# Review of Ongoing Clinical Trials in Metastatic NSCLC

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강 다 현


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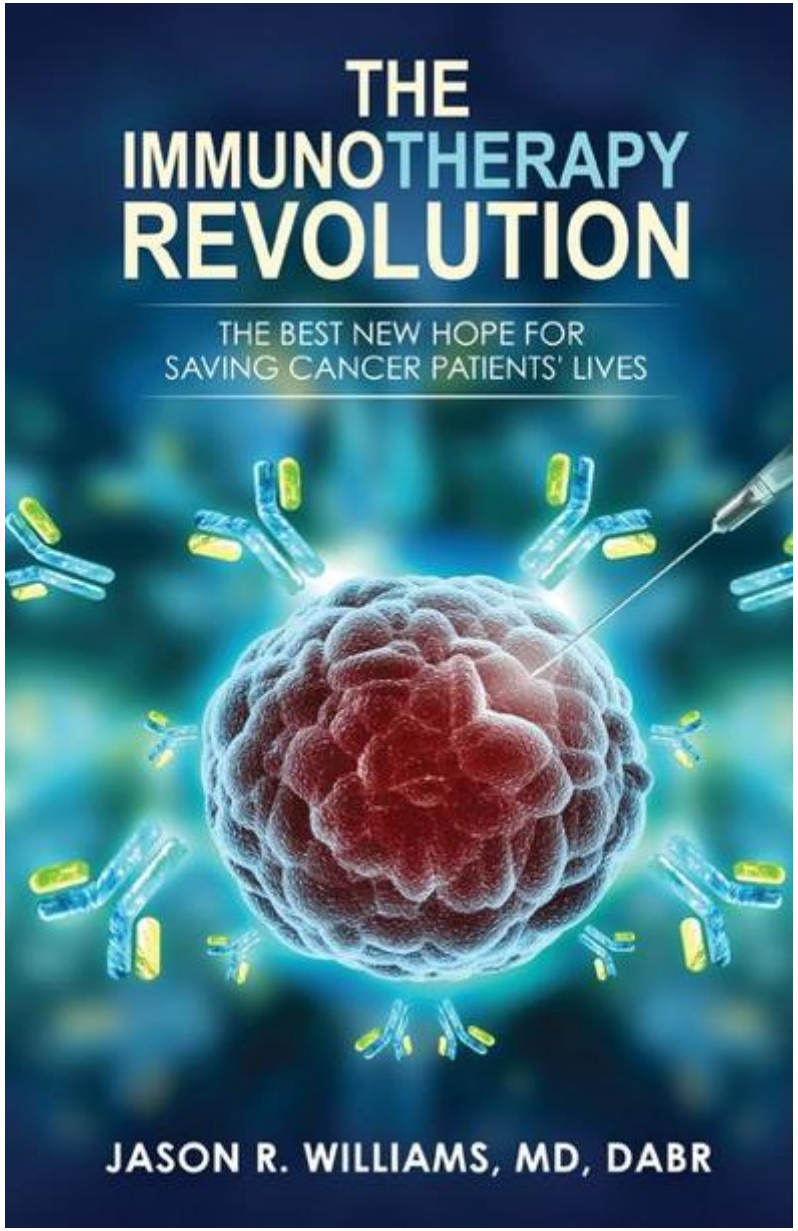
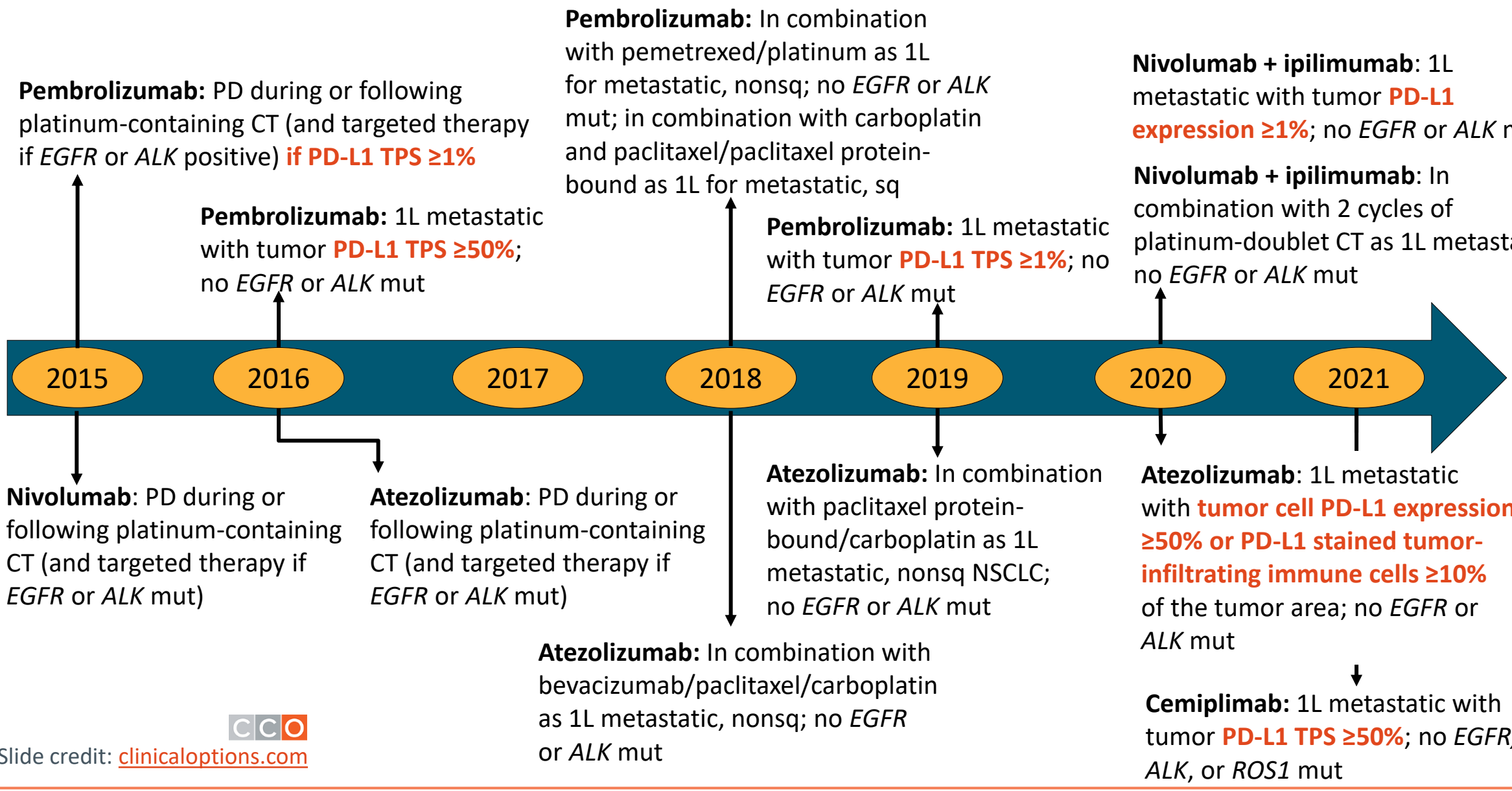


# FDA-approved immune checkpoint inhibitors

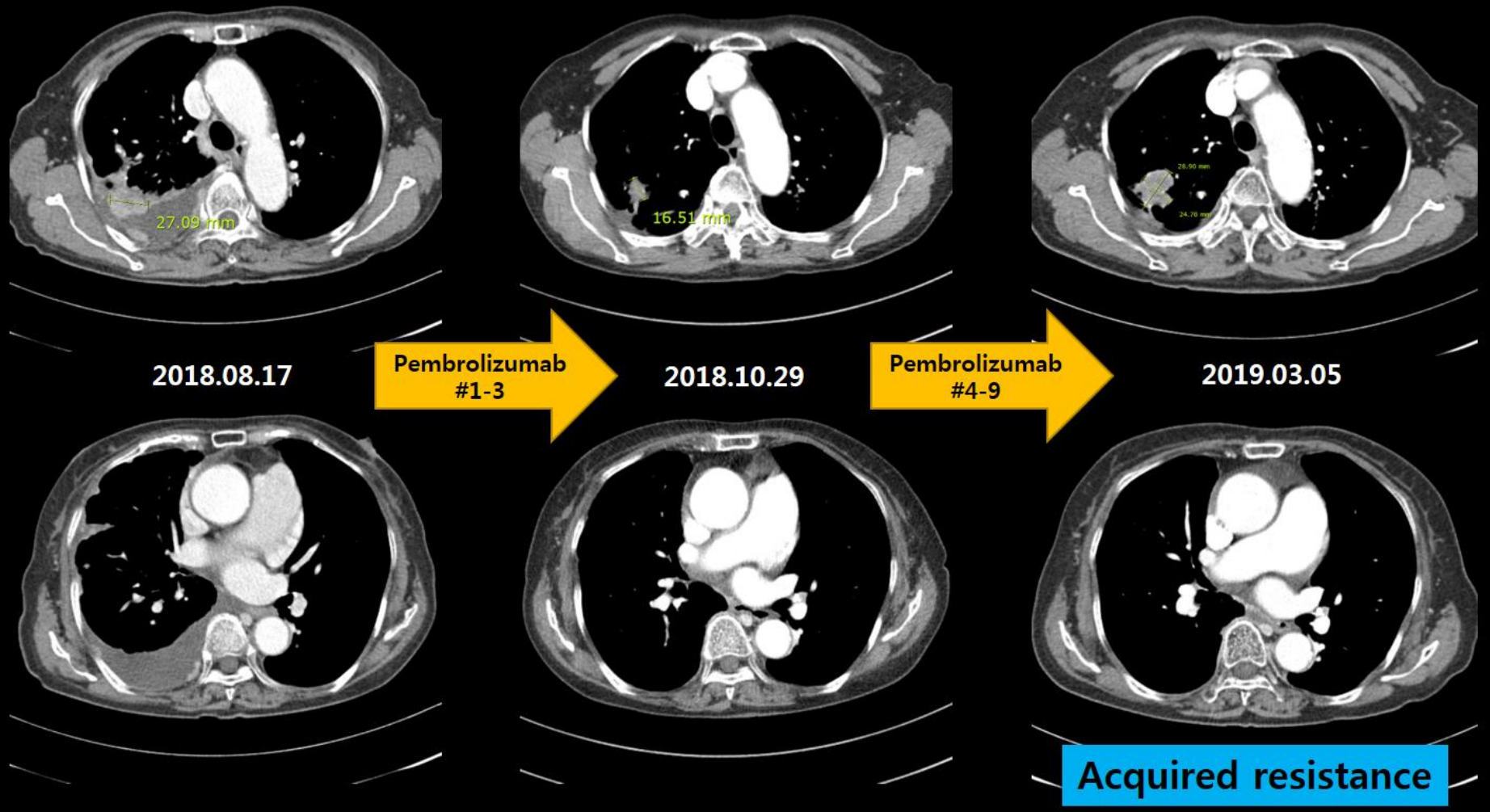
| Drug | Target | Approval |
|---|---|---|
| Ipilimumab | CTLA-4 | 2011 |
| Nivolumab | PD-1 | 2014 |
| Pembrolizumab | PD-1 | 2014 |
| Atezolizumab | PD-L1 | 2016 |
| Durvalumab | PD-L1 | 2017 |
| Avelumab | PD-L1 | 2017 |
| Cemiplimab | PD-1 | 2019 |
| Dostarlimab | PD-1 | 2021 |
| Relatlimab/Nivolumab | LAG-3/PD-1 | 2022 |

# Current FDA Approvals of ICIs for Metastatic NSCLC

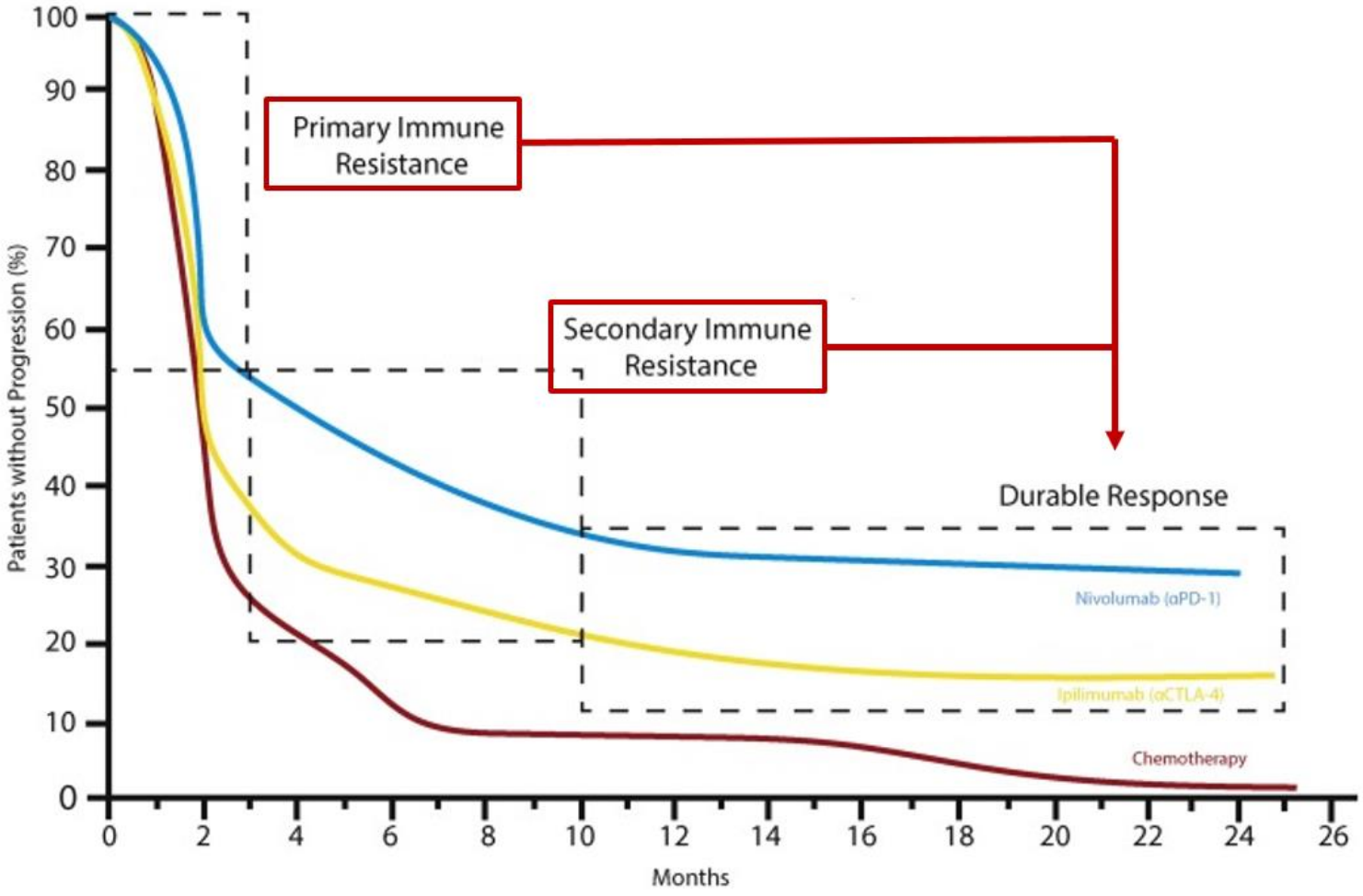



Slide credit: clinicaloptions.com

# Acquired resistance to ICI treatment



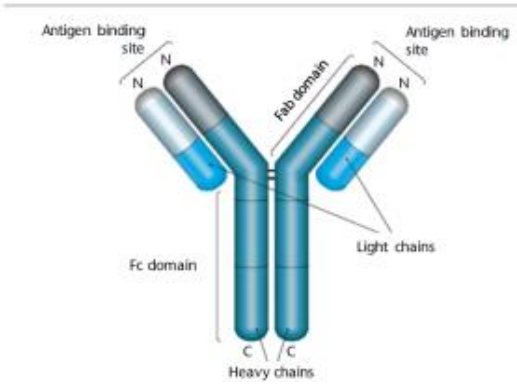
# Immune resistance → Durable response

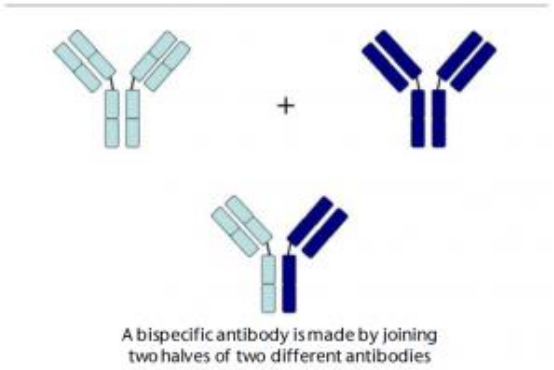



*Cytokine & growth factor reviews* 36 (2017): 5-15.

# Development for improving efficacy of ICI

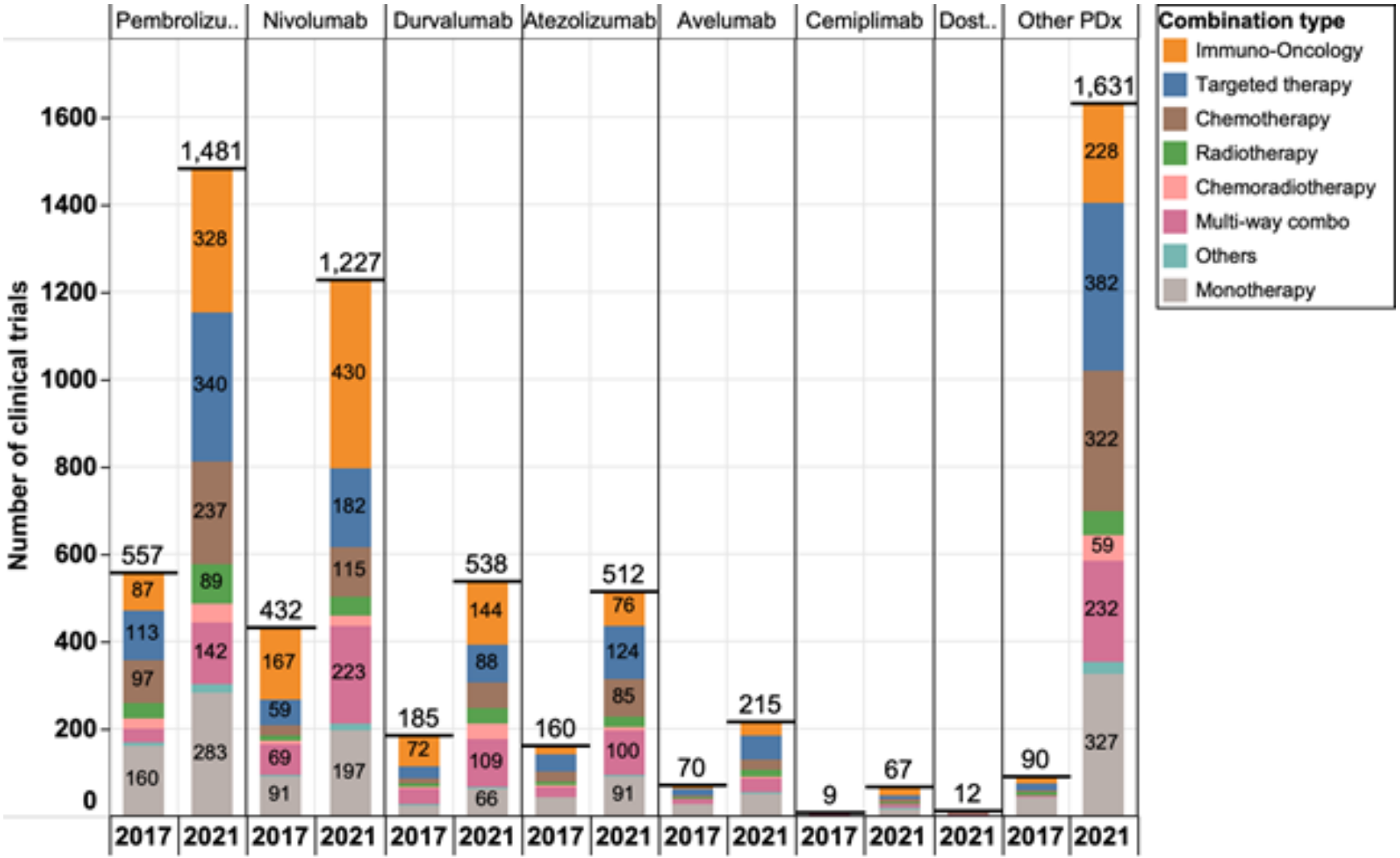
- **Combination treatment**
- **Bispecific antibodies**



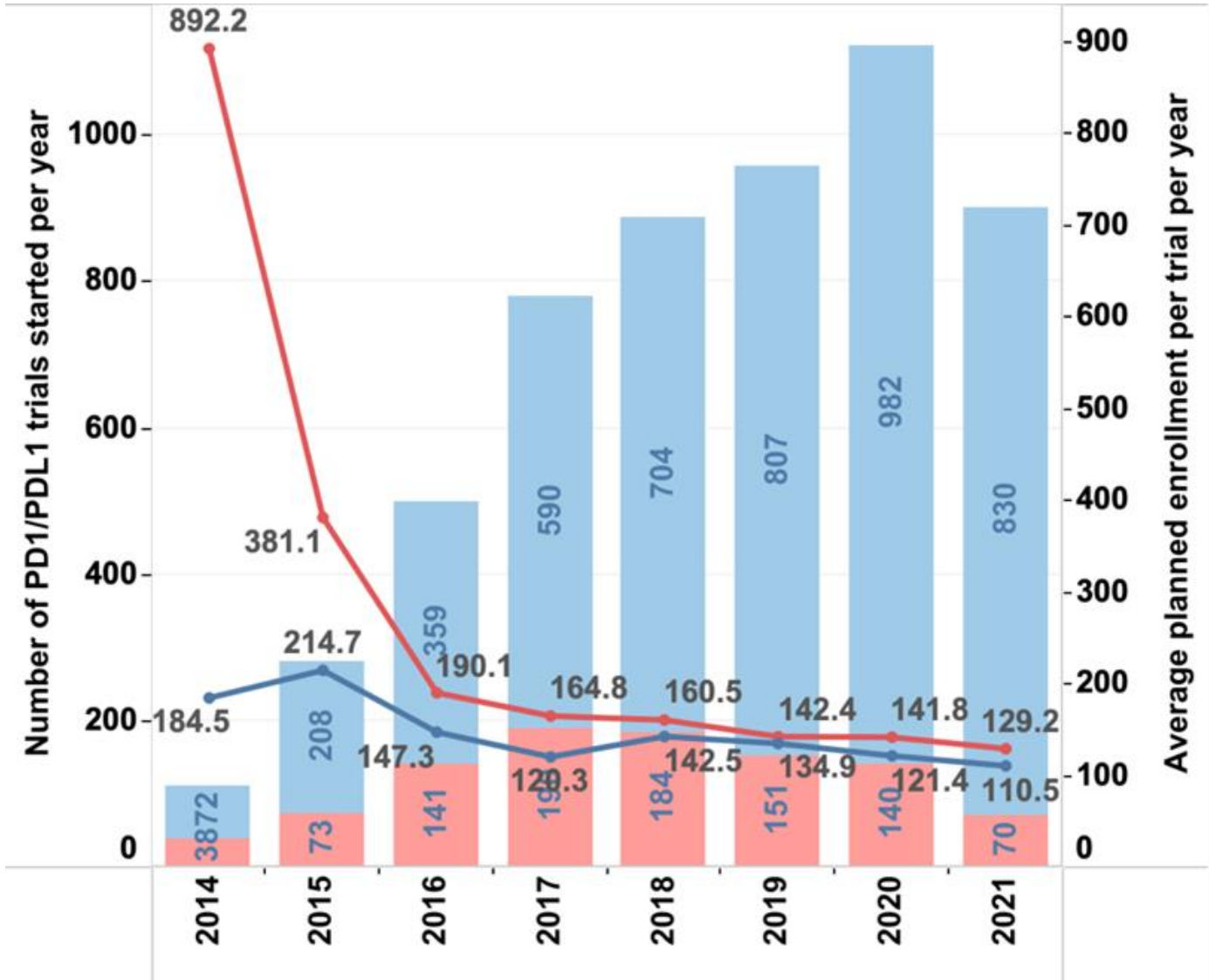

- **Fixed drug combination**

# Landscape of anti-PD1/PDL1 mAb clinical trials



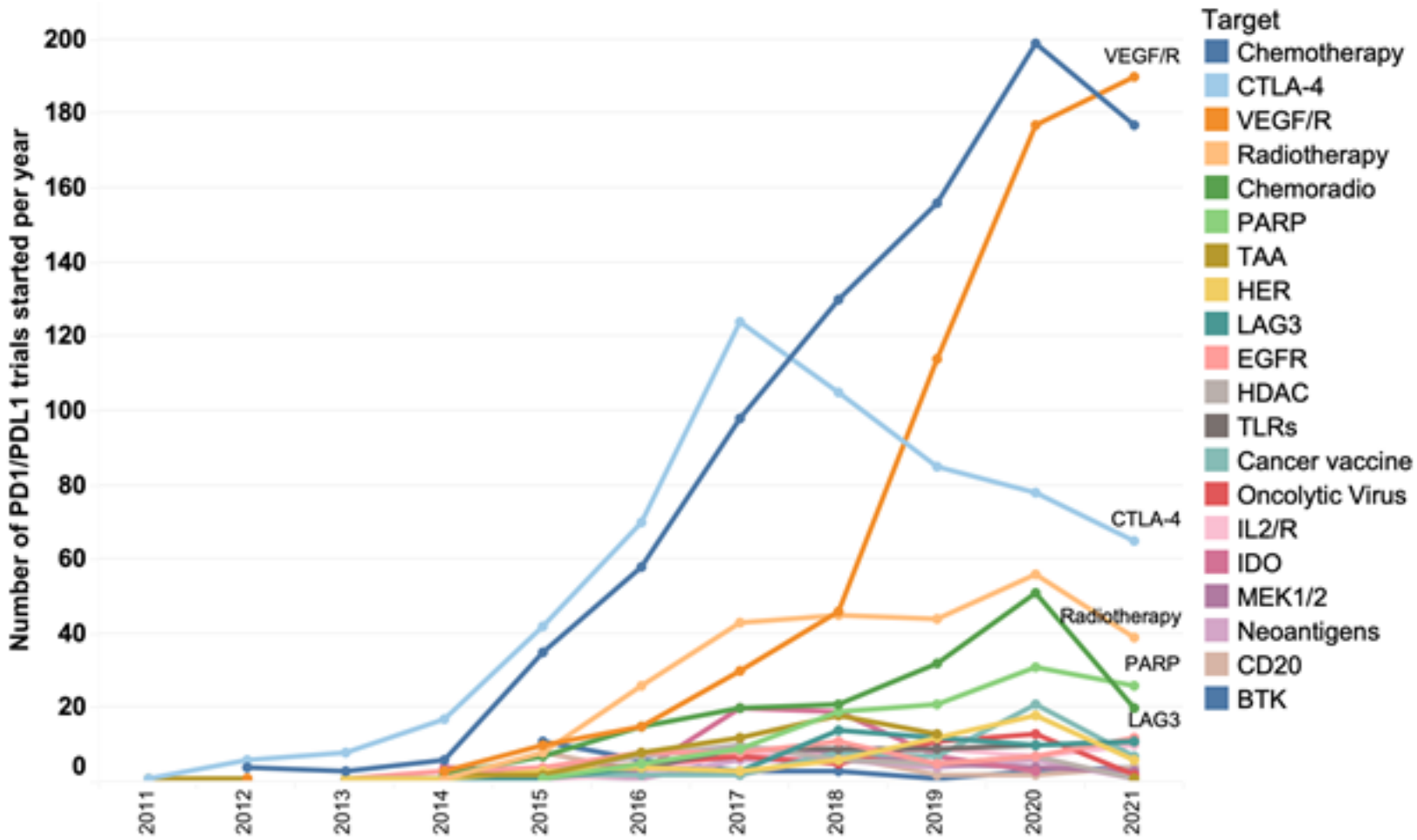

https://www.cancerresearch.org/en-us/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape

