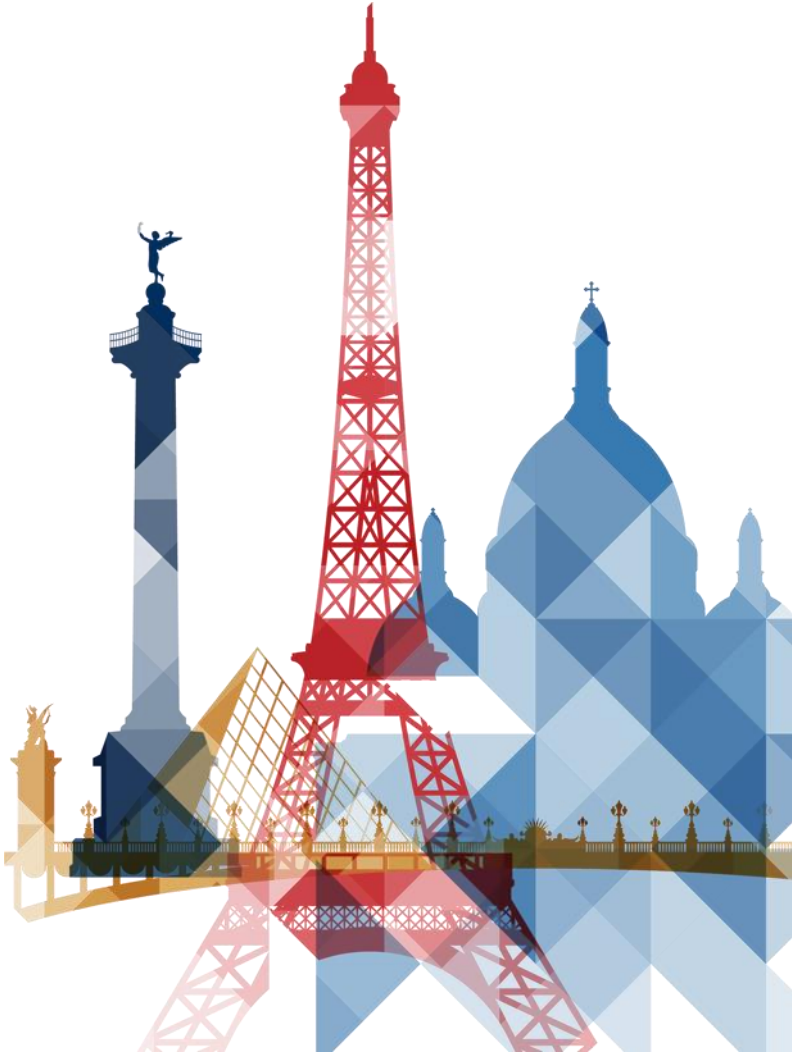
PARIS 2022 ESMO congress

What's next?

Emerging next-generation immunotherapy in lung cancer

Natasha Leighl MD MMSc FRCPC FASCO
Princess Margaret Cancer Centre

Toronto, Canada
12 September 2022



DECLARATION OF INTERESTS

Natasha Leighl (previous 24 months)

Institutional grant funding (University Health Network):

- Amgen, Array, Astra Zeneca, Bayer, BMS, Eli Lilly, EMD Serono, Guardant Health, Inivata, MSD, Novartis, Pfizer, Roche, Takeda

Honoraria (independent CME lectures):

- Amgen, Astra Zeneca, BMS, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi Genzyme, Takeda

Consulting fees:

- Bayer, GlaxoSmithKline, Puma Biotechnology

Objectives

- To highlight some emerging immunotherapeutics in lung cancer targeting:
  - Co-inhibitory receptors
  - Tumor Immune Microenvironment
  - Bispecifics
  - Antigen-directed therapy (very briefly!)

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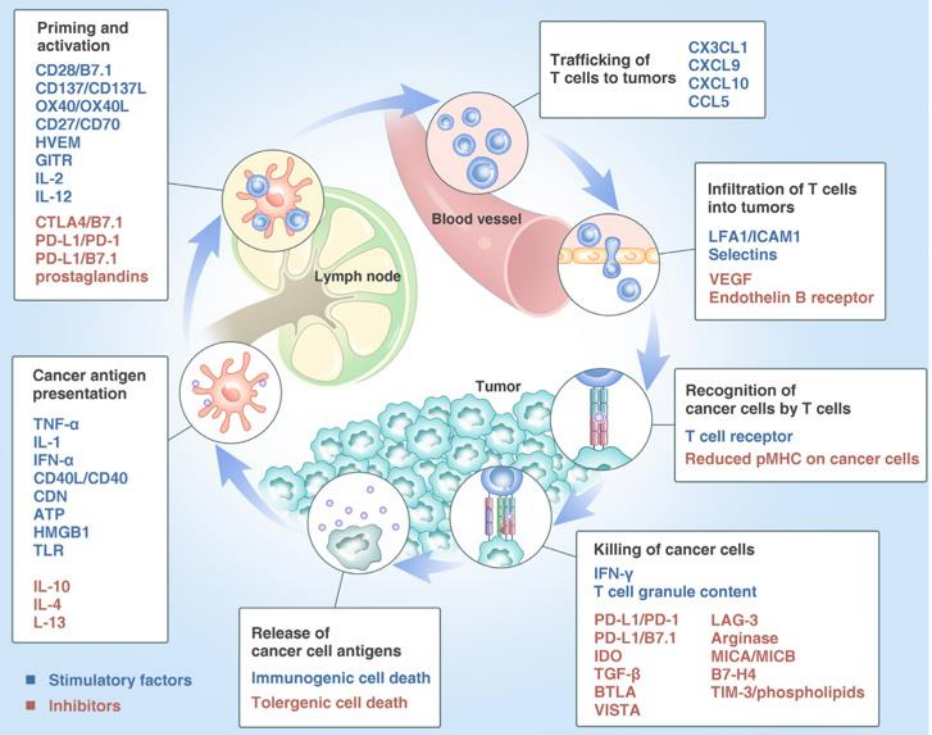
Cancer Immunity Cycle

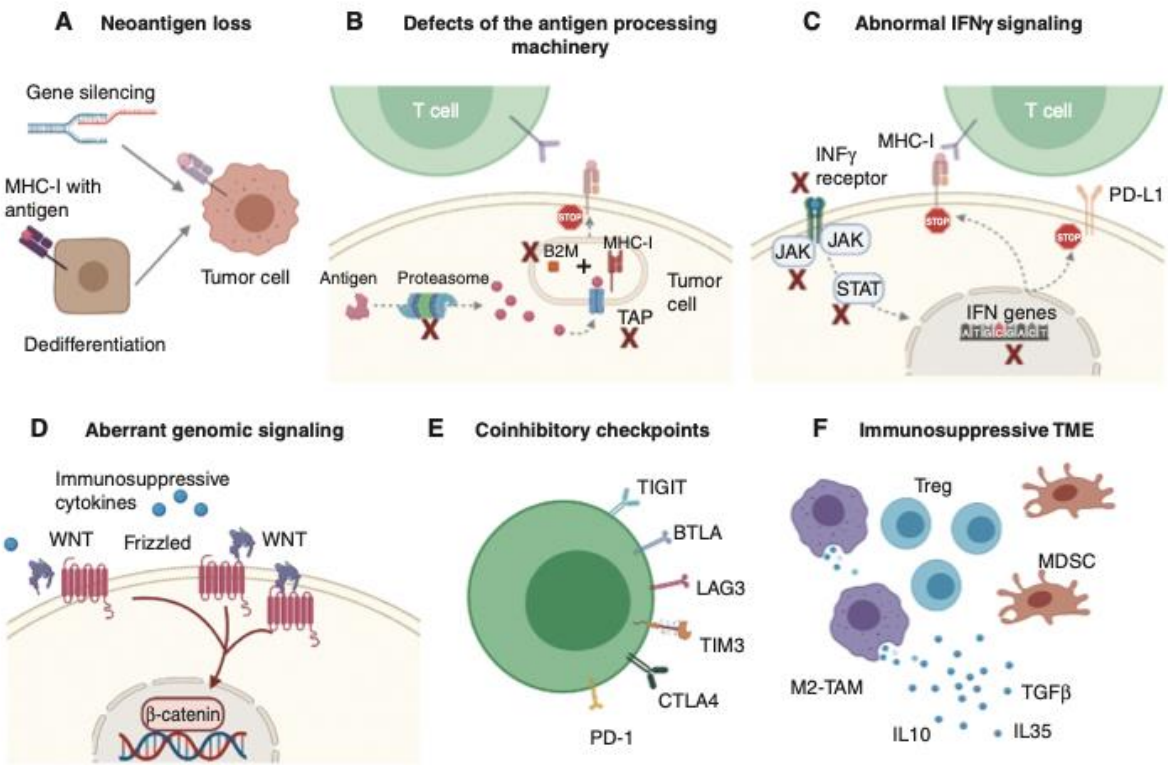


Luo Precision Clin Med 2021

Resistance Mechanisms to Checkpoint Inhibition

Immune desert phenotype

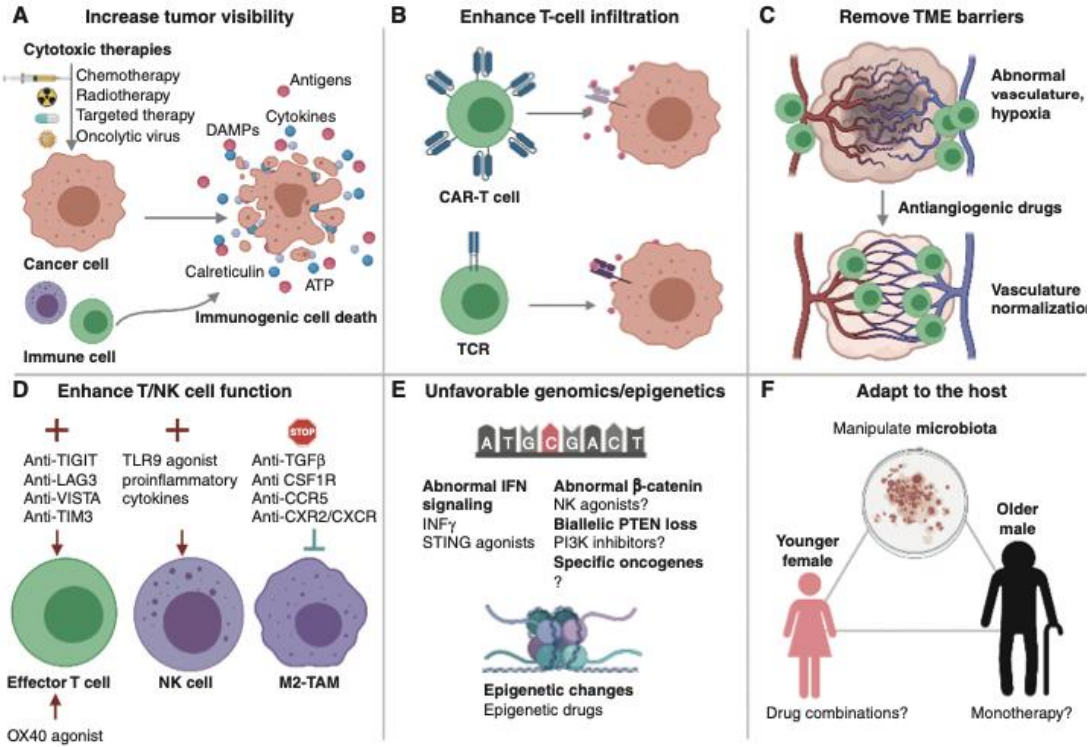
Differences by organ location



Impact of microbiome

Aldea Cancer Disc 2021

Overcoming resistance



Aldea Cancer Disc 2021

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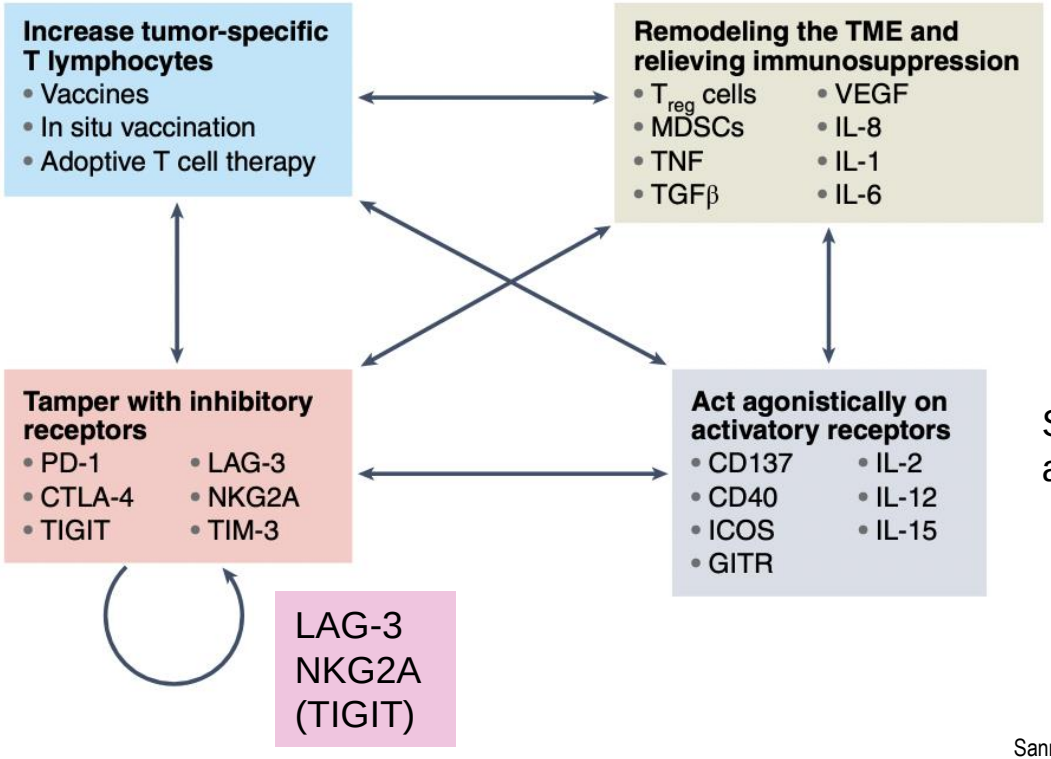
Potential for rational combinations of novel therapies

