# UPDATES IN IMMUNOTHERAPY IN METASTATIC LUNG CANCER

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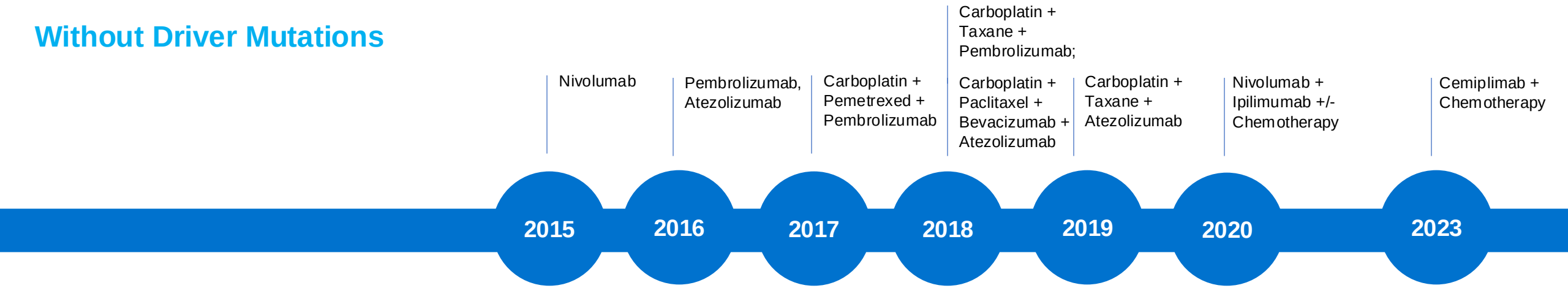
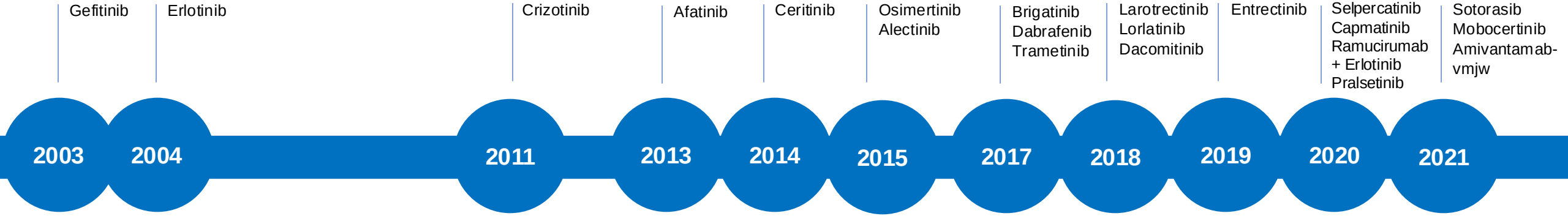
# Treatment Approvals in Metastatic NSCLC with and without Driver Mutations

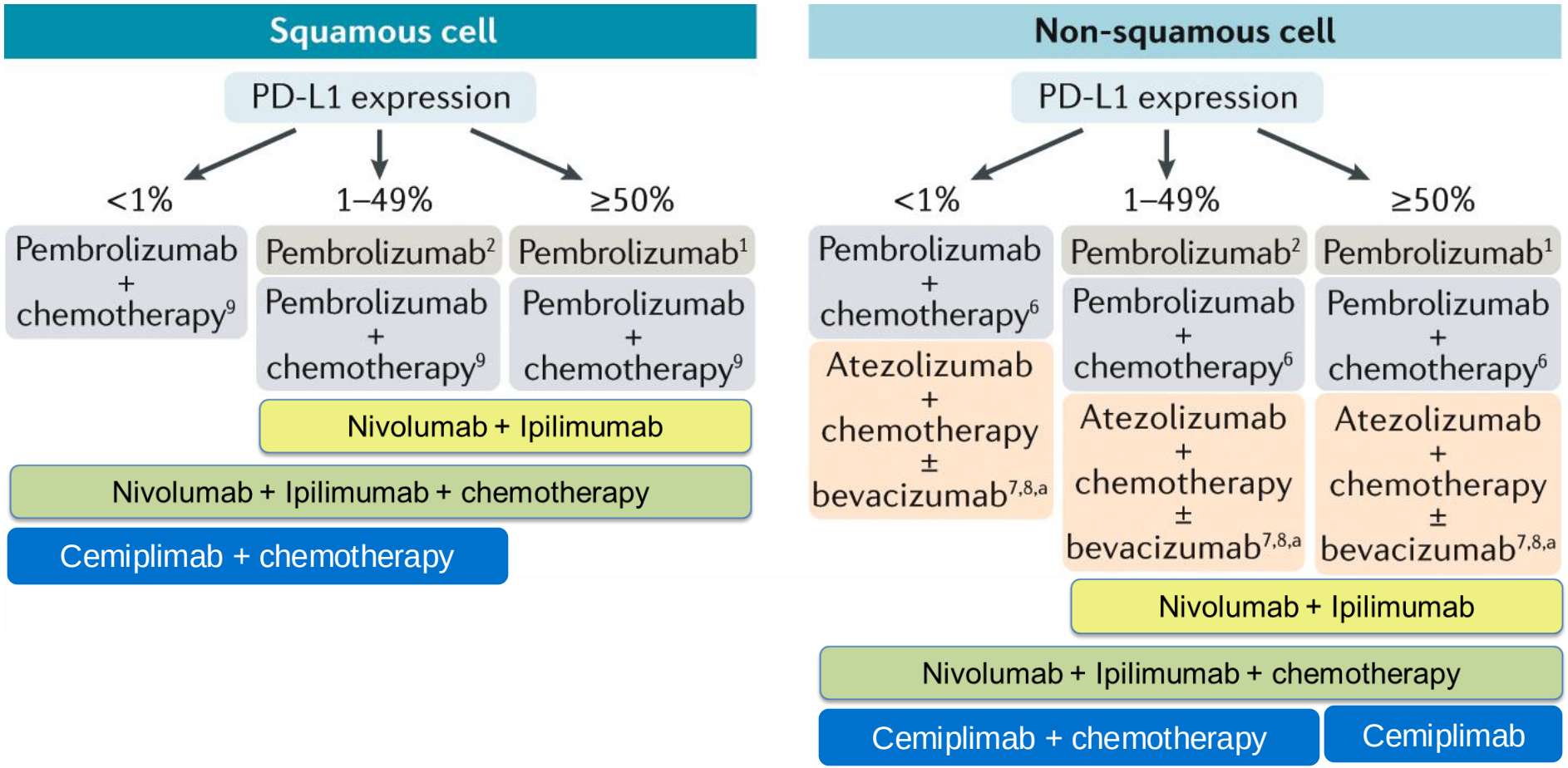
## Without Driver Mutations




## With Driver Mutations



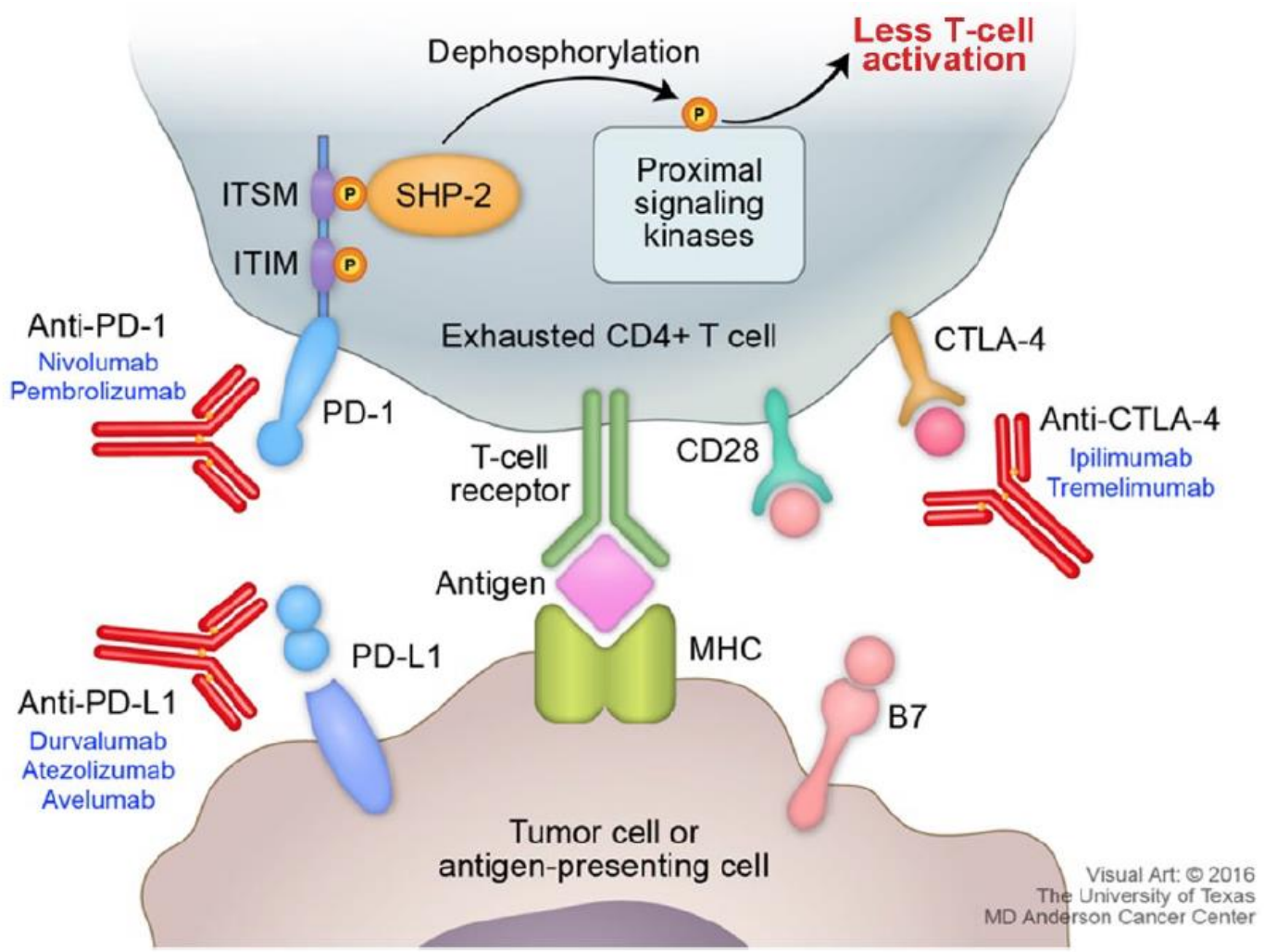
# Current First-Line Treatment in Metastatic NSCLC (No Driver Mutations)






*Adapted from Chiang A& Herbst RS, Nature Reviews Clinical Oncology 2020*

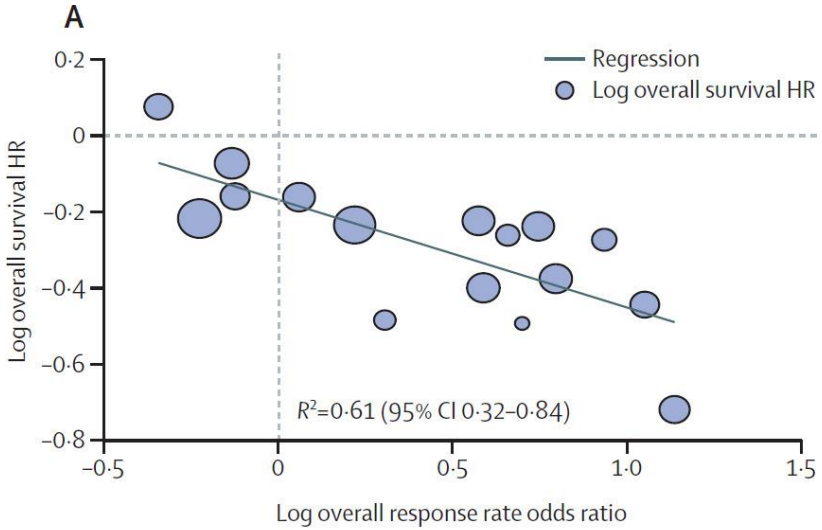
# PD-1/PD-L1 Pathway and Immunotherapy Targets