# Monotherapy vs. Combination trials




https://www.cancerresearch.org/en-us/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape

# Targets in combination with anti-PD-1/PD-L1 mAbs

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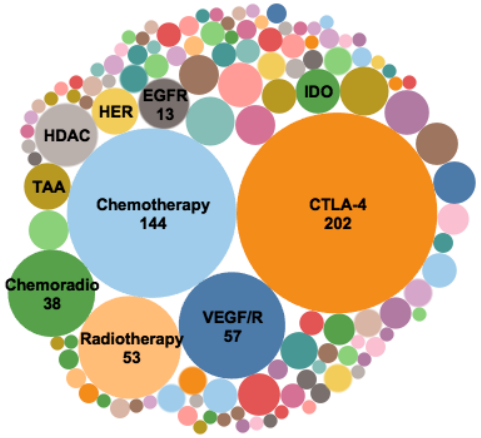
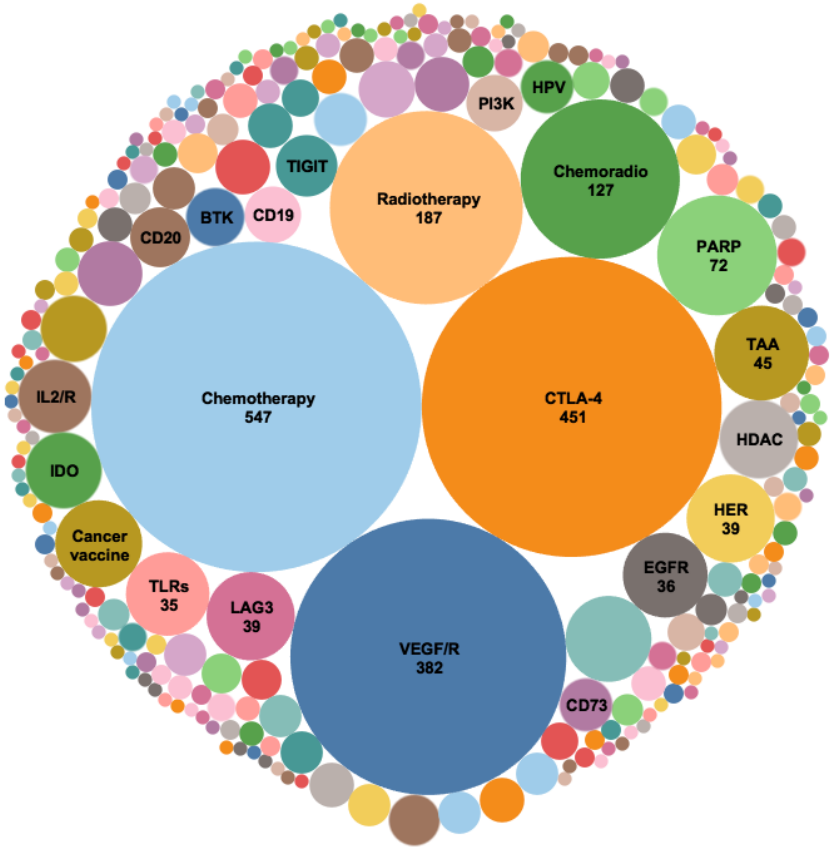
# Target landscapes of combination trials

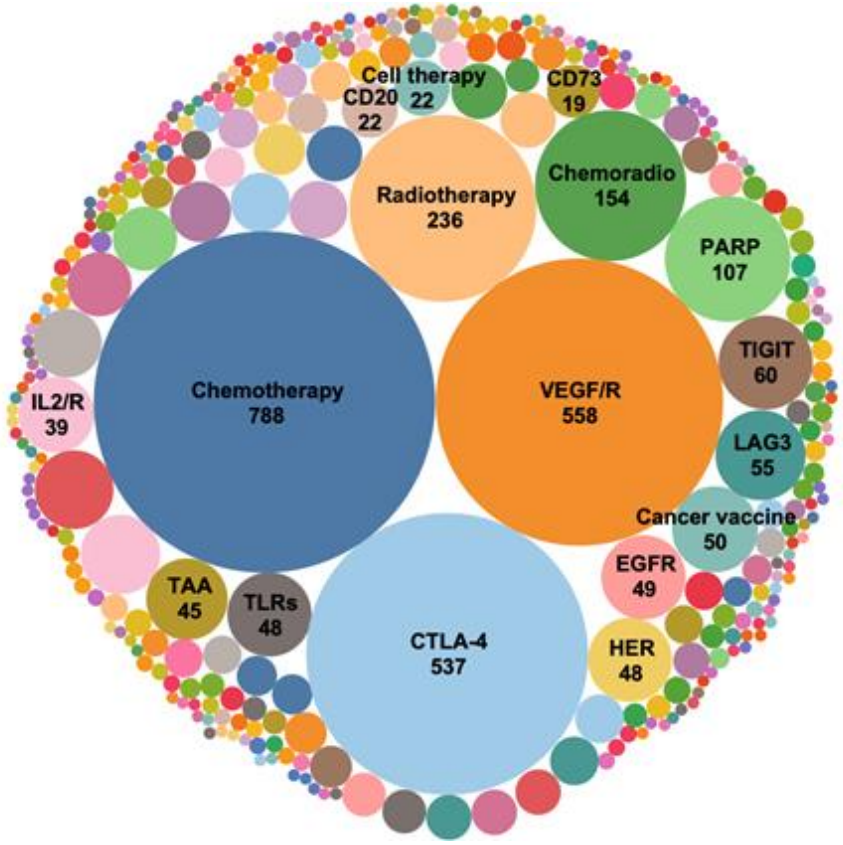
2017




2020




2021

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# Ongoing clinical trials in Metastatic NSCLC

- **PD-1/PD-L1 blockade combination with**
  - **Antiangiogenic drug**
  - **Other checkpoint inhibitors (LAG-3, TIGIT, TIM-3, OX-40)**
  - **PARP inhibitors**
- **Route of PD-1/PD-L1 blockade administration**

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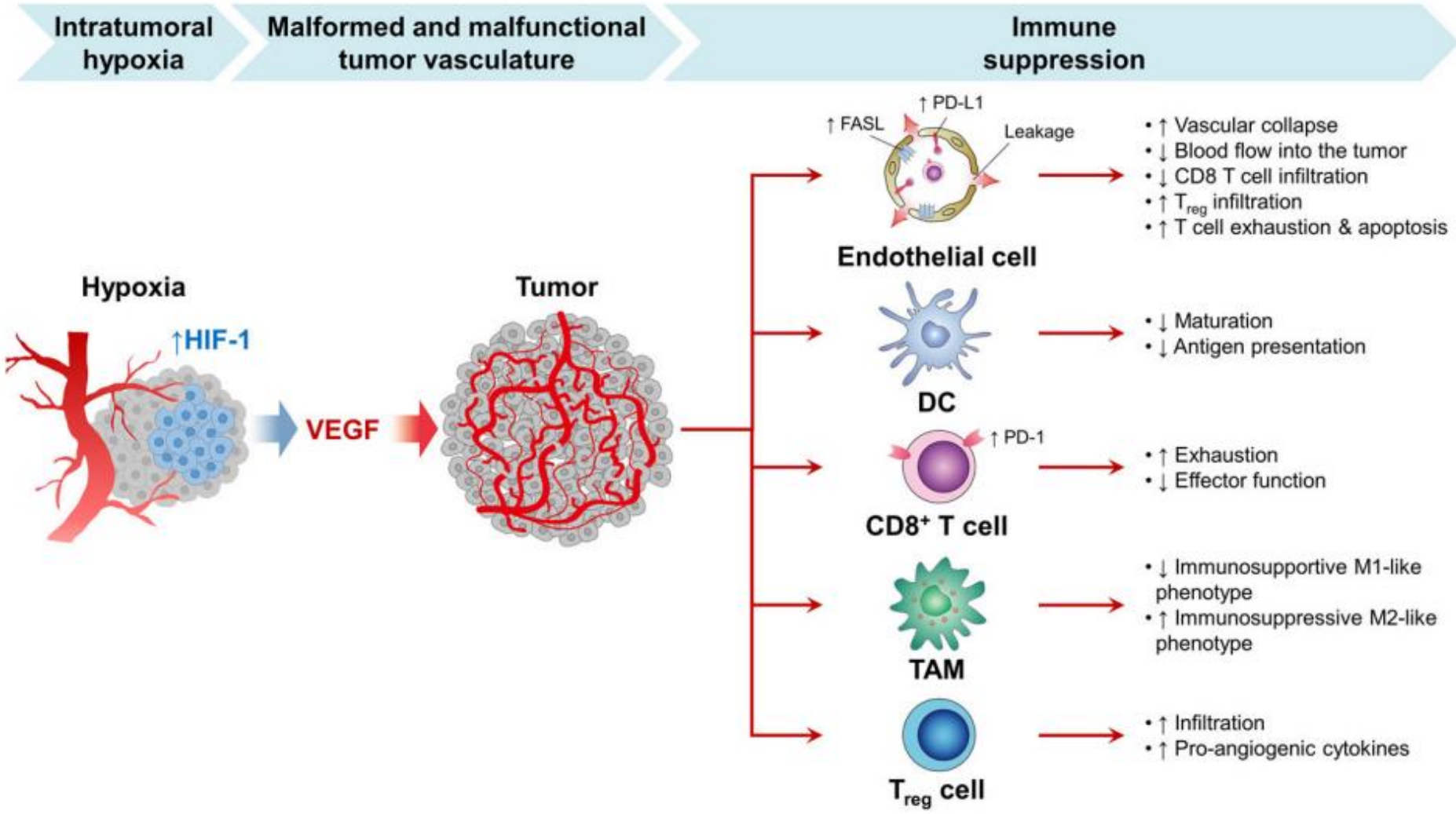
# Abnormal tumor vasculature elicits immune suppression




Experimental & Molecular Medicine (2020) 52:1475–1485

# Ongoing clinical trials combining ICIs with antiangiogenics (phase II)

| Trial | Cancer | Line | Antiangiogenic agent | Treatment | Phase |
|---|---|---|---|---|---|
| NCT03896074 (BEAT) | NSCLC (high PD-L1) | 1 | Bevacizumab | Atezolizumab+Bevacizumab vs. Atezolizumab | II |
| NCT03713944 | Non-squamous NSCLC | 1 | Bevacizumab | Atezolizumab+chemotherapy | II |
| NCT03689855 (RamAtezo-1) | NSCLC | ≥2 | Ramucirumab | Atezolizumab | II |
| NCT03527108 | NSCLC | ≥2 | Ramucirumab | Atezolizumab | II |
| NCT02954991 | NSCLC | ≥2 | Sitravatinib | Nivolumab | II |

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Meeting Abstract | 2021 ASCO Annual Meeting I

LUNG CANCER—NON-SMALL CELL METASTATIC

# Phase II trial of atezolizumab (A) + carboplatin (C) + pemetrexed (P) + bevacizumab (B) in pts with stage IV non-squamous non-small cell lung cancer (NSq-NSCLC): Big Ten Cancer Research Consortium Study LUN 17-139.

**Background:** The addition of A to C+ Paclitaxel (Pac) + plus B improved progression free survival (PFS) and overall survival (OS) compared with C + Pac + B alone in pts with metastatic NS-NSCLC. However, C + Pem is more commonly used for this patient population with a shorter infusion time and favorable toxicity profile compared with Pac. **Methods:** Multicenter single arm phase II clinical trial of chemo and immunotherapy-naïve pts with stage IV NSq-NSCLC. All pts received A (1200 mg, D1) + C (AUC 5, D1) + P (500 mg/m2, D1) + B (15mg/kg D1) q3 week x4. If non-PD, pts could receive maintenance APB until PD or intolerable side effects. The primary endpoint was 1 yr. PFS. Sample size of 42 planned with 87% power and two-sided type I error of 0.05 for 1 yr PFS. Secondary endpoints included ORR, disease control rate (DCR) [defined by CR + PR + SD], and toxicity. **Results:** 30 pts were enrolled from 11/15/2018 to 10/5/2020. The study was closed early due to 3 patient deaths, possibly related to treatment (VTE, Febrile neutropenia, colonic perforation). Median age 64 (range 38-83); M/F 20/10; mutations in EGFR/ALK/KRAS/BRAF (5/1/4/2); PD-L1 TPS $<$ 1%/1-49%/ $>$ 50% (9/14/6) and one pt did not have PDL-1 status. Median f/u was11.6 mos (range 1-20). ORR 35.71% (95% CI: 18.64%-55.95%), DCR 92.85% (95% CI: 83%-100%). 1yr PFS and OS were 55.27% and 82.90% respectively. The most common G III and G II toxicity were HTN (20%) and fatigue (33.3%).3 pts had G IV toxicity (Anemia, Febrile neutropenia and colonic perforation) and 2 pts had Grade (G) V toxicity (VTE, Hypoxia/Sepsis). **Conclusions:** Atezolizumab + Carboplatin + Pemetrexed + Bevacizumab was associated with longer DCR, PFS, and OS than historical controls. 3 on-treatment deaths, possibly related to therapy (more likely bevacizumab), prompted early closure. A phase 3 study evaluating this regimen is ongoing by another group NCT03786692. Clinical trial information: NCT03713944. Research Sponsor: Genentech.

- 1st line, Stage IV non-squamous NSCLC
- 30 patients enrolled (2018.11.15~2020.10.5)
- ORR 35.7%, DCR 92.9%
- 1yr PFS 55.3%, 1yr OS 82.9%

- The study was closed early due to 3 patients deaths (VTE, Febrile neutropenia, colonic perforation), possibly related to treatment (more likely bevacizumab).

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# Ramucirumab and Atezolizumab After Progression on Any Immune Checkpoint Blocker in NSCLC (RamAtezo-1)

- Combining ramucirumab with immunotherapy in non-small cell lung cancer (NSCLC) patients who have previously received immune checkpoint blockers (ICBs) may be more effective than traditional therapy

- 21 patients
- ORR 4.8% (1/21), CBR 76.2% (16/21)
- Median length of treatment to date is 91.5 days
- All-cause mortality 61.9% (13/21), Serious AEs 47.6% (10/21)

https://clinicaltrials.gov/ct2/show/results/NCT03689855

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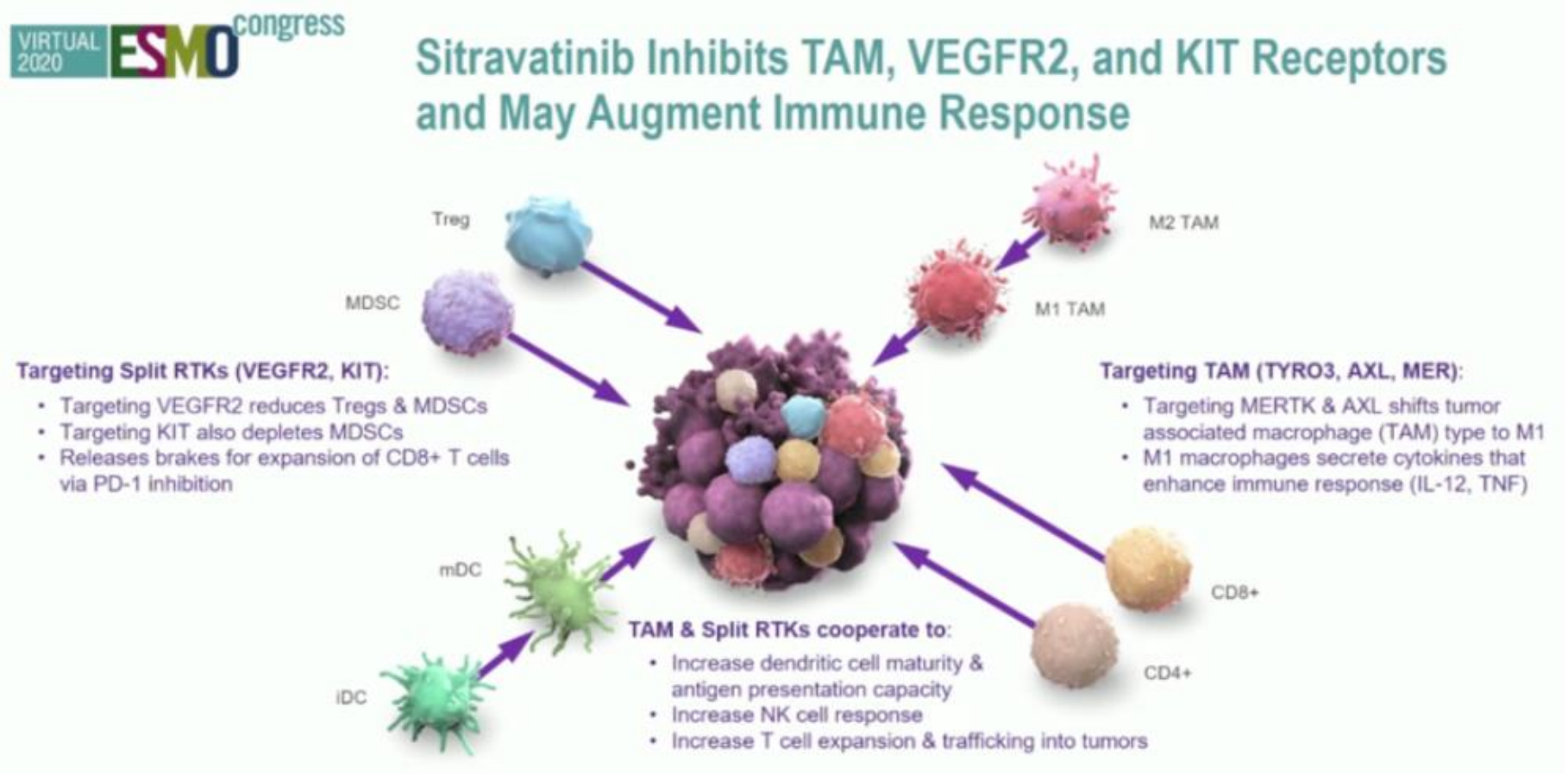
# Sitravatinib inhibits TAM, VEGFR2, KIT receptors




2020 ESMO

**Proffered Paper session - NSCLC, metastatic 2**

**Phase III trial of sitravatinib plus nivolumab vs. docetaxel for treatment of NSCLC after platinum-based chemotherapy and immunotherapy (SAPPHIRE).**

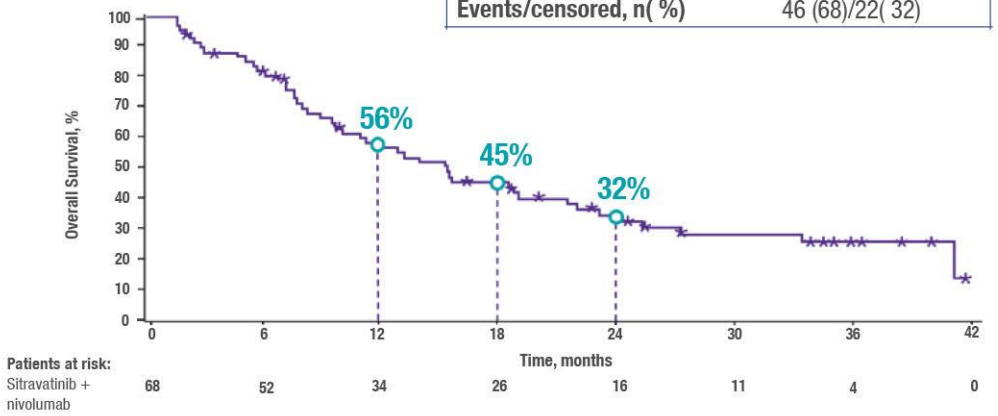
# 11910 - MRTX-500: Phase II trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

**Date**
20 Sep 2021

**Presenters**
Ticiana Leal

OS (n=68)

| | 2L/3Ls itravatinib+ nivolimumab |
|---|---|
| Median OS (95% CI) | 14.9 (9.3,2 1.1) |
| Events/censored, n( %) | 46 (68)/22( 32) |




Data as of June 1, 2021. Median follow-up: 33.6 months.
CI, confidence interval.

Sitra + nivo demonstrated antitumor activity and encouraging OS

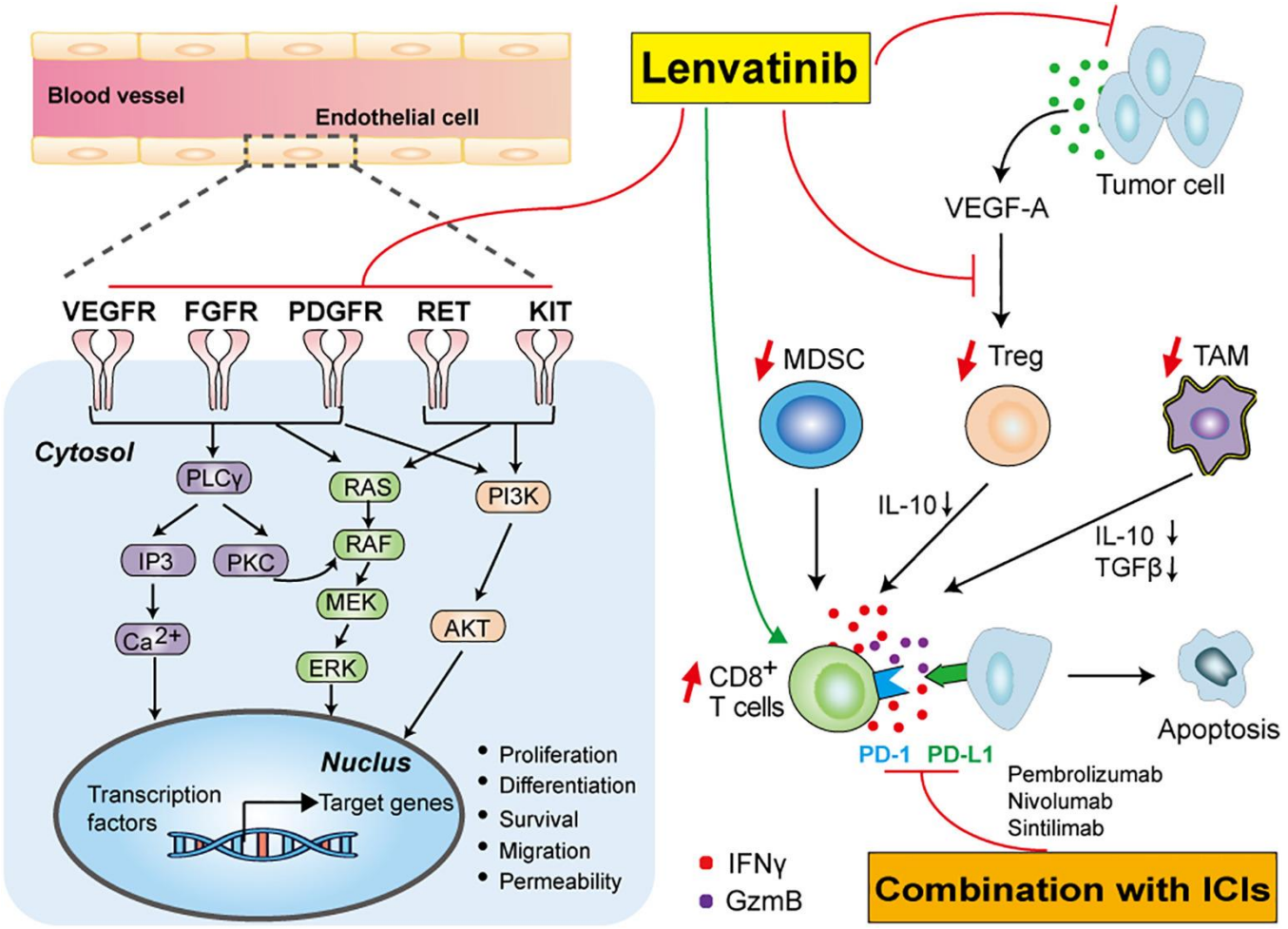
- Phase II study evaluating sitra (120 mg QD) + nivo (Q2W or Q4W) in pts with NSQ NSCLC who have progressed on or after treatment, with a CPI-based regimen (anti-PD1/PD-L1) and/or platinum doublet chemotherapy.
- Median OS was 15 months (95% CI 9.3, 21.1), 1- and 2-year OS rates were 56% and 32%
- Median PFS was 6 months, and ORR was 16% (11/68), including 2 CRs.
- Median duration of response was 13 months
- In all CPI-experienced pts evaluable for safety (n=124), treatment related adverse events (TRAEs) occurred in 91% of pts, with Gr 3/4 TRAEs occurring in 60% of pts. There were no Gr 5 TRAEs.
- Discontinuation rates for sitra and nivo due to any AE were 30% and 27%, respectively.

2021 ESMO

# Ongoing clinical trials combining ICIs with antiangiogenics (phase III)

| Trial | Cancer | Line | Antiangiogenic agent | Treatment | Phase |
|---|---|---|---|---|---|
| NCT39766375 (LEAP-006) | Non-SqCC NSCLC | 1 | Lenvatinib | Lenvatinib+pembrolizumab+chemotherapy vs. pembrolizumab+chemotherapy | III |
| NCT03829332 (LEAP-007) | NSCLC (PD-L1+) | 1 | Lenvatinib | Lenvatinib+pembrolizumab vs. pembrolizumab | III |
| WJOG11218L (APPLE study) | NSCLC | 1 | Bevacizumab | Atezolizumab+bevacizumab+chemotherapy vs. atezolizumab+chemotherapy | III |
| NCT03976375 (LEAP-008) | NSCLC | ≥2 | Lenvatinib | Lenvatinib vs. Lenvatinib+pembrolizumab vs. docetaxel (patients who failed prior immunotherapy and platinum-doublet chemotherapy) | III |
| NCT03906071 (SAPPHIRE) | NSCLC | ≥2 | Sitravatinib | Sitravatinib+nivolumab vs. docetaxel | III |
| NCT04471428 (CONTACT-01) | NSCLC | ≥2 | Cabozantinib | Cabozantinib+Atezolizumab vs. Docetaxel | III |

# Targets signaling pathways and underlying immunomodulatory activity of lenvatinib




*Drugs* 79.6 (2019): 665-674.

# Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors

Matthew H. Taylor, MD[1]; Chung-Han Lee, MD, PhD[2]; Vicky Makker, MD[2]; Drew Rasco, MD[3]; Corina E. Dutcus, MD[4]; Jane Wu, PhD[4]; Daniel E. Stepan, MD[5]; Robert C. Shumaker, PhD[4]; and Robert J. Motzer, MD[2]

**TABLE 4.** Efficacy Outcomes (investigator review, immune-related RECIST)

| Parameter | RCC (n = 30) | Endometrial (n = 23) | SCCHN (n = 22) | Melanoma (n = 21) | NSCLC (n = 21) | Urothelial (n = 20) |
|---|---|---|---|---|---|---|
| Best overall response | | | | | | |
| Complete response | 0 (0) | 2 (9) | 1 (5) | 1 (5) | 1 (5) | 1 (5) |
| Partial response | 21 (70) | 10 (44) | 9 (41) | 9 (43) | 6 (29) | 4 (20) |
| Stable disease | 8 (27) | 10 (44) | 10 (46) | 7 (33) | 10 (48) | 9 (45) |
| Progressive disease | 1 (3) | 1 (4) | 0 (0) | 3 (14) | 2 (10) | 2 (10) |
| Unknown | 0 (0) | 0 (0) | 2 (9) | 1 (5) | 2 (10) | 4 (20) |
| ORR[a] | 21 (70) | 12 (52) | 10 (46) | 10 (48) | 7 (33)[b] | 5 (25) |
| (95% CI) | (50.6 to 85.3) | (30.6 to 73.2) | (24.4 to 67.8) | (25.7 to 70.2) | (14.6 to 57.0) | (8.7 to 49.1) |
| $ORR_{Week24}$ | 19 (63) | 12 (52) | 8 (36) | 10 (48) | 7 (33) | 5 (25) |
| (95% CI) | (43.9 to 80.1) | (30.6 to 73.2) | (17.2 to 59.3) | (25.7 to 70.2) | (14.6 to 57.0) | (8.7 to 49.1) |
| Median DOR, months (95% CI) | 20.0 (9.0 to 22.9) | NE (2.6 to NE) | 8.2 (2.2 to 12.6) | 12.5 (2.7 to NE) | 10.9 (2.4 to NE) | NE (6.5 to NE) |
| Median PFS, months (95% CI) | 19.8 (9.9 to 24.1) | 9.7 (4.2 to NE) | 4.7 (4.0 to 9.8) | 5.5 (2.6 to 15.8) | 5.9 (2.3 to 13.8) | 5.4 (1.3 to NE) |

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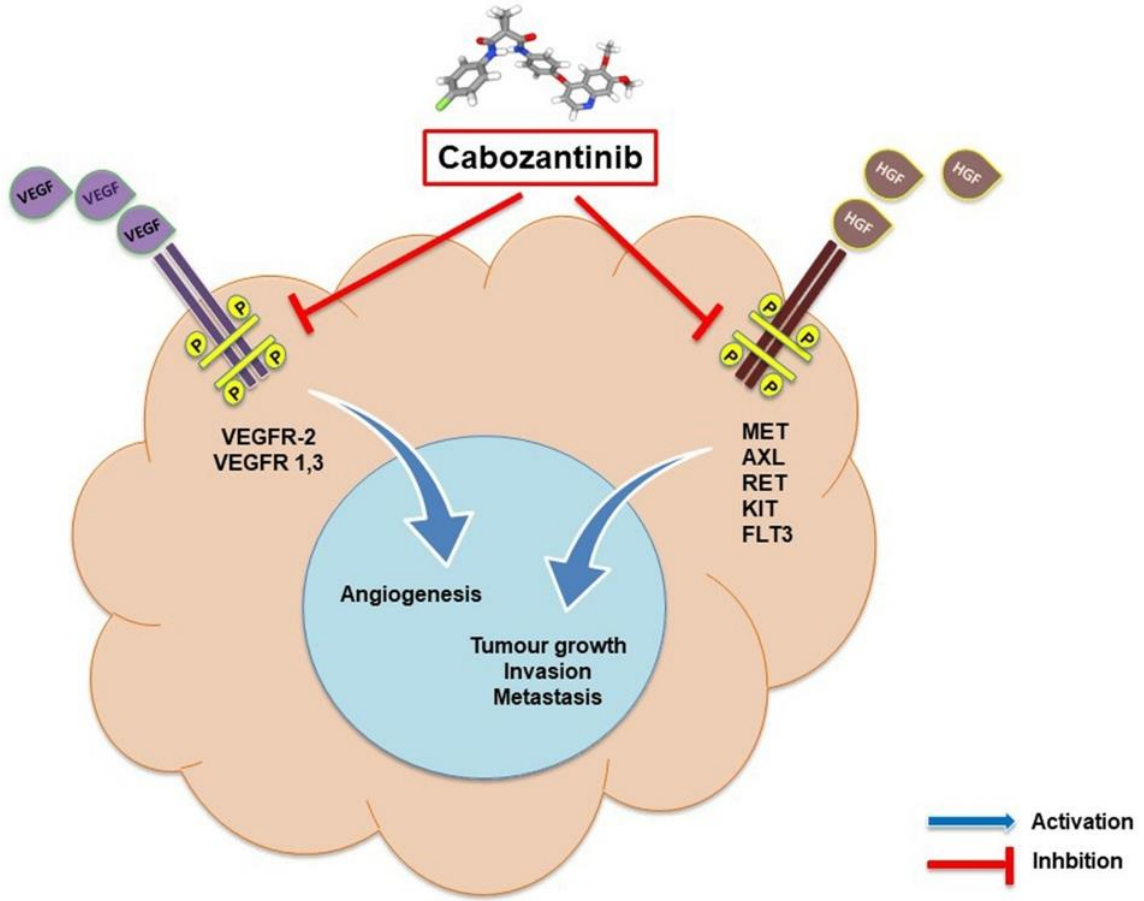
# Mechanism of action of cabozantinib




*Critical Reviews in Oncology/Hematology* 149 (2020): 102921.

# CONTACT-01
## *Study design*

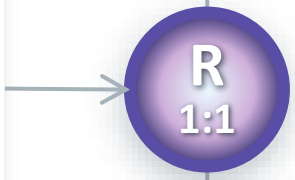
CONTACT-01
GO41892

**Metastatic NSCLC**

> Progression on or after immune checkpoint inhibitor (ICI) therapy AND platinum-based chemotherapy

> Absence of sensitizing EGFR mutation or ALK fusion oncogene

*N =350*




**Atezolizumab** (1200 mg Q3W)
+
**Cabozantinib** (40 mg QD)

→ *PD* or loss of clinical benefit*

NO crossover allowed

**Docetaxel**
(75 mg/m² Q3W)

→ *PD*

**Stratification Factors:**

> Histology (SQ vs NSQ)

> Prior NSCLC treatment regimen(s) at following 4 levels:

1. Concurrent platinum-containing chemo and anti-PD(L)1 Ab combo
2. Platinum-containing chemo first, followed by anti-PD(L)1 Ab
3. Anti-PD(L)1 Ab monotherapy first, followed by platinum-containing chemo
4. Anti-PD(L)1 Ab monotherapy first, with platinum-containing chemo added at progression

**Primary Endpoints:**

> OS

**Secondary Endpoints:**

> PFS, ORR and DOR assessed INV, PRO

***Treatment may be continued beyond PD (see next slide)**

Ab: antibody; NSQ: non-squamous; PD: disease progression; SQ: squamous

# Ongoing clinical trials in Metastatic NSCLC

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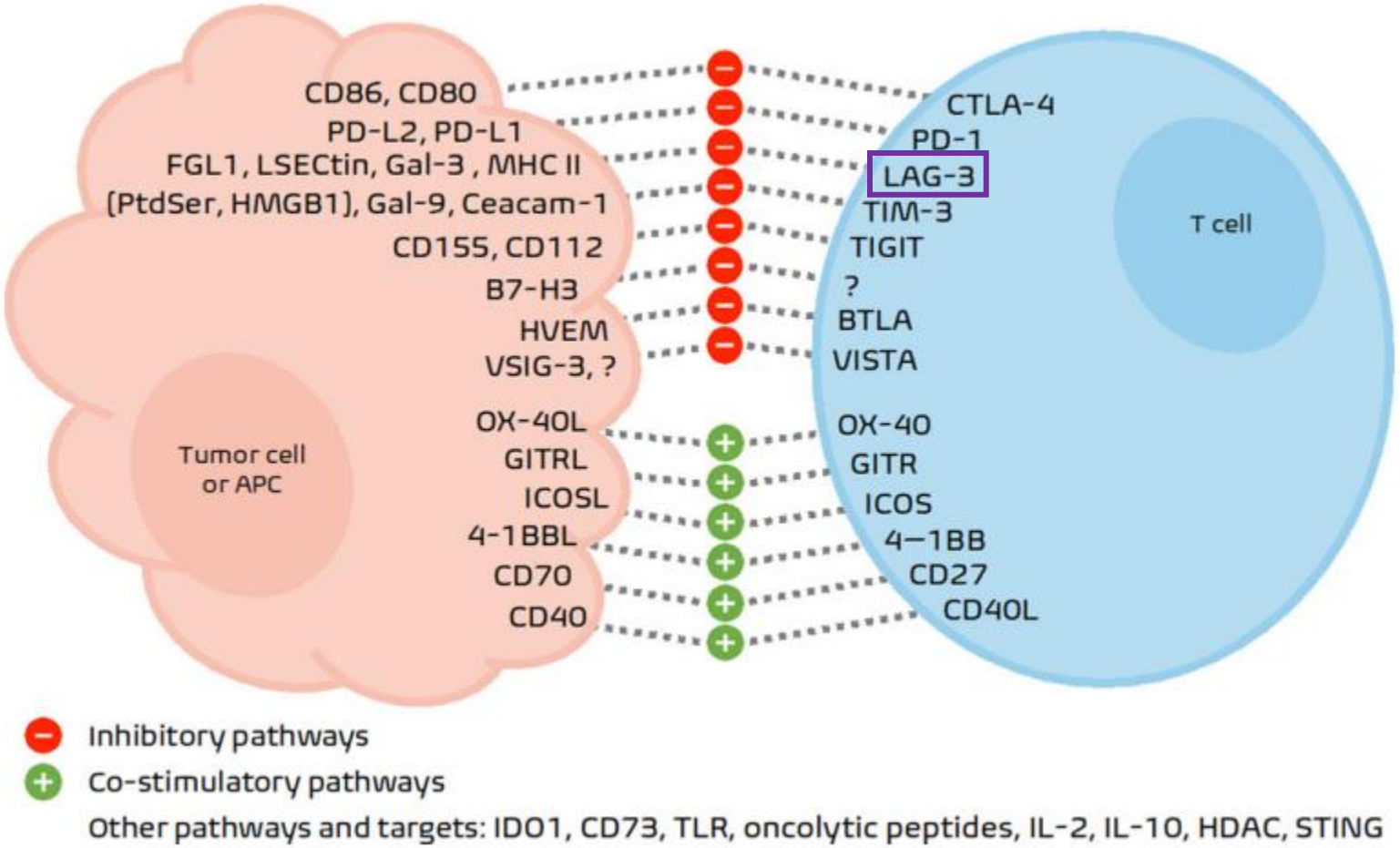
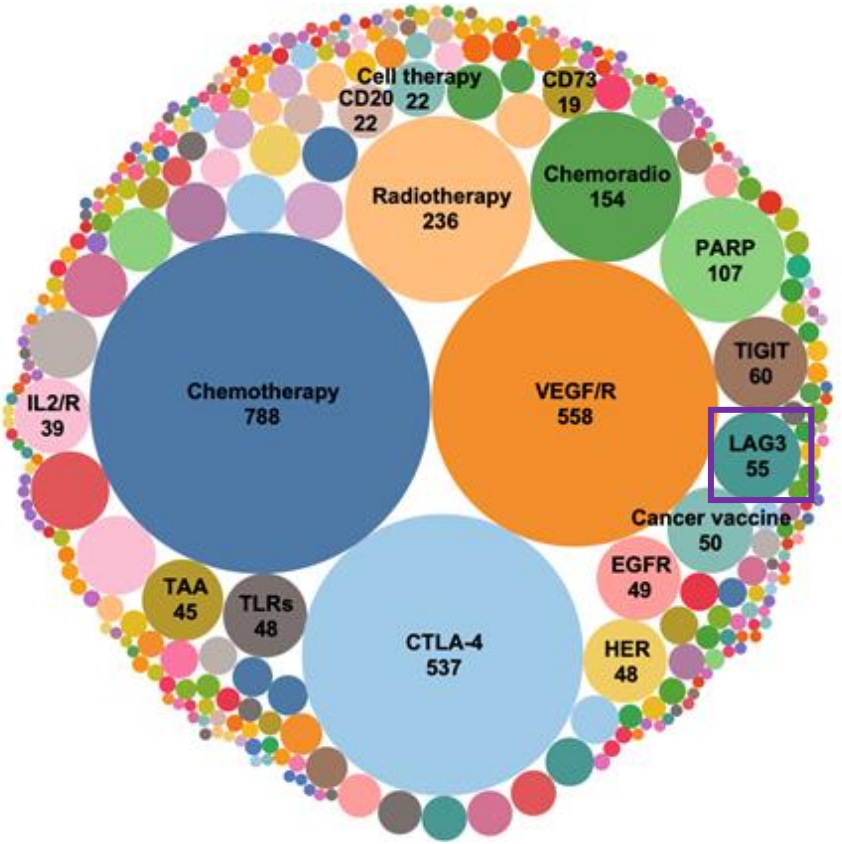
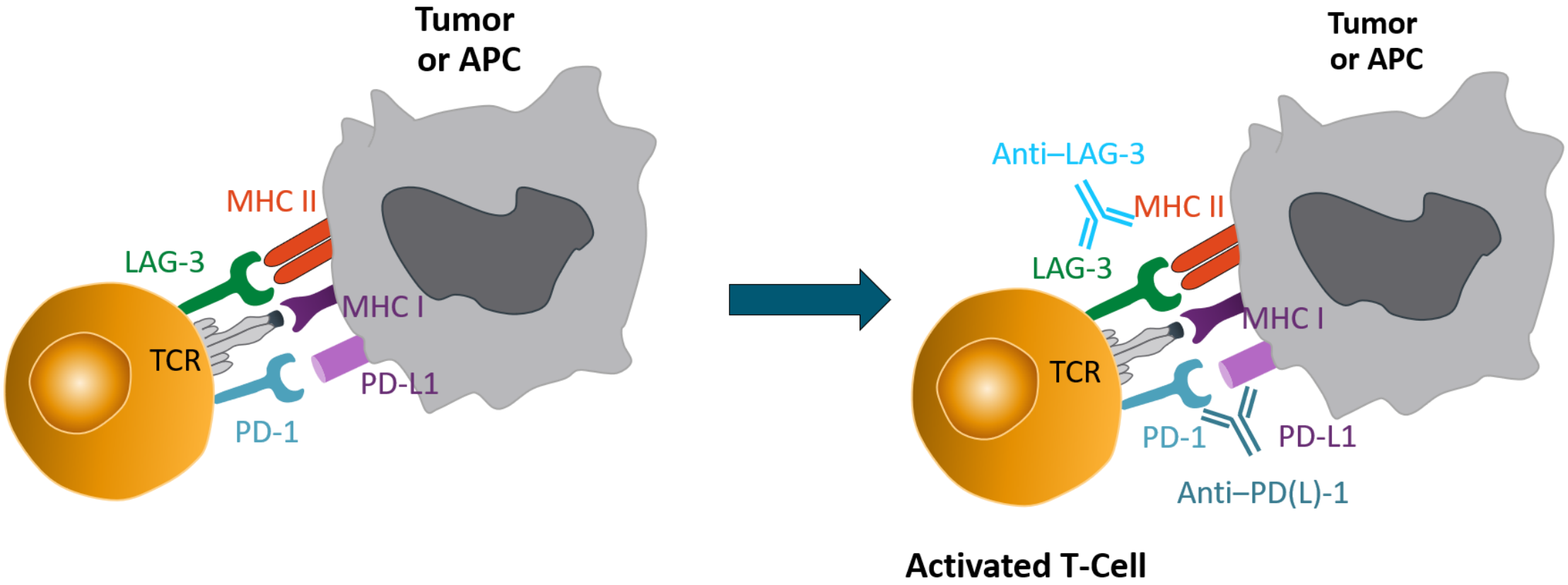
# Immune checkpoints




*memo-Magazine of European Medical Oncology* 14.2 (2021): 135-142.

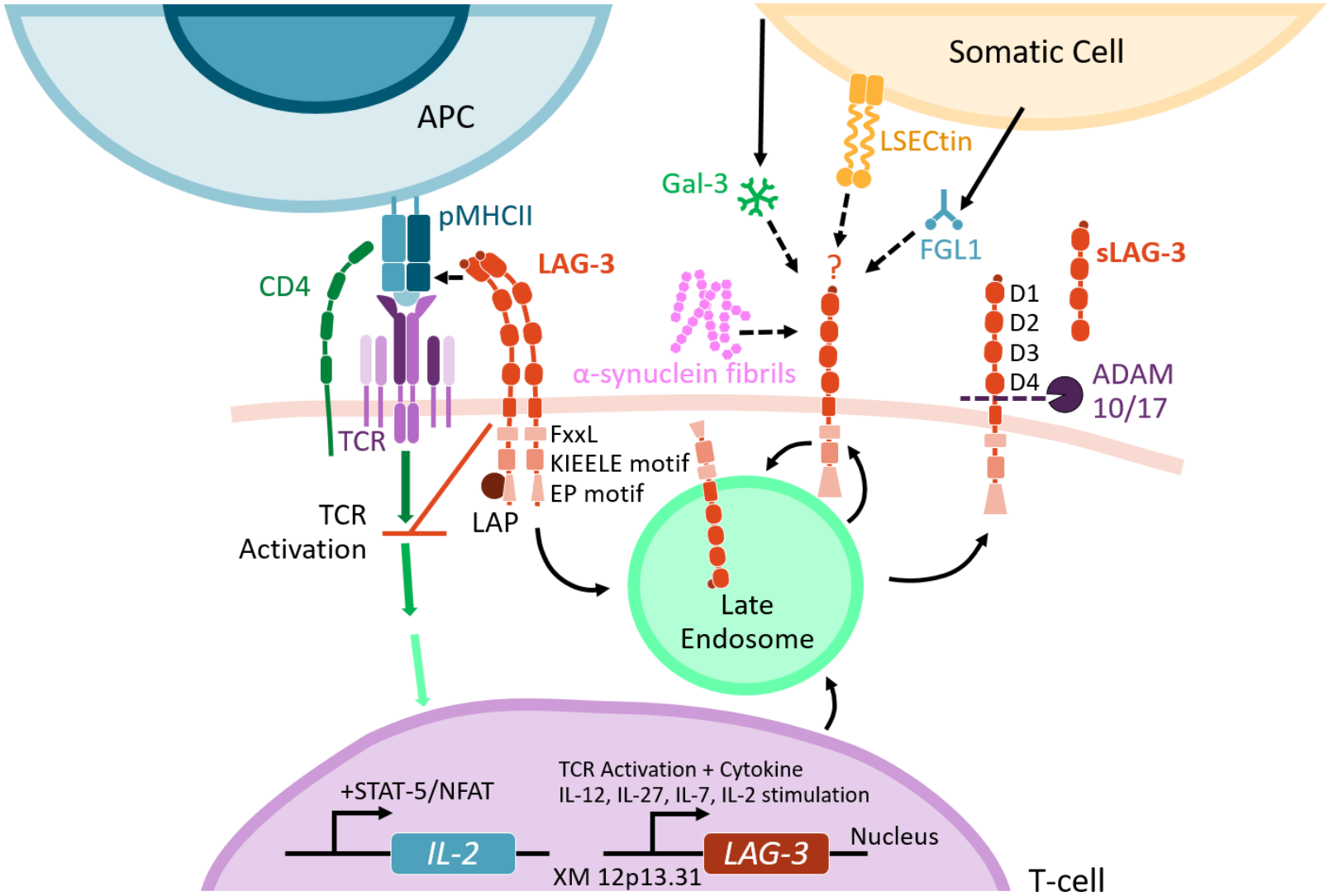
# LAG-3 and PD-1/PD-L1 as Targets in Cancer Therapy




Nguyen. Nature Rev Immunol. 2014;15:45.

# Mechanism of LAG-3

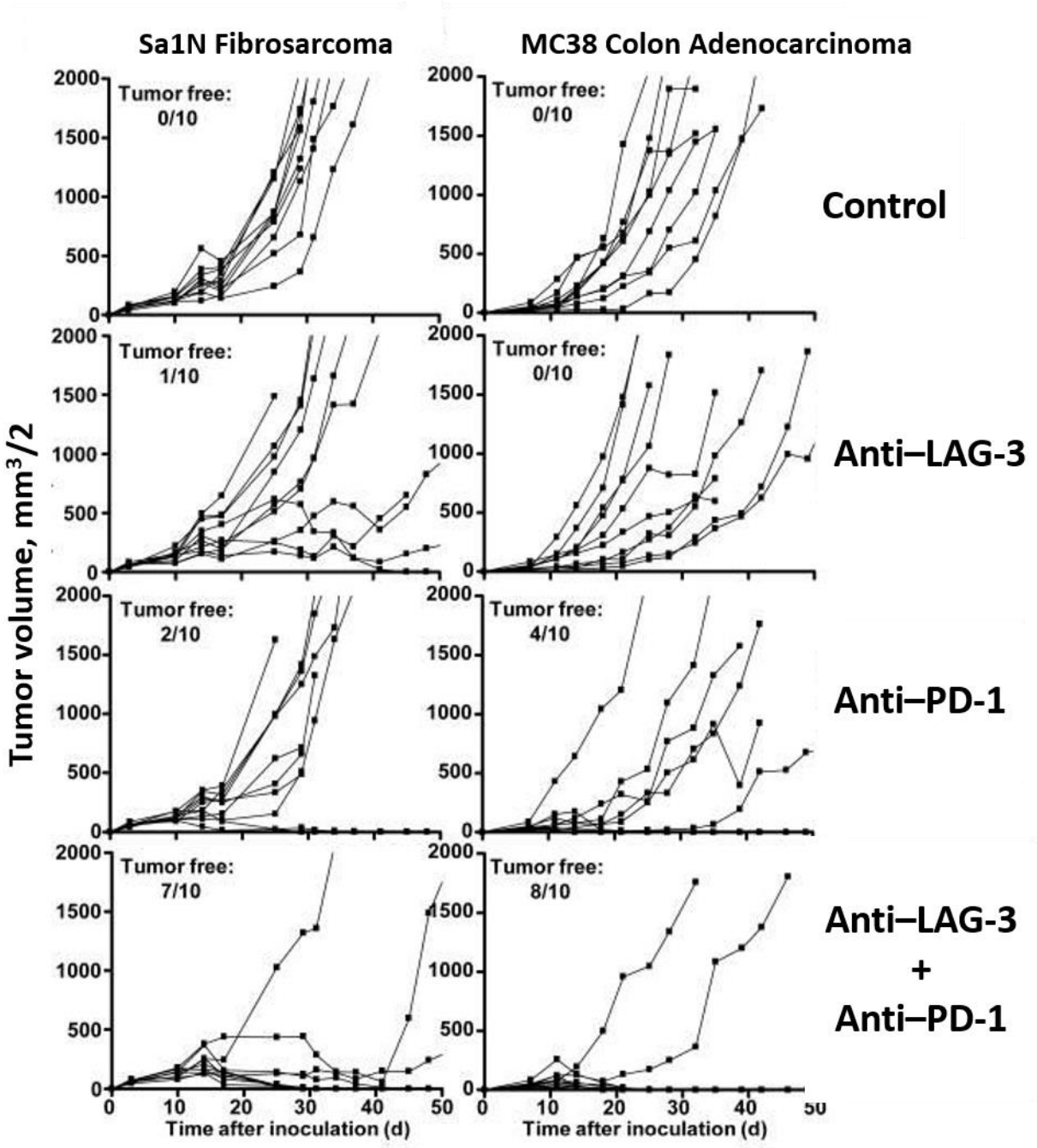
- Negatively regulates cellular proliferation and activation[1,2]
  - Similar to, but not redundant with PD-1, CTLA-4
- LAG-3 is expressed on multiple cell types including CD4+ and CD8+ T-cells and T-regulatory cells, and helps maintain self and tumor tolerance[3,4]
- The major ligand for LAG-3 is MHC class II[5]




1. Workman. J Immunol. 2004;172:5450. 2. Workman. J Immunol. 2005;174:688. 3. Huang. Immunity. 2004;21:503.
4. Grosso. J Clin Invest. 2007;117:3383. 5. MacLachlan. Eur J Immunol. 2021;52:331.

# Preclinical Evidence of Synergy Between Anti–LAG-3 and Anti–PD-1

- LAG-3 and PD-1 blockade in mice with Sa1N fibrosarcoma or MC38 colon adenocarcinoma
- Blockade demonstrates synergy




Woo. Cancer Res. 2012;72:917.

