ESMO ON AIR

Advanced NSCLC: Non-oncogene addicted

ESMO DEEP DIVE WEBINAR SERIES: LUNG CANCER

Solange Peters, *Chair*

Centre Hospitalier Universitaire Vaudois (CHUV)

Switzerland

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Programme

2 April 2025

5 min	**Welcome and introduction** Solange Peters
15-20 min	**Beyond PD-1 axis inhibition** Martin Reck
15-20 min	**ADCs – designer drugs?** Egbert Smit
15-20 min	**Targeting the microbiome** Bertrand Routy
15 min	**QnA and Discussion** All speakers

Solange Peters
Chair
Centre Hospitalier Universitaire Vaudois (CHUV)
Oncology Department, Lausanne

Martin Reck
Speaker
Department of Thoracic Oncology
Lung Clinic Grosshansdorf
Grosshansdorf

Egbert Smit
Speaker
Netherlands Cancer Institute

Bertrand Routy
Speaker
Associate professor of Hemato-Oncology, University of Montreal (CHUM)
Director of the CHUM Microbiome Centre
University of Montreal Research Centre (CRCHUM)

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NSCLC Outcome: TNM 9th Edition

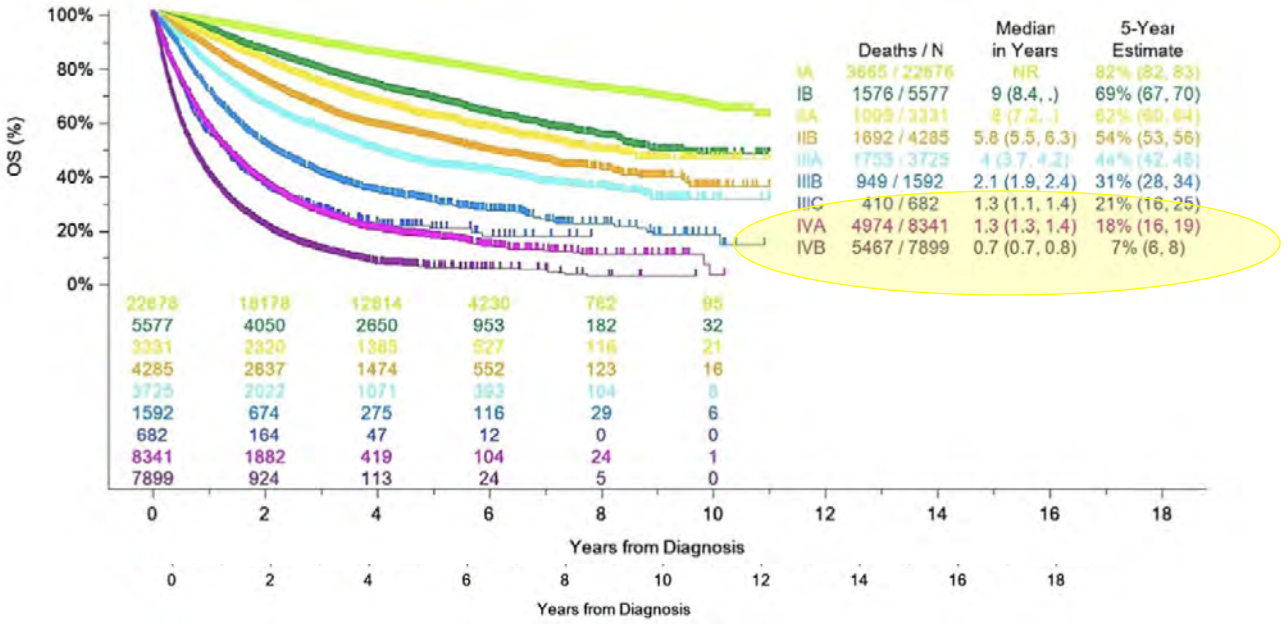
Tx	Primary tumor cannot be assessed[a]
T0	No evidence of primary tumor
Tis	Carcinoma in situ[b]
T1	Tumor surrounded by lung or visceral pleura or in a lobar or more peripheral bronchus[c]
T1mi	Minimally invasive adenocarcinoma[d]
T1a	Tumor ≤1 cm in greatest dimension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor with any of the following features:
T2a	Tumor >3 cm but ≤4 cm in greatest dimension invades visceral pleura invades an adjacent lobe involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis, extending to the hilar region, involving either part of or the entire lung
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor with any of the following features: tumor >5 cm but ≤7 cm in greatest dimension invades parietal pleura or chest wall invades pericardium, phrenic nerve, or azygos vein[e] invades thoracic nerve roots (i.e., T1, T2) or stellate ganglion separate tumor nodule(s) in the same lobe as the primary
T4	Tumor with any of the following features: tumor >7 cm in greatest dimension invades mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus, or diaphragm invades heart, great vessels (aorta, superior or inferior vena cava, intrapericardial pulmonary arteries or veins), supra-aortic arteries, or brachiocephalic veins invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (i.e., trunks, divisions, cords, or terminal nerves) separate tumor nodule(s) in a different ipsilateral lobe than that of the primary
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial or ipsilateral hilar or intrapulmonary lymph nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal or subcarinal lymph node(s)
N2a	Metastasis(es) in a single ipsilateral mediastinal or in the subcarinal nodal station
N2b	Metastases in multiple ipsilateral mediastinal nodal stations with or without involvement of the subcarinal nodal station
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Tumor with pleural or pericardial nodules or malignant pleural or pericardial effusions,[f] separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis in a single organ system[g]
M1c	Multiple extrathoracic metastases in a single or multiple organ system(s)
M1c1	Multiple extrathoracic metastases in a single organ system[h]
M1c2	Multiple extrathoracic metastasis in multiple organ systems

M1c2 Multiple extrathoracic metastasis in multiple organ systems

Proposed 9th Ed TNM Categories

T/M	Description	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural / pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

	N0	N1	N2		N3
			N2a	N2b	
	IA1	IIA	IIB	IIIA	IIIB
	IA2	IIA	IIB	IIIA	IIIB
	IA3	IIA	IIB	IIIA	IIIB
	IB	IIB	IIIA	IIIB	IIIB
	IB	IIB	IIIA	IIIB	IIIB
	IIA	IIB	IIIA	IIIB	IIIB
	IIB	IIIA	IIIA	IIIB	IIIC
	IIB	IIIA	IIIA	IIIB	IIIC
	IIB	IIIA	IIIA	IIIB	IIIC
	IIIA	IIIA	IIIB	IIIB	IIIC
	IIIA	IIIA	IIIB	IIIB	IIIC
	IIIA	IIIA	IIIB	IIIB	IIIC
ion	IVA	IVA	IVA	IVA	IVA



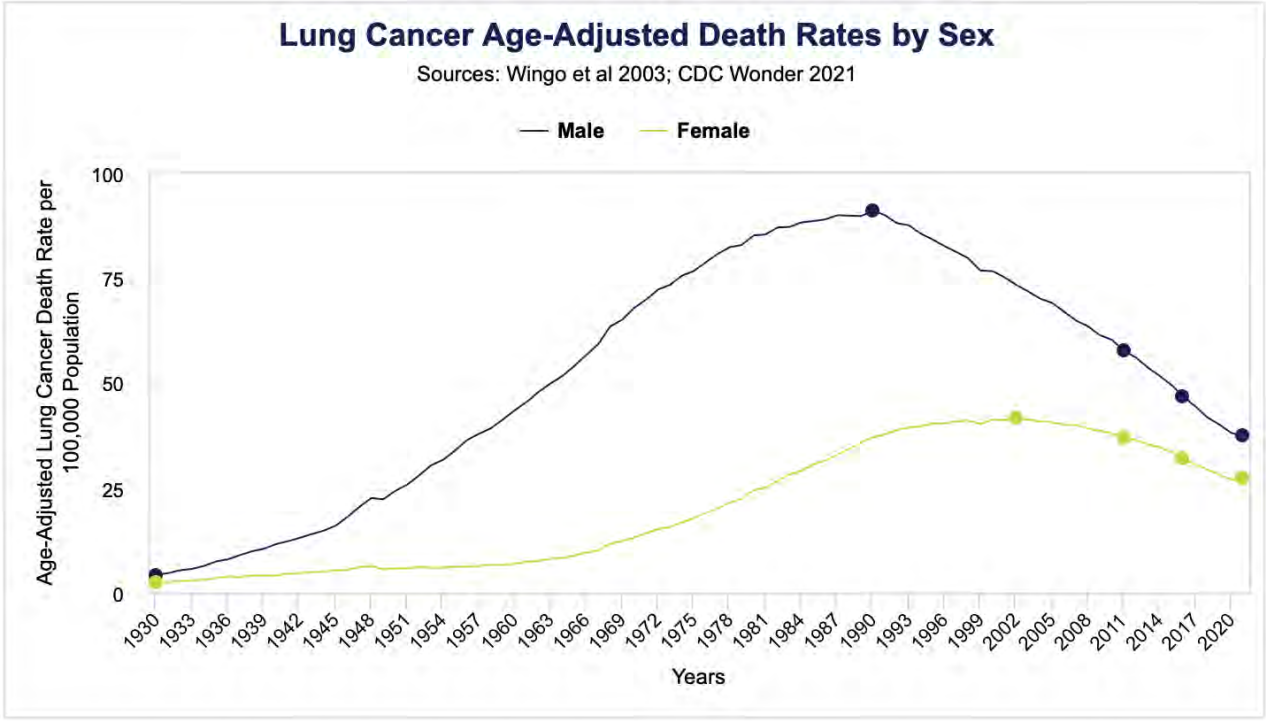
TNM staging classification for lung cancer, mesothelioma, and thymic cancer, 9th Edition.

Immunotherapy contributes to the mortality drop

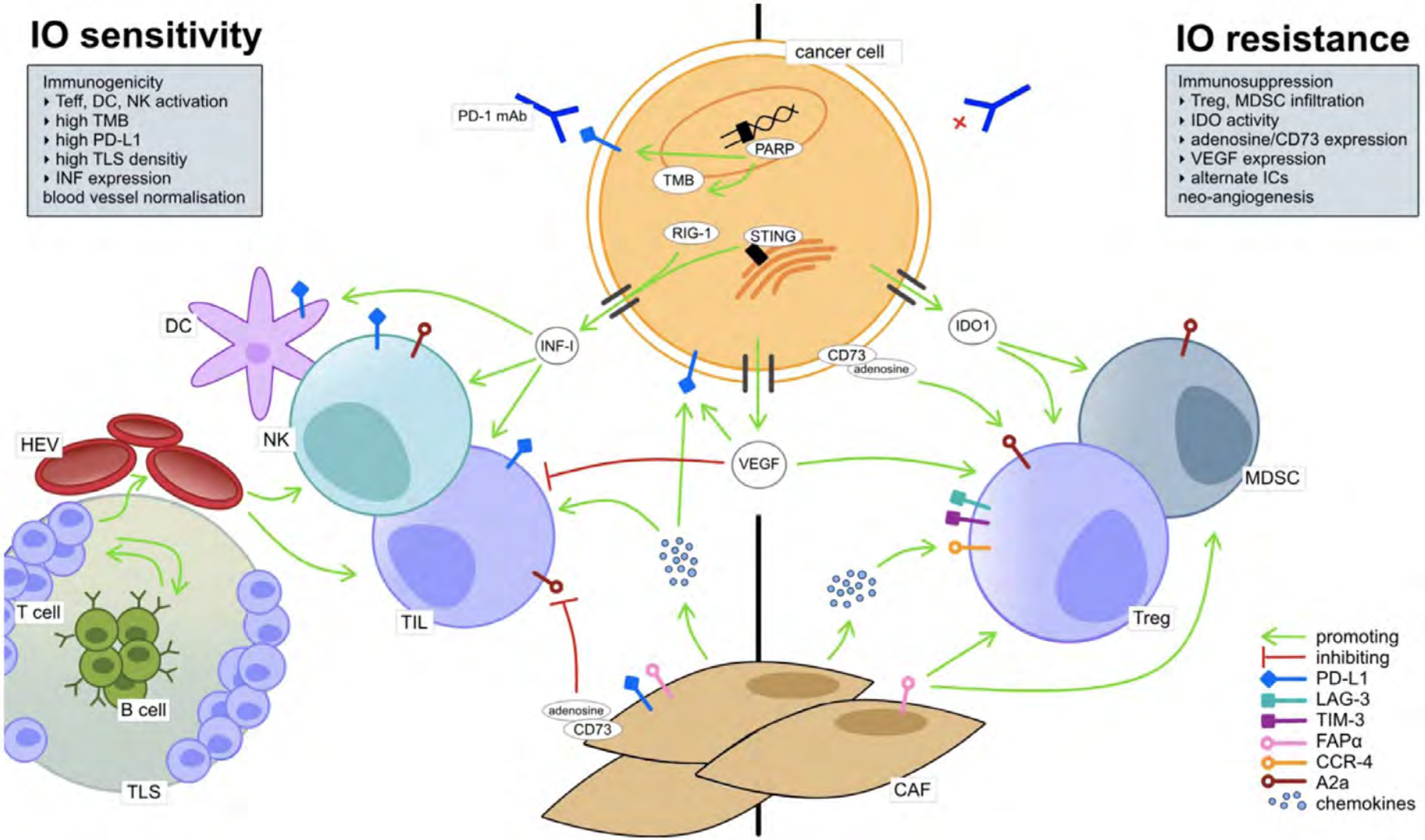
New Report Shows Significant Lung Cancer Survival Rate Gains, Lingering Disparities and Urgent Need for Increased Screening

American Lung Association.

- Death rates increased for both men and women from 1930 until peaking in 1990 at 91.1 per 100,000 for men and in 2002 at 41.6 per 100,000 for women.
- Since peaking, rates have decreased by 59% for men and 34% for women.
- Over the last 10 years, rates have decreased by 35% for men and 26% for women.
- Over the last 5 years, rates have decreased by 20% for men and 14% for women.



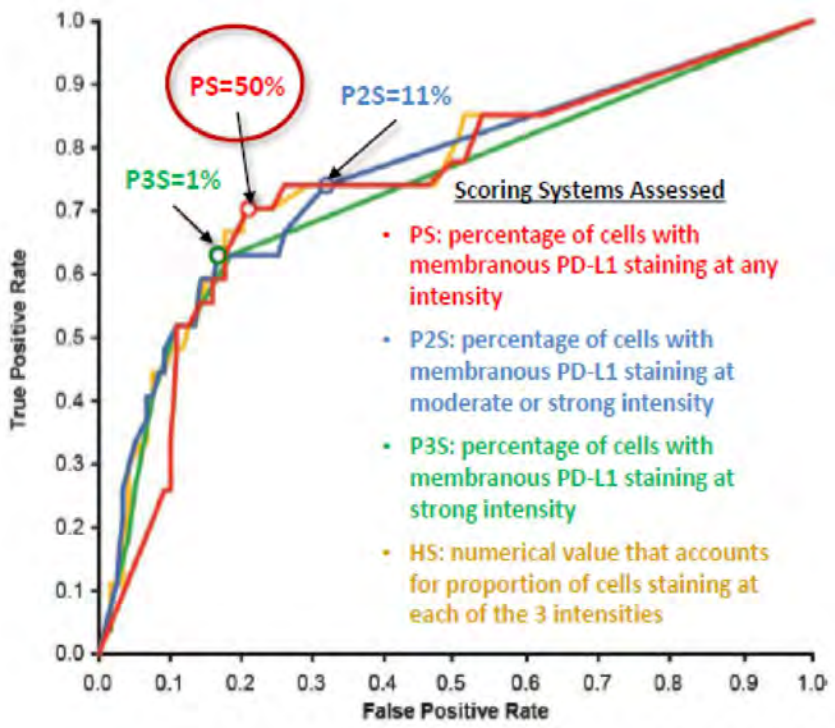
Cellular TME composition and molecular pathways associated with IO sensitivity and resistance



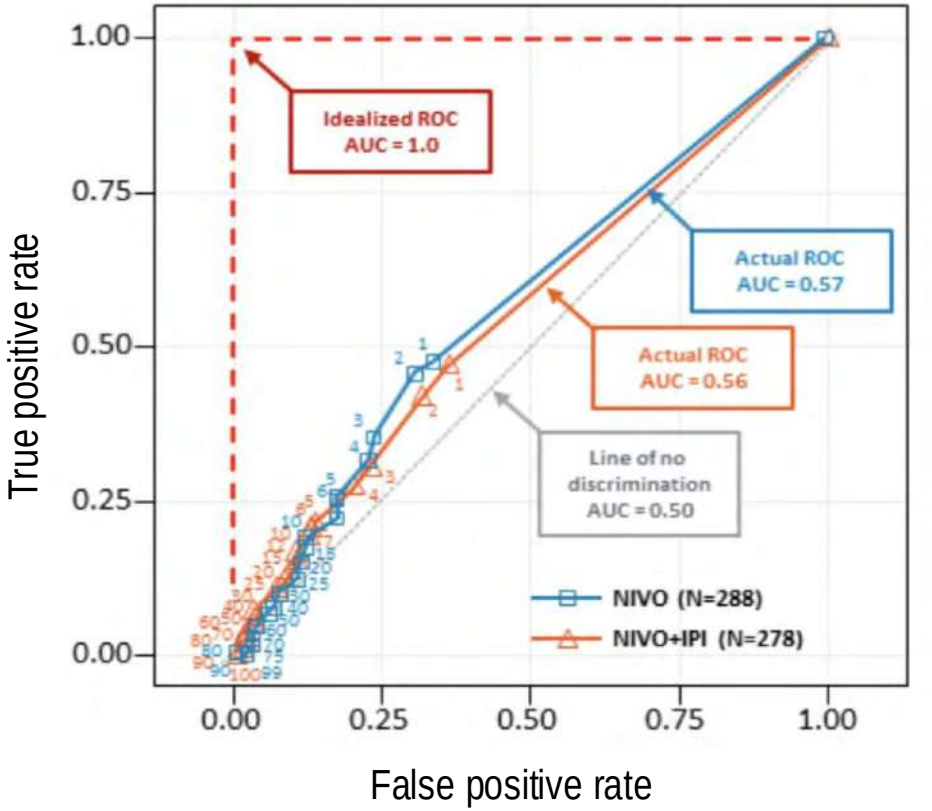
Horvath L, et al 2020, Mol Cancer

Performance of PD-L1 is variable across cancer types

NSCLC



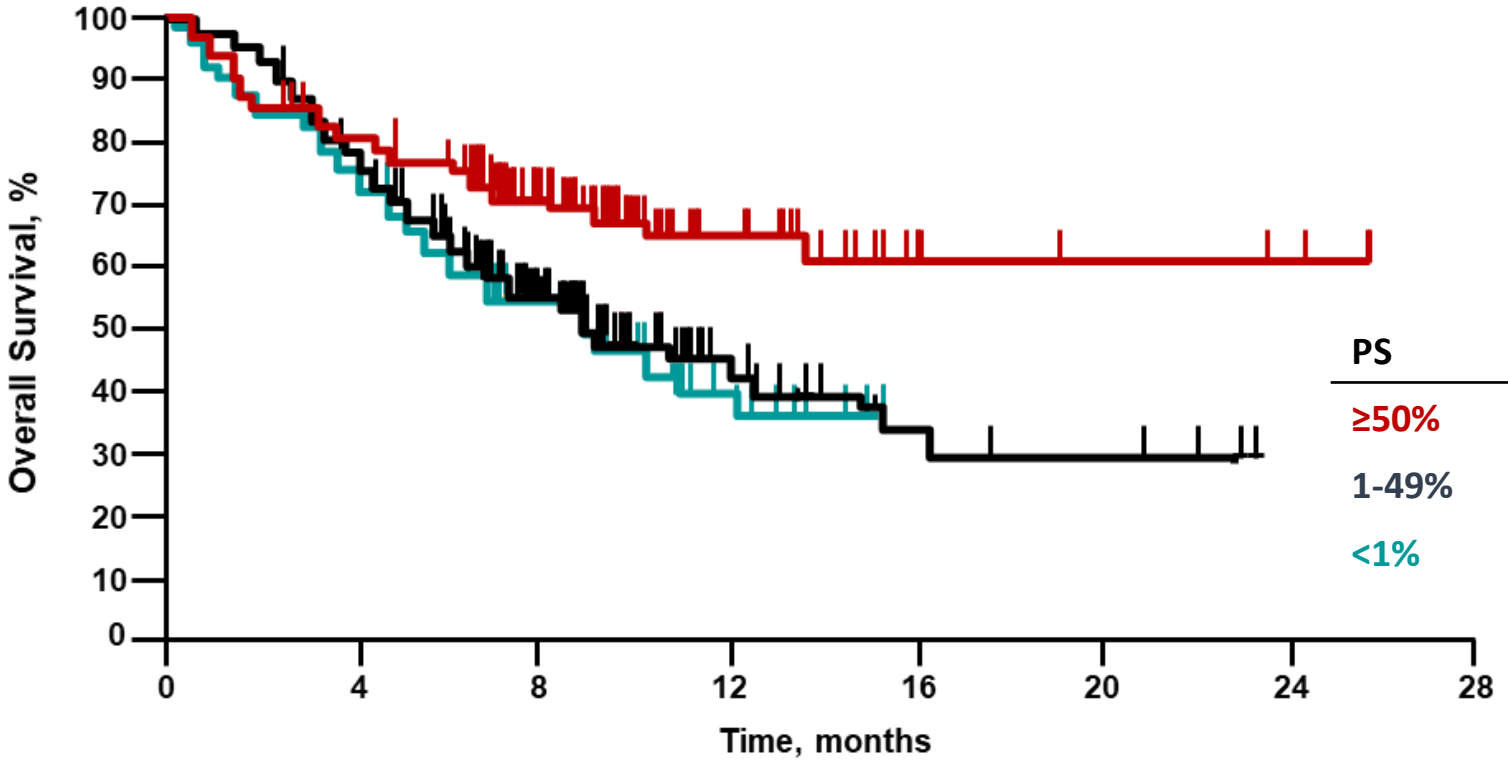
Melanoma



- A cut off value of 50% has been defined in NSCLC
- The shoulder of the ROC curve is taken to be the point that achieves the best true positive and the best false positive rate

Wolchok NEJM 2017; Garon NEJM 2015

OS by PD-L1 Expression : Pembrolizumab KEYNOTE-001



PS	Median (95% CI), mo
≥50%	NR (13.7-NR)
1-49%	8.8 (6.8-12.4)
<1%	8.8 (5.5-12.0)

n at risk

PS ≥50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

Garon EB et al. N Engl J Med. 2015;372(18):1700-1709.

First-line treatment for non-AGA NSCLC must include ICIs

PD-L1 ≥50%

- ICI alone
- Chemotherapy plus CPI
- ICI/ICI combination
- ICI/ICI/chemotherapy combinations

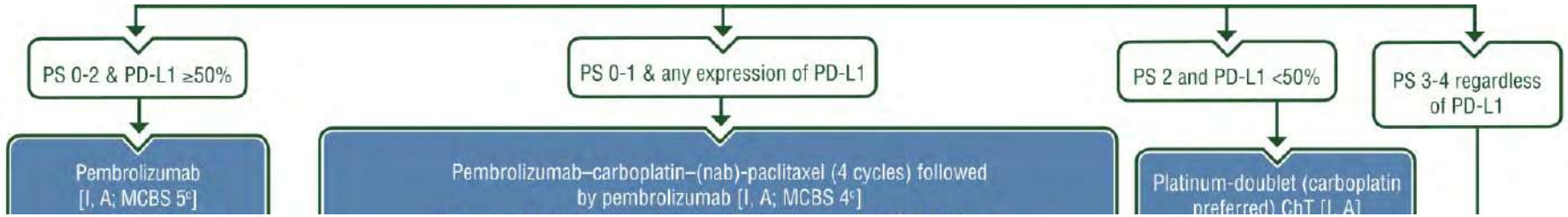
PD-L1 <1-49%

- Chemotherapy plus ICI
- ICI/ICI combination
- ICI/ICI/chemotherapy combinations

PD-L1 <1%

- ICI/ICI combination
- ICI/ICI/chemotherapy combinations

ESMO CPG first line ICB metastatic Non-AGA NSCLC

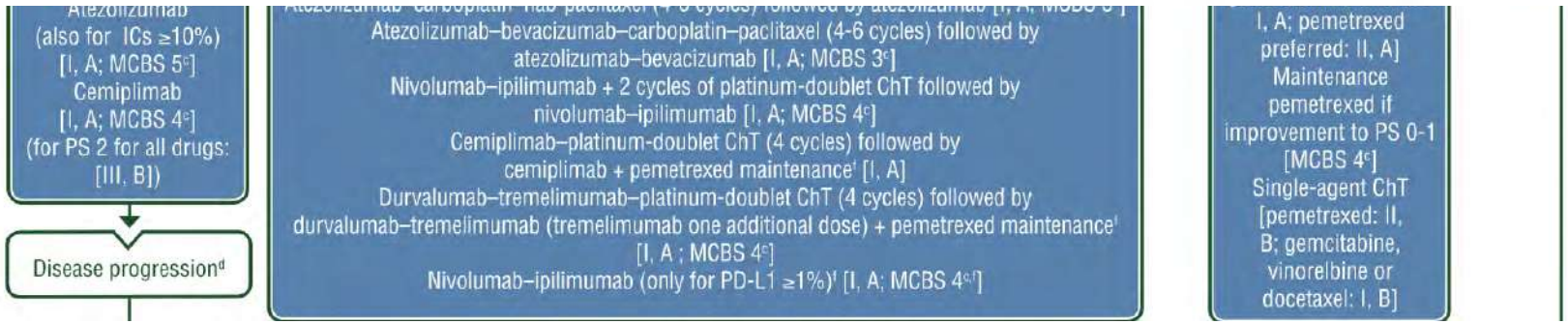


ESMO Non-Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guideline

Version:
v1.1 - March 2024

To cite this living guideline, please include the original Clinical Practice Guideline citation "Ann Oncol. 2023;34(4):358-376" and this online publication, including date and version number: "ESMO Non-Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guidelines, v1.1 March 2024"

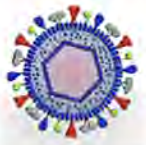
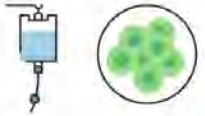
This living guideline was prepared by L Hendriks, F Cortiula, E Mariamidze, L Castelo-Branco, D Martins-Branco, C Sessa, G Pentheroudakis and M Reck, on behalf of the Clinical Practice Guideline author group.



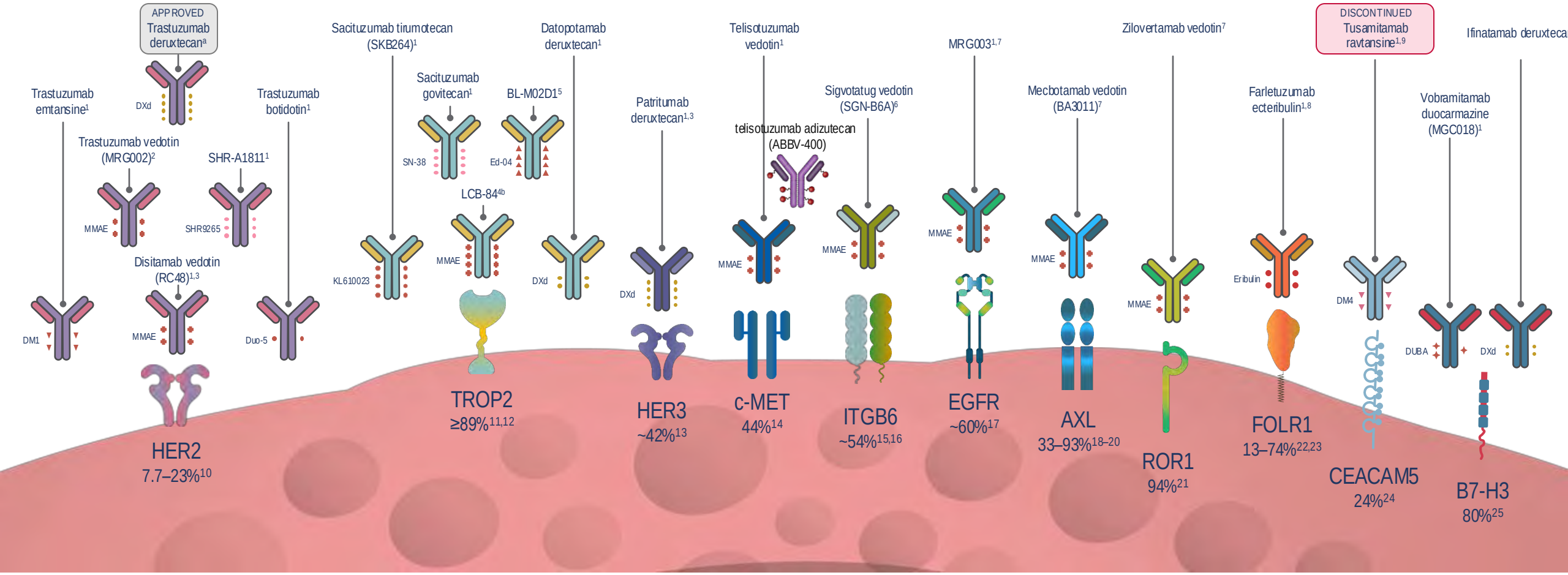
Non-squamous

Hendriks Ann Oncol 2023

Approved Immunotherapy Anticancer Agents

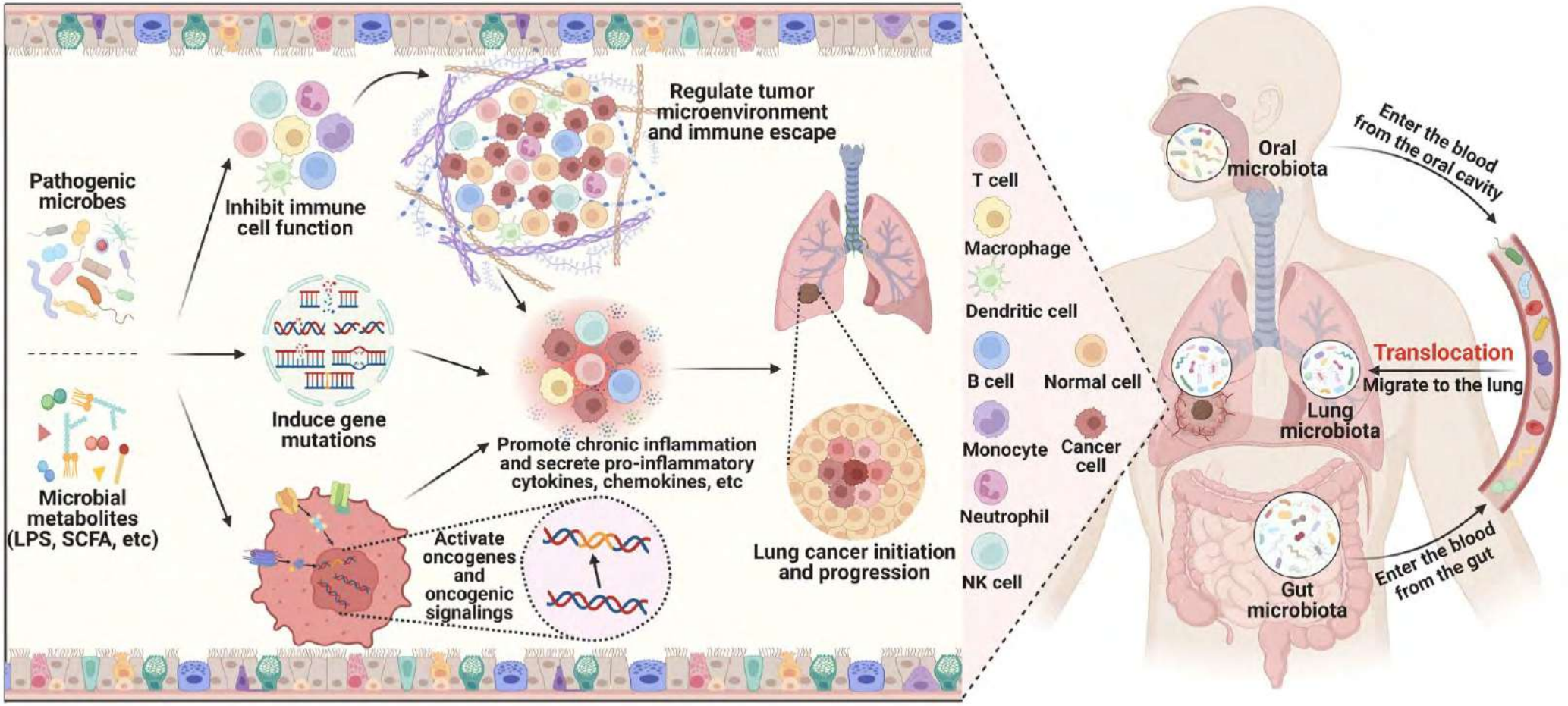
						
Drug Class	Monoclonal Ab	Bispecifics	Immuno-cytokines	Cancer vaccines	CAR-T cells	TCR-T cells
Targets	CD20 CD38 SLAMF7 (CD319) CD52 CD19 PD-1 PD-L1 CTLA-4 LAG3	CD3 x CD19 CD3 x gp100 CD3 x GPRC5D CD3 x CD20 CD3 x BCMA CD3 x DLL3 (PD-L1 x CTLA4) (EGFR x cMET)	IL-2 IL-12 IL-15 Interferons	Bacillus Calmette-Guerin Sipuleucel-T	Idecabtagene vicleucel (MM) Lisocabtagene maraleucel (B cell lymphoma) Ciltacabtagene autoleucel (MM) Tisagenlecleucel (DLBCL and ALL) Breuxcabtagene autoleucel (MCL and ALL) Axicabtagene ciloleucal (B cell and follicular lymphoma)	Afamitresgene autoleucel (synovial sarcoma)
						
			Oncolytic Virus	Tumor Infiltrating Lymphocytes		
			Talimogene Laherparepvec (TVEC)	Lifileucel		

Targets for ADCs approved or in development for lung cancer



1. Liu, Front Immunol 2023;14:1335252; 2. Li, Antib Ther 2021;4:175–184; 3. Grinda Curr Treat Options Oncol 2023;24:442–465; 4. Passaro, JCO 2023 5. Mountzios, CTR 2025

Can microbiome by a diagnostic/therapeutic tool?