Steer the car

Vaccines, cell therapy bispecifics



? Pave the road

Targeting VEGF, TAM

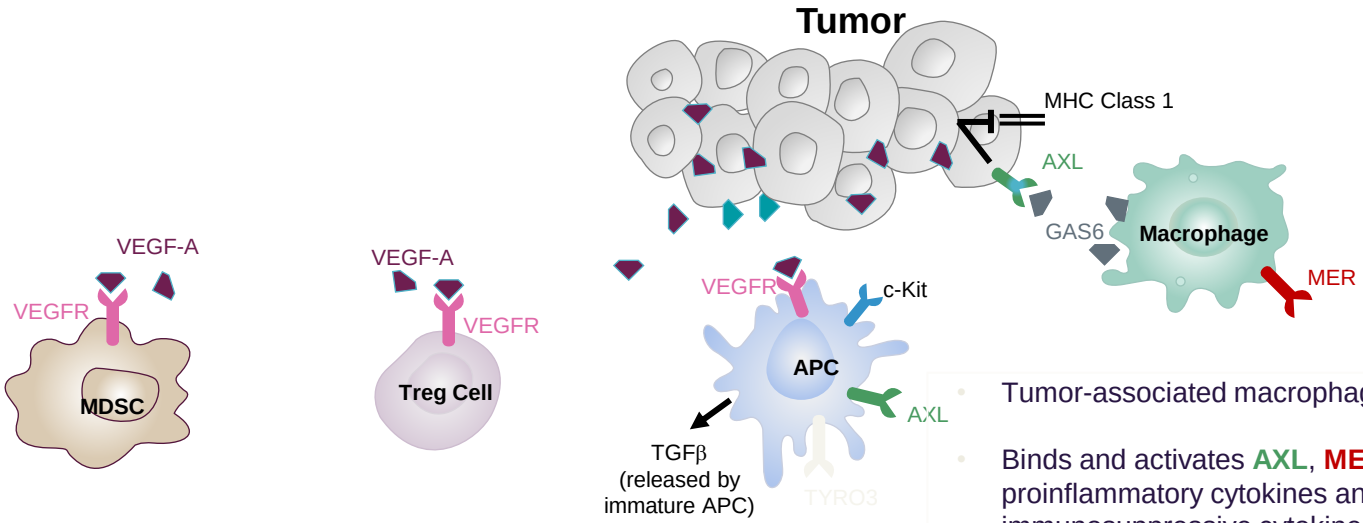
Release the "brakes"

Step on the accelerator

LAG-3
NKG2A
(TIGIT)

Sanmamed et al Nat Cancer 2022

TAM RTKs can lead to an immune suppressive tumor microenvironment and Resistance



VEGF released by tumor cells
- Increases number of MDSCs and Tregs
- Inhibits maturation and function of DCs

- Tumor-associated macrophages release **GAS6**
- Binds and activates **AXL**, **MER** and **TYRO3**, which inhibits proinflammatory cytokines and stimulates immunosuppressive cytokines
- **MER** inhibits M1 (immune stimulating) polarization of macrophages and induces immunosuppressive M2 polarization

Modified from Carbone WCLC2022

Bergerot Mol Cancer Ther 2019; Carbone WCLC 2022

Treatment	Phase	TYRO3	AXL	MER	VEGFR	KIT
Sitravatinib[1,2]	3	●	●	●	●	●
Cabozantinib[1,3]	3	●	●	●	●	●
Bemcentinib[1,4]	2		●			
Ramucirumab	2				●	
Lenvatinib	3				●	
PF-07265807/ ARRAY-067[1,5]	1		●	●		
INCB081776[1,6]	1		●	●		
BA3011[1,7]	2		●			
TP-0903[1,8]	1		●			

1. Leal ASCO 2021; 2. Du W, et al. JCI Insight. 2018. 3. Cabometyx Prescribing information, Exelixis, 2021. 4. Ludwig KF, et al. Cancer Res. 2018; Subbiah V, et al. Presented at ASCO Annual Meeting 2021. 6. Rios-Doria J, et al. Front Oncol 2020. 7. Ahnert JR, et al. Presented at ASCO Annual Meeting 2018. 8. Mangelson R, et al. Cancer Res. 201

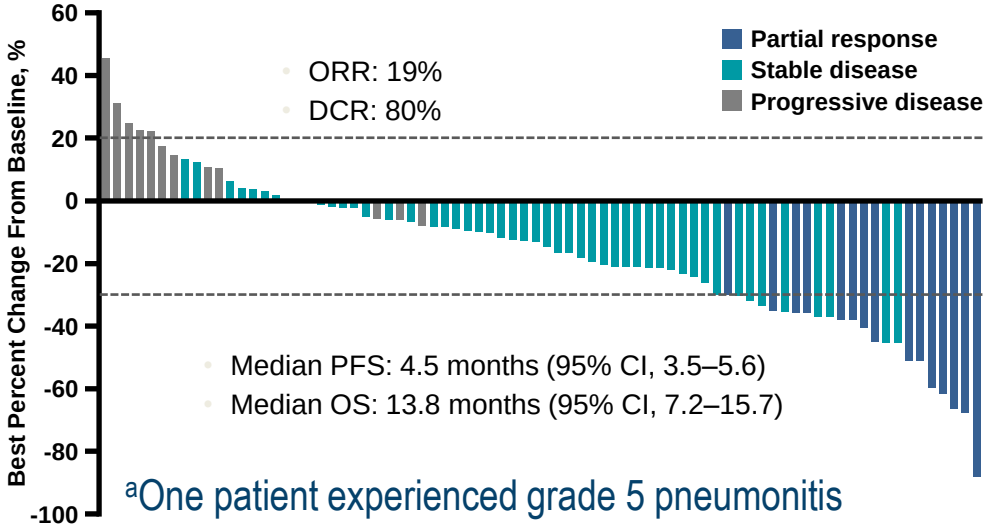
Trials targeting TAM RTKs

Trials	Phase	Treatment Arm(s)	Primary Endpoint(s)
MRTX-500[1,2] NCT02954991	2	**Sitravatinib** + nivolumab	ORR
SAPPHIRE[3] NCT03906071	3	**Sitravatinib** + nivolumab vs docetaxel	OS
NCT04921358[4]	3	**Sitravatinib** + tislelizumab vs docetaxel	OS and PFS
COSMIC-021 Cohort 7[5] NCT03170960	1/2	**Cabozantinib** + atezolizumab	ORR
CONTACT-01[6] NCT04471428	3	**Cabozantinib** + atezolizumab vs docetaxel	OS
BGBC008[7] NCT03184571	2	**Bemcentinib** + pembrolizumab	ORR
NCT03522142[8]	1	**INCB081776** ± retifanlimab	AEs, Recommended Dose for Expansion
NCT04681131[9]	2	**BA3011** ± PD-1 inhibitor	ORR, AEs
NCT02729298[10]	1	**TP-0903** monotherapy	DLT, AEs

NCT02954991. Leal TA, et al. ESMO 2021. 3. ciNCT03906071.4. NCT04921358. NCT03170960. /NCT04471428. NCT03184571. NCT03522142. /NCT04681131. /NCT02729298.

COSMIC-021: Phase 1/2, Non-randomized, Open-Label Study of Cabozantinib in Combination With Atezolizumab in NSCLC

Efficacy



[a]One patient experienced grade 5 pneumonitis

Safety

TRAEs (≥10%), n=81	Any Grade, n (%)	Grade ≥3[a], n (%)
Diarrhea	36 (44)	1 (1)
Decreased appetite	30 (37)	1 (1)
Fatigue	29 (36)	4 (5)
Nausea	28 (35)	2 (2)
Asthenia	24 (30)	5 (6)
Constipation	21 (26)	0
Pyrexia	20 (25)	0
AST increase	19 (23)	2 (2)
Hypertension	19 (23)	5 (6)
Vomiting	19 (23)	0
ALT increase	17 (21)	3 (4)
PPE	17 (21)	3 (4)
Hypomagnesemia	16 (20)	1 (1)
Weight decrease	16 (20)	3 (4)

Neal JW, et al. ASCO Annual Meeting 2022

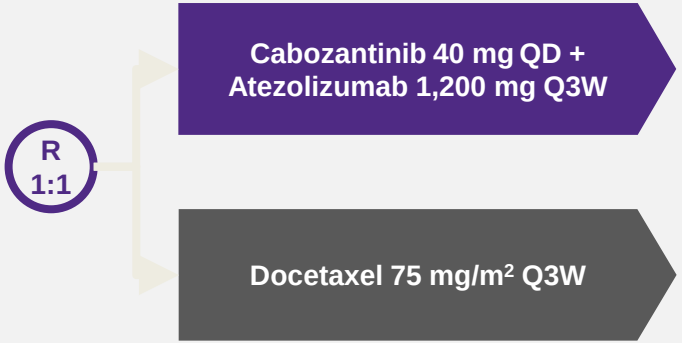
CONTACT-01: Phase 3 Study of Cabozantinib + Atezolizumab vs Docetaxel After Prior CPI and Platinum-Based Chemotherapy in NSCLC

Screening / Enrollment

Key Eligibility Criteria (N=366)

- Metastatic NSCLC
- Progression on or following platinum-containing chemotherapy and anti-PD-1/L1 therapy
- Excludes patients with a sensitizing EGFR mutation or ALK translocation

Phase 3
Randomized Combination Treatment vs Docetaxel



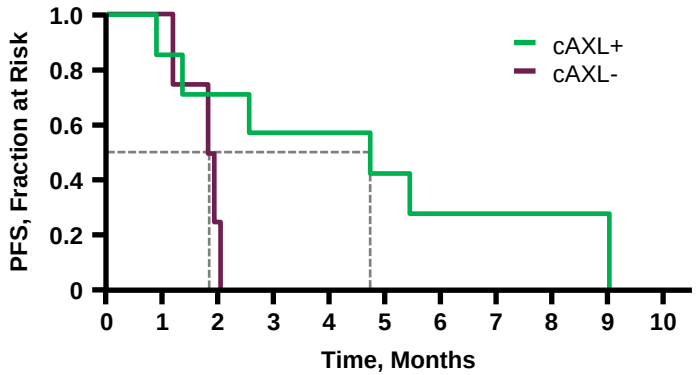
Study Objectives

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DOR, PROs, safety

ClinicalTrials.gov. NCT04471428. clinicaltrials.gov/ct2/show/NCT04471428. Accessed August 4, 2022

BGBC008: Phase 2, Non-randomized, Open-Label Study of Bemcentinib in Combination With Pembrolizumab in Advanced NSCLC

Cohort B Efficacy



Efficacy	cAXL+[a]	cAXL-	p
PFS, months	4.73	1.87	0.066
ORR, %	14	0	-

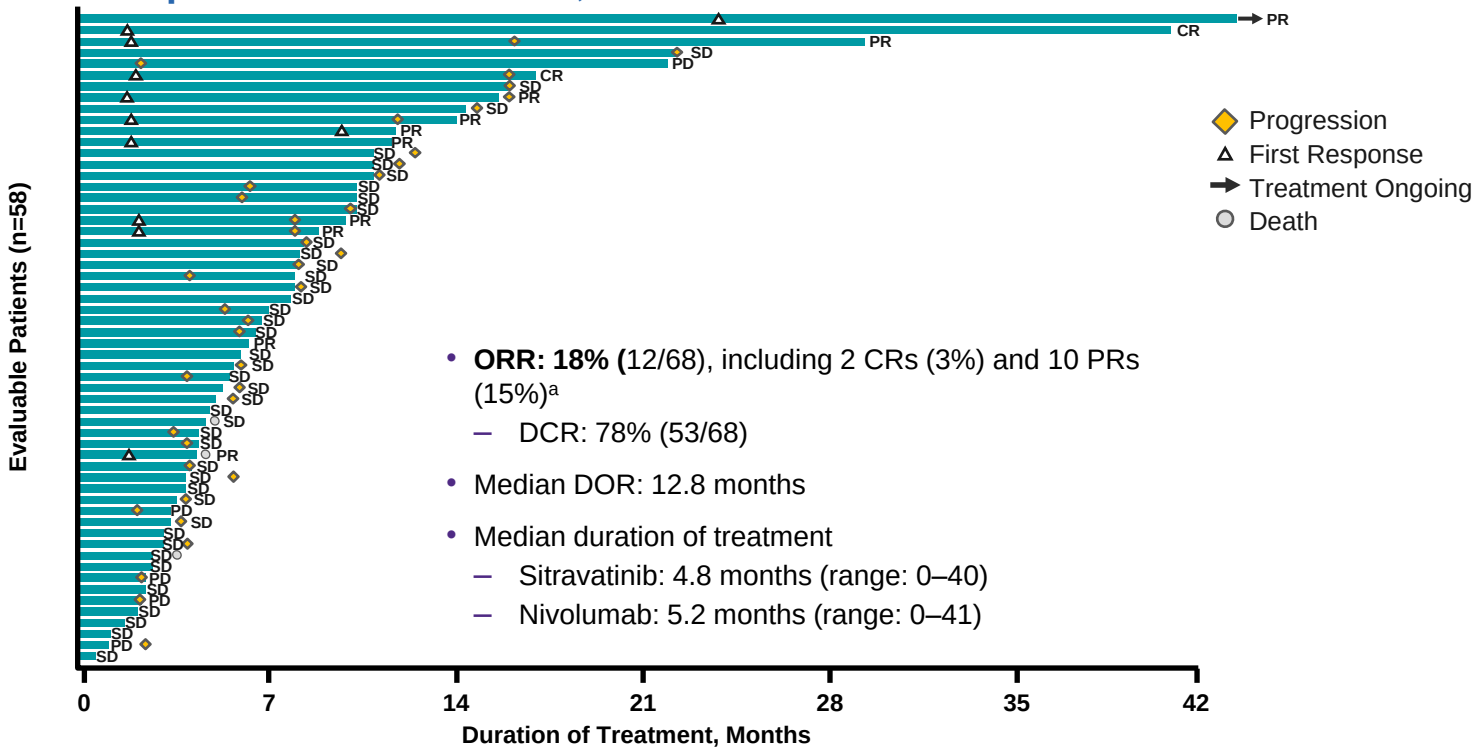
Cohort A and B Safety

TRAEs (≥10%)	Any Grade, n (%)	Grade ≥3,[b] n (%)
Diarrhea	20 (30)	0
ALT increase	19 (29)	7 (11)
AST increase	18 (27)	3 (5)
Asthenia	11 (17)	4 (6)
QT prolongation	10 (15)	2 (3)
Anemia	9 (14)	2 (3)
Blood creatinine increase	9 (14)	0
Fatigue	9 (14)	1 (2)
Nausea	9 (14)	0