# Investigational LAG-3-Targeted Monoclonal Antibodies

| Agent | Ongoing Clinical Trials | Trial Identifier |
|---|---|---|
| Ieramilimab (LAG-525) | Phase II, melanoma, with spartalizumab | NCT03484923 |
| Favezelimab/ pembrolizumab coformulation (MK-4280A) | Phase III vs SoC in mCRC<br>Phase I/II, NSCLC<br>Phase I/II, ES-SCLC<br>Phase I/II, RCC | NCT05064059<br>NCT03516981<br>NCT04938817<br>NCT04626479, NCT04626518 |
| Fianlimab (REGN3767) | Phase I, advanced cancers ± cemiplimab | NCT03005782 |
| INCAGN-2385 | Phase I/II, advanced cancers, with anti–TIM-3 ± anti–PD-1 | NCT04370704 |
| Miptenalimab (BI 754111) | Phase I, advanced solid tumors, with anti–PD-1 ± MDM2 inhibitor | NCT03964233 |
| LBL-007 | Phase Ib/II, advanced tumors | NCT05102006 |
| Sym022 | Phase I, biliary tract carcinoma with anti–PD-1 | NCT04641871 |
| Encelimab (GSK-4074386, TSR-033) | Phase I, advanced solid tumors, + anti–PD-1<br>Phase I, advanced solid tumors + anti–TIM-3 | NCT03250832<br>NCT02817633 |
| IBI110 | Phase II, ES-SCLC, + sintilimab<br>Phase I, NSCLC, + sintilimab (neoadjuvant) | NCT05026593<br>NCT05088967 |

Slide credit: clinicaloptions.com

# Ongoing clinical trials of anti-LAG-3 agents combined with PD-1/PD-L1 blocker

| Trial | Cancer | Line | Anti-LAG-3 | Treatment | Phase |
|---|---|---|---|---|---|
| NCT04623775 (RELATIVITY-104) | Stage IV NSCLC | 1 | Relatlimab | Nivolumab+Relatlimab+PDCT Vs. Nivolumab+PDCT | II |
| NCT01968109 | Advanced solid tumors | ≥2 | Relatlimab | Relatlimab+Nivolumab vs. Relatlimab | Ib/II |
| NCT02460224 | Advanced solid tumors | ≥2 | Ieramilimab (LAG-525) | Ieramilimab+spartalizumab(anti-PD-1, PDR001) vs. Ieramilimab | I/II |

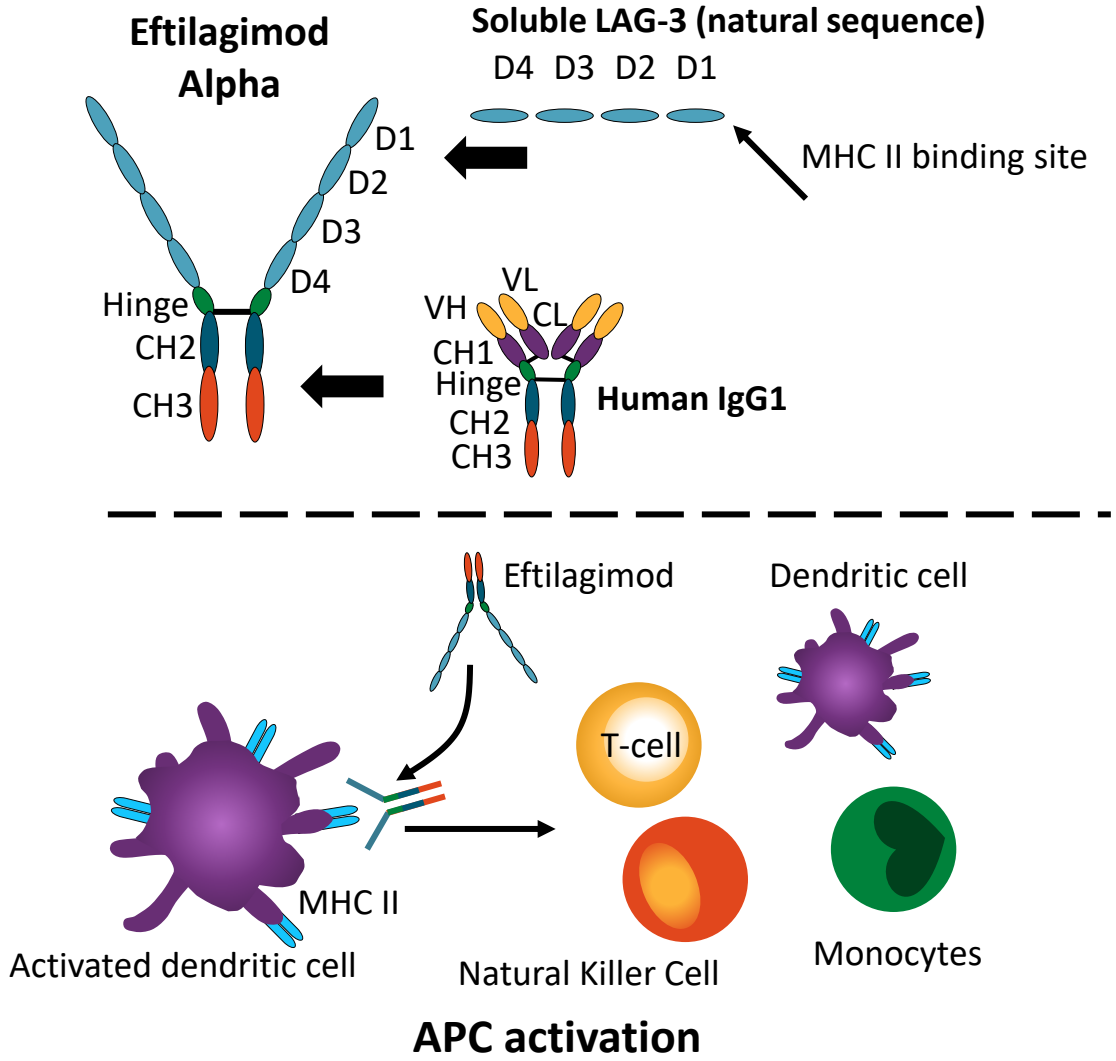
# Anti–LAG-3 Bispecific Antibodies in Development

| Agent | Targets | Clinical Development | Trial Identifier |
|---|---|---|---|
| Tebotelimab (MDG-013)[1,2] | LAG-3/PD-1 | Phase II in HNSCC<br>Phase III; MAHOGANY; gastric/GEJ HER2 with margetuximab | NCT04634825<br>NCT04082364 |
| EMB-02 | LAG-3/PD-1 | Phase I/II in solid tumors | NCT04618393 |
| RG6139 | LAG-3/PD-1 | Phase I study in advanced solid tumors | NCT04140500 |
| IBI-323 | LAG-3/PD-1 | Phase I in adv malignancies | NCT04916119 |
| FS 118[1,3] | LAG-3/PD-L1 | Phase I /II in adv malignancies | NCT03440437 |
| Pavunalimab (XmAb-841) | LAG-3/CTLA-4 | Phase I w/pembrolizumab in solid tumors | NCT03849469 |

1. Maruhashi. J ImmunoTher Cancer. 2020;8e001014. 2. Wang. ASH 2020. Abstr 3022. 3. Yap. SITC 2020. Abstr 395.

# Eftilagimod Alpha Dimeric Recombinant LAG-3

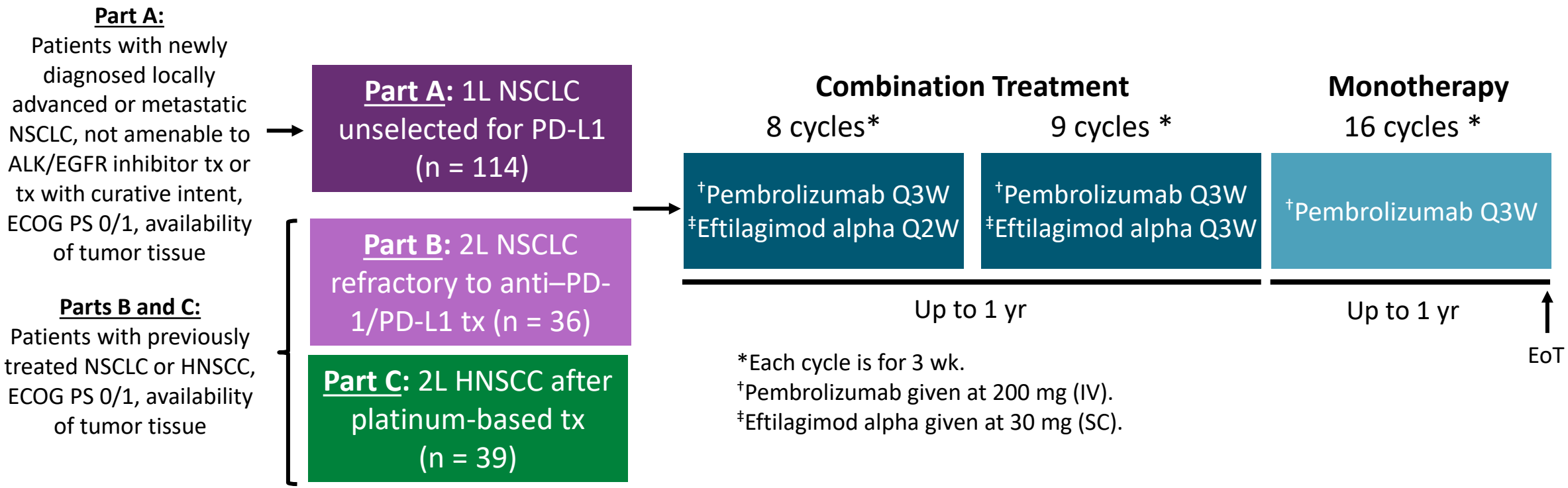
- Recombinant, soluble LAG-3 fusion protein
- Mechanism of action is different from antibodies or bispecific antibodies targeting LAG-3
- MHC class II agonist
  - Binds to MHC class II on APC leading to APC activation
- Activated APCs leads to increased T-cell activation




Felip. ASCO 2020. Abstr 3100. Clay. ASCO 2021. Abstr 9046.

# TACTI-002: Eftilagimod Alpha Plus Pembrolizumab in NSCLC or HNSCC

- Nonrandomized, parallel assignment, open-label phase II trial

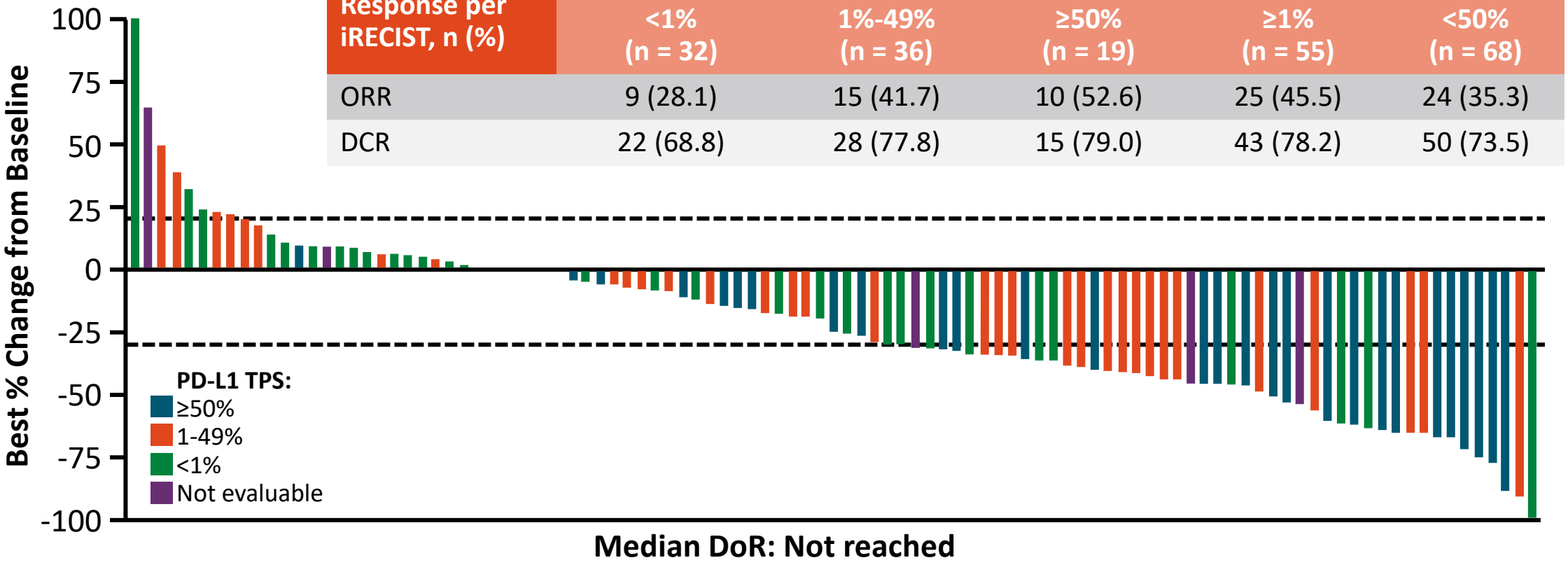



- **Primary endpoint:** ORR per iRECIST
- **Secondary endpoints:** ORR by RECIST 1.1, PFS, OS, DoR, safety and PK/PD (including potential biomarkers)

Felip. ASCO 2020. Abstr 3100. Clay. ASCO 2021. Abstr 9046. Felip. ASCO 2022. Abstr 9003. NCT03625323.

# TACTI-002 Part A: Response Rates by PD-L1 TPS in Treatment Naive NSCLC

| Tumor Response per iRECIST, n (%) | Tumor Response by Central PD-L1 Status (iRECIST, Unconfirmed; n = 87) | | | | |
|---|---|---|---|---|---|
| | <1% (n = 32) | 1%-49% (n = 36) | ≥50% (n = 19) | ≥1% (n = 55) | <50% (n = 68) |
| ORR | 9 (28.1) | 15 (41.7) | 10 (52.6) | 25 (45.5) | 24 (35.3) |
| DCR | 22 (68.8) | 28 (77.8) | 15 (79.0) | 43 (78.2) | 50 (73.5) |




- 8.6% of patients with confirmed response experienced PD in ≤6 mo

# TACTI-002 Part A: AEs in ≥15% of Patients

| AE, n (%) | All Patients (n = 114) | | | |
|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Grade 5 |
| Dyspnea | 39 (34.2) | 13 (11.4) | 1 (0.9) | 1 (0.9) |
| Asthenia | 35 (30.7) | 2 (1.8) | -- | -- |
| Decreased appetite | 27 (23.7) | 1 (0.9) | -- | -- |
| Cough | 27 (23.7) | 2 (1.8) | -- | -- |
| Anemia | 24 (21.1) | 3 (2.6) | -- | -- |
| Fatigue | 23 (20.2) | 1 (0.9) | -- | -- |
| Pruritus | 22 (19.3) | -- | -- | -- |
| Constipation | 20 (17.5) | 1 (0.9) | -- | -- |
| Diarrhea | 18 (15.8) | 1 (0.9) | -- | -- |
| Nausea | 18 (15.8) | 2 (1.8) | -- | -- |

- 11 patients (9.6%) discontinued treatment due to TRAEs

| AE, n (%) | All Patients (n = 114) | | | |
|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Grade 5 |
| Hypothyroidism* | 10 (8.8) | -- | -- | -- |
| Pneumonitis | 4 (3.5) | -- | 1 (0.9) | 1 (0.9) |
| Hyperthyroidism | 6 (5.3) | -- | -- | -- |
| Diarrhea | 18 (15.8) | 1 (0.9) | -- | -- |
| Thyroiditis | 1 (0.9) | -- | -- | -- |
| Hepatitis* | 3 (2.6) | -- | 1 (0.9) | -- |
| Nephritis + acute kidney injury | 1 (0.9) | 1 (0.9) | -- | -- |
| Adrenal insufficiency | 1 (0.9) | -- | -- | -- |
| Infusion-related reaction | 1 (0.9) | 1 (0.9) | -- | -- |

*Immune related.

Felip. ASCO 2022. Abstr 9003.

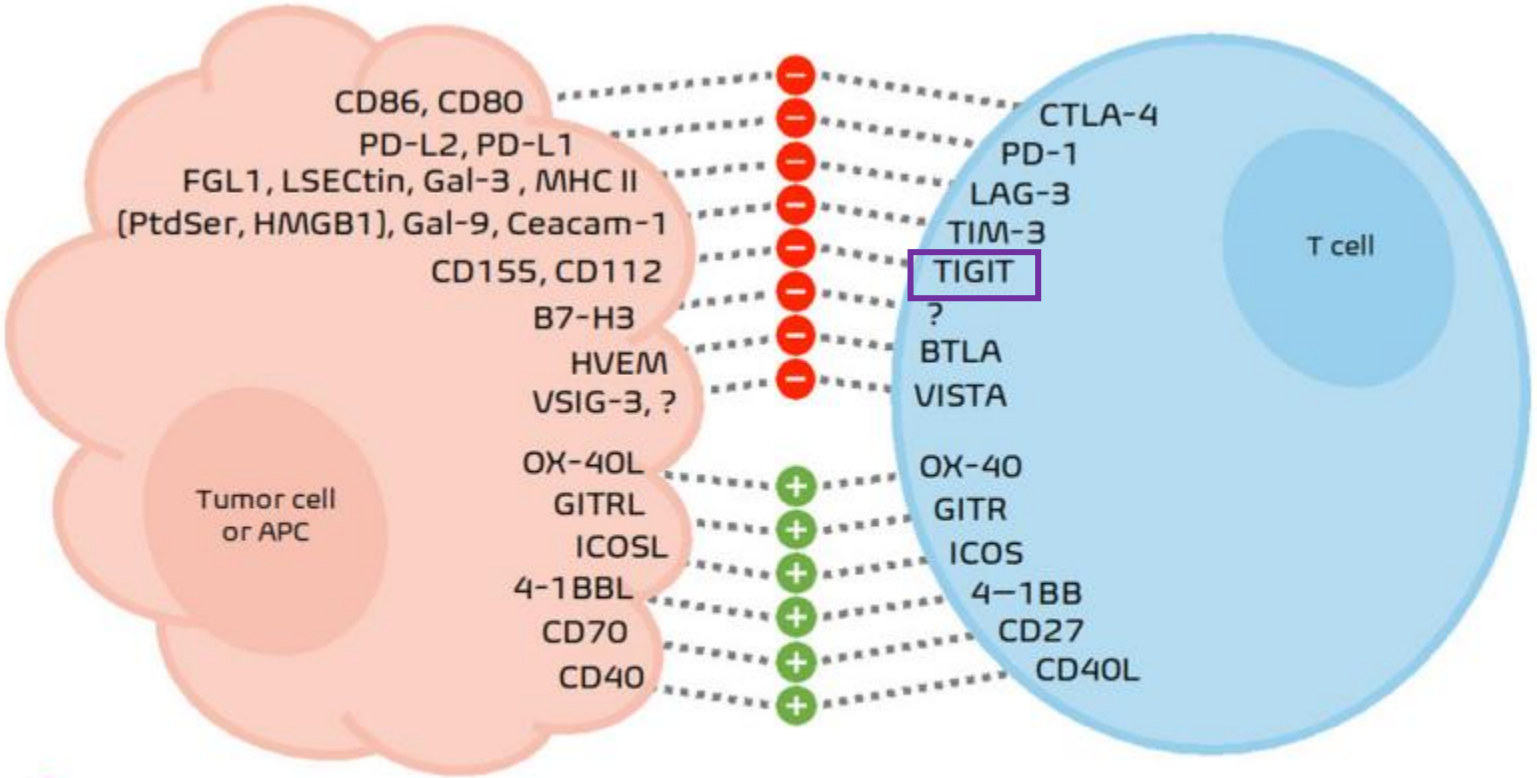
# TACTI-002 Part B: Efficacy as Second-line Therapy in NSCLC After PD-1/PD-L1 Therapy

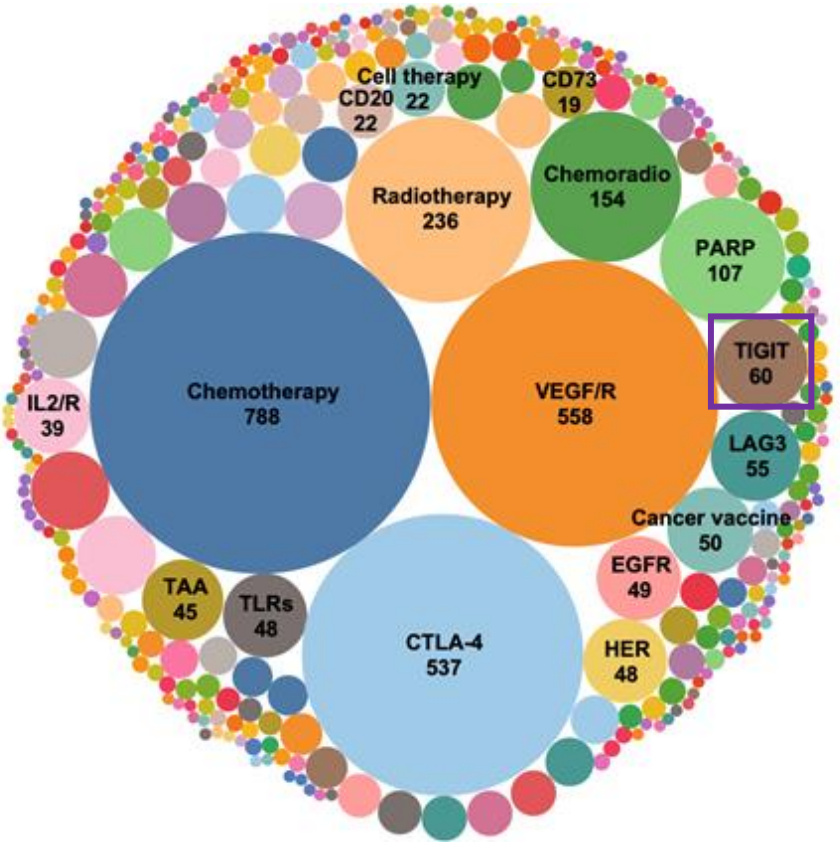
| Baseline Characteristics, n (%) | Stage 1 (n = 23) |
|---|---|
| Median age, yr (range) | 67.0 (46-84) |
| Female | 10 (43.5) |
| Male | 13 (56.5) |
| ECOG PS<br>▪ 0<br>▪ 1 | <br>7 (30.4)<br>16 (69.6) |
| Current or former smoker | 21 (91.3) |
| Histology<br>▪ Squamous<br>▪ Non-squamous | <br>5 (21.7)<br>18 (78.3) |
| Prior PD-1/PD-L1<br>▪ With CT | 100%<br>61% |

| Tumor Response per RECIST 1.1, n (%) | Stage 1 (n = 23) |
|---|---|
| ORR [95% CI] | 1 (4.4) [0.11-21.95] |
| PR | 1 (4.4) |
| SD | 7 (30.4) |
| PD | 14 (60.9) |
| NE | 1 (4.4) |
| DCR | 8 (34.8) |

Triebel. Non-Small Cell Cancer Drug Development Summit. 2021.

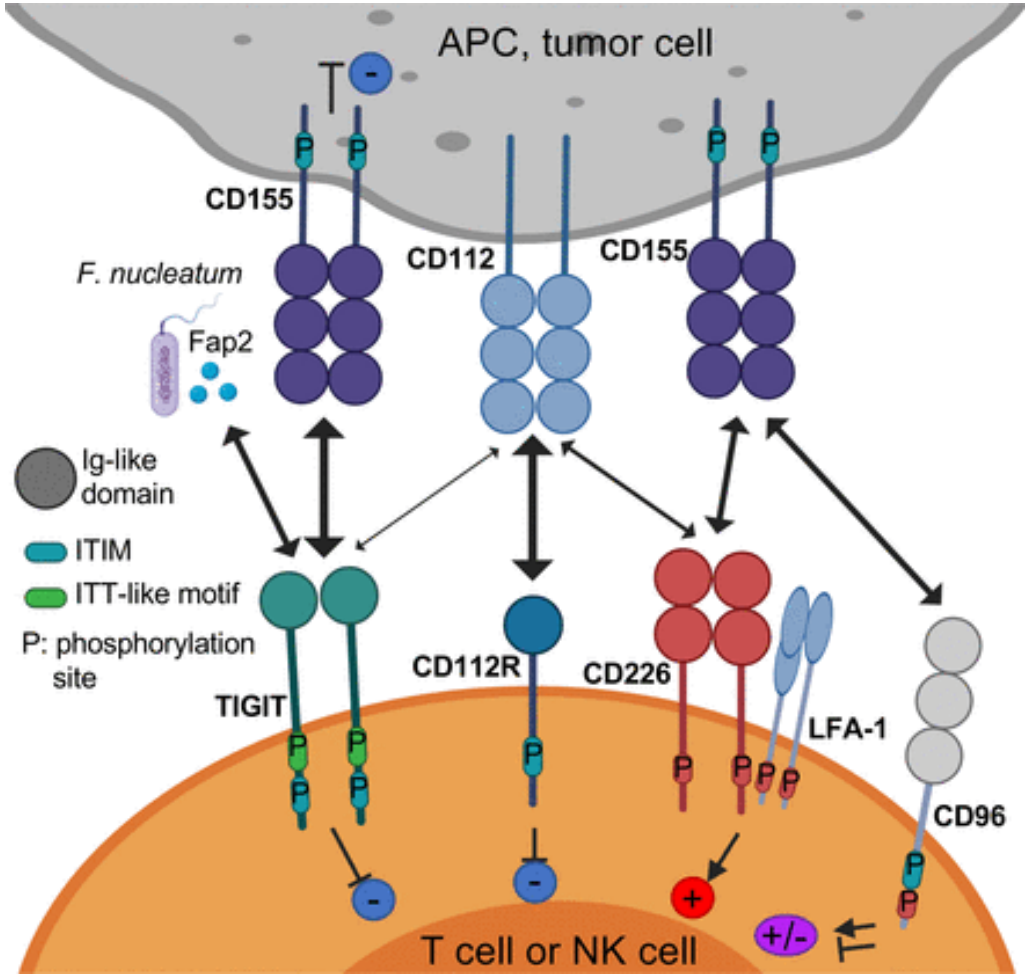
# Immune checkpoints



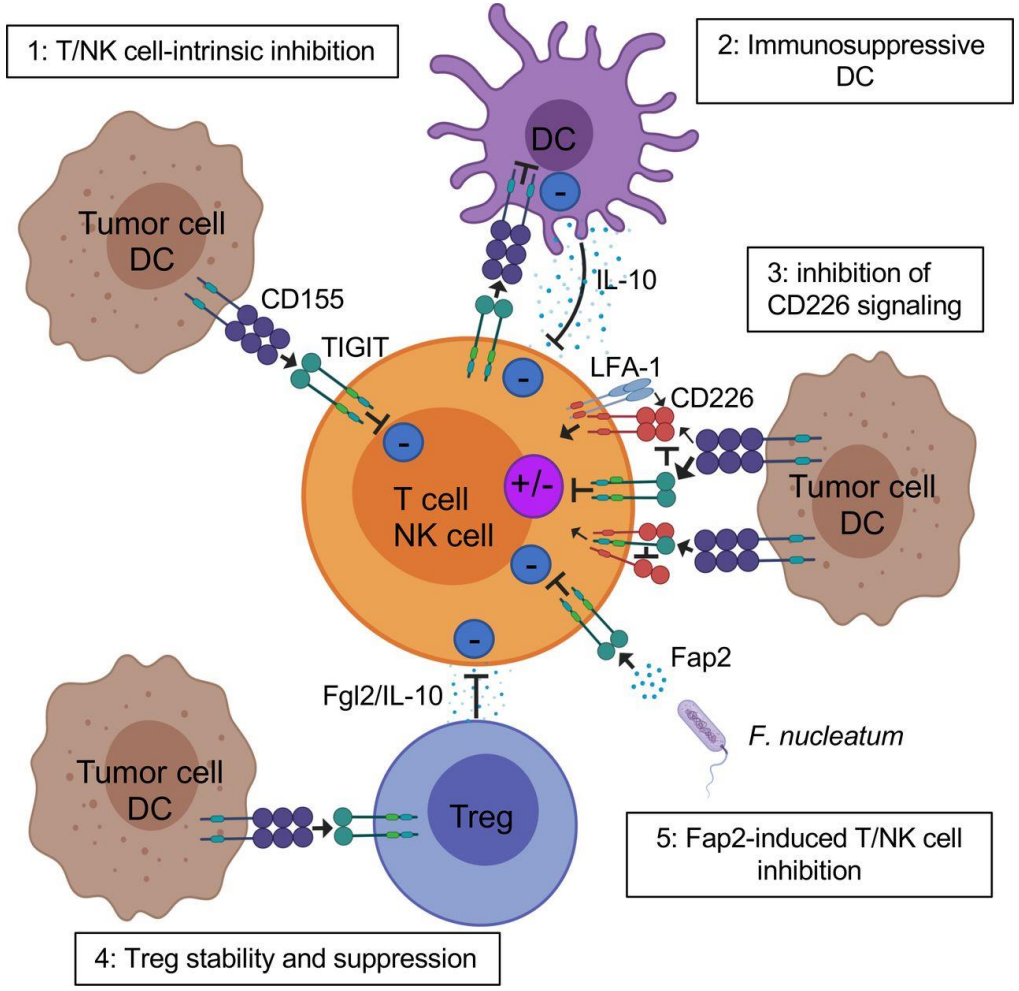




*memo-Magazine of European Medical Oncology* 14.2 (2021): 135-142.

# TIGIT/CD226/CD96/CD112R Axis in Cancer



# TIGIT Axis Inhibits Innate and Adaptive Immunity Through Multiple Mechanisms



# Multiple TIGIT mAb Are Currently in Development

| Agent | Fc Structure | Indication | Phase |
|---|---|---|---|
| **AB-154 (domvanalimab)** | Fc inactive | NSCLC, melanoma | II/III |
| **AB-308** | Fc active | Advanced solid tumors | I |
| **BGB-A1217 (ociperlimab)** | Fc active | Advanced solid tumors | I/II/III |
| **BMS-986207** | Nondisclosed | Advanced solid tumors | I/II |
| **COM-902** | Nondisclosed | Advanced solid tumors | I |
| **EOS-448** | Fc active | Advanced solid tumors | I/II |
| **IBI-939** | Nondisclosed | Advanced solid tumors, lung | I |
| **JS006** | Nondisclosed | Advanced solid tumors | I |
| **MK-7684 (vibostolimab)** | Nondisclosed | Advanced solid tumors, NSCLC, ES-SCLC | I/II/III |
| **Tiragolumab** | Fc active | Advanced solid tumors, cervical, esophageal/gastric/GEJ, head and neck, melanoma, NSCLC, rectal, SCLC | I/II/III |

Clinicaltrials.gov.