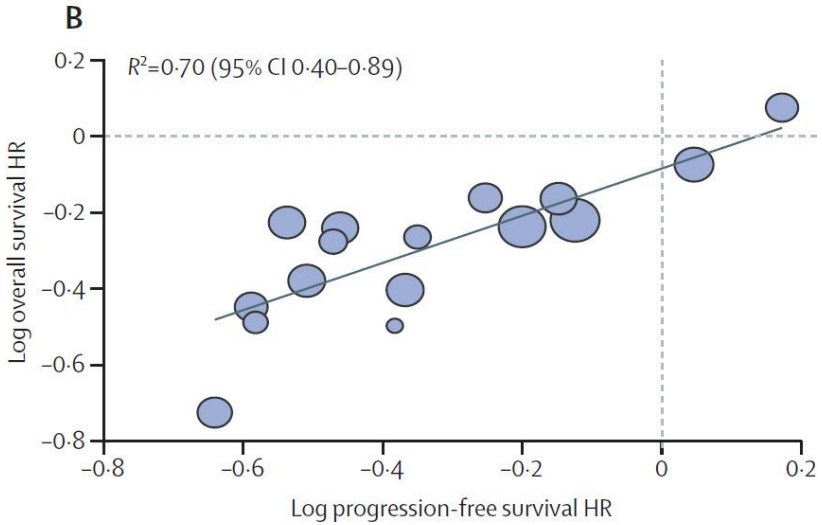


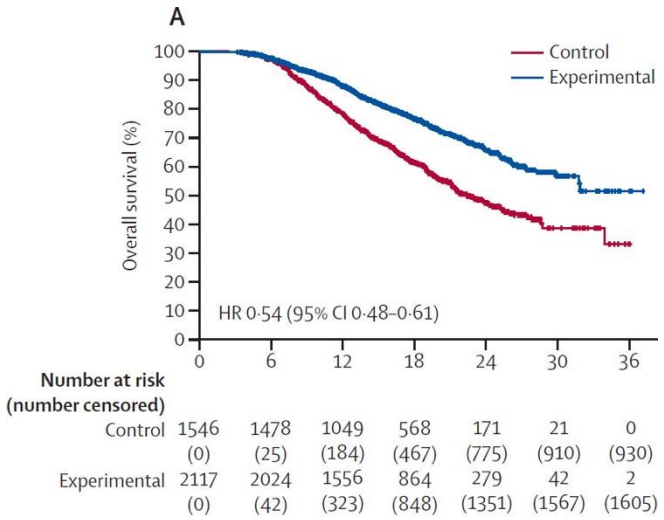



*Schvartsman G, Ferrarotto R and Massarelli E. Ther Adv Med Oncol 2016*

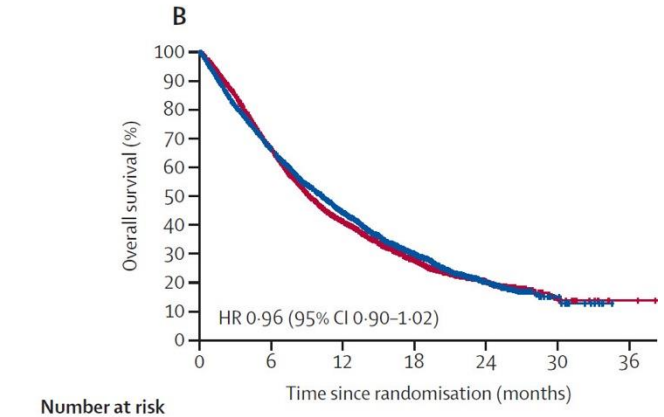
# FDA Pooled Analysis: Response Rate and Progression-Free Survival with Overall Survival in Immunotherapy




| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 1546 | 1478 | 1049 | 568 | 171 | 21 | 0 |
| | (0) | (25) | (184) | (467) | (775) | (910) | (930) |
| Experimental | 2117 | 2024 | 1556 | 864 | 279 | 42 | 2 |
| | (0) | (42) | (323) | (848) | (1351) | (1567) | (1605) |



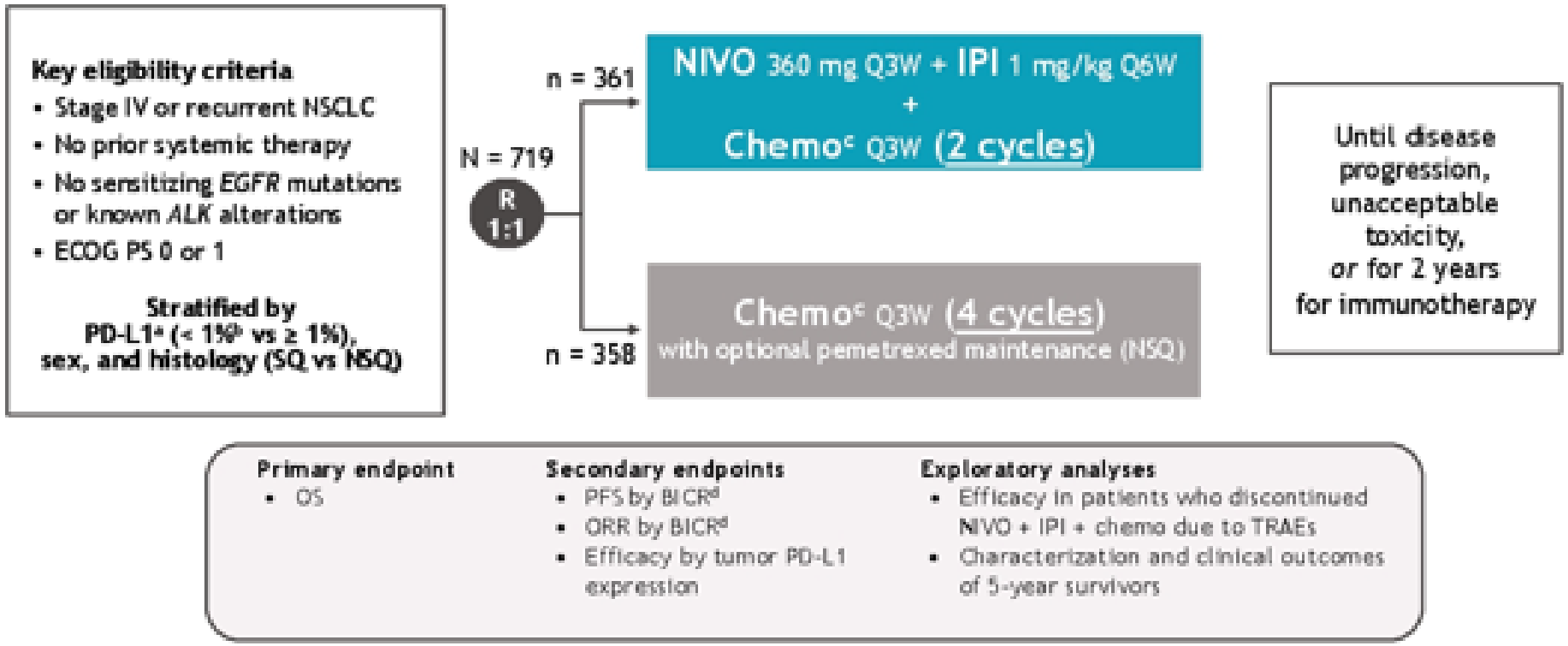

| Number at risk (number censored) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control | 3214 | 2000 | 1094 | 526 | 151 | 15 | 2 |
| | (0) | (171) | (355) | (606) | (879) | (994) | (1007) |
| Experimental | 3138 | 1981 | 1163 | 531 | 136 | 14 | 0 |
| | (0) | (132) | (321) | (632) | (903) | (1005) | (1017) |



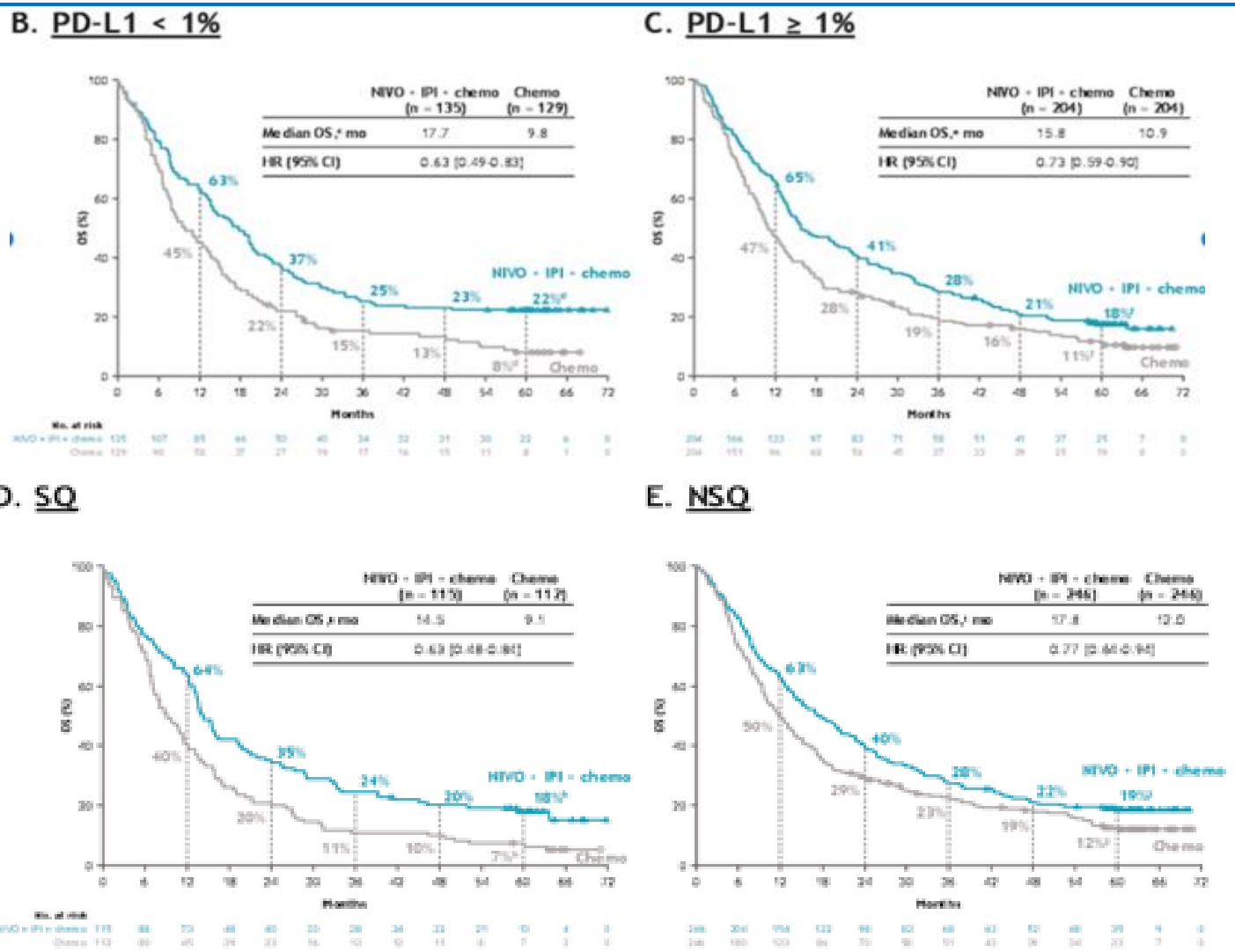
*Goulart BHL et al, Lancet 2024*

# DOUBLE CHECKPOINT INHIBITION

# CHECKMATE 9LA: 5 years survival update



# CHECKMATE 9LA: Survival by PDL1 status and histology




*Presented by Reck M et al. ASCO 2024*

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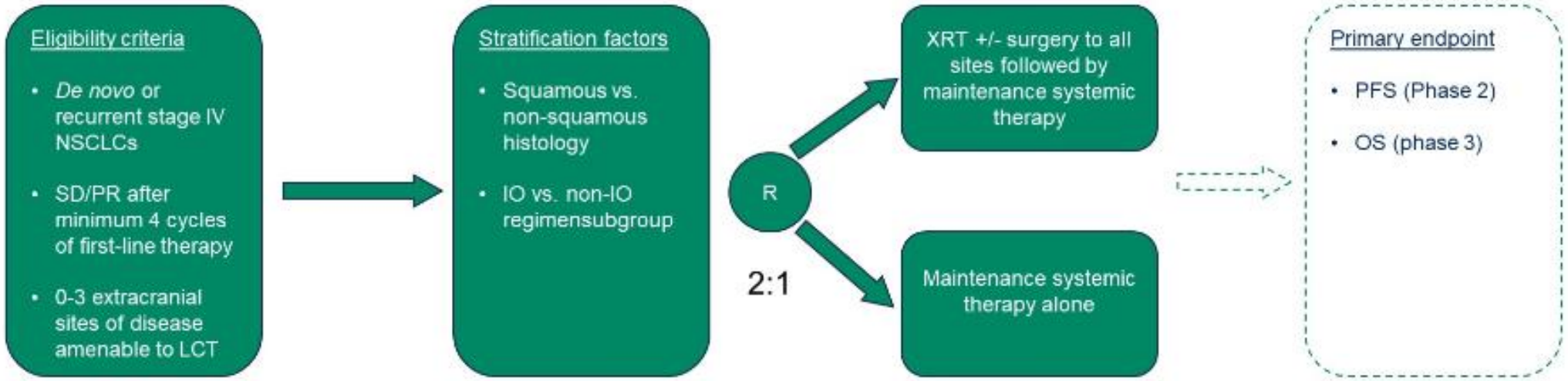
# CHECKMATE 9LA: Survival in patients with TRAE

# IMMUNOTHERAPY+ RADIATION THERAPY

# NRG-LU002: Maintenance Systemic Therapy vs. Local Consolidative Therapy + Maintenance Therapy for Limited Metastatic NSCLC

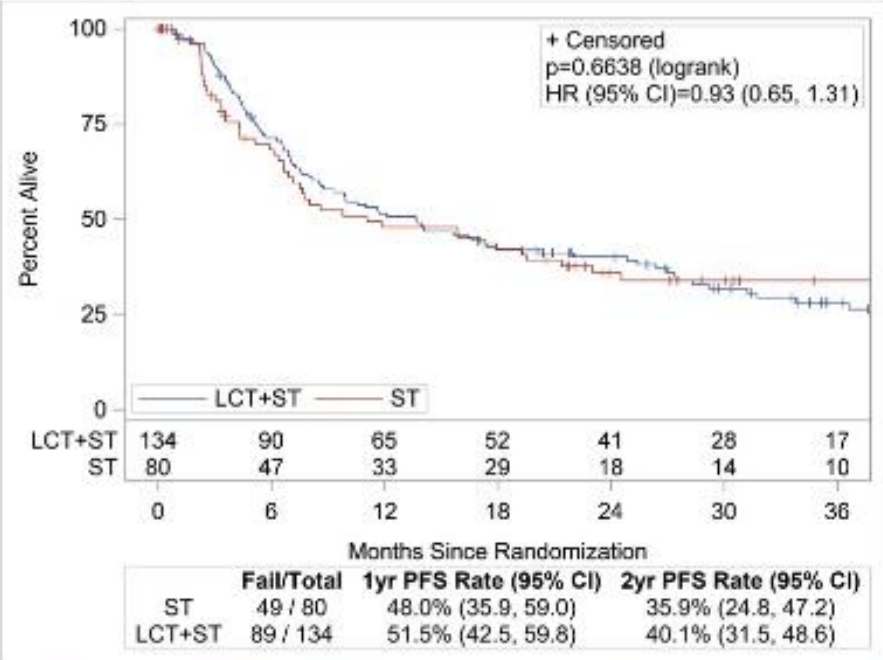



## Key features

- 91% patients received immunotherapy-based systemic treatment
- 85% patients had 1-2 lesions after 1st line Tx
- **Patients had up to 25 lesions at baseline**
- XRT to primary tumor in 31% patients only
- **No subgroup analysis yet (clinical factors or biomarkers)**

