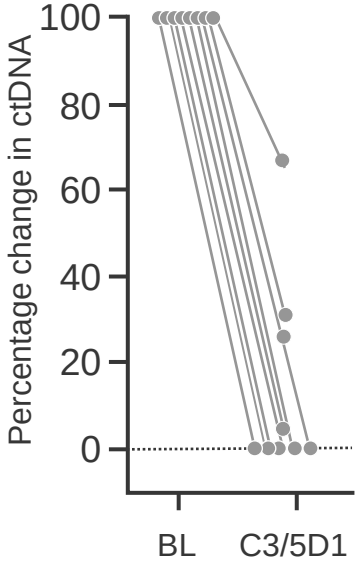
- **Methods**
  - Mutational sequencing of 235,761 cases with NSCLC
  - Phase 1 study to examine the potency of BDTX-1535 (100 and 200 mg/day) against classical, non-classical and acquired resistance mutations following progression on third generation EGFR TKIs (osimertinib, furmonertinib and lazertinib)

Dardenne E, et al. AACR; 2024. Abstract nr 1229

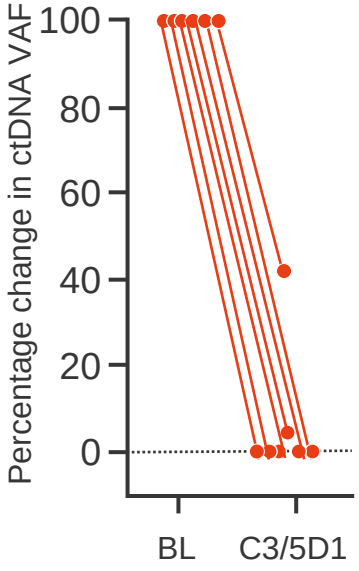
1229: BDTX-1535: A MasterKey EGFR inhibitor targeting classical and non-classical oncogenic driver mutations and the C797S acquired resistance mutation to address the evolving molecular landscape of EGFR mutant NSCLC – Dardenne E, et al

- **Key results**

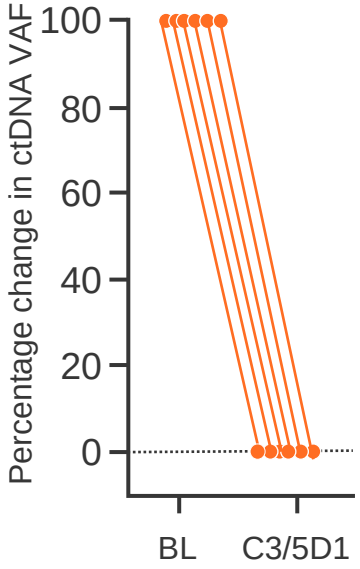
Clearance of plasma ctDNA (9/9 patients)



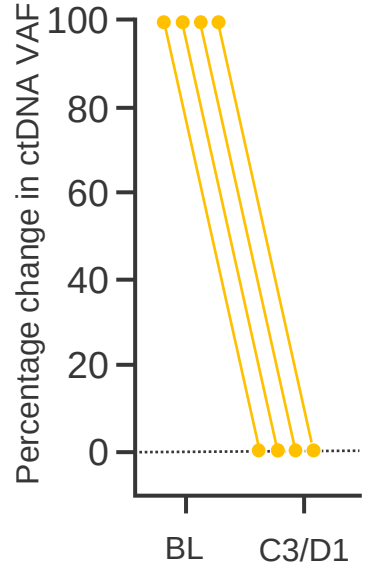
Clearance of classical mutations (7/7 patients)