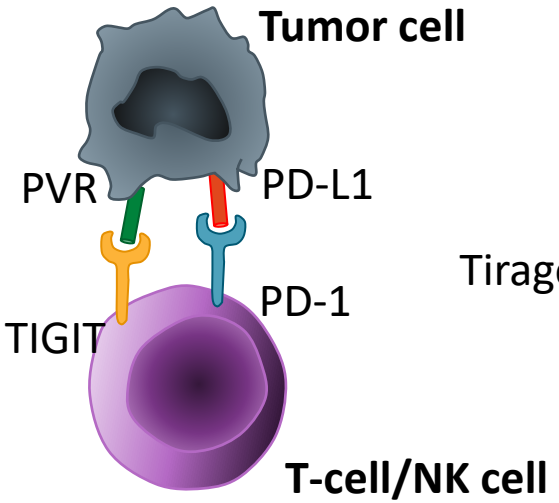
Slide credit: clinicaloptions.com

# Ongoing clinical trials of anti-TIGIT agents combined with PD-1/PD-L1 blockade

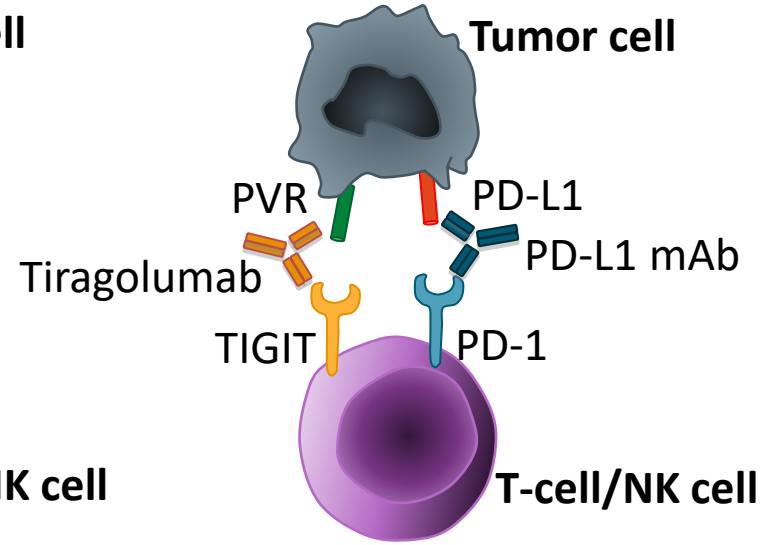
| Trial | Cancer | Line | Anti-TIGIT | Treatment | Phase |
|---|---|---|---|---|---|
| NCT04294810 (SKYSCRAPER-01) | Advanced NSCLC (high PD-L1) | 1 | Tiragolumab | Tiragolumab+atezolizumab vs. atezolizumab | III |
| NCT04619797 (SKYSCRAPER-06) | Advanced non-squamous NSCLC | 1 | Tiragolumab | Tiragolumab+atezolizumab+pemetrexed+platinum vs. pembrolizumab+pemeterexed+platinum | II/III |
| NCT04738487 (KEYVIBE-003) | Stage IV NSCLC (PD-L1+) | 1 | Vibostolimab | Vibostolimab+pembrolizumab vs. pembrolizumab | III |
| NCT05226598 (KEYVIBE-007) | Stage IV NSCLC | 1 | Vibostolimab | Vibostolimab+pembrolizumab+chemo vs. pembrolizumab+chemo | III |

# Tiragolumab (MTIG7192A) is an Anti-TIGIT mAb That Blocks TIGIT/PVR Interaction

- Tiragolumab is a fully human IgG1 κ Fc-active anti-TIGIT mAb that blocks binding of TIGIT with PVR[1,2]

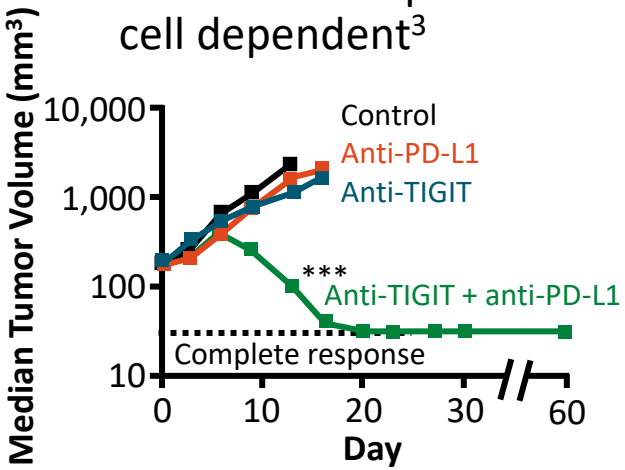


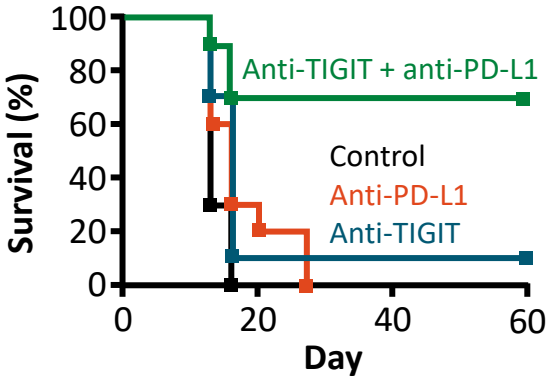

TIGIT binds to PVR, resulting in inhibitory response

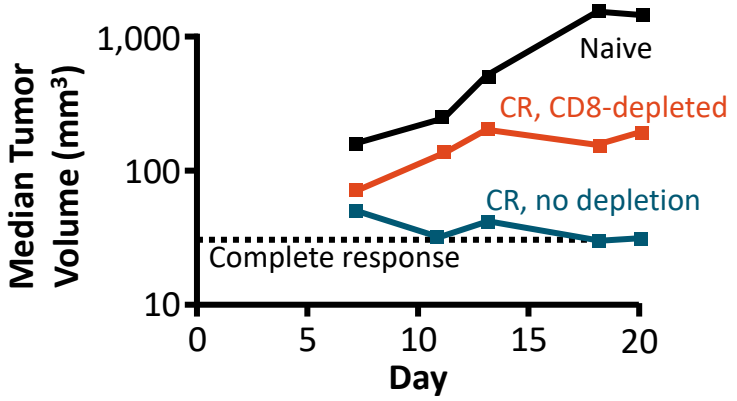



Blocking TIGIT binding restores antitumor response and complements PD-1/PD-L1 activity

- In preclinical models, combination TIGIT and PD-L1 blockade with mAb acts synergistically to control tumors and improve survival; these effects are T-cell dependent[3]



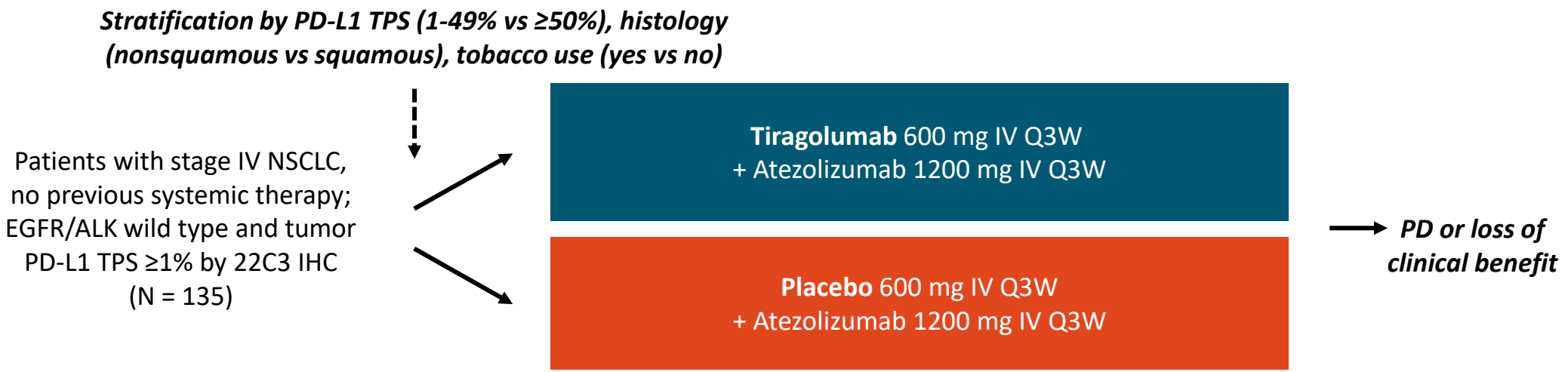




***$P$ <.001.

1. Rodriguez-Abreu. ASCO 2020. Abstr 9503. 2. Manieri. Trends Immunol. 2017;38:20. 3. Johnston. Cancer Cell. 2014;26:923.

# CITYSCAPE: Phase II Trial of Tiragolumab + Atezolizumab vs Atezolizumab in Patients With PD-L1+ NSCLC

- Randomized, double-blind phase II trial

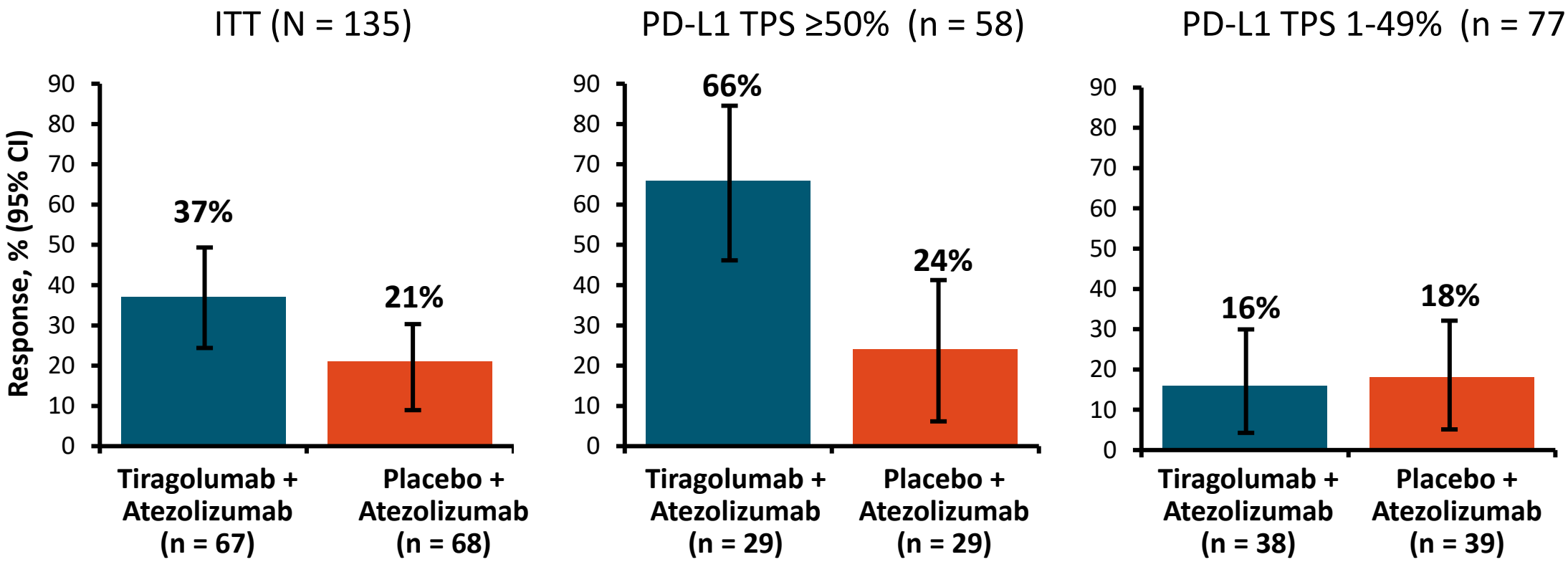



- Primary endpoint: ORR and PFS
- Secondary endpoints: Safety, DoR, OS, PROs, efficacy analysis by PD-L1

Cho. ESMO 2021. Abstr LBA2. Rodriguez-Abreu. ASCO 2020. Abstr 9503.

# CITYSCAPE: Overall Response Rate with Atezolizumab ± Tiragolumab

**Confirmed ORR at Median Follow-up of 5.9 Mo**



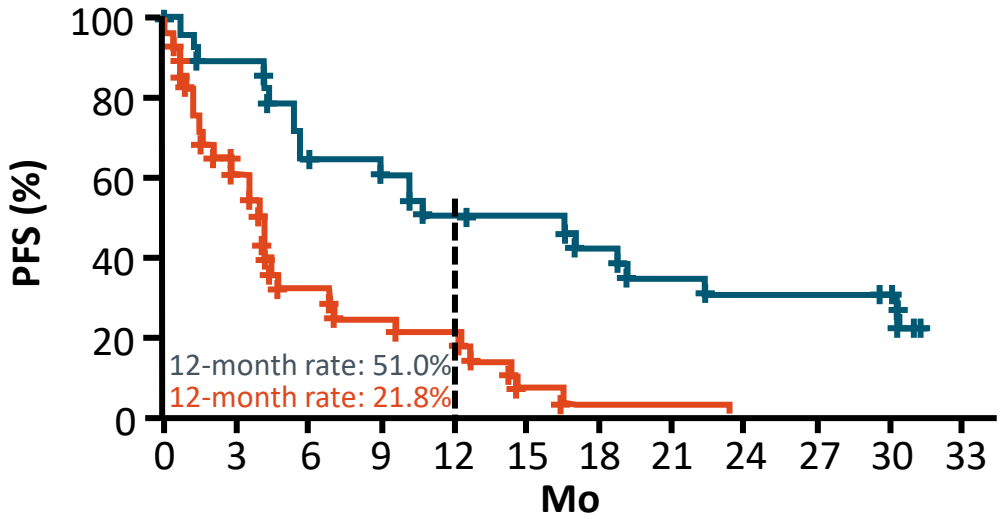

Updated data cutoff: December 2, 2019

Rodriguez-Abreu. ASCO 2020. Abstr 9503.

# CITYSCAPE: Progression-Free Survival with Atezolizumab ± Tiragolumab

## PD-L1 TPS ≥50% (n = 58)

| | Events n (%) | Median PFS, mo (95% CI) | PFS HR (95% CI) | ORR, % | Median DoR mo (95% CI) |
|---|---|---|---|---|---|
| Tira + atezo | 21 (72.4) | 16.6 (5.5–22.3) | 0.29* | 69.0 | 15.7 (9.1–NE) |
| Placebo + atezo | 28 (96.6) | 4.1 (2.1–6.8) | (0.15–0.53) | 24.1 | 8.2 (5.6–10.4) |

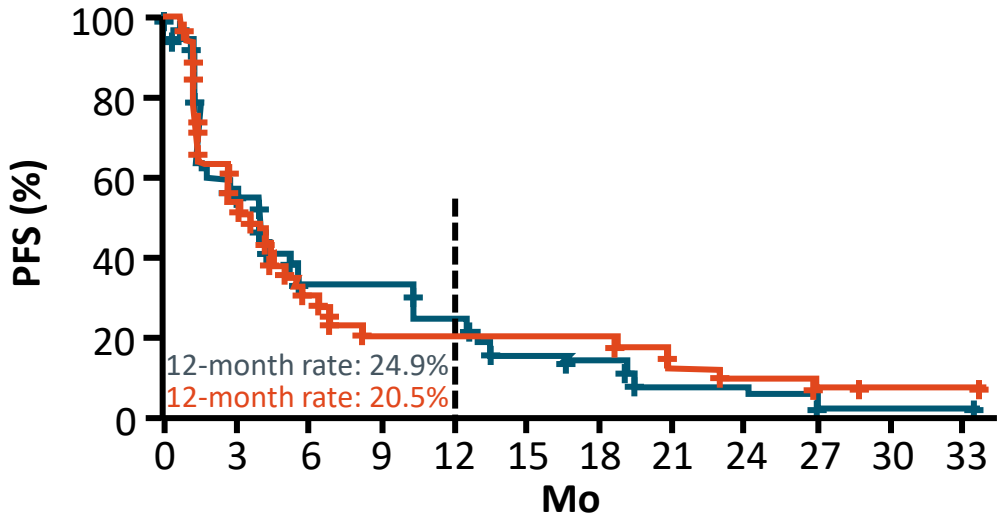



No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T + A | 29 | 26 | 19 | 17 | 14 | 13 | 11 | 9 | 8 | 8 | 7 | NE |
| P + A | 29 | 17 | 9 | 7 | 6 | 2 | 1 | 1 | NE | NE | NE | NE |

## PD-L1 TPS 1-49% (n = 77)

| | Events n (%) | Median PFS, mo (95% CI) | PFS HR (95% CI) | ORR, % | Median DoR mo (95% CI) |
|---|---|---|---|---|---|
| Tira + atezo | 36 (94.7) | 4.0 (1.6–5.6) | 1.07* | 15.8 | 17.8 (8.3–24.2) |
| Placebo + atezo | 36 (92.3) | 3.6 (1.4–5.5) | (0.67–1.71) | 17.9 | 18.8 (15.9–22.8) |




No. at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T + A | 38 | 22 | 12 | 12 | 9 | 6 | 5 | 3 | 3 | 1 | 1 | 1 |
| P + A | 39 | 21 | 12 | 8 | 8 | 8 | 8 | 5 | 4 | 3 | 2 | 2 |

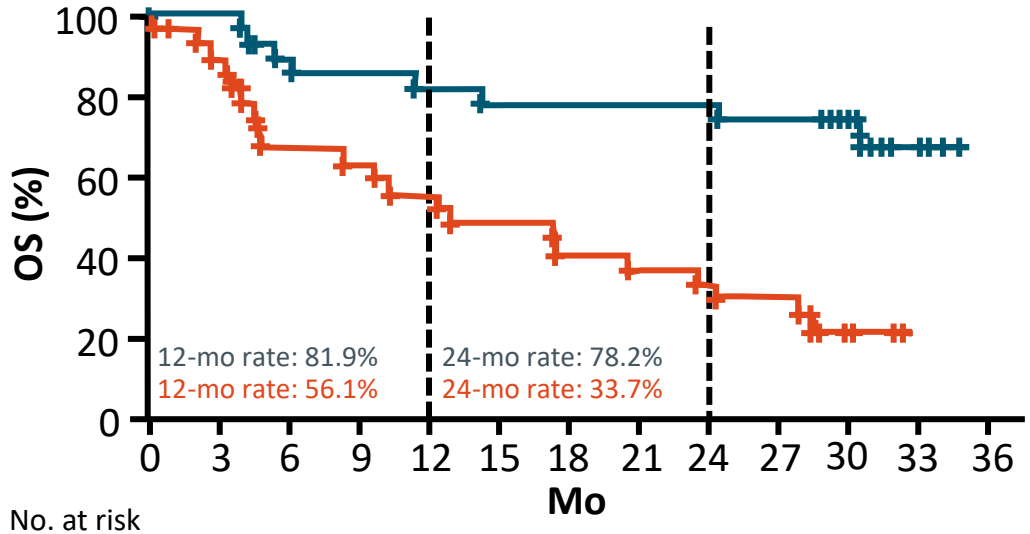
* Unstratified.

Median follow-up of 30.4 mo

# CITYSCAPE: Overall Survival with Atezolizumab ± Tiragolumab

## PD-L1 TPS ≥50% (n = 58)

| | Events n (%) | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Tira + atezo | 8 (27.6) | NE (30.3–NE) | 0.23* (0.10–0.53) |
| Placebo + atezo | 21 (72.4) | 12.8 (4.7–24.2) | |

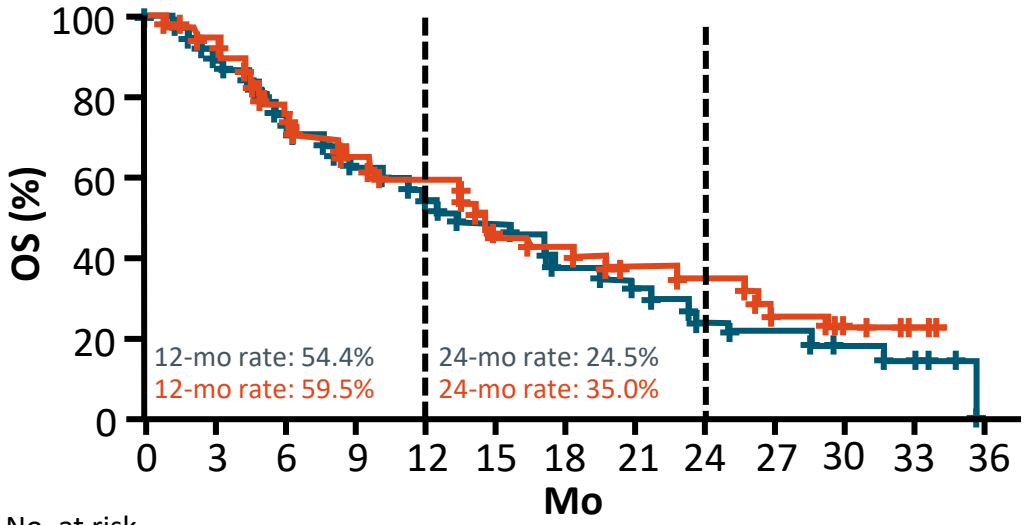



No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T + A | 29 | 29 | 24 | 23 | 22 | 21 | 21 | 21 | 21 | 20 | 15 | 4 | NE |
| P + A | 29 | 25 | 18 | 17 | 15 | 13 | 11 | 10 | 9 | 8 | 3 | NE | NE |

## PD-L1 TPS 1-49% (n = 77)

| | Events n (%) | Median OS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Tira + atezo | 32 (84.2) | 13.3 (8.0–20.7) | 1.16* (0.70–1.94) |
| Placebo + atezo | 28(71.8) | 14.5 (8.3–25.6) | |




No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T + A | 38 | 34 | 28 | 23 | 20 | 18 | 14 | 12 | 9 | 8 | 5 | 4 | NE |
| P + A | 39 | 35 | 28 | 24 | 22 | 17 | 16 | 13 | 12 | 9 | 5 | 2 | NE |

* Unstratified.

Median follow-up of 30.4 mo

Cho. ESMO IO 2021. Abstr LBA2.

# CITYSCAPE: Safety with Atezolizumab ± Tiragolumab

| Event | Tiragolumab + Atezo (n = 67) | Placebo + Atezo (n = 68) |
|---|---|---|
| Median treatment duration, mo (range) | 4.99 (0-34.5) | 2.81 (0-30.3) |
| Any-cause AEs, n (%) | 66 (98.5) | 66 (97.1) |
| ▪ Grade 3/4 | 35 (52.2) | 27 (39.7) |
| ▪ Grade 5 | 3 (4.5) | 7 (10.3) |
| ▪ Serious AEs | 35 (52.2) | 28 (41.2) |
| Treatment-related AEs, n (%) | 55 (82.1) | 48 (70.6) |
| ▪ Grade 3/4 | 15 (22.4) | 17 (25.0) |
| ▪ Grade 5 | 2 (3.0) | 0 |
| ▪ Serious AEs | 14 (20.9) | 12 (17.6) |
| Immune-mediated AEs, n (%) | 51 (76.1) | 32 (47.1) |
| ▪ Grade 3/4 | 13 (19.4) | 11 (16.2) |
| AEs leading to dose modification/interruption, n (%) | 33 (49.3) | 24 (35.3) |
| AEs leading to treatment discontinuation, n (%) | 10 (14.9) | 9 (13.2) |

Median follow-up of 30.4 mo

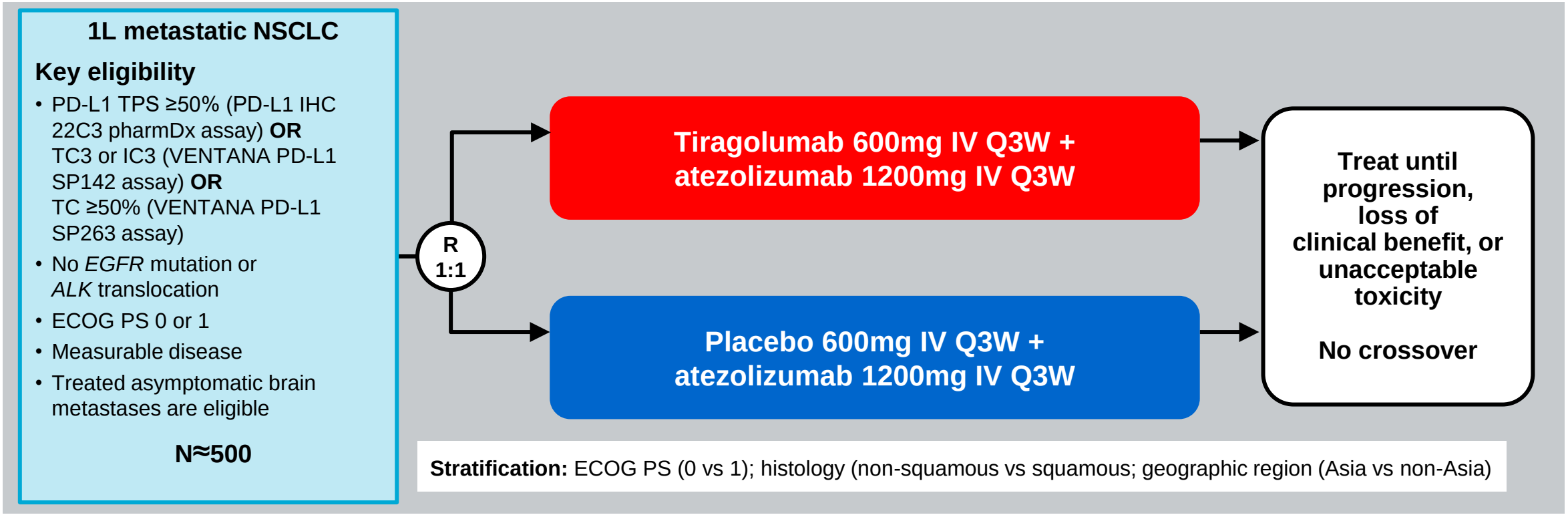
# skySCRAPER-01

GO41717

**A phase III, randomised, double-blinded, placebo-controlled study of tiragolumab, an anti-TIGIT antibody, in combination with atezolizumab compared with placebo in combination with atezolizumab in patients with previously untreated locally advanced** unresectable **or metastatic PD-L1–high non-small cell lung cancer**

Clinicaltrials.gov (NCT04294810)

# SKYSCRAPER-01: study design and co-primary endpoints




**Co-primary endpoints**
- PFS by investigator assessment according to RECIST v1.1
- OS

Clinicaltrials.gov (NCT04294810)

