



Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

# Ongoing Immunotherapy Clinical Trials in Advanced NSCLC

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#LearnACI

# Disclosures

- Research Funding (to Institution): Bristol Meyers Squibb, IOVANCE, NextCure, Genentech
- Trial Safety Board: Bristol Myers Squibb
- Trial Steering Committee: IOVANCE
- I may be discussing non-FDA approved indications during my presentation.

# Current Challenges with IO in Lung Cancer

1. Too many first line options
2. How long should IO be continued (CM 153)?
3. Role of immunotherapy in NSCLC with driver mutations uncertain
4. How best to use radiotherapy with immunotherapy
5. Majority of patients do not respond to IO alone (primary resistance)
6. The majority of responders will develop resistance
7. Management of IO toxicity/ use of IO with autoimmune dis./ transplant
  - How are we addressing these questions in clinical trials?

283 Studies found for: **Recruiting, Not yet recruiting, Active, not recruiting Studies | (Non Small Cell Lung Cancer OR non-small cell lung carcinoma OR non-small cell lung cancer) AND (Immunotherapy OR immune checkpoint OR cytokine OR Cellular OR Costimulatory OR Vaccine OR Angiogenesis OR intratumoral OR Epigenetic) | Phase 3**

Applied Filters: ☒ Recruiting ☒ Not yet recruiting ☒ Active not recruiting ☒ Phase 3

- Excluded trials evaluating adjuvant/ neoadjuvant therapy

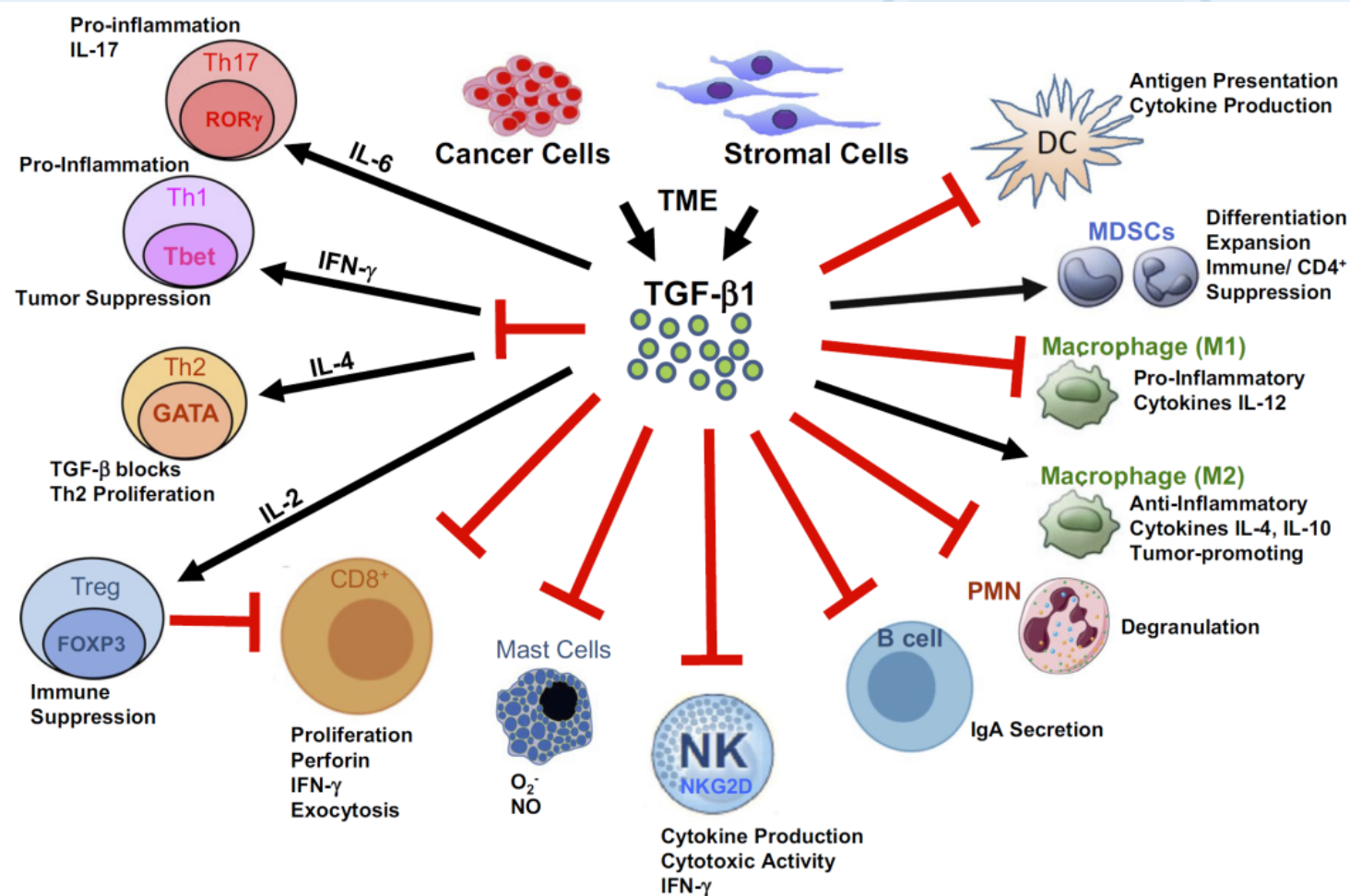
# How often/ long should IO be cont.?

| Trial/ NCT              | Setting (Location)                                  | Treatment                                                                                                                                                                    | 1° EndPt         | Results |
|-------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|---------|
| DICIPLE<br>03469960     | 1L; PD-L1, 1-49%<br>(France)                        | Nivolumab/ Ipilimumab for 6 months →<br>Continuation versus Observation                                                                                                      | PFS              | 2023    |
| REFINE-Lung<br>05085028 | 1L<br>(UK)                                          | Pembrolizumab +/- Chemotherapy x 6 months →<br>Pembrolizumab every 6/9/12/15 or 18 weeks                                                                                     | OS at<br>2 years | 2027    |
| DIAL<br>05255302        | 1L<br>(France)                                      | Platin Doublet/ Pembrolizumab x 6 months → Observation<br>(Maintenance Pemetrexed in Non-Sq)<br>Platin Doublet/ Pembrolizumab →<br>Pembrolizumab (with Pemetrexed in Non-Sq) | OS               | 2029    |
| EDEN<br>03542461        | 1L, Sq NSCLC<br>(Italy)                             | Platin Doublet → Switch Maintenance Nivolumab vs. Delayed<br>Nivolumab (on Progression)                                                                                      | OS               | 2022    |
| INSIGNA<br>03793179     | 1L; Non-Sq NSCLC<br>PDL1 ≥ 1%<br>(US, Canada, Guam) | Pembrolizumab, on Progression → Carboplatin/ Pemetrexed<br>plus/minus Pembrolizumab (Arms A and B)<br>Pemetrexed/Carboplatin/ Pembrolizumab                                  | OS               | 2022    |
| 04909684                | 1L<br>(Netherlands)                                 | SOC Pembrolizumab (200/400mg Q3/6 Weeks)<br>Pembrolizumab 300 mg Q 6 Weeks                                                                                                   | OS at<br>1 year  | 2024    |

# Immunotherapy for EGFR (and other driver) Mutant NSCLC?

| Trial/ NCT              | Setting (Location)                        | Treatment                                                                                                                                                | 1° EndPt  | Results |
|-------------------------|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------|
| CM722<br>02864251       | EGFRm, Prior- TKI<br>(International, INT) | Platin/ Pemetrexed plus/ minus Nivolumab<br>Nivolumab/ Ipilimumab (arm closed)                                                                           | PFS       | 2022    |
| KEYNOTE 789<br>03515837 | EGFRm, Prior TKI<br>(INT)                 | Platin/ Pemetrexed/ Pembrolizumab<br>Platin/ Pemetrexed/ Placebo                                                                                         | OS<br>PFS | 2023    |
| 03924050                | EGFRm, Prior TKI<br>(China)               | Platin/ Pemetrexed/ Toripalimab (anti-PD-1)<br>Platin/ Pemetrexed/ Placebo                                                                               | PFS       | 2022    |
| 05132413                | EGFRm, Prior TKI<br>(China)               | Platin/ Pemetrexed/ SH-1701 (anti-PD-L1/ TGFbetaRII)<br>Platin/ Pemetrexed/ SH-1701/ Bevacizumab - <b>1° Endpoint met</b><br>Platin/ Pemetrexed/ Placebo | PFS       | 2024    |
| ORIENT-31<br>03802240   | EGFRm, Prior TKI<br>(China)               | Cisplatin/ Pemetrexed/ Sintilimab (anti-PD1)<br>Cisplatin/ Pemetrexed/ Sintilimab/ IBI305 (Anti-VEGF)<br>Cisplatin/ Pemetrexed/ Placebo                  | PFS       | 2022    |
| 05184712                | EGFRm, Prior TKI<br>(China)               | Carboplatin/Pemetrexed/ AK112 (anti-PD-1/VEGF)<br>Carboplatin/Pemetrexed/ Placebo                                                                        | PFS       | 2024    |
| 03991403                | EGFR/ ALK+, Prior TKI<br>(Korea)          | Carboplatin/ Paclitaxel/ Bevacizumab/ Atezolizumab<br>Platin/Pemetrexed                                                                                  | PFS       | 2022    |

| Trial/ NCT              | Setting (Location)                        | Treatment                                    |
|-------------------------|-------------------------------------------|----------------------------------------------|
| CM722<br>02864251       | EGFRm, Prior- TKI<br>(International, INT) | Platin/ Per<br>Nivolumab                     |
| KEYNOTE 789<br>03515837 | EGFRm, Prior TKI<br>(INT)                 | Platin/ Per<br>Platin/ Per                   |
| 03924050                | EGFRm, Prior TKI<br>(China)               | Platin/ Per<br>Platin/ Per                   |
| 05132413                | EGFRm, Prior TKI<br>(China)               | Platin/ Per<br>Platin/ Per<br>Platin/ Per    |
| ORIENT-31<br>03802240   | EGFRm, Prior TKI<br>(China)               | Cisplatin/ P<br>Cisplatin/ P<br>Cisplatin/ P |
| 05184712                | EGFRm, Prior TKI<br>(China)               | Carboplati<br>Carboplati                     |
| 03991403                | EGFR/ ALK+, Prior TKI<br>(Korea)          | Carboplati<br>Platin/Pem                     |