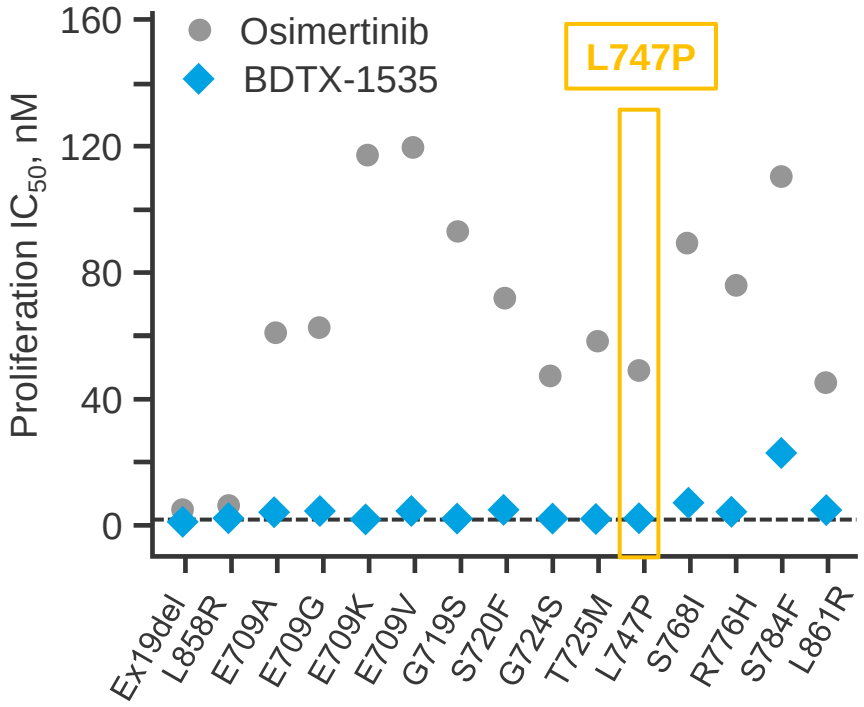
Clearance of C797S (6/6 patients)



Clearance of non-classical mutations (4/4 patients)



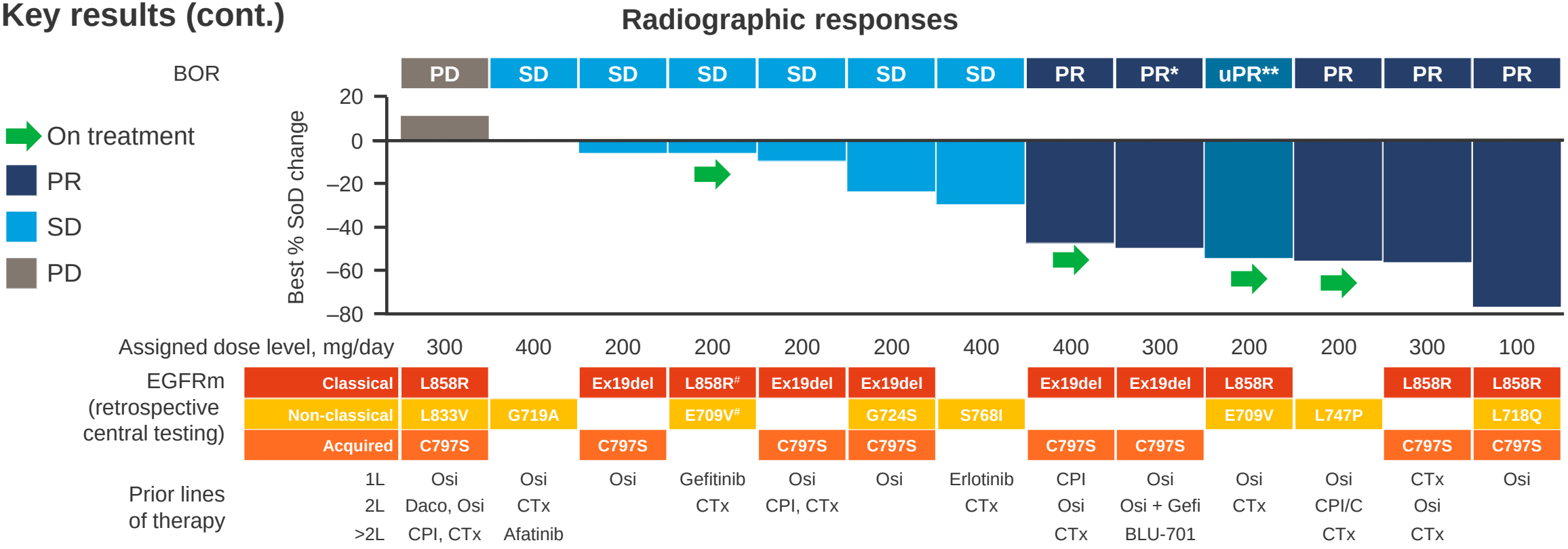
BDTX-1535: inhibition of non-classical mutations that are insensitive to osimertinib