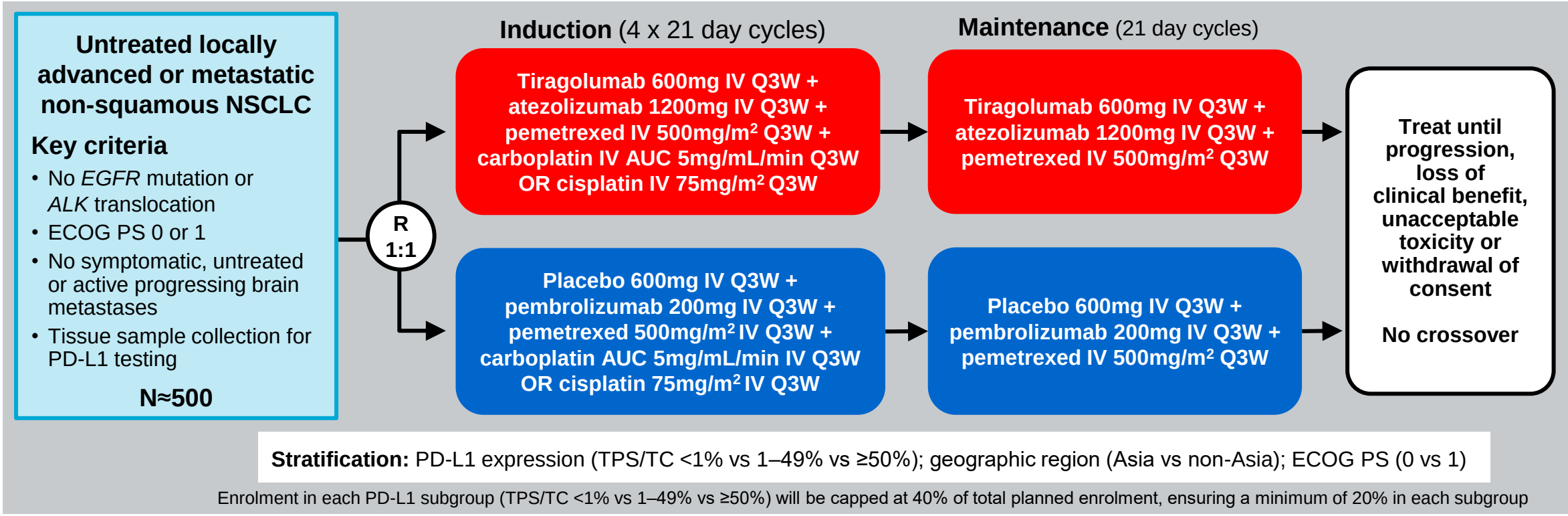
# skySCRAPER·06

BO42592

**A phase II/III, randomised, double-blind, placebo-controlled study of tiragolumab in combination with atezolizumab plus pemetrexed and carboplatin/cisplatin versus pembrolizumab plus pemetrexed and carboplatin/cisplatin in patients with previously untreated advanced non-squamous non-small cell lung cancer**

Clinicaltrials.gov (NCT04619797)

# SKYSCRAPER-06: study design and co-primary endpoints




**Co-primary endpoints**
- Phase II: ORR (INV-assessed)
- Phase II/III: PFS (INV-assessed)
- Phase III: OS

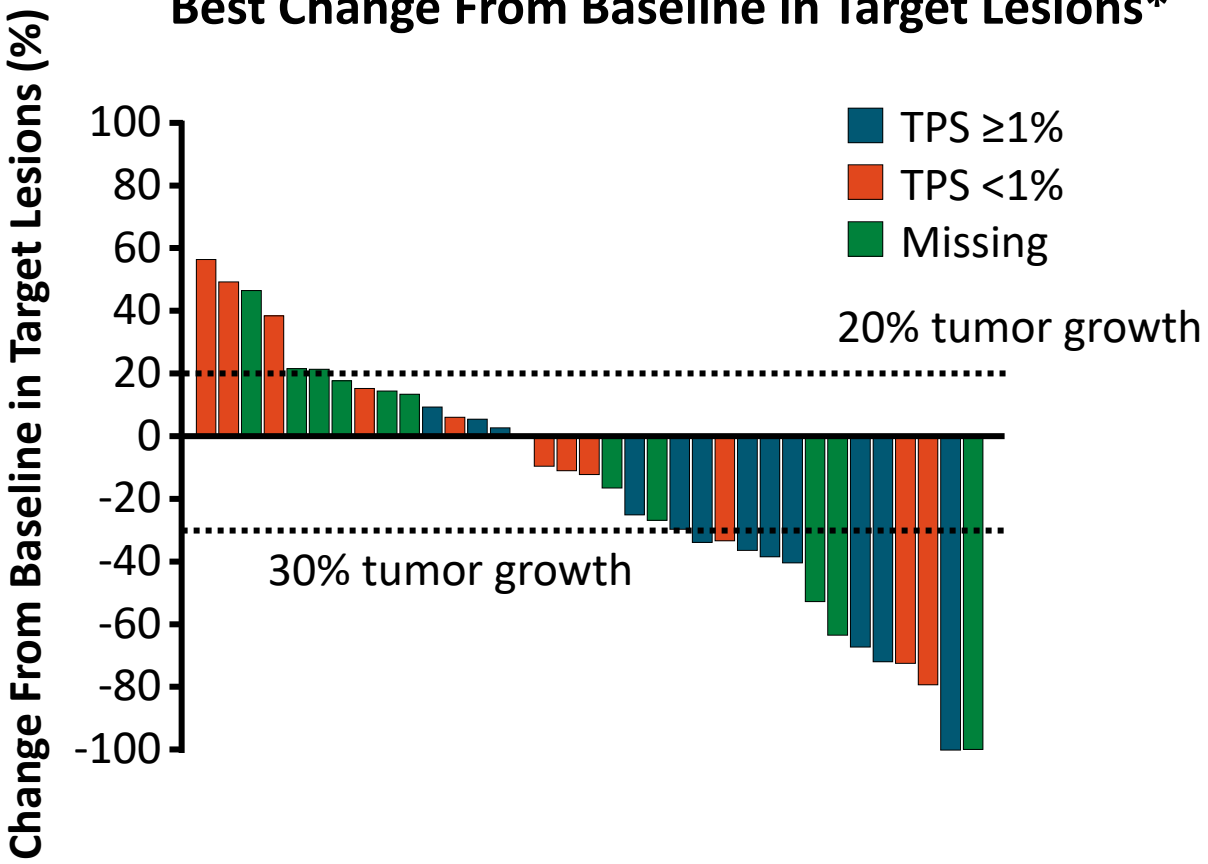
Clinicaltrials.gov (NCT04619797)

# Ongoing clinical trials of anti-TIGIT agents combined with PD-1/PD-L1 blockade

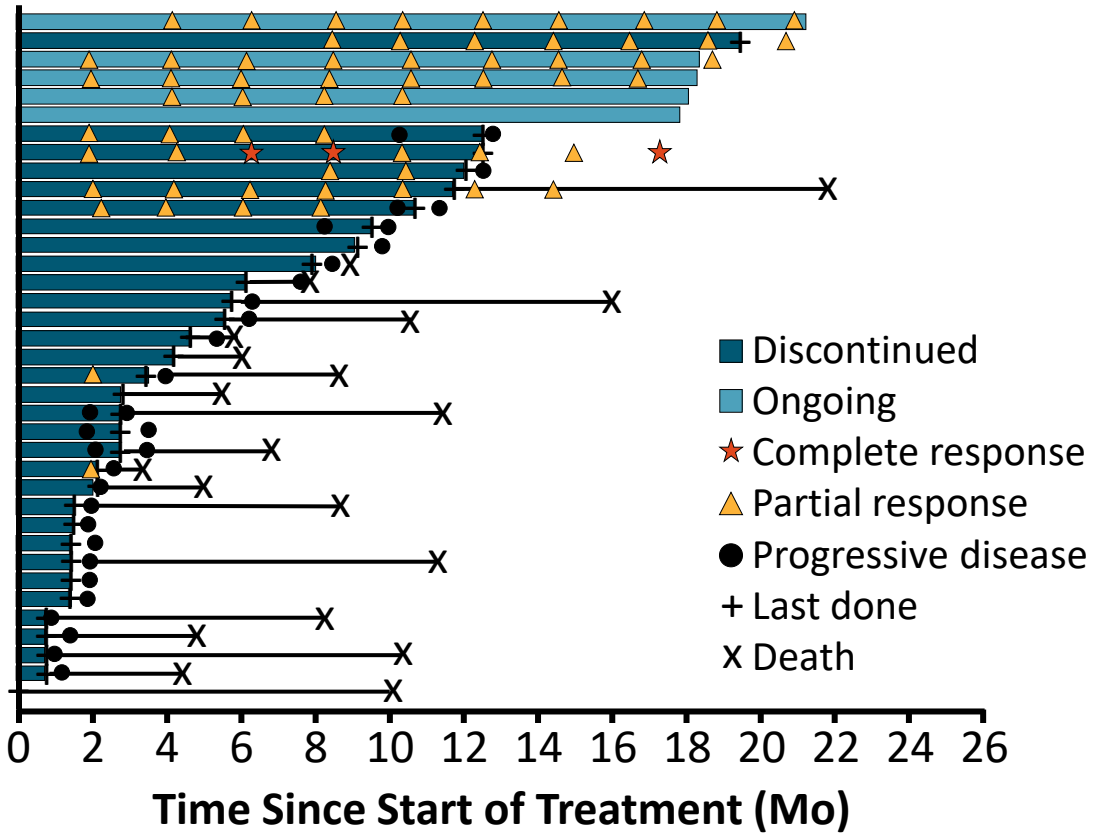
| Trial | Cancer | Line | Anti-TIGIT | Treatment | Phase |
|---|---|---|---|---|---|
| NCT04294810 (SKYSCRAPER-01) | Advanced NSCLC (high PD-L1) | 1 | Tiragolumab | Tiragolumab+atezolizumab vs. atezolizumab | III |
| NCT04619797 (SKYSCRAPER-06) | Advanced non-squamous NSCLC | 1 | Tiragolumab | Tiragolumab+atezolizumab+pemetrexed+platinum vs. pembrolizumab+pemeterexed+platinum | II/III |
| NCT04738487 (KEYVIBE-003) | Stage IV NSCLC (PD-L1+) | 1 | Vibostolimab | Vibostolimab+pembrolizumab vs. pembrolizumab | III |
| NCT05226598 (KEYVIBE-007) | Stage IV NSCLC | 1 | Vibostolimab | Vibostolimab+pembrolizumab+chemo vs. pembrolizumab+chemo | III |

# Phase I Trial of Vibostolimab + Pembrolizumab in Patients With NSCLC: Investigator-Assessed Response

## Best Change From Baseline in Target Lesions*




## Response Duration

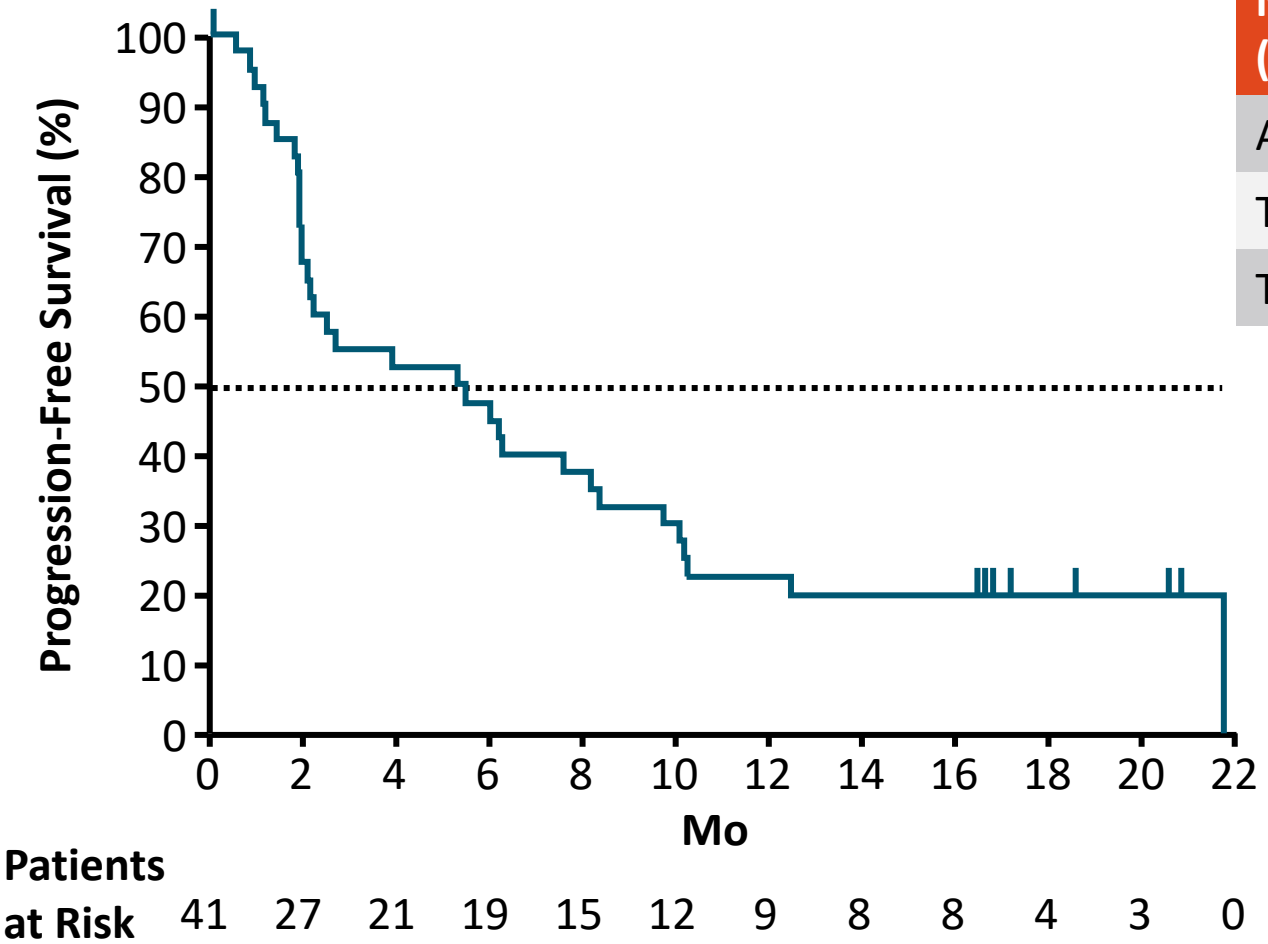



*Includes all patients with at least 1 post-baseline target lesion measurement (n = 35).
Database cutoff date: March 3, 2020.

Niu. ESMO 2020. Abstr 1410P.

Slide credit: clinicaloptions.com

# Phase I Trial of Vibostolimab + Pembrolizumab in Patients With NSCLC: PFS




| Median PFS, Mo (95% CI) | Vibostolimab + Pembro (n = 41) |
|---|---|
| All patients (N = 41) | 5.4 (2.1-8.2) |
| TPS ≥1% (n = 13) | 8.4 (3.9-10.2) |
| TPS <1% (n = 12) | 4.1 (1.9-NR) |

Niu. ESMO 2020. Abstr 1410P.

Slide credit: clinicaloptions.com

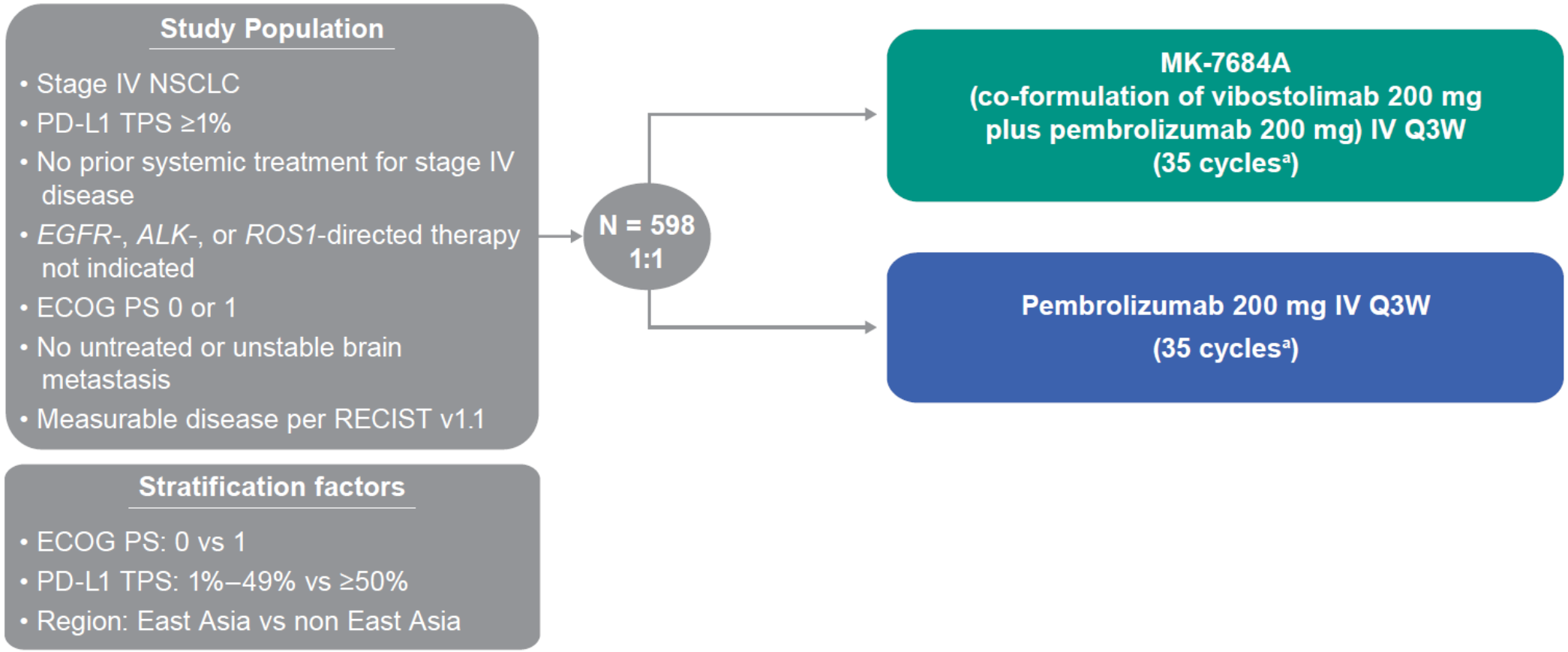
# KEYVIBE-003: Randomized, Double-Blind, Phase 3 Study of First-Line Pembrolizumab With and Without Vibostolimab (Anti-TIGIT) in Patients With PD-L1–Positive Metastatic NSCLC

B.C. Cho[1]; R.A. Juergens[2]; Y. Cheng[3]; G. de Castro, Jr[4]; M. Erman[5]; J.R. Bauman[6]; T. Takahashi[7]; P. Schwarzenberger[8]; C. Li[8]; M.C. Pietanza[8]; J.C.-H. Yang[9]

[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [2]McMaster University, Juravinski Cancer Centre, Hamilton, ON, Canada; [3]Jilin Cancer Hospital, Changchun, China; [4]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [5]Hacettepe University Cancer Institute, Ankara, Turkey; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Shizuoka Cancer Center, Sunto-gun, Japan; [8]Merck & Co., Inc., Kenilworth, NJ, USA; [9]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan

Presented at the American Association for Cancer Research Annual Meeting (AACR)
April 8 – 13, 2022
New Orleans, LA, USA

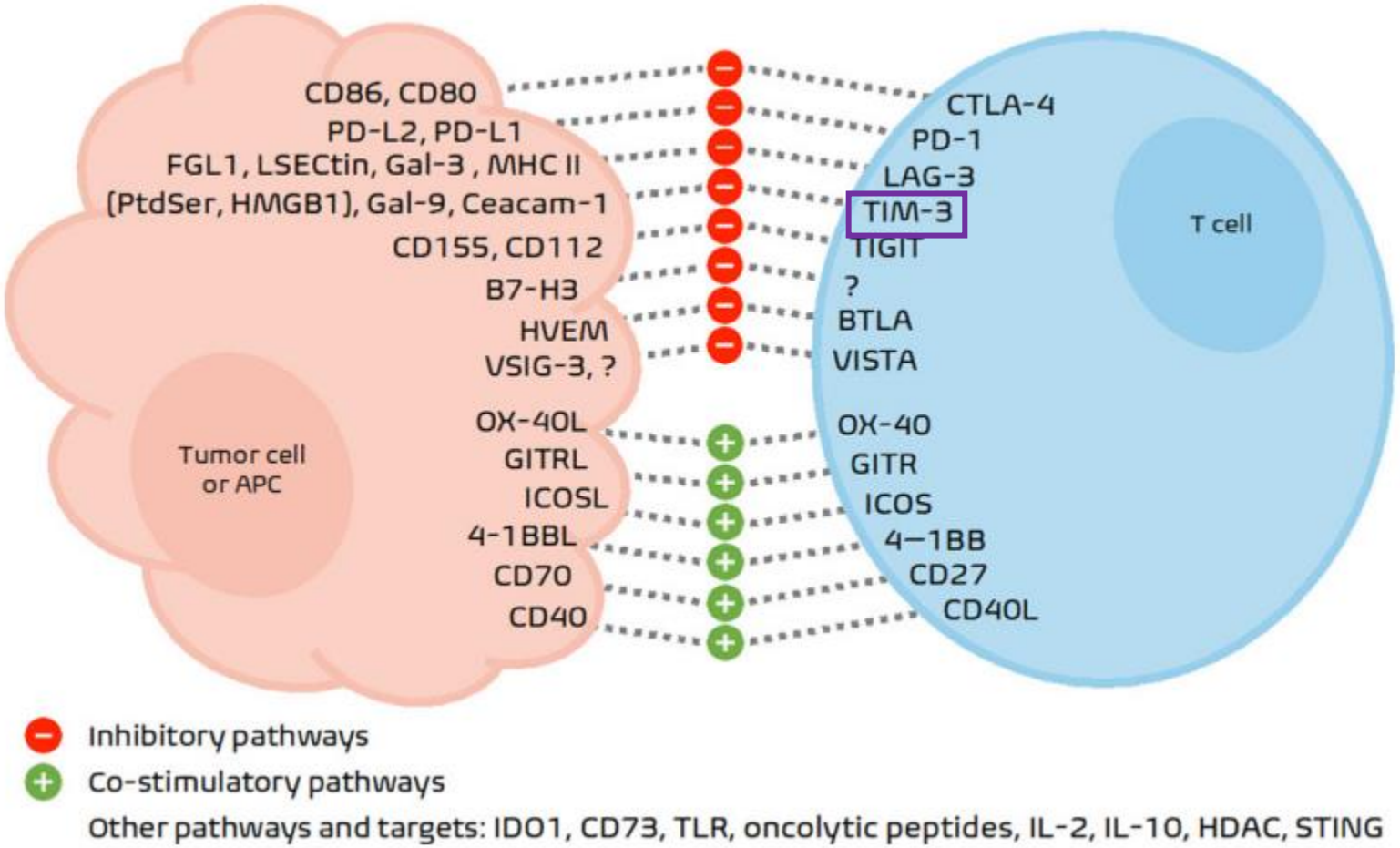
# KEYVIBE-003 Study Design

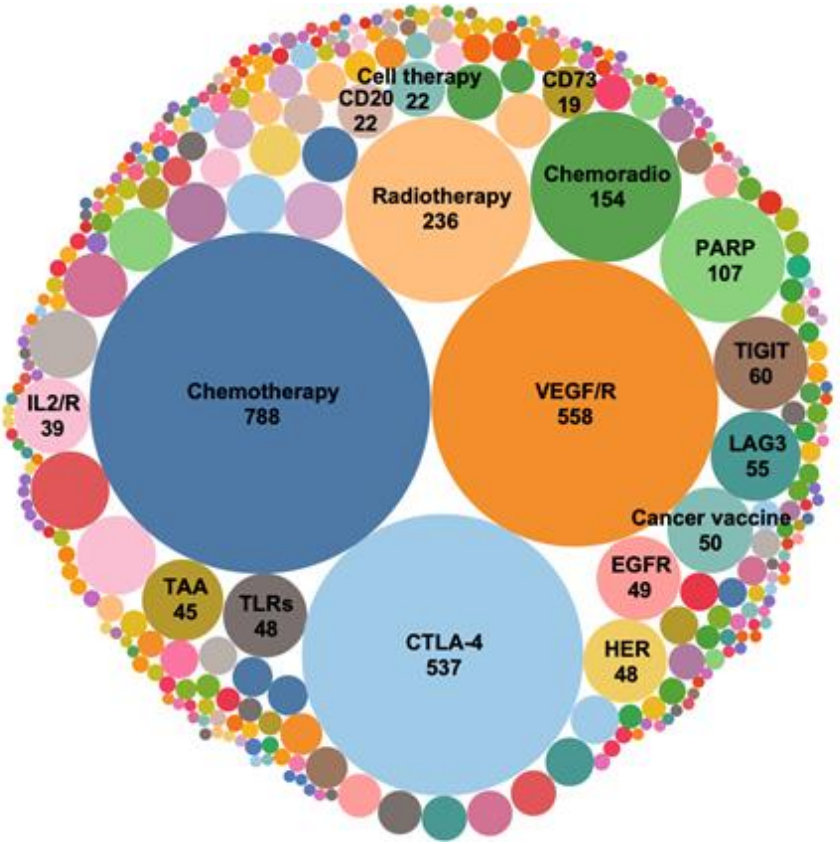



AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PD, progressive disease; Q3W, every 3 weeks; SD, stable disease; TPS, tumor proportion score.

[a] Treatment to continue until completion of 35 cycles (~2 years) or until confirmed PD, unacceptable AEs, intercurrent illness, or investigator decision. Eligible patients with ≥SD may be eligible for 17 additional cycles (~1 year; second course) of MK-7684A or pembrolizumab based on initial randomization upon experiencing PD if there is BICR verified radiographic PD by RECIST v1.1 after initial treatment or the first course is completed or stopped for confirmed CR.