Liu, Critical Reviews in Oncology / Hematology 2024

Learning objectives

- To acquire a deeper understanding of the clinical course of lung cancer.
- To understand biological hypotheses on classification and risk stratification, ongoing/required research in therapeutics and knowledge of use of omics technologies for biomarker-enabled precision medicine for lung cancer.
- To develop skills and abilities for critical analysis, interpretation of research data and therapeutic strategies.
- To become better equipped for informed, innovative thinking and engagement in ongoing or new research projects.

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Beyond PD-L1 axis inhibition

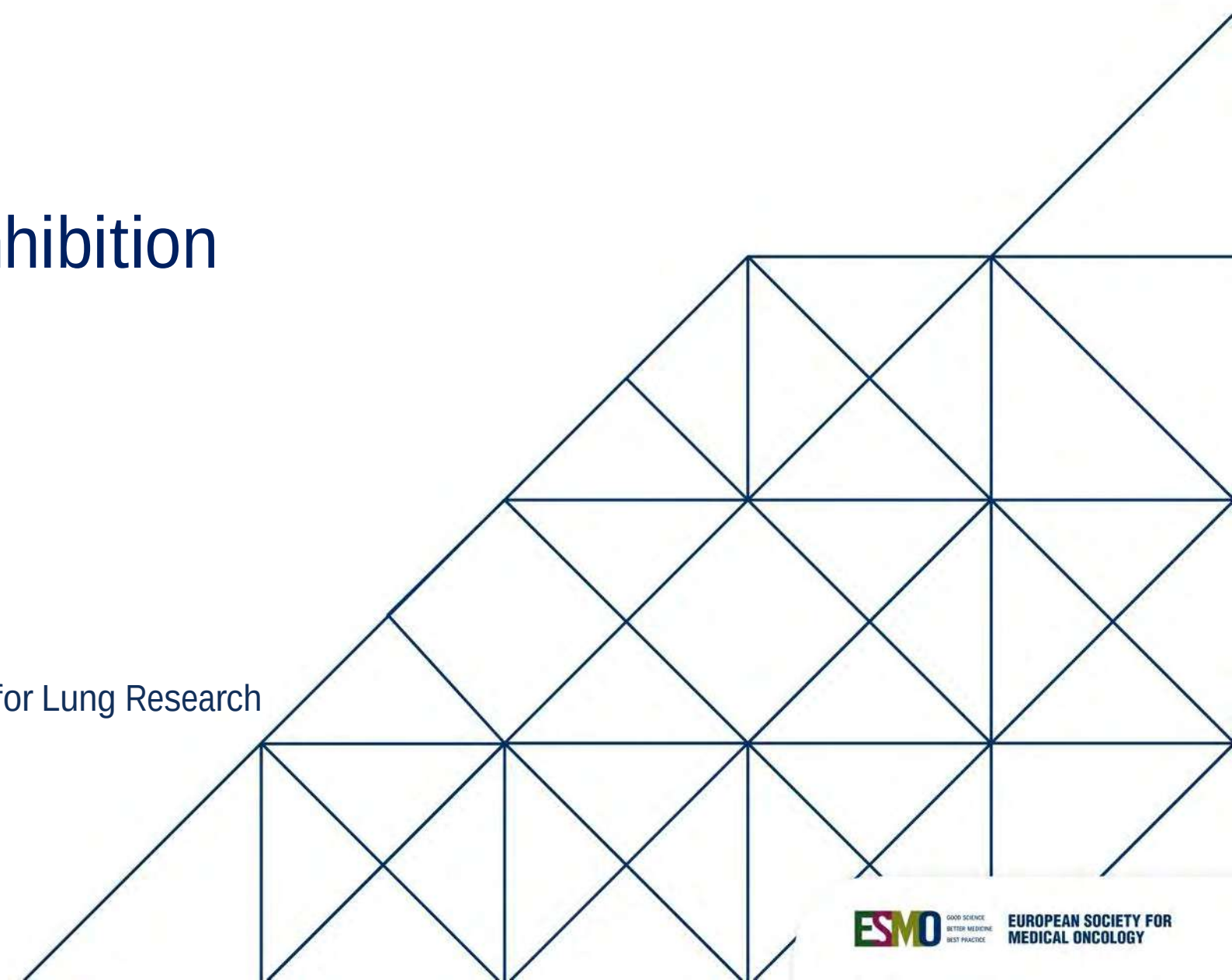
Where are we going?

Martin Reck

Airway Research Center North, German Center for Lung Research

LungenClinic

Grosshansdorf, Germany



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DECLARATION OF INTERESTS

- Martin Reck

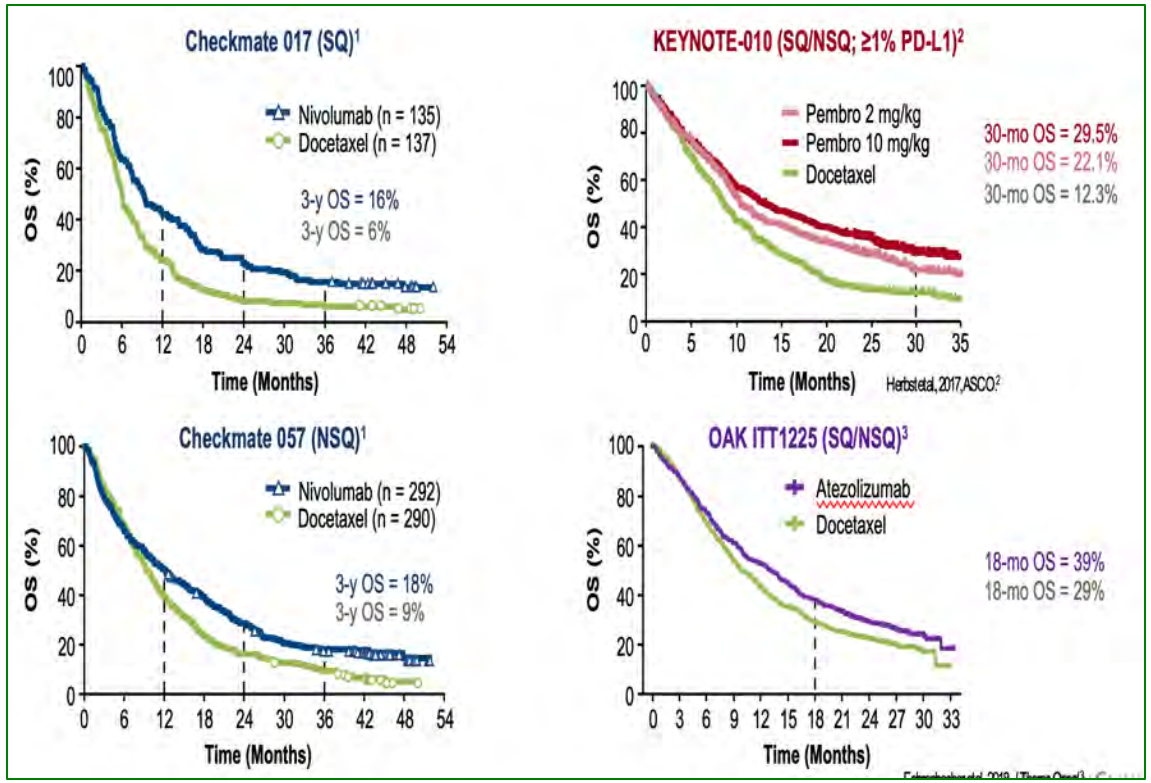
- Honoraria for lectures and consultancy from:
- Amgen, AstraZeneca, Beigene, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Mirati, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, Samsung Bioepis

- Compensated Membership in Study Steering Committees:
- Amgen, AstraZeneca, Beigene, Daiichi-Sankyo, Mirati, Merck, MSD, Novartis, Pfizer, Roche, Sanofi

- Compensated Membership in Data Safety Monitoring Committees:
- Daiichi-Sankyo, Sanofi

Immunotherapy - The Game Changer

Pretreated Patients

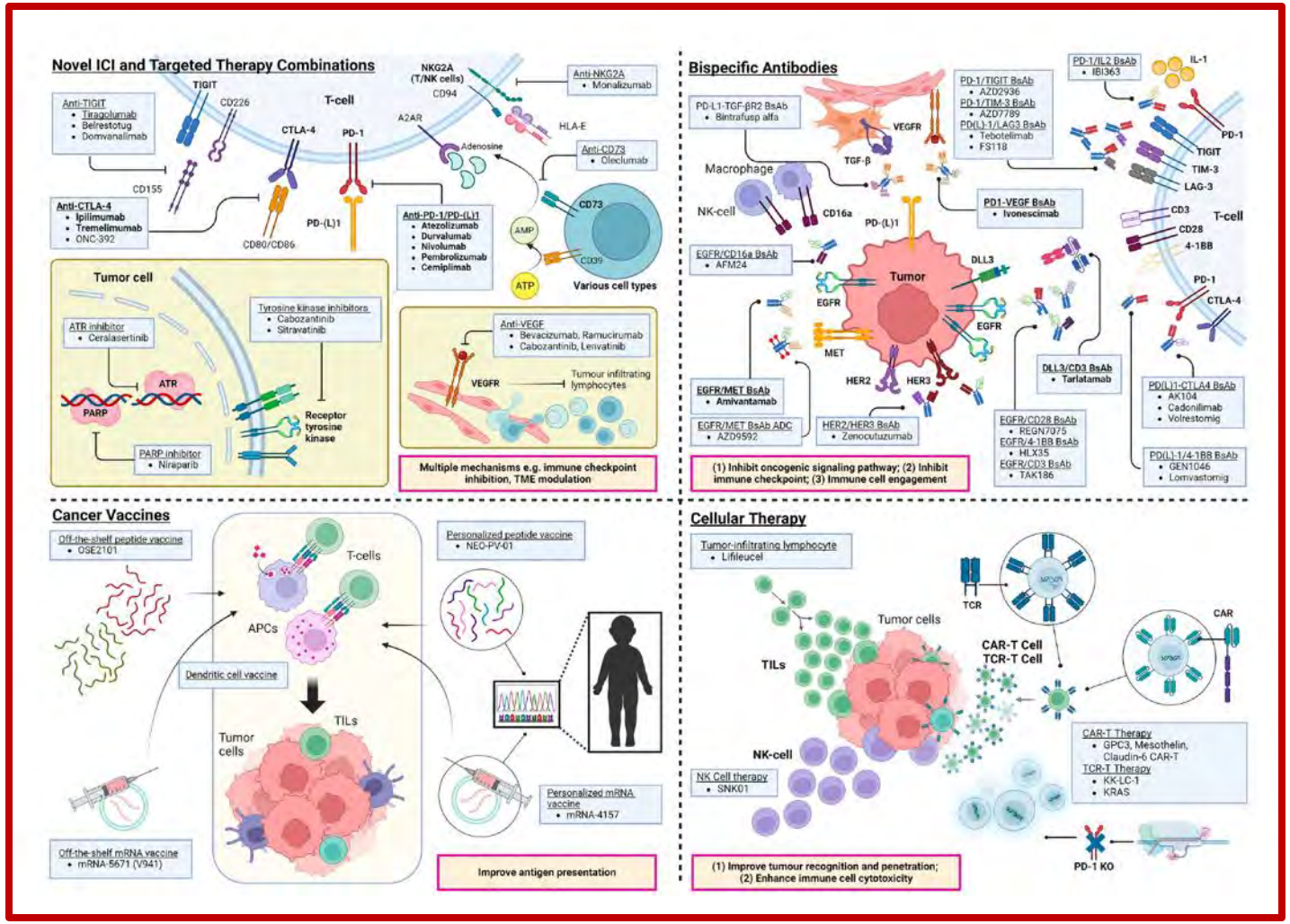


Untreated Patients

Trial			PFS / OS (months)	Treatment-Related AEs, grade 3-5 (* *All toxicities*)
KEYNOTE-024	PD-L1 TPS ≥50%	Pembro Plat/Pem or Gem or Pacli	10.3 / 30.0 6.0 / 14.2	31% vs 53%
CheckMate 026	PD-L1 ≥5%	Nivo Plat/Pem or Gem or Pacli	4.2 / 14.4 5.9 / 13.2	18% vs 52%
KEYNOTE-042	PD-L1 TPS ≥1%	Pembro Plat/Pem or Pacli	5.4 / 16.7 6.5 / 12.1	18% vs 41%
IMPower150	Nonsquamous	Atezo + Beva + Plat/Pacli Plat/Pacli	8.3 / 23.2 6.8 / 14.7	59% vs 50%
KEYNOTE-189	Nonsquamous	Pembro + Plat/Pem Plat/Pem	8.8 / NR 4.9 / 11.3	67% vs 66%*
IMPower132	Nonsquamous	Atezo + Plat/Pem Plat/Pem	7.6 / 18.1 5.2 / 13.6	57% vs 42%
IMPower130	Nonsquamous	Atezo + Carbo/nabPacli Carbo/nabPacli	7.0 / 18.6 5.5 / 13.9	75% vs 61%
KEYNOTE-407	Squamous	Pembro + Plat/Tax Plat/Tax	6.4 / 15.9 4.8 / 11.3	70% vs 68%*
IMPower131	Squamous	Atezo + Carbo/nabPacli Carbo/nabPacli	6.3 / 14 5.6 / 13.9	69% vs 58%
CheckMate 227	PD-L1 neg (*only PFS*)	Nivo + Plat/Pem or Gem Plat/Pem or Gem	5.6 4.7	54% vs 38%
CheckMate 227	TMB ≥10 mut/Mb	Nivo + Ipi Plat/Pem or Gem	7.2 / 17.1 5.5 / 10.7	32% vs 37%
MYSTIC	PD-L1 ≥25%	Durvalumab Plat/Pem or Gem or Pacli	4.7 / 14.3 5.4 / 12.9	15% vs 35%
MYSTIC	PD-L1 ≥25%	Durva + Treme Plat/Pem or Gem or Pacli	3.9 / 11.9 5.4 / 12.9	24% vs 35%
MYSTIC	TMB ≥16 mut/Mb (*only OS*)	Durva + Treme Plat/Pem or Gem or Pacli	16.5 10.5	24% vs 35%

Peters S et al, Ann Oncol 2019

Multiple Approaches to enhance immunogenicity...



- Novel Checkpoint-Inhibitors
- Bispecifc Antibodies
- Vaccinations
- Cellular Therapies

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Molly SC et al, Therapeutic Advances in Medical Oncology 2024

The Concept of T-Cell Immunoreceptor with Ig and ITIM domains (TIGIT)

- TIGIT is a co-inhibitory immunomodulatory checkpoint receptor
- Expressed on effector T-cells (CD4+ and CD8+), Tregs, and NK cells[1]
- TIGIT binds to ligands expressed on tumor cells and APCs (CD112 and CD155) [1,3,4,5]
- The costimulatory receptor CD226 competes with TIGIT for the binding of CD112 and CD155[1]
- Binding of CD226 with CD155 has been shown to strengthen the activity of TILs, which can restore a functioning immune antitumor response[6]

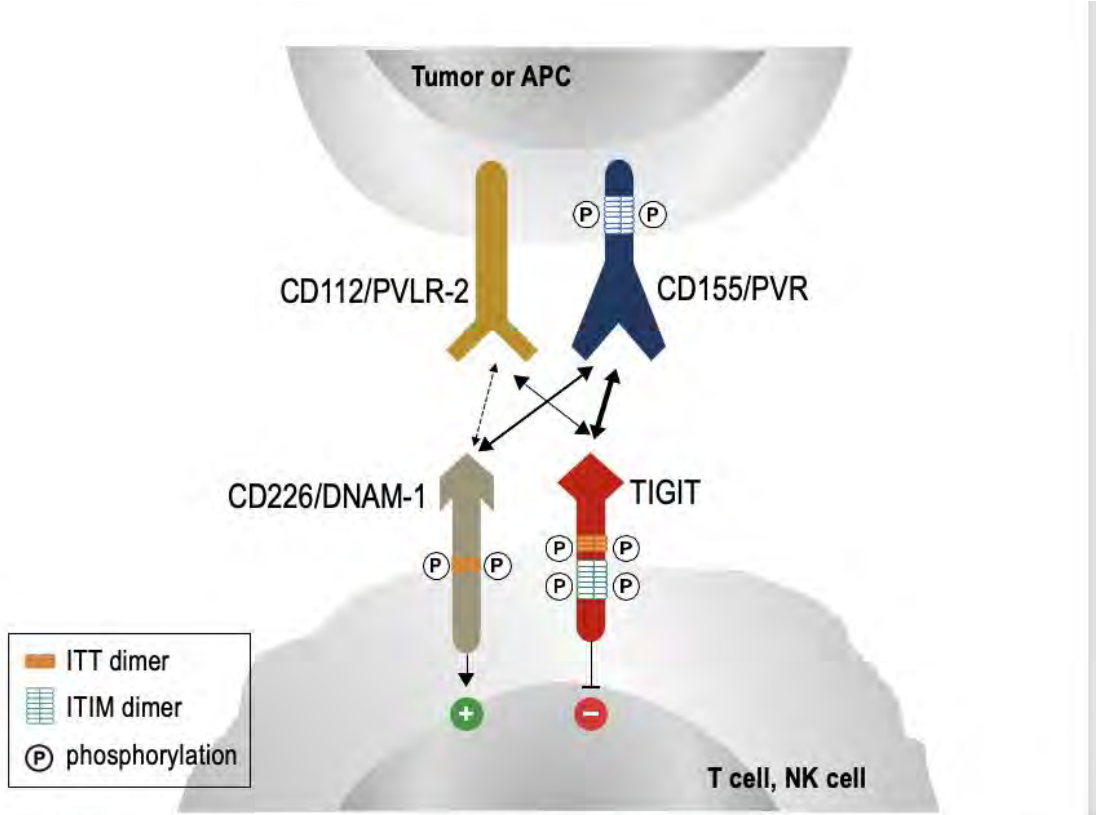


Image adapted from Anderson AC et al. Immunity. 2016;44(5):989-1004. and Harjunpaa H and Guillerey C. Clinical and Experimental Immunology. 2020;200:108-119.

1. Anderson AC, et al. *Immunity*. 2016;44(5):989-1004. 2. Kurtulus S, et al. *J Clin Invest*. 2015;125(11):4053-62. 3. Stanietsky N, et al. *PNAS U S A*. 2009;106(42):17858-63. 4. Liu S, et al. *Cell Death Differ*. 2013;20(3):456-64. 5. Manieri N, et al. *Trends Immunol*. 2017 Jan;38(1):20-28. 6. Gilfillan S, et al. *J Exp Med*. 2008;205(13):2965-73.

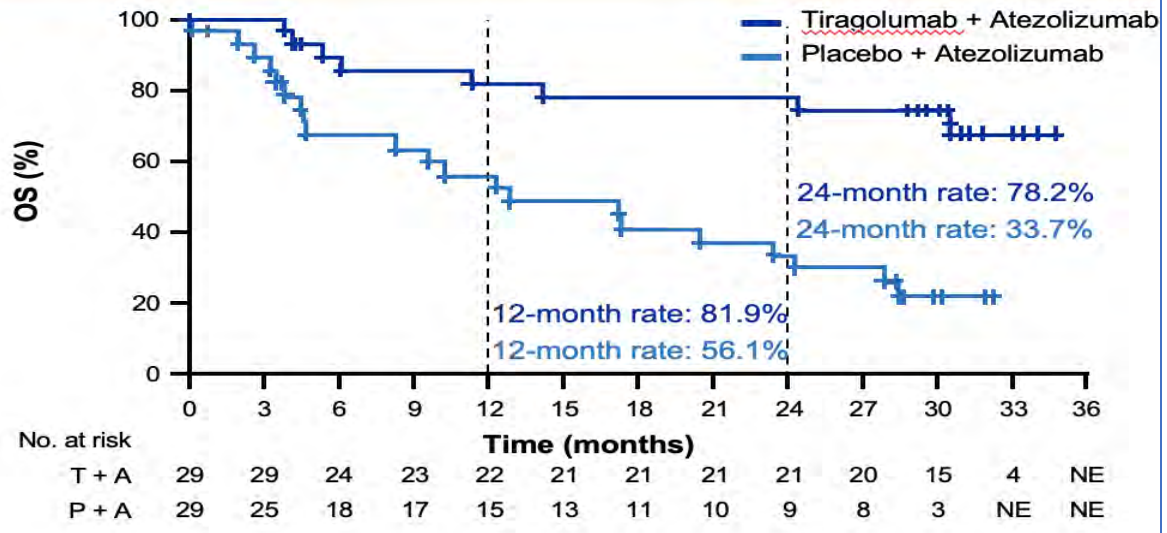
- Martin Reck

Potential signals in phase II trials

Cityscape Trial

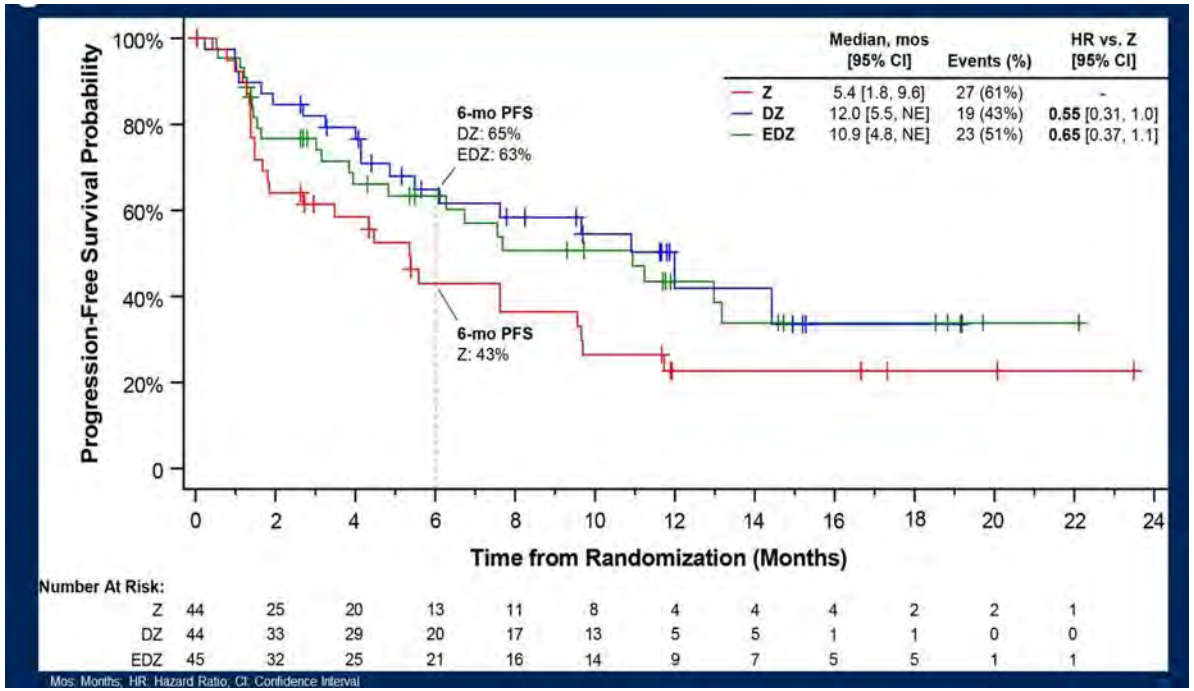
PD-L1 TPS ≥50% (n=58)

	Events n (%)	Median OS, months (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)	



Cho BC, ESMO IO 2021, Lancet Oncology, Johnson M et al, ASCO Plenary Discussion 12/2022

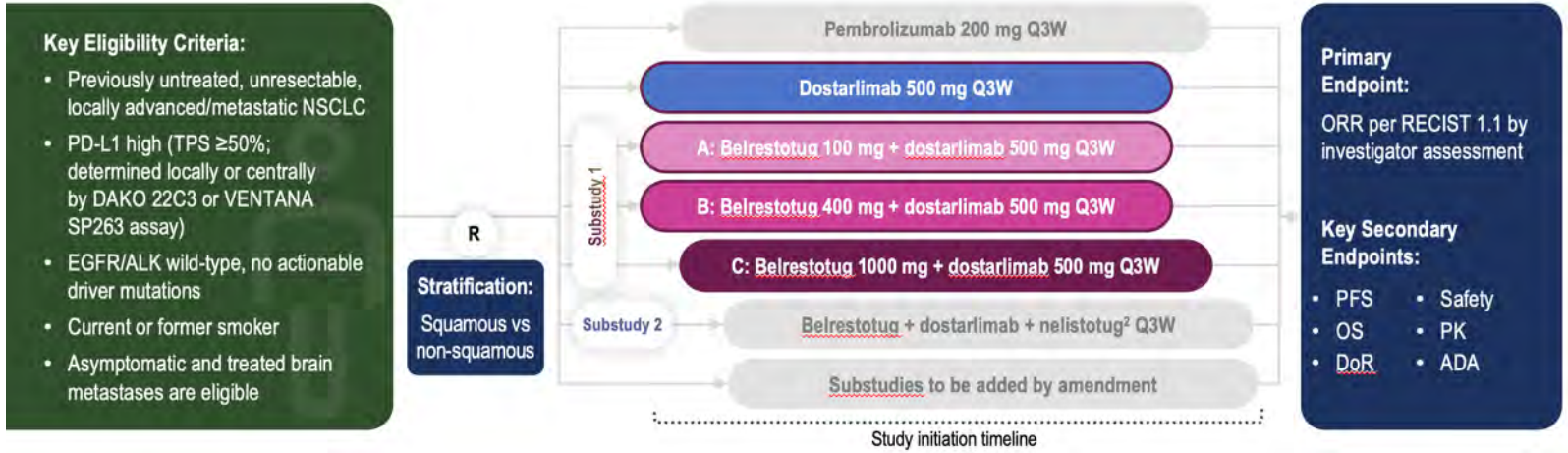
ARC-07 Trial



Med PFS 10.9 vs 5.4 m (HR 0.65) (Arm 3 vs 1)
RR: 40% vs 27% (Arm 3 vs 1)

GALAXIES - Lung201

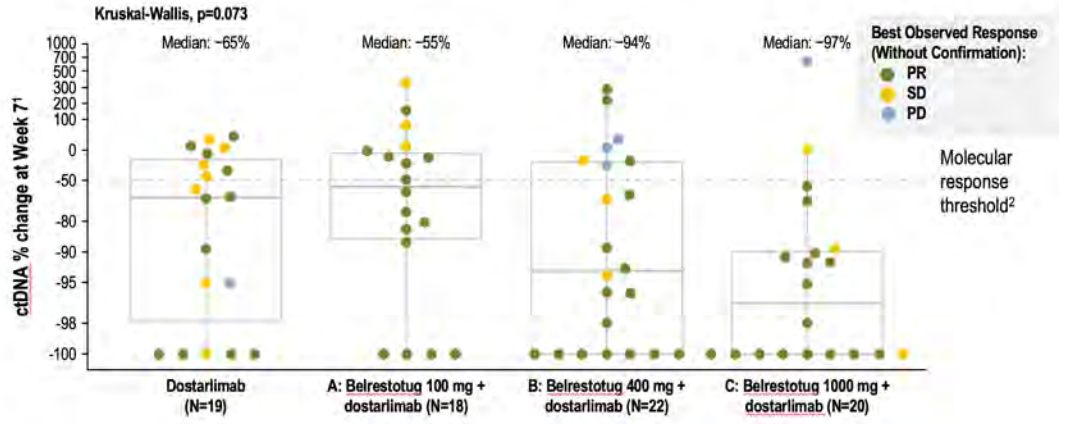
Belrestotug + Dostarlimab in PD-L1 =/> 50%



- RR: 60.0 - 63.3%
- Higher Decrease of ctDNA in Belrestotug combinations
- Grade 3+ TRAE: 22% - 44%
- Grade 3+ TR-irAE: 16% - 37%

Ongoing phase III trial: Galaxies-Lung 301 (NCT 06472076)

Response measure in mITT	Dostarlimab N=32	A: Belrestotug 100 mg + dostarlimab N=30	B: Belrestotug 400 mg + dostarlimab N=32	C: Belrestotug 1000 mg + dostarlimab N=30
Median follow-up, months (range)[1]	7.0 (0.2–16.6)	8.5 (0.3–14.3)	8.5 (0.4–16.2)	6.7 (2.4–9.7)
ORR,[2,3] % n (95% CI)	**37.5%** n=12 (21.1–56.3)	**63.3%** n=19 (43.9–80.1)	**65.6%** n=21 (46.8–81.4)	**76.7%** n=23 (57.7–90.1)
Complete response, n (%)	0	0	0	0
Partial response, n (%)	12 (37.5%)	19 (63.3%)	21 (65.6%)	23 (76.7%)
Stable disease, n (%)	14 (43.8%)	5 (16.7%)	4 (12.5%)	5 (16.7%)
Progressive disease, n (%)	2 (6.3%)	4 (13.3%)	3 (9.4%)	2 (6.7%)
Not evaluable/no assessment,[4] n (%)	4 (12.5%)	2 (6.7%)	4 (12.5%)	0
Confirmed ORR,[3,5] % n (95% CI)	**28.1%** n=9 (13.7–46.7)	**60.0%** n=18 (40.6–77.3)	**59.4%** n=19 (40.6–76.3)	**63.3%** n=19 (43.9–80.1)

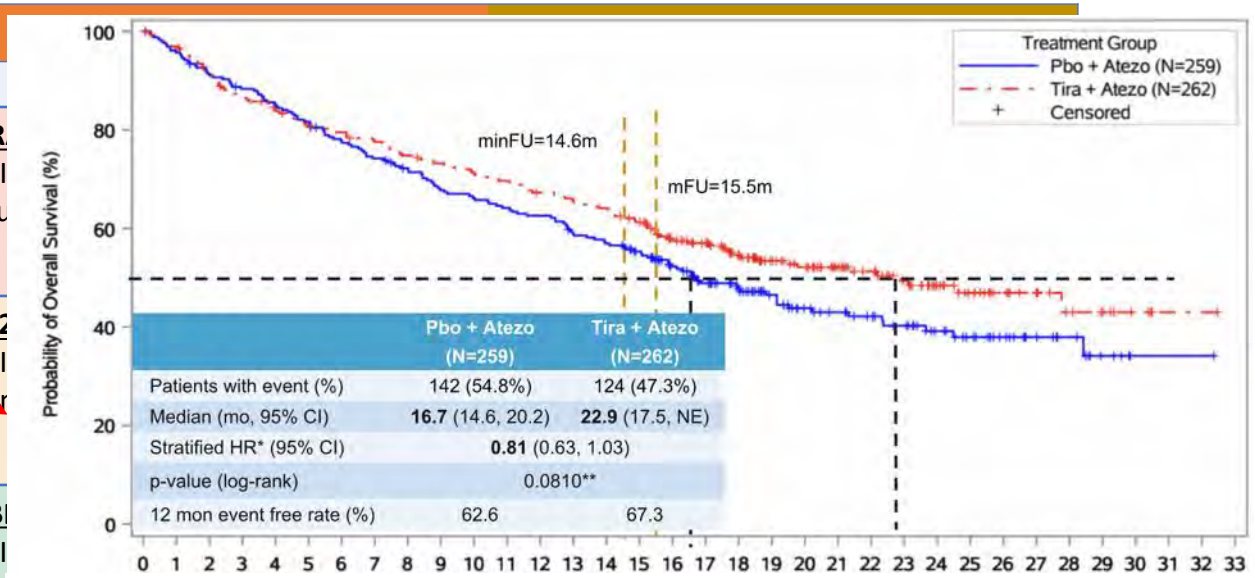


Spigel D et al, ESMO 2024

New results for anti-TIGIT therapies in NSCLC

(courtesy of Solange Peters)

	1L NSCLC	
	PD-L1 positive	
Roche **Tiragolumab**	**SKYSCRAPER-01**[1] Phase III Tiragolumab + atezolizumab PD-L1 high	**SKYSCR** Phase II Tiragolu
ARCUS BIOSCIENCES GILEAD **Domvanalimab**	**ARC-10**[4] Phase III Domvanalimab + zimberelimab PD-L1 ≥50%	**STAR-12** Phase II Domvar
MERCK **Vibostolimab**	**KEYVIBE-003**[7] Phase III MK-7684A* PD-L1 ≥1%	**KEYVIB** Phase II MK-768
NOVARTIS BeiGene **Ociperlimab**	**AdvanTIG-302**[10] Phase III Ociperlimab + tislelizumab PD-L1 ≥50%	AdvanT Phase II Ociperli
iTEOS THERAPEUTICS GSK **Belrestotug**	**GALAXIES Lung-301** Phase III Dostarlimab + belrestotug PD-L1 ≥50%	



	Pbo + Atezo (N=259)	Tira + Atezo (N=262)
Patients with event (%)	142 (54.8%)	124 (47.3%)
Median (mo, 95% CI)	**16.7** (14.6, 20.2)	**22.9** (17.5, NE)
Stratified HR* (95% CI)	**0.81** (0.63, 1.03)	
p-value (log-rank)	0.0810**	
12 mon event free rate (%)	62.6	67.3

Basel, 26 November 2024 - Roche (SIX: RO, ROG; OTCQX: RHHBY) reports an update on the phase III SKYSCRAPER-01 study, evaluating tiragolumab combined with Tecentriq® (atezolizumab) compared to Tecentriq alone for patients with PD-L1-high, locally advanced or metastatic non-small cell lung cancer (NSCLC).