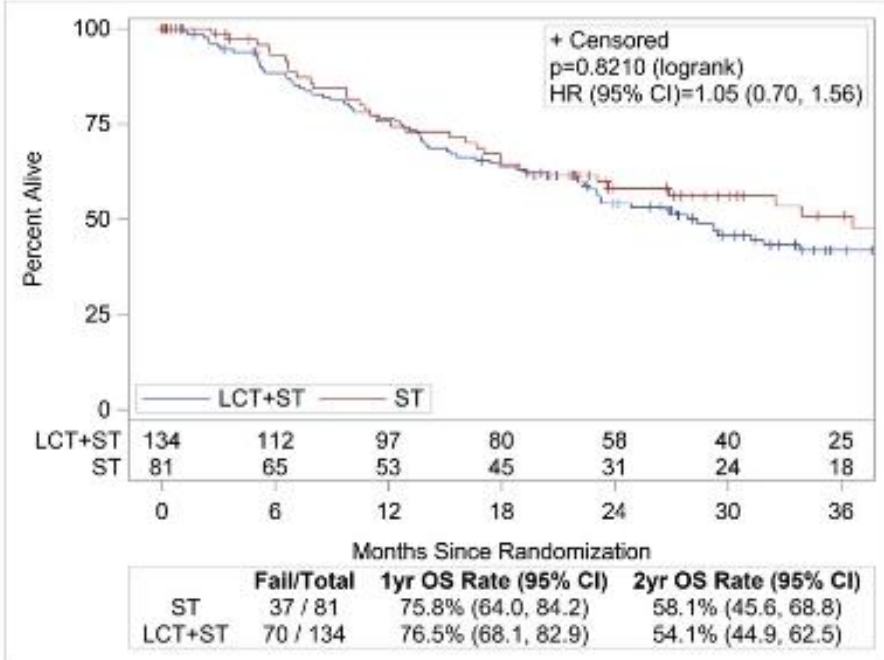
# NRG-LU002: PFS and OS

Progression-free survival




| | Fail/Total | 1yr PFS Rate (95% CI) | 2yr PFS Rate (95% CI) |
|---|---|---|---|
| ST | 49 / 80 | 48.0% (35.9, 59.0) | 35.9% (24.8, 47.2) |
| LCT+ST | 89 / 134 | 51.5% (42.5, 59.8) | 40.1% (31.5, 48.6) |

Overall survival

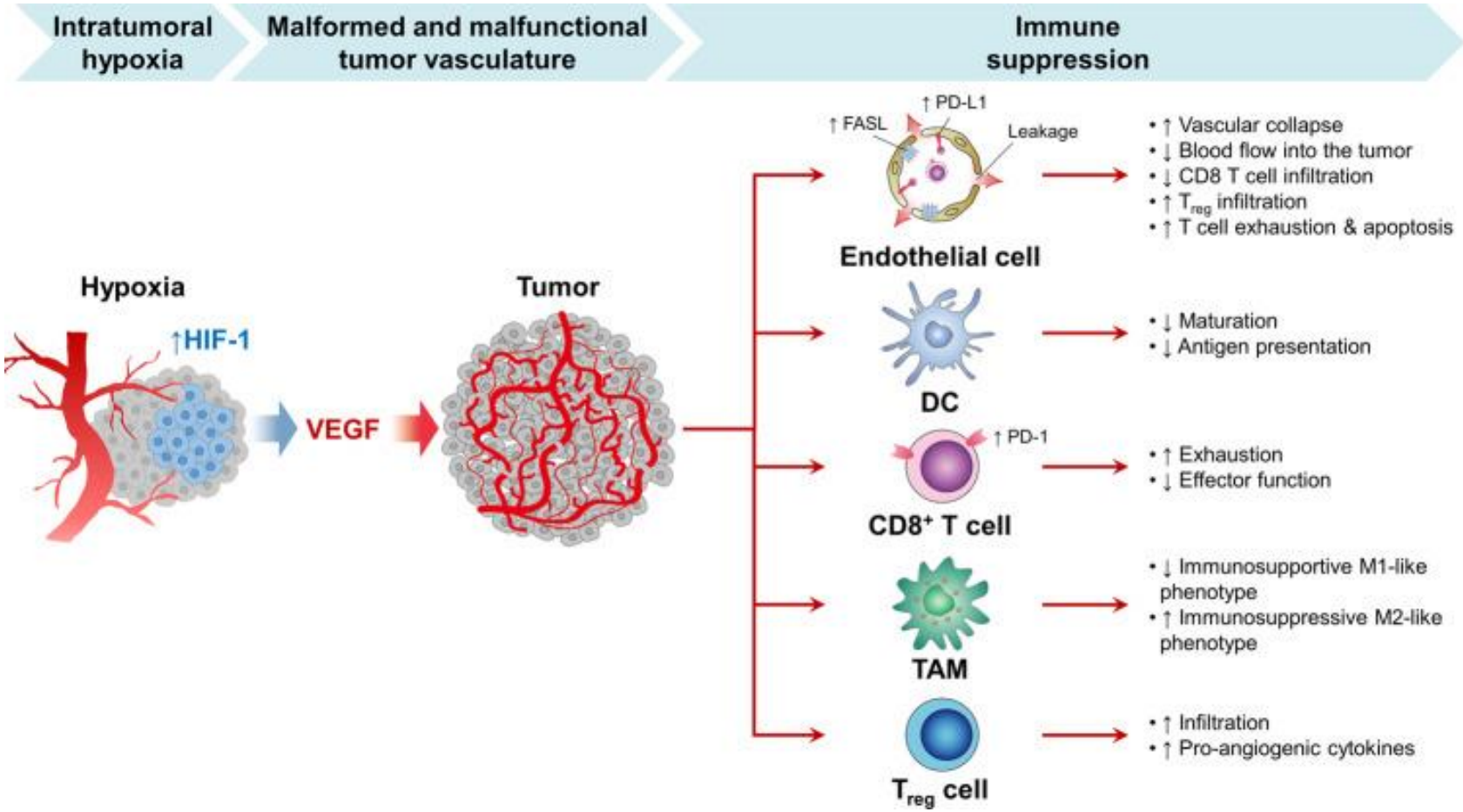



| | Fail/Total | 1yr OS Rate (95% CI) | 2yr OS Rate (95% CI) |
|---|---|---|---|
| ST | 37 / 81 | 75.8% (64.0, 84.2) | 58.1% (45.6, 68.8) |
| LCT+ST | 70 / 134 | 76.5% (68.1, 82.9) | 54.1% (44.9, 62.5) |

- None of the HRs were statistically significant, although there was a trend towards a delay in in-filed recurrences and new lesion development in the LCT arm
- More grade 2+ toxicities (84% vs 73%) and grade 3+ pneumonitis (10% vs 1%) in LCT arm

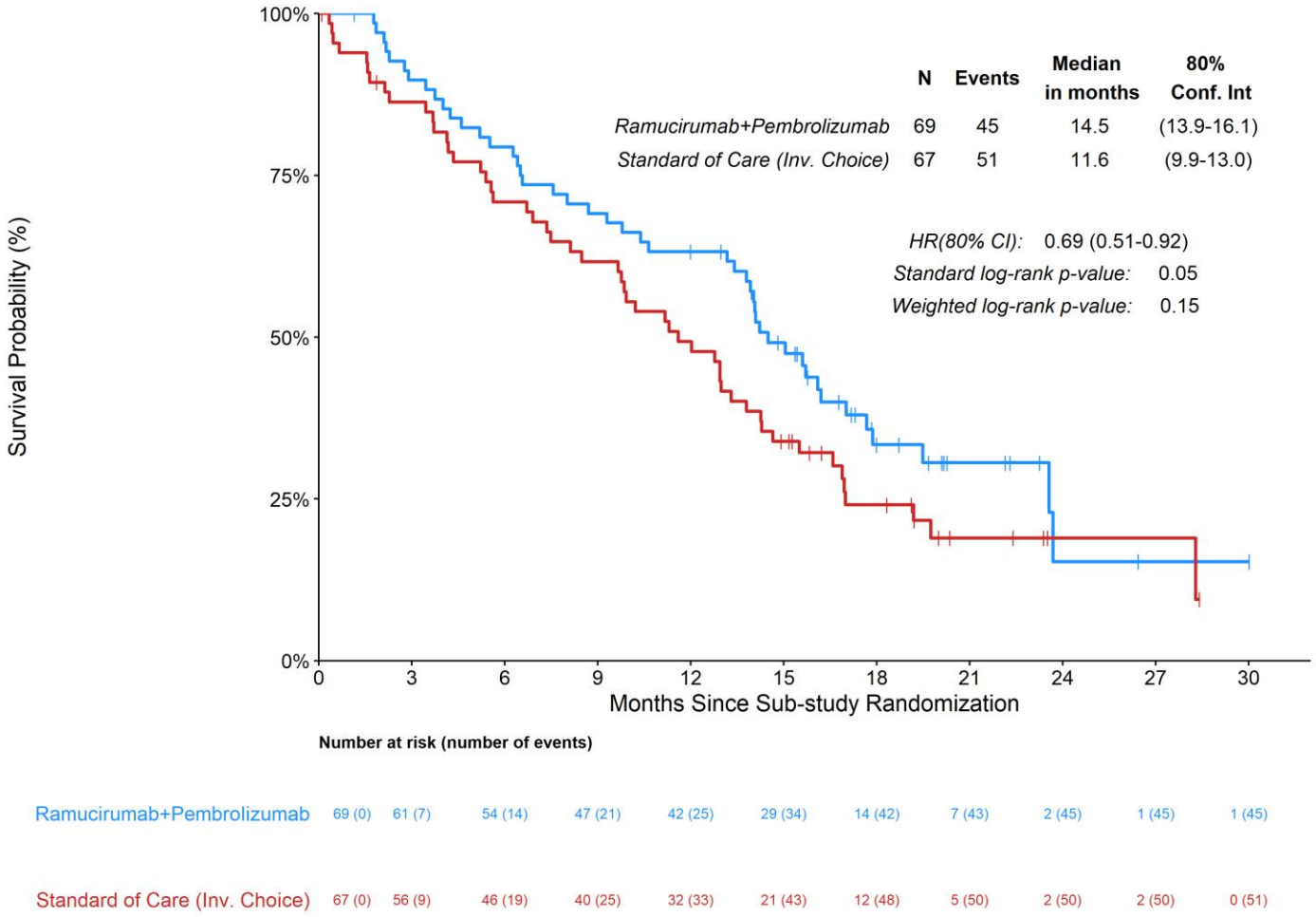
# IMMUNOTHERAPY+ ANTIANGIOGENIC AGENTS

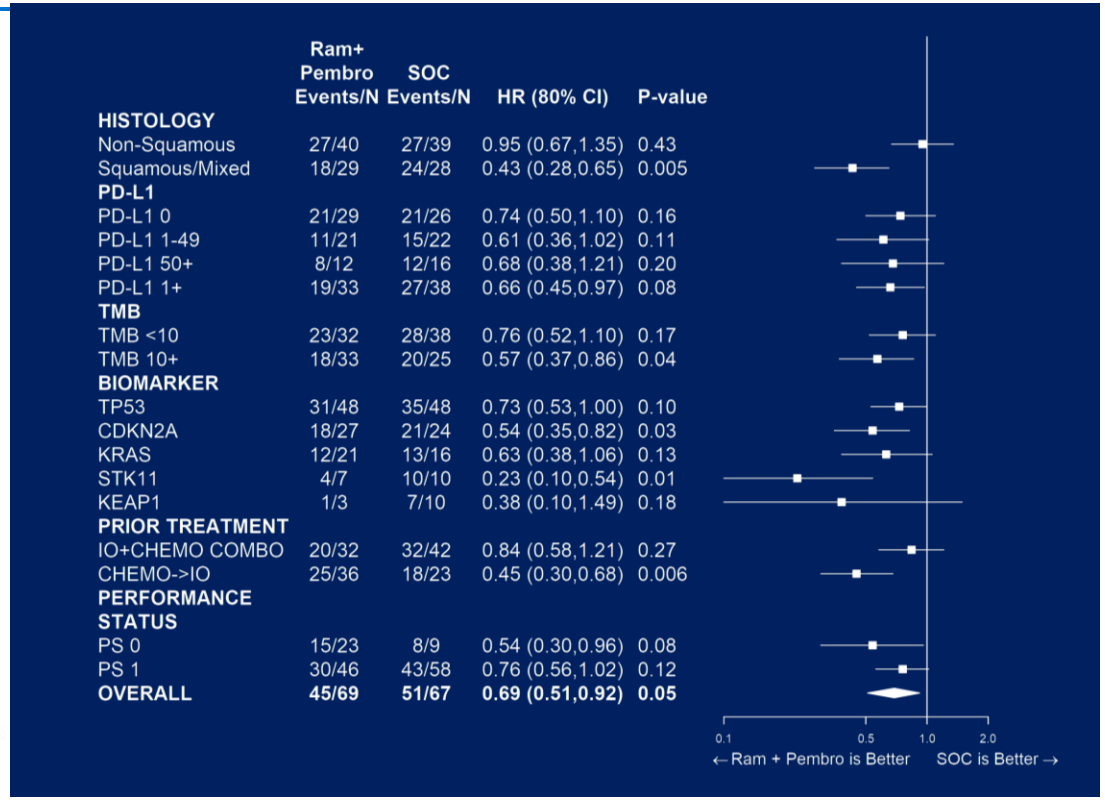
# Role of hypoxia and tumor vasculature in immune suppression




Lee WS, et al. Exp Mol Med, 2020

# S1800A: Pembrolizumab plus Ramucirumab




- **<u>Standard of care therapy received</u>**:
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