# Immune checkpoints



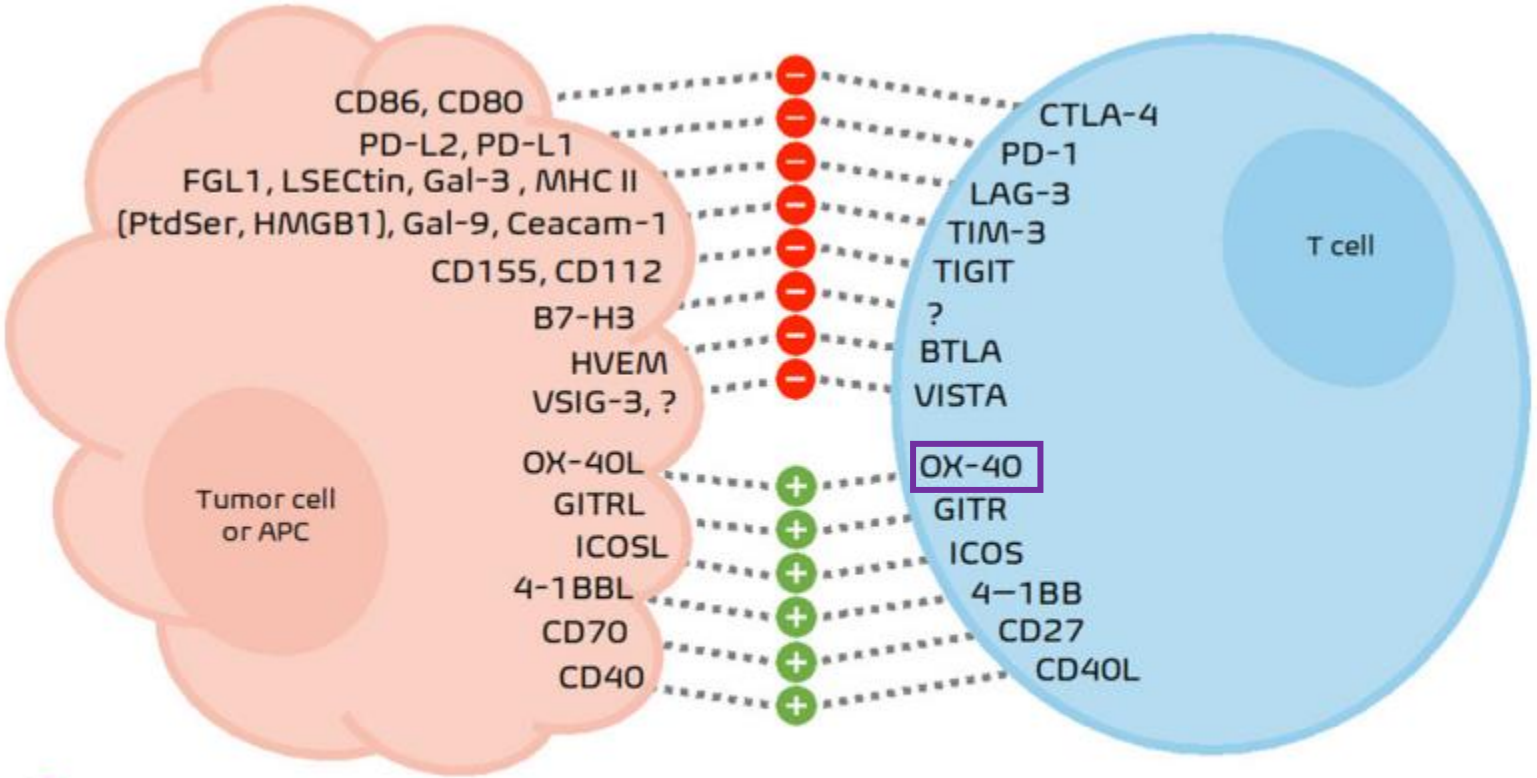

*memo-Magazine of European Medical Oncology* 14.2 (2021): 135-142.

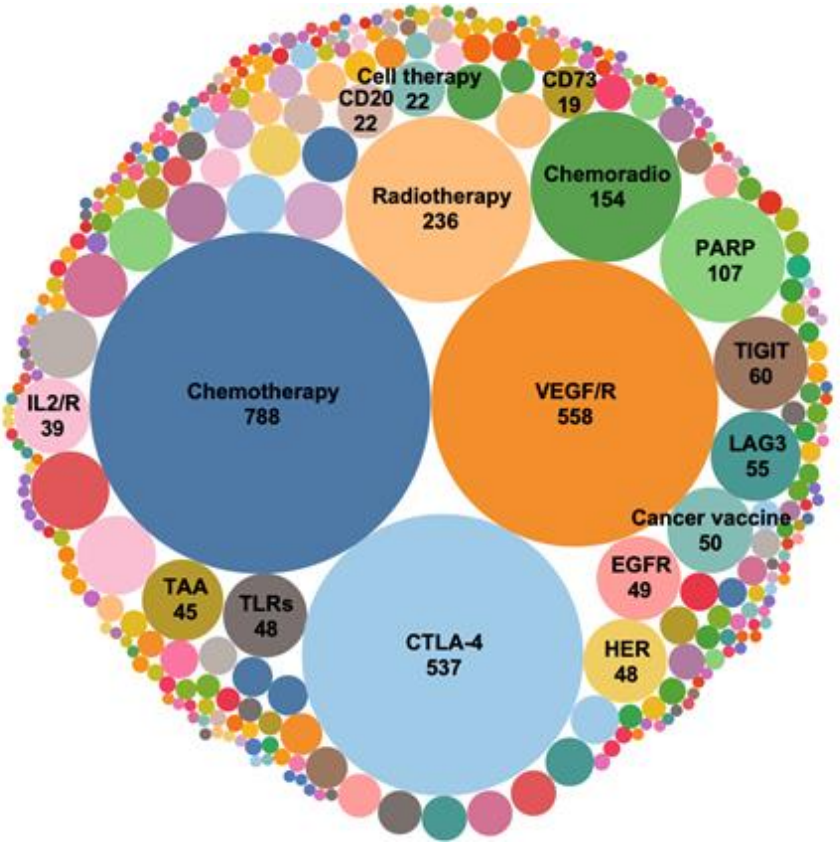
# Ongoing Trials of anti-Tim-3 agents combined with PD-1/PD-L1 blockade

| Clinical Trial | Cancer Type | Treatment Line | Anti-Tim-3 Agent | Immunotherapy | Phase |
|---|---|---|---|---|---|
| NCT03099109 | Advanced solid tumors | ≥2 | LY3321367 | LY3300054 (anti-PD-L1 mAb) | I |
| NCT03307785 | Advanced solid tumors | ≥2 | TSR-022 | TSR-042 (anti-PD-L1 mAb) | I |
| NCT03311412 | Advanced solid tumors and/or lymphomas | ≥2 | Sym023 | Sym021 (anti-PD-1 mAb) | I |
| NCT02817633 (AMBER) Part 1 Part2 cohort B (NSCLC) | Advanced solid tumors | ≥2 | TSR-022 | Nivolumab or TSR-042 (anti-PD-1 mAb) | I |
| NCT03708328 | Advanced solid tumors | ≥2 | RO7121661 (anti-PD-1/ TIM-3 bispecific mAb) | – | I |
| NCT03744468 | Advanced solid tumors | ≥2 | BGB-A425 | Tislelizumab (anti-PD-1 mAb) | I/II |

*ImmunoTargets and therapy* 10 (2021): 9.

# Immune checkpoints




*memo-Magazine of European Medical Oncology* 14.2 (2021): 135-142.

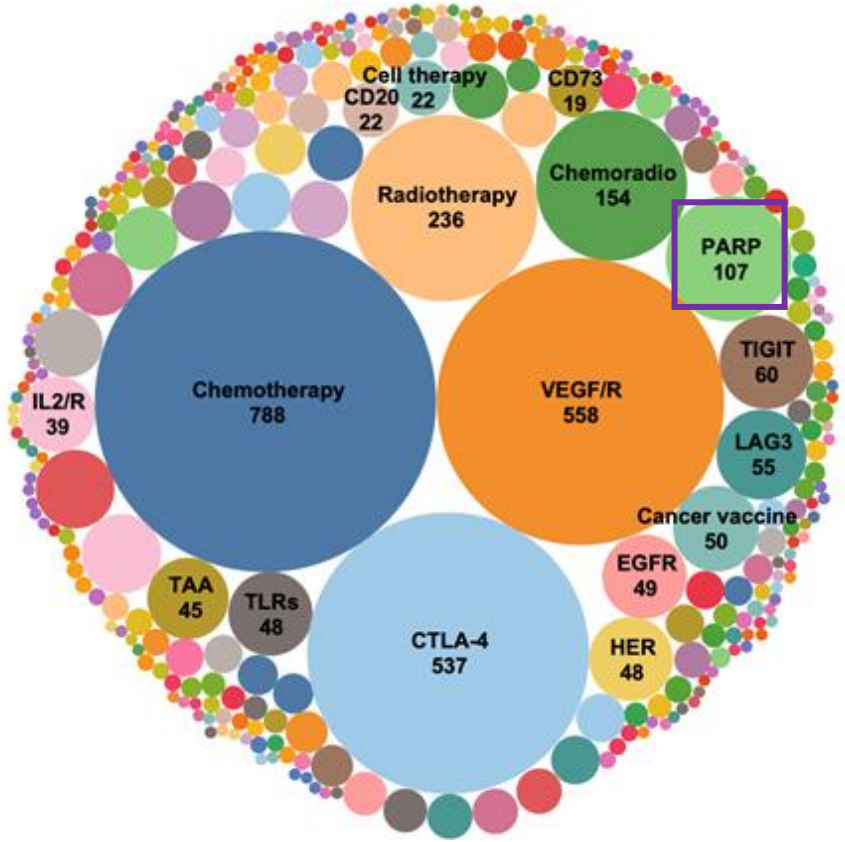
# Ongoing Trials of OX40 agonistic agents combined with PD-1/PD-L1 blockade

| Clinical Trial | Cancer Type | Treatment Line | OX40 Agonistic mAb | Immunotherapy | Phase |
|---|---|---|---|---|---|
| NCT02528357 | Advanced solid tumors | ≥2 | GSK3174998 | Pembrolizumab | I |
| NCT02410512 | Advanced solid tumors | ≥2 | MOXR0916 | Atezolizumab | Ib |
| NCT02554812 | Advanced solid tumors | ≥2 | PF-04518600 (OX40 agonist mAb) | Avelumab | Ib/II |
| NCT02221960 | Advanced solid tumors | ≥2 | MEDI6383 (recombinant human OX40L IgG4P Fc fusion protein) | Durvalumab | I |
| NCT03241173 | Advanced Malignancies | ≥2 | INCAGN01949 | Nivolumab or ipilimumab | I/II |

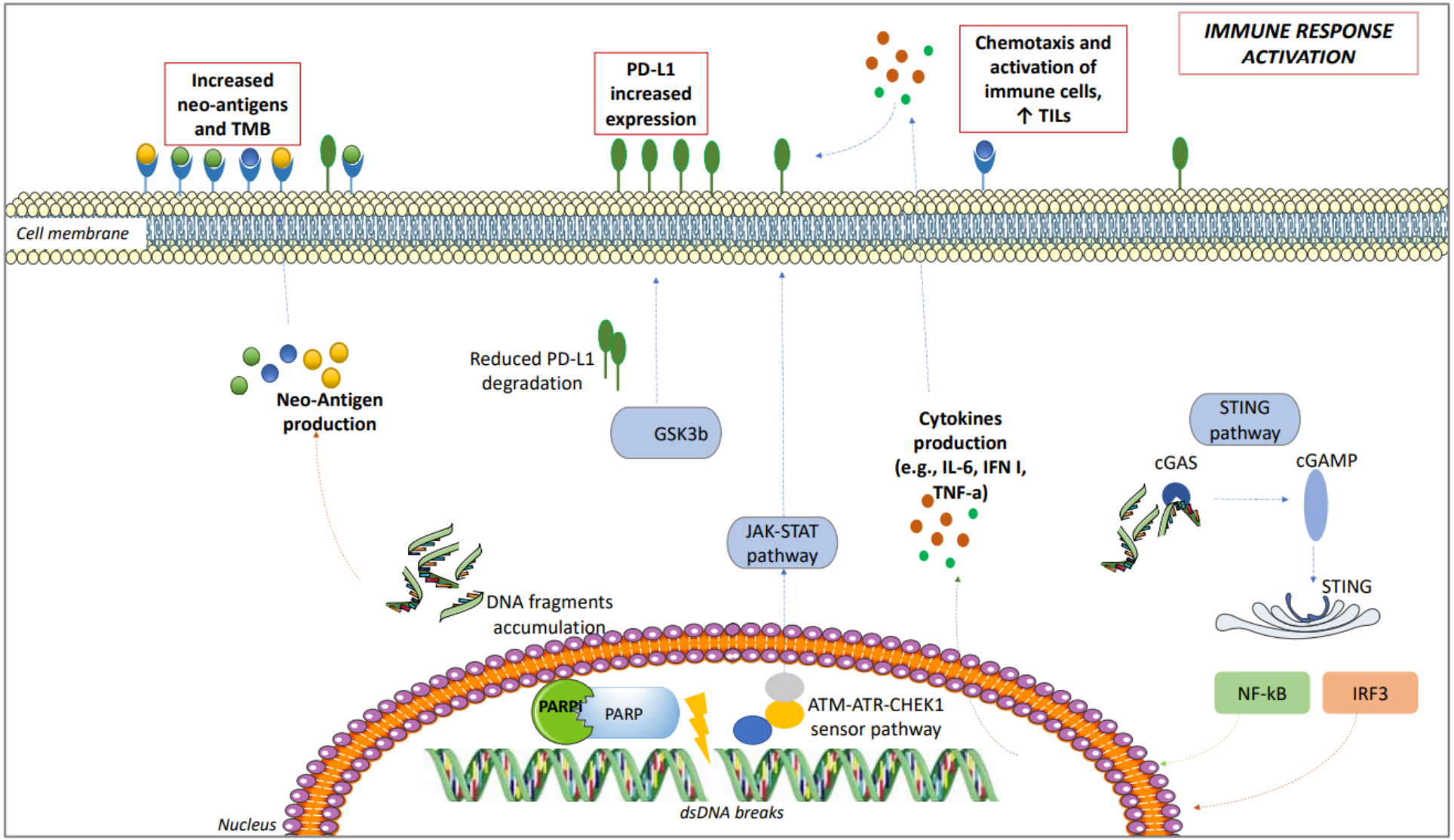
*ImmunoTargets and therapy* 10 (2021): 9.

# Ongoing clinical trials in Metastatic NSCLC

- **PD-1/PD-L1 blockade combination with**
  - **Antiangiogenic drug**
  - **Other checkpoint inhibitors (LAG-3, TIGIT, TI**
  - **PARP inhibitors**
- **Route of PD-1/PD-L1 blockade administra**



# Interplay between PARP inhibitors and ICIs




*International Journal of Molecular Sciences* 23.7 (2022): 3871.

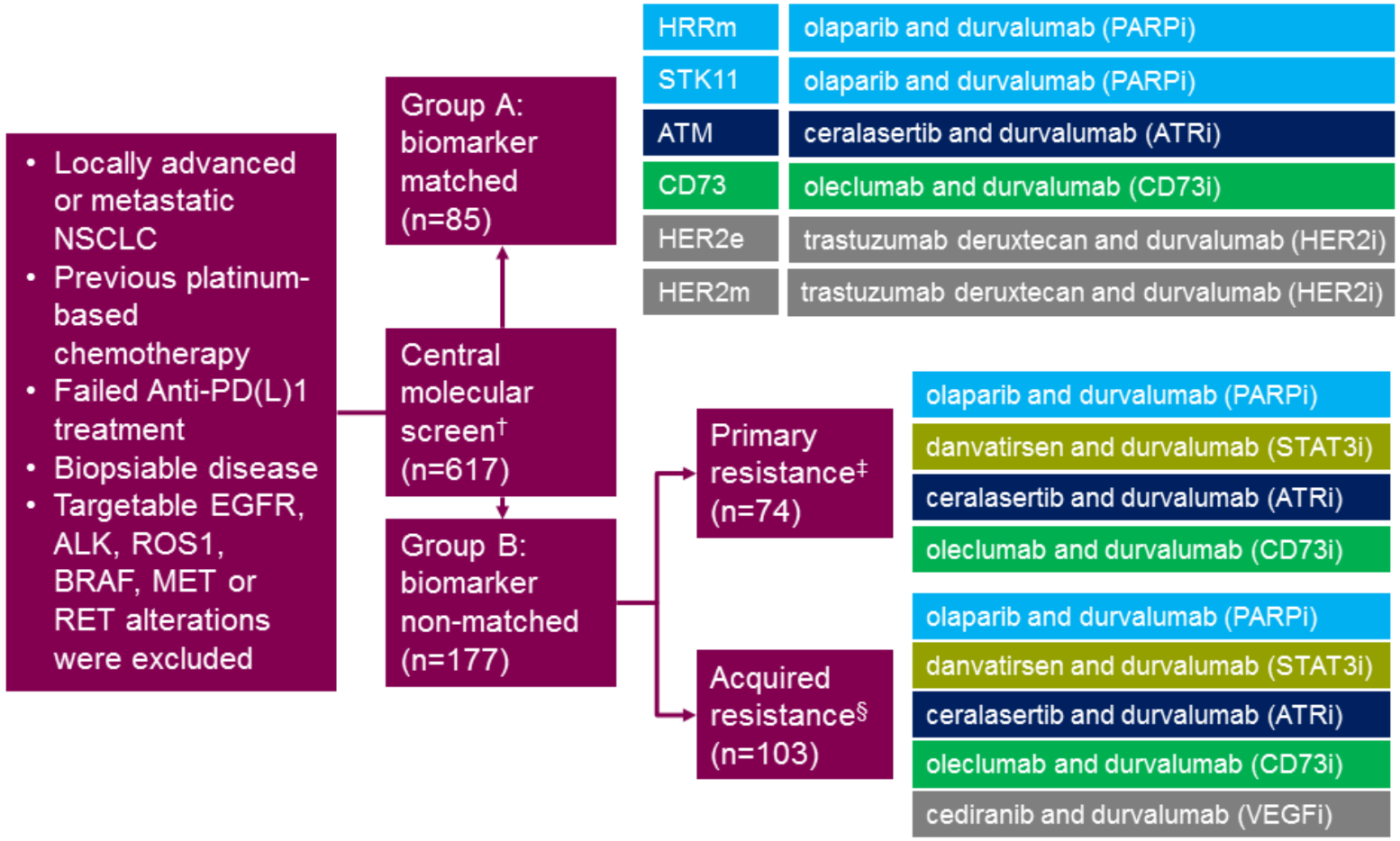
# Ongoing trials of PARPi combined with ICIs

**Olaparib**
**Rucaparib**
**Niraparib**
**Talazoparib**

| Trial | Cancer Type | Line of Treatment | PARP Inhibitor | Immunotherapy | Phase |
|---|---|---|---|---|---|
| NCT03308942 | NSCLC | 1/2 | Niraparib | Pembrolizumab/TSR-042 (anti-PD-1 mAb) | II |
| NCT03330405 | NSCLC, TNBC, HR+ breast cancer, ovarian cancer, UC, CRPC. | ≥1 | Talazoparib | Avelumab | II |
| NCT03334617 (HUDSON) | NSCLC | ≥2 | Olaparib | Durvalumab | II |
| NCT03775486 (ORION) | NSCLC | Maintenance | Olaparib | Durvalumab Compared to: Durvalumab | II |
| NCT03976323 (KEYLYNK-006) | Non-squamous NSCLC | Maintenance | Olaparib | Pembrolizumab Compared to: Pembrolizumab + chemotherapy | III |
| NCT03976362 (KEYLYNK-008) | Squamous NSCLC | Maintenance | Olaparib | Pembrolizumab Compared to: Pembrolizumab + chemotherapy + placebo | III |
| NCT04380636 (KEYLYNK −012) | NSCLC | Maintenance | Olaparib | Pembrolizumab Compared to: Pembrolizumab + placebo Compared to: Durvalumab | III |
| NCT04173507 Lung-MAP | Non-squamous STK11-positive NSCLC | ≥2 | Talazoparib | Avelumab | II |

*ImmunoTargets and therapy* 10 (2021): 9.

# HUDSON: Open-Label, Multidrug Umbrella Phase II Study in Patients With Advanced NSCLC After Progression on PD-1/PD-L1 Inhibitor Therapy




- Multidrug, nonrandomized umbrella phase II study (data cutoff April 14, 2021)
- **Primary endpoint:** ORR
- **Secondary endpoints:** DCR, PFS, OS, safety

Besse. WCLC 2022. Abstr OA15.05.

# HUDSON: Efficacy by Treatment (Groups A + B)

| Efficacy Parameter | Durvalumab + Ceralasertib (n = 66) | Durvalumab + Olaparib (n = 87) | Durvalumab + Danvatirsen (n = 45) | Durvalumab + Oleclumab (n = 57) |
|---|---|---|---|---|
| ORR (primary endpoint), % | 16.7 | 4.6 | 0 | 1.8 |
| Median tx duration, mo | | | | |
| ▪ Durvalumab | 7.3 | 3.7 | 2.8 | 2.9 |
| ▪ Other tx agent | 6.3 | 3.2 | 2.8 | 2.9 |
| 12-wk disease control rate, % | 60.6 | 36.8 | 26.7 | 29.8 |
| 24-wk disease control rate, % | 42.4 | 17.2 | 13.3 | 15.8 |

- Due to low activity (ORR <5%) seen in durvalumab + olaparib, durvalumab + danvatirsen, and durvalumab + oleclumab groups, these 3 regimens were pooled as an internal control

Besse. WCLC 2022. Abstr OA15.05.

Slide credit: clinicaloptions.com

# HUDSON: PFS & OS by Treatment (Groups A + B)

| PFS, OS Parameter | Durvalumab + Ceralasertib (n = 66) | Other Regimens* (n = 189) | Durvalumab + Olaparib (n = 87) | Durvalumab + Danvatirsen (n = 45) | Durvalumab + Oleclumab (n = 57) |
|---|---|---|---|---|---|
| Median PFS, mo (80% CI) | 6.0 (4.6-7.5) | 2.7 (1.8-2.8) | 2.7 (1.6-3.0) | 2.9 (1.7-3.1) | 1.8 (1.6-2.7) |
| 6-mo PFS, % (80% CI) | 46.3 (37.9-54.2) | 18.0 (14.5-21.9) | 18.7 (13.5-24.5) | 18.8 (11.5-27.6) | 16.6 (10.8-23.6) |
| Median OS, mo (80% CI) | 15.9 (14.1-20.3) | 9.4 (7.5-10.6) | 9.4 (6.9-10.8) | 7.9 (6.0-10.6) | 11.0 (7.6-13.5) |
| 12-mo OS, % (80% CI) | 61.6 (53.4-68.8) | 39.7 (35.1-44.3) | 40.8 (34.0-47.5) | 28.8 (20.2-38.0) | 46.2 (37.5-54.5) |

*Pooled internal control of durvalumab + olaparib, durvalumab + danvatirsen, and durvalumab + oleclumab.

Besse. WCLC 2022. Abstr OA15.05.

Slide credit: clinicaloptions.com

# HUDSON: Efficacy by Cohort (Durvalumab + Ceralasertib)

| Efficacy Parameter | Biomarker Matched (ATM) (n = 21) | Biomarker Nonmatched | |
|---|---|---|---|
| | | Primary Resistance (n = 20) | Acquired Resistance (n = 25) |
| ORR, %<br>▪ PR | 28.6<br>28.6 | 15.0<br>15.0 | 8.0<br>8.0 |
| SD ≥40 days, %<br>▪ Unconfirmed PR | 47.6<br>9.5 | 45.0<br>0 | 64.0<br>0 |
| Progression, %<br>▪ RECIST disease progression<br>▪ Death | 19.0<br>19.0<br>0 | 35.0<br>30.0<br>5.0 | 24.0<br>16.0<br>8.0 |
| 12-wk disease control rate, % | 71.4 | 55.0 | 56.0 |
| 24-wk disease control rate, % | 57.1 | 40.0 | 32.0 |
| Median PFS, mo (80% CI)<br>▪ 6-mo PFS, % | 8.4 (6.0-9.7)<br>64.3 | 4.9 (1.9-6.8)<br>41.5 | 4.6 (3.6-6.0)<br>35.2 |
| Median OS, mo (80% CI)<br>▪ 12-mo PFS, % | 22.8* (12.6-29.9)<br>70.2 | 11.8 (6.6-18.8)<br>45.0 | 19.1 (14.1-20.3)<br>68.0 |

*Data still accruing.

Besse. WCLC 2022. Abstr OA15.05.

Slide credit: clinicaloptions.com

# HUDSON: Safety by Treatment (Groups A + B)

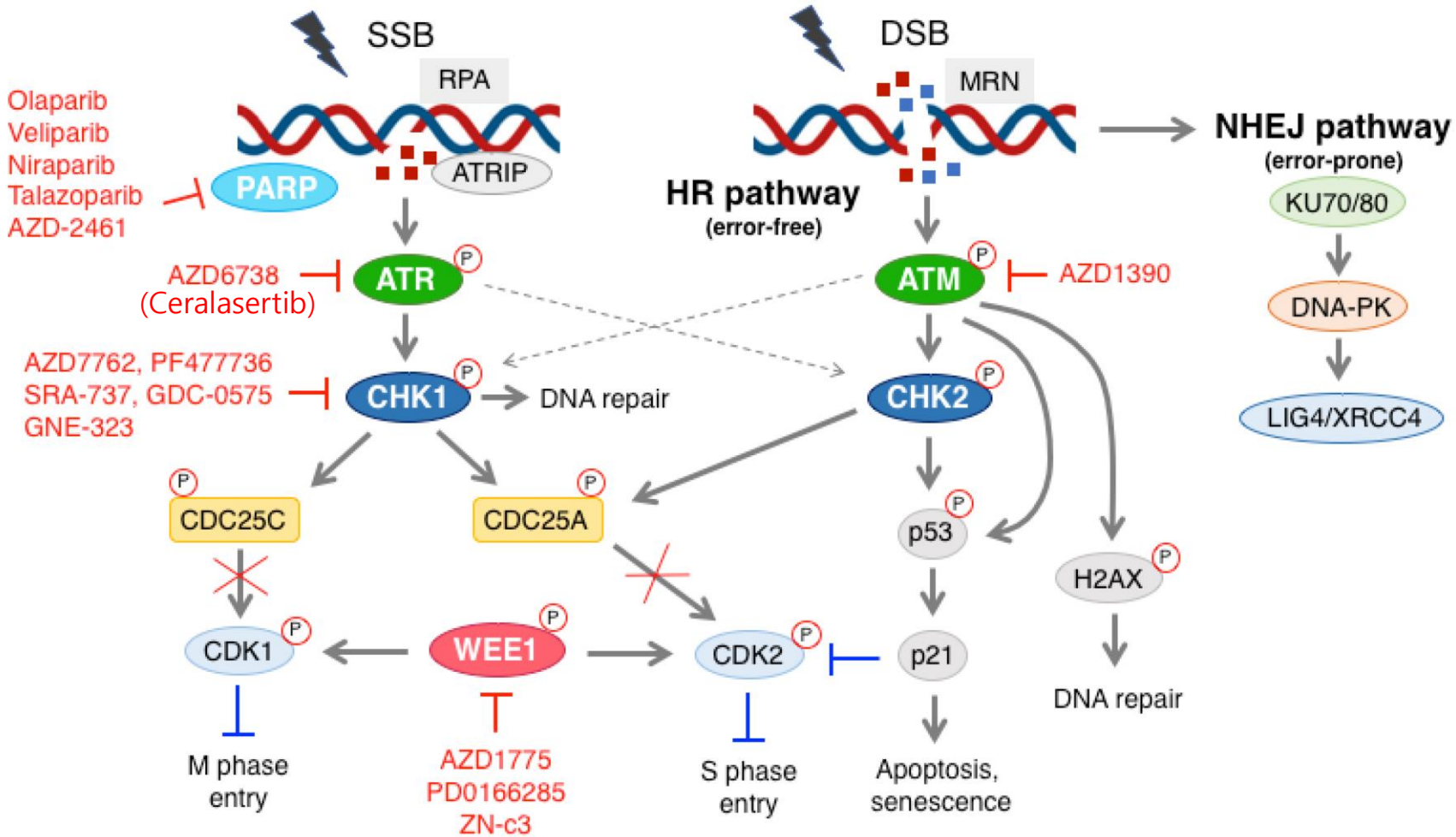
| Safety Parameter, n (%) | Durvalumab + Ceralasertib (n = 66) | Durvalumab + Olaparib (n = 87) | Durvalumab + Danvatirsen (n = 45) | Durvalumab + Oleclumab (n = 57) |
|---|---|---|---|---|
| Any TEAE | 64 (97.0) | 80 (92.0) | 43 (95.6) | 48 (84.2) |
| ▪ Related to any tx | 52 (78.8) | 67 (77.0) | 33 (73.3) | 34 (59.6) |
| Any grade ≥3 TEAE | 33 (50.0) | 47 (54.0) | 28 (62.2) | 23 (40.4) |
| ▪ Related to any tx | 15 (22.7) | 30 (34.5) | 17 (37.8) | 9 (15.8) |
| ▪ Resulted in death | 2 (3.0) | 1 (1.1) | 3 (6.7) | 1 (1.8) |
| Any SAE | 28 (42.4) | 33 (37.9) | 20 (44.4) | 16 (28.1) |
| ▪ Related to any tx | 8 (12.1) | 9 (10.3) | 3 (6.7) | 4 (7.0) |
| Any TEAE resulting in discontinuation | 8 (12.1) | 9 (10.3) | 10 (22.2) | 7 (12.3) |
| ▪ Related to any tx | 5 (7.6) | 8 (9.2) | 7 (15.6) | 3 (5.3) |
| Most common TRAEs (≥15%*) | | | | |
| ▪ Nausea | 34 (51.5) | 37 (42.5) | 1 (2.2) | 4 (7.0) |
| ▪ Vomiting | 19 (28.8) | 18 (20.7) | 2 (4.4) | 1 (1.8) |
| ▪ Decreased appetite | 15 (22.7) | 8 (9.2) | 2 (4.4) | 4 (7.0) |
| ▪ Anemia | 14 (21.2) | 22 (25.3) | 4 (8.9) | 2 (3.5) |
| ▪ Fatigue | 11 (16.7) | 18 (20.7) | 6 (13.3) | 8 (14.0) |
| ▪ Diarrhea | 10 (15.2) | 11 (12.6) | 5 (11.1) | 7 (12.3) |

*In the durvalumab + ceralasertib treatment group.