SKYSCRAPER-01 is a global phase III, randomised, double-blind study evaluating tiragolumab plus Tecentriq compared to Tecentriq alone in 534 patients with PD-L1-high previously untreated, locally advanced unresectable or metastatic NSCLC. Patients were randomised 1:1 to receive either tiragolumab plus Tecentriq or placebo plus Tecentriq, until disease progression, loss of clinical benefit, or unacceptable toxicity. The study did not reach the primary endpoint of overall survival at the final analysis. The overall safety profile observed remained consistent with longer follow-up, and no new safety signals were identified. The detailed data will be presented at a medical meeting in 2025.

*MK-7684 = pembrolizumab + vibostolimab coformulation.

cCRT, concurrent chemoradiation; CT, chemotherapy; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

References in slide notes.

New results for anti-TIGIT therapies in NSCLC

(courtesy of Solange Peters)

	1L NSCLC		Stage III NSCLC
	PD-L1 positive	All comers	Unresectable
Roche Tiragolumab	**SKYSCRAPER-01**[1] Phase III Tiragolumab + atezolizumab PD-L1 high	**SKYSCRAPER-06**[2] Phase II / III Tirag	**SKYSCRAPER-03**[3] Phase III atezolizumab
ARCUS BIOSCIENCES GILEAD Domvanalimab	ARC-10[4] Phase III Domvanalimab + zimberelimab PD-L1 ≥50%	STA Phas Dom	AstraZeneca + durvalumab
MERCK Vibostolimab	**KEYVIBE-003**[7] Phase III MK-7684A* PD-L1 ≥1%	**KEYVIBE-007**[8] Phase III MK-7684A* + CT	**KEYVIBE-006**[9] Phase III MK-7684A* + cCRT → MK-7684A
NOVARTIS BeiGene Ociperlimab	**AdvanTIG-302**[10] Phase III Ociperlimab + tislelizumab PD-L1 ≥50%	AdvanTIG-306[11] Phase III Ociperlimab + tislelizumab +	
iTEOS THERAPEUTICS GSK Belrestotug			

No success in SCLC
KeyVibe 008 : OS HR 0.97
SKY-2 : OS HR 1.09

Discontinued: Futility by IDMC (12/2024)

Discontinued subsequently

Genentech Provides Update on Phase II/III SKYSCRAPER-06 Study in Metastatic Non-Squamous Non-Small Cell Lung Cancer

PUBLISHED
JUL 4, 2024 1:10AM EDT

– SKYSCRAPER-06 evaluating tiragolumab plus Tecentriq and chemotherapy did not meet the primary endpoints of progression-free survival at primary analysis and overall survival at first interim analysis –

– The combination of tiragolumab plus Tecentriq and chemotherapy showed reduced efficacy compared to the comparator arm –

– Safety was consistent with previous studies, however we intend to halt the trial due to reduced efficacy compared to the comparator arm –

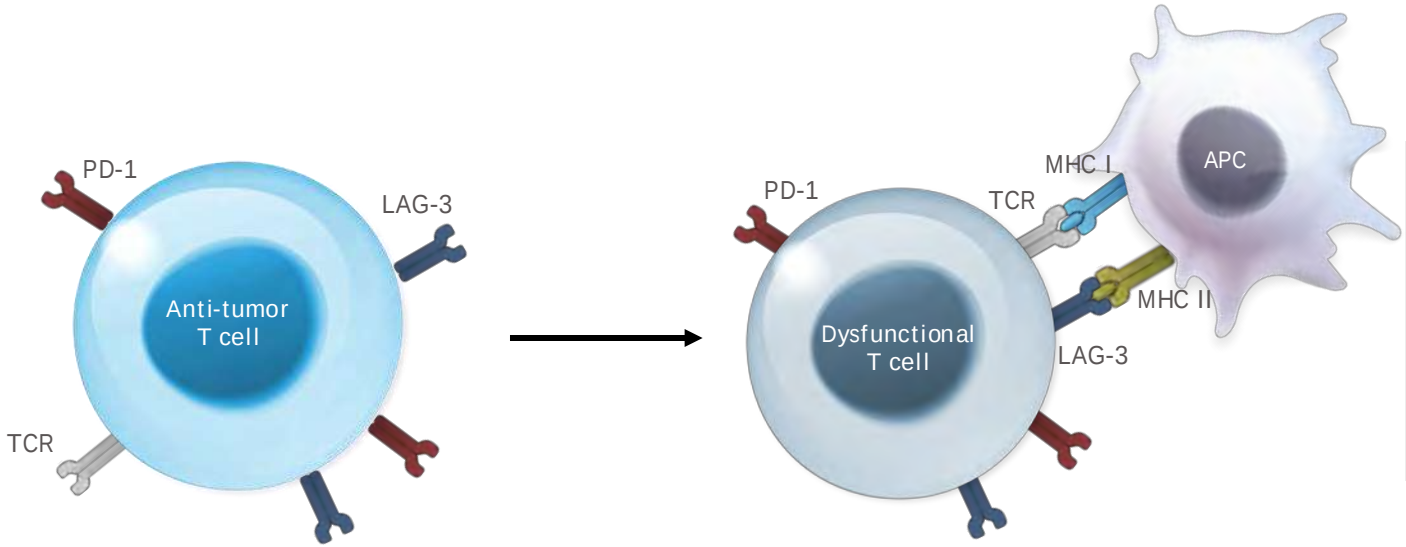
*MK-7684 = pembrolizumab + vibostolimab coformulation.

cCRT, concurrent chemoradiation; CT, chemotherapy; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

LAG-3 biology and pathway

LAG-3 is a cell-surface molecule expressed on T cells and other immune cells that has diverse inhibitory biologic effects on the function of T cells[1,2]

Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially when co-expressed with PD-1, inhibits effector T-cell function[1,3-5]



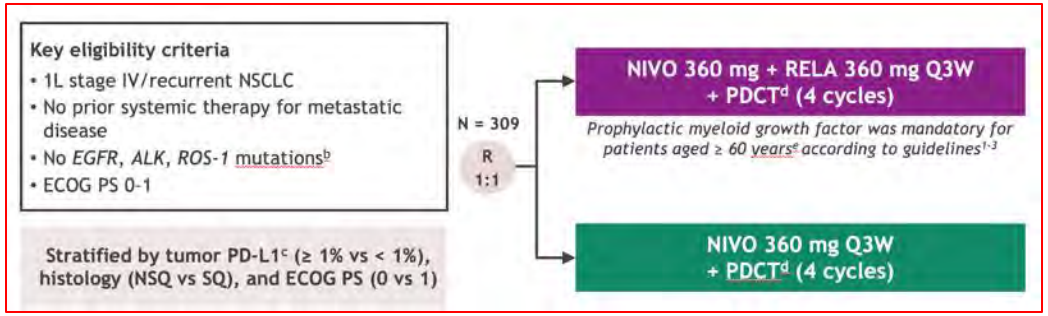
Preclinical data suggest that simultaneous activation of the LAG-3 and PD-1 pathways in TILs results in a greater degree of T-cell dysfunction than either pathway signaling alone[4,6,7]

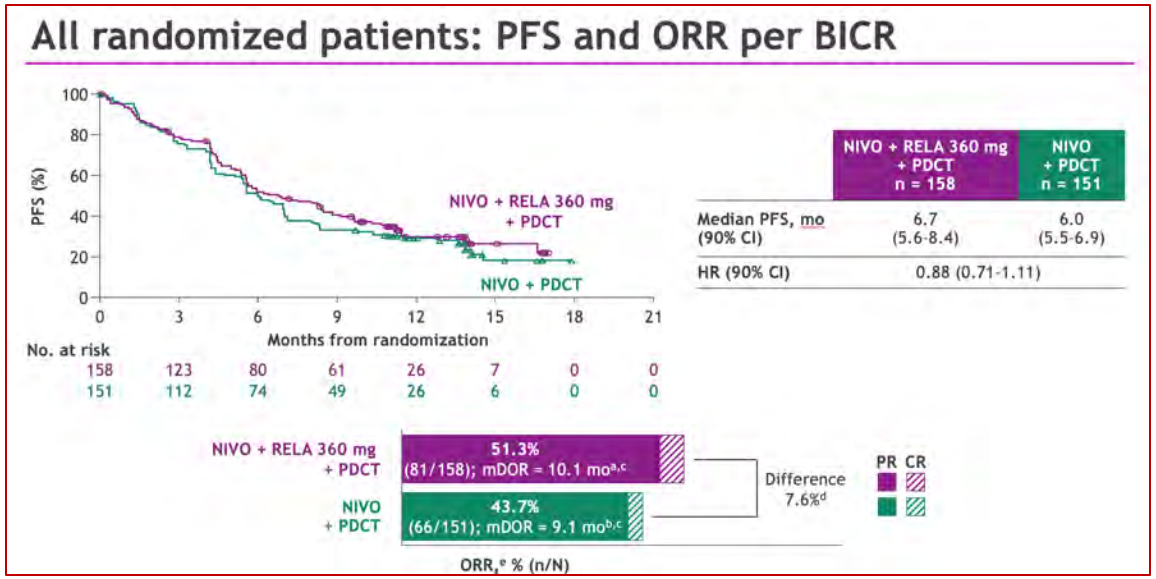
Interaction of LAG-3 with its ligands triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to fight tumor cells and an increased potential for tumor growth[1,5]

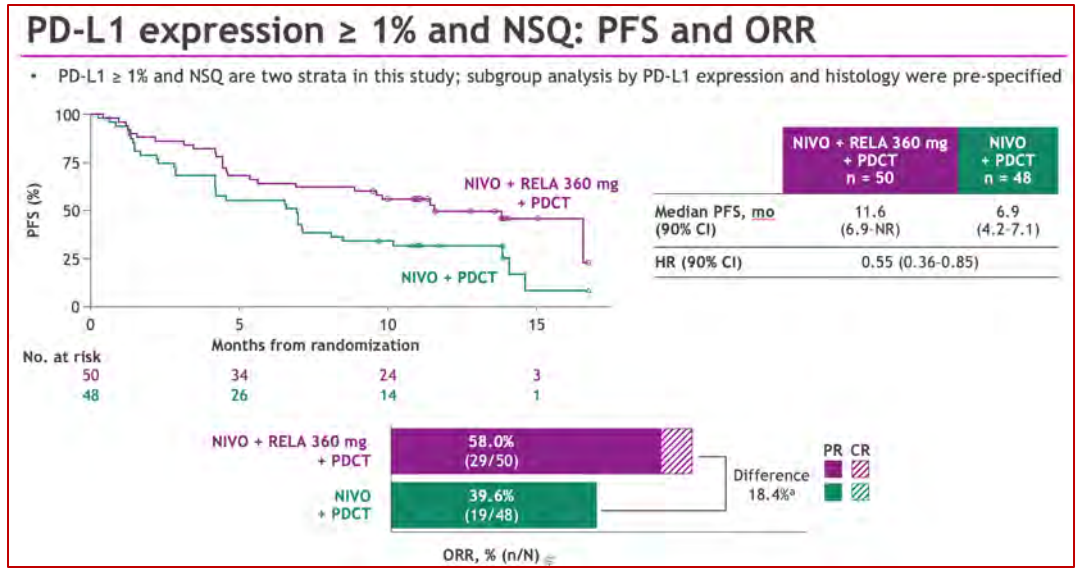
Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints, such as PD-1 or CTLA-4. Among its ligands, the most well established is MHC II; others are emerging, including FGL1[1,5,8,9]

1. Long L et al. Genes Cancer. 2018;9:176–189. 2. Grosso JF et al. J Clin Invest. 2007;117:3383–3392. 3. Workman CJ et al. J Immunol. 2004;172:5450–5455. 4. Woo SR et al. Cancer Res. 2012;74:917–927. 5. Wang J et al. Cell. 2019;176:334–347.e12. 6. Nguyen LT et al. Nat Rev Immunol 2015;15:45–56. 7. Anderson AC et al. Immunity. 2016;44:989–1004. 8. Huang R-Y et al. Oncoimmunology. 2017;6:e1249561. 9. Maçon-lemaître L, Triebel F. Immunology. 2005;115:170–178.

Relativity-104 Part 2 / Relatlimab + Nivo + CT







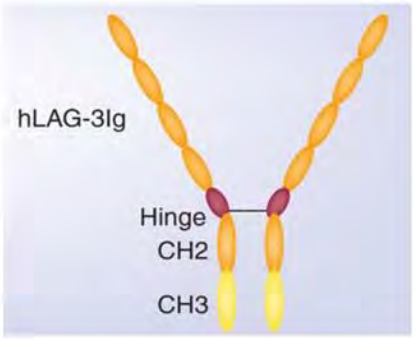
RR: 51.3% vs 43.7%
Med PFS: 6.7 vs 6.0 m (HR 0.88)

RR: 58% vs 39.6%
Med PFS: 11.6 vs 6.9 m (HR 0.55)

Eftilagimod Alpha (Soluble Lag-3)

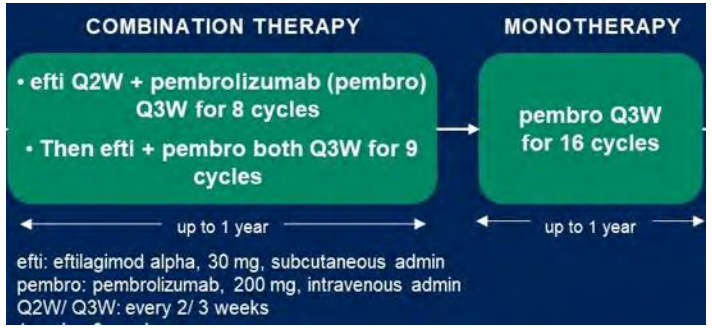
Promising phase II results, confirmation pending

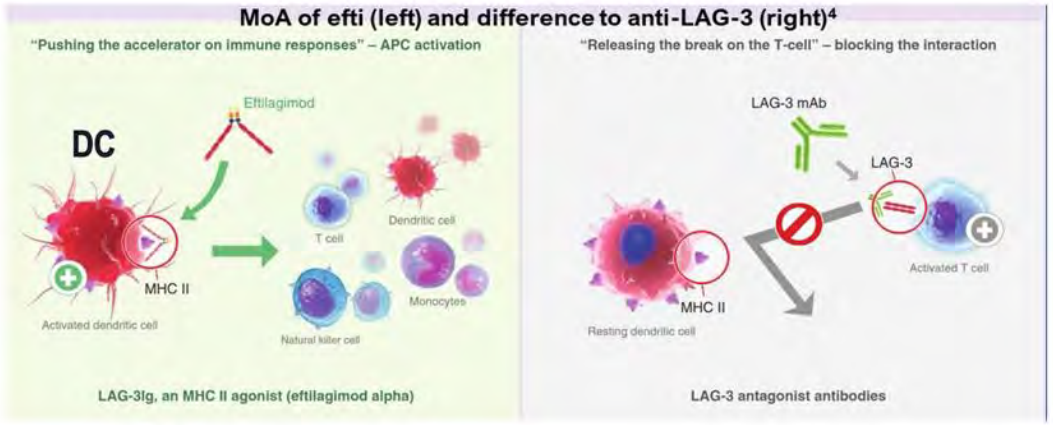
114 patients



Efti structure
Fc part can activate APC

PART A ONLY
- Advanced/metastatic (stage IIIb /IV) NSCLC (SQ & NSQ)
- Not amenable to ALK/EGFR based therapies or therapy with curative intent
- Treatment naive for advanced or metastatic disease





Tumor Response by central PD-L1[1], N=90

Efficacy parameter	<1%[1], n (%), N=32	1-49%[1], n (%), N=38	≥50%[1], n (%), N=20	≥1%[1], n (%), N=58
ORR[2,3], % (95% CI)[4]	31.3 (16.1-50.0)	44.7 (28.6-61.7)	55.0 (31.5-76.9)	48.3 (35.0-61.8)
mPFS[2], mo (% events)	4.2 (90.6)	9.3 (71.1)	16.5 (70.0)	11.2 (70.7)
mDoR[2], mo (% events)	20.7 (57.1)	NR (35.7)	18.7 (63.6)	24.2 (48.0)
mOS, mo (% events)	15.5 (71.9)	23.4 (52.6)	NR (40.0)	35.5 (48.3)

[1] N=90; Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx; [2] iRECIST; [3] unconfirmed; [4] calculated using Clopper Pearson method; NR: not reached.
Note: results for PD-L1 central + local (N=108) were as follows (<1% / 1-49% / ≥50% / ≥1%):
mOS, mo: 14.4 / 23.4 / 38.8 / 35.5; mPFS[2]: 4.2 / 8.3 / 16.3 / 9.8; mDoR[2]: 20.7 / 21.6 / 18.7 / 21.6.

Felip E, ASCO 2022, Carcereny E, ESMO 2023

LAG-3 Ongoing Research

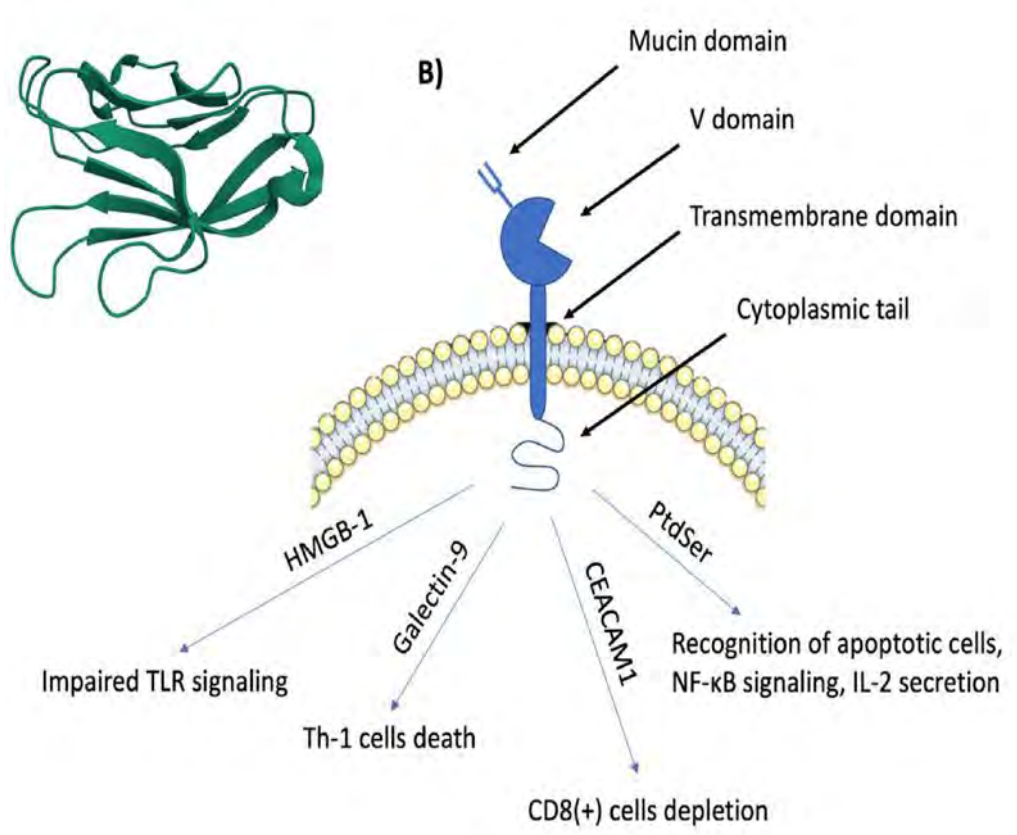
Reference	Drugs	Phase	N	Population	Primary Endpoint
NCT03252938	Eftilagimod alpha	1	45	IT, IP, SC alone or in combination in advanced solid tumors	Feasibility rate
NCT03005782	Fianlimab with or without REGN2810 (Anti-PD1)	1	333	Advanced malignancies	DLTs AEs Serious AEs
NCT05352672	Fianlimab + cemiplimab vs. pembrolizumab	3	1590	Previously untreated unresectable LA or metastatic melanoma	PFS
NCT04140500	RO7247669 (PD1-LAG3 bispecific antibody)	1	320	Advanced and/or metastatic solid tumors	DLTs, AEs, ORR, DCR, DOR, PFS
NCT05419388	RO7247669	1/2	80	Previously untreated unresectable or metastatic melanoma	PFS
NCT05645692	RO7247669 +/− tiragolumab vs. atezolizumab	2	240	Previously untreated advanced or metastatic UC ineligible for platinum-containing chemotherapy	ORR
NCT04785820	RO7247669 vs. RO7121661 (PD1-TIM3 bispecific antibody) vs. nivolumab	2	210	Relapsed or intolerant to platinum-containing regimens in A/M SCCE	OS
NCT05508867 (KEYFORM-008)	favezelimab + pembrolizumab vs. physician's choice chemotherapy	3	360	PD-(L)1-refractory, R/R classical Hodgkin lymphoma	PFS
NCT05064059 (MK-4280A-007)	favezelimab + pembrolizumab vs. SOC	3	432	Previously treated metastatic PD-L1 positive CRC	OS
NCT03598608 (MK-4280-003)	Favezelimab + pembrolizumab	1/2	174	Hematologic malignancies	DLTs, AEs, treatment discontinuation due to AEs
NCT04938817 (MK-3475-B98/KEYNOTE-B98)	Pembrolizumab + favezelimab or quavonlimab	1/2	80	PD-(L)1 refractory extensive-stage SCLC	DLTs AEs TRAEs ORR
NCT05695898	XmAb23104 (PD1-ICOS) + XmAb22841 (CTLA-4-LAG3)	1/2	46	Metastatic melanoma refractory to prior ICI with and without CNS disease	TEAEs, irAEs, DLTs
NCT04150965	BMS-986016 + Pomalidomide + dexamethasone (Arm B)	1/2	104	Relapsed and/or refractory MM	ORR, AEs

- Multiple trials ongoing with the combination of Relatlimab and Nivolumab in several tumor types
- Multiple trials ongoing with different anti-LAG 3 antibodies
- Agents of interest:
- Fianlimab, Favezelimab, Eftilagimod Alpha, Ieramilimab…
- …and several bispecific antibodies

Reference	Drugs	Phase	N	Population	Primary Endpoint
NCT04811027 (TACTI-003)	Eftilagimod alpha + pembrolizumab	2	154	First-line: unresectable R/M HNSCC	ORR
NCT04252768 (AIPAC-002)	Eftilagimod alpha + paclitaxel	1	24	HR+ metastatic breast cancer	Safety and tolerability
NCT05747794 (AIPAC-003)	Eftilagimod alpha or placebo + paclitaxel	3	849	HER2-neg/low metastatic breast cancer	OS, Aes, OBD

Ibrahim R et al, Biomedicines 2023

T-cell immunoglobulin and mucin-domain containing protein 3 (TIM 3)



- Expressed on Th1, Th17, Monocytes, Dendritic Cell, Macrophages, NK cells…
- Ligands: Galectin 9, CEACAM 1, Phosphatidylserine (PtdSer), HMBG1
- Function: Immune Regulation (Induction of immune tolerance)
- Prognostic Factor in several tumors
- Lung Cancer: Correlation with shorter survival, nodal involvement, advanced stage

Sauer N et al, Cancer Immunology 2023

Early Clinical Experience with anti TIM antibodies

In pretreated patients: RR 0 - 8.3%, SD 21 - 41%, few data on PFS/OS

aTIM-3 mAb	Type	Study	Phase	Setting	N	Intervention	1st Endpoint	Results with aTIM-3
Cobolimab (TSR-022/GSK4069889)	Humanized IgG4	AMBER	I	Metastatic, ≥2nd line after aPD-1/PD-L1	84	Cobo + dostar (aPD-1)	ORR	• ORR 8.3% • DCR 21.4% • Grade ≥ 3 TRAE 13.1%
Sabatolimab (MGB453)	Humanized IgG4	Mach et al.	I	Metastatic, ≥2nd line after aPD-1/PD-L1	17 with NSCLC	Saba + sparta (aPD-1)	ORR	• SD 41.2% • Grade ≥ 3 TRAE 11.8%
LY3321367	Humanized IgG1λ, Fc-null	Harding et al.	I	Metastatic, ≥2nd line	65 with NSCLC	LY3321367 +/−LY300054 (aPD-L1)	Safety, RP2D	• PD as the best immunotherapy response in previous lines: ORR 0%, DCR 34.8%, mPFS 1.9 mo • SD or PR as the best immunotherapy response in previous lines: ORR 7%, DCR 50%, mPFS 7.3 mo • Grade ≥ 3 TRAE 3%with LY3321367 monotherapy

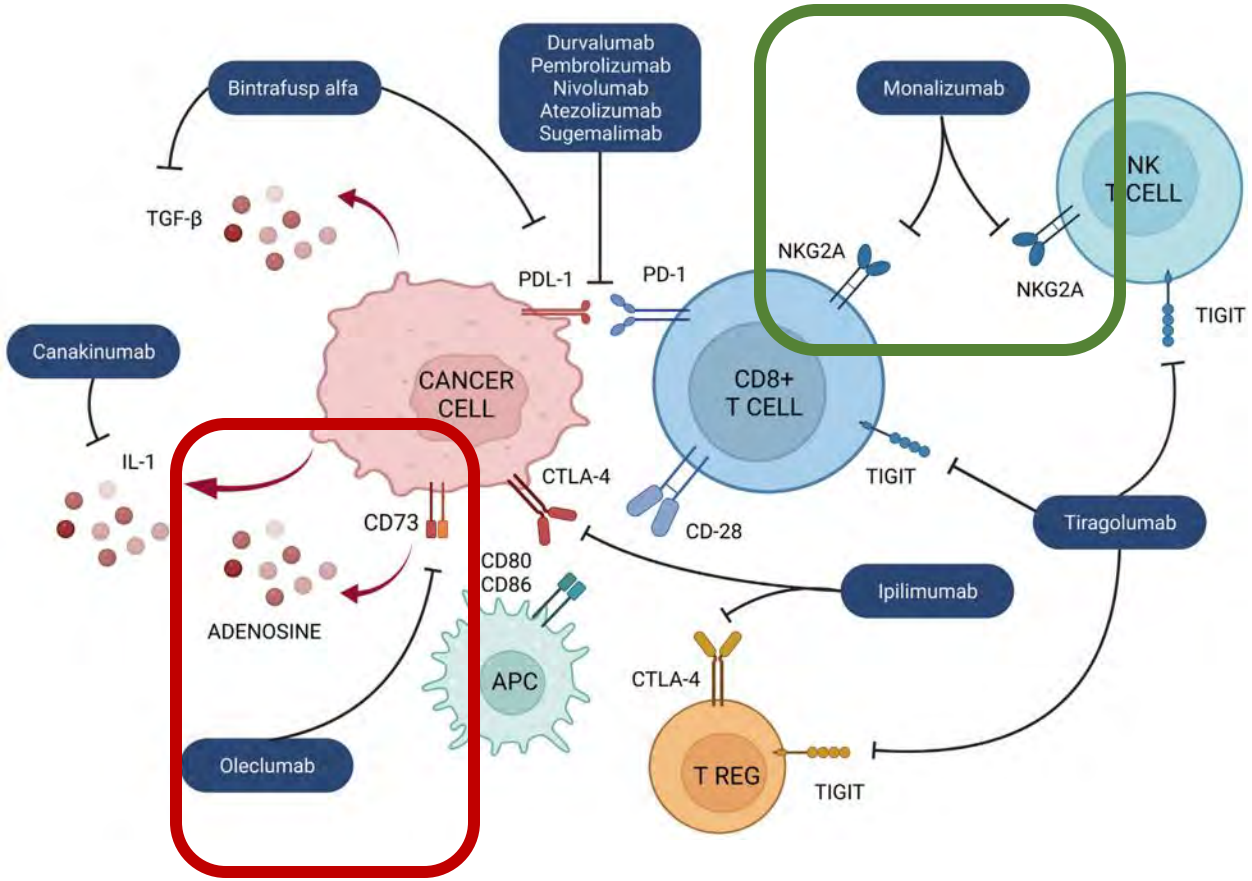
Agents/Concepts of interest in clinical trials:

- Anti-TIM3 antibodies: MBG453, TSR-022, BGB-A425, TQB2618, INCAGN02390, LY3321367, SYM023
- Bispecific Antibodies (anti-TIM3 + anti PD-L1)
- TIM-3 CAR T-cells
- Adoptive T-cells

Roussot N et al, Cancer 2025; Sauer N et al, Cancer Immunology 2023

aNKG2A & aCD73

(Natural Killer Group Protein 2A - Immune Modulator on NK and T-cells
CD 73 - overexpressed on TAMs, TREGS, exhausted Tcells - mediates catabolism of ATP)



NKG2A

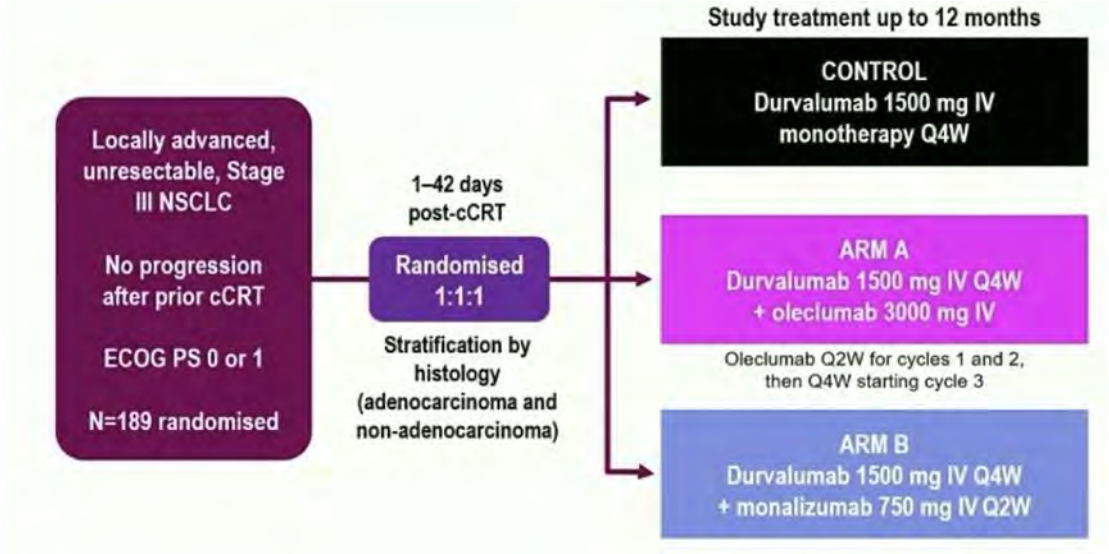
- Overexpressed as Heterodimer with CD94 on subsets of T cells and NK cells
- Binds to HLA-E
- Triggers Immunosuppression:
  - Suppression of Cytokine Secretion
  - Cytotoxicity of T- and NK Cells
  - …
- Poor prognostic factor in NSCLC