[a]Axl expression on membranes of tumor and immune cells. [b]No grade 5 TRAEs were reported

Gabra H, et al. Next Gen Immuno-Oncology 2020

MRTX-500: Sitravatinib + Nivolumab in Patients With Non-Squamous NSCLC with prior benefit from checkpoint inhibitors - ORR, DOR



- **ORR: 18% (**12/68), including 2 CRs (3%) and 10 PRs (15%)[a]
  - DCR: 78% (53/68)
- Median DOR: 12.8 months
- Median duration of treatment
  - Sitravatinib: 4.8 months (range: 0–40)
  - Nivolumab: 5.2 months (range: 0–41)

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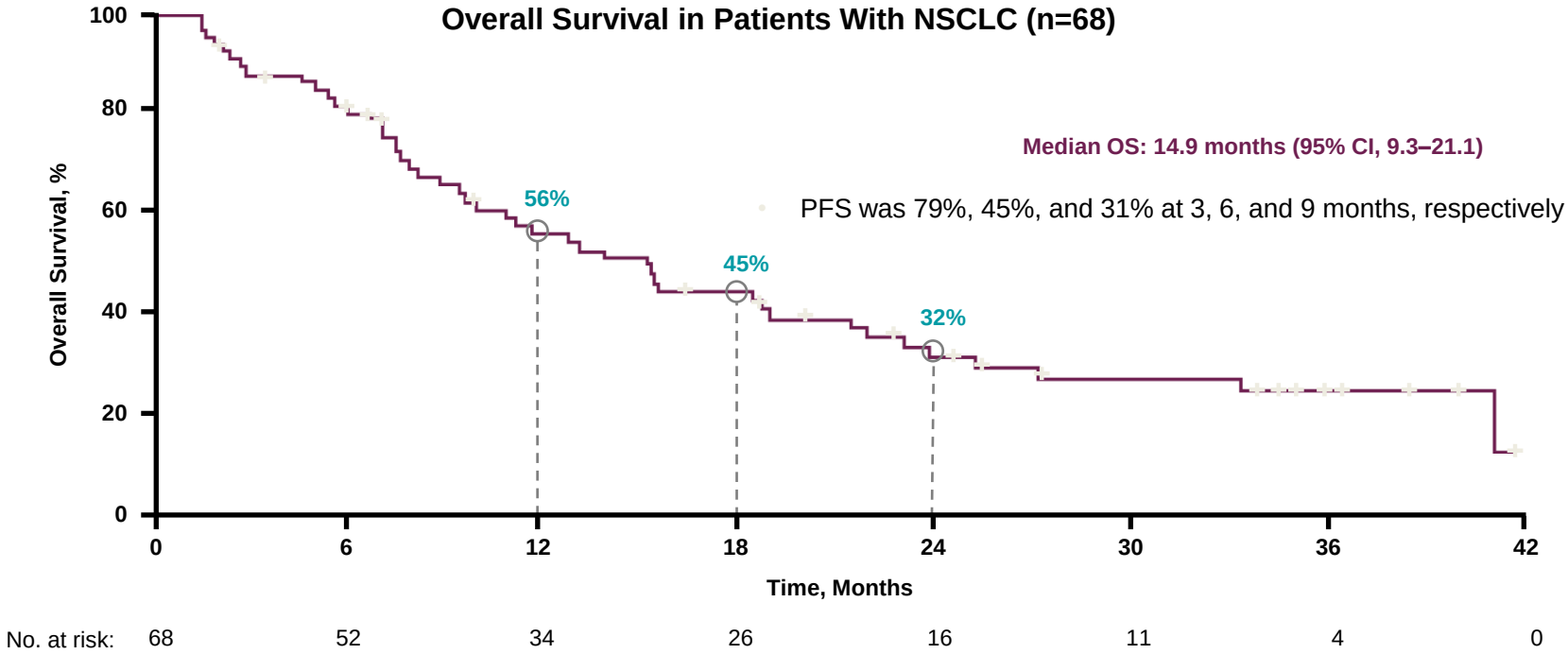
Leal TA, et al. Presented at ESMO Congress 2021

MRTX-500: Sitravatinib + Nivolumab in Patients who had Prior Clinical Benefit (PCB) on CPI but Subsequently Experienced PD



Leal TA, et al. Presented at ESMO Congress 2021

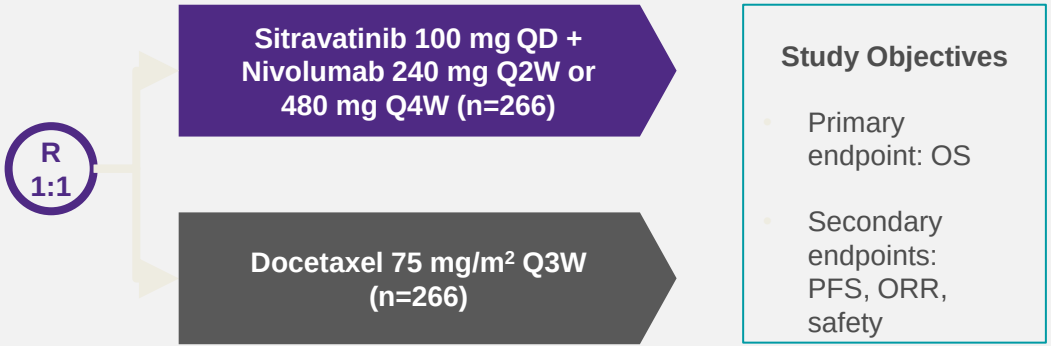
SAPPHIRE

Screening / Enrollment

Key Eligibility Criteria (N=532)

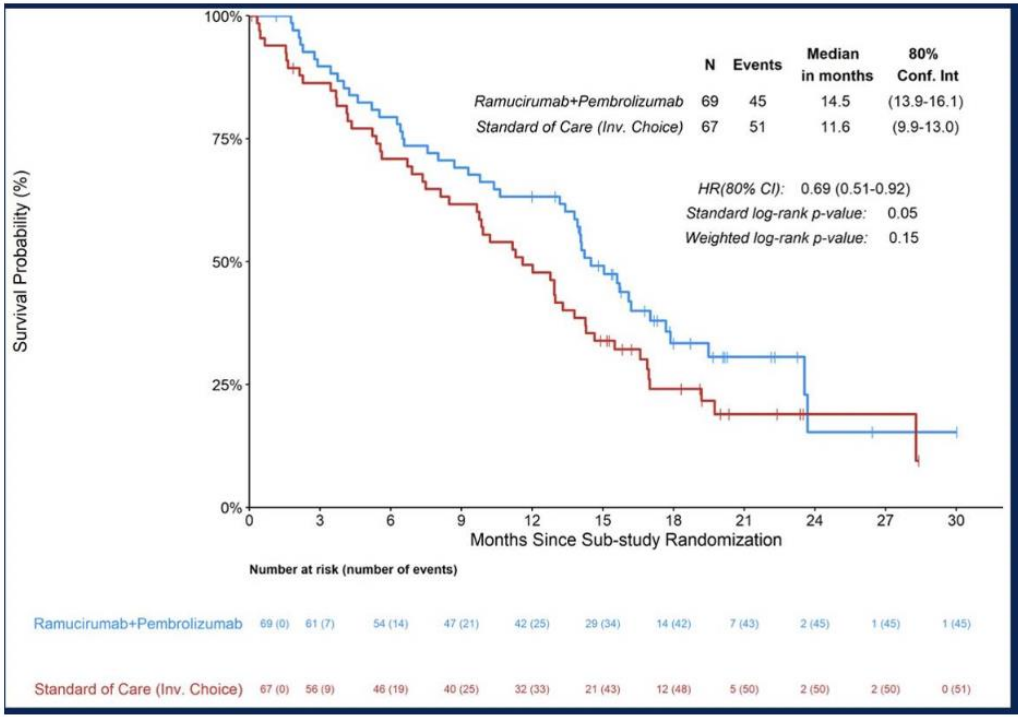
- Advanced, non-squamous NSCLC
- Prior PD-1/L1 inhibitor for ≥4 months (prior anti-CTLA-4 therapy allowed)
- Progression on or following PD-1/L1 inhibitor in combination with or following chemotherapy
- Excludes patients with known driver mutations

Phase 3
Randomized Combination Treatment vs Docetaxel



NCT03906071.

Lung MAP S1800A (Prior platinum, CPI for >3 months)



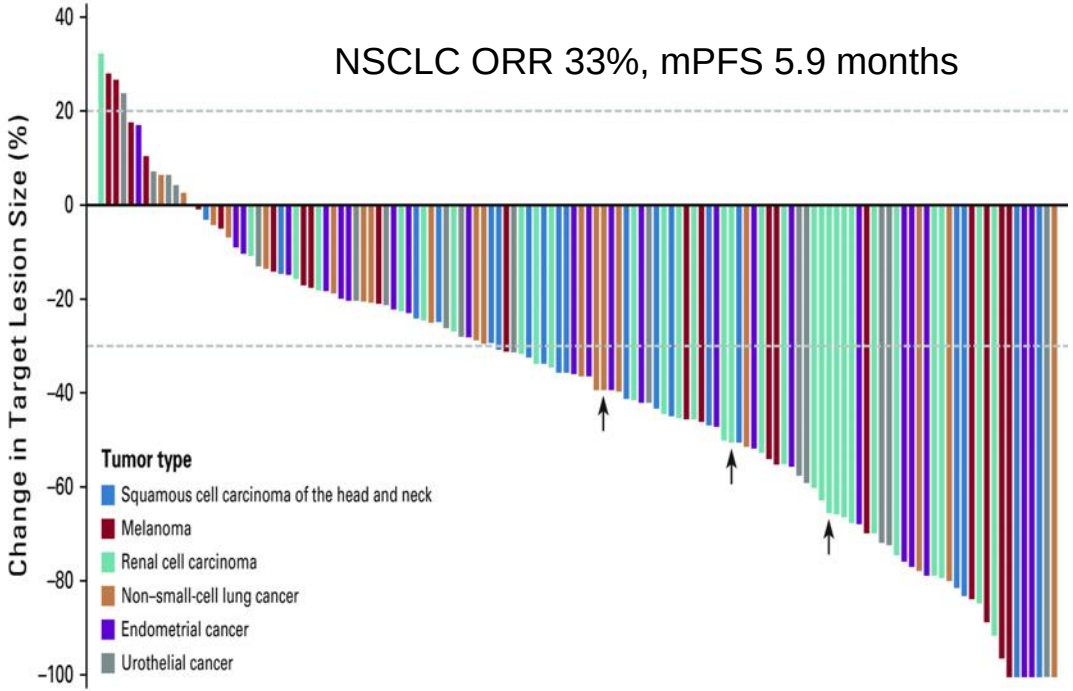
- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

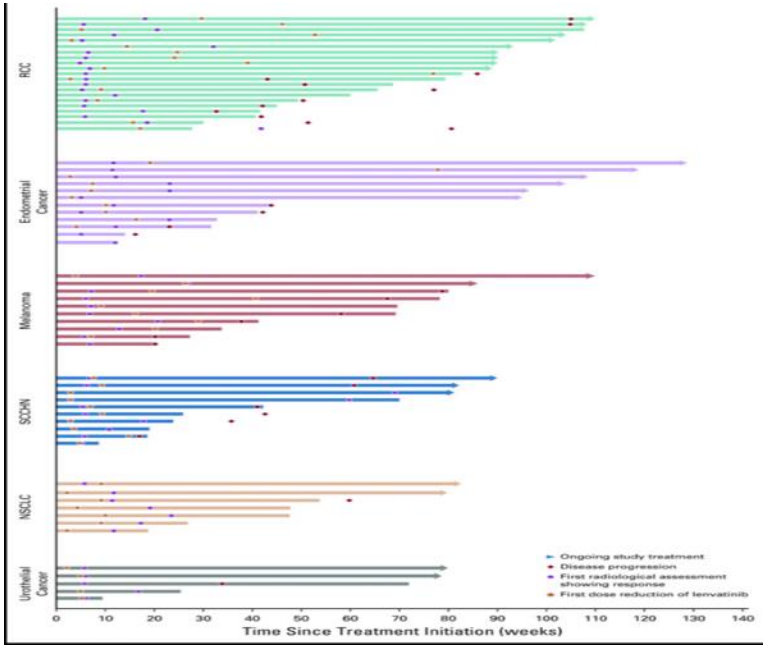
Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Reckamp et al J Clin Oncol 2022

Lenvatinib + Pembrolizumab Phase Ib/II





Taylor et al J Clin Oncol 2020

LEAP-006 | NCT03829319 | **1L**
Non-squamous NSCLC

Phase 3 | 726 participants
Placebo controlled | Randomized | International
Estimated study completion date | June 21, 2024
Arm 1: Pemetrexed + Platinum Chemotherapy + Pembrolizumab + Lenvatinib
Arm 2: Pemetrexed + Platinum Chemotherapy + Pembrolizumab + Placebo
Endpoints:
Part 1: DLTs 3-wk | AEs 27-mo
Part 2: PFS 24-mo | OS 60-mo

LEAP-007 | NCT03829332 | **1L**
NSCLC

Phase 3 | 620 participants
Active controlled | Randomized | International
Estimated study completion date | March 8, 2024
Arm 1: Lenvatinib + Pembrolizumab
Arm 2: Pembrolizumab + Placebo
Endpoints: PFS 24-mo | OS 60-mo