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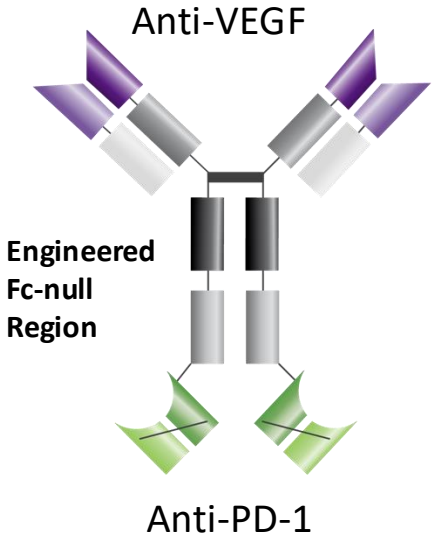
Reckamp KL et al ASCO 2022; J Clin Oncol 2022

# Ivonescimab (PD-1/VEGF bispecific antibody)




**Key Inclusion:**
- First-line Stage IV squamous NSCLC

**Key Exclusion:**
- Known actionable mutations for which 1L approved agents are available
- Symptomatic central nervous system (CNS) metastases
- Major blood vessel invasion or encasement by cancer; intratumor cavitation
- History of bleeding tendencies or coagulopathy or clinically significant bleeding symptoms or risk (including GI bleeding, hemoptysis)
- Active autoimmune disease

Randomization 1:1

Ivonescimab 20 mg/kg q3w + carboplatin AUC 5 or 6 q3w + paclitaxel 175 or 200 mg/m² q3w (or nab-paclitaxel 100 mg/m² q3w) x 4 cycles → Ivonescimab (maintenance up to 24 months)

Pembrolizumab 200 mg q3w + carboplatin AUC 5 or 6 q3w + paclitaxel 175 or 200 mg/m² q3w (or nab-paclitaxel 100 mg/m² q3w) x 4 cycles → Pembrolizumab (maintenance up to 24 months)

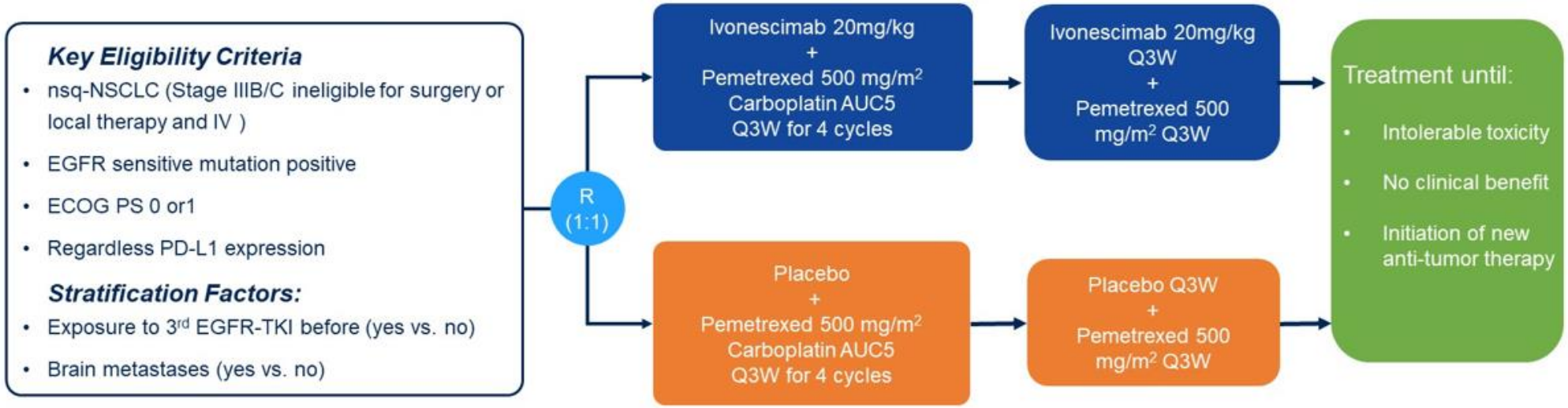
**Treatment until:**
- Disease progression
- Unacceptable toxicity
- Withdrawal of consent/death

**Stratification factors:**
- Sex (female vs male)
- Age (<65 vs ≥65 years)
- Geographical region: East Asia vs Rest of the world (ROW)
- Liver or brain metastases at study entry (present vs absent)

JW Riess et al. ENA 2023

On May 30, 2024 It was announced that the Phase III clinical trial, HARMONi-2 or AK112-303, met its primary endpoint of progression-free survival (PFS). HARMONi-2 evaluated monotherapy ivonescimab against monotherapy pembrolizumab in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have positive PD-L1 expression (PD-L1 TPS ≥1%).

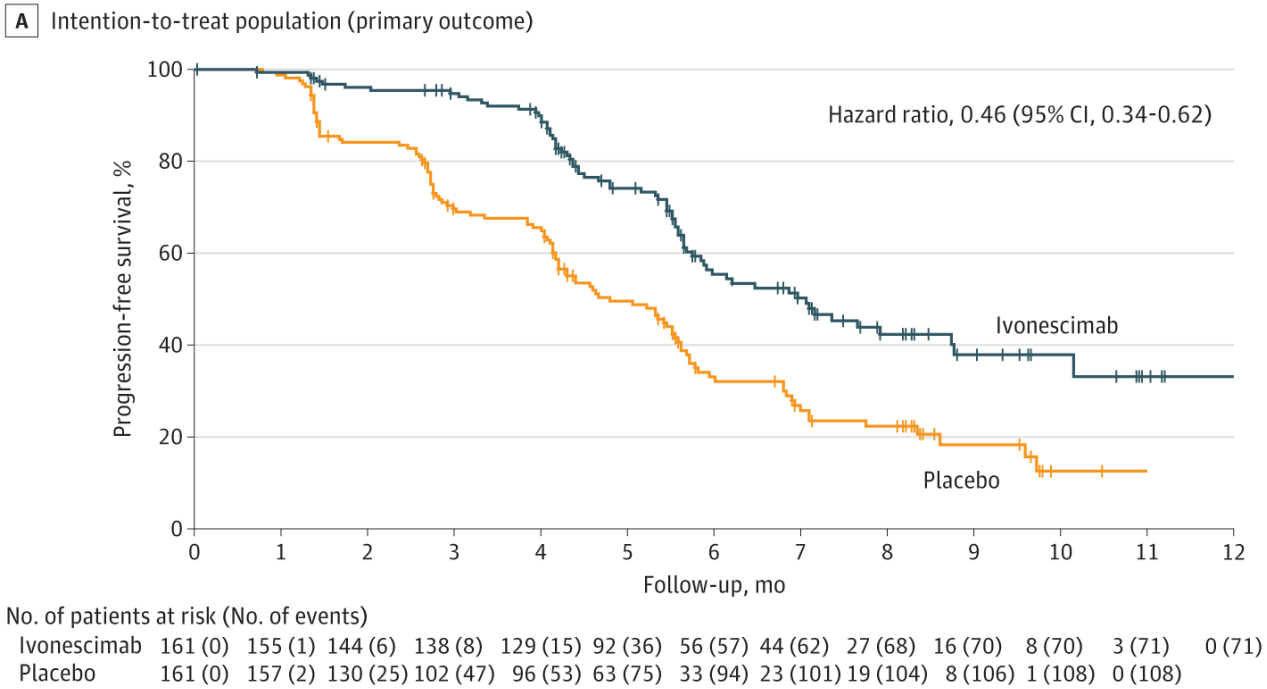
# HARMONi-A: Ivonescimab + Chemotherapy in *EGFR*+ NSCLC After EGFR TKI Progression

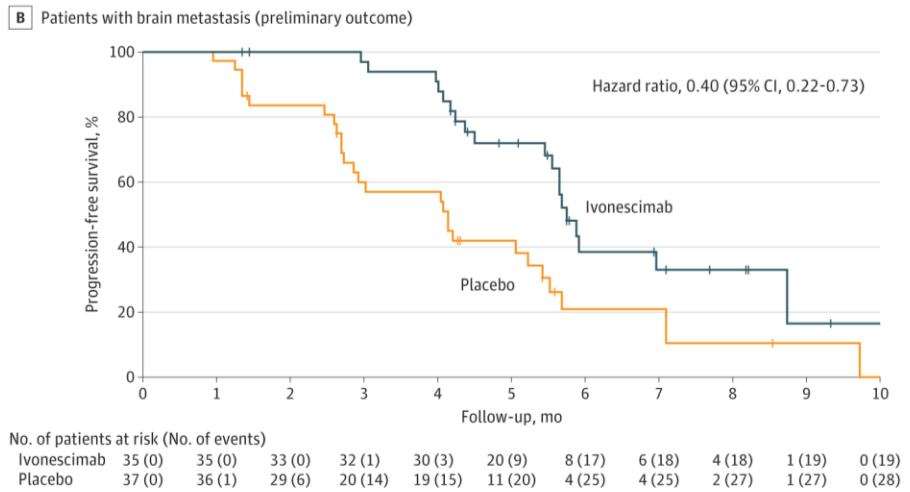


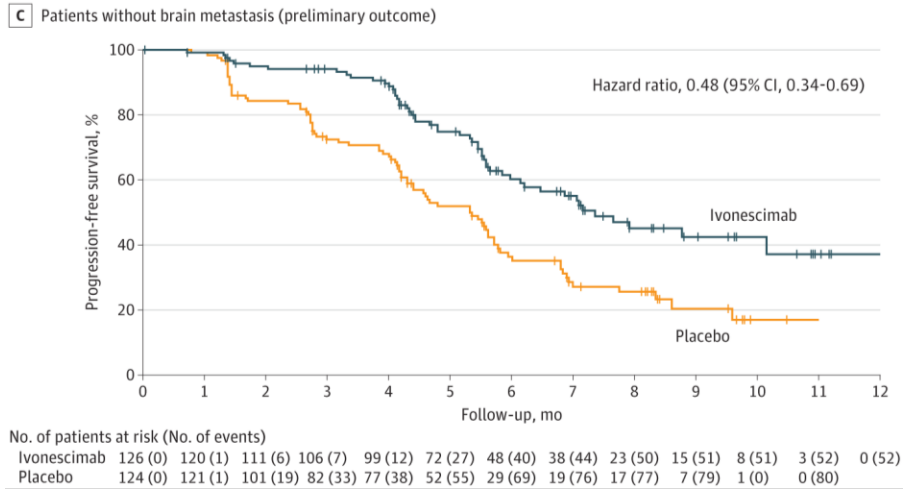

## Key features

- Multi-center, placebo-controlled study
- Brain mets allowed (present in 22% of pts)
- 19% non-exon-19 del / L858R EGFR mutations (slightly higher in experimental arm)
- 86% exposed to 3rd Gen TKI (only 33% 3rd Gen TKI upfront - pts switched to 3rd Gen TKI irrespective of T790M)
- **No anti-VEGF in the control arm**
- No biomarker data yet (e.g., PD-L1)