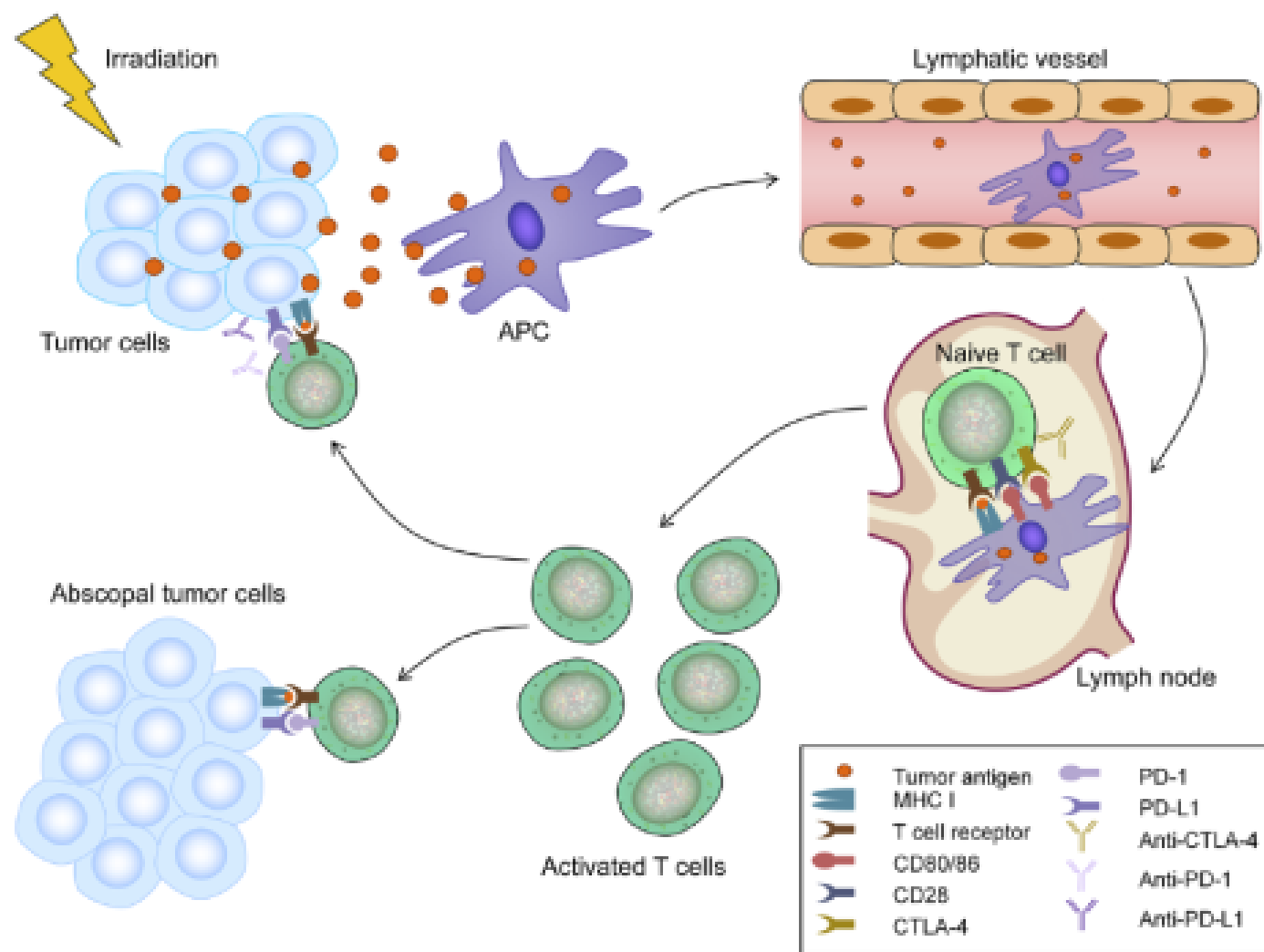


# How best to use radiotherapy with immunotherapy?

| Trial/ NCT                | Setting (Location)                            | Treatment                                                                                                                                                        | 1° EndPt       | Results |
|---------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|---------|
| LONESTAR<br>03391869      | IO naïve<br>(US)                              | Nivolumab/ Ipilimumab plus Local Treatment (Surgery/RT)<br>Nivolumab/ Ipilimumab                                                                                 | OS<br>OS oligo | 2022    |
| NIRVANA<br>03774732       | IO naïve<br>(France)                          | Platin Doublet/ Pembrolizumab plus Concurrent Radiation<br>Platin Doublet/ Pembrolizumab                                                                         | OS             | 2024    |
| 04929041<br>RPh2/3        | 1L, PD-L1<1%<br>(US)                          | Standard IO w or w/out Chemotherapy plus Radiation<br>Standard IO w or w/out Chemotherapy                                                                        | OS<br>PFS      | 2027    |
| 03867175                  | 1L, Maint.<br>(US)                            | ChemoIO → Pembrolizumab plus SBRT<br>Pembrolizumab                                                                                                               | PFS            | 2027    |
| TRAILOCLORI01<br>05111197 | 1 <sup>st</sup> line,<br>Oligomet<br>(France) | Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 + Stereotactic Radiation Therapy (up to 5 FDG avid lesions)<br>Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 | OS             | 2024    |
| 04702009                  | 1L, Central<br>Lesion (China)                 | Platinum Doublet/ anti-PD1/L1/ Bronch. Assist. Interventional Tx<br>Platinum Doublet/ anti-PD1/L1                                                                | ORR            | 2026    |

# How best to use radioth

| Trial/ NCT             | Setting (Location)                      | Treatment                                                                                                                                                        |
|------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LONESTAR 03391869      | IO naïve (US)                           | Nivolumab/ Ipil<br>Nivolumab/ Ipil                                                                                                                               |
| NIRVANA 03774732       | IO naïve (France)                       | Platin Doublet/<br>Platin Doublet/                                                                                                                               |
| 04929041<br>RPh2/3     | 1L, PD-L1<1% (US)                       | Standard IO w c<br>Standard IO w c                                                                                                                               |
| 03867175               | 1L, Maint. (US)                         | ChemoIO → Pe<br>Pe                                                                                                                                               |
| TRAILOCLORI01 05111197 | 1 <sup>st</sup> line, Oligomet (France) | Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 + Stereotactic Radiation Therapy (up to 5 FDG avid lesions)<br>Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 |
| 04702009               | 1L, Central Lesion (China)              | Platinum Doublet/ anti-PD1/L1/ Bronch. Assist. Interventional Tx<br>Platinum Doublet/ anti-PD1/L1                                                                |



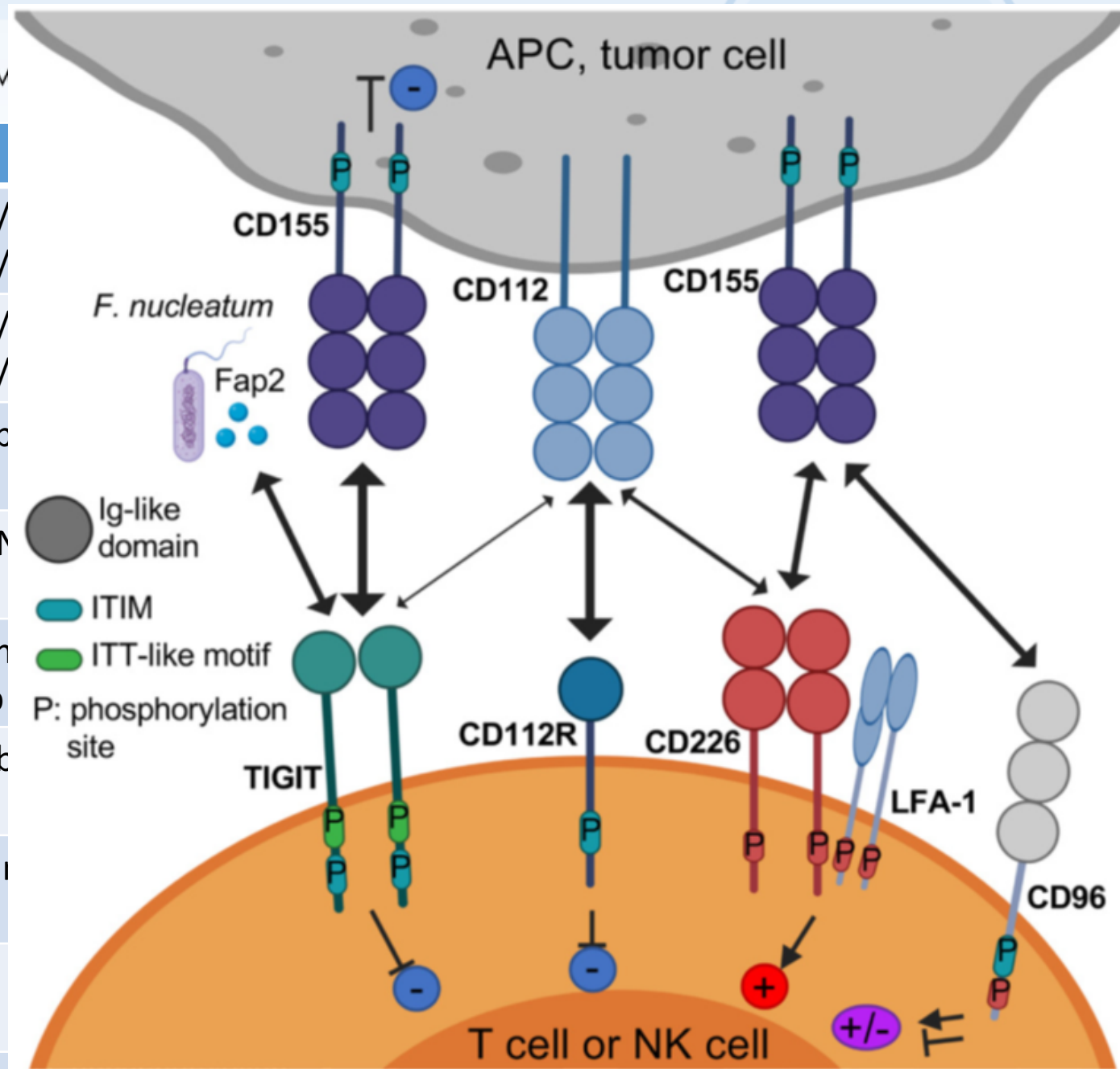
# How best to use radiotherapy with immunotherapy?