CD-73

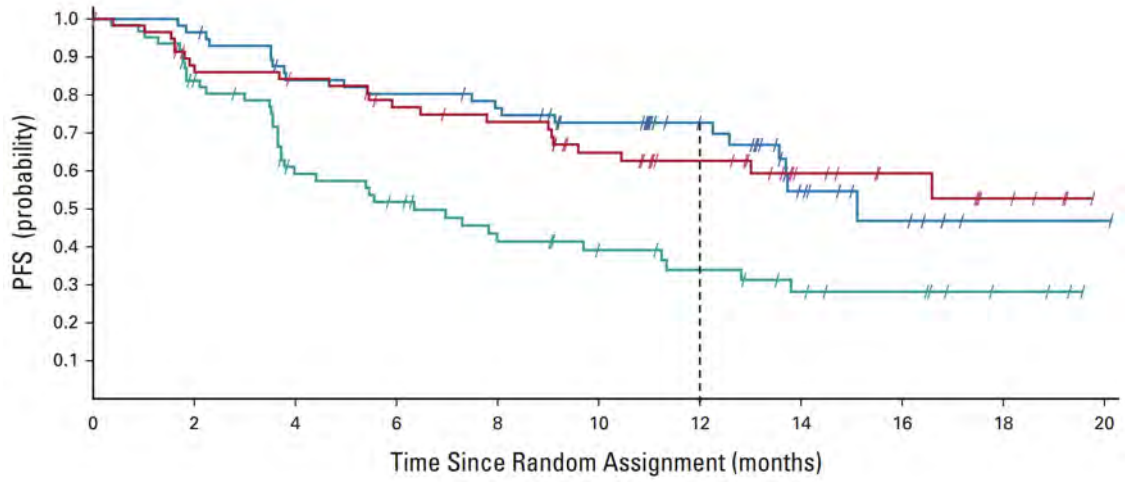
- Expressed on Cancer and Immune Cells
- Increases extracellular Adenosine
  - Immune Suppression of the tumor microenvironment
- Poor prognostic factor in NSCLC and other tumors

Cortiula Ann Oncol 2022 ; Vijayan D Nat Rev Cancer 2017; Inoue Y, Oncotarget 2017; Andre P, Cell 2018

COAST-TRIAL IN STAGE III NSCLC



PFS



Response:

- 30.0% (Oleclumab/Durvalumab) vs 17.9% (Durvalumab)
- 35.5% (Monalizumab/Durvlaumab) vs 17.9% (Durvalumab)

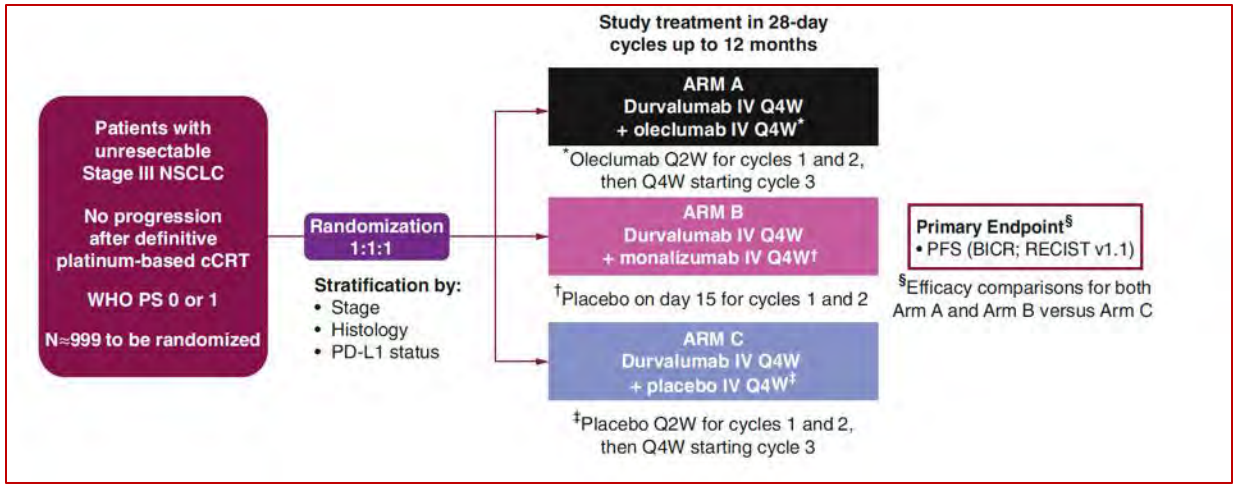
PFS

- nr (median) / 62.6% (1 y PFS) vs 6.3 m (median) / 33.9% (1 y PFS) (HR 0.44)
- 15.1 m (median) / 72.7% (1 y PFS) vs 6.3 (med) / 33.9%) (1 y PFS) (HR 0.42)

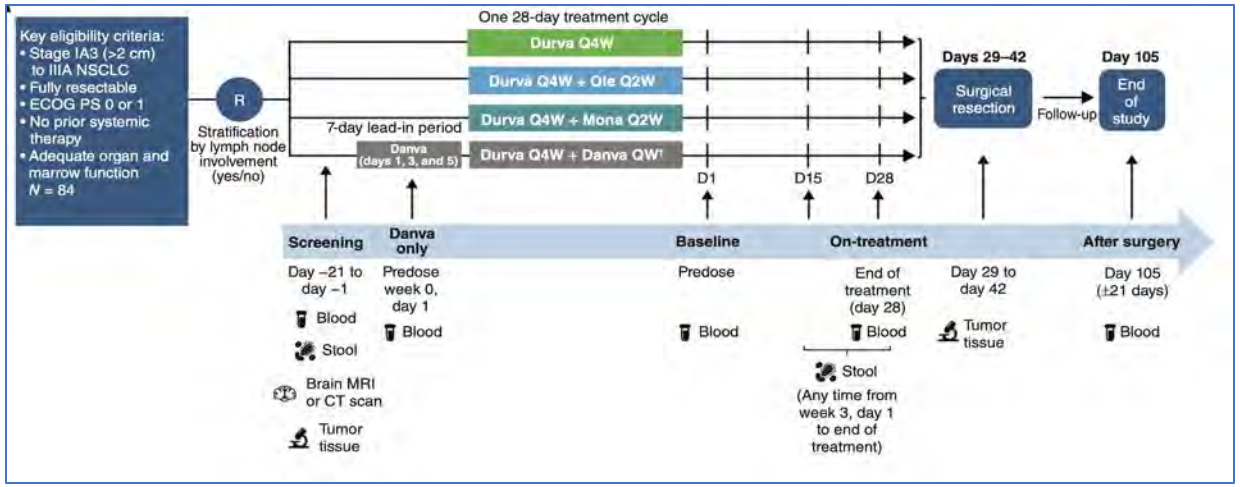
Herbst R et al, J Clin Oncol2022

Follow up trials

Pacific 9 - NCT05221890



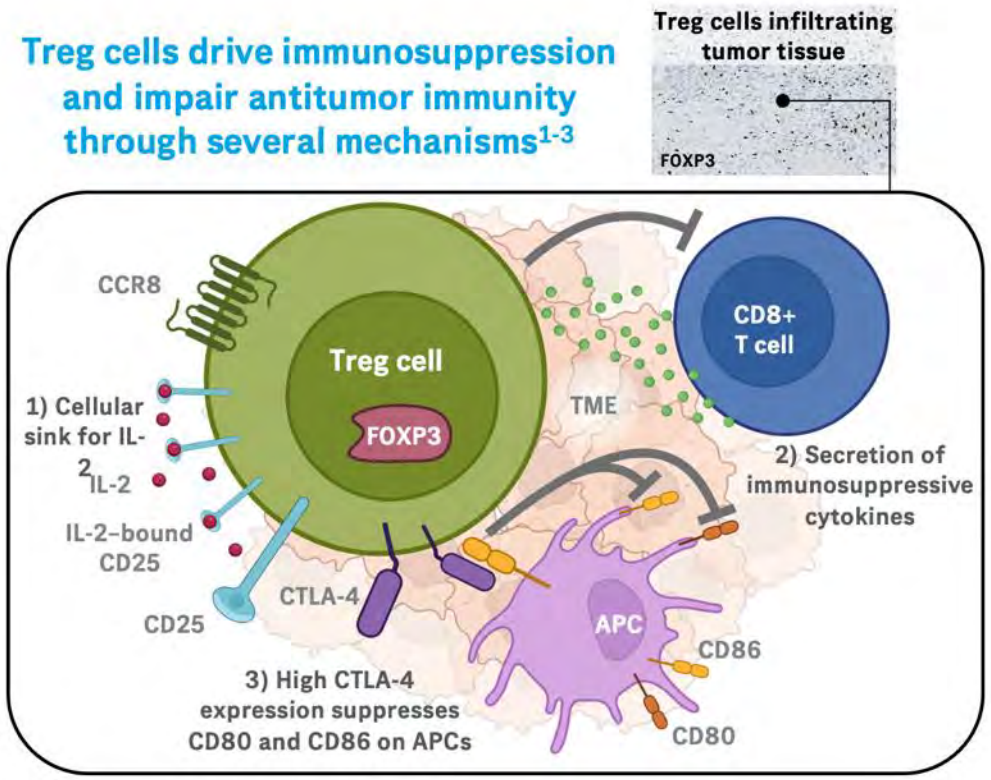
NeoCOAST - IA3-IIIa resectable NSCLC



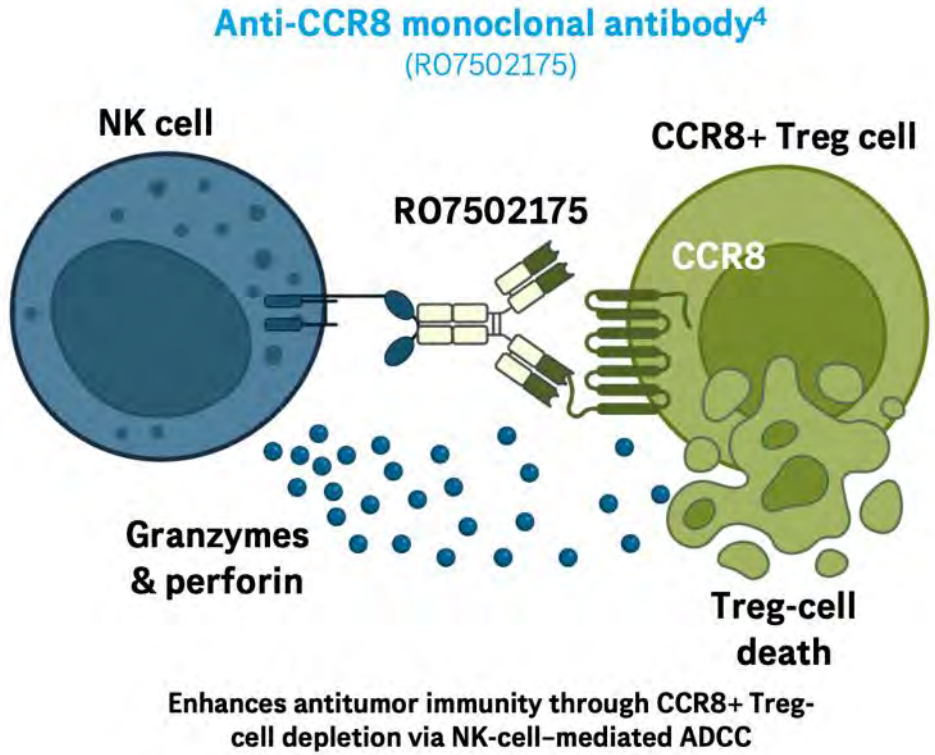
MPR:
Durva 11.1%, Durva+Ole 19%, Durva+Mona 30%, Durva+Danva 31.3%

Barlesi F et al, Future Oncology 2024; Cascone T et al, Cancer Discovery 2023

CCR-8 on Treg cells - a new kid on the block?



A therapeutic target? Example RO7502175



Currently mainly safety data from phase 1 trials available, but…

1. Wing JB, et al. *Immunity*. 2019;50(2):302-316. 2. Plitas G, Rudensky AY. *Annu Rev Cancer Biol*. 2020;4:459-477. 3. Zhang A, et al. *Mol Cancer*. 2024;23:251. 4. Gampa G, et al. *Br J Pharmacol*. 2024;181(13):2033-2052

Impressive list of anti-CCR8 antibodies in development....

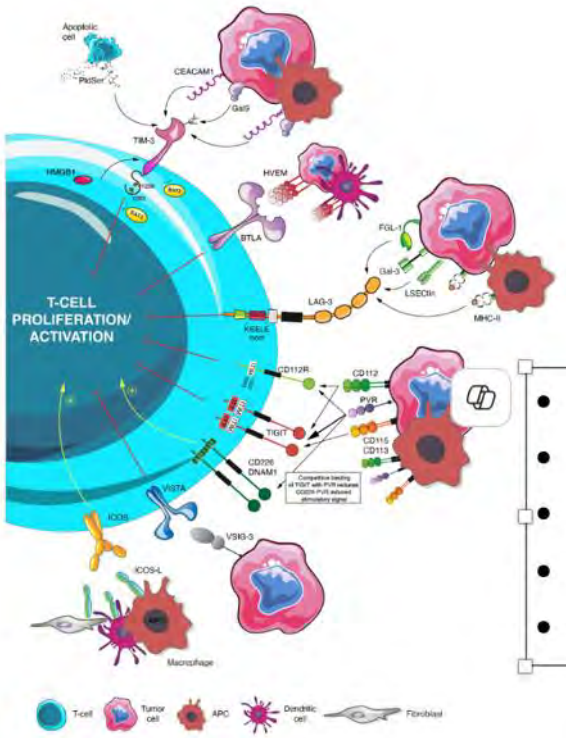
Clinical-stage anti-CCR8 antibodies

Project	Company	Status	Target enrolment
BMS-986340	Bristol Myers Squibb	Ph1/2 solid tumours, +/- Opdivo or docetaxel	665
LM-108	LaNova Medicines	Ph1/2 solid tumours, +/- Loqtorzi	476
S-531011	Shionogi	Ph1/2 AcceleR8-001 trial in solid tumours, +/- Keytruda	274
AMG 355/ FPA157	Amgen (ex Five Prime)	Ph1 solid tumours, +/- Keytruda, started Mar 2024	515
GS-1811/ JTX-1811	Gilead (ex Jounce)	Ph1 solid tumours, +/- zimberelimab	376
RO7502175/ RG6411	Roche	Ph1 solid tumours, +/- Tecentriq	365
BGB-A3055	BeiGene	Ph1 solid tumours, +/- Tevimbra	318
BAY 3375968	Bayer	Ph1 solid tumours, +/- Keytruda	270
ABBV-514	AbbVie	Ph1 solid tumour, +/- budigalimab	215
IPG7236	Immunophage Biotech	Ph1 solid tumours	196
QLP2117	Qilu Pharmaceutical	Ph1 solid tumours	180
CM369	InnoCare Pharma	Ph1 solid tumours	146
HC006	HC Biopharma	Ph1 solid tumour trial started Feb 2024	76
ZL-1218	Zai Lab	Ph1 solid tumours, +/- Keytruda	60
CHS-114/ SRF114	Coherus (ex Surface)	Ph1 solid tumours, +/- Loqtorzi	47

https://www.oncologypipeline.com/apexonco/ccr8-expectations

Additional targets for development

Additional inhibitory checkpoints



- VISTA
- BTLA
- PVRIG / CD112R
- CD376 / B7-H3
- ...

Multiple additional inhibitory targets on tumor cells, T lymphocytes and APCs

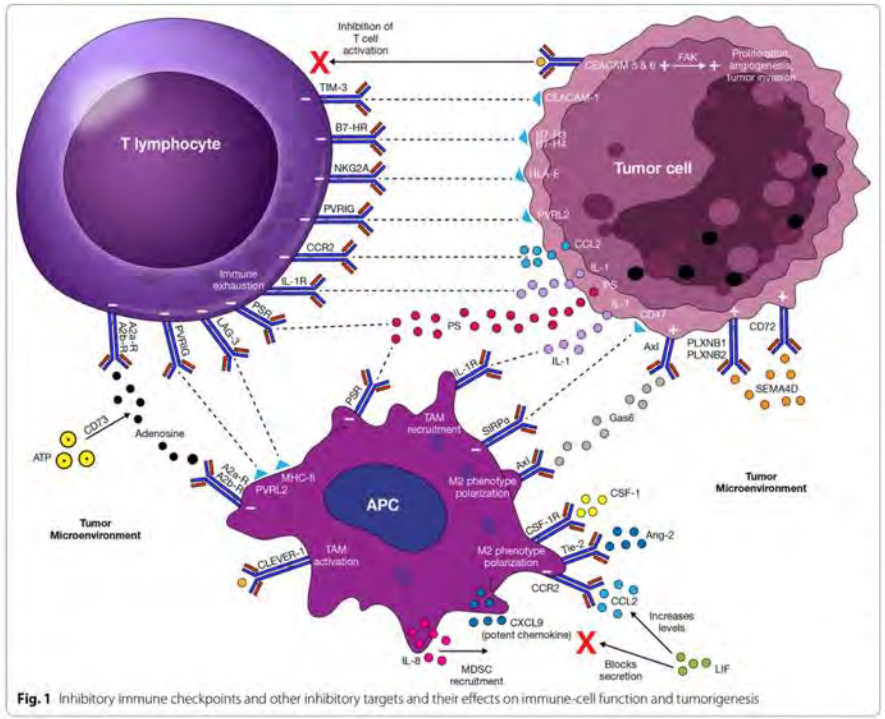
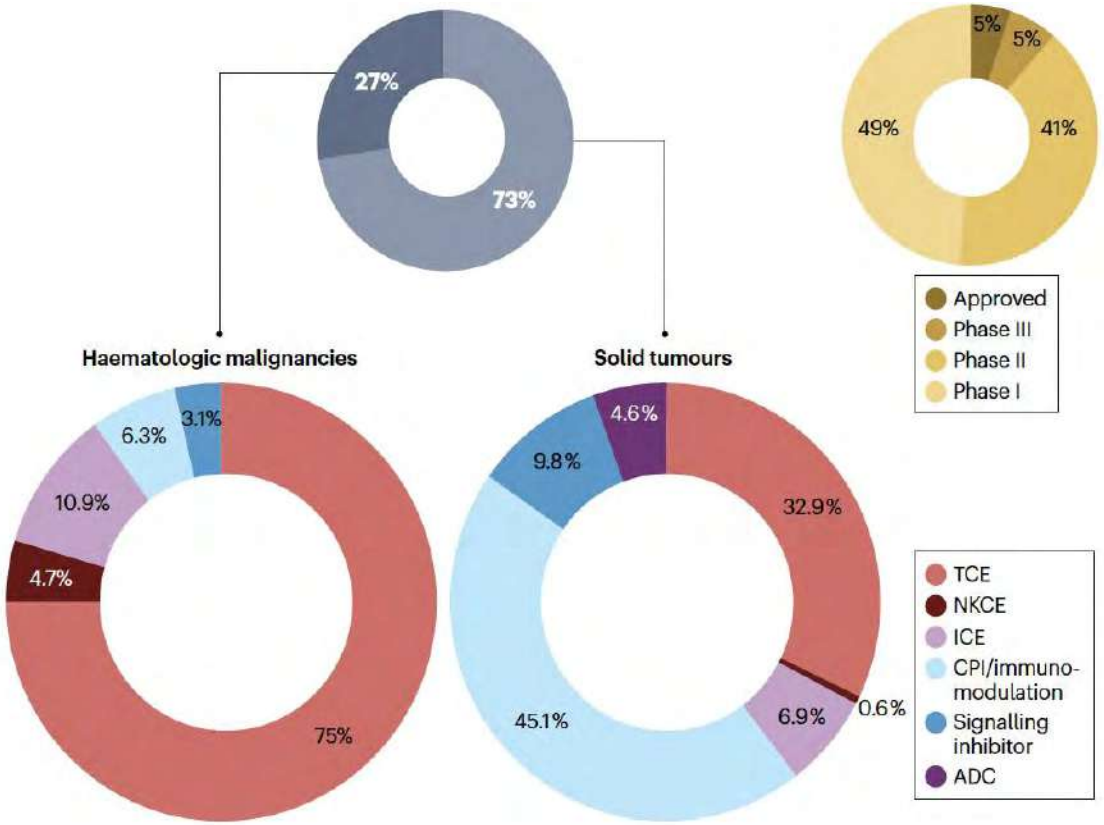


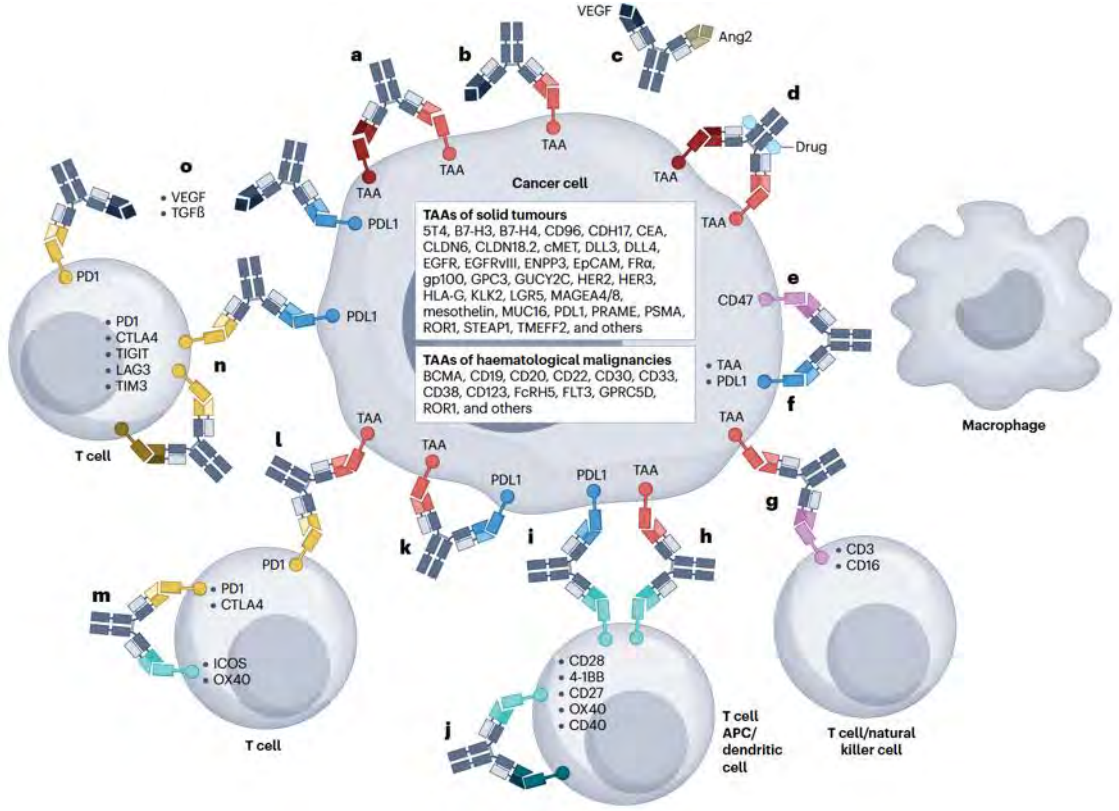
Fig. 1 Inhibitory immune checkpoints and other inhibitory targets and their effects on immune-cell function and tumorigenesis

- CEACAM 1,5,6 and FAK
- CCL2 / CCR2
- LIF
- CD47 / SIRPα
- IL1 / IL-R1
- IL8
- Semaphorins
- Ang-2
- CLEVER-1
- Axl
- Phosphatidylserine

Marin Acevedo JA, J Hematol Oncol 2021; Borgeaud M et al, Cancer Treatment Rev 2023

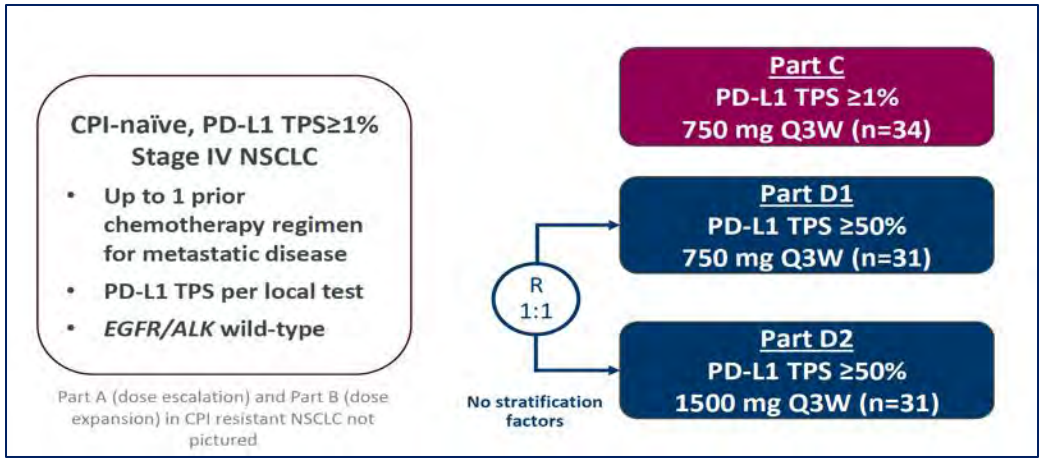
Bispecific Antibodies - a new universe of Immunotherapies

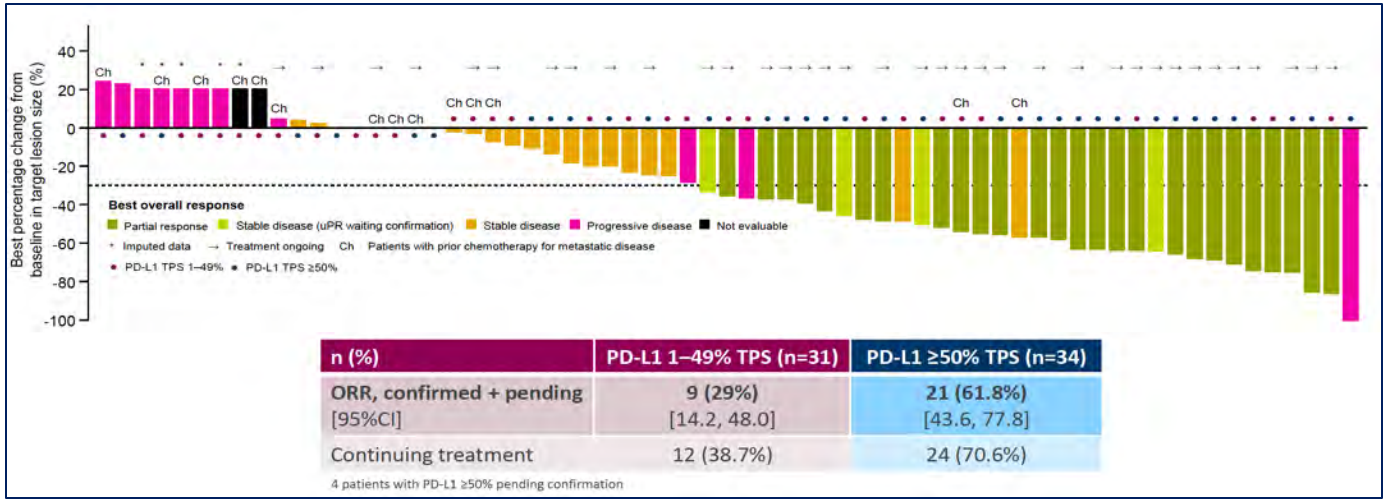




Kleinstein C et al Nature Drug Discovery 2024

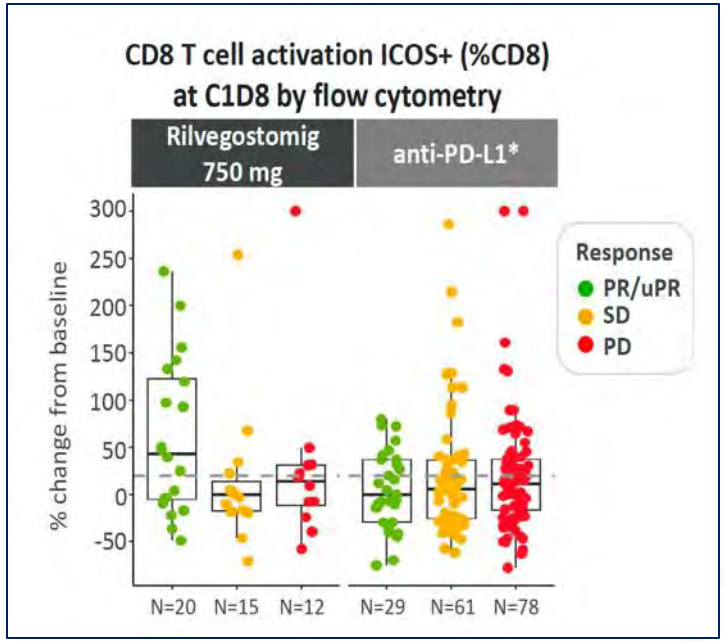
Rilvegostomig (anti PD-1/TIGIT) in CPI naive patients - ARTEMIDE-01 (cohorts C & D)





n (%)	PD-L1 1–49% TPS (n=31)	PD-L1 ≥50% TPS (n=34)
ORR, confirmed + pending [95%CI]	9 (29%) [14.2, 48.0]	21 (61.8%) [43.6, 77.8]
Continuing treatment	12 (38.7%)	24 (70.6%)

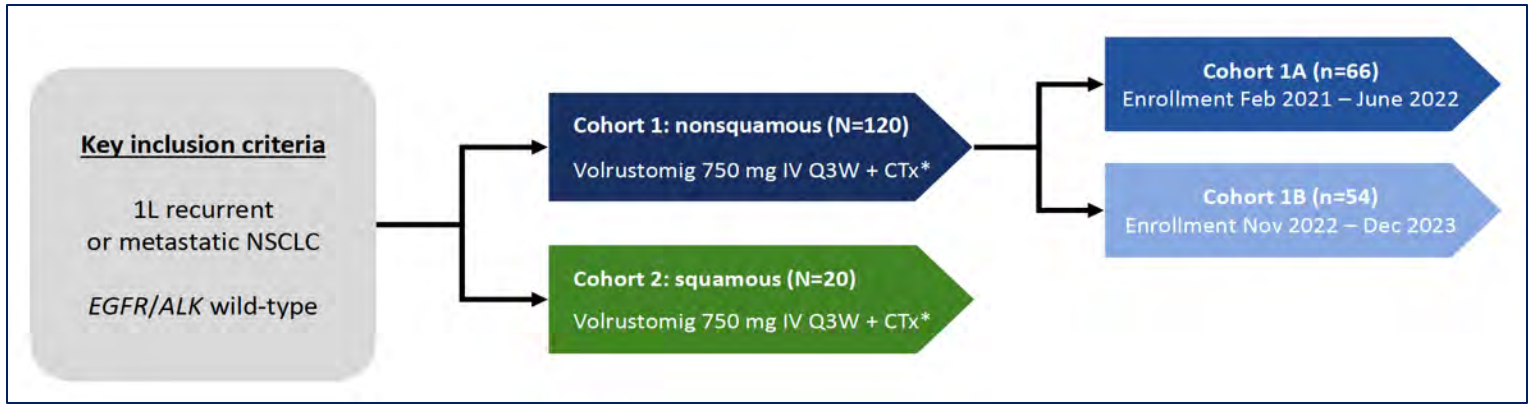
4 patients with PD-L1 ≥50% pending confirmation