Dardenne E, et al. AACR; 2024. Abstract nr 1229

1229: BDTX-1535: A MasterKey EGFR inhibitor targeting classical and non-classical oncogenic driver mutations and the C797S acquired resistance mutation to address the evolving molecular landscape of EGFR mutant NSCLC – Dardenne E, et al

- **Key results (cont.)**



- **Conclusions**
  - In patients with EGFRm NSCLC, BDTX-1535 demonstrated preliminary activity against classical, non-classical and acquired C797S resistance mutations

*%SoD was updated to -50% from prior data release; **1 patient had a PR on a post-baseline scan, but the radiologist was unable to confirm response on a subsequent scan; #mutations were absent on confirmatory test

Dardenne E, et al. AACR; 2024. Abstract nr 1229

Advanced NSCLC
Not radically treatable stage III and stage IV

ADCs and other therapies

6580: A novel EGFR x cMET bispecific ADC PRO1286 demonstrated broad antitumor activity and promising tolerability in preclinical models – Xiao Y, et al

- **Study objective**
  - To evaluate the antitumor activity of PRO1286, an EGFR and cMET bispecific ADC, in mouse xenograft models

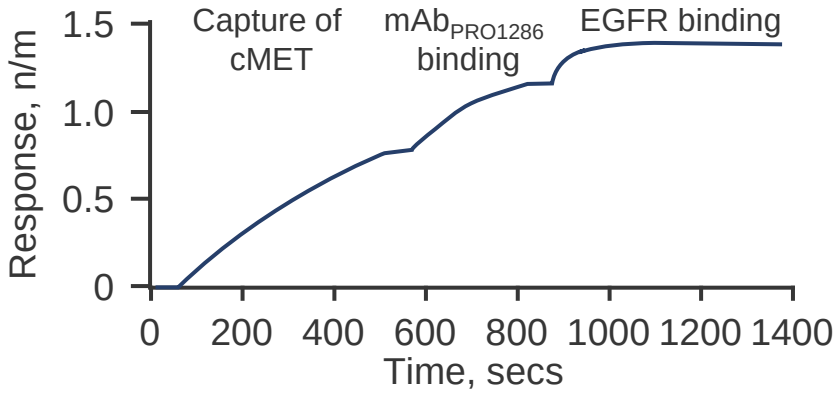
- **Methods**
  - The antitumor activity of PRO1286 was assessed in mouse xenograft models of head and neck, lung, esophageal, gastric and colorectal tumor types
  - The toxicity and PK of PRO1286 were assessed in cynomolgus monkeys

Presented by Zhu Chen
Xiao Y, et al. AACR; 2024. Abstract nr 6580

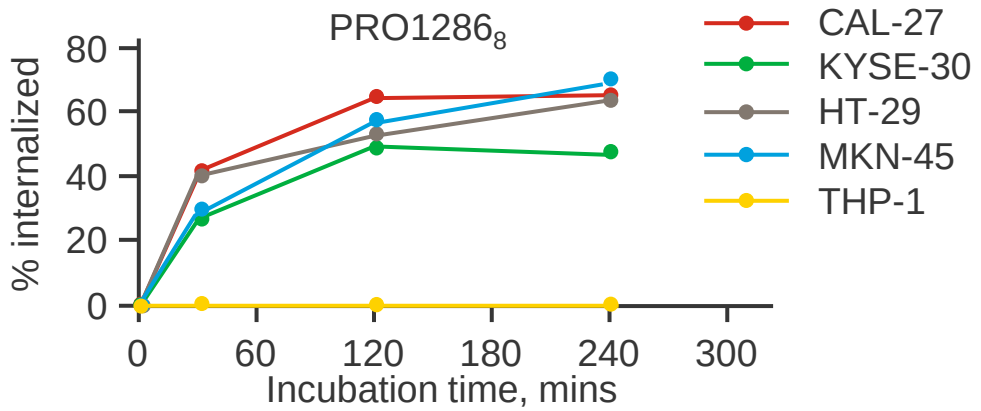
6580: A novel EGFR x cMET bispecific ADC PRO1286 demonstrated broad antitumor activity and promising tolerability in preclinical models – Xiao Y, et al