LEAP-008 | NCT03976375 | **≥2L**
NSCLC

Phase 3 | 405 participants
Active comparators | Randomized | Open-label | International
Estimated study completion date | February 23, 2026
Arm 1: Lenvatinib + Pembrolizumab
Arm 2: Docetaxel
Arm 3: Lenvatinib
Endpoints: PFS 36-mo | OS 48-mo

	Pembro + Lenva n = 309[a]	Pembro + Pbo n = 314[a]
OS		
Events, n (%)	149 (48.2)	137 (43.6)
Median[b] (95% CI), mo	14.1 (11.4–19.0)	16.4 (12.6–20.6)
HR[c] (95% CI)	1.10 (0.87–1.39)	
P value[d,e]	0.79744	
PFS		
Events, n (%)	202 (65.4)	217 (69.1)
Median[b] (95% CI), mo	6.6 (6.1–8.2)	4.2 (4.1–6.2)
HR[c] (95% CI)	0.78 (0.64–0.95)	
P value[d,e]	0.00624	
ORR, % (95% CI)	40.5 (34.9–46.2)	27.7 (22.8–33.0)
Difference[f], % (95% CI)	12.8 (5.4–20.1)	
P value[d,f]	0.00037	

Taylor et al Future Oncol 2020; Csoszi et al ESMO 2021

Conclusions – Targeting TAM

Acquired resistance to CPI therapy is not yet fully understood, including how to define the patient population in clinical trials, and the molecular and cellular mechanisms

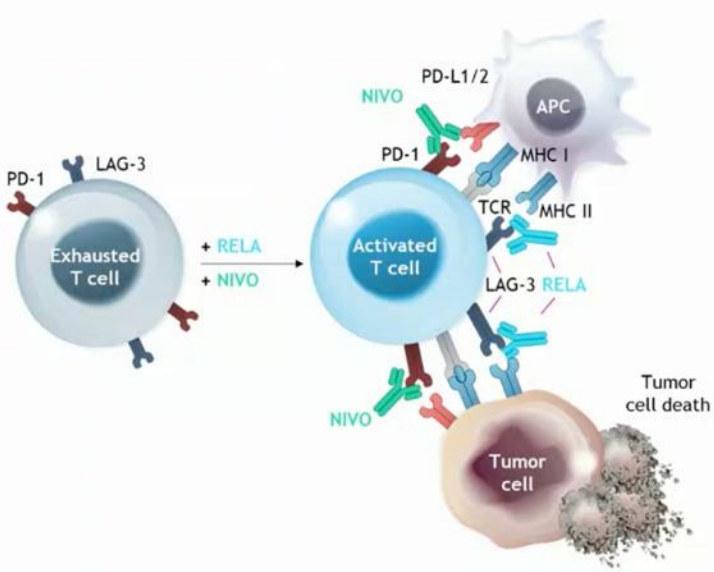
The development of an immune suppressive tumor microenvironment (TME) may be a contributing factor to acquired resistance

TAM receptor signaling can increase immunosuppressive factors in the TME

Targeting of TAM receptors, to shift the TME towards a more immunostimulatory state, is one approach under investigation to address acquired CPI resistance

Initial results with several TAM inhibitors, including sitravatinib and cabozantinib, have demonstrated promise in patients whose disease has progressed on or after CPI therapy

Lymphocyte activation gene 3 (LAG-3, CD223)



LAG3 expressed on activated T, NK, B, dendritic cells

Downregulates cell proliferation, activation

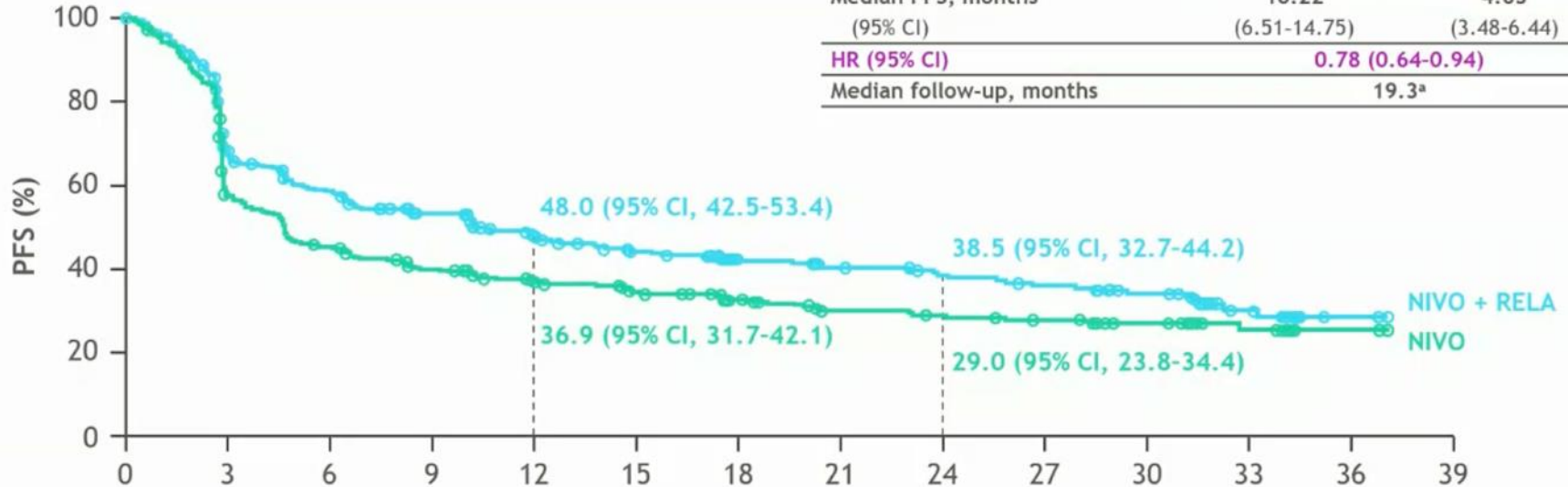
Helps maintain self tolerance, T cell exhaustion

Combination of LAG-3 inhibitor + PD-1 inhibitor active

Approval for nivolumab and relatlimab in melanoma based on PFS benefit

Progression-free survival significantly improved with RELA+NIVO

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	
Median follow-up, months	19.3[a]	



No. at risk														
NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Statistical model for HR and *P* value: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF*, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients. Database lock date: October 28, 2021.
[a]Minimum potential follow-up (time from last patient randomized to last patient, last visit) was 8.7 months.

Long et al, ASCO 2022

PARIS 2022 ESMO congress

A randomized phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer

NEOpredict-Lung

Martin Schuler[1], Kristof Cuppens[2], Till Ploenes[1], Michel Vanbockrijck[2], Marcel Wiesweg[1], Kaid Darwiche[1], Alexander Schramm[1], Brigitte Maes[2], Balazs Hegedus[1], Hans-Ulrich Schildhaus[1], Hubertus Hautzel[1], Dirk Theegarten[1], Paul Baas[3], Koen Hartemink[3], Bert Du Pont[2], and Clemens Aigner[1]

[1]West German Cancer Center, University Medicine Essen, Essen, Germany
[2]Jessa Hospital, Hasselt, Belgium
[3]Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, N

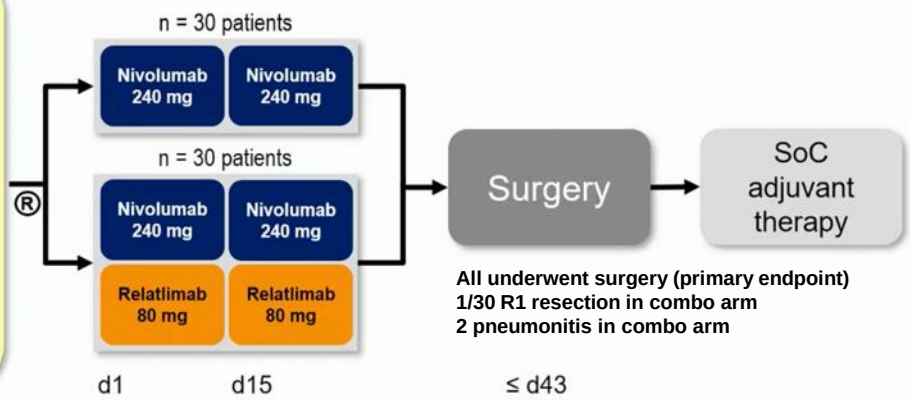
Study design

NEOpredict-Lung (NCT04205552)

Key eligibility

- Histologically confirmed non-small-cell lung cancer
- Stage I B, II or III A (UICC 8th edition)
- Curative resectability as determined by the multidisciplinary lung cancer board
- Sufficient organ function

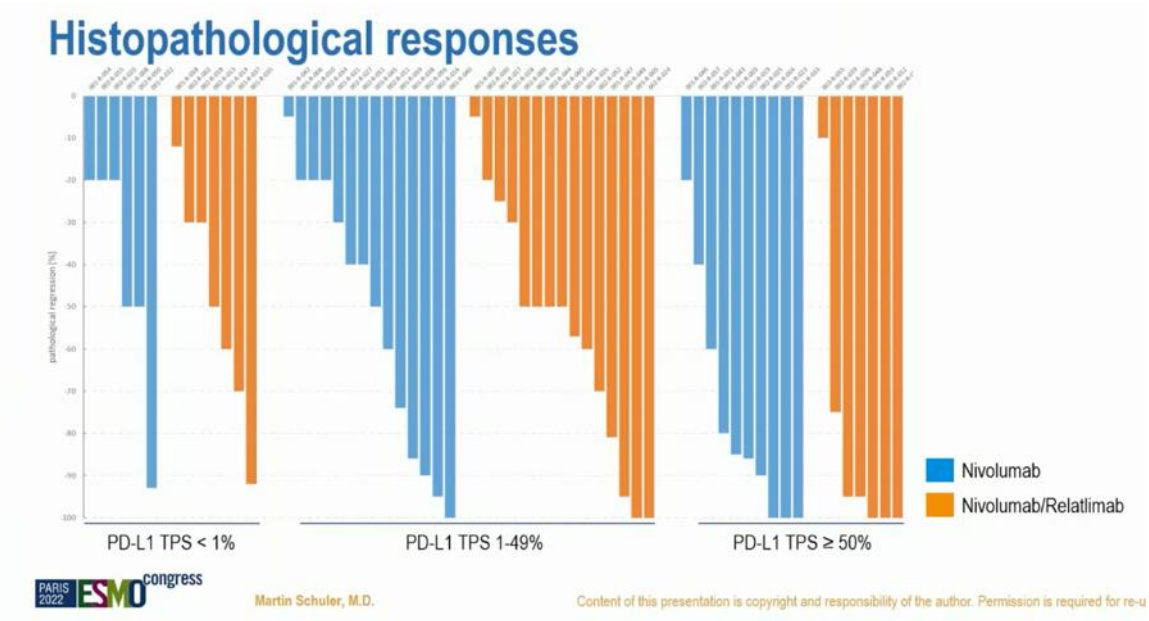
Most stage II



All underwent surgery (primary endpoint)
1/30 R1 resection in combo arm
2 pneumonitis in combo arm

Schuler ESMO 2022

▪ ORR (RECIST version 1.1)	10%	27%
▪ ORR (PERCIST version 1.0)*	38%	38%
▪ Complete/major pathological response**	27%	30%
▪ DFS at 12 months	92% (70-98%)	91% (66-98%)
▪ OS at 12 months	92% (70-98%)	100%



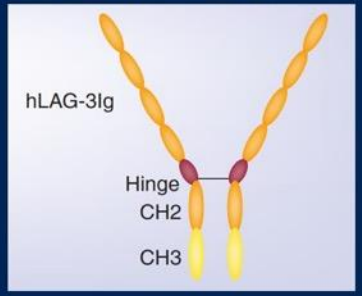
Peripheral blood effector T cells associated with major response

Next steps to increase relatlimab dose and explore receptor occupancy, LAG expression and more

Schuler ESMO 2022

Eftilagimod alpha (efti) – soluble LAG-3

STRUCTURE OF EFTI[4]



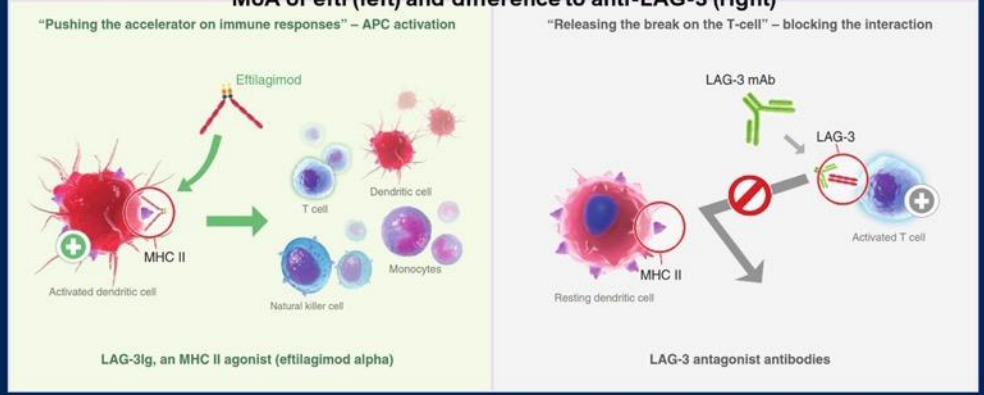
- **MoA: efti** (figure, left) is a **soluble LAG-3 protein** (LAG-3 domains fused to human IgG backbone) **targeting** a subset of **MHC class II molecules** to mediate antigen presenting cells (APCs) and CD8 T-cell activation (figure below left).
- **Difference to Anti-LAG-3:** Efti does not bind to the LAG-3 on the T cell (figure, below right).
- **Rationale:** efti activates APCs, leading to an increase in activated T cells, potentially reducing the number of non-responders to PD-1/PD-L1 antagonists.

- In preclinical models, the antitumor activity of PD-1 antagonists was synergistically enhanced when combined with efti[1].
- Recommended phase II dose of 30 mg efti s.c. every two weeks was determined in phase I studies[2,3].