| Trial/ NCT                | Setting (Location)                            | Treatment                                                                                                                                                        | 1° EndPt       | Results |
|---------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|---------|
| LONESTAR<br>03391869      | IO naïve<br>(US)                              | Nivolumab/ Ipilimumab plus Local Treatment (Surgery/RT)<br>Nivolumab/ Ipilimumab                                                                                 | OS<br>OS oligo | 2022    |
| NIRVANA<br>03774732       | IO naïve<br>(France)                          | Platin Doublet/ Pembrolizumab plus Concurrent Radiation<br>Platin Doublet/ Pembrolizumab                                                                         | OS             | 2024    |
| 04929041<br>RPh2/3        | 1L, PD-L1<1%<br>(US)                          | Standard IO w or w/out Chemotherapy plus Radiation<br>Standard IO w or w/out Chemotherapy                                                                        | OS<br>PFS      | 2027    |
| 03867175                  | 1L, Maint.<br>(US)                            | ChemoIO → Pembrolizumab plus SBRT<br>Pembrolizumab                                                                                                               | PFS            | 2027    |
| TRAILOCLORI01<br>05111197 | 1 <sup>st</sup> line,<br>Oligomet<br>(France) | Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 + Stereotactic Radiation Therapy (up to 5 FDG avid lesions)<br>Anti- PD-1/L1 with or w/out Chemo → Anti-PD-1/L1 | OS             | 2024    |
| 04702009                  | 1L, Central<br>Lesion (China)                 | Platinum Doublet/ anti-PD1/L1/ Bronch. Assist. Interventional Tx<br>Platinum Doublet/ anti-PD1/L1                                                                | ORR            | 2026    |



| Trial/ NCT (Loc)                | Target         | Treatment                                                                                                           | 1° EndPt   | RESULTS |
|---------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------|------------|---------|
| PACIFIC 8<br>05211895 (INT)     | TIGIT<br>(INT) | ChemoRT → Durvalumab/ Domvanalimab or Placebo<br>ChemoRT → Durvalumab/ Placebo                                      | PFS        | 2027    |
| PACIFIC 9<br>05221840 (INT)     | CD73<br>NKG2A  | ChemoRT → Durvalumab/ Oleclumab plus/minus Monalizumab<br>ChemoRT → Durvalumab/ Placebo                             | PFS        | 2026    |
| SKYSCRAPER-03<br>04513925 (INT) | TIGIT          | ChemoRT → Atezolizumab/ Tiragolumab<br>ChemoRT → Durvalumab                                                         | PFS        | 2024    |
| CM73L<br>04026412 (INT)         |                | ChemoRT/ Nivolumab → Nivolumab plus/minus Ipilimumab<br>ChemoRT → Durvalumab                                        | PFS        | 2025    |
| KEYVIBE-006<br>05298423         | TIGIT          | ChemoRT/ MK-7684A (Pembrolizumab/Vibostolimab) → MK7648A<br>ChemoRT → Durvalumab                                    | OS<br>PFS  | 2028    |
| KEYLYNK-012<br>04380636 (INT)   | PARP           | ChemoRT/ Pembrolizumab → Pembrolizumab with Olaparib or Placebo<br>ChemoRT → Durvalumab                             | OS<br>PFS  | 2026    |
| 04866017<br>(US/ AU)            | TIGIT          | ChemoRT/ Tislelizumab (anti-PD1) plus/minus Ociperlimab<br>ChemoRT → Durvalumab                                     | PFS<br>CCR | 2025    |
| 04092283<br>(US)                |                | ChemoRT/Durvalumab → Durvalumab<br>ChemoRT → Durvalumab                                                             | OS         | 2028    |
| 04325763<br>(China)             | VEGFR          | ChemoRT → TQB2450 (anti-PDL1)/ Placebo or TQB2450/ Anlotinib<br>ChemoRT → Placebo (Anlotinib- RTKi including VEGFR) | PFS        | 2022    |

| Trial/ NCT (Loc)                | Target         | Treatment                                        |
|---------------------------------|----------------|--------------------------------------------------|
| PACIFIC 8<br>05211895 (INT)     | TIGIT<br>(INT) | ChemoRT → Durvalumab/<br>ChemoRT → Durvalumab/   |
| PACIFIC 9<br>05221840 (INT)     | CD73<br>NKG2A  | ChemoRT → Durvalumab/<br>ChemoRT → Durvalumab/   |
| SKYSCRAPER-03<br>04513925 (INT) | TIGIT          | ChemoRT → Atezolizumab<br>ChemoRT → Durvalumab   |
| CM73L<br>04026412 (INT)         |                | ChemoRT/ Nivolumab → M<br>ChemoRT → Durvalumab   |
| KEYVIBE-006<br>05298423         | TIGIT          | ChemoRT/ MK-7684A (Per<br>ChemoRT → Durvalumab   |
| KEYLYNK-012<br>04380636 (INT)   | PARP           | ChemoRT/ Pembrolizumab<br>ChemoRT → Durvalumab   |
| 04866017<br>(US/ AU)            | TIGIT          | ChemoRT/ Tislelizumab (a<br>ChemoRT → Durvalumab |
| 04092283<br>(US)                |                | ChemoRT/Durvalumab →<br>ChemoRT → Durvalumab     |
| 04325763<br>(China)             | VEGFR          | ChemoRT → TQB2450 (an<br>ChemoRT → Placebo       |



## Trial/ NCT (Loc)

PACIFIC 8  
05211895 (INT)

PACIFIC 9  
05221840 (INT)

SKYSCRAPER-03  
04513925 (INT)

CM73L  
04026412 (INT)

KEYVIBE-006  
05298423

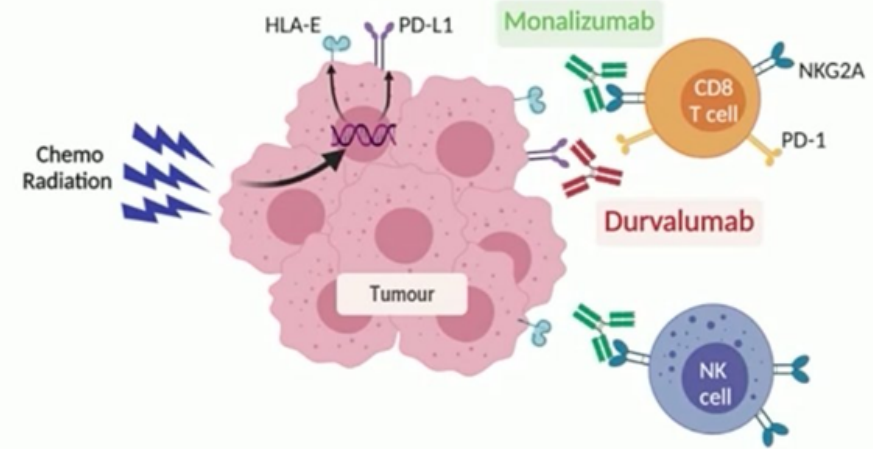
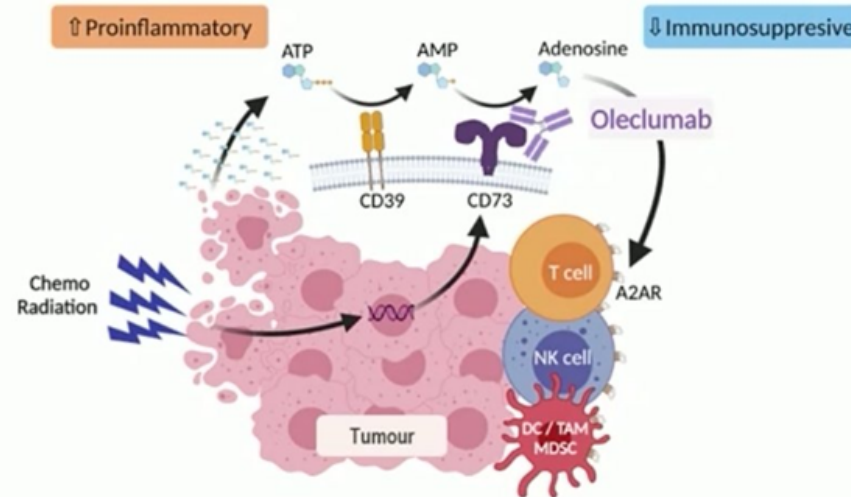
KEYLYNK-012  
04380636 (INT)