Besse. WCLC 2022. Abstr OA15.05.

Slide credit: clinicaloptions.com

# Schematic representation of the DDR pathway and DDR inhibitors




*Cells* 11.9 (2022): 1466.

# HUDSON: Conclusions

- In this umbrella phase II study, durvalumab + ceralasertib showed promising activity in both biomarker matched (ATM) and nonmatched patients with advanced NSCLC who failed previous PD-1/PD-L1 therapy and platinum-based chemotherapy with an ORR of 16.7% compared with 0% to 4.8% in other evaluated regimens
- Median OS was notable for biomarker matched (22.8 mo), primary resistance (11.8 mo), and acquired resistance (19.1 mo) cohorts for durvalumab + ceralasertib
- All 4 reported regimens seem to have tolerable safety profiles according to investigators
- HUDSON remains ongoing, with patients continuing to enroll in ceralasertib-based treatment regimens in both biomarker matched and nonmatched cohorts

Besse. WCLC 2022. Abstr OA15.05.

# Ongoing clinical trials in Metastatic NSCLC

- **PD-1/PD-L1 blockade combination with**
  - **Antiangiogenic drug**
  - **Other checkpoint inhibitors (LAG-3, TIGIT, TIM-3, OX-40)**
  - **PARP inhibitors**
- **Route of PD-1/PD-L1 blockade administration**

# IMscin002: study design

**A phase II, randomised, multicenter, open-label cross-over study to evaluate participant and healthcare professional reported preference for subcutaneous TECENTRIQ compared with intravenous TECENTRIQ formulation in participants with NSCLC**

- Resected stage IIB-IIIB (T3-N2) eNSCLC [1]
- Completed adjuvant chemotherapy
- ECOG 0–1
- PD-L1 positive [2]

- Stage IV NSCLC [1]
- Chemotherapy-naïve
- ECOG 0–1
- PD-L1 high [3]

R

1:1 [4]

N= ~140

**Treatment Crossover Period**

| | |
|---|---|
| TECENTRIQ SC 1875mg, Q3W<br>3 cycles | TECENTRIQ IV 1200mg, Q3W<br>3 cycles |
| TECENTRIQ IV 1200mg, Q3W<br>3 cycles | TECENTRIQ SC 1875mg, Q3W<br>3 cycles |

**Treatment Continuation Period**

Patient selected regimen

(TECENTRIQ SC or TECENTRIQ IV)

for a total of 16 cycles (eNSCLC) or until loss of clinical benefit (Stage IV NSCLC)

FOLLOW UP

[1] Histological or cytological diagnosis per UICC/AJCC staging system, 8th Ed.

[2] PD-L1 positive defined as minimum TC ≥ 1% by VENTANA PD-L1 (SP263) IHC assay or TPS ≥ 1% by Dako PD-L1 IHC 22C3 pharmDx assay performed by a local or central laboratory.

[3] PD-L1 high defined as minimum TC ≥ 50% by VENTANA PD-L1 (SP263) IHC assay, minimum TPS ≥ 50% by Dako PD-L1 IHC 22C3 pharmDx assay, or TC3 or IC3 by VENTANA PD-L1 (SP142) IHC assay, performed by a local or central laboratory.

[4] Stratification: disease stage and type of surgery.

eNSCLC = early non-small cell lung cancer; IV = intravenous; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; R = randomization; SC = subcutaneous; TC = tumour cells.

TECENTRIQ® atezolizumab

CONNECT WITH PURPOSE

**Study of Pembrolizumab (MK-3475) Subcutaneous (SC) Versus Pembrolizumab Intravenous (IV) Administered With Platinum Doublet Chemotherapy in Participants With Metastatic Squamous or Nonsquamous Non-Small Cell Lung Cancer (NSCLC) (MK-3475-A86)**

- A Randomized, Phase 3, Open-label Study to Investigate the Pharmacokinetics and Safety of Subcutaneous Pembrolizumab Versus Intravenous Pembrolizumab, Administered With Platinum Doublet Chemotherapy
- In the First-Line Treatment of Participants With Metastatic NSCLC
  - A: Pembrolizumab SC + Platinum Doublet Chemotherapy
  - B: Pembrolizumab IV + Platinum Doublet Chemotherapy

# Positive Results Announced from Phase III IMscin001 Study Evaluating Subcutaneous Formulation of Tecentriq® with ENHANZE® in Advanced Non-Small Cell Lung Cancer

NEWS PROVIDED BY
**Halozyme Therapeutics, Inc.** →
Aug 02, 2022, 00:55 ET



*Subcutaneous formulation with ENHANZE® reduced treatment time to 3-8 minutes compared to 30-60 minutes for standard intravenous infusion*

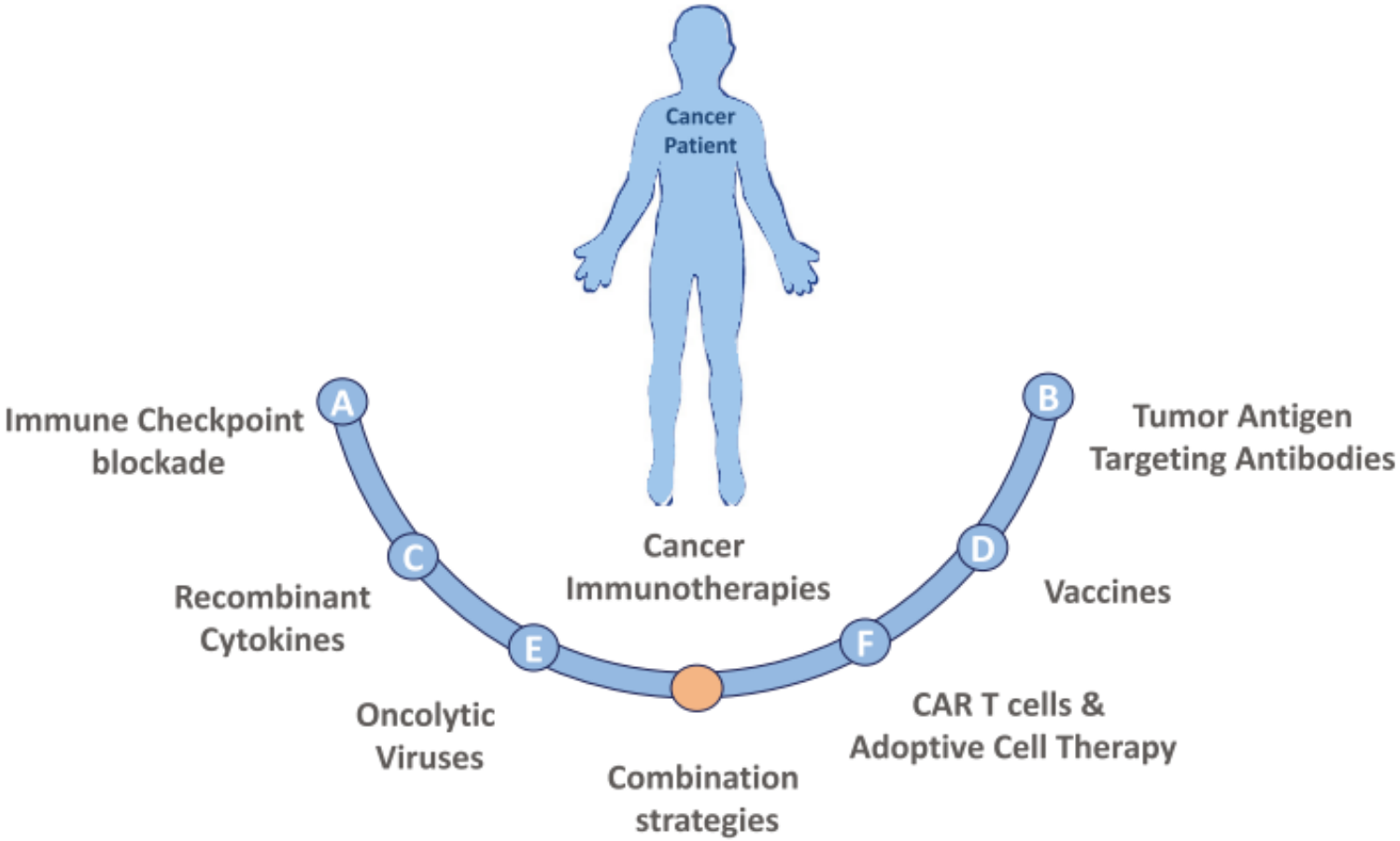
SAN DIEGO, Aug. 2, 2022 /PRNewswire/ -- Halozyme Therapeutics, Inc. (NASDAQ: HALO) ("Halozyme") today announced that Roche's Phase III IMscin001 study evaluating a subcutaneous (SC) formulation of Tecentriq® (atezolizumab) with Halozyme's ENHANZE® technology met its co-primary endpoints.

The study showed non-inferior levels of Tecentriq® in the blood (pharmacokinetics), when injected subcutaneously, compared with intravenous (IV) infusion in cancer immunotherapy-naïve patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) for whom prior platinum therapy has failed. The safety profile of the SC formulation was consistent with IV Tecentriq®.

"These positive results further demonstrate the opportunity for a coformulation of ENHANZE to potentially benefit patients by reducing the treatment time of Tecentriq to 3-8 minutes as a SC delivery from 30-60 minutes for IV treatment," commented Dr. Helen Torley, president and chief executive officer of Halozyme. "We are delighted to announce these positive results, which represent our second positive Phase III trial announcement this year for our Wave Three products."

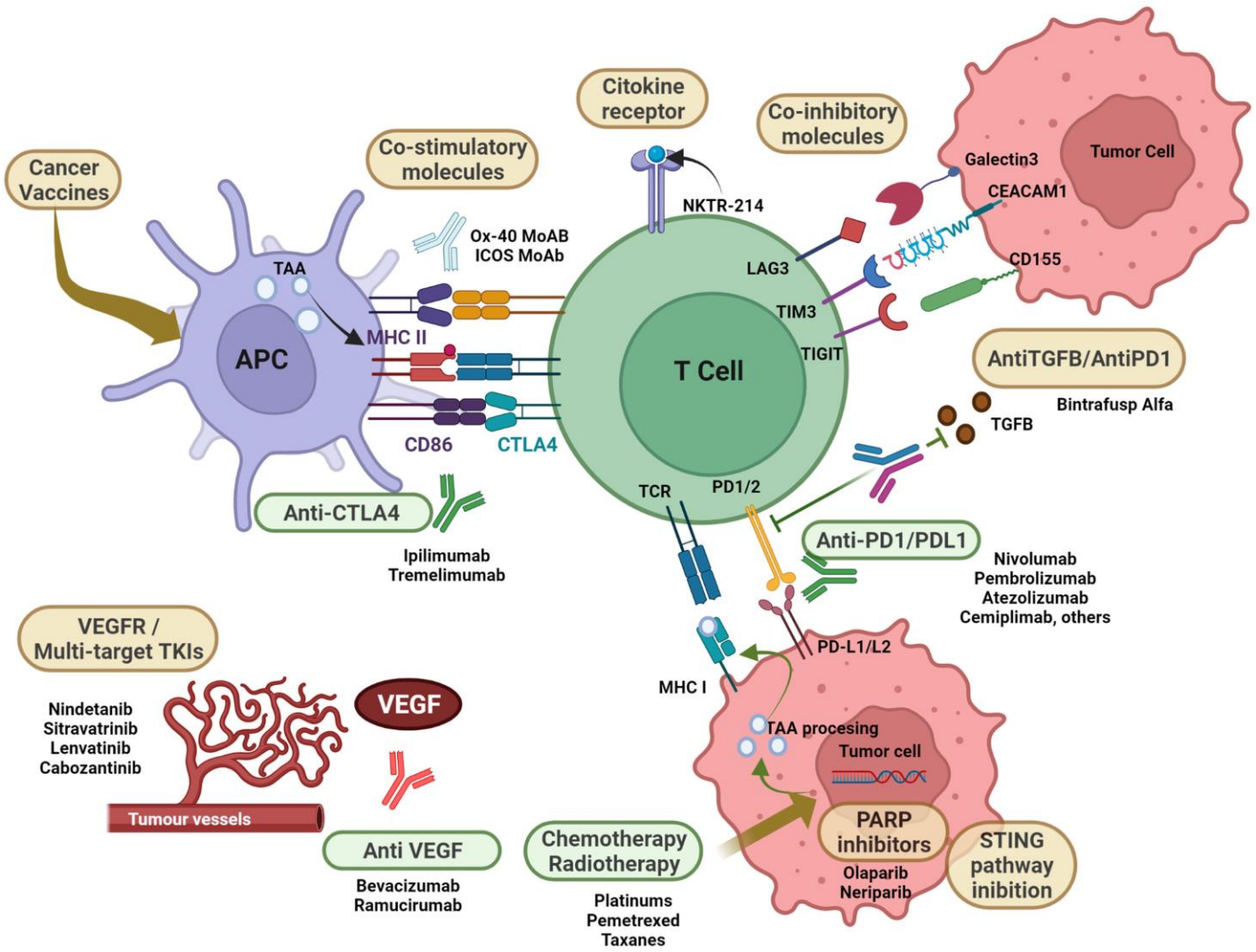
Roche will share detailed findings of the IMscin001 study at an upcoming medical meeting and submit the data for regulatory approval to health authorities globally, including the U.S. Food and Drug Administration and the European Medicines Agency.

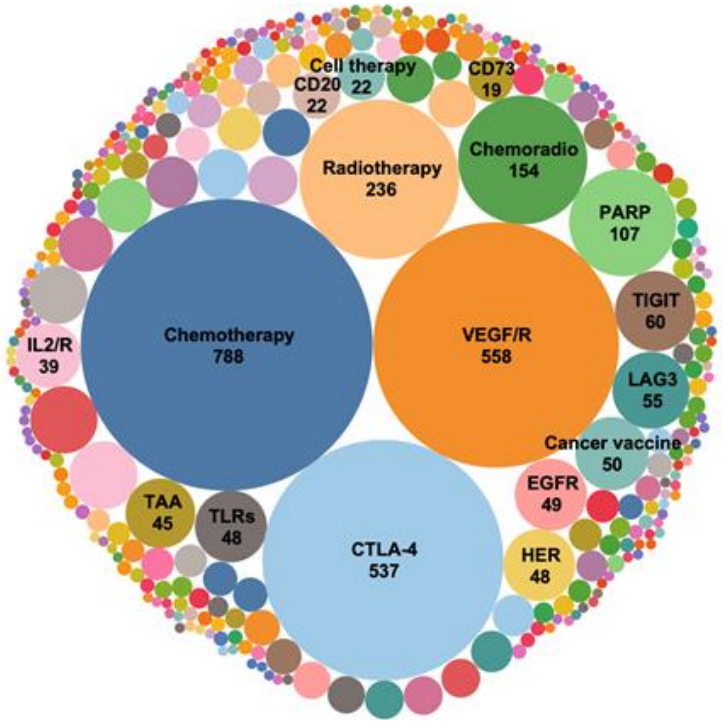
# Types of cancer immunotherpies




*Frontiers in Pharmacology* 11 (2021): 566401.

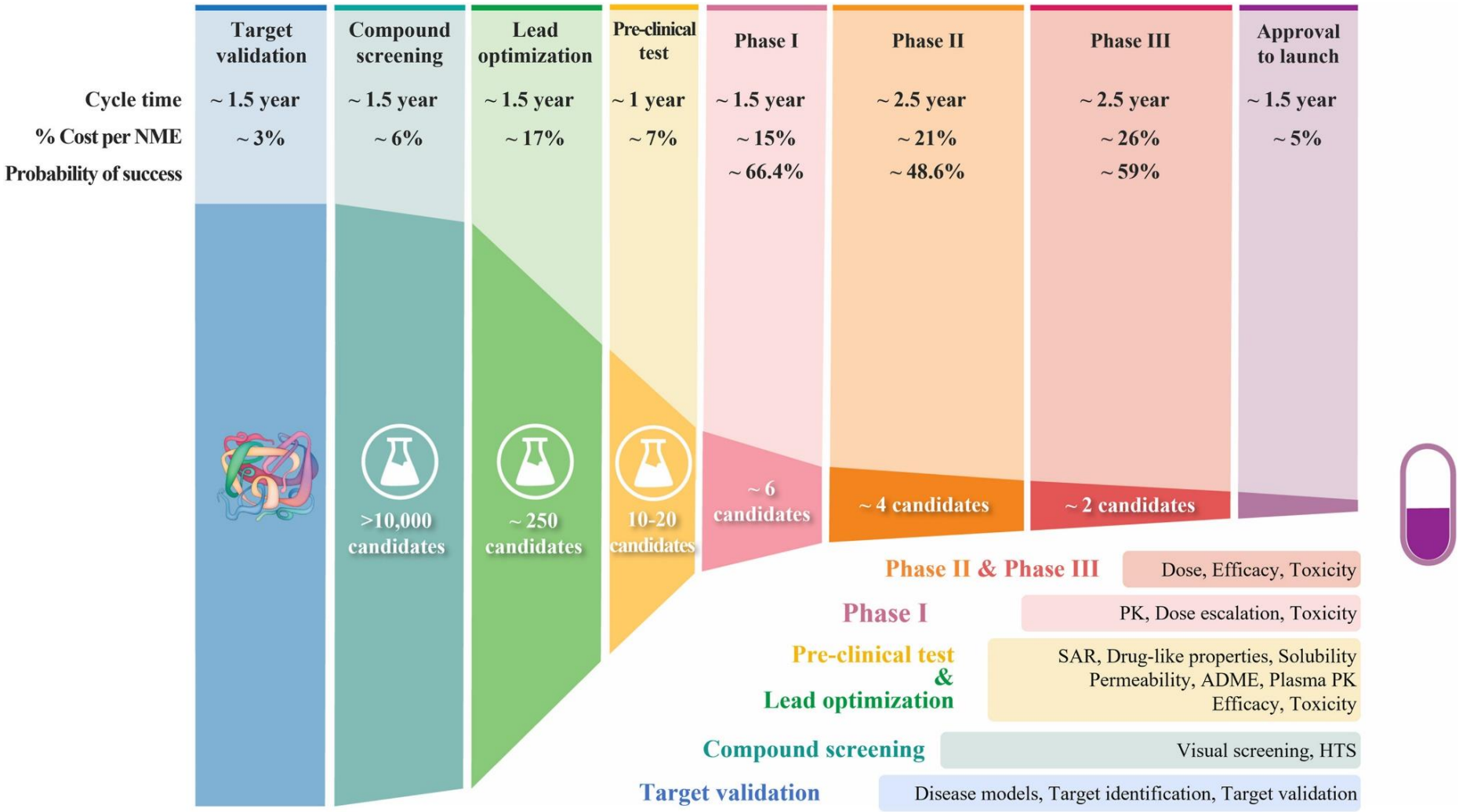
# Current and potential therapeutic targets for NSCLC



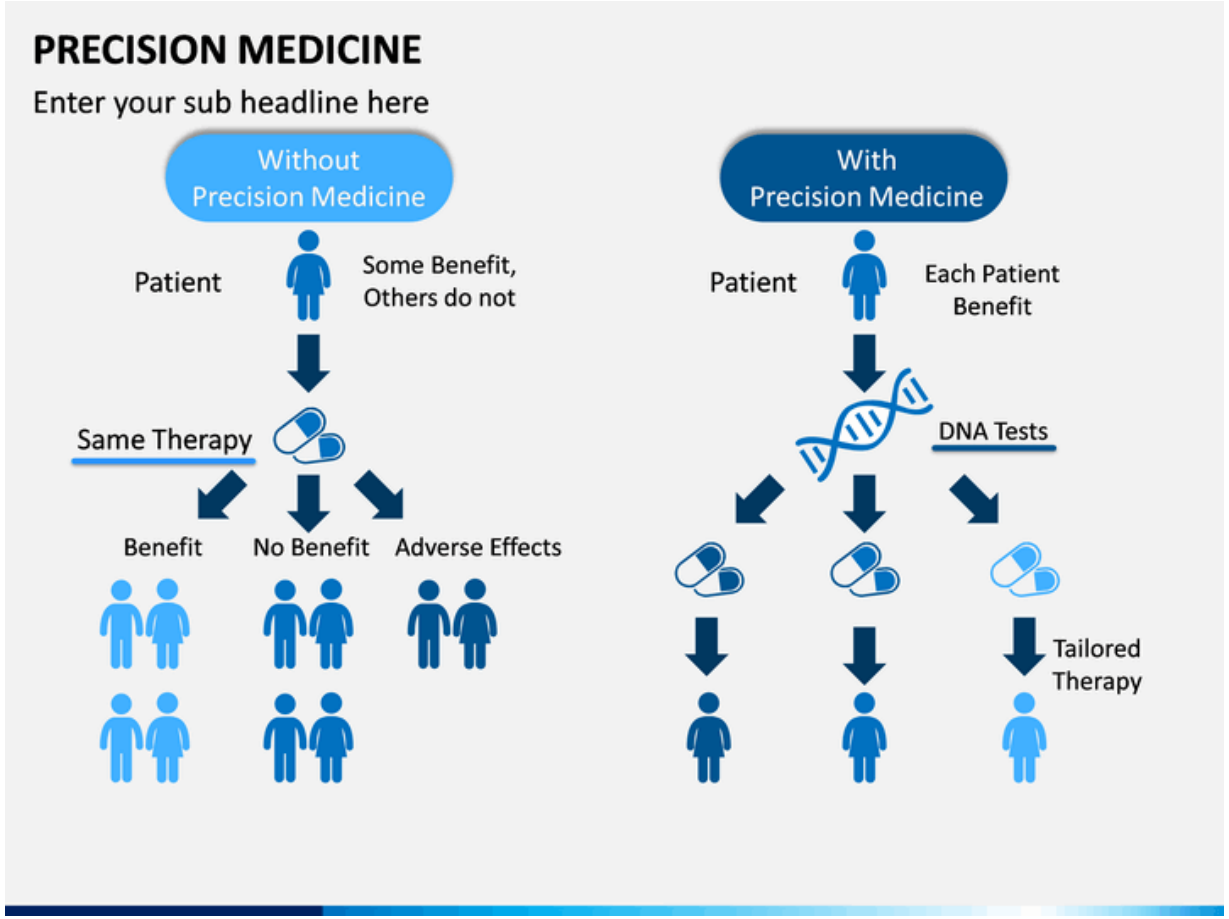

*Clinical Lung Cancer* (2022)

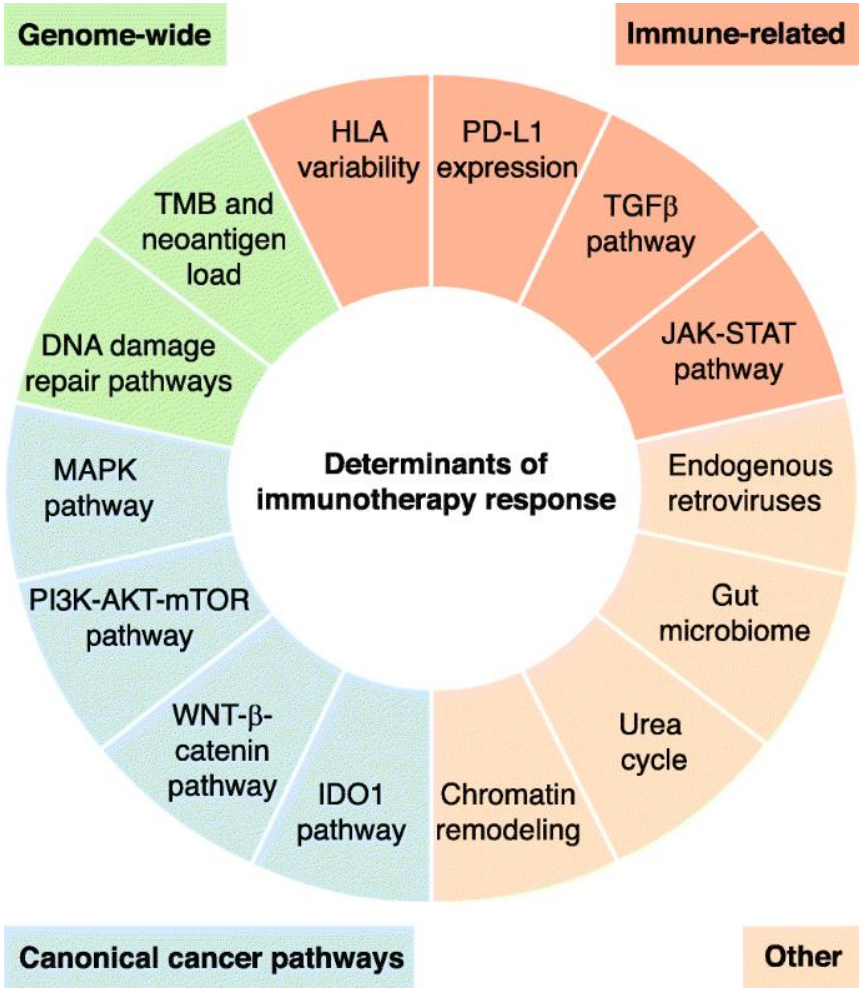
# Clinical drug development




*Acta Pharmaceutica Sinica B* (2022).

# Precision Medicine




https://www.sketchbubble.com/en/presentation-precision-medicine.html

*Genome medicine* 10.1 (2018): 1-18.

# Summary

- Numerous preclinical and clinical trials, many still ongoing, have attempted to evaluate the safety and efficacy of anti-PD-1/PD-L1 mAbs combination with other treatment methods including antiangiogenic drug, other checkpoint inhibitors (LAG-3, TIGIT, TIM-3, OX-40, etc.), and PARP inhibitors.

- Indication : 1$^{st}$ line, ≥2$^{nd}$ line - progression after PD-1/PD-L1 blocker

- Yet, not all patients respond similarly to the present immunotherapy methods since various factors impact the treatment outcome.

- Immunotherapy is moving toward a personalized method of therapy.
- It is important to the usage of biomarkers to predict treatment efficacy and choose the best therapeutic option for a given patient.

# Thank you

# for your attention