MoA: mechanism of action
PD-1/PD-L1: programmed death-(ligand) 1
s.c.: subcutaneous

[1] Internal data, Immutep, not yet published.
[2] Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.
[3] Atkinson V, J Immunoth Cancer. 2020; 8(2):e001681.
[4] Dirix L, Triebel F. Future Oncol. 2019;15(17):1963-1973.

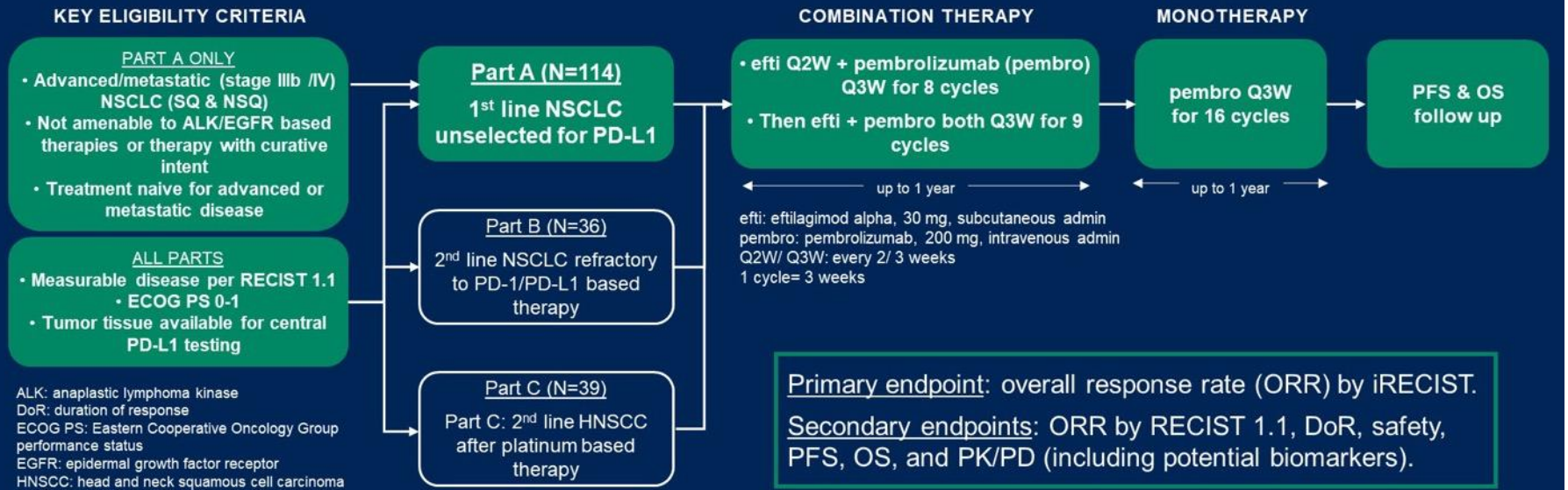
MoA of efti (left) and difference to anti-LAG-3 (right)[4]



Felip et al ASCO 2022 abstr 9003

Trial Design – TACTI-002

TACTI-002 is a Phase II, multinational, open label trial with patients from 3 indications unselected for PD-L1.



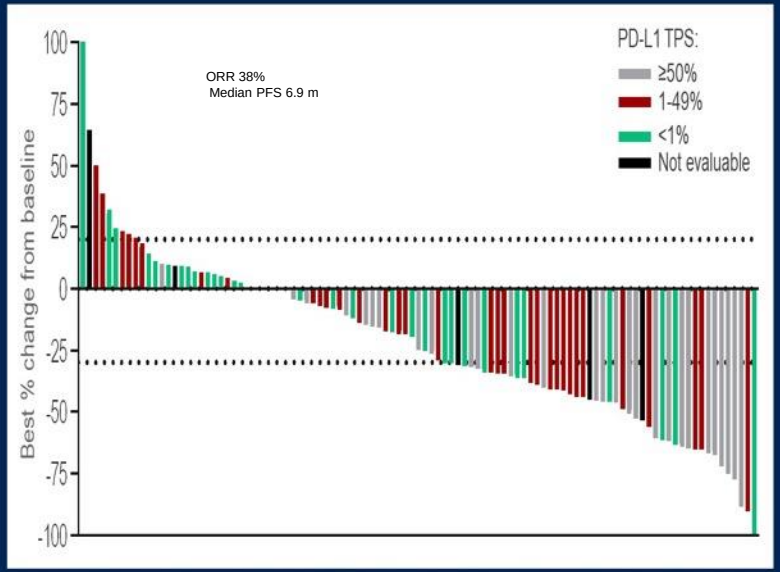
ALK: anaplastic lymphoma kinase
DoR: duration of response
ECOG PS: Eastern Cooperative Oncology Group performance status
EGFR: epidermal growth factor receptor
HNSCC: head and neck squamous cell carcinoma
NSCLC: non-small cell lung cancer
NSQ: non squamous
OS: overall survival
PD: pharmacodynamics
PFS: progression free survival
PK: pharmacokinetics
SQ: squamous

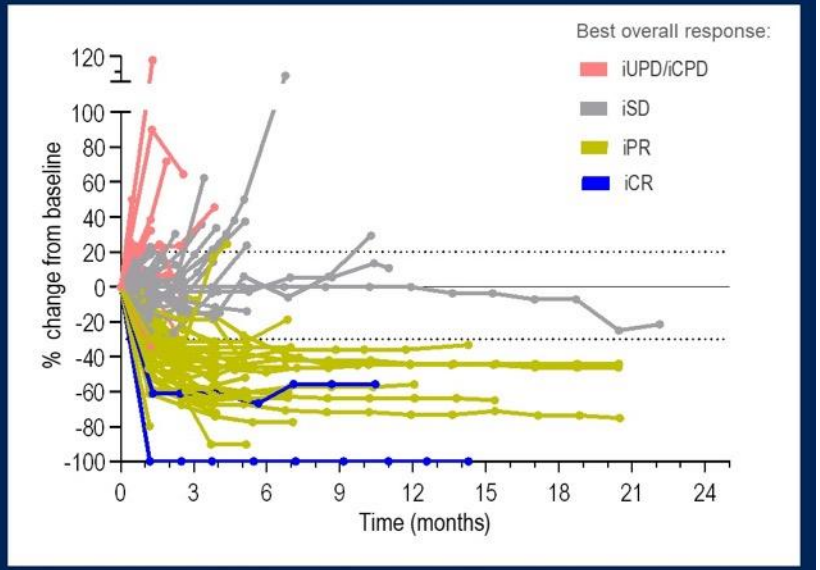
Primary endpoint: overall response rate (ORR) by iRECIST.

Secondary endpoints: ORR by RECIST 1.1, DoR, safety, PFS, OS, and PK/PD (including potential biomarkers).

Felip et al ASCO 2022 abstr 9003

Efficacy – Waterfall plot[1] – TACTI-002





[1] all patients with ≥1 post-baseline CT scan n=103; [2] PD-L1 assessed by central assessment (Dako kit); n=79; [3] local assessment included due to non evaluable central assessment results, n=19; [4] no results available for neither central nor local testing, n=5.

- 2 complete responses and 19.4% of patients with a target lesion decrease ≥50%.
- 68/103 (66.0%) of patients with a post-baseline assessment had a decrease in target lesions.

Data cut-off date: April 15, 2022

Fewer than 10% stopped for toxicity

PRESENTED BY:
Enriqueta Felip. A Phase II study (TACTI-002) in 1st line metastatic NSCLC investigating eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab: updated results from a PD-L1 unselected population

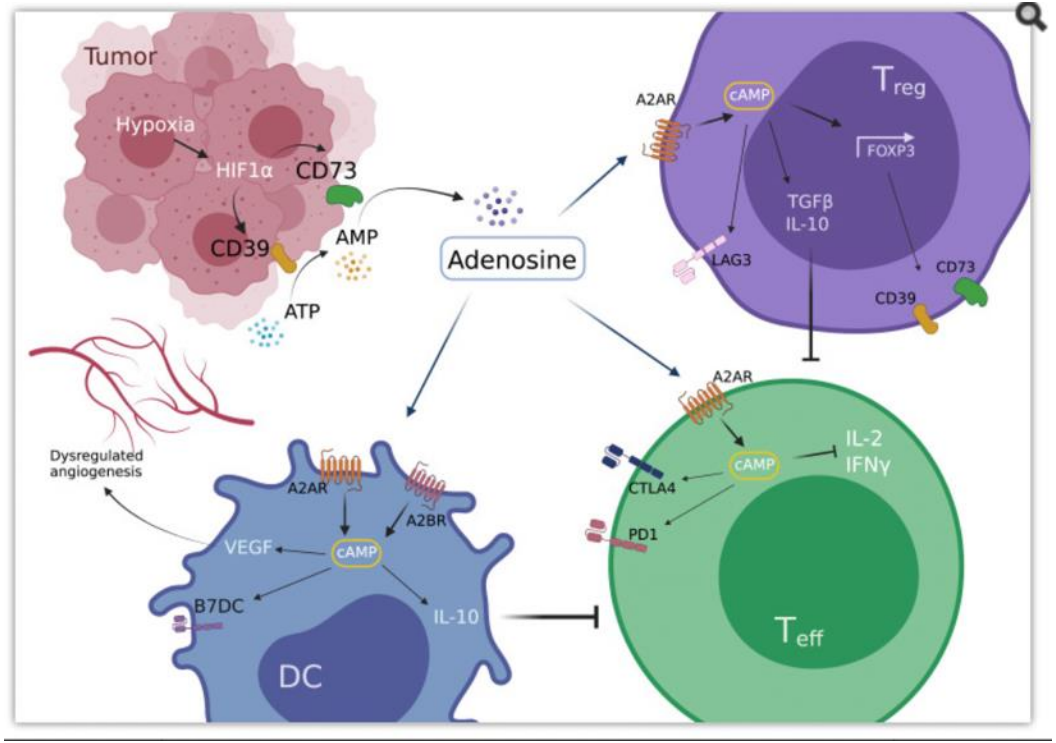
Felip et al ASCO 2022 abstr 9003

LAG-3 Agents in Development

Name	Description	Target disease	Clinical trial*	Combination†
Relatlimab	Antagonistic Ab	Tumors	I (5), I/II (6), II (13)	PD-1
LAG525	Antagonistic Ab	Tumors	I (1), I/II (1), II (3)	PD-1, M-CSF, IL-1β, A2AR
BI754111	Antagonistic Ab	Tumors	I (3), Ia/Ib (1), II (1)	PD-1
MK-4280	Antagonistic Ab	Tumors	I (1), I/II (1), II (1)	PD-1
Sym022	Antagonistic Ab	Tumors	I (2)	PD-1
TSR-033	Antagonistic Ab	Tumors	I (2)	PD-1, Tim3
REGN3767	Antagonistic Ab	Tumors	I (1), II (1)	PD-1
INCAGN2385-101	Antagonistic Ab	Tumors	I (1)	–
MGD013	Bispecific to LAG-3/PD-1	Tumors	I (2), I/II (1), II/III (1)	–
FS118	Bispecific to LAG-3/PD-L1	Tumors	I (1)	–
XmAb22841	Bispecific to LAG-3/CTLA-4	Tumors	I (1)	PD-1
GSK2831781	Depleting Ab	Autoimmune diseases	I (2), II (1)	–
IMP321	Soluble LAG-3-Ig	Tumors	I (8), II (2)	PD-1, PD-L1, vaccination

NCT04623775 Phase 2 randomized study of relatlimab plus nivolumab with chemotherapy versus nivolumab plus chemotherapy

Targeting Adenosine



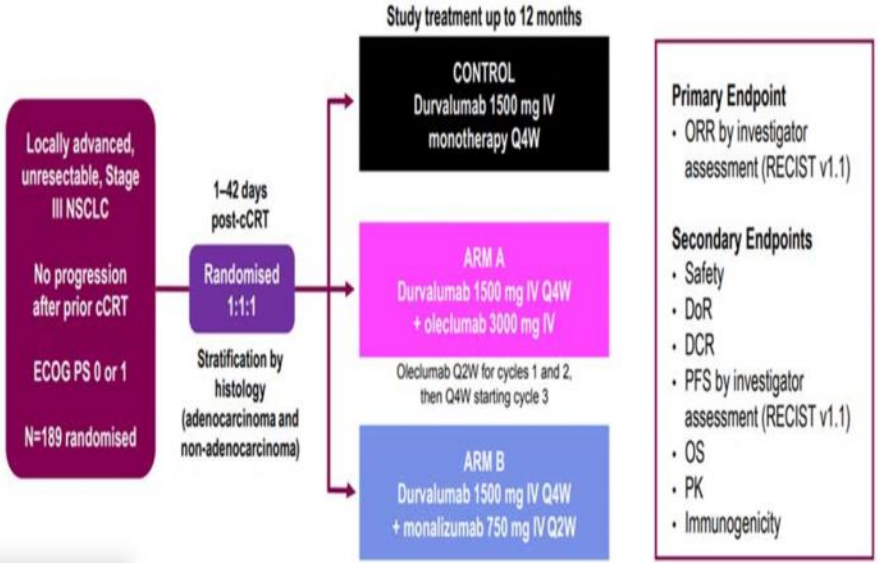
CD73 antagonists
Oleclumab- MEDI-9447
Uliledlimab-
Mupadolimab- CPI-006
SYM024
INCA00186
BMS-986179

CD39 antagonists
TTX-030
IPH-5201
SRF-617

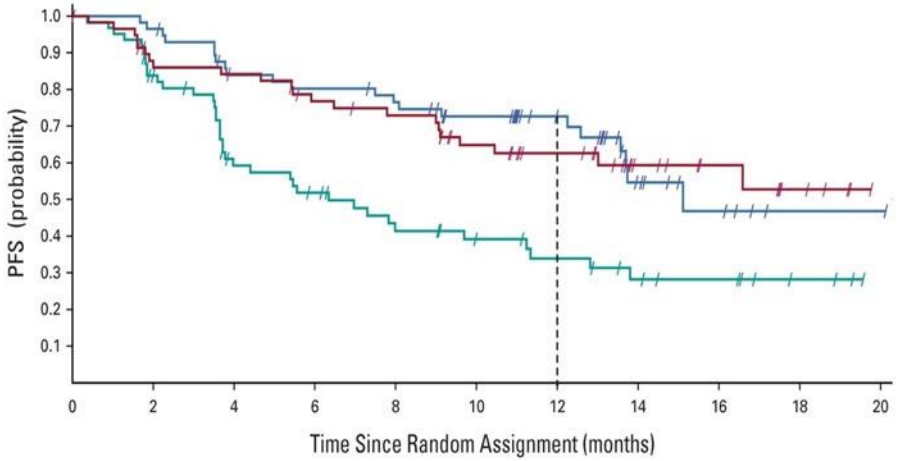
A2AR antagonists
Ciforadenant- CPI-444
Imaradenant- AZD4635
Etrumadenant- AB928
Inupadenant- EOS100850