# HARMONi-A: Progression-Free Survival & Key Results

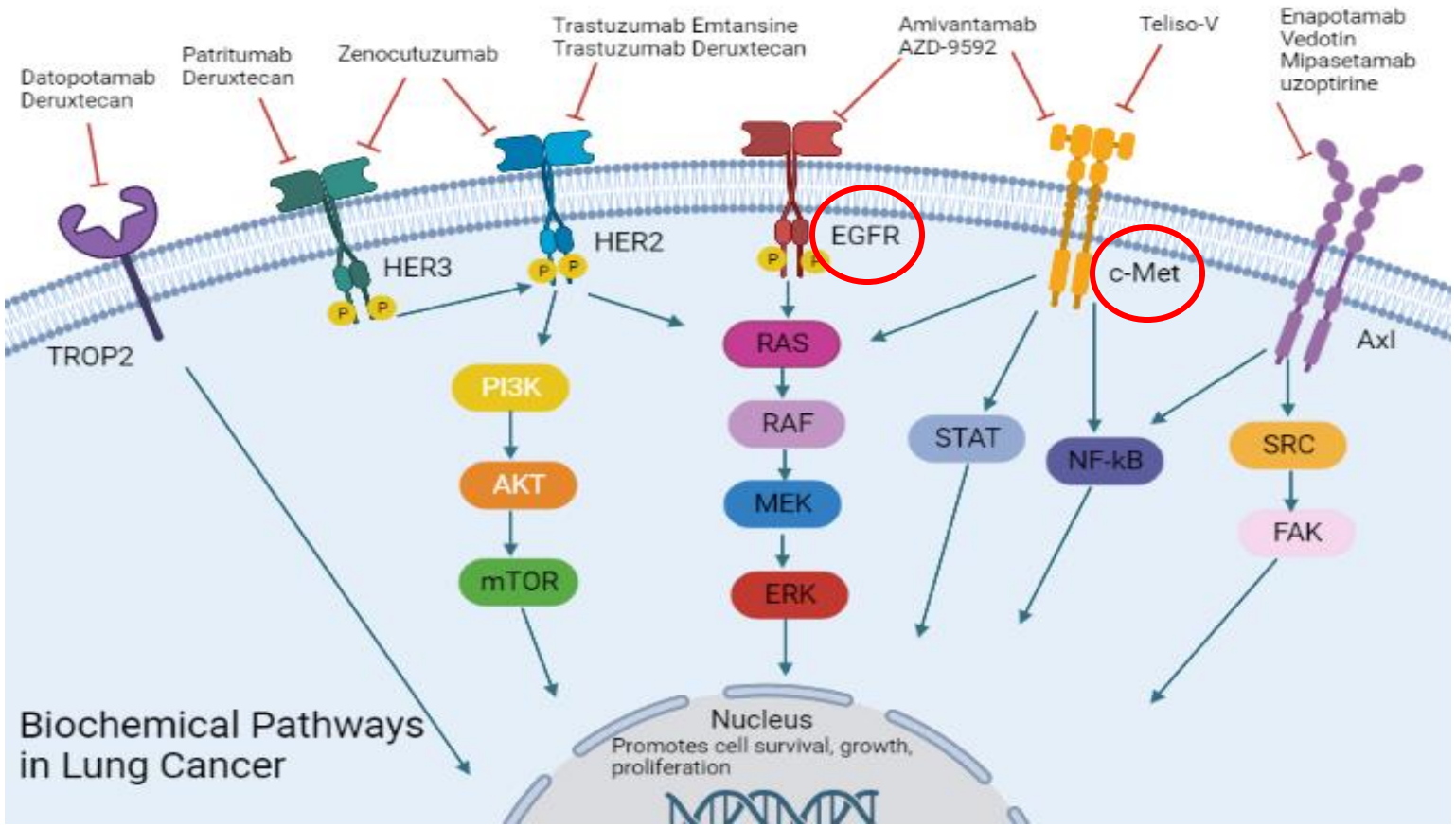


# IMMUNOTHERAPY
# NOVEL TARGETS

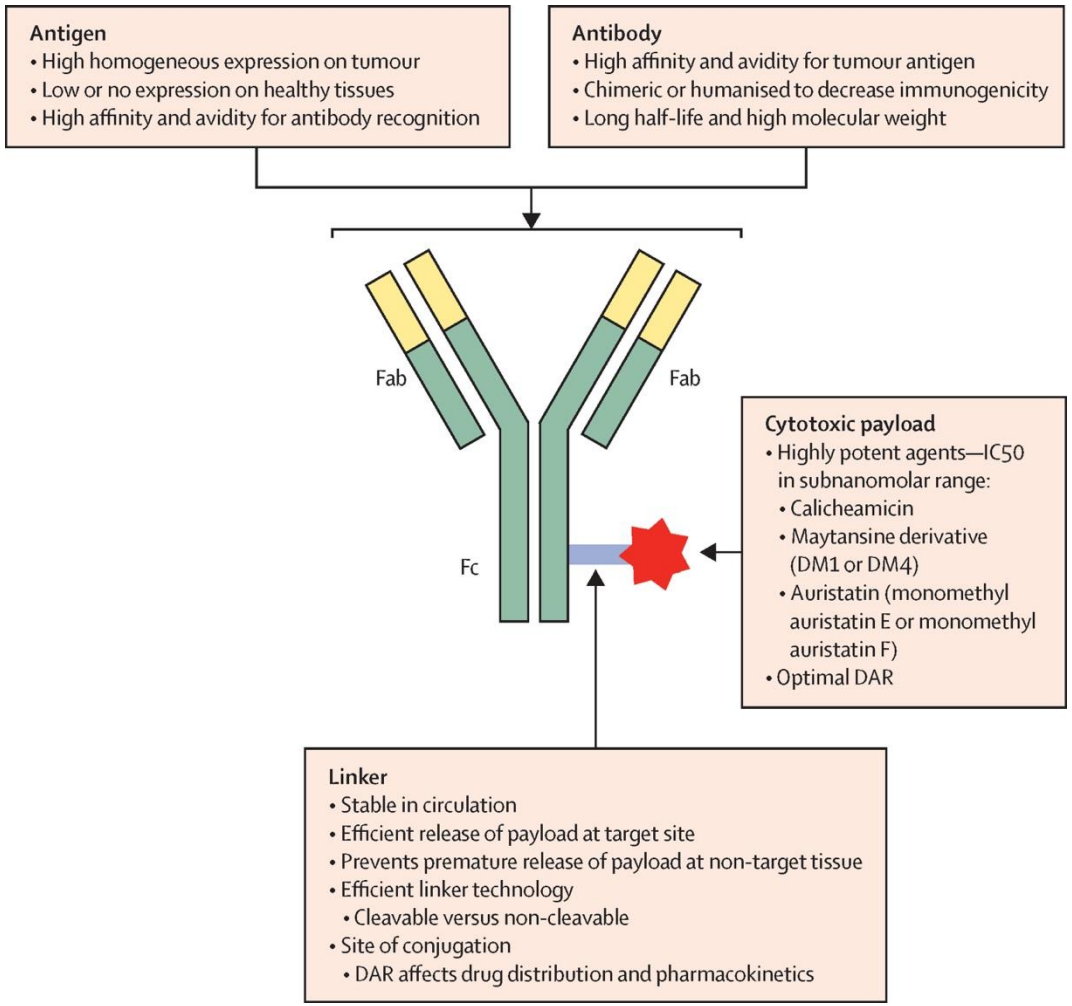
# Novel Targets: Antibody-Drug Conjugates and Bispecifics






Reyes A… Massarelli E. Cancers 2023

# Novel Targets: Antibody-Drug Conjugates






*Chau CH et al. Therapeutics 2019*

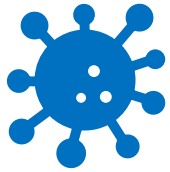
# Antibody-Drug Conjugates: The Antibody

| | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|
| **Antibodies** |  |  |  |  |
| *Serum half-life* | 21 days | 21 days | 7 - 21 days | 21 days |
| *C1q binding* | Yes | Yes | Yes | No |
| *Fcγ avidity* | High | Low | High | Moderate |



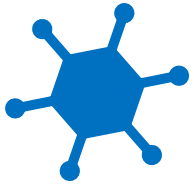
*Created with BioRender.com; Drago. Nat Rev Clin Oncol. 2021*

# Antibody-Drug Conjugates: The Antibody



**High antigen density** in tumors, not normal tissue, to limit on-/off-target toxicity

**Rapid internalization** to facilitate rapid transmembrane trafficking enhancing intracellular ADC toxicity

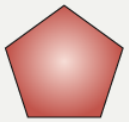
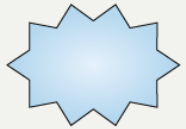


**Surface localization**, affecting antigen presentation after exosomes are taken up by antigen-presenting cell



*Theocharopoulos C et al, Vacines 2021*

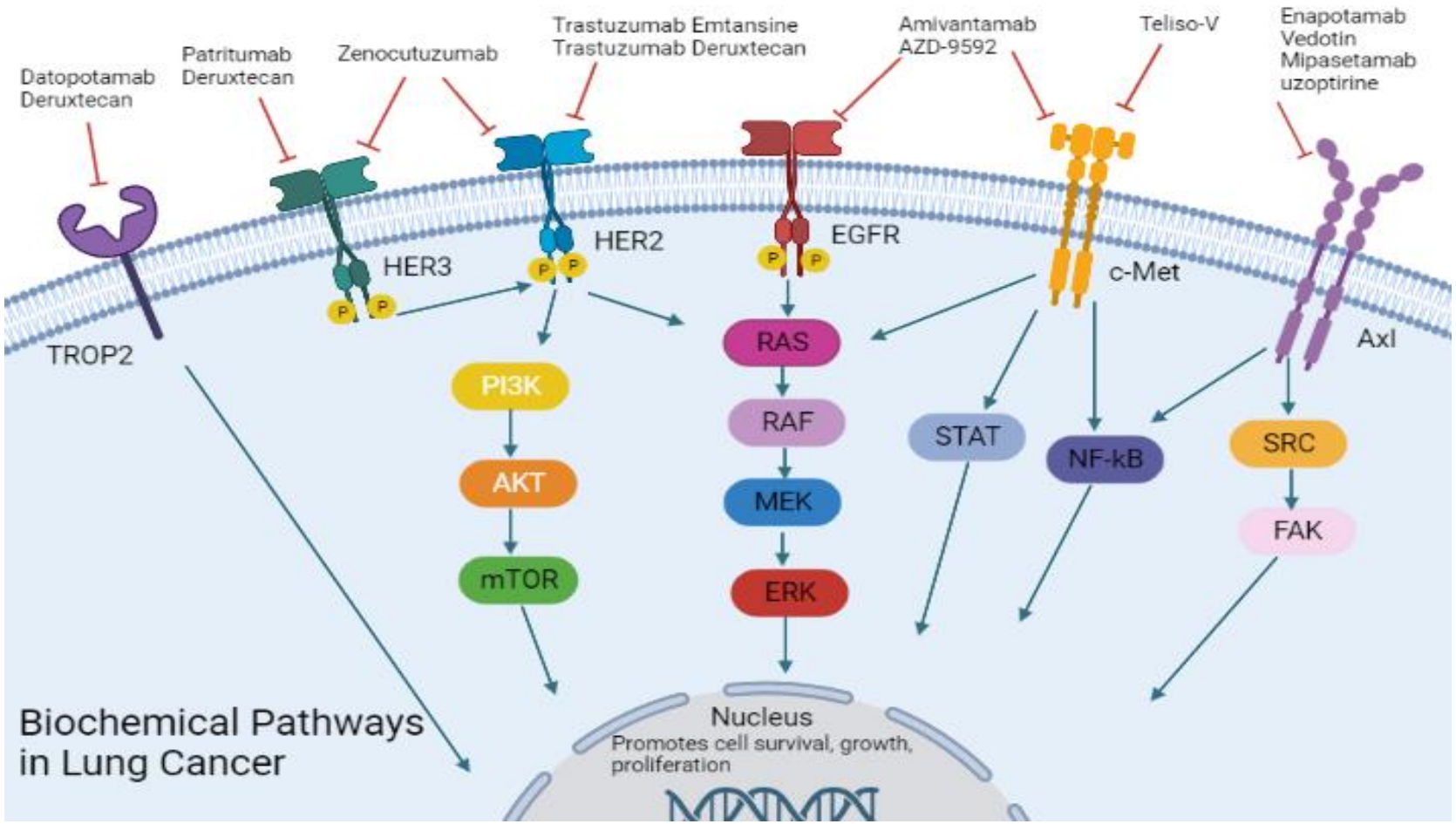
# Antibody-Drug Conjugates: The Warhead

| | | | | |
|---|---|---|---|---|
| **Warhead class** |  Auristatins |  Maytansinoids |  Calicheamicins |  Camptothecins |
| **Mechanism** | Anti-microtubule | Anti-microtubule | DNA cleavage | Topoisomerase 1 inhibition |
| **Payload** | MMAE, MMAF | DM1 | Ozogamicin | Deruxtecan (TDXd) |
| **Drug** | Telisotuzumab vedotin | Ado Trastuzumab Emstansine | Gemtuzumab ozogamicin | Trastuzumab deruxtecan |



*Drago. Nat Rev Clin Oncol. 2021*

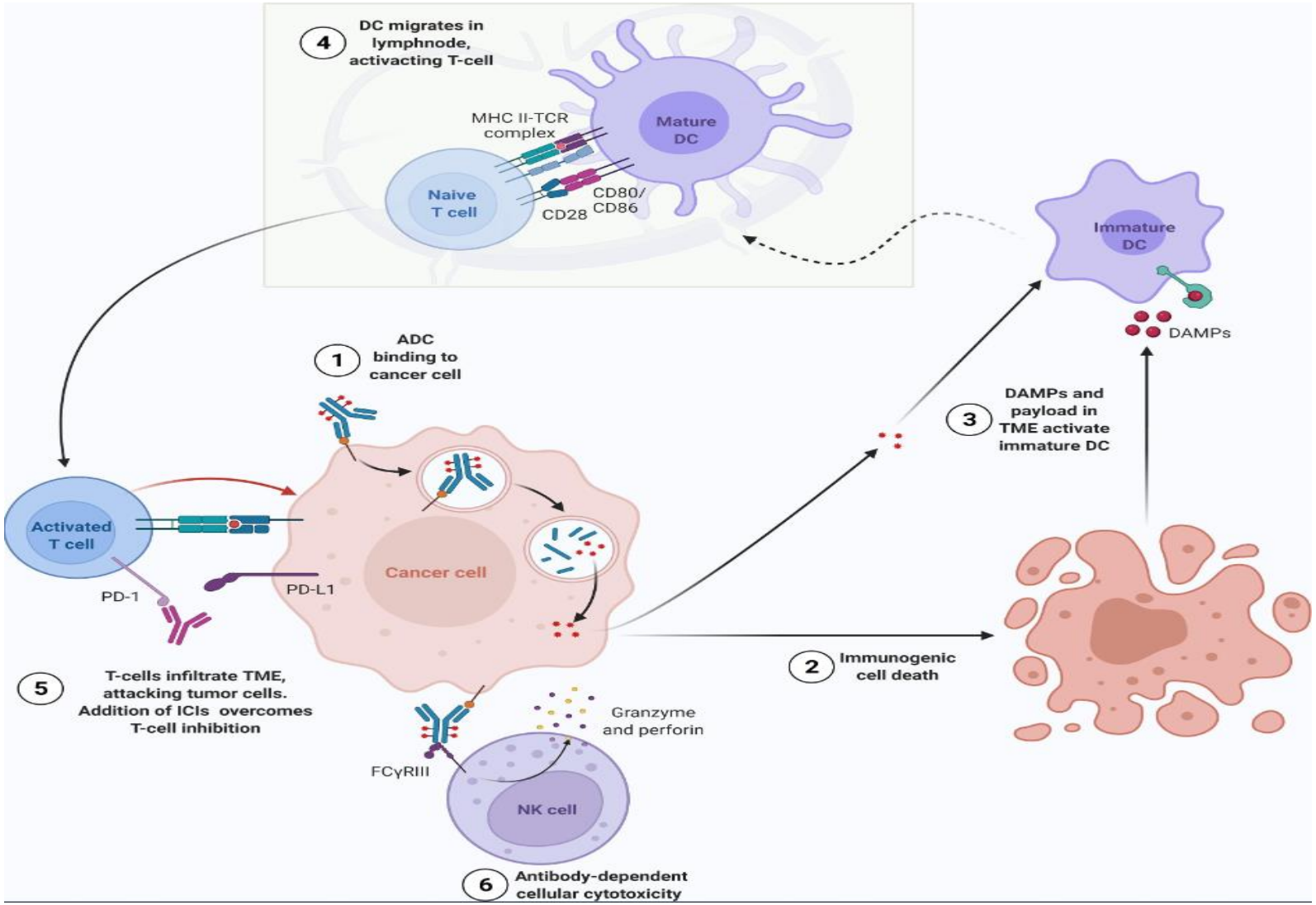
# Antibody-Drug Conjugates: Mechanism of Action