04866017  
(US/ AU)

04092283  
(US)

04325763  
(China)

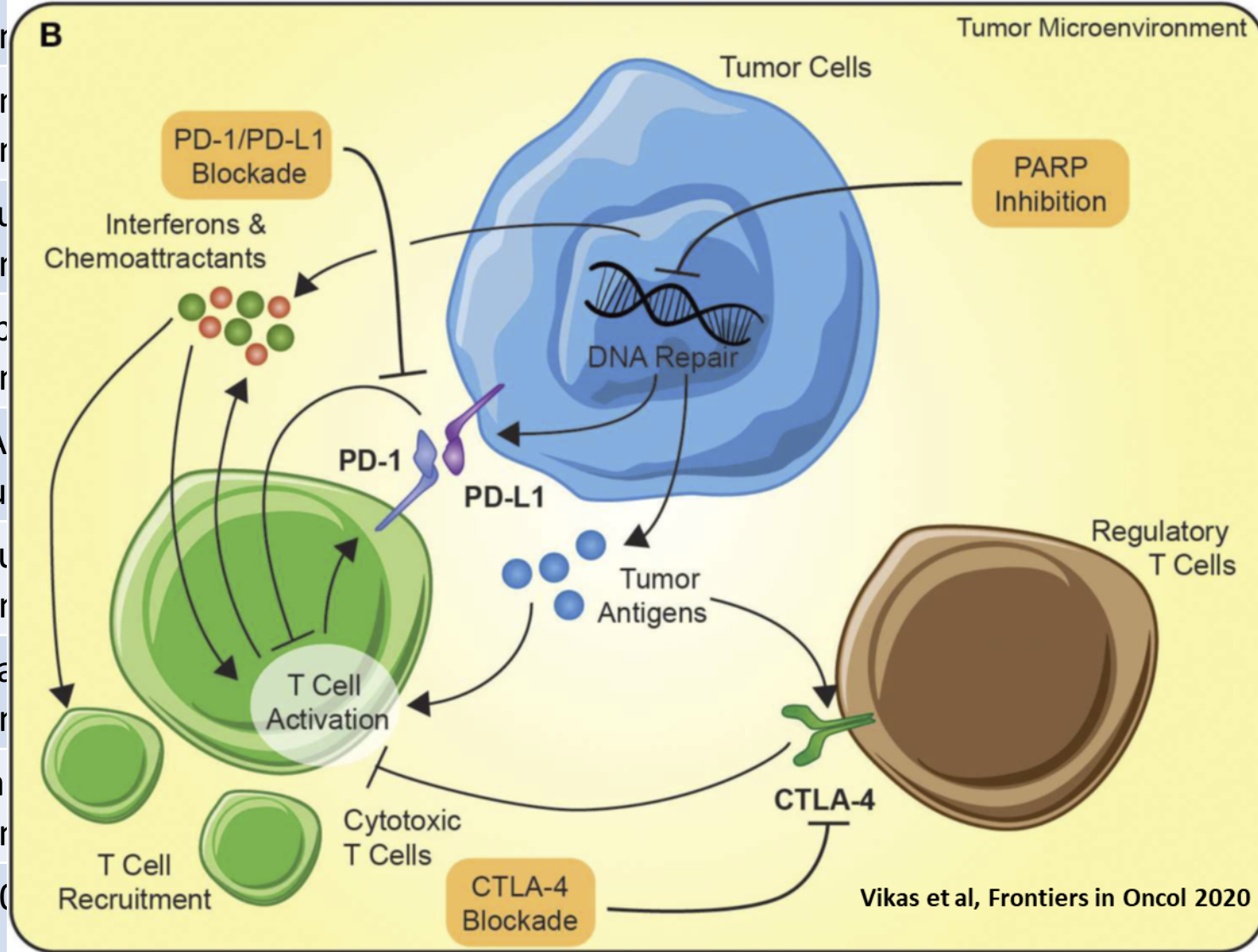
## Rationale for combining durvalumab with oleclumab (anti-CD73) or monalizumab (anti-NKG2A)



- RT induces expression of CD73 and HLA-E (NKG2A ligand), which inhibit antitumour immune response<sup>1-4</sup>
- Oleclumab inhibits CD73 to reduce extracellular adenosine production, thereby promoting antitumour immunity.<sup>5</sup> Oleclumab combined with durvalumab produced durable responses with manageable safety in a Ph I study of advanced *EGFR*m NSCLC<sup>6</sup>
- Monalizumab blocks NKG2A to reduce inhibition of NK and CD8+ T cells.<sup>7</sup> Monalizumab combined with cetuximab had promising activity with manageable safety in a Ph I/II trial of patients with R/M HNSCC<sup>8</sup>
- Combinations of RT and anti-CD73/NKG2A ± anti-PD-(X) show increased antitumour activity in preclinical models<sup>1,2,4</sup>

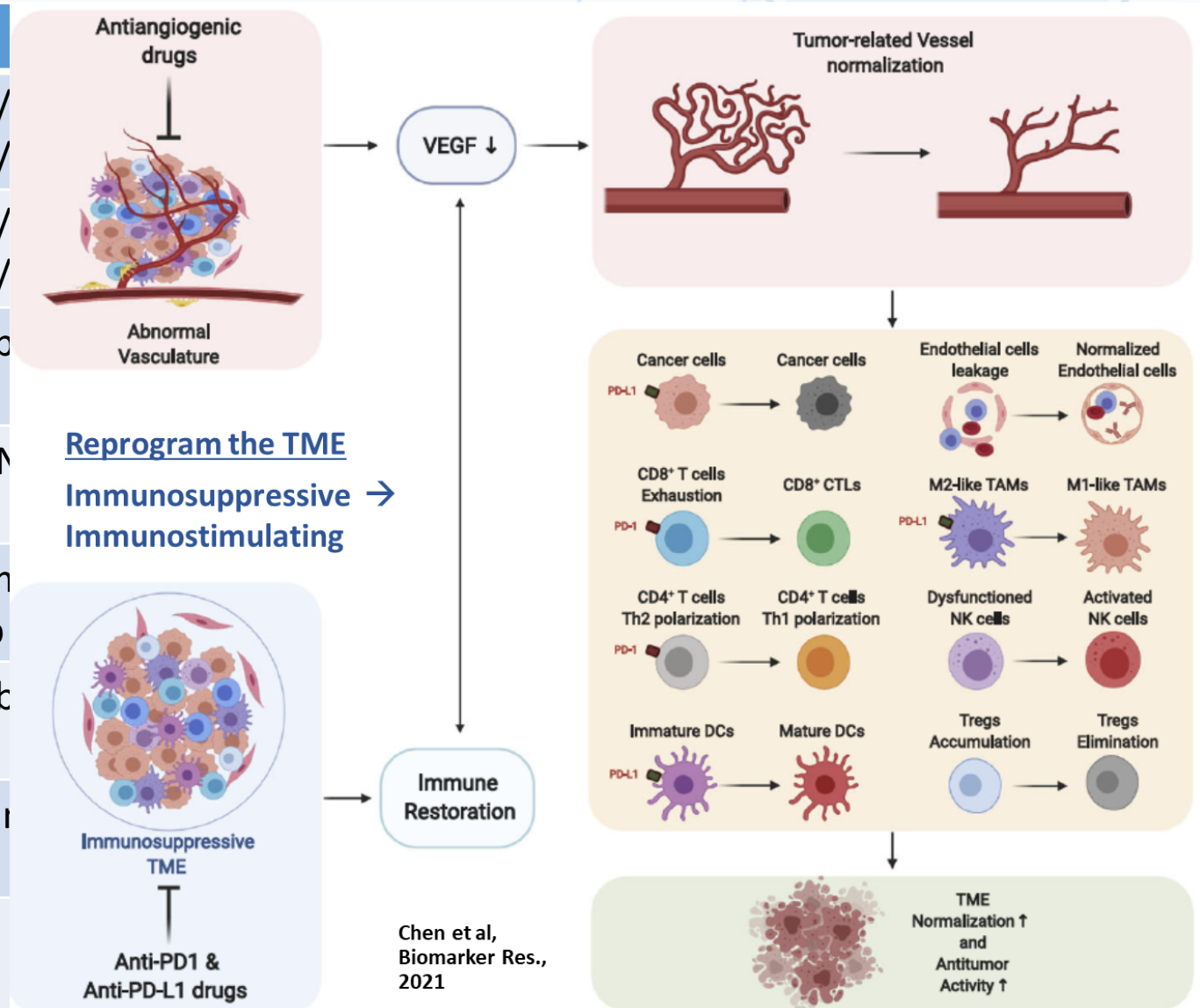
ATP, adenosine triphosphate; AMP, adenosine monophosphate; DC, dendritic cell; *EGFR*m, epidermal growth factor receptor mutant; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-(L)1, programmed cell death (ligand) 1; R/M HNSCC, recurrent/metastatic head and neck squamous cell carcinoma; RT, radiotherapy; TAM, tumour-associated macrophages  
 1. Wennerberg E, et al. Cancer Immunology Res 2020;8:465-478; 2. Tsukui H, et al. BMC Cancer 2020;20:411; 3. Nguyen AM, et al. Mol Cell Proteomics, 2020;19:375-389;  
 4. Battaglia NG, et al. J Immunol 2020;204:241-24; 5. Geoghegan JC, et al. MABs 2016;8:454-467; 6. Bendell J, et al. J Clin Oncol 2021;39.no. 15\_suppl.9047;  
 7. André P, et al. Cell 2018;175:1731-1743 e13; 8. Cohen RB et al. J Clin Oncol 38: 2020 (suppl; abstr 6516). Figures created with BioRender.com.