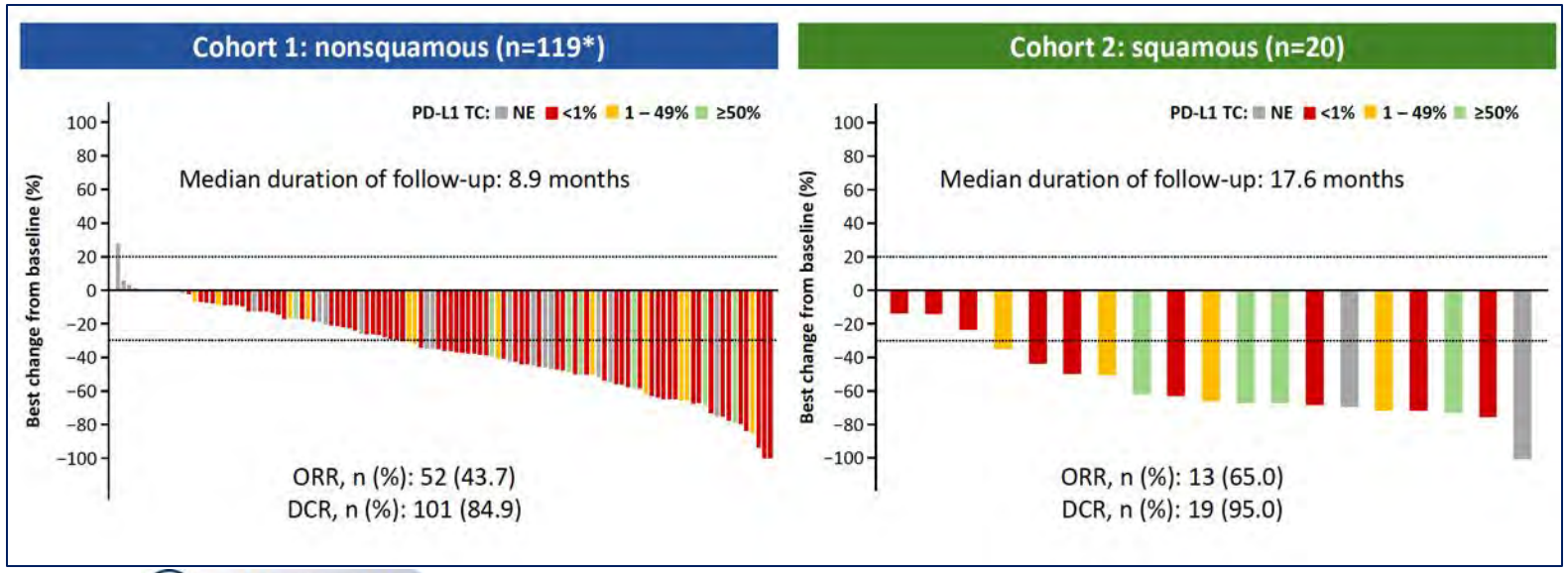


ESMO ON AIR

Hiltermann J et al, WCLC 2024

Volrustomig (anti-PD1/CTLA4) + CT / Phase 1 trial



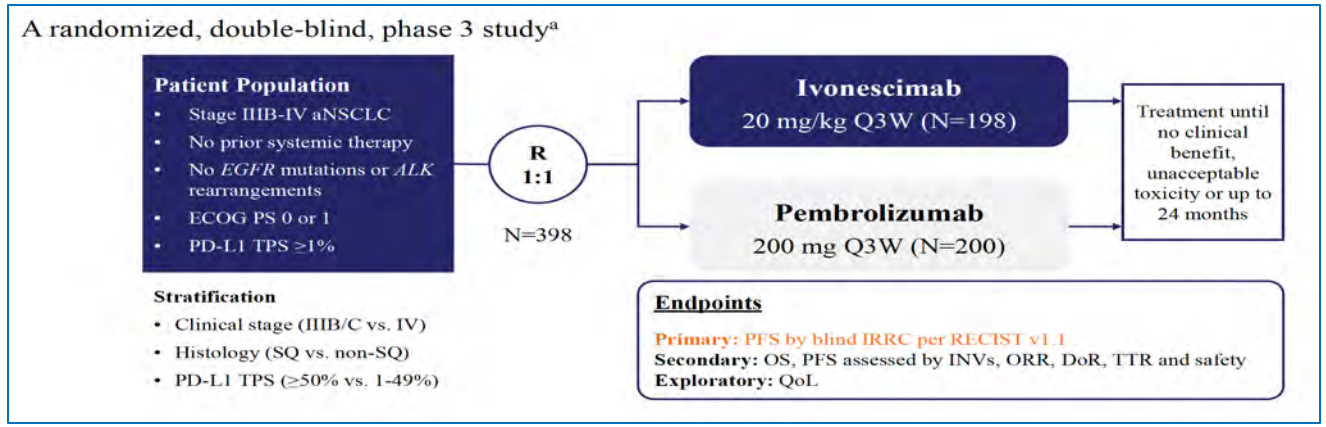


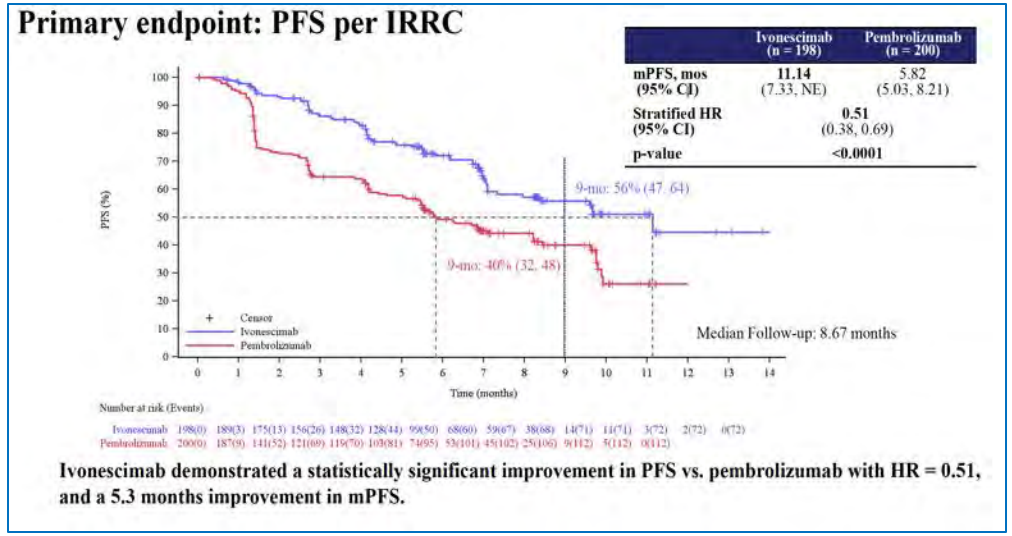
Volrustomig 750 mg + CTx	All (N=140)
Median volrustomig exposure (range), months	4.8 (0.3–28.3)
Any TEAE, n (%)	139 (99.3)
Any TRAE, n (%)	136 (97.1)
Grade 3/4 TRAE	106 (75.7)
TRAE leading to volrustomig discontinuation	42 (30.0)
TRAE leading to death*	7 (5.0)

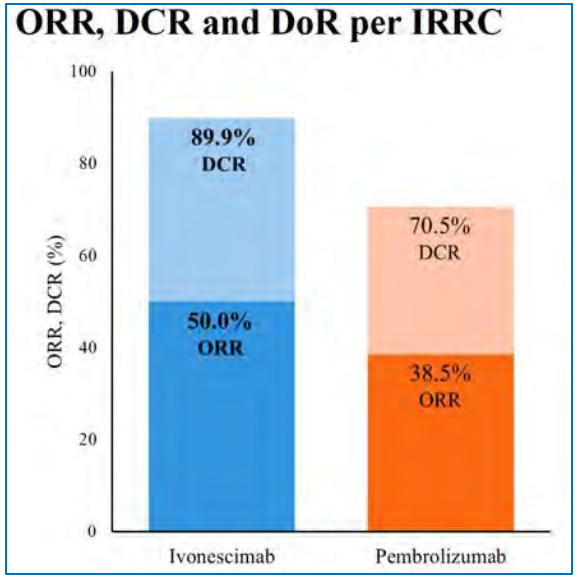
Spigel D et al, WCLC 2024

A new standard of IO Monotherapy?

Ivonescimab (anti-PD-1/anti-VEGF) vs Pembrolizumab in PD-L1+ NSCLC (Harmoni-A Study)







Med PFS: 11.1 vs 5.8 M
HR 0.51, p<0.0001

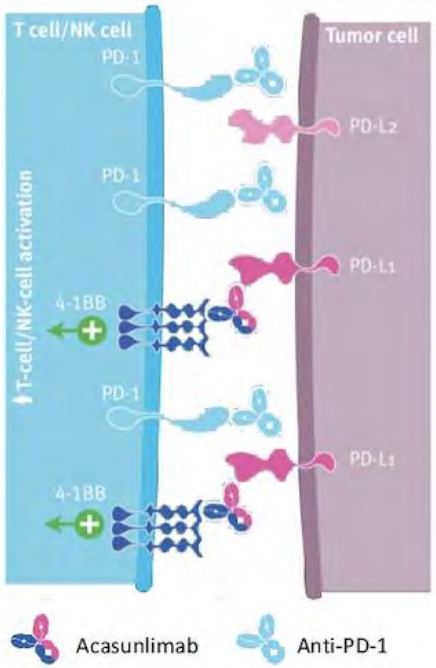
ESMO ON AIR

Zhou C et al, WCLC 2024; Lancet 2025

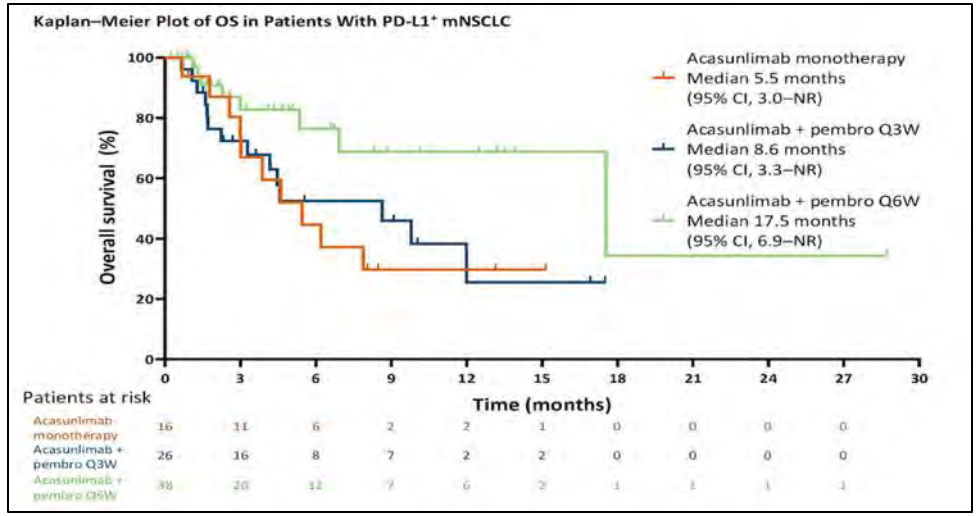
Rapid Development…

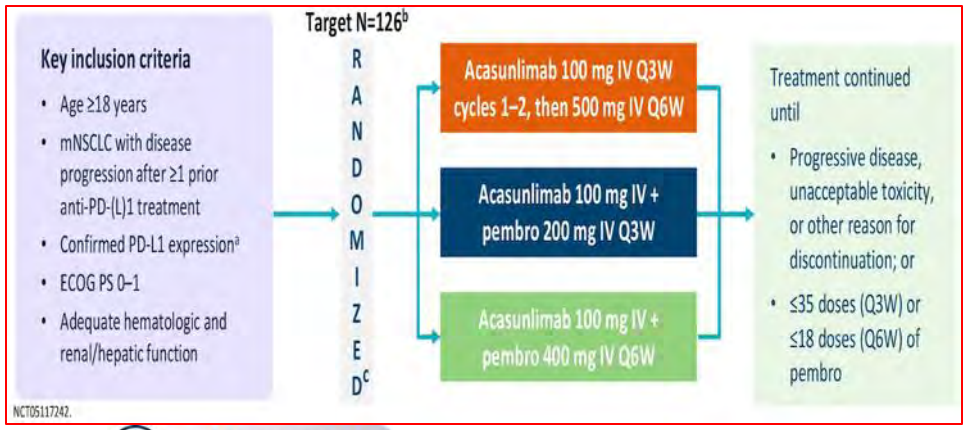
Name	Company	Target	Status	NCT
Ivonescimab (AK112/SMT112)	Akeso Biopharma Summit Pharmaceutics	PD-1, VEGF-A	Phase III Approved China	NCT05899608
BNT237	Biontech	PD-L1, VEGF-A	Phase III (SCLC) Phase III (NSCLC)	NCT06712355 NCT06712316
LM-299	LaNova Medicines Merck	PD-1, VEGF-A	Phase I	NCT06650566
HB0025	Hanchor Bio	PD-L1, VEGFR1	Phase I	NCT06758557
AI 081	OncoC4	PD-1, VEGF	Phase I	NCT06635785

Acasunlimab +/- Pembrolizumab - second line



	Acasunlimab Monotherapy (n=16)	Acasunlimab + Pembro Q3W (n=22)[a]	Acasunlimab + Pembro Q6W (n=24)[b]
Unconfirmed ORR, % (95% CI)	31.3 (11.0–58.7)	20.8 (7.1–42.2)	29.6 (13.8–50.2)
Confirmed ORR, % (95% CI)	12.5 (1.6–38.3)	18.2 (5.2–40.3)	16.7 (4.7–37.4)
Confirmed DCR, % (95% CI)	50.0 (24.7–75.3)	59.1 (36.4–79.3)	75.0 (53.3–90.2)
Median DOR, mo (95% CI)	2.0 (1.6–NR)	5.2 (3.5–NR)	NR (NR–NR)
6-month PFS rate, % (95% CI)	0 (NA)	14 (3–31)	34 (13–56)
12-month OS rate, % (95% CI)	30 (9–54)	26 (6–52)	69 (43–85)





Highest Efficacy for Pembro q6 w + Acasunlimab
RR 29.6% (unconfirmed)
DOR nr
Med OS: 17.5 m
12m OS rate: 69%

Aerts J et al, ASCO 2024

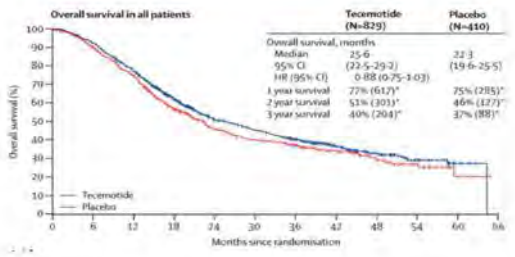
Multiple ongoing trials with Bispecifics in NSCLC & SCLC

Target	Study agent	Setting	Ph	Status	NCT
BsAb					
PD-1, CTLA-4	Volrustomig Chemotherapy	First-line metastatic NSCLC	III	R	NCT05984277
	Volrustomig Chemotherapy	Perioperative treatment in resectable NSCLC	II	R	NCT05061550
	Cadonilimab chemotherapy	NSCLC failed first-line immunotherapy	II	R	NCT06467500
	Cadonilimab ± chemotherapy	ES-SCLC failed first-line chemotherapy	II	R	NCT05901584
	Cadonilimab Pemetrexed Anlotinib	NSCLC failed EGFR TKI Chemotherapy and ICI naïve	II	R	NCT06277674
	AK104 Chemotherapy	Perioperative NSCLC	II	R	NCT05377658
	AK104 Chiauranib	ES-SCLC failed immunochemotherapy	I/II	A, nR	NCT05505825
	KN406	First-line metastatic NSCLC	II	R	NCT05420220
	Lorigertimab	NSCLC failed standard therapy	I	A, nR	NCT03761017
PD-1 TIGIT	AZD2936	First-line metastatic NSCLC or NSCLC failed ICI	I/II	A, nR	NCT04995523
	HLX301	NSCLC failed standard therapy	I/II	R	NCT05102214
PD-1 VEGF	AK112 Chemotherapy	First-line metastatic NSCLC	III	R	NCT05899608
	AK112	NSCLC, multiple cohorts	I/II	R	NCT04900363
	PM8002	ES-SCLC failed chemotherapy	II	R	NCT05879068
PD-1 PD-L1	IBI318 Lenvatinib	NSCLC failed ICI	I	R	NCT04777084
PD-1 TIM-3	AZD7789	NSCLC, ICI pretreated or ICI-naïve	I/II	R	NCT04931654
	Lomvastomig	NSCLC failed standard therapy	I	A, nR	MCT03708328
PD-1 LAG3	RO7247669	NSCLC failed ICI	I/II	R	NCT04140500
PD-L1 4-1BB	GEN1046 ± Pembrolizumab	NSCLC failed ICI	II	A, nR	NCT05117242
PD-L1 CD47	IMM2520	NSCLC failed standard therapy	I	R	NCT05780307
PD-1 ILT4	CDX-585	NSCLC failed standard therapy	I	R	NCT05788484
EGFR 4-1BB	HLX35	NSCLC failed standard therapy	I	A, nR	NCT05360381
EGFR CD28	REGN7075 Cemiplimab	ICI-naïve advanced NSCLC	I/II	R	NCT04626635
EGFR HER-3	SI-B001 Docetaxel	NSCLC failed first-line immunochemotherapy	III	R	NCT05943795
	SI-B001 Osimertinib	EGFR-mutation-positive NSCLC	II/III	R	NCT05020769
	SI-B001 SI-B003	NSCLC failed standard therapy or untreated	I/II	R	NCT05949606
	SI-B001	NSCLC failed standard therapy	I	R	NCT04603287
EGFR MET	MCLA-129	NSCLC failed standard therapy	I/II	R	NCT04868877
	EMB-01	EGFR-mutant or MET aberrant NSCLC failing standard treatment	I/II	R	NCT03797391
HER-2 HER-3	Zenocutuzumab	Tumor harboring NRG rearrangement	II	R	NCT02912949
HER-2 SIRPα	IMM2902	HER-2 altered	I/II	R	NCT05805956
B7H3 CD28	XmAb808 Pembrolizumab	NSCLC failed standard therapy	I	R	NCT05585034
BiTe					
DLL3 CD3 T cell	BI764532 PD-1 antibody Chemotherapy	First line in ES-SCLC	I	R	NCT06077500
	BI764532	SCLC failed standard therapy	I	R	NCT04429087
	BI764532	SCLC failed standard therapy	II	R	NCT05882058
	Tarlatamab	SCLC failed standard therapy	I	A, nR	NCT03319940
	Tarlatamab	SCLC failed standard therapy	II	A, nR	NCT05060016
	Tarlatamab	SCLC failed chemotherapy	III	A, nR	NCT05740566
	Tarlatamab	LS-SCLC after chemoradiotherapy	III	R	NCT06117774
	Tarlatamab Durvalumab	Maintenance after first-line immunochemotherapy in ES-SCLC	III	R	NCT06211036
	Tarlatamab PD-1 antibody Chemotherapy	First-line in ES-SCLC	I	R	NCT05361395
	HPN328 ± Atezolizumab or Ifinatamab deruxtecan	ES-SCLC failed first-line treatment	I/II	R	NCT04471727
EGFR CD3 T cell	TAK-186	NSCLC failed standard therapy	I/II	R	NCT04844073
Two HER-2 domains	ZW25	HER-2 expressing cancer	I	A, nR	NCT02892123
ROR1 CD3 T cell	NVG-111	ROR1+ tumor failing standard therapy	I	R	NCT04763083
B7H4 CD3 T cell	GEN1047	NSCLC failed standard therapy	I/II	R	NCT05180474
Bispecific NK cell engager					
EGFR CD16A	AFM24 Atezolizumab	NSCLC failed standard therapy	I/II	R	NCT05109442
Tri-specific NK cell engager					
EGFR NK cell	DF9001	EGFR expressed	I/II	R	NCT05597839
Bispecific antibody linking to radioisotope					
EGFR MET	AC225-FPI_2068	NSCLC failed standard therapy	I	R	NCT06147037

Li MC et al, Therapeutic Advances in Medical Oncology 2024

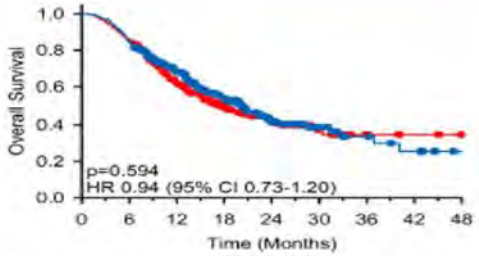
Vaccination in NSCLC - so far not a success story

Tecemotide (L-BLP25)
MUC 1 peptide



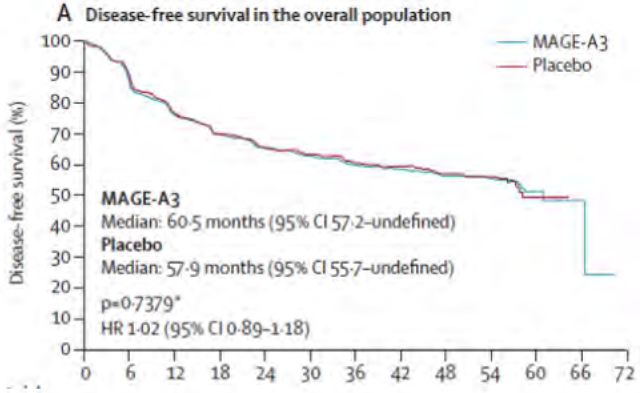
Butts, Lancet Onc, 2013

Belagenpumatucel-L
Whole cell vaccine



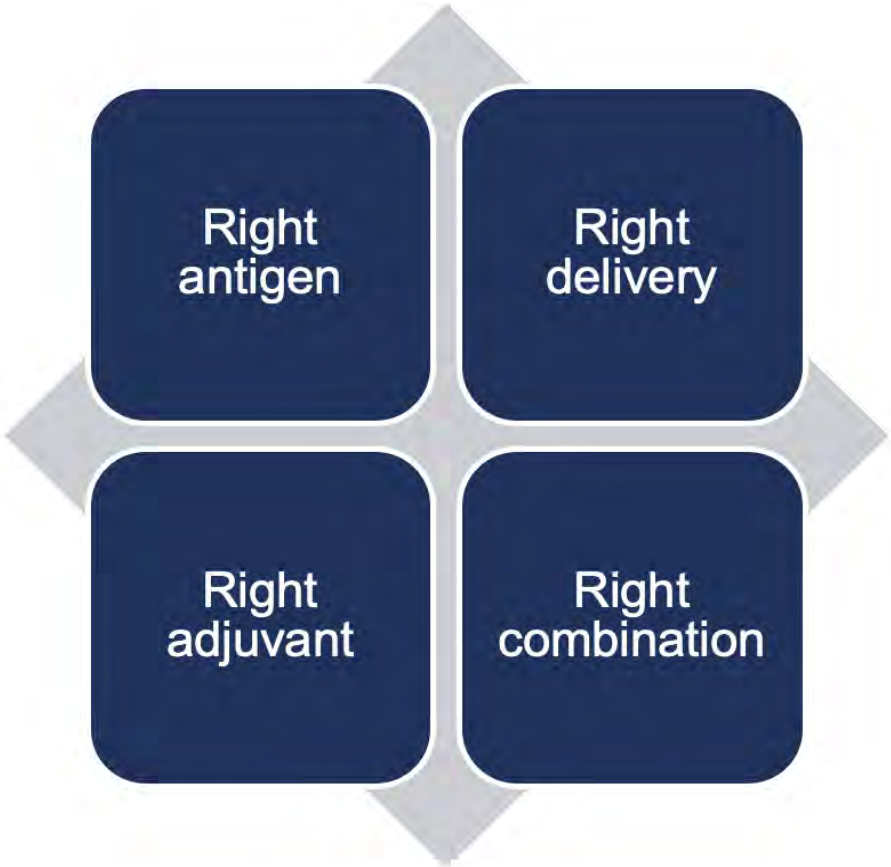
Giaccone, European Journal of cancer_2015

(MAGE-A3) peptide



Vansteenkiste JF, et al. Lancet Oncol 2016

Relevant steps in optimization



Courtesy of Lyudmila Bhazenova

Vaccines – ph III ATALANTE trial

- Advanced/metastatic NSCLC
- EGFRwt, ALK-negative, all PD-L1 status
- HLA-A2+ (blood)
- Failure to platinum-based CT and IO, combined or sequenced
- IO last line with primary or secondary resistance*
- Brain metastases allowed if asymptomatic & treated
- ECOG PS 0 to 1

R 2:1

Arm A: OSE2101 Q3W for 6 subcutaneous injections, then Q8W up to Year 1, then Q12W until progression or toxicity

Arm B: SoC (docetaxel or pemetrexed) Q3W until progression or toxicity

Primary endpoint: OS

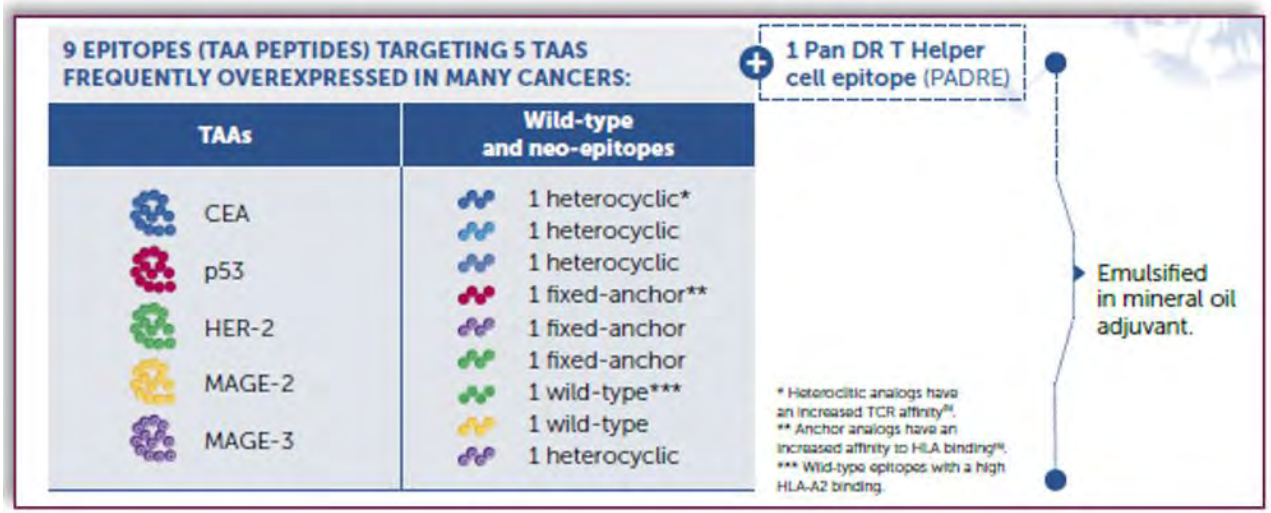
Stratification:
- Histology
- Best response to 1st line
- Line rank of prior IO

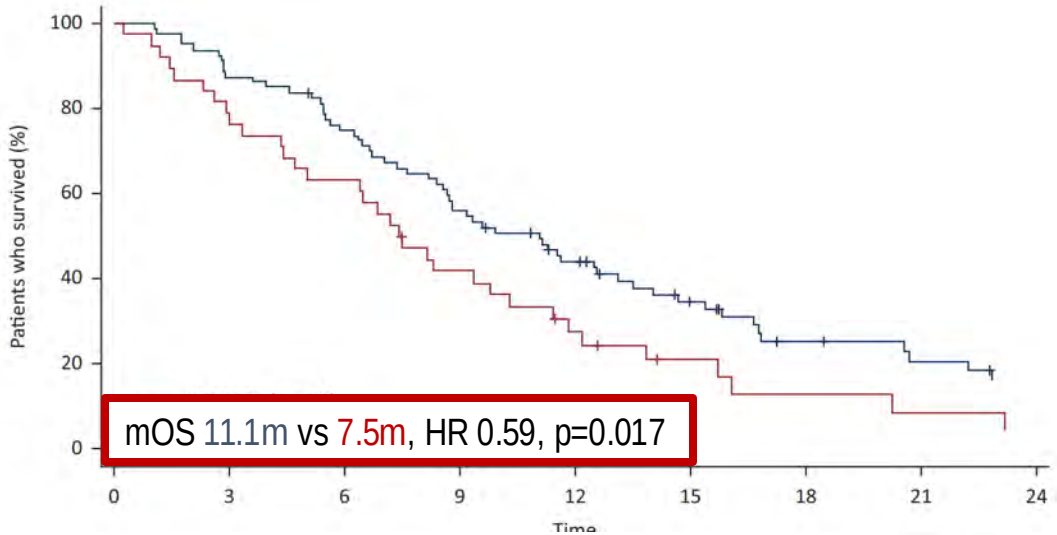
COVID: prematurely closed (219/400 enrolled)

Final primary analysis in IO secondary resistance

(>12 weeks IO, N=118, 68% of total)

Stats revised: HR 0.55, power 80%, 2-sided level 5%



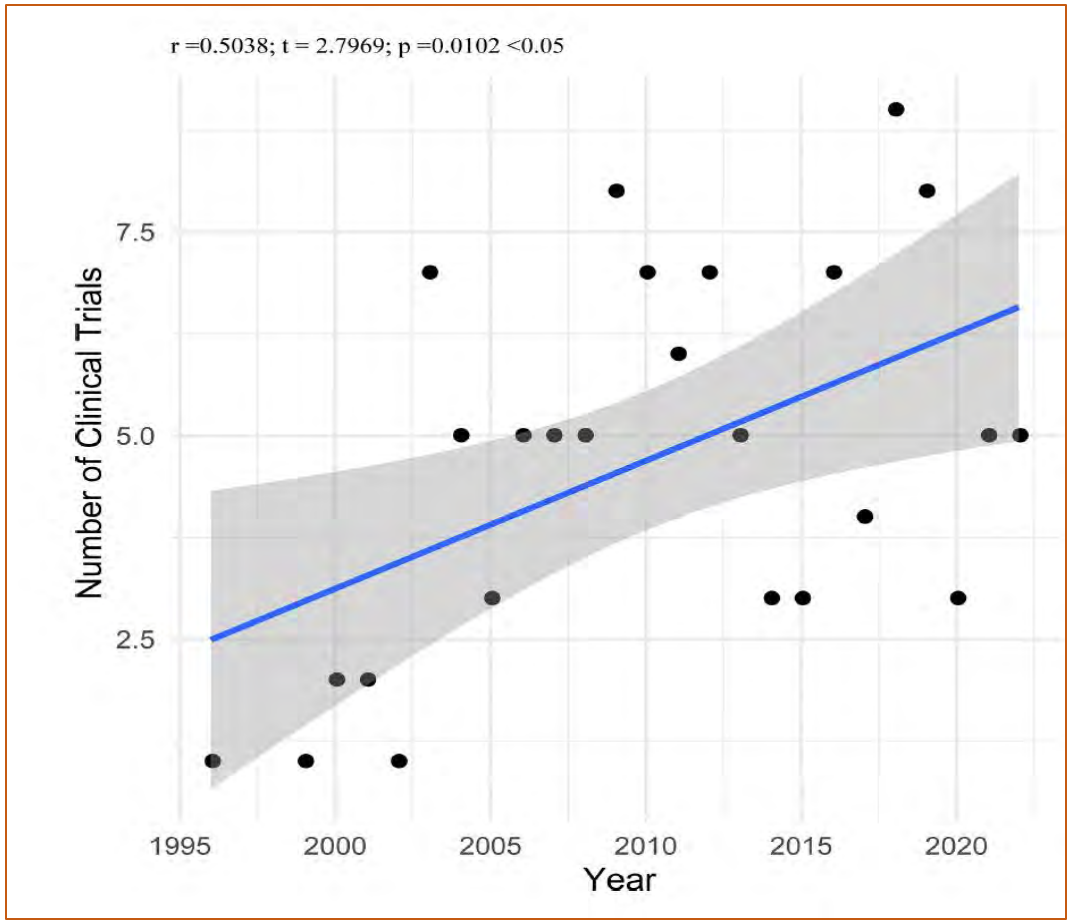


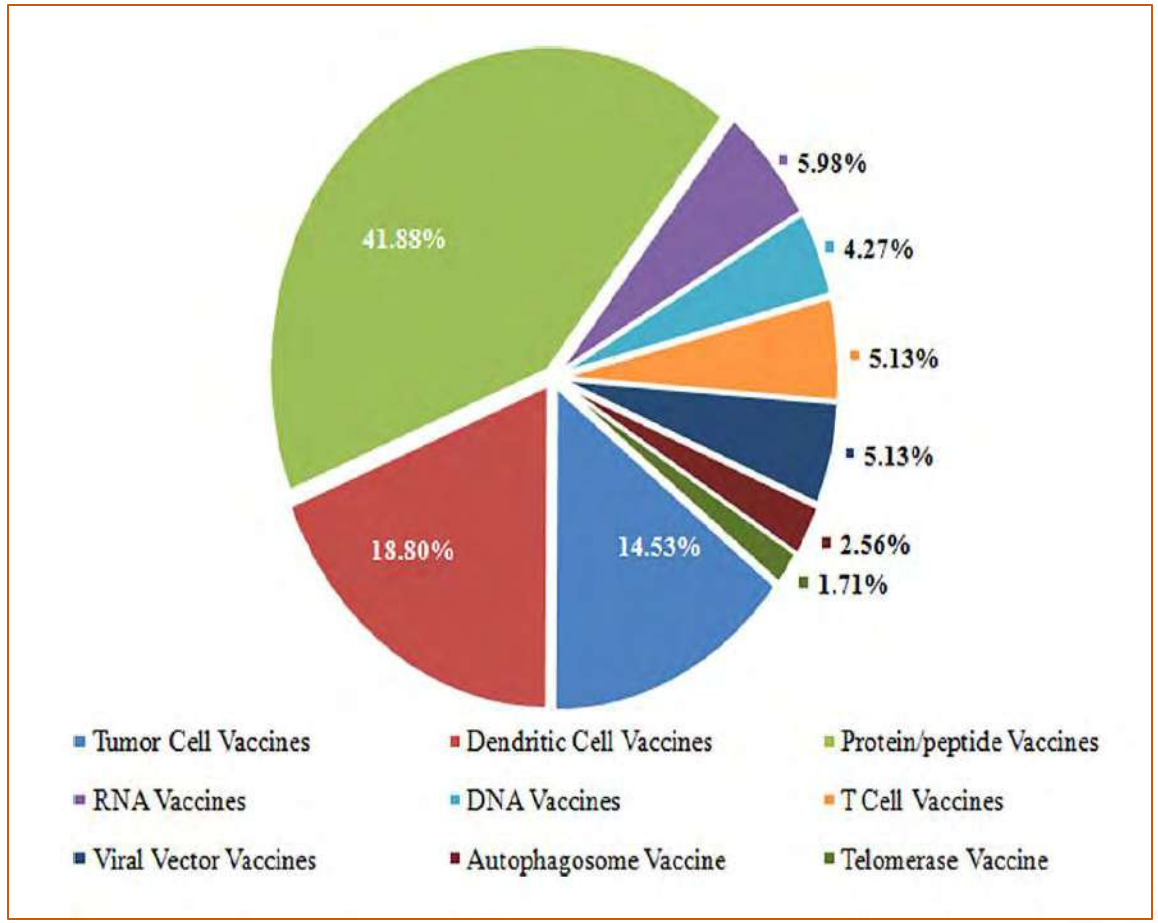
ESMO ON AIR

Besse Ann Oncol 2023

Courtesy of L Hendriks

Evolution of NSCLC Vaccines studies (www.trial.gov registered)