Augustin JITC 2022; Gadgeel ASCO 2022

COAST (PACIFIC 9)

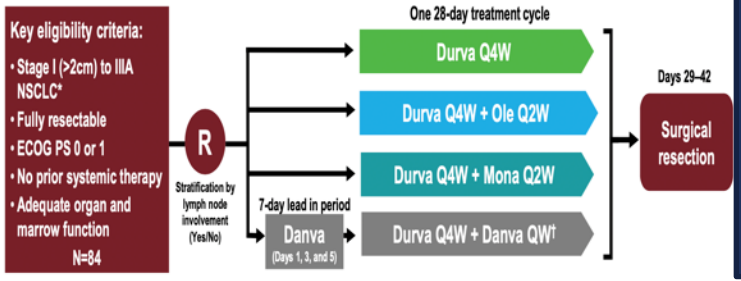


Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–



Herbst J Clin Oncol 2022

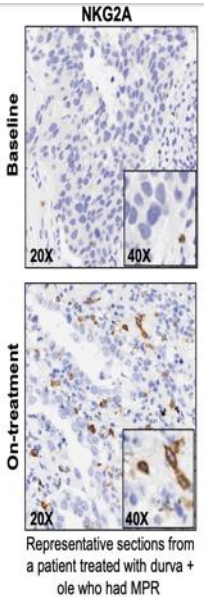
NeoCOAST: Study design and objectives



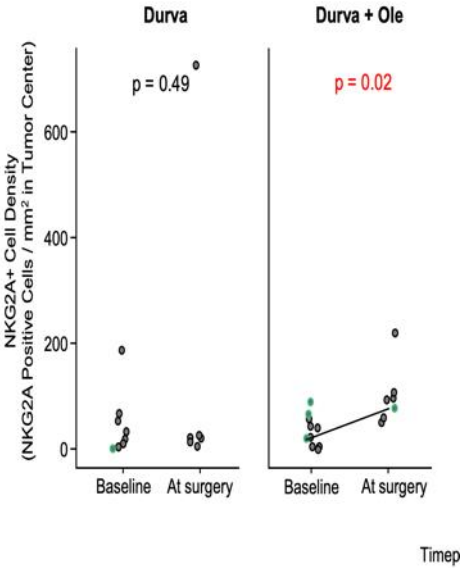
MPR	pCR.	ORR
11%	4%	7%
19%.	10%	5%
30%	11%	15%
31%	13%	6%

Endpoints:

- **Primary**: MPR rate (proportion of patients with ≤10% residual viable tumor cells in resected tumor specimen and sampled nodes at surgery) per investigator assessment.
- **Secondary**: pCR rate (no viable tumor cells in resected tumor specimen or sampled nodes at surgery), safety and tolerability, feasibility of planned surgery, pharmacokinetics, and immunogenicity.
- **Exploratory**: Tumor, blood, and stool microbiome biomarkers; investigator-assessed best overall response and ORR (per RECIST v1.1).

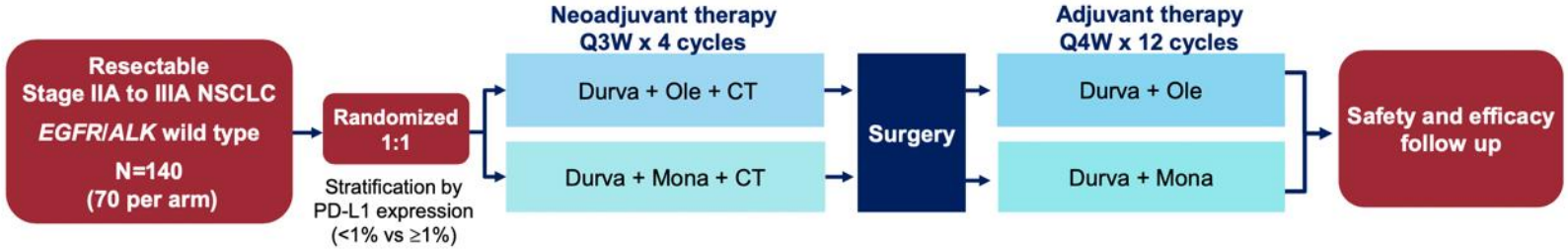


Representative sections from a patient treated with durva + ole who had MPR



Cascone et al AACR 2022

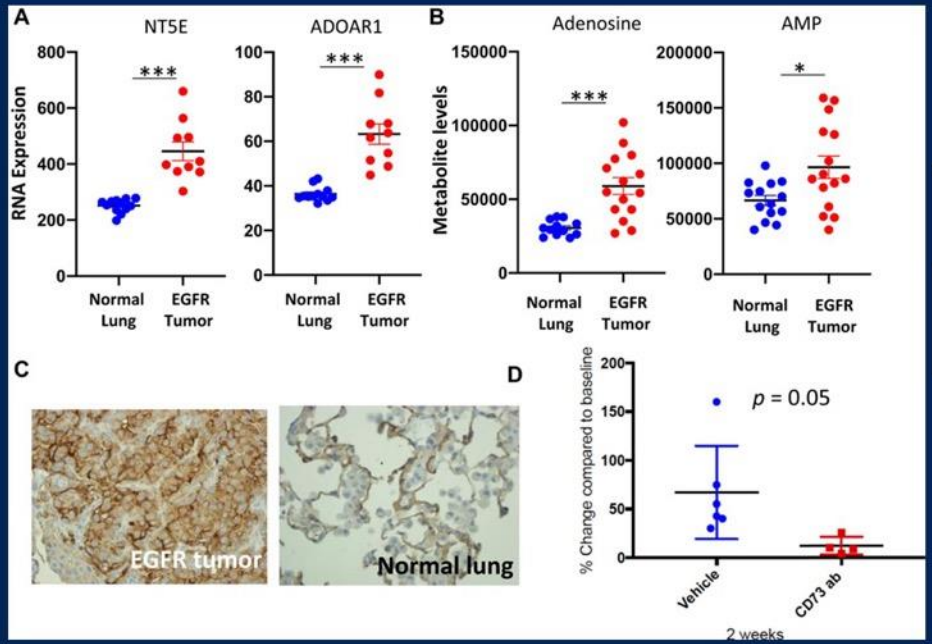
NeoCOAST-2: Study design



- NeoCOAST-2 (NCT05061550) is a phase 2, randomized study of neoadjuvant durva combined with chemo and either ole or mona, followed by surgery and adjuvant durva plus ole or mona, in patients with resectable, Stage IIA–IIIA NSCLC.[1]
  - Primary endpoints: pCR, safety and tolerability
  - Secondary endpoints: EFS, DFS, OS, and ORR per RECIST v1.1; MPR; feasibility of surgery; pharmacokinetics; immunogenicity; baseline tumor PD-L1 expression; changes in ctDNA
  - Recruitment initiated in January 2022.

Cascone T, et al. AACR 2022 (poster CT124).

EGFR +ve NSCLC and Adenosine Pathway



Le, et al, J Thorac Oncol 2021

Oleclumab and Durvalumab in EGFR +ve NSCLC. N=42

RR	DOR	PFS
9.5%	14.8 mo (95% CI- 5.6-24.0)	1.8 mo (95% CI- 1.7-1.9)

Bendell, et al, ASCO 2021

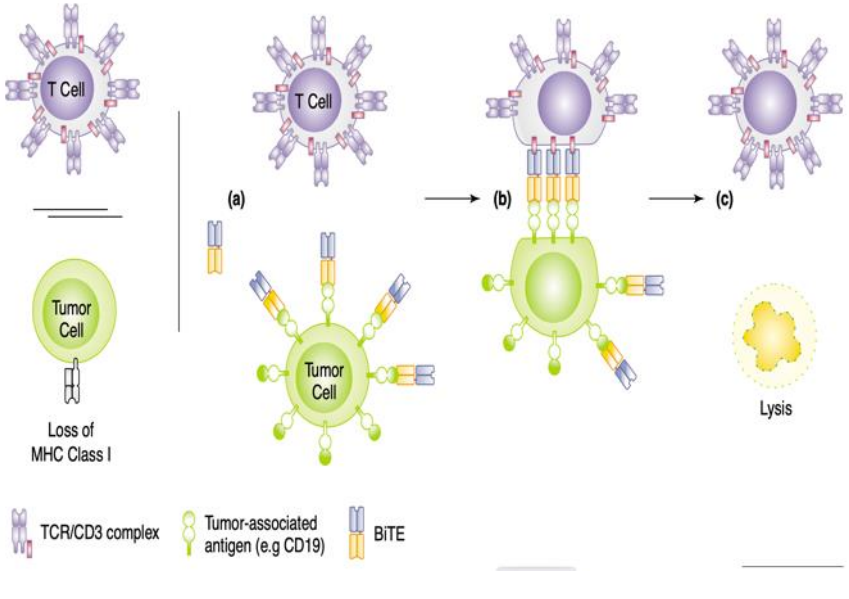
Turning on the “gas” – targeting co-stimulatory receptors

Co-stimulatory receptors			
GITR  GITRL	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
OX40  OX40L	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
4-1BB  4-1BBL	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
ICOS  ICOSL	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

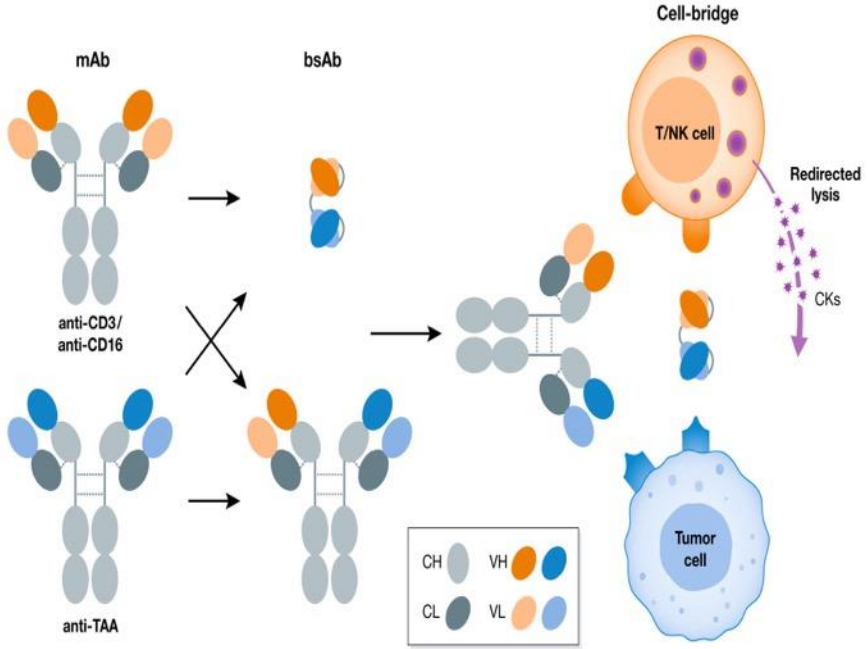
Kraehanbuehl Nat Rev Clin Oncoll 2022

Bispecific Compounds

Bi Tcell Engagers

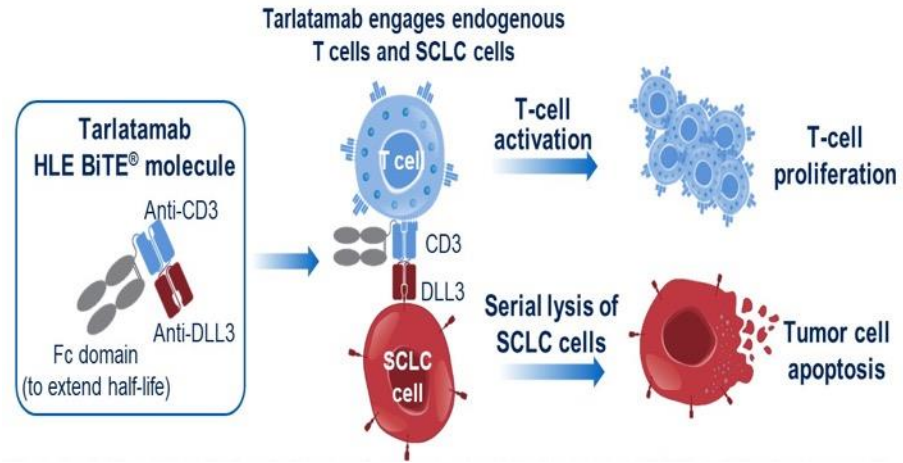


Bispecific Antibodies



EMBO Mol Med 2021

BiTEs in Lung Cancer – Tarlatamab in SCLC



Phase I in pretreated SCLC

N=66

CRS (mostly gr 1,2) in 44%

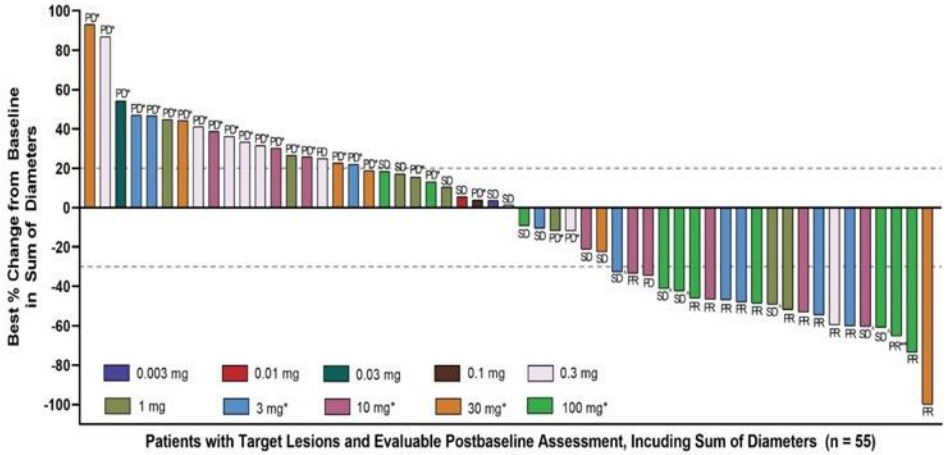
DLT gr 5 pneumonitis, gr 3 encephalopathy