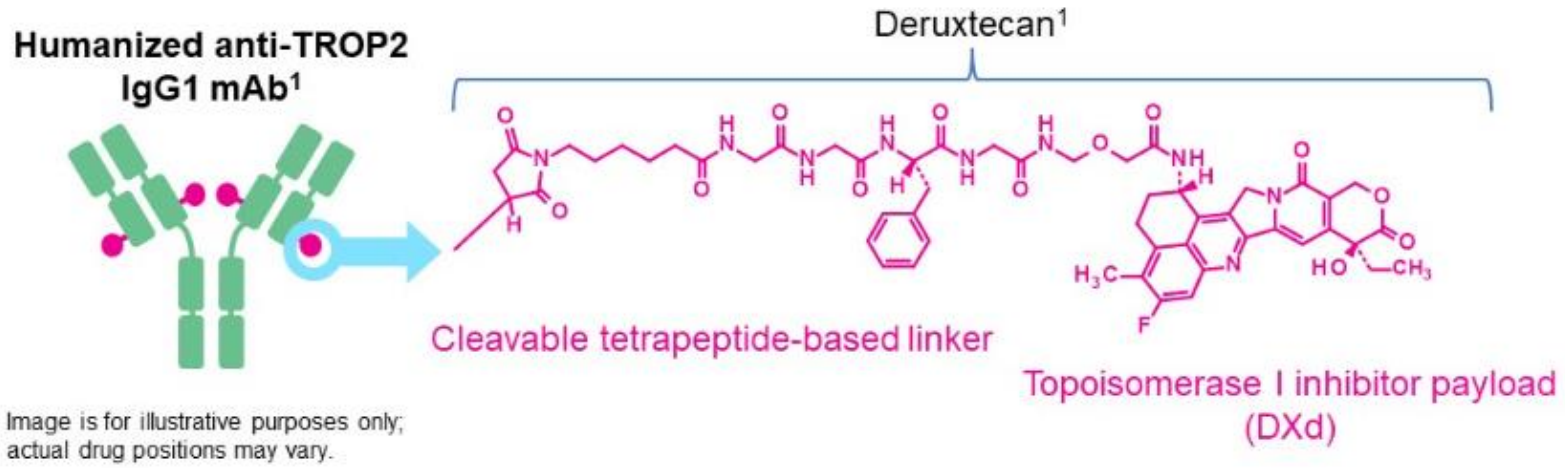

Reyes A… Massarelli E. Cancers 2023

# ADCs may interact with immunotherapy in many ways

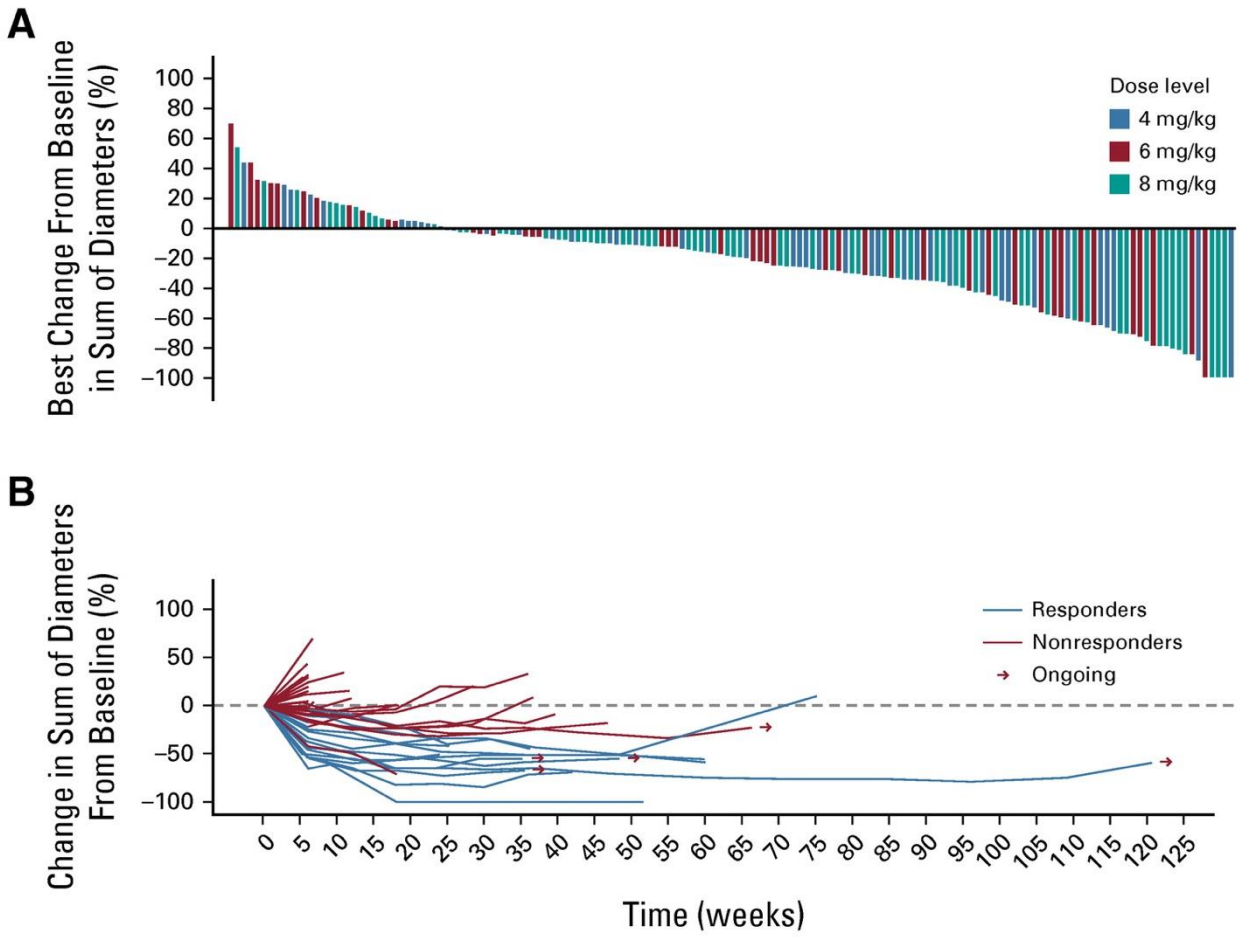


# TROP2: Datopotamab Deruxtecan (Dato-DXd)

- TROP2-directed monoclonal antibody
- Highly potent cytotoxic payload
- Tetrapeptide-based cleavable linker



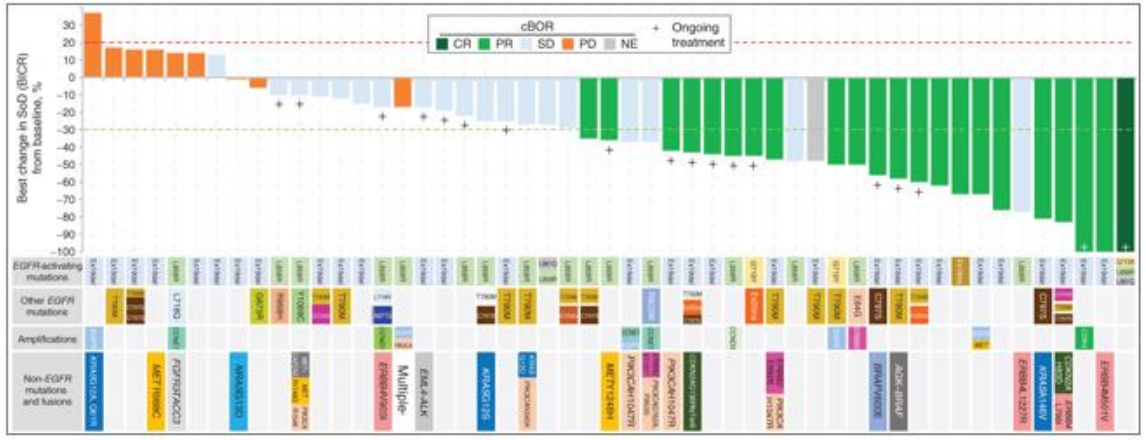
# TROPION-PanTumor01: Antitumor activity of Dato-DXd in NSCLC & Safety Results




| Event | Events, No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Dato-DXd 4 mg/kg (n = 50) | | Dato-DXd 6 mg/kg (n = 50) | | Dato-DXd 8 mg/kg (n = 80) | |
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| TEAE observed in ≥15% of patients | | | | | | |
| Preferred term | | | | | | |
| Nausea | 24 (48) | 0 | 32 (64) | 2 (4) | 43 (53.8) | 1 (1.3) |
| Stomatitis | 21 (42) | 0 | 30 (60) | 1 (2) | 44 (55) | 4 (5) |
| Alopecia | 13 (26) | 0 | 21 (42) | 0 | 38 (47.5) | 0 |
| Fatigue | 8 (16) | 0 | 14 (28) | 0 | 38 (47.5) | 2 (2.5) |
| Vomiting | 7 (14) | 0 | 9 (18) | 1 (2) | 29 (36.3) | 0 |
| Decreased appetite | 10 (20) | 0 | 13 (26) | 1 (2) | 21 (26.3) | 0 |
| Constipation | 8 (16) | 0 | 12 (24) | 0 | 23 (28.8) | 1 (1.3) |
| Infusion-related reaction | 12 (24) | 1 (2) | 10 (20) | 1 (2) | 20 (25) | 0 |
| Dry eye | 8 (16) | 0 | 8 (16) | 0 | 23 (28.8) | 0 |
| Anemia | 4 (8) | 2 (4) | 11 (22) | 2 (4) | 22 (27.5) | 4 (5) |
| Rash | 10 (20) | 0 | 4 (8) | 0 | 21 (26.3) | 0 |
| Dyspnea | 5 (10) | 0 | 8 (16) | 0 | 16 (20) | 5 (6.3) |
| Diarrhea | 5 (10) | 0 | 9 (18) | 0 | 15 (18.8) | 0 |
| Cough | 6 (12) | 0 | 8 (16) | 0 | 15 (18.8) | 1 (1.3) |
| Mucosal inflammation | 6 (12) | 1 (2) | 6 (12) | 1 (2) | 16 (20) | 4 (5) |
| ILD observed in any patients | | | | | | |
| Potential ILD[a] | 7 (14) | 3 (6) | 7 (14) | 4 (8) | 14 (17.5) | 6 (7.5) |
| ILD adjudicated as drug-related[b] | 5 (10) | 1 (2) | 3 (6) | 1 (2) | 11 (13.8) | 4 (5) |

# The importance of Patient Selection

## HER3-DXd in *EGFR*-mut NSCLC

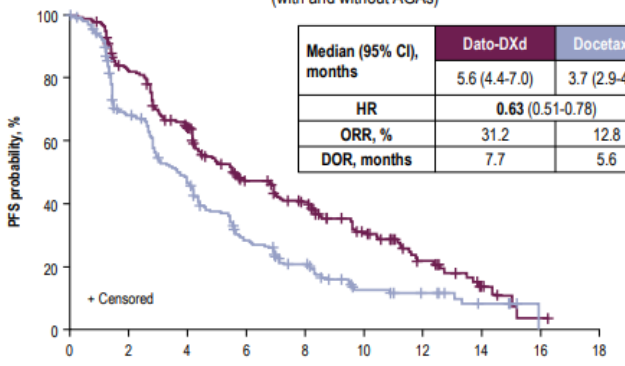



## TROPION-Lung01: Dato-DXd vs docetaxel

### PFS by Histology

**Non-squamous**
(with and without AGAs)

| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 5.6 (4.4-7.0) | 3.7 (2.9-4.2) |
| HR | 0.63 (0.51-0.78) | |
| ORR, % | 31.2 | 12.8 |
| DOR, months | 7.7 | 5.6 |

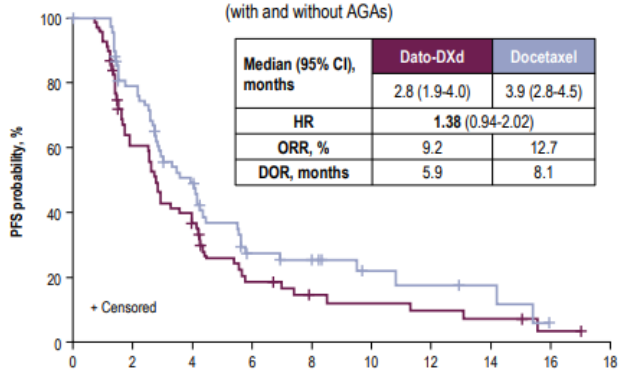



No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 229 | 178 | 134 | 86 | 68 | 41 | 20 | 7 | 1 | 0 |
| Docetaxel | 232 | 135 | 90 | 50 | 32 | 14 | 10 | 4 | 0 | 0 |

**Squamous**
(with and without AGAs)

| Median (95% CI), months | Dato-DXd | Docetaxel |
|---|---|---|
| | 2.8 (1.9-4.0) | 3.9 (2.8-4.5) |
| HR | 1.38 (0.94-2.02) | |
| ORR, % | 9.2 | 12.7 |
| DOR, months | 5.9 | 8.1 |




No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dato-DXd | 70 | 38 | 22 | 10 | 6 | 5 | 4 | 3 | 1 | 0 |
| Docetaxel | 73 | 51 | 30 | 13 | 10 | 5 | 4 | 3 | 0 | 0 |

**PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)**

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

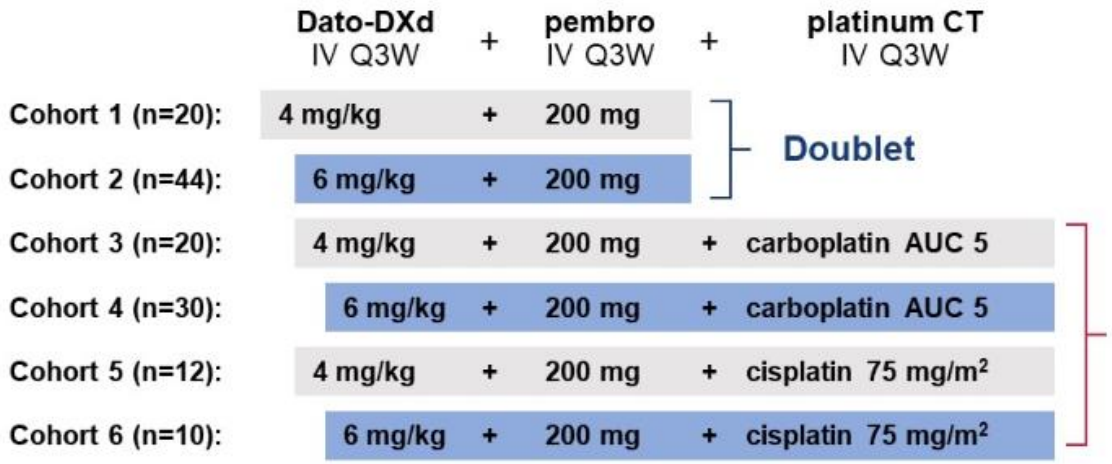
MADRID 2023 ESMO congress

Aaron Lisberg

# TROPION-Lung02: Dato-DXd + Pembrolizumab with or without Platinum Chemotherapy in NSCLC

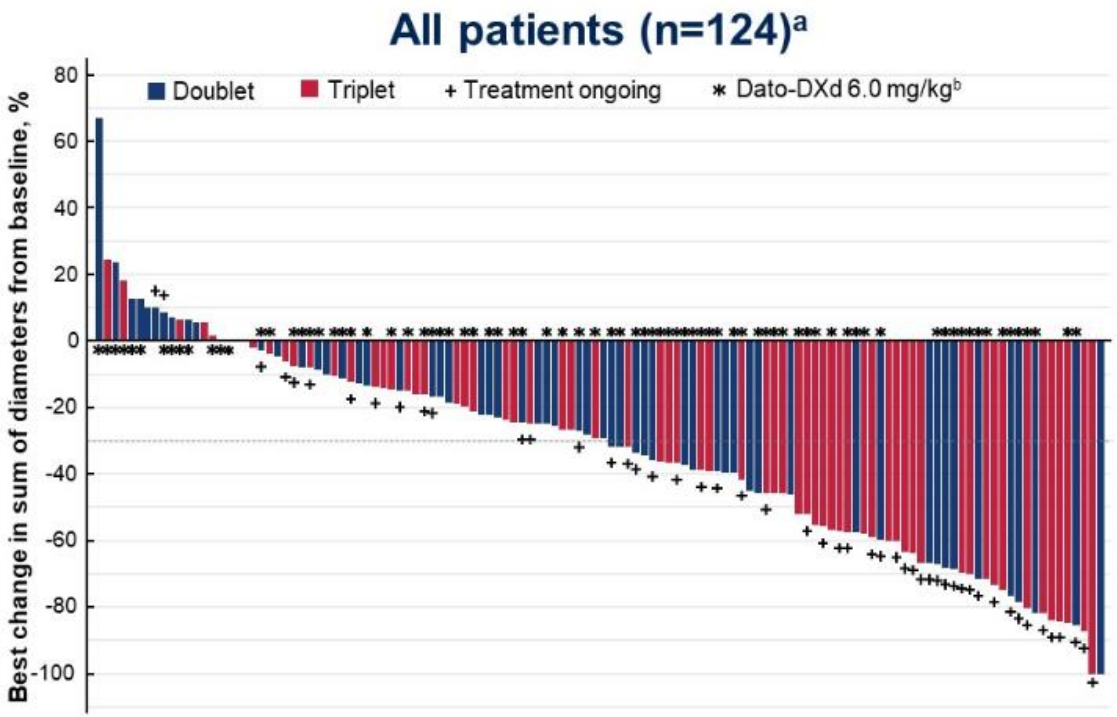
**Key eligibility criteria**

- **Advanced/metastatic NSCLC**
- **Dose escalation**[c]: ≤2 lines of prior therapy[d]
- **Dose expansion**
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[d]
  - Treatment naive (cohort 2; enrollment after Jun 30, 2022)[d]
  - Treatment naive (cohorts 3-6)[d]

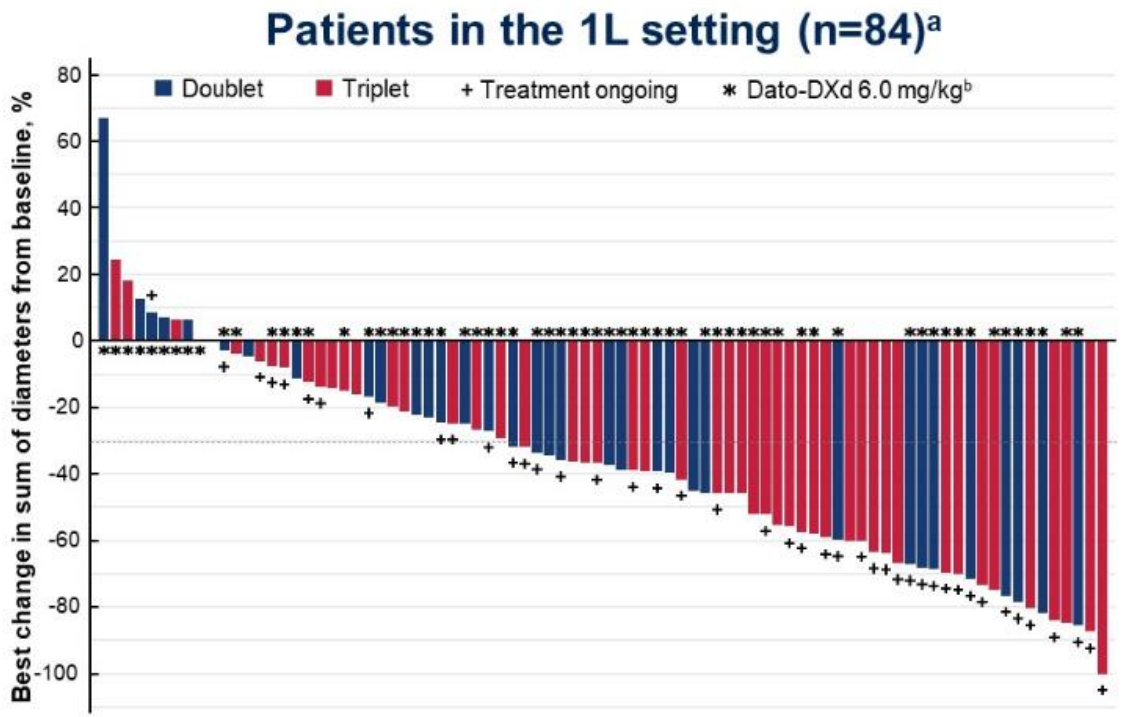



- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, and antidrug antibodies

# TROPION-Lung02: Best Overall Tumor Change from Baseline

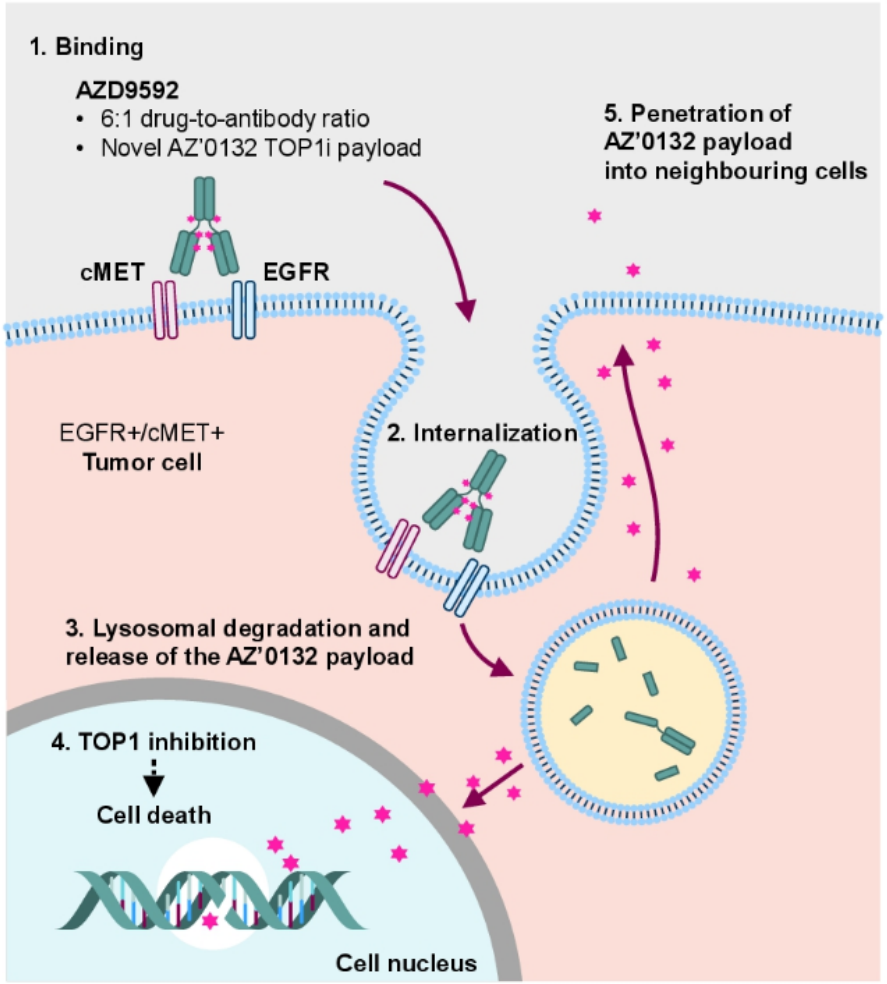



ORR for any line of therapy 38%




ORR 1L doublet 60%
ORR 1L triplet 55%

# AZD9592: Mechanism of Action




**1.** AZD9592 binds to EGFR and cMET on the tumor cell surface.

**2.** The ADC complex is internalized and trafficked to the lysosome.

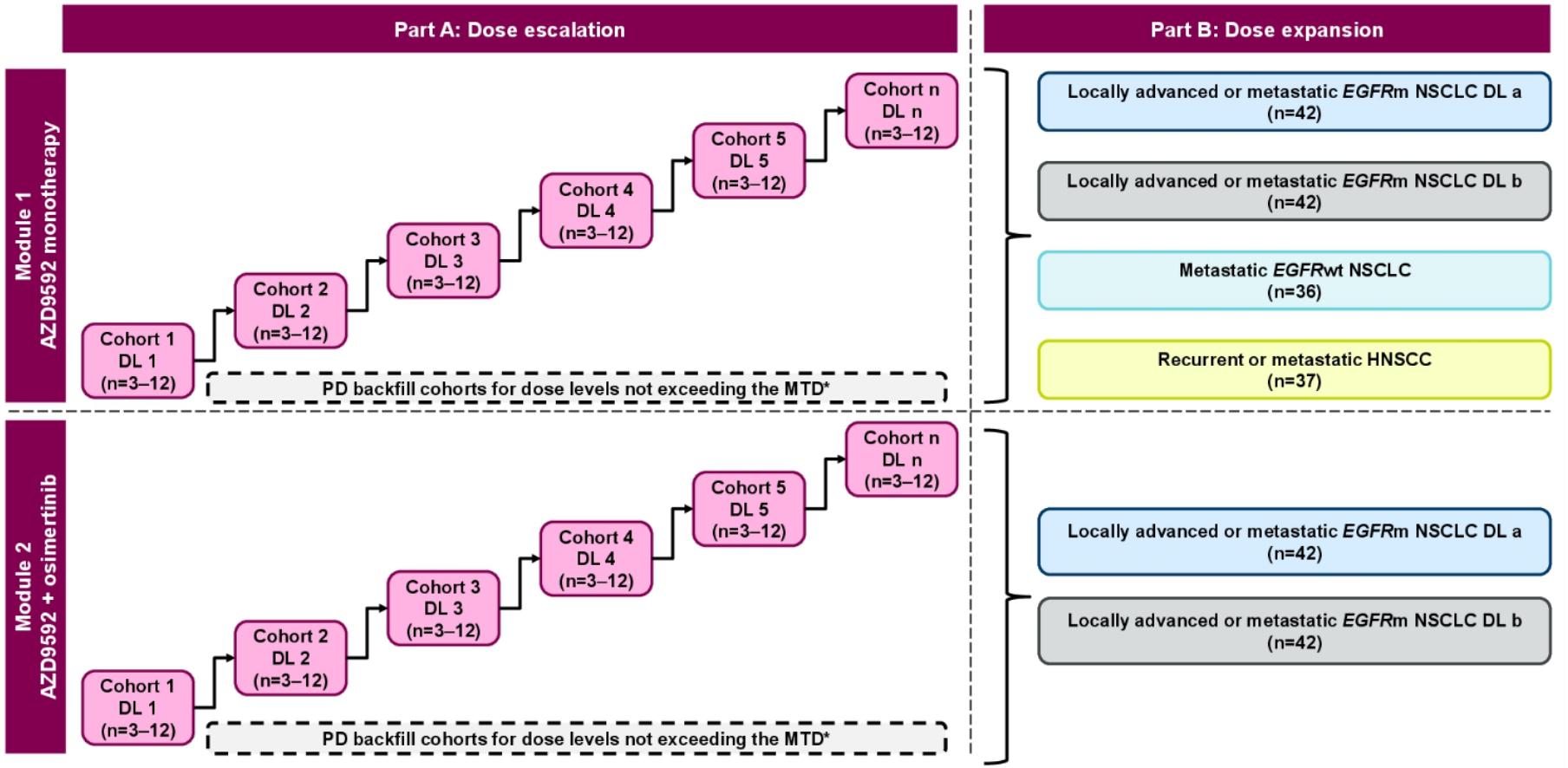
**3.** The linker is cleaved and cytotoxic TOP1i is released into the cell.

**4.** The TOP1i prevents topoisomerases from relieving stress at the replication fork, causing DNA double-strand breaks that, when unrepaired, can result in apoptosis and cell death.

**5.** The TOP1i may also penetrate into neighboring cells (i.e., potentially show a bystander effect).

ADC, antibody-drug conjugate; cMET, mesenchymal-epithelial transition tyrosine kinase receptor; EGFR, epidermal growth factor receptor; TOP1i, topoisomerase 1 inhibitor.