| Trial/ NCT (Loc)                | Target         | Treatment                                                             | 1° EndPt | RESULTS |
|---------------------------------|----------------|-----------------------------------------------------------------------|----------|---------|
| PACIFIC 8<br>05211895 (INT)     | TIGIT<br>(INT) | ChemoRT → Durvalumab/ Domvanalimab or Placebo<br>ChemoRT → Durvalumab | PFS      | 2027    |
| PACIFIC 9<br>05221840 (INT)     | CD73<br>NKG2A  | ChemoRT → Durvalumab<br>ChemoRT → Durvalumab                          |          |         |
| SKYSCRAPER-03<br>04513925 (INT) | TIGIT          | ChemoRT → Atezolizumab<br>ChemoRT → Durvalumab                        |          |         |
| CM73L<br>04026412 (INT)         |                | ChemoRT/ Nivolumab<br>ChemoRT → Durvalumab                            |          |         |
| KEYVIBE-006<br>05298423         | TIGIT          | ChemoRT/ MK-7684A<br>ChemoRT → Durvalumab                             |          |         |
| KEYLYNK-012<br>04380636 (INT)   | PARP           | ChemoRT/ Pembrolizumab<br>ChemoRT → Durvalumab                        |          |         |
| 04866017<br>(US/ AU)            | TIGIT          | ChemoRT/ Tislelizumab<br>ChemoRT → Durvalumab                         |          |         |
| 04092283<br>(US)                |                | ChemoRT/Durvalumab<br>ChemoRT → Durvalumab                            |          |         |
| 04325763<br>(China)             | VEGFR          | ChemoRT → TQB2450<br>ChemoRT → Placebo                                |          |         |



# Can we Improve Upon PACIFIC?

| Trial/ NCT (Loc)                | Target         | Treatment                                                                                                           |
|---------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------|
| PACIFIC 8<br>05211895 (INT)     | TIGIT<br>(INT) | ChemoRT → Durvalumab/<br>ChemoRT → Durvalumab/                                                                      |
| PACIFIC 9<br>05221840 (INT)     | CD73<br>NKG2A  | ChemoRT → Durvalumab/<br>ChemoRT → Durvalumab/                                                                      |
| SKYSCRAPER-03<br>04513925 (INT) | TIGIT          | ChemoRT → Atezolizumab<br>ChemoRT → Durvalumab                                                                      |
| CM73L<br>04026412 (INT)         |                | ChemoRT/ Nivolumab → M<br>ChemoRT → Durvalumab                                                                      |
| KEYVIBE-006<br>05298423         | TIGIT          | ChemoRT/ MK-7684A (Per<br>ChemoRT → Durvalumab                                                                      |
| KEYLYNK-012<br>04380636 (INT)   | PARP           | ChemoRT/ Pembrolizumab<br>ChemoRT → Durvalumab                                                                      |
| 04866017<br>(US/ AU)            | TIGIT          | ChemoRT/ Tislelizumab (a<br>ChemoRT → Durvalumab                                                                    |
| 04092283<br>(US)                |                | ChemoRT/Durvalumab →<br>ChemoRT → Durvalumab                                                                        |
| 04325763<br>(China)             | VEGFR          | ChemoRT → TQB2450 (anti-PDL1)/ Placebo or TQB2450/ Anlotinib<br>ChemoRT → Placebo (Anlotinib- RTKi including VEGFR) |



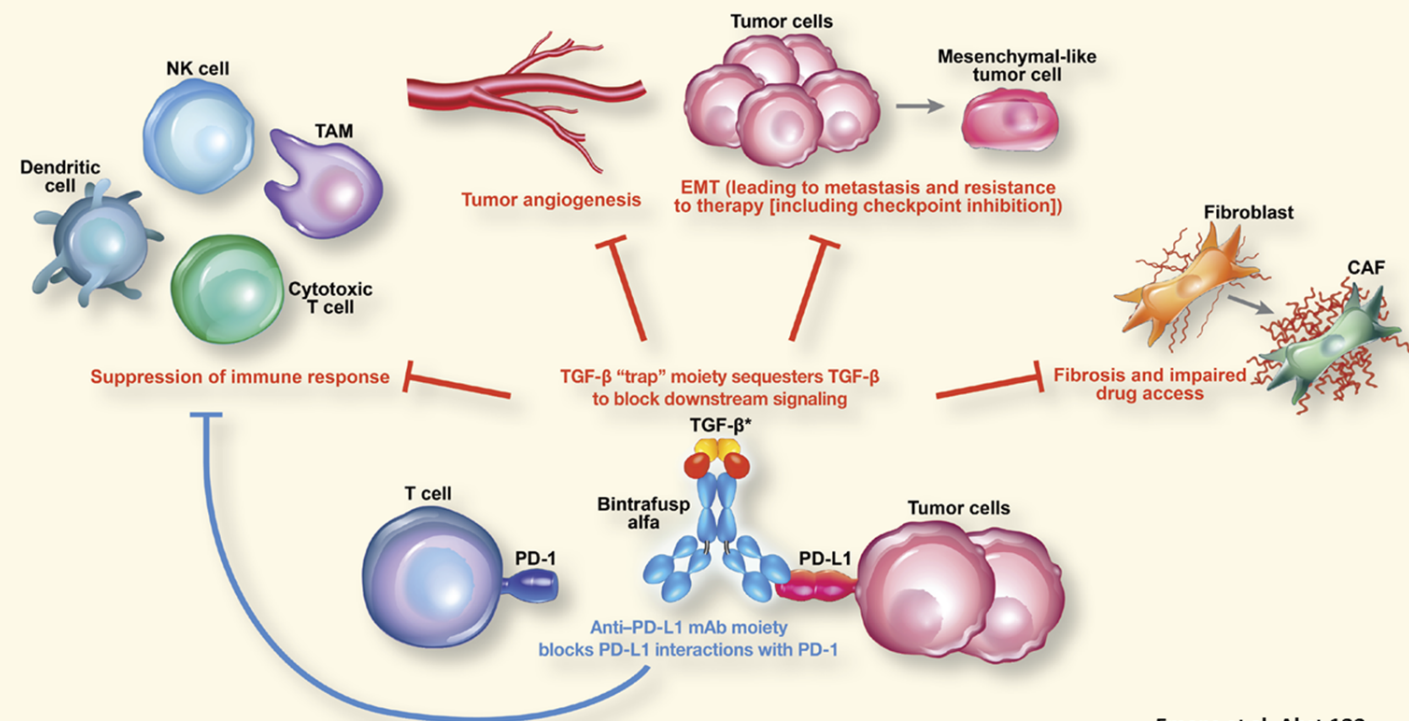
PFS

2022

# Overcoming 1° Resistance to IO (High PD-L1)

| Trial/ NCT                | Setting (Location)                 | Target       | Treatment                                                                | 1° EndPt  | Results |
|---------------------------|------------------------------------|--------------|--------------------------------------------------------------------------|-----------|---------|
| Skyscraper-01<br>04294810 | 1 Line, PD-L1 $\geq$ 50%<br>(INT)  | TIGIT        | Atezolizumab/ Tiragolumab<br>Atezolizumab/ Placebo                       | OS<br>PFS | 2025    |
| INTR@PID 037<br>03631706  | 1 Line, PD-L1 $\geq$ 50%<br>(INT)  | TGF- $\beta$ | Bintrafusp alfa (anti-PDL1/ TGFbetaRII Fusion Protein)<br>Pembrolizumab  | OS<br>PFS | 2022    |
| 04746924                  | 1L, PDL1 $\geq$ 50%<br>(INT)       | TIGIT        | Tislelizumab (anti-PD1) plus/minus Tociperlimab<br>Pembrolizumab/placebo | OS<br>PFS | 2025    |
| PERSEE<br>04547504        | 1L, PDL1 $\geq$ 50%<br>(France)    |              | Platin Doublet/ Pembrolizumab<br>Pembrolizumab                           | PFS       | 2025    |
| 05047250                  | 1L, PDL1 Hi (TC/IC)<br>(China)     |              | Platin Doublet<br>Atezolizumab                                           | PFS       | 2024    |
| TROPION-08<br>05215340    | 1L, PDL1 $\geq$ 50%<br>(US, Japan) | TROP2        | Pembrolizumab/ Dato-DXd (TROP2 ADC)<br>Pembrolizumab                     | OS<br>PFS | 2026    |