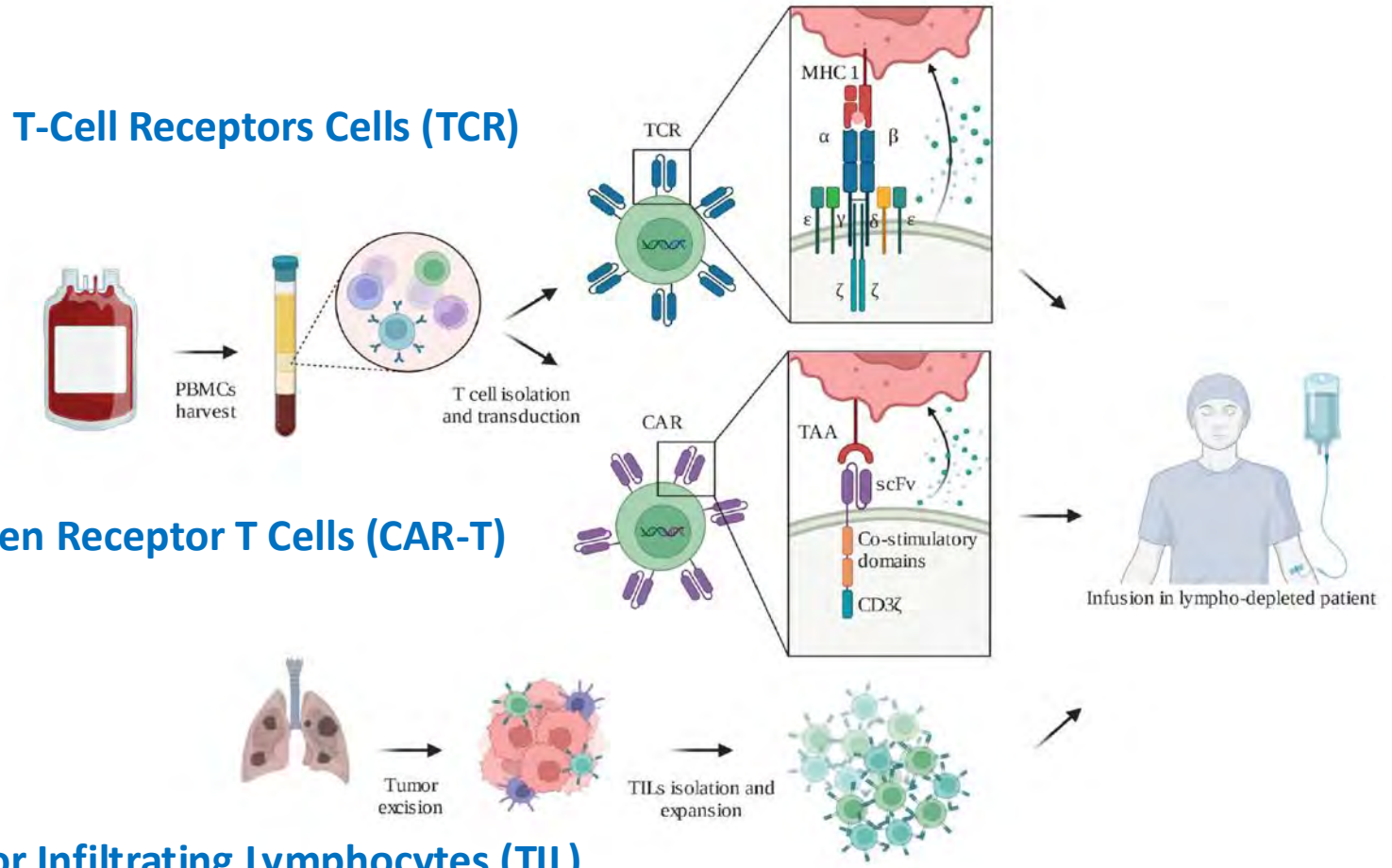
Gu W et al, Frontiers Immunology 2022

Cellular Therapies - a fascinating concept

T-Cell Receptors Cells (TCR)

Chimeric Antigen Receptor T Cells (CAR-T)

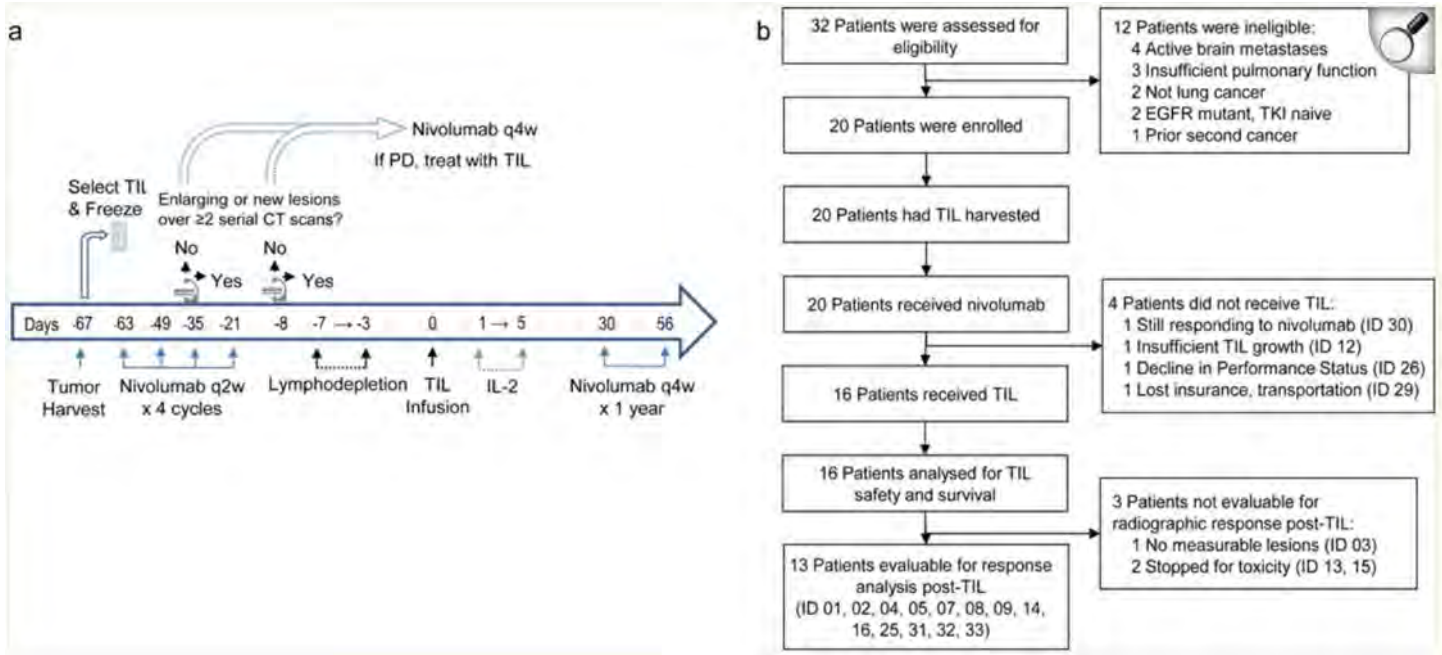
Tumor Infiltrating Lymphocytes (TIL)



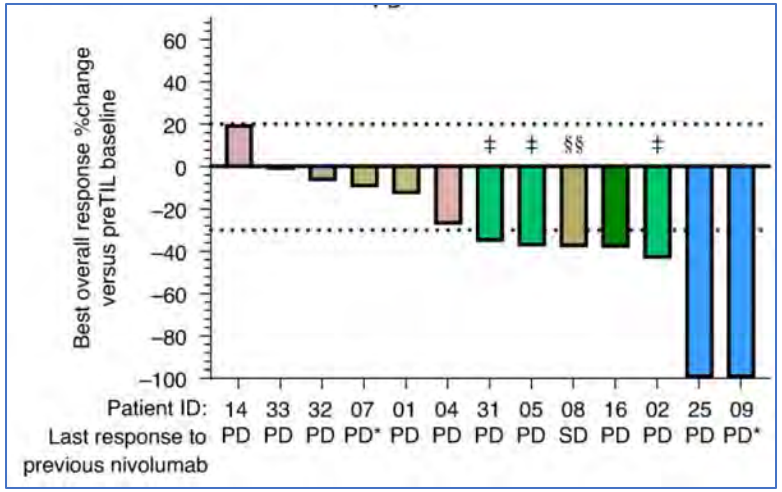
Imbimbo M et al, Lung Cancer 2023

Proof of concept - TILs in Nivolumab pretreated patients

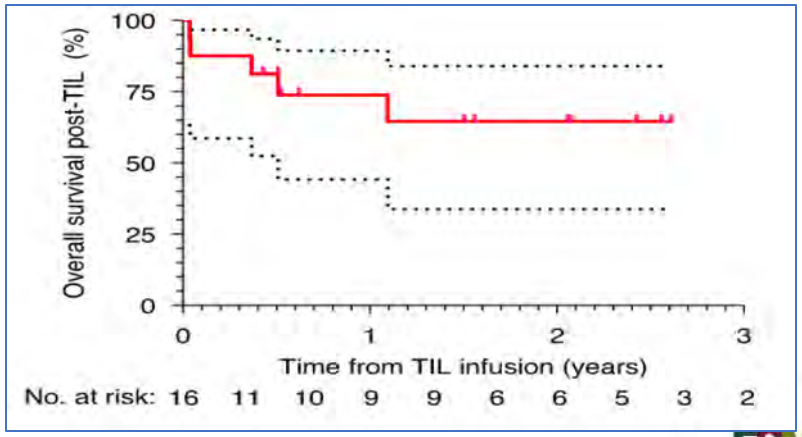
Highly selected group of patients
16/32 enrolled patients evaluable for TIL safety and OS



Responses



Survival post TIL (years!)

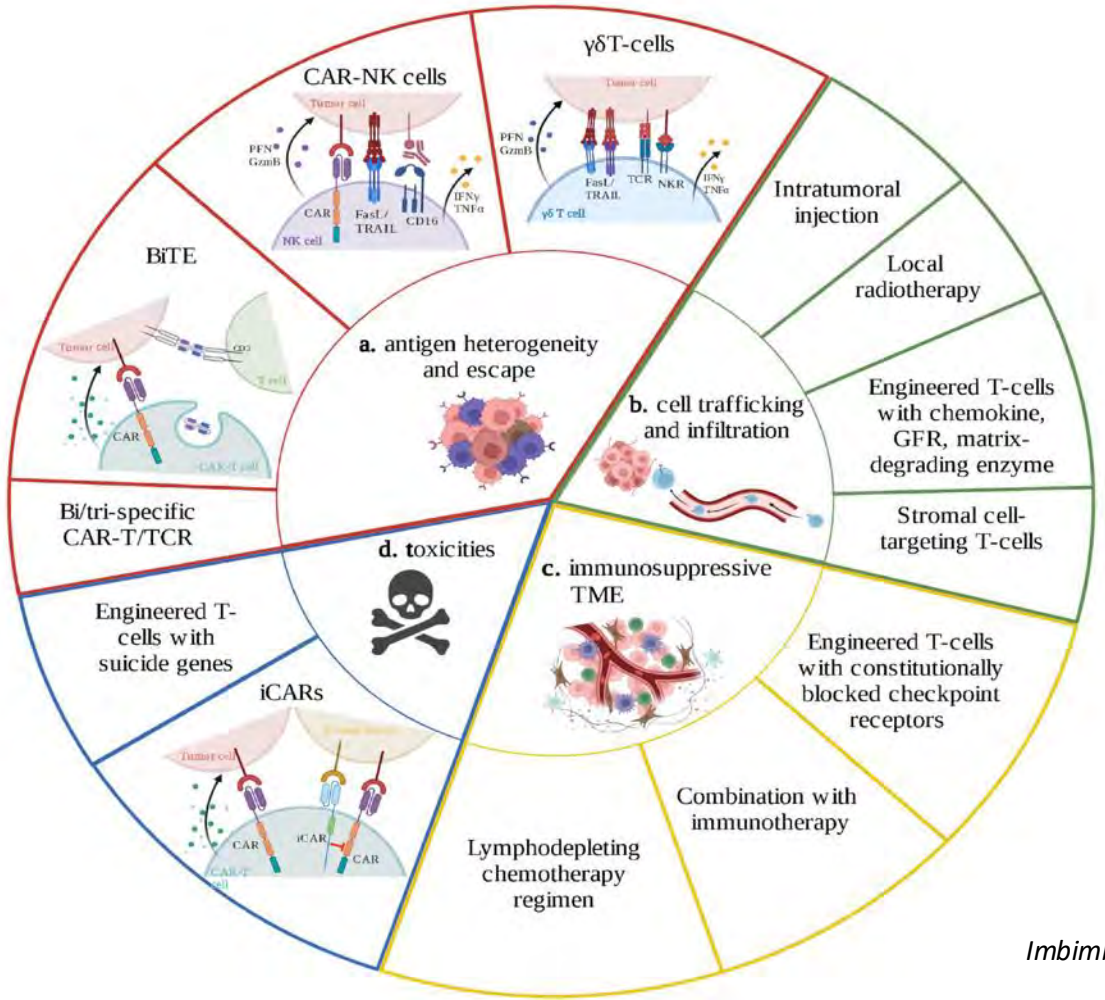


Creelan B et al, Nature Med 2021

A couple of remaining challenges...

Antigen Heterogeneity

On target / off tumor toxicities



Limitation of immune cell trafficking and penetration

Overcoming immunosuppressive TME

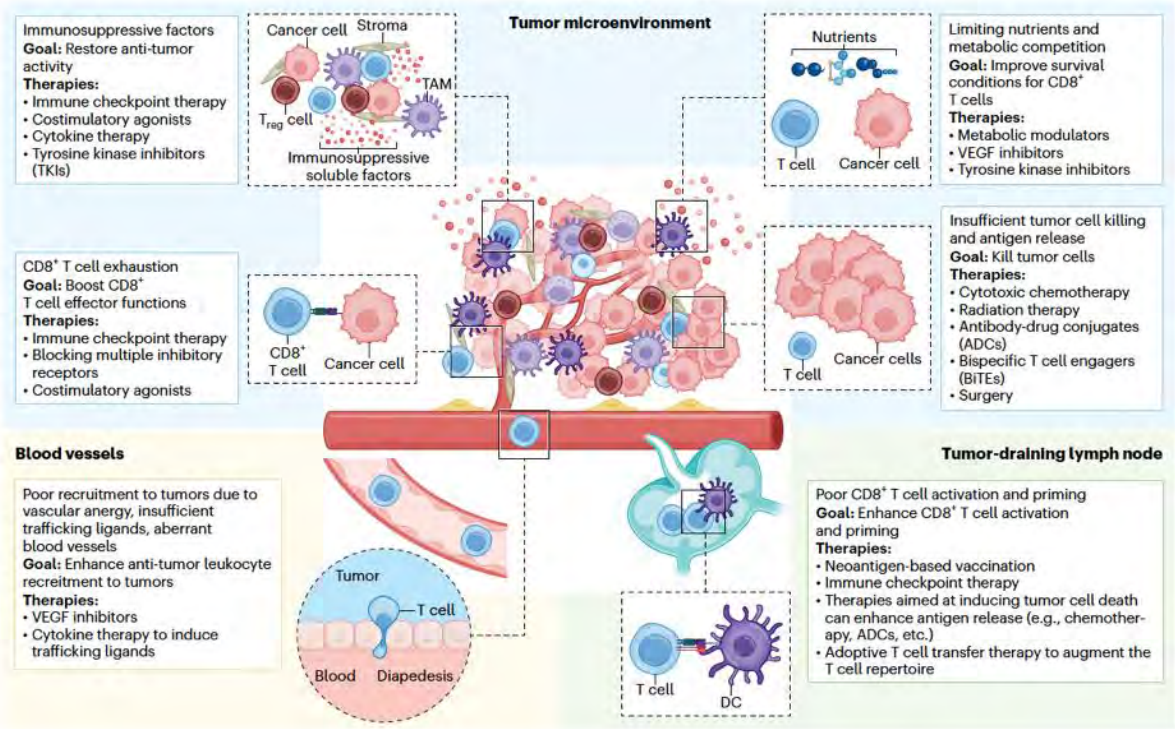
Imbimbo M et al, Lung Cancer 2023

Conclusions

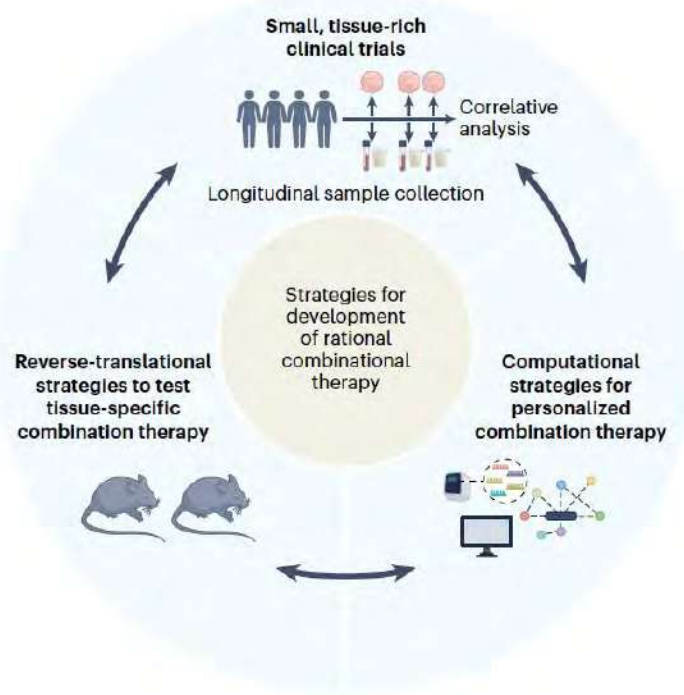
- Beyond anti PD(L)-1 and anti-CTLA4 antibodies multiple novel checkpoint inhibitors in development
- In general novel Checkpoint Inhibitors require backbone of anti PD(L)-1 activity
- Bispecific antibodies - a novel model of combined checkpoint inhibition with oncoing clinical investigation
- Emerging Development of Vaccines with different new new concepts (personalized and non personalized vaccines)
- Cellular Therapies on the horizon for selected patients
- Superior clinical efficacy to be confirmed
- For further development of immunotherapies - perhaps a more personalized approach might be more promising…

Potential next steps...

Understanding of tumor specific „enrichment“ strategies



Individual Development in „tissue rich“ clinical trials



Goswamy S et al, Nature Immunology 2024

Thank you!!

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ADC – DESIGNER DRUGS?

Egbert F. Smit MD PhD

Dept Pulmonary Diseases

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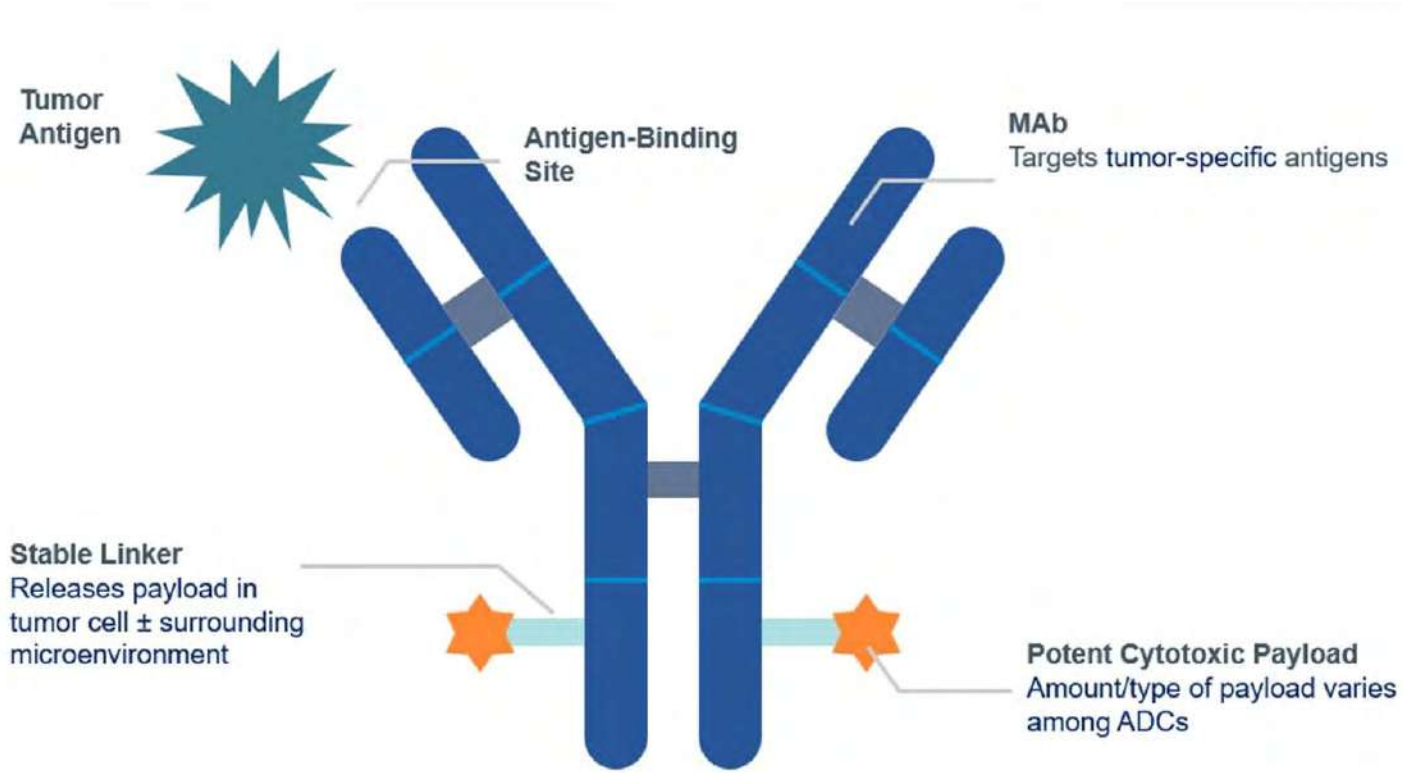
DECLARATION OF INTERESTS

Personal financial interests: None

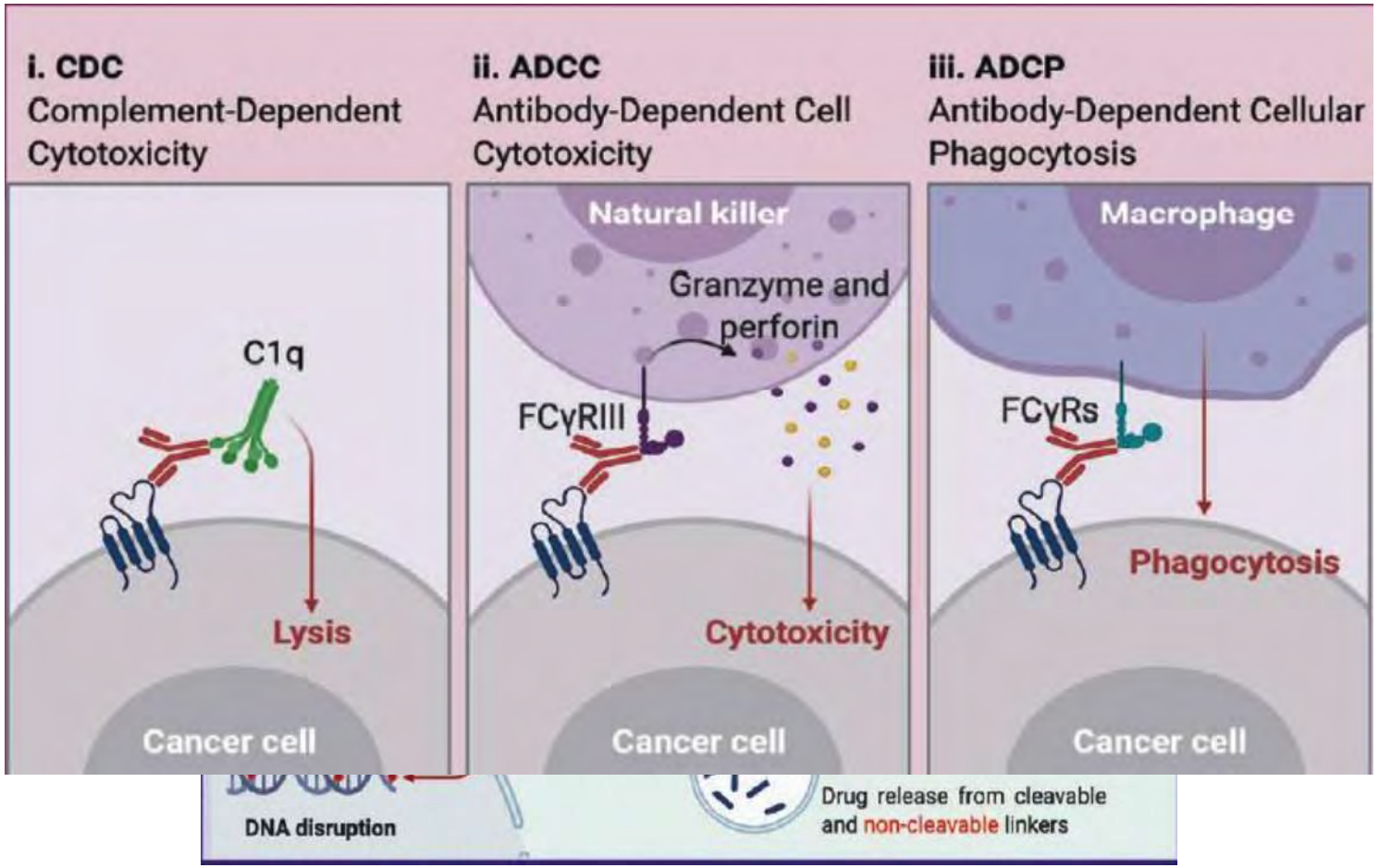
Institutional financial interests:

- Fees have been paid to my institution for speaker engagements and attendance to advisory boards of Astra Zeneca, Bristol Myers Squibb, Bayer, DSI, Eli Lilly, MSD, Merck, Novartis, Pfizer, Takeda, Regeneron, Roche Genentech, Roche Diagnostics.
- Research support: Astra Zeneca, Bristol Myers Squibb, Merck, MSD, Roche Genentech, DSI.
- PI for clinical studies sponsored by Novartis, PharmaMar, Takeda, Bayer, Eli Lilly, Amgen, DSI.