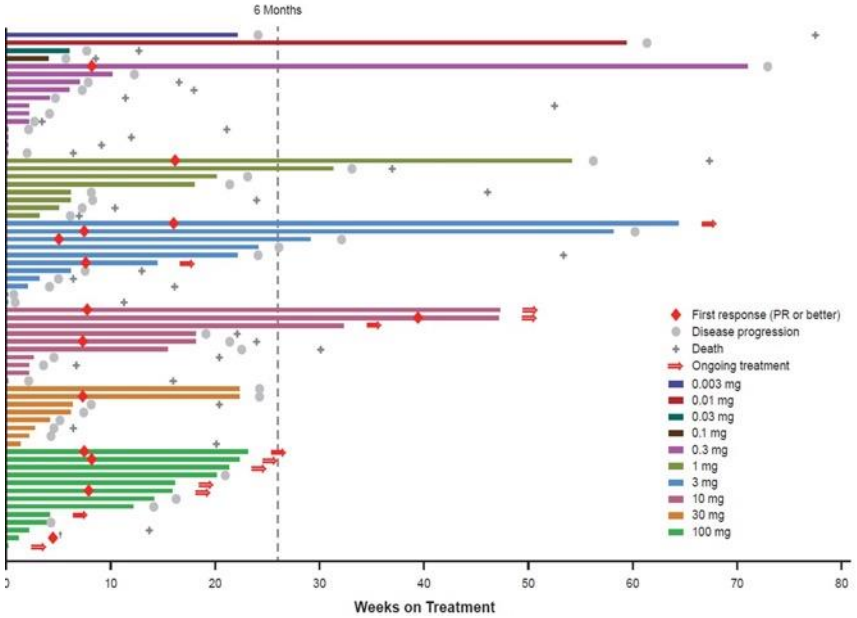
Ongoing studies with chemotherapy 1L, single agent 3rd line+

Owonikoko ASCO 2021

Activity seen across a range of doses

ORR 20-22%, Median duration of response 8.7 months



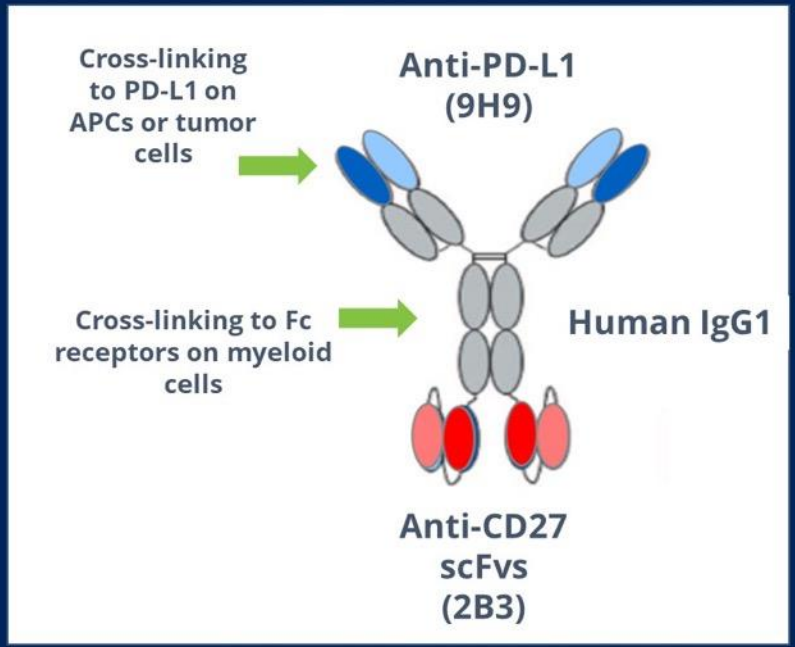


Owonikoko ASCO 2021

Dual-Immunomodulator Bispecific Antibodies

- 2 checkpoint inhibitor targets
  - PD(L)-1, CTLA-4, Lag-3, TIM-3, TGFβ
- Agonistic antibodies to costimulatory targets
  - CD27, CD28, OX-40, …

Example: CDX527



Sanborn et al, ASCO 2021 (Poster)

PARIS 2022 ESMO congress

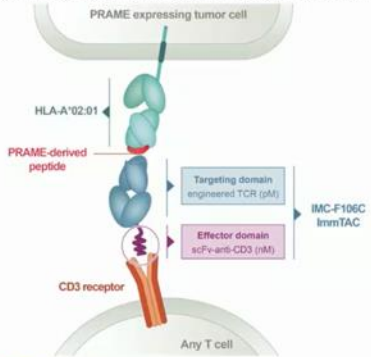
Phase 1 dose escalation of IMC-F106C, the first PRAME × CD3 ImmTAC bispecific protein in solid tumors

Omid Hamid,[1] Takami Sato,[2] Diwakar Davar,[3] Margaret Callahan,[4] Fiona Thistlethwaite,[5] Raid Aljumaily,[6] Melissa Johnson,[7] Hendrik-Tobias Arkenau,[8] Ecaterina Dumbrava,[9] Benjamin Izar,[10] Hui Amy Chen,[11] Shannon Marshall,[12] Yuan Yuan,[12] Mugdha Deo,[12] Sarah Stanhope,[12] Laura Collins,[12] Renee Mundy,[12] Shaad Abdullah,[12] Juanita Lopez[13]

[1]The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA, US; [2]Thomas Jefferson University Hospital, Philadelphia, PA, US; [3]UPMC Hillman Cancer Center, Pittsburgh, PA, US; [4]Memorial Sloan Kettering Cancer Center, New York, NY, US; [5]The Christie NHS Foundation Trust and University of Manchester, Manchester, UK; [6]University of Oklahoma Peggy and Charles Stephenson Cancer Center, Oklahoma City, OK, US; [7]Sarah Cannon Research Institute, Nashville, TN, US; [8]Sarah Cannon Research Institute, London, UK; [9]MD Anderson Cancer Center, Houston, TX, US; [10]Columbia University Medical Center, New York, NY, US; [11]University of California Davis Comprehensive Cancer Center, Sacramento, CA, US; [12]Immunocore Ltd, Abingdon, UK; [13]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, UK

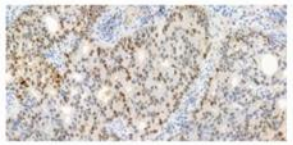
IMC-F106C: ImmTAC targeting HLA-A2-presented peptide from PRAME (PRAME × CD3)

- TCR bispecific proteins redirect polyclonal T cells to target intra- or extra-cellular cancer proteins (>90% of proteome)
- ImmTAC molecules are validated by tebentafusp (gp100 × CD3) with OS benefit in uveal melanoma (HR 0.51)[1]

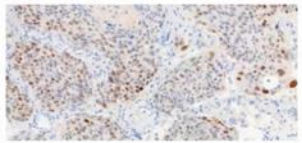


PRAME: most broadly expressed cancer-testis antigen in several tumor types but with minimal normal tissue expression

Adeno NSCLC



Squamous NSCLC



Tumor	Prevalence of PRAME expression
Melanoma, endometrial, NSCLC, TNBC, SCLC, ovarian	
RCC, esophageal, SCCHN, cervical	
Bladder, HCC, gastric	

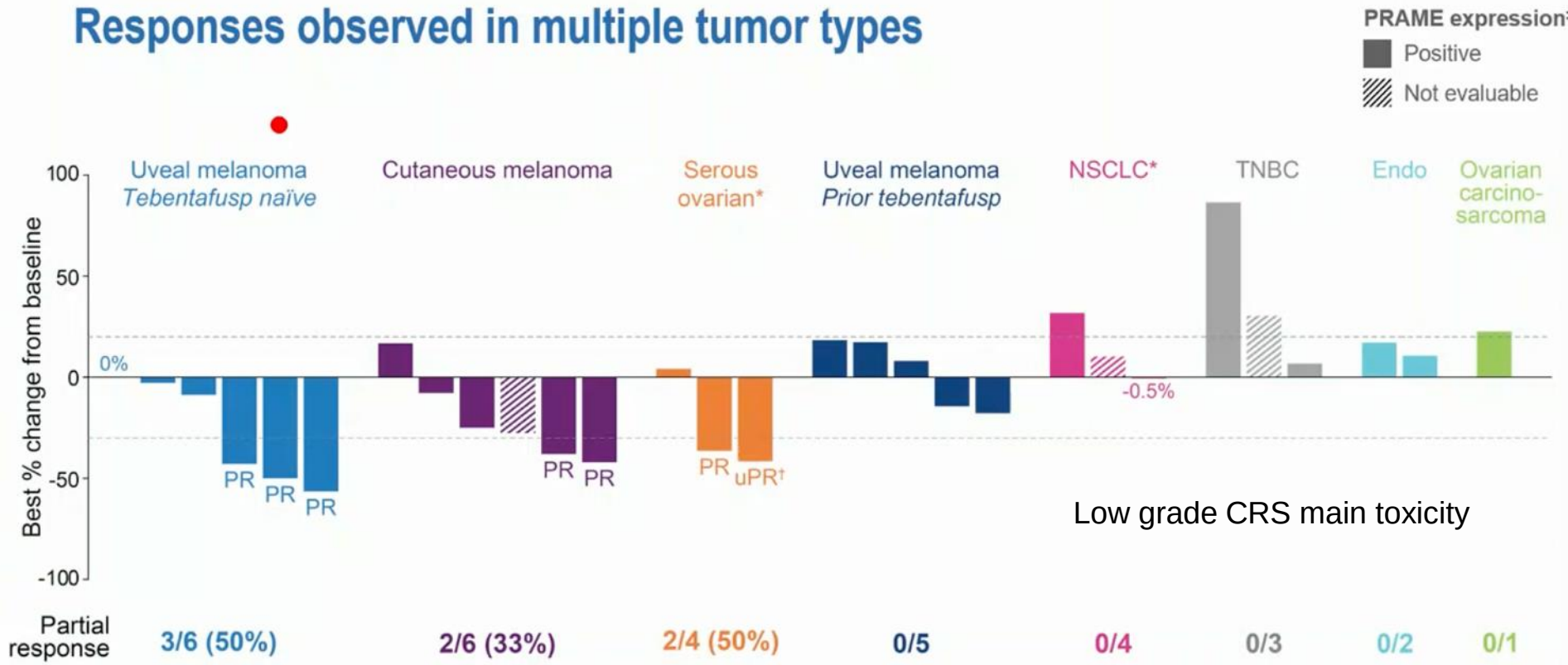
LOW — HIGH

PARIS 2022 ESMO congress

ImmTAC, Immune mobilizing T cell receptor Against Cancer; TCR, T cell receptor

1. Nathan P, et al. N Engl J Med 2021;385:1196-206;

Responses observed in multiple tumor types



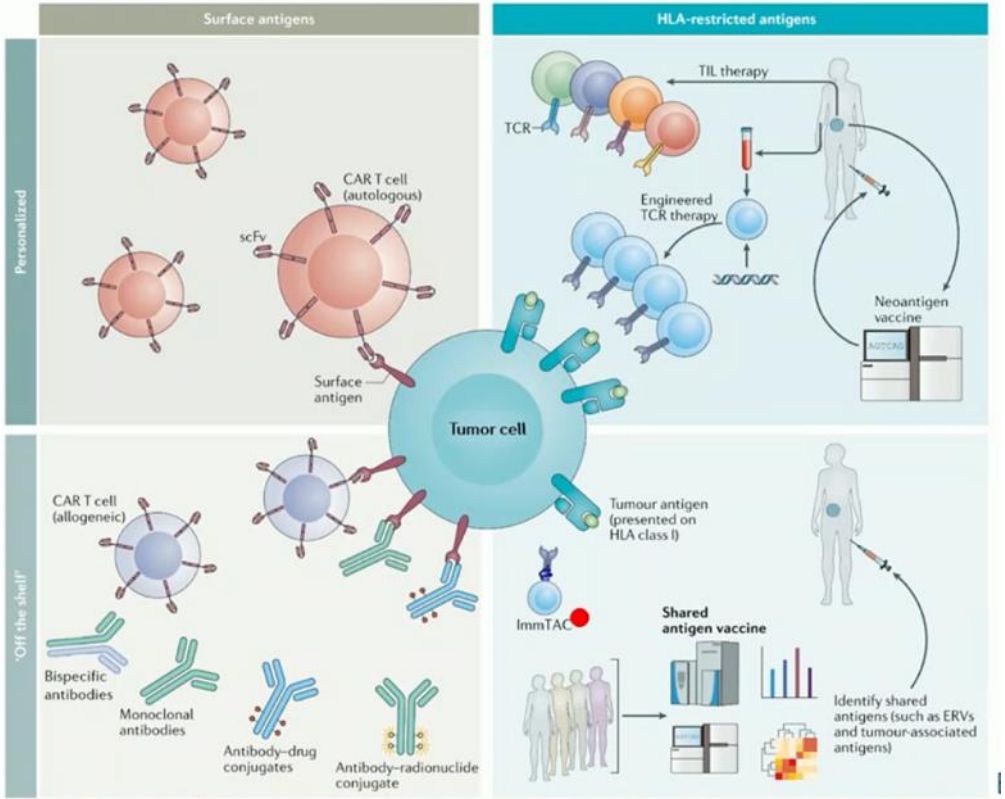
Low grade CRS main toxicity

* Two patients (1 with NSCLC, 1 serous ovarian) discontinued treatment due to PD with scan data not available at DCO
† Ovarian cancer patient with unconfirmed PR (uPR) remains on treatment and eligible for confirmation
‡ PRAME expression assessed by IHC H-score
Two PRAME-negative patients both had PD (not shown)
Endo, endometrial carcinoma; NSCLC, non small cell lung carcinoma; TNBC, triple-negative breast cancer;