# Overcoming 1° Resistance to IO (High PD-L1)

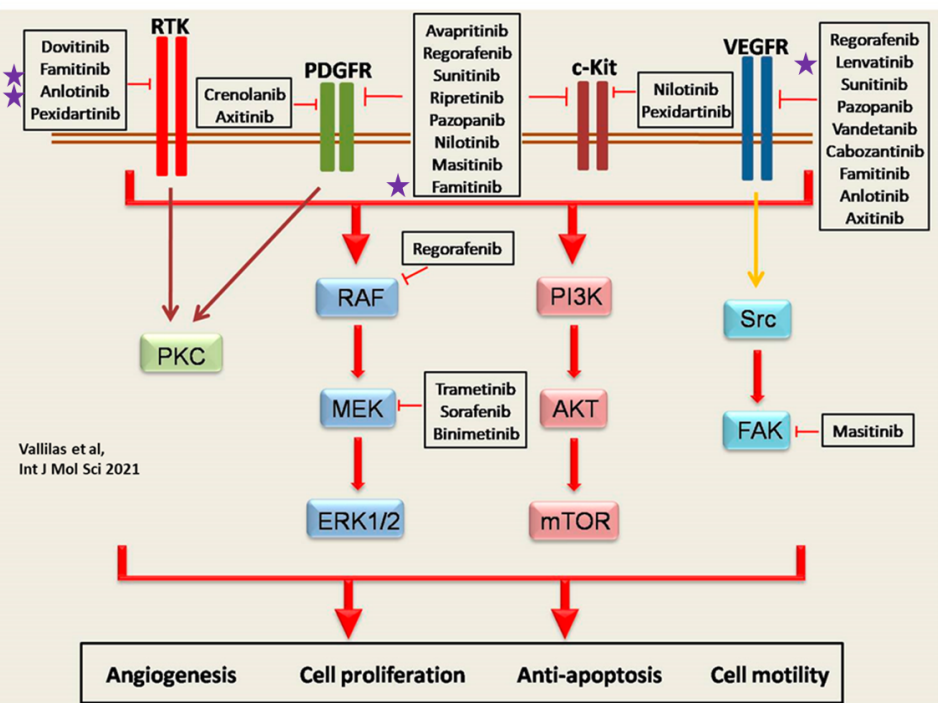
| Trial/ NCT                | Setting (Location)                 | Target       | Treatment                                                                            | 1° EndPt  | Results |
|---------------------------|------------------------------------|--------------|--------------------------------------------------------------------------------------|-----------|---------|
| Skyscraper-01<br>04294810 | 1 Line, PD-L1 $\geq$ 50%<br>(INT)  | TIGIT        | Atezolizumab/ Tiragolumab<br>Atezolizumab/ Placebo                                   | OS<br>PFS | 2025    |
| INTR@PID 037<br>03631706  | 1 Line, PD-L1 $\geq$ 50%<br>(INT)  | TGF- $\beta$ | Bintrafusp alfa (anti-PDL1/ TGFbetaRII Fusion Protein)<br>Pembrolizumab              | OS<br>PFS | 2022    |
| 04746924                  | 1L, PDL1 $\geq$ 50%<br>(INT)       | TIGIT        |  |           |         |
| PERSEE<br>04547504        | 1L, PDL1 $\geq$ 50%<br>(France)    |              |                                                                                      |           |         |
| 05047250                  | 1L, PDL1 Hi (TC/IC)<br>(China)     |              |                                                                                      |           |         |
| TROPION-08<br>05215340    | 1L, PDL1 $\geq$ 50%<br>(US, Japan) | TROP2        |                                                                                      |           |         |

# Overcoming 1° Resistance to IO (any PD-L1)

| Trial/ NCT               | Setting (Location)              | Target | Treatment                                                                             | 1° EndPt      | Results |
|--------------------------|---------------------------------|--------|---------------------------------------------------------------------------------------|---------------|---------|
| LEAP-007*<br>03829332    | 1 Line, PDL1 $\geq$ 1%<br>(INT) | VEGFR  | Pembrolizumab/ Lenvatinib * <b>Did not meet 1° Endpoint</b><br>Pembrolizumab/ Placebo | OS and<br>PFS | *       |
| MK-7684A-003<br>04738487 | 1L, PDL1 $\geq$ 1%<br>(INT)     | TIGIT  | MK-7684A (Pembrolizumab/ Vibostolimab)<br>Pembrolizumab                               | OS<br>PFS     | 2025    |
| 04964479<br>China        | 1L; PDL1 $\geq$ 1%<br>(China)   | VEGFR  | TQB2450 (anti-PDL1)/ Anlotinib (RTKi including VEGFR)<br>Pembrolizumab/ Placebo       | PFS           | 2022    |
| 04203485                 | 1L, PDL1 pos/<br>(China)        | VEGFR  | Camrelizumab (anti-PD1) +/- Apatinib (RTKi incl VEGFR)<br>Platin Doublet              | OS<br>PFS     | 2022    |
| 05042375                 | 1L, PDL1 pos.<br>(China)        | VEGFR  | Camrelizumab/Famitinib (RTKi incl VEGFR)<br>Pembrolizumab                             | OS<br>PFS     | 2024    |

# Overcoming 1° Resistance to IO (any PD-L1)

| Trial/ NCT               | Setting (Location)              | Target | Treatment                                                                             | 1° EndPt      | Results |
|--------------------------|---------------------------------|--------|---------------------------------------------------------------------------------------|---------------|---------|
| LEAP-007*<br>03829332    | 1 Line, PDL1 $\geq$ 1%<br>(INT) | VEGFR  | Pembrolizumab/ Lenvatinib * <b>Did not meet 1° Endpoint</b><br>Pembrolizumab/ Placebo | OS and<br>PFS | *       |
| MK-7684A-003<br>04738487 | 1L, PDL1 $\geq$ 1%<br>(INT)     | TIGIT  | MK-7684A (Pembrolizumab/ Vibostolimab)<br>Pembrolizumab                               | OS<br>PFS     | 2025    |
| 04964479                 | 1L; PDL1 $\geq$ 1%              | VEGFR  | TQB2450 (anti-PDL1)/ Anlotinib (RTKi including VEGFR)<br>Pembrolizumab/ Placebo       | PFS           | 2022    |
|                          |                                 |        | Camrelizumab (anti-PD1) +/- Apatinib (RTKi incl VEGFR)<br>Platin Doublet              | OS<br>PFS     | 2022    |
|                          |                                 |        | Camrelizumab/Famitinib (RTKi incl VEGFR)<br>Pembrolizumab                             | OS<br>PFS     | 2024    |



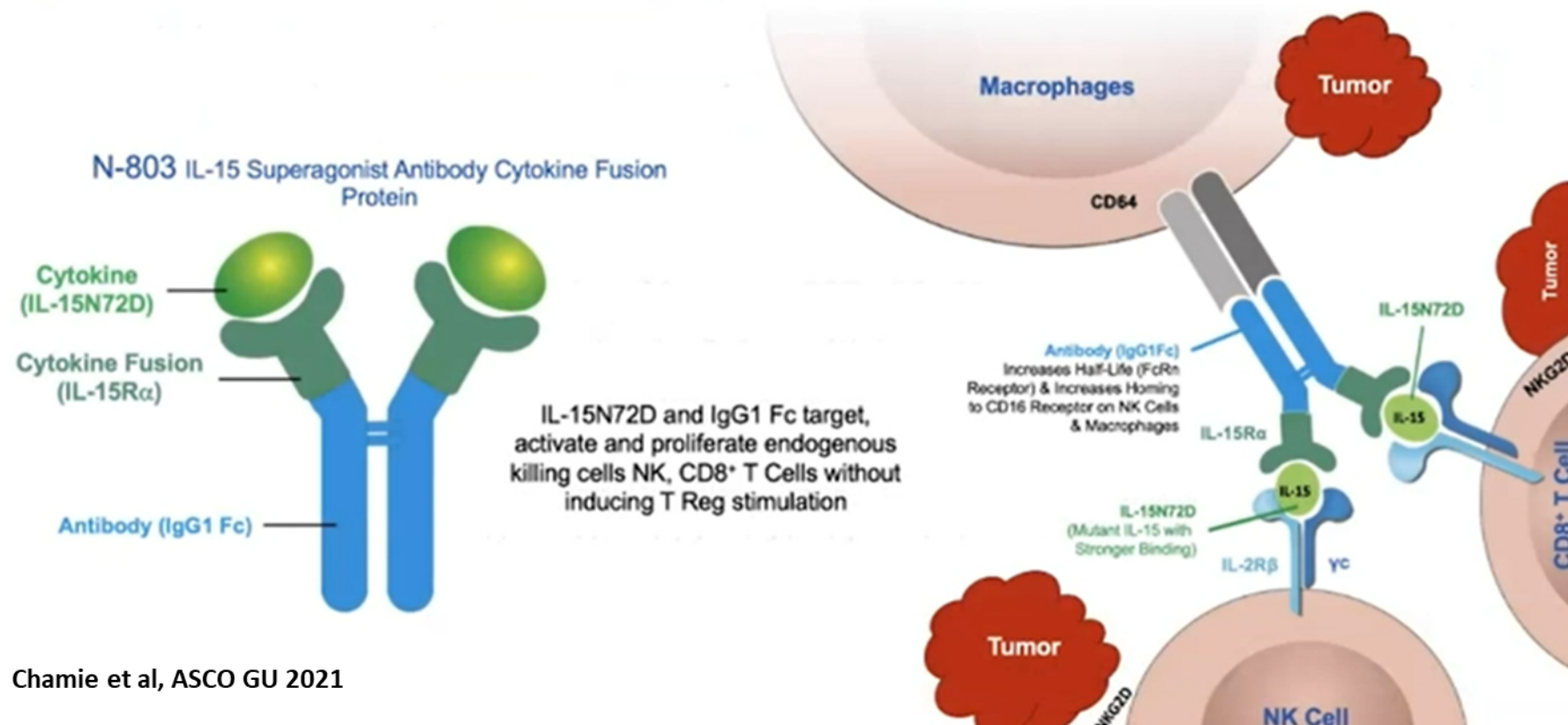
# Overcoming 1° Resistance to IO (PDL1 Independent)

| Trial/ NCT                | Setting (Location)      | Target        | Treatment                                                                               | 1° EndPt           | Results |
|---------------------------|-------------------------|---------------|-----------------------------------------------------------------------------------------|--------------------|---------|
| SKYSCRAPER 06<br>04619797 | 1L, Non-Sq<br>(INT)     | TIGIT         | Platin/Pemetrexed/Atezolizumab/ Tiragolumab<br>Platin/Pemetrexed/Pembrolizumab/ Placebo | OS<br>PFS          | 2024    |
| LEAP-006<br>03829318      | 1 Line, N-Sq<br>(INT)   | VEGFR         | Platin/Pemetrexed/Pembrolizumab/ Lenvatinib<br>Platin/Pemetrexed/Pembrolizumab/ Placebo | DLT, OS<br>and PFS | 2023    |
| IPOWER151<br>04194203     | 1L, Non-Sq<br>(China)   |               | Platin Doublet/Bevacizumab/ Atezolizumab<br>Platin Doublet/Bevacizumab/ Placebo         | PFS                | 2023    |
| ENREACH-L-01<br>04474119  | 1L, Sq NSCLC<br>(China) |               | Catboplatin/ Paclitaxel/ KN046 (anti-PDL1/CTLA4)<br>Catboplatin/ Paclitaxel/ Placebo    | PFS<br>OS          | 2022    |
| KEYVIBE-007<br>05226598   | 1L                      | TIGIT         | Platin Doublet/ MK-7684A (Pembrolizumab/Vibostolimab)<br>Platin Doublet/ Pembrolizumab  | OS<br>PFS          | 2025    |
| QUILT 2.023<br>03520686   | 1L<br>(US)              | IL15<br>SupAg | Pembrolizumab/N-803 +/- Platin Doublet Chemo<br>Pembrolizumab +/- Platin Doublet Chemo  | PFS                | 2023    |
| CANOPY-1<br>03631199      | 1 Line<br>(INT)         | IL-1β         | Platin Doublet/ Pembrolizumab/ Canakinumab<br>Platin Doublet/ Pembrolizumab/ Placebo    | OS<br>PFS          | -       |