- **Key results**

Concurrent binding of the antigens

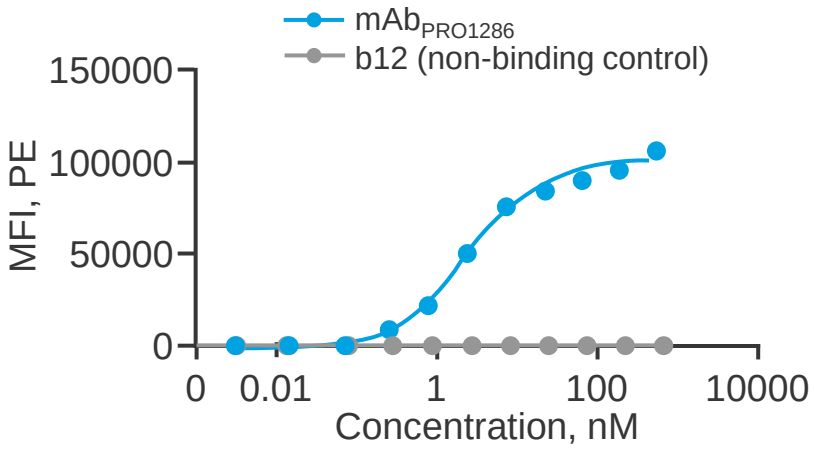


Internalization



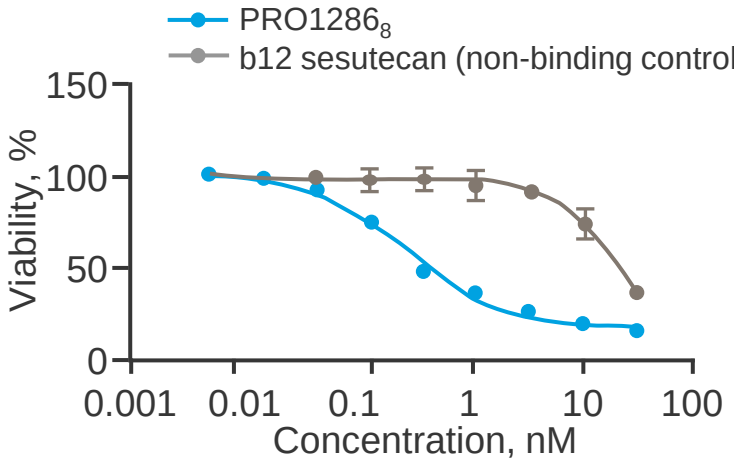
Binding to tumor cells

NCI-H292 (NSCLC)



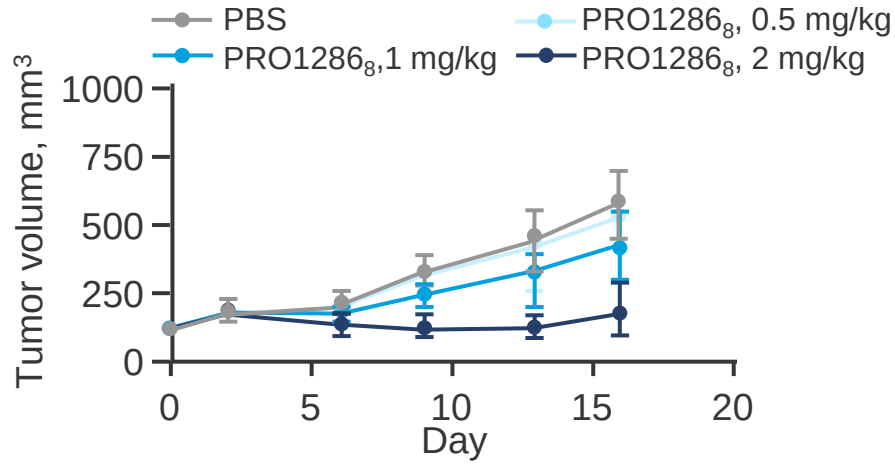
Cytotoxicity

NCI-H292 (NSCLC)



Antitumor activity

NCI-H1975 (NSCLC, EGFR T790M/L858R)



Xiao Y, et al. AACR; 2024. Abstract nr 6580

6580: A novel EGFR x cMET bispecific ADC PRO1286 demonstrated broad antitumor activity and promising tolerability in preclinical models – Xiao Y, et al

- **Key results (cont.)**
  - Administration of $PRO1286_8$ 30 mg/kg IV q3w (x2) in cynomolgus monkeys had a payload-driven toxicity profile with decreased erythropoiesis and leukocytes and a principal toxicity residing in bone marrow

- **Conclusions**
  - The preclinical characterization of PRO1286 showed encouraging antitumor activity, PK and tolerability profile