# EGRET - AZD9592 as Monotherapy or with Other Anticancer Agents in Patients with Advanced Solid Tumors: Study Design



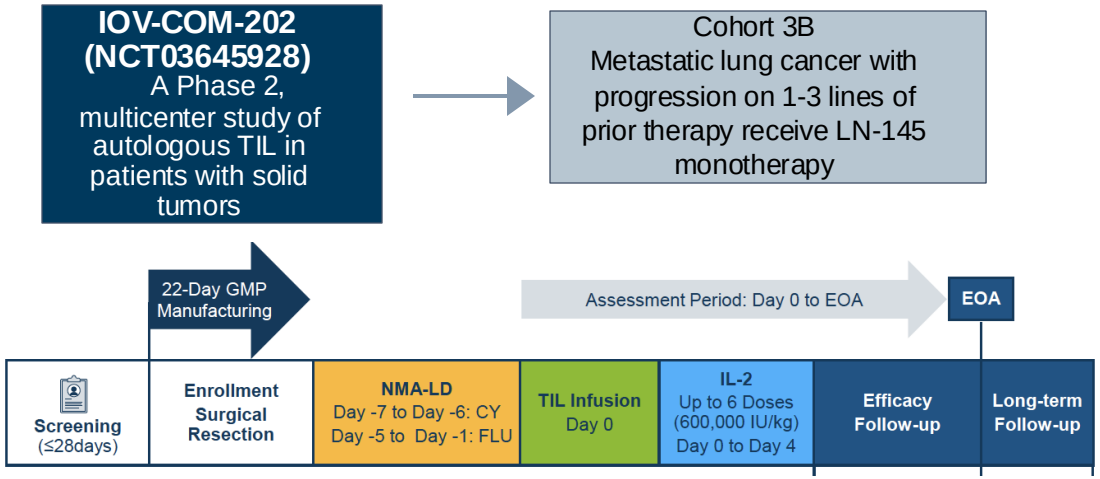

In Part A, dose escalation will utilize the modified toxicity probability interval-2 algorithm. *In Part A, any dose level not exceeding the MTD may be expanded by an additional number of patients as part of the PD backfill cohorts. Module 1 PD backfill cohorts: locally advanced or metastatic *EGFR*m NSCLC (n=~6), metastatic *EGFR*wt NSCLC (n=~6) and recurrent or metastatic HNSCC (n=~6). Module 2 PD backfill cohorts: locally advanced or metastatic *EGFR*m NSCLC (n=~10).

DL, dose level; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; m, mutation; MTD, maximum tolerated dose; NSCLC, non-small-cell lung cancer; PD, pharmacodynamic; wt, wild-type

# CELL THERAPY

# Preliminary experience with TIL in PD-(L)1 therapy resistant lung cancer

## Phase 2 multicenter study of TIL monotherapy (LN-145)



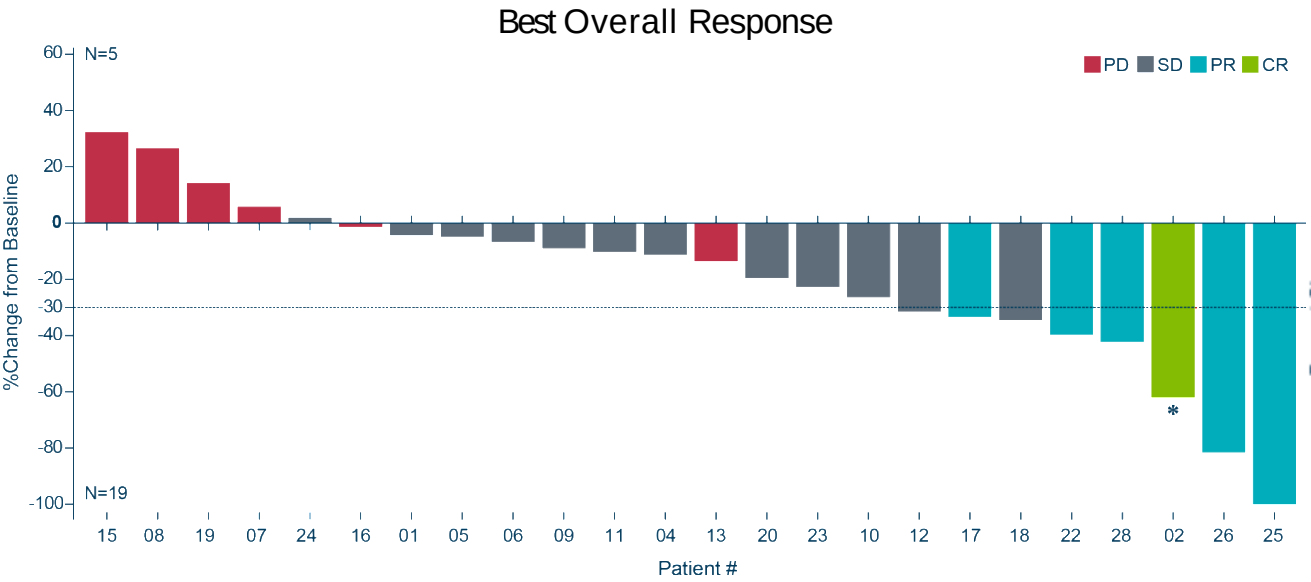

- Resection after resistance to last line of therapy
- TIL monotherapy
- Up to 6 doses of high dose IL2

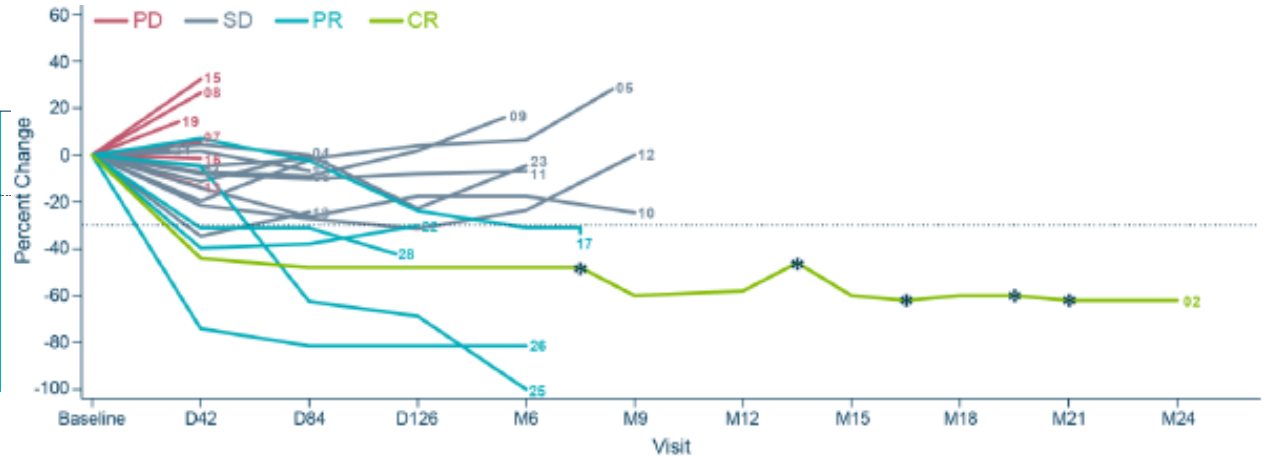
| Endpoints | IOV-COM-202 |
|---|---|
| Primary | • ORR<br>• Incidence of Grade ≥3 TEAEs |
| Secondary | • CR rate, DOR, DCR, PFS, OS |

- **Key eligibility criteria**
  - ≥1 resectable lesion for TIL manufacturing (diameter ≥1.5 cm post-resection)
  - ≥1 measurable lesion for response assessment (by investigator per RECIST v1.1)
  - ECOG performance status 0–1
- **Methods**
  - Patients were enrolled from March 2019 to August 2021 at sites across North America and the EU
  - Concomitant anticancer therapy was not permitted
  - Responses were evaluated per RECIST v1.1
- **Data cutoff:** 24 August 2021

Schoenfeld SITC 2021

# Preliminary experience with TIL in PD-(L)1 therapy lung cancer




For patient 2, the overall response of CR was based on investigator assessment of a complete metabolic response via negative FDG-PET scan.

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# Preliminary Clinical Results for IOV-LUN-202 Cohorts 1 and 2

## All Patients Progressed On or After Anti-PD-1 Therapy and Chemotherapy

| | Cohort 1 + 2 (n=23)[2] |
|---|---|
| Objective Response Rate, n (%)[1] | 6 (26.1) |
| (95% CI) | (10.2, 48.4) |
| Best overall response, n (%) | |
| CR | 1 (4.3) |
| PR | 5 (21.7) |
| SD | 13 (56.5) |
| PD | 2 (8.7) |
| NE | 2 (8.7) |

TEAEs were consistent with the underlying disease and known AE profiles of NMA-LD and IL-2

ORR= 26.1% by RECIST 1.1

DCR= 82.6%

Regardless of PD-L1 Status

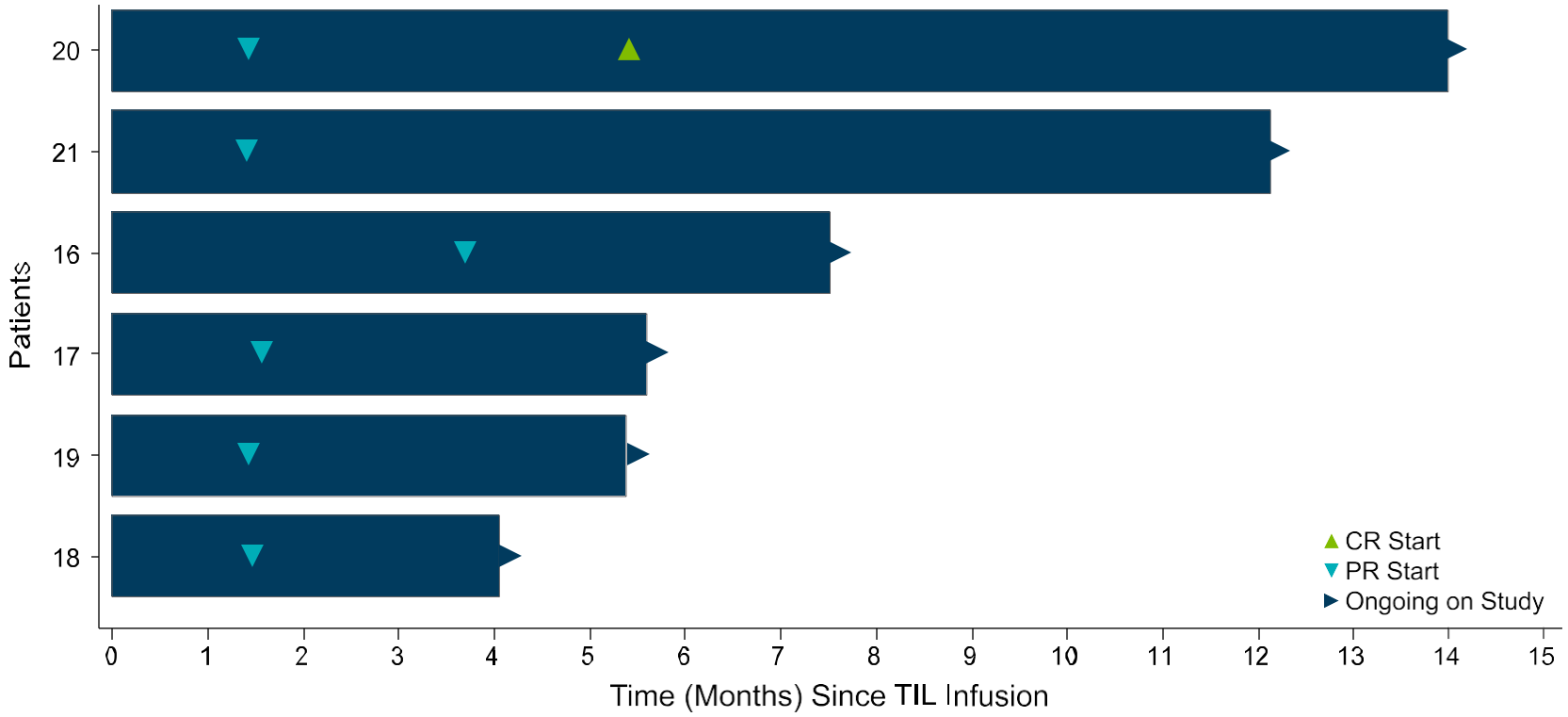
**All Responses remain ongoing at time of data cut**

1. Data cut: July 6, 2023. Responses were assessed by investigator.
2. Patients who have progressed on or after chemotherapy and anti-PD-1 therapy for advanced (unresectable or metastatic) NSCLC without EGFR, ROS or ALK genomic mutations and had received at least one line of an FDA-approved targeted therapy if indicated by other actionable tumor mutations.

Abbreviations: AE, adverse event; CI, confidence interval; CR, complete response; ICI, immune checkpoint inhibitor; NE, not evaluable; NMA-LD, non-myeloablative lymphodepletion; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent AE.

# Preliminary Clinical Results for IOV-LUN-202 Cohorts 1 and 2

## All Responses Remain Ongoing at Time of Data Cut




Data cut: July 6, 2023.
A bar is presented for each patient starting from date of LN-145 infusion up to date of new anti-cancer therapy, end of assessment, death, or data cutoff date, whichever occurs earlier.
Abbreviations: CR, complete response; DOR, duration of response; NSCLC, non-small-cell lung cancer; PR, partial response.

# CONCLUSIONS

- Novel bispecific antibodies poised for changing practice in lung cancer.
- Cooperative binding properties of bispecifics may provide advantages enhancing the therapeutic index.
- Next generation ICI agents have the potential to increase activity and reduce toxicity.
- Patient selection is needed to improve efficacy of ADCs.
- Cell therapy is a good option for patients who are fit as early as first line therapy for NSCLC


City of Hope