Basic structure of antibody-drug-conjugates (as we know them)



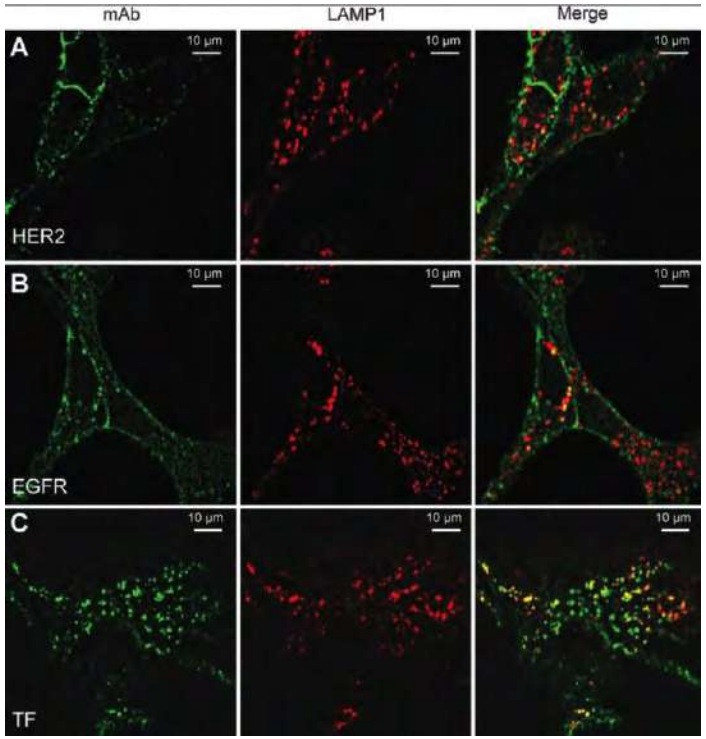
Mechanism of action

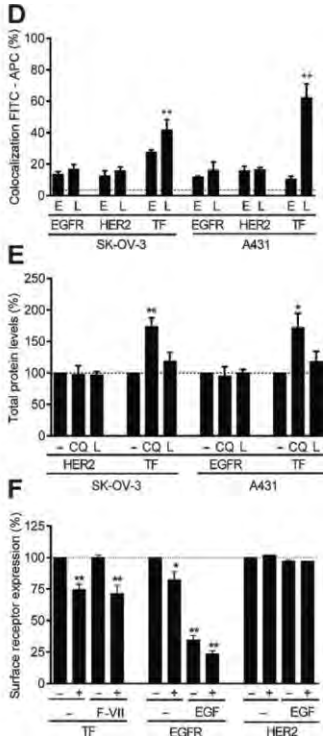


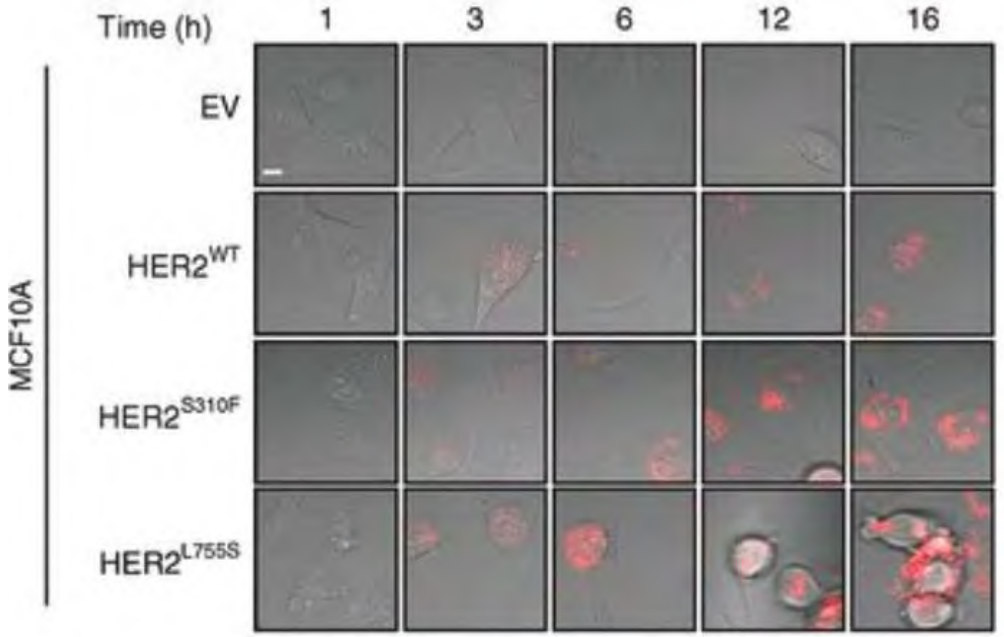
Considerations in ADC design: The antibody

- Mainly IgG1:
  - General stability in circulation; terminal half life 14-21 days
  - Engagement with innate immune system through Fcy receptors
  - Minimizing risk of formation of ADA's
- Recognizes (more or less) tumor specific antigens
  - Off target toxicities
  - Tumor specific variants e.g. EGFR variant III
- Turnover and internalization (probably) more important than surface antigen expression

Turnover and internalization important







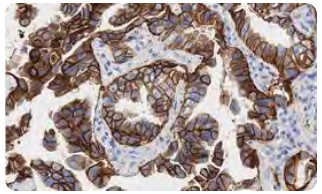
De Goeij. Mol. Cancer Ther. 2015

Li. Cancer Disc. 2020

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

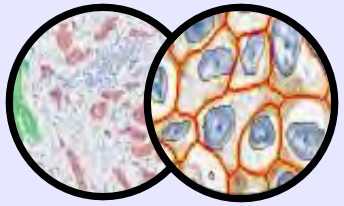
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay

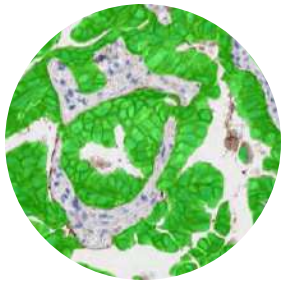


2 Whole Slide Imaging

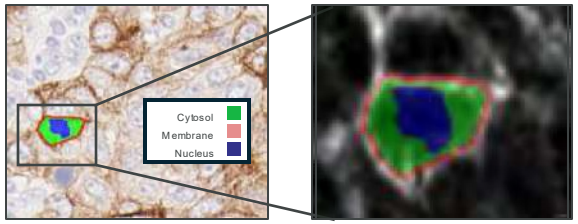
3 Automated Image Analysis (QCS)



Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

Lower NMR → higher cytoplasm proportion

4 Patient Biomarker Status Determination

\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

OD, optical density (a measure of staining intensity).
*Or >25% of cells with an NMR >0.56

TROPION-Lung01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

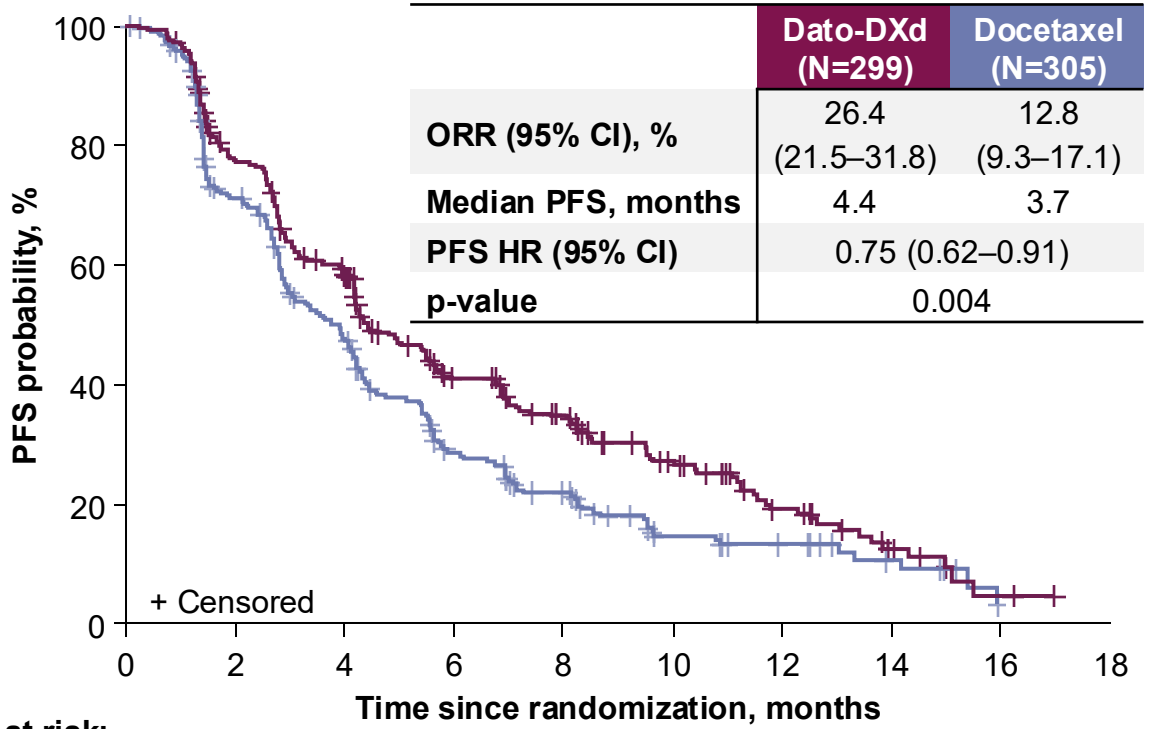
Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR[1]



	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

No. at risk:

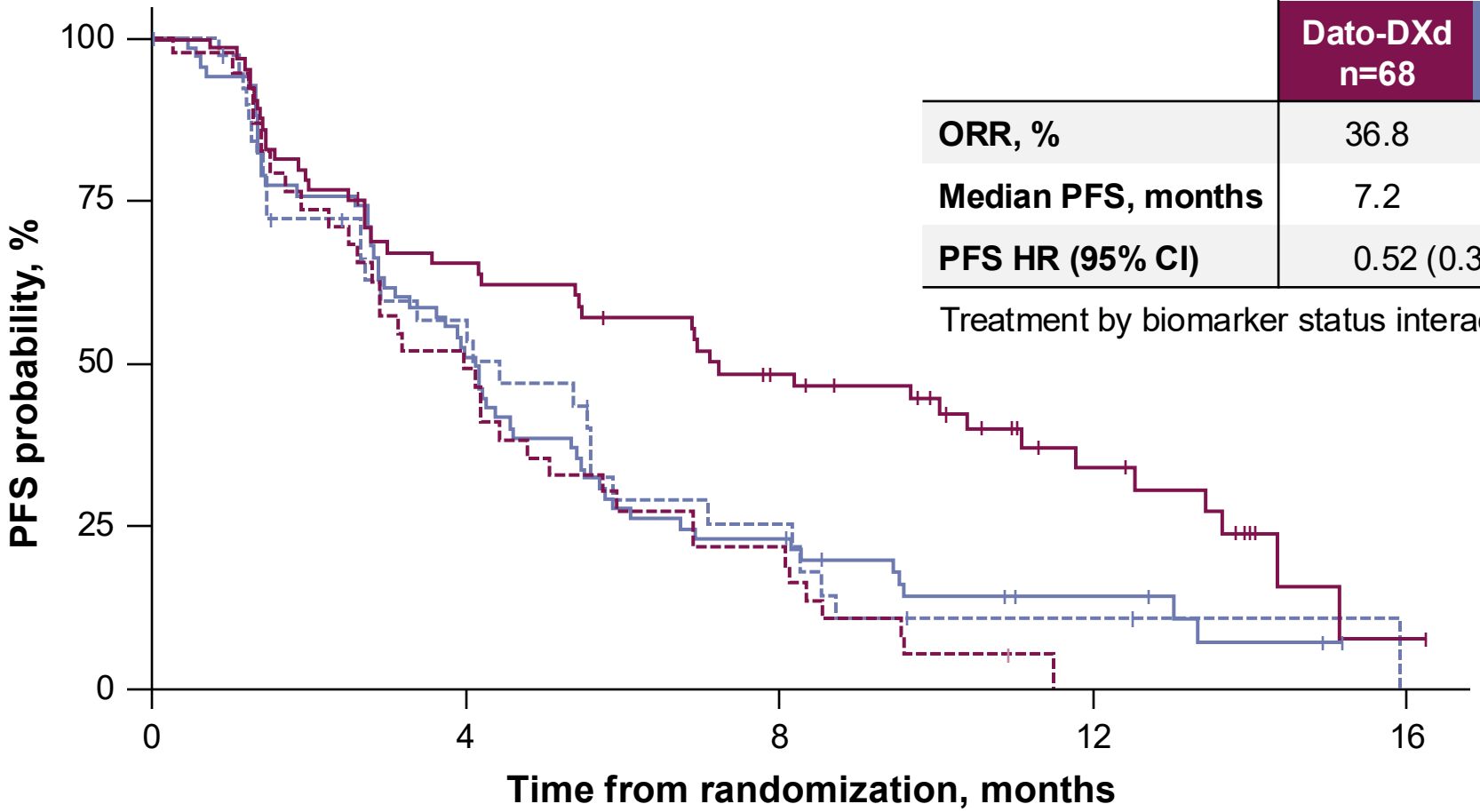
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).
Enrollment period: February 19, 2021, to November 7, 2022. Data cutoff: March 29, 2023.
AGA, actionable genomic alterations; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; q3w, every 3 weeks; R, randomized.
*Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. †Squamous vs non-squamous. ‡Presence vs absence. §United States/Japan/Western Europe vs other geographic regions.

NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the NSQ/non-AGA biomarker-evaluable population

NSQ/non-AGA BEP, n=221



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

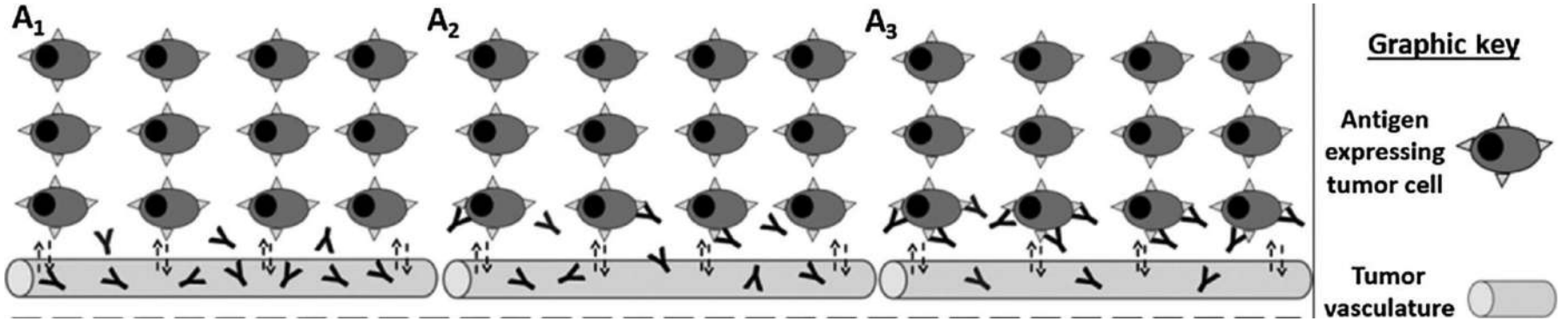
Data cutoff: March 29 2023

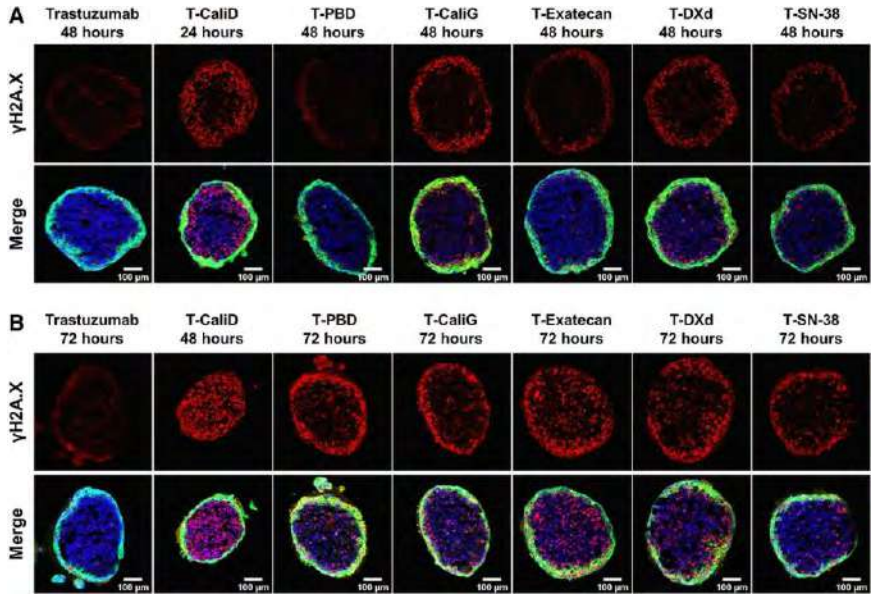
PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.40 [0.25-0.64]; Docetaxel:0.94 [0.60-1.49]

Considerations in ADC design: The antibody

- Mainly IgG1:
  - General stability in circulation; terminal half life 14-21 days
  - Engagement with innate immune system through Fcy receptors
  - Minimizing risk of formation of ADA's
- Recognizes (more or less) tumor specific antigens
  - Off target toxicities
  - Tumor specific variants e.g. EGFR variant III
- Turnover and internalization (probably) more important than surface antigen expression
- Affinity for the antigen
  - Binding-site barrier effect

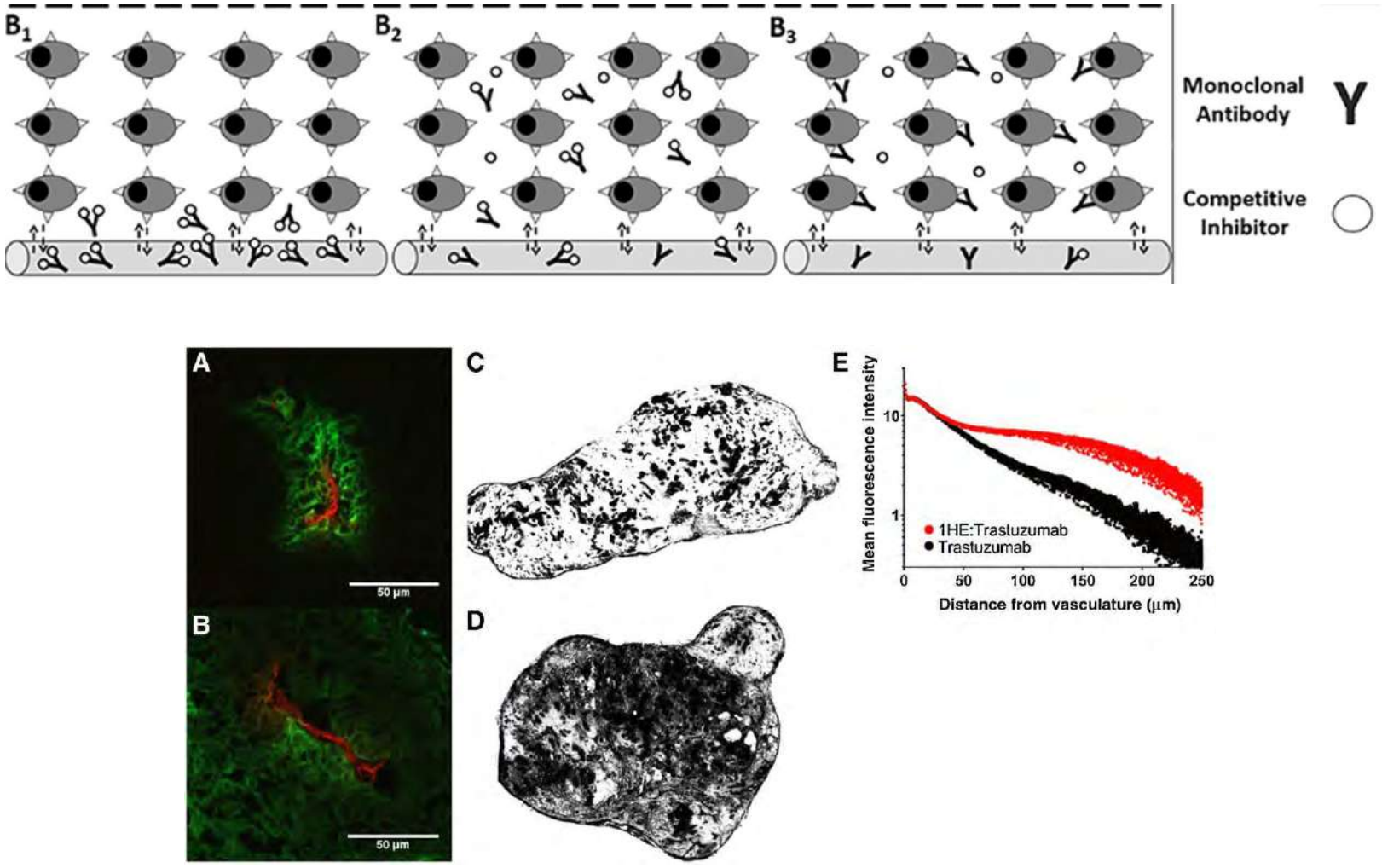
High affinity antibody precludes sufficient tumor infiltration





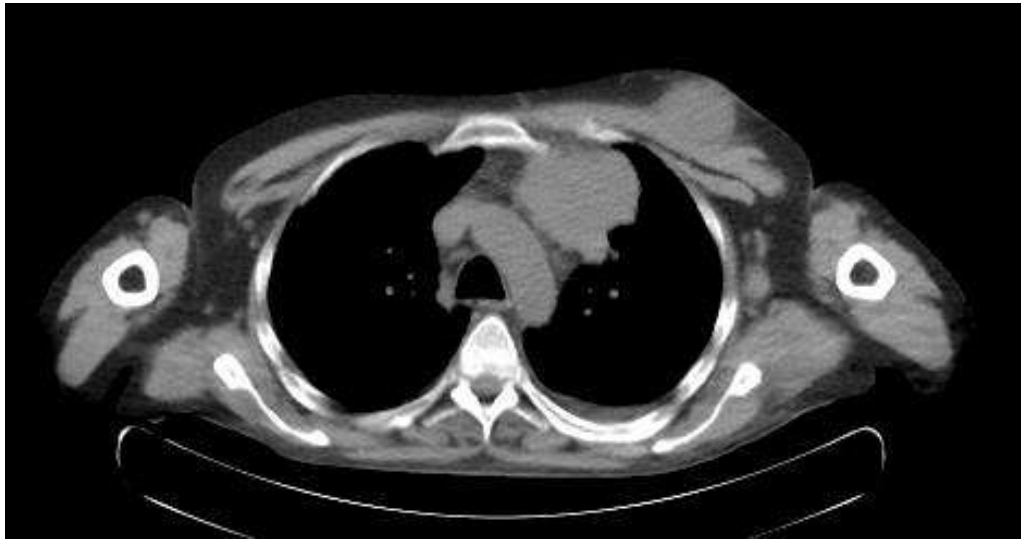
Bordeau. Cancer Res 2021

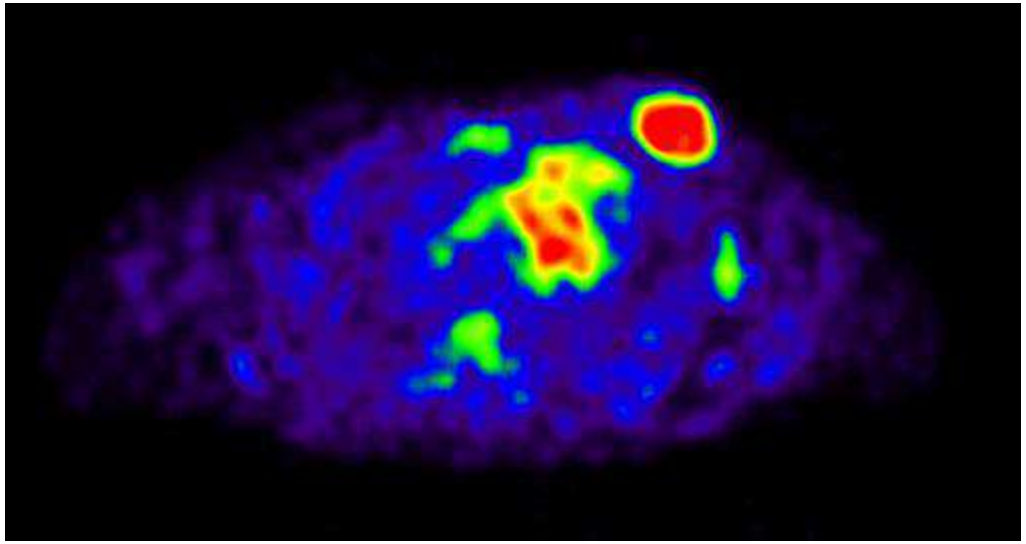
High affinity antibody precludes sufficient tumor infiltration

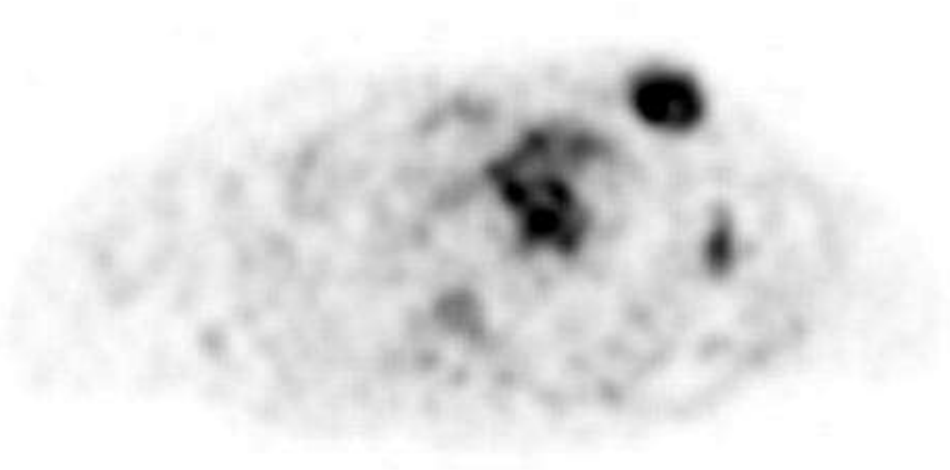


Bordeau. Cancer Res. 2021

Intrapatient ^{89}Zr-nivolumab uptake heterogeneity

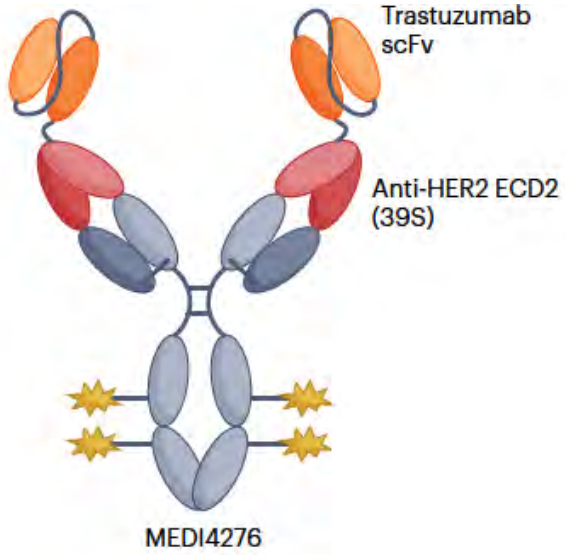


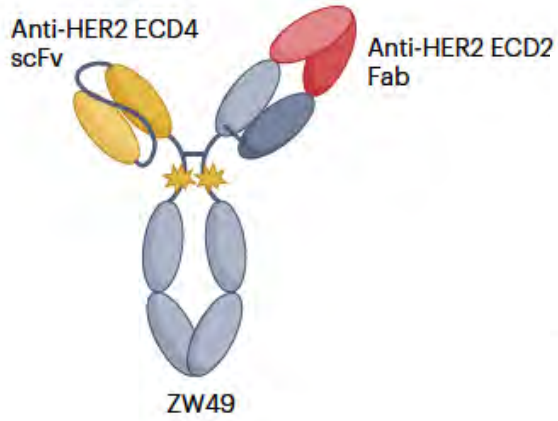


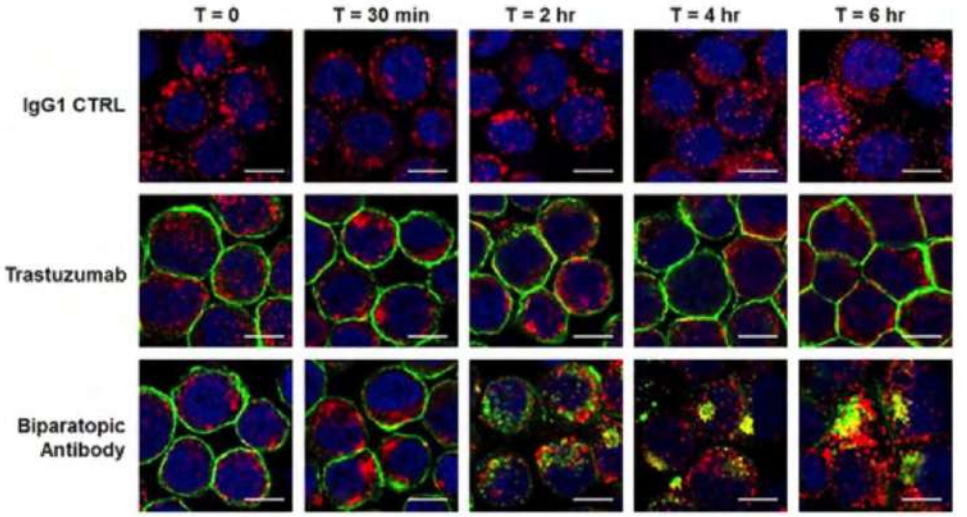


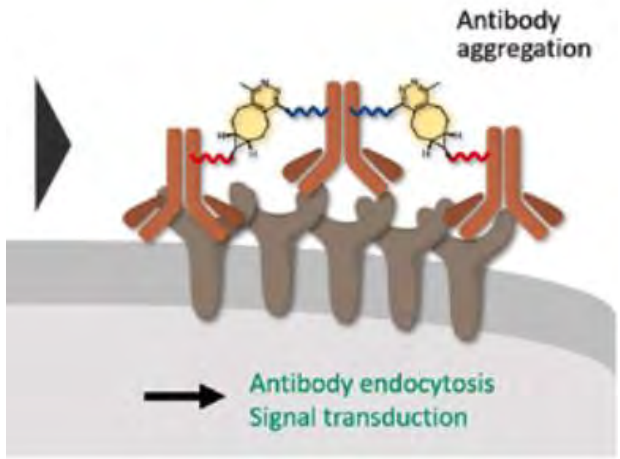
NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK
1913 2013

Considerations in ADC design: The antibody Biparatopics



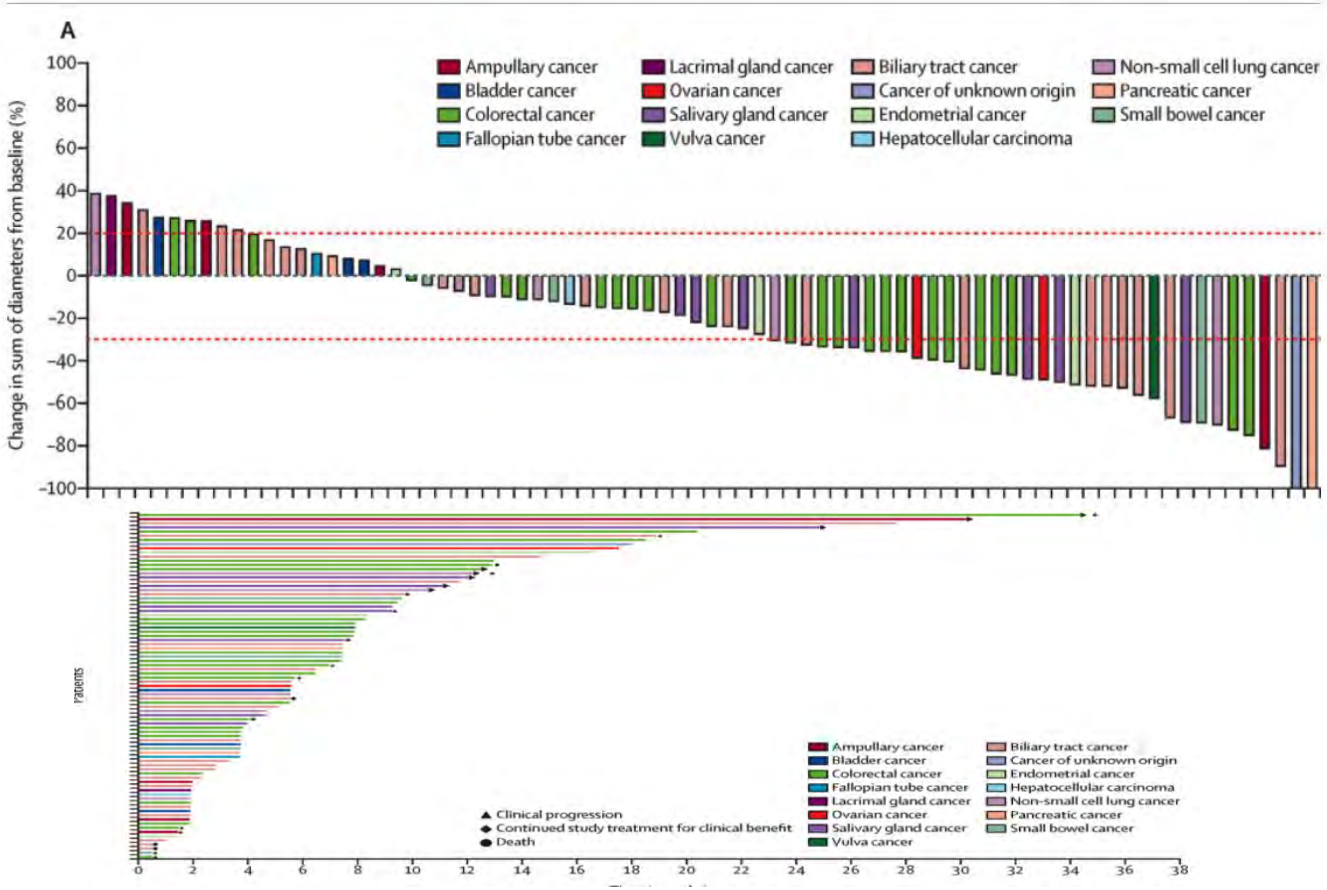


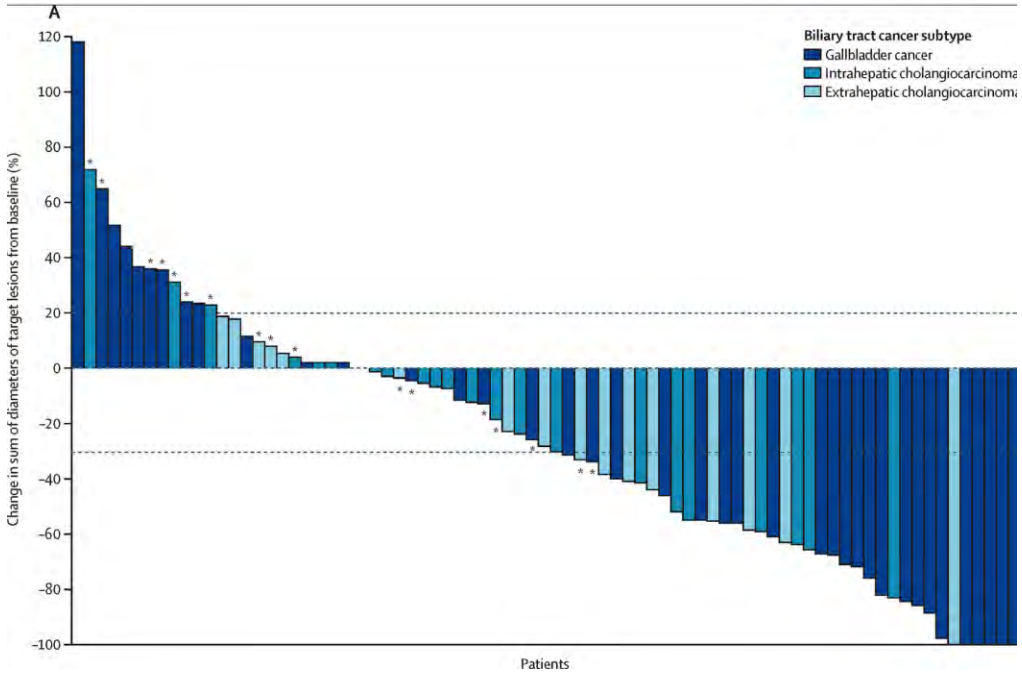




Li. Cancer Cell 2016

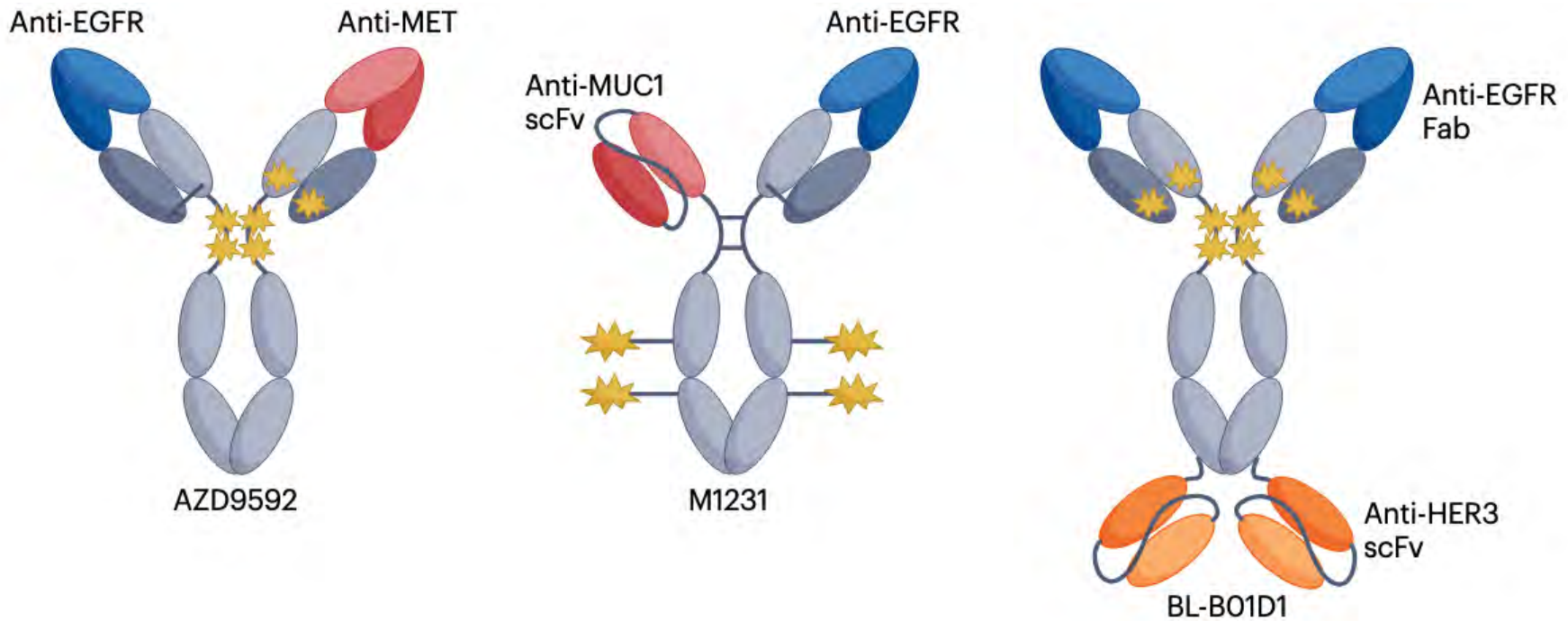
Zanidatamab phase I and II study in BTC





Meric-Bernstam. Lancet Oncol 2021 (left) Harding. Lancet Oncol 2023 (right)