# Overcoming

## N-803 Mechanism of Action

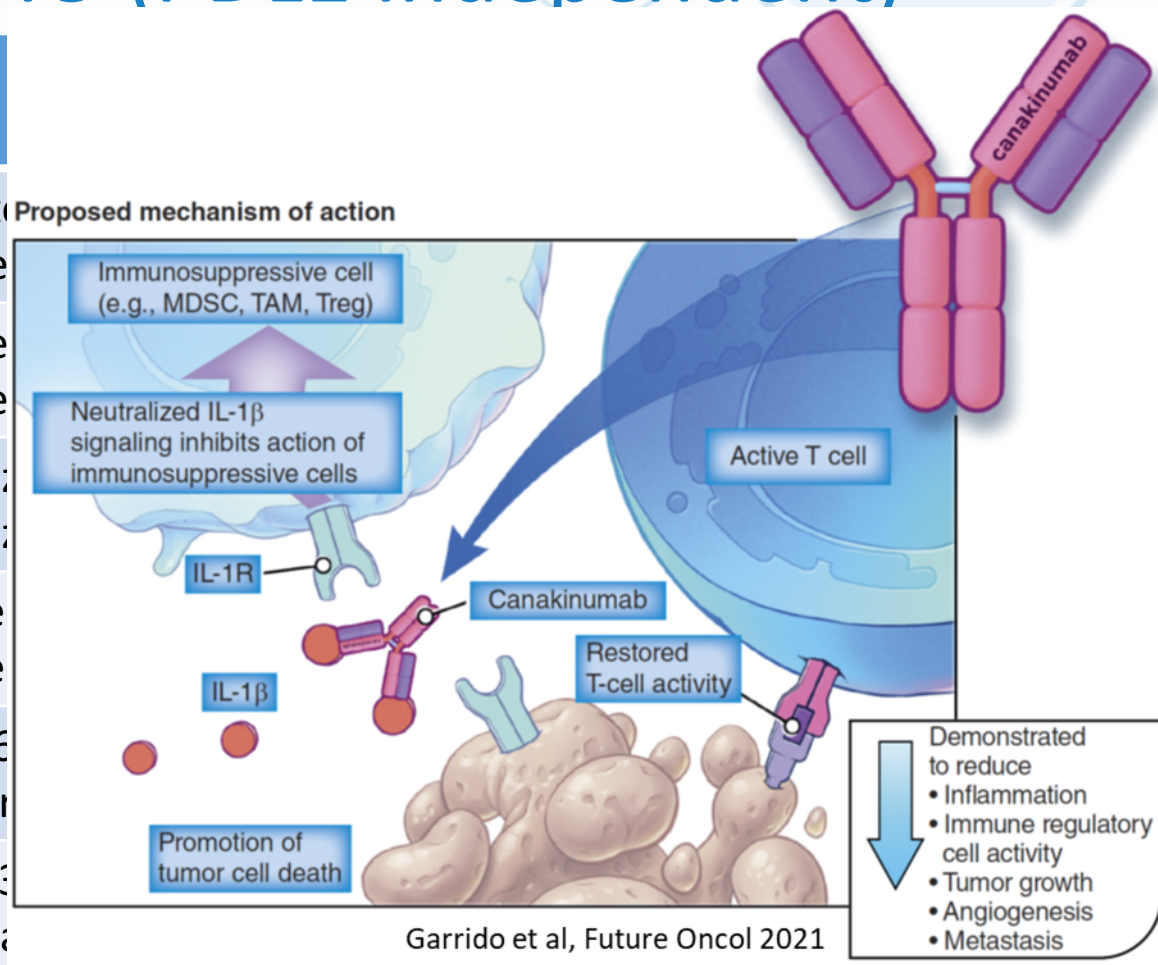
| Trial/ NCT                | Setting (Location)   |
|---------------------------|----------------------|
| SKYSCRAPER 06<br>04619797 | 1L, Non-Sq (INT)     |
| LEAP-006<br>03829318      | 1 Line, N-Sq (INT)   |
| IPOWER151<br>04194203     | 1L, Non-Sq (China)   |
| ENREACH-L-01<br>04474119  | 1L, Sq NSCLC (China) |
| KEYVIBE-007<br>05226598   | 1L                   |
| QUILT 2.023<br>03520686   | 1L (US)              |
| CANOPY-1<br>03631199      | 1 Line (INT)         |



|                         |              |            |                                                                                        |           |      |
|-------------------------|--------------|------------|----------------------------------------------------------------------------------------|-----------|------|
| QUILT 2.023<br>03520686 | 1L (US)      | IL15 SupAg | Pembrolizumab/N-803 +/- Platin Doublet Chemo<br>Pembrolizumab +/- Platin Doublet Chemo | PFS       | 2023 |
| CANOPY-1<br>03631199    | 1 Line (INT) | IL-1β      | Platin Doublet/ Pembrolizumab/ Canakinumab<br>Platin Doublet/ Pembrolizumab/ Placebo   | OS<br>PFS | -    |

# Overcoming 1° Resistance to IO (PDL1 Independent)

| Trial/ NCT                | Setting (Location)   | Target     | Treatment                                                                            |    |   |
|---------------------------|----------------------|------------|--------------------------------------------------------------------------------------|----|---|
| SKYSCRAPER 06<br>04619797 | 1L, Non-Sq (INT)     | TIGIT      | Platin/Pemetrexed/At<br>Platin/Pemetrexed/Pe                                         |    |   |
| LEAP-006<br>03829318      | 1 Line, N-Sq (INT)   | VEGFR      | Platin/Pemetrexed/Pe<br>Platin/Pemetrexed/Pe                                         |    |   |
| IPOWER151<br>04194203     | 1L, Non-Sq (China)   |            | Platin Doublet/Bevac<br>Platin Doublet/Bevac                                         |    |   |
| ENREACH-L-01<br>04474119  | 1L, Sq NSCLC (China) |            | Catboplatin/ Paclitaxe<br>Catboplatin/ Paclitaxe                                     |    |   |
| KEYVIBE-007<br>05226598   | 1L                   | TIGIT      | Platin Doublet/ MK-76<br>Platin Doublet/ Pemb                                        |    |   |
| QUILT 2.023<br>03520686   | 1L (US)              | IL15 SupAg | Pembrolizumab/N-803<br>Pembrolizumab +/- Pl                                          |    |   |
| CANOPY-1<br>03631199      | 1 Line (INT)         | IL-1β      | Platin Doublet/ Pembrolizumab/ Canakinumab<br>Platin Doublet/ Pembrolizumab/ Placebo | OS | - |
|                           |                      |            | <b>* Did not meet 1° Endpoint</b>                                                    |    | * |



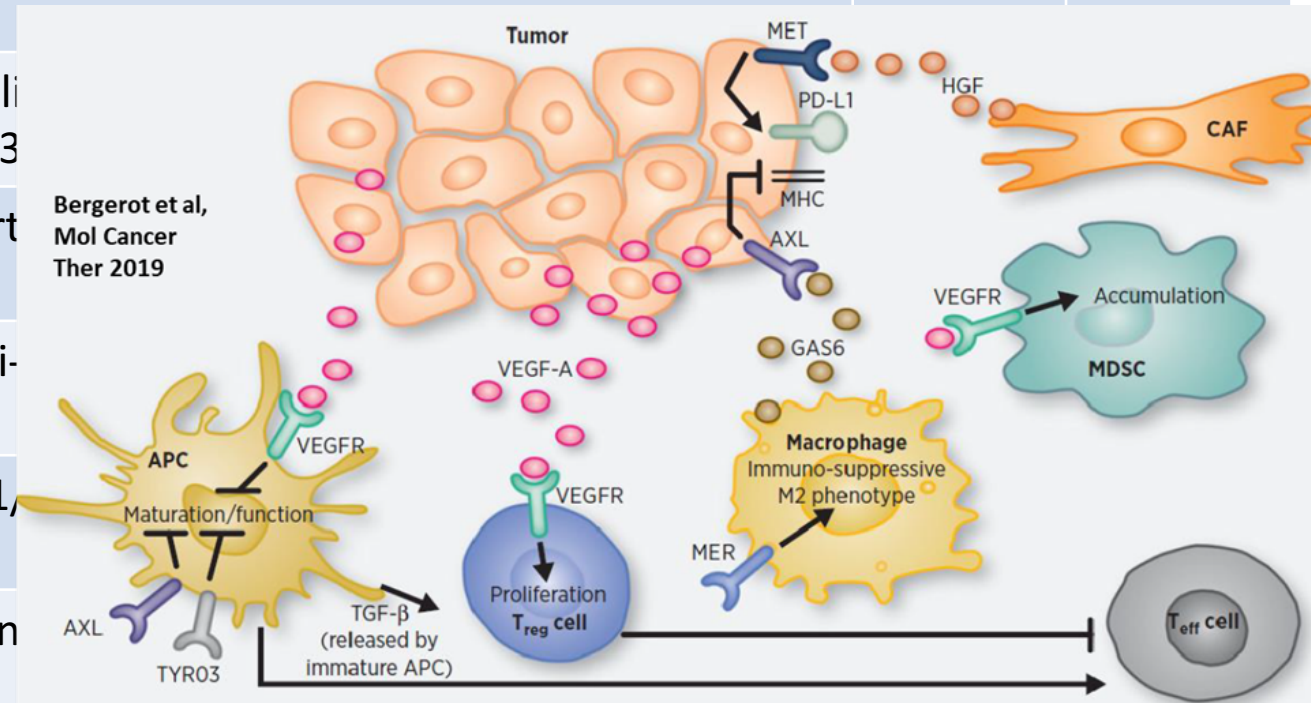
# Overcoming 1° Resistance to IO (PDL1 Independent)