Hamid ESMO 2022

Many strategies for antigen-directed therapy (”Steering the car”)

e.g. CAR-T targeting mesothelin



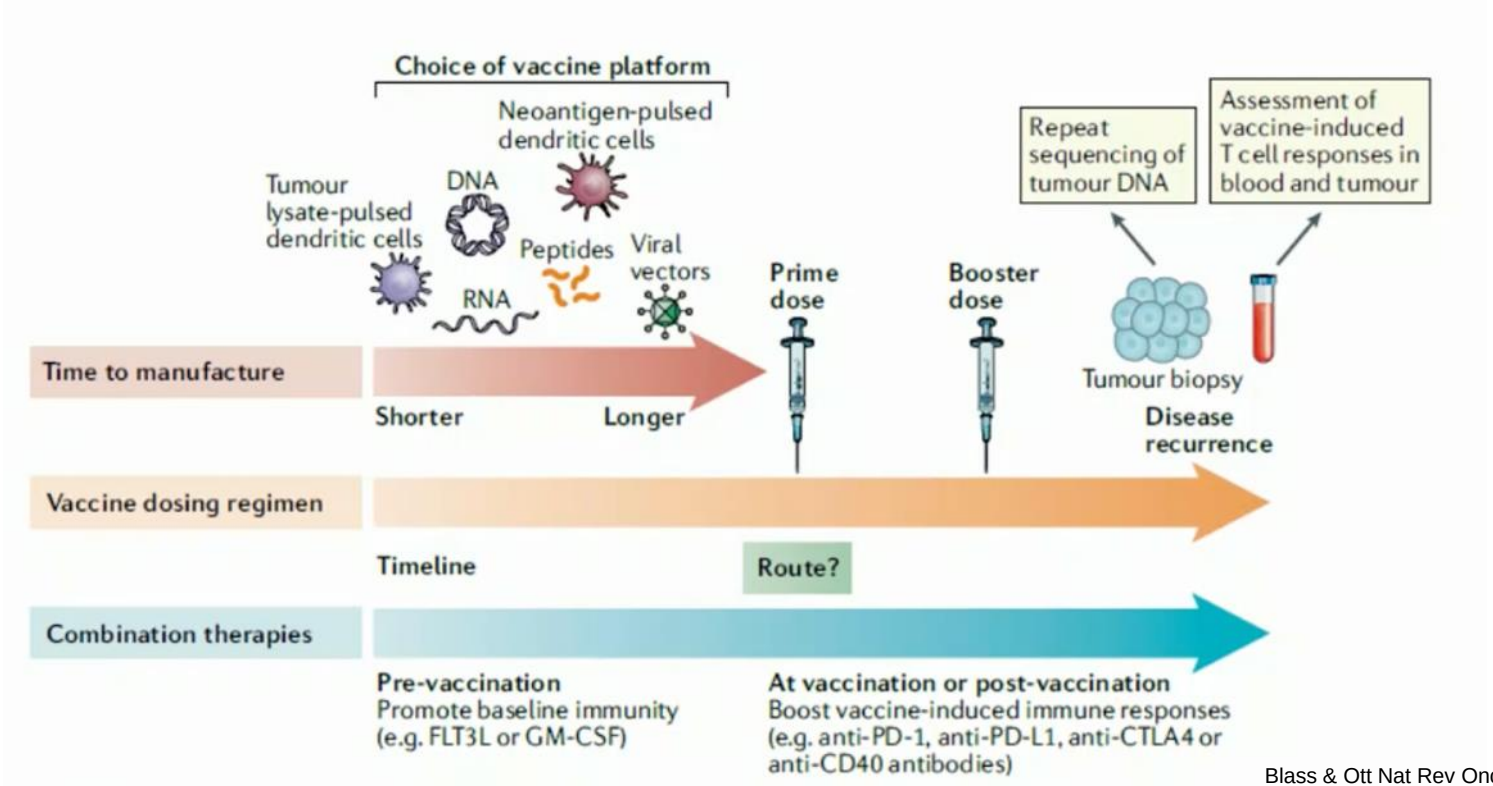
TILs – expanded or engineered

Creelan et al
Iovance etc

Non personalized, Personalized vaccines

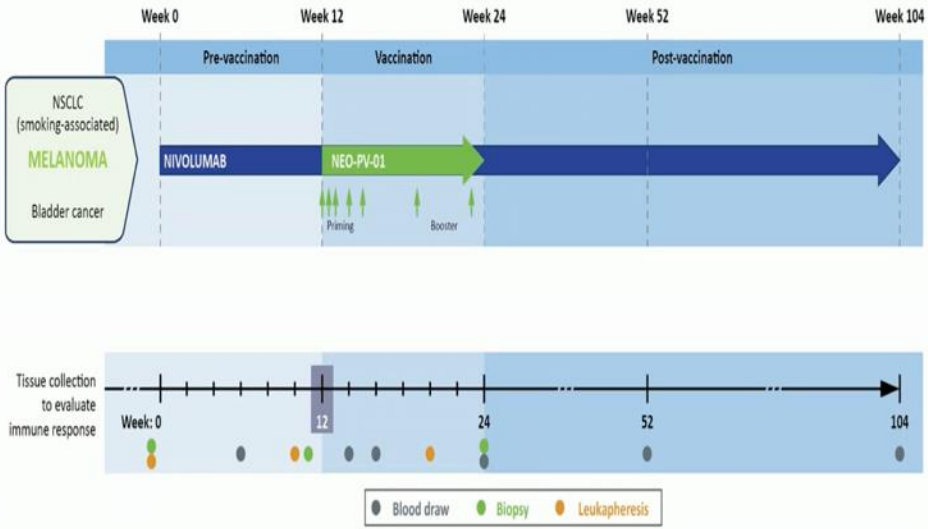
Braun Nat Rev Clin Oncol 2021
Braun ESMO 2022

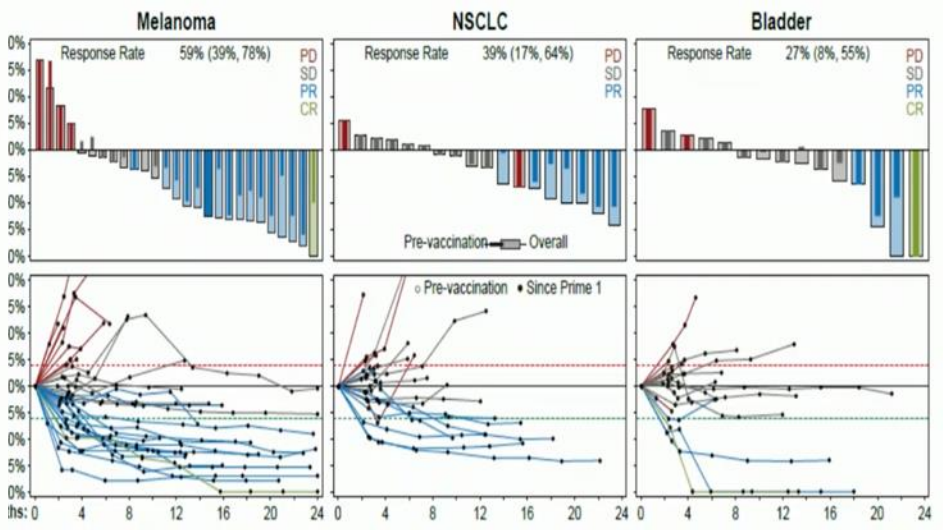
Vaccines – timing, dosing, combinations…



Blass & Ott Nat Rev Oncol 2021

NT-001: Personalized peptide vaccine (PV-01) + Nivolumab in metastatic patients (melanoma, NSCLC, and urothelial cancer)





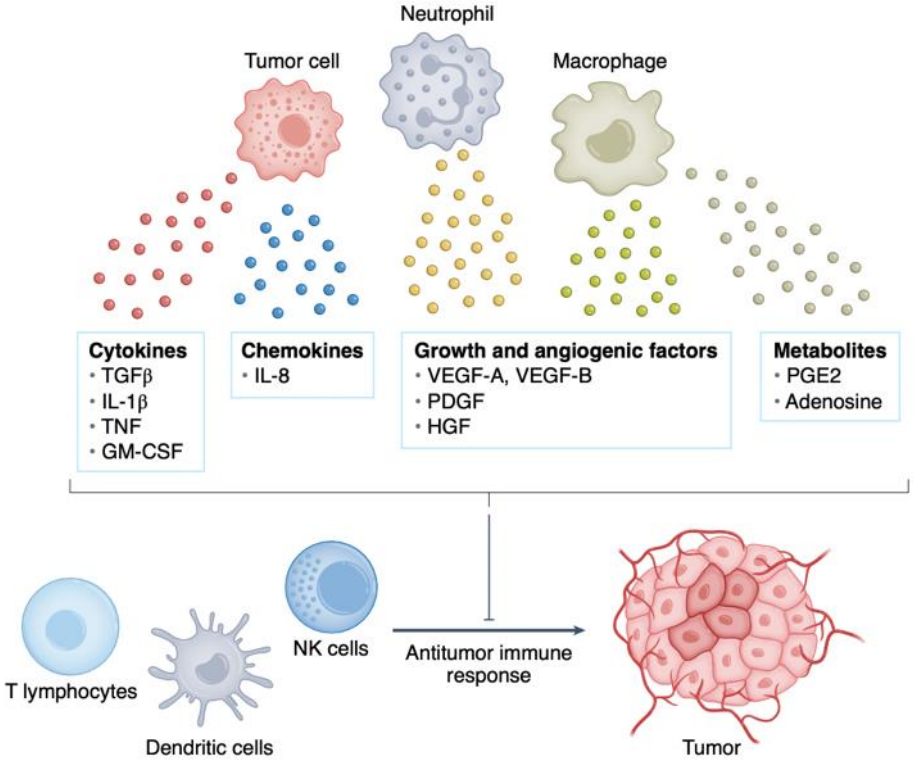
Ott Cell 2020

Snapshot of ongoing personalized cancer vaccine studies

NCT	Phase	Agent	Tumor Types	Targets
NCT03953235	I/II	GRT-C903/GRT-R904	Multiple including NSCLC	BRAF, ERBB2, KRAS, NRAS, TP53, others
NCT05195619	Ib	PEP-DC	NSCLC	Autologous dendritic cell with personalized peptides
NCT04266730	I	PANDA-VAC	Multiple including NSCLC	6 personalized neoantigens + Pembro
NCT04397003	II	Polyepitope DNA via electroporation	SCLC	Personalized neoantigen DNA vaccine + Durva
NCT05269381		PNeoVCA (IV)	Numerous including NSCLC	Personalized neoantigen peptide +Pembrolizumab

PRESENTED BY:
Rachel E. Sanborn, M.D.
Earle A. Chiles Research Institute, Providence Cancer Institute

Cytokines, chemokines, metabolomics..



Ott 2022

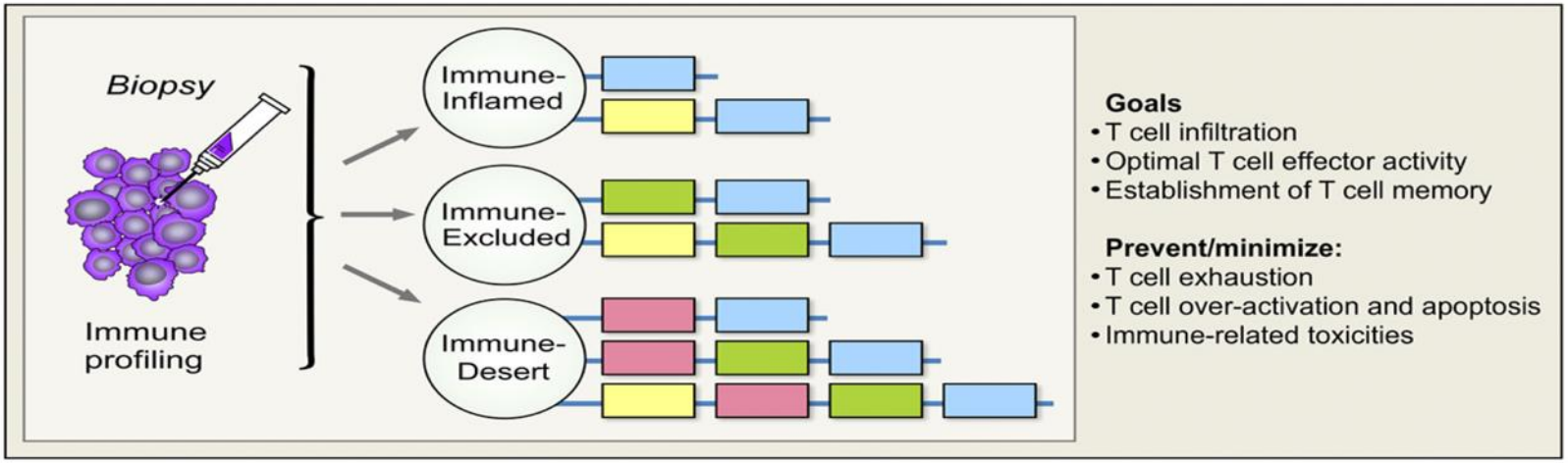
Promoting T cell infiltration and Function

Prime/expand T cells
- Oncolytic viruses
- STING/TLR agonists
- Radiation
- Chemotherapy
- Vaccines
- Adoptive cell therapy

Overcome T cell exclusion
- Oncogenic pathway inhibitors
- Anti-VEGF
- TGF-β inhibitors

Modulate T cells
- Checkpoint inhibitors
- Co-stimulatory agonists
- Cytokines

Reverse immunosuppression
- TGF-β inhibitors
- Chemotherapy
- Targeted therapies



Goals
- T cell infiltration
- Optimal T cell effector activity
- Establishment of T cell memory

Prevent/minimize:
- T cell exhaustion
- T cell over-activation and apoptosis
- Immune-related toxicities

Anandappa et al. Cancer Discov 2020

To Sum Up…

Many promising directions in many areas, ongoing combinations

Still need greater translation understanding of the who, what, when and how to use our new strategies

Thank you!