Considerations in ADC design: The antibody Bispecifics



All three agents currently in clinical testing

Izalontamab Brengitecan: EGFRxHER3 Bispecific ADC

- Phase Ia/Ib dose escalation and dose expansion study

Patients ≥18 yr and ≤75 yr of age (phase Ia) or ≥18 yr of age (phase Ib) with locally advanced or metastatic NSCLC or other solid tumors, ECOG PS 0-1, measurable disease per RECIST V1.1, failure of standard therapy or without feasible treatment options (Q3W safety cohort: N = 369; NSCLC cohort: N = 113)

Dose Escalation

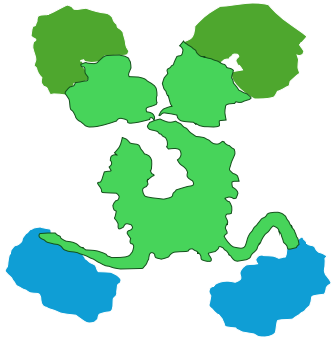
BL-B01D1
QW dosing
0.27, 1.5, 3.0 mg/kg IV

BL-B01D1
D1D8 Q3W dosing
2.5, 3.0, 3.5 mg/kg IV

BL-B01D1
D1 Q3W dosing
4.5, 5.0, 6.0 mg/kg IV

Dose Expansion

- **NSCLC**
- **SCLC**
- **Nasopharyngeal carcinoma**
- **Head and neck squamous cell carcinoma**



αEGFR
Human EGFR affinity: high

Cat B cleavable linker
Ed-04 (TOPI inhibitor)

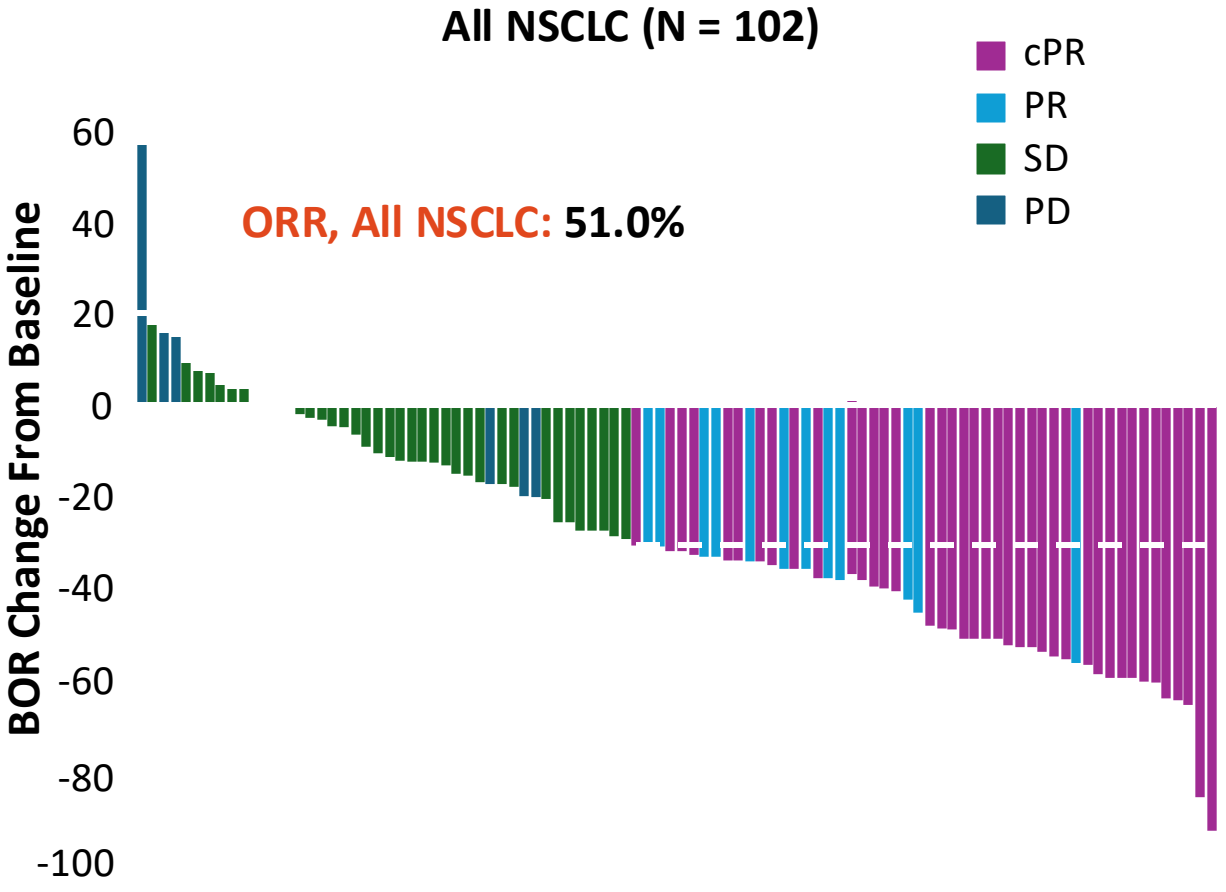
wt Fc IgG1

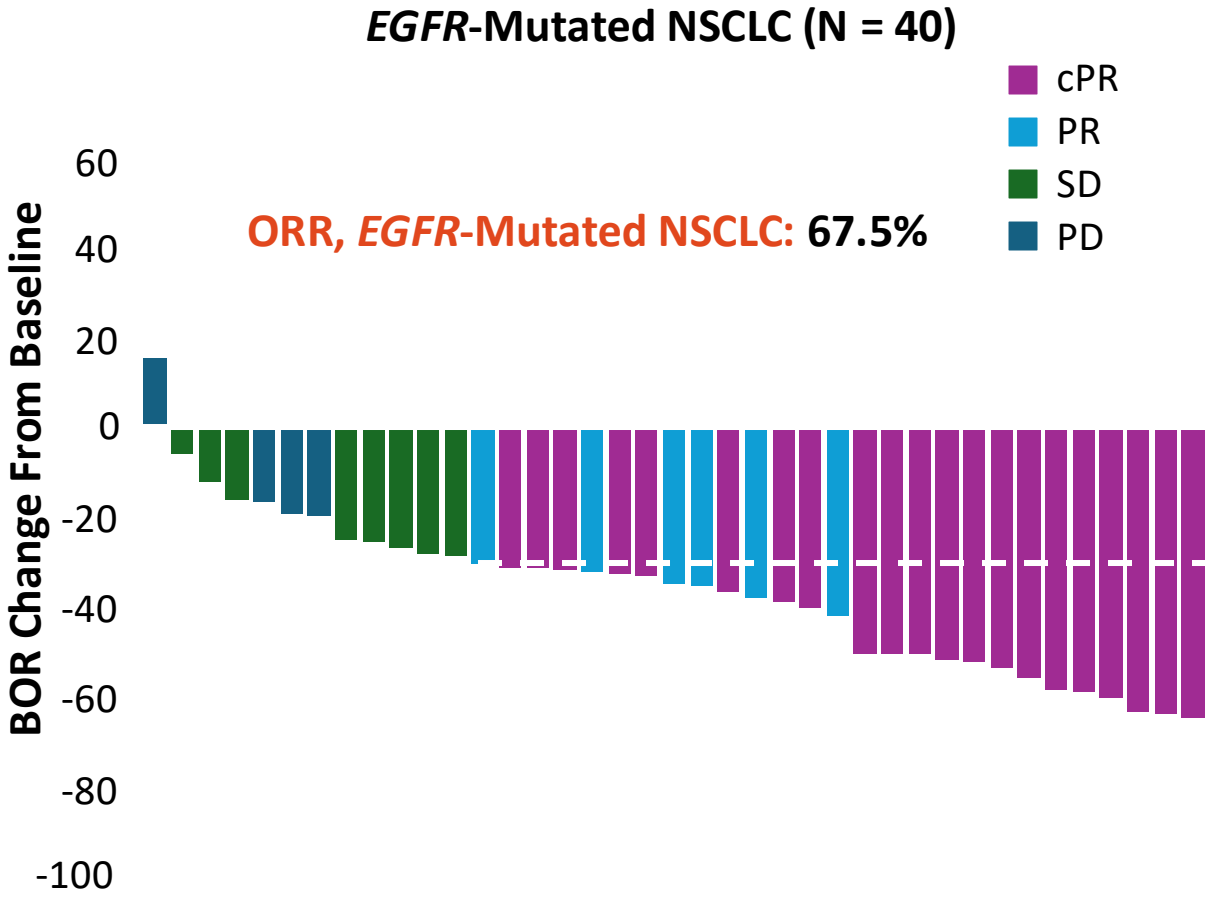
αHER3
Human HER3 affinity: low

- **Primary endpoint:** DLT, MTD, RP2D
- **Secondary endpoints:** PK, ADA, ORR, DCR, DoR

Zhang. ESMO 2023. Abstr 1316MO. Ma. Lancet Oncol. 2024;25:901.

Izalontamab Brengitecan: Tumor Response in NSCLC





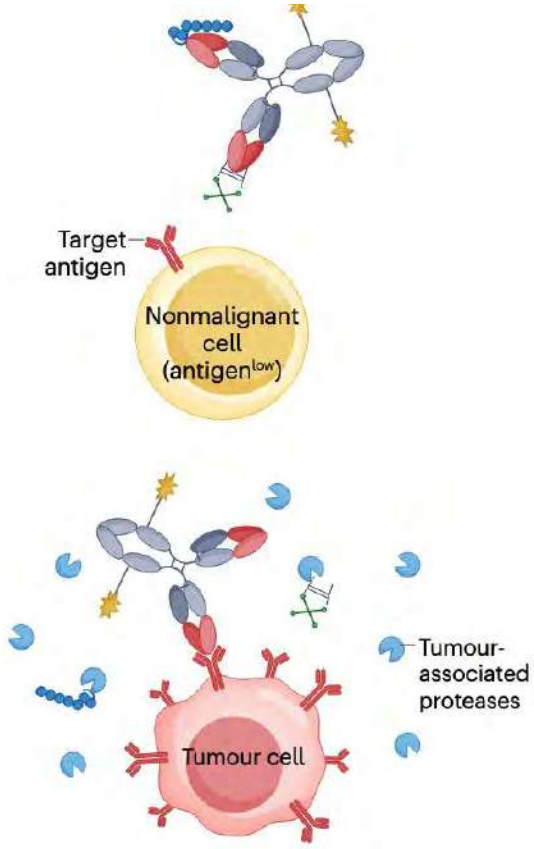
Zhang. ESMO 2023. Abstr 1316MO. Ma. Lancet Oncol. 2024;25:901.

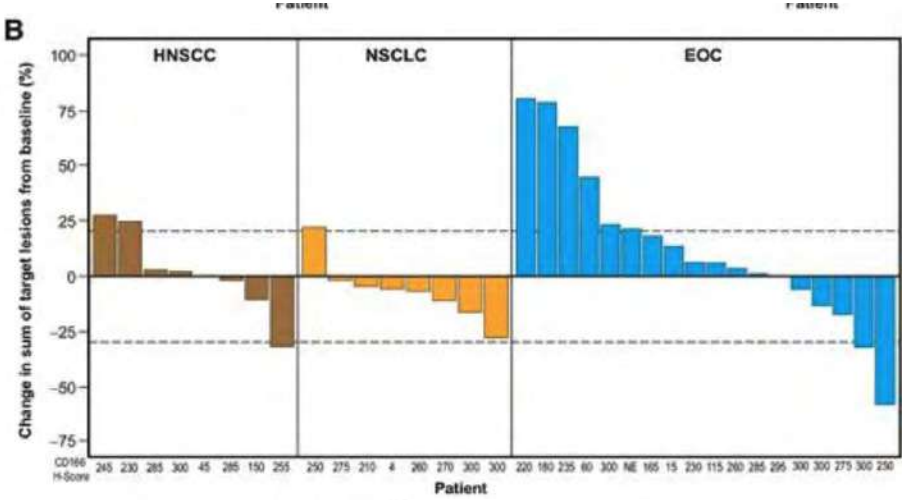
Considerations in ADC design: The antibody Probodies

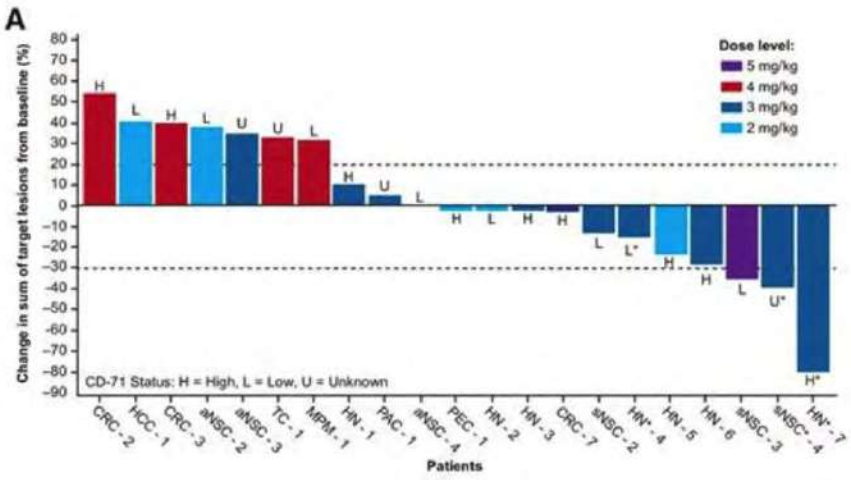
- Designed to circumvent on target off tumor toxicities

- Conditionally active antibodies
  - Fusion with self masking moieties undergoing pH dependent cleavage
  - Antigen binding sites that undergo pH dependent conformational change

PDC's targeting CD166 and CD71







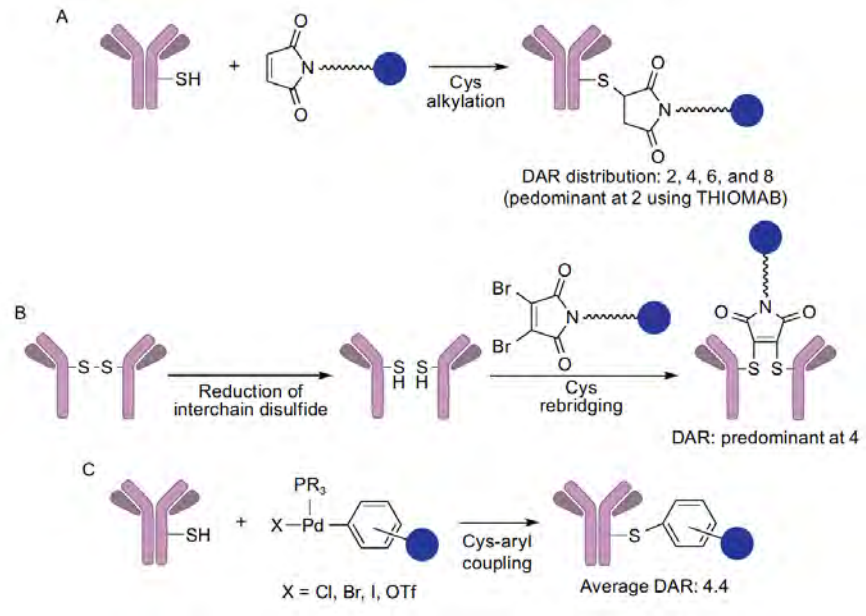
Boni. Clin Cancer Res 2022, Johnson Clin Cancer Res 2021

Considerations in ADC design: Linkers

- Sufficient stability in plasma
- Rapid cleavage and release of payload once internalized
- Avoid hydrophilic payloads with hydrophilic linkers
  - Promotion of ADC aggregates, hepatotoxicity, immune responses

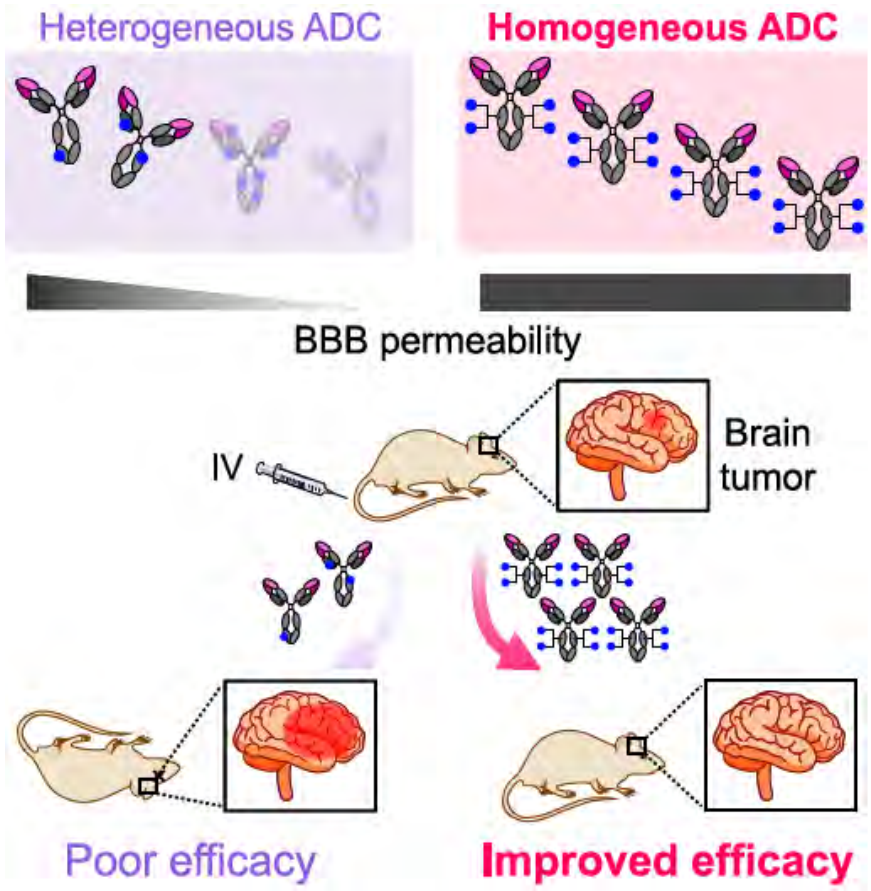
Considerations in ADC design: Linker conjugation

- Chemical conjugation
  - Using lysine and cysteine residues: heterogeneous DAR
  - Engineered strategies: THIOMAB (DAR 2), cysteine rebridging



Tsuchikama. Protein Cell 2018

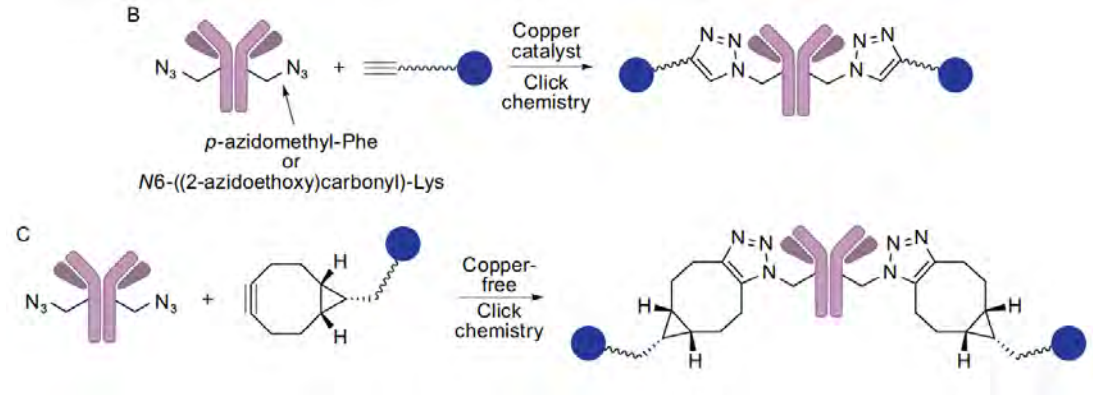
DAR homogeneity matters



Anami. Cell Rep. 2022

Considerations in ADC design: Linker conjugation

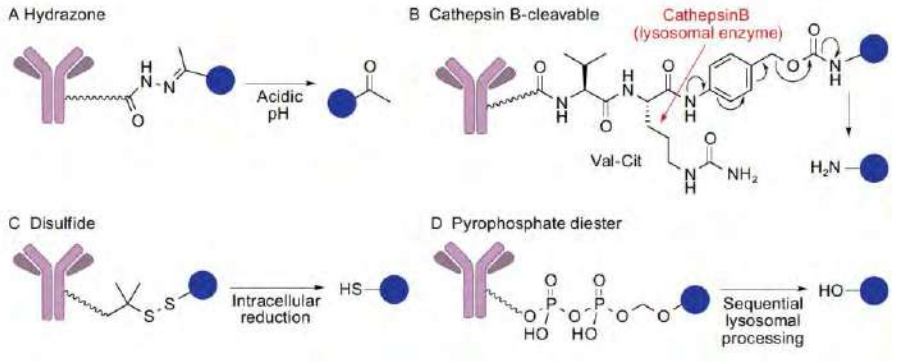
- Non-natural amino acid incorporation
  - Click chemistry
  - Tight control of DAR
  - Allows for multi-payload homogeneous ADC
- Enzymatic conjugation
- Affinity labelling
- Glycans



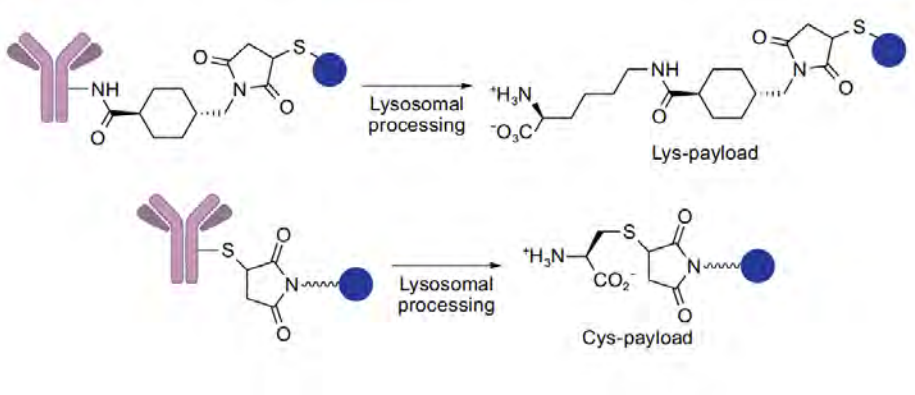
Tsuchikama. Protein Cell 2018

Considerations in ADC design: Cleavable vs Non-cleavable Linker

- Cleavable linker
  - Bond cleavage in response to difference extra vs intracellulair milieu
  - Release of payload in circulation

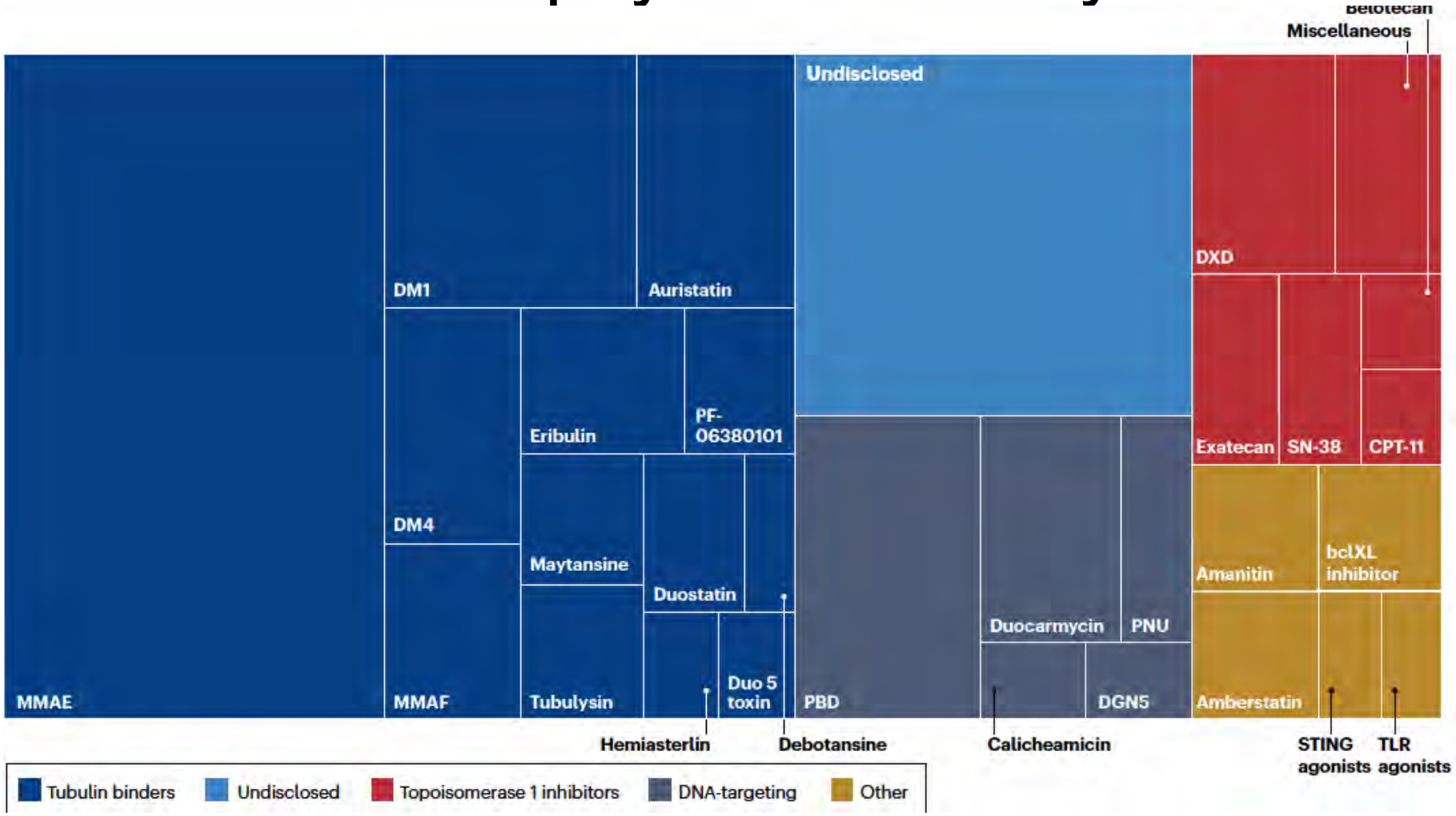


- Non-Cleavable linker
  - Degradation of ADC releases payload
  - Modified payload
  - Stability in circulation



Tsuchikama. Cell Protein 2018

Considerations in ADC design: Current payload diversity

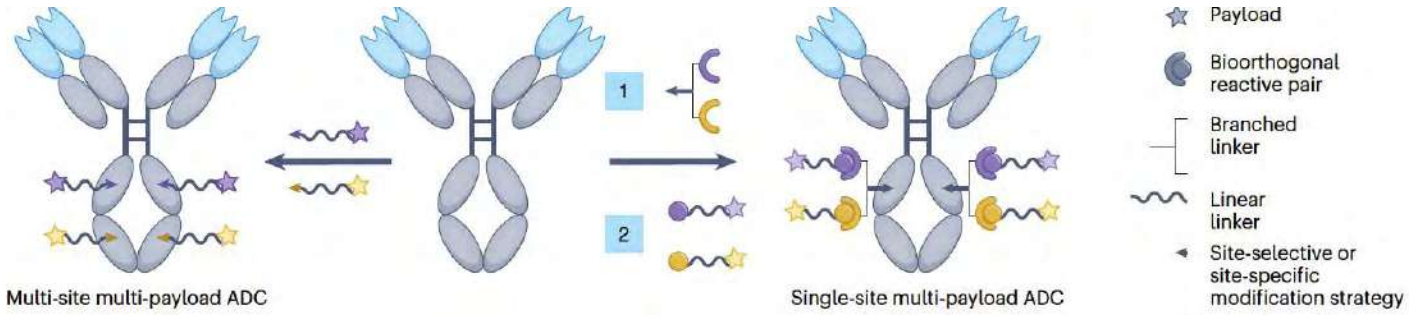


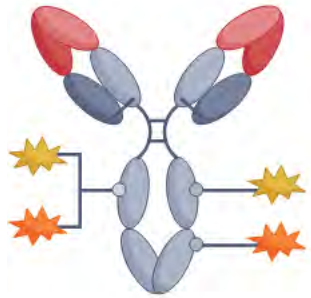
Dumontet. Nat.Rev. Drug Disc. 2023

Considerations in ADC design: Dual/Multi payloads

- Combination regimen more effective as single agent therapy

- Development of ADC's with 2 distinct payloads
  - Additive or synergistic activity
  - More toxicity?