| Trial/ NCT              | Setting (Location)                   | Target | Treatment                                                                                                 | 1° EndPt  | Results |
|-------------------------|--------------------------------------|--------|-----------------------------------------------------------------------------------------------------------|-----------|---------|
| 04619433                | 1L<br>(China)                        | VEGFR  | Carboplatin/Pemetrexed/Camrelizumab (anti-PD1)/ Famitinib<br>Carboplatin/Pemetrexed/Camrelizumab/ Placebo | PFS       | 2022    |
| KEYLYNK-006<br>03976323 | 1 Line, N-Sq<br>Maintenance<br>(INT) | PARP   | Platin/Pemetrexed/Pembrolizumab →<br>Pembrolizumab/ Olaparib<br>Pembrolizumab/ Pemetrexed                 | OS<br>PFS | 2024    |
| KEYLYNK-008<br>03976362 | 1 Line, Sq<br>Maintenance<br>(INT)   | PARP   | Platin/nab-Paclitaxel)/Pembrolizumab →<br>Pembrolizumab/ Olaparib<br>Pembrolizumab/ Placebo               | OS<br>PFS | 2024    |
| ZEAL<br>04475939        | 1L-Maint<br>(INT)                    | PARP   | Platinum Doublet/ Pembrolizumab →<br>Pembrolizumab/ Niraparib<br>Pembrolizumab/ Placebo                   | OS<br>PFS | 2024    |



| Trial/ NCT (Loc)             | Setting                    | Target        | Treatment                                                                                 | 1° EndPt  | Results |
|------------------------------|----------------------------|---------------|-------------------------------------------------------------------------------------------|-----------|---------|
| LEAP-008<br>03976375 (INT)   | Post CT and<br>ICI         | VEGFR         | Pembrolizumab/ Lenvatinib<br>Docetaxel                                                    | OS<br>PFS | 2023    |
| Sapphire<br>03906071 (INT)   | Post CT and<br>ICI; Non-Sq | VEGFR<br>TAM  | Nivolumab/Sitravatinib (RTKI incl. VEGFR, TAM)<br>Docetaxel                               | OS        | 2022    |
| CONTACT-01<br>04471428 (INT) | Post CT and<br>ICI         | VEGFR<br>TAM  | Atezolizumab/ Cabozantinib (RTKi incl. VEGFR, TAM)<br>Docetaxel                           | OS        | 2022    |
| LUNG MAP<br>05096663 (US)    | 2/3 Line<br>Prior IO       | IL15<br>SupAg | ALT-803/ Pembrolizumab<br>SOC salvage 2 <sup>nd</sup> / 3 <sup>rd</sup> Line Chemotherapy | OS        | 2024    |
| COSTAR<br>04655976 (INT)     | Prior IO and<br>Chemo      | TIM3          | Docetaxel/Dostartalimab (anti-PD1) plus/minus Cobolimab<br>Docetaxel                      | OS        | 2024    |
| 04921358<br>(China and AU)   | Prior<br>ChemoIO           | VEGFR<br>TAM  | Tislelizumab (anti-PD1) plus Sitravatinib<br>Docetaxel                                    | OS<br>PFS | 2024    |
| 05001724<br>(China)          | Prior IO/<br>ChemoIO       |               | KN046 (anti-PDL1/CTLA4) versus Lenvatinib<br>Docetaxel                                    | OS<br>PFS | 2024    |
| 05106335<br>(China)          | Prior IO and<br>Chemo      | VEGFR         | Camrelizumab (anti-PD1)/ Famitinib or Famitinib alone<br>Docetaxel                        | OS        | 2025    |
| 03944980<br>(China)          | 2L                         |               | Docetaxel/ anti-PD1 Activated Peripheral T cell<br>Docetaxel                              | PFS       | 2022    |

| Trial/ NCT (Loc)             | Setting                    | Target        | Treatment                                                               | 1° EndPt  | Results |
|------------------------------|----------------------------|---------------|-------------------------------------------------------------------------|-----------|---------|
| LEAP-008<br>03976375 (INT)   | Post CT and<br>ICI         | VEGFR         | Pembrolizumab/ Lenvatinib<br>Docetaxel                                  | OS<br>PFS | 2023    |
| Sapphire<br>03906071 (INT)   | Post CT and<br>ICI; Non-Sq | VEGFR<br>TAM  | Nivolumab/Sitravatinib (RTKI incl. VEGFR, TAM)<br>Docetaxel             | OS        | 2022    |
| CONTACT-01<br>04471428 (INT) | Post CT and<br>ICI         | VEGFR<br>TAM  | Atezolizumab/ Cabozantinib (RTKi incl. VEGFR, TAM)<br>Docetaxel         | OS        | 2022    |
| LUNG MAP<br>05096663 (US)    | 2/3 Line<br>Prior IO       | IL15<br>SupAg | ALT-803/ Pembrolizumab<br>SOC salvage 2 <sup>nd</sup> / 3 <sup>rd</sup> |           |         |
| COSTAR<br>04655976 (INT)     | Prior IO and<br>Chemo      | TIM3          | Docetaxel/Dostarlimab<br>Docetaxel                                      |           |         |
| 04921358<br>(China and AU)   | Prior<br>ChemoIO           | VEGFR<br>TAM  | Tislelizumab (anti-VEGFR)<br>Docetaxel                                  |           |         |
| 05001724<br>(China)          | Prior IO/<br>ChemoIO       |               | KN046 (anti-PDL1)<br>Docetaxel                                          |           |         |
| 05106335<br>(China)          | Prior IO and<br>Chemo      | VEGFR         | Camrelizumab (anti-PD-1)<br>Docetaxel                                   |           |         |
| 03944980<br>(China)          | 2L                         |               | Docetaxel/ anti-PD-1<br>Docetaxel                                       |           |         |





| Trial/ NCT (Loc)             | Setting                    | Target        | Treatment                                                                                 | 1° EndPt  | Results |
|------------------------------|----------------------------|---------------|-------------------------------------------------------------------------------------------|-----------|---------|
| LEAP-008<br>03976375 (INT)   | Post CT and<br>ICI         | VEGFR         | Pembrolizumab/ Lenvatinib<br>Docetaxel                                                    | OS<br>PFS | 2023    |
| Sapphire<br>03906071 (INT)   | Post CT and<br>ICI; Non-Sq | VEGFR<br>TAM  | Nivolumab/Sitravatinib (RTKI incl. VEGFR, TAM)<br>Docetaxel                               | OS        | 2022    |
| CONTACT-01<br>04471428 (INT) | Post CT and<br>ICI         | VEGFR<br>TAM  | Atezolizumab/ Cabozantinib (RTKi incl. VEGFR, TAM)<br>Docetaxel                           | OS        | 2022    |
| LUNG MAP<br>05096663 (US)    | 2/3 Line<br>Prior IO       | IL15<br>SupAg | ALT-803/ Pembrolizumab<br>SOC salvage 2 <sup>nd</sup> / 3 <sup>rd</sup> Line Chemotherapy | OS        | 2024    |
| COSTAR<br>04655976 (INT)     | Prior IO and<br>Chemo      | TIM3          | Docetaxel/Dostartalimab (anti-PD1) plus/minus Cobolimab<br>Docetaxel                      | OS        | 2024    |
| 04921358<br>(China and AU)   | Prior<br>ChemoIO           | VEGFR<br>TAM  | Tislelizumab (anti-PD1) plus Sitravatinib<br>Docetaxel                                    | OS<br>PFS | 2024    |
| 05001724<br>(China)          | Prior IO/<br>ChemoIO       |               | KN046 (anti-PDL1/CTLA4) versus Lenvatinib<br>Docetaxel                                    | OS<br>PFS | 2024    |
| 05106335<br>(China)          | Prior IO and<br>Chemo      | VEGFR         | Camrelizumab (anti-PD1)/ Famitinib or Famitinib alone<br>Docetaxel                        | OS        | 2025    |
| 03944980<br>(China)          | 2L                         |               | Docetaxel/ anti-PD1 Activated Peripheral T cell<br>Docetaxel                              | PFS       | 2022    |

# Other IO Being Evaluated in NSCLC (Phase I, II)

*Generally combined with PD-1 axis Inhibitors*

- Other ICI and Stimulatory Agonists
- Anti-Angiogenesis Agents
- Epigenetic Therapy
- Vaccines (including personalized vaccines)
- Cellular Therapies
- Cytokine Therapies
- Microbiome-based Therapy
- Intratumoral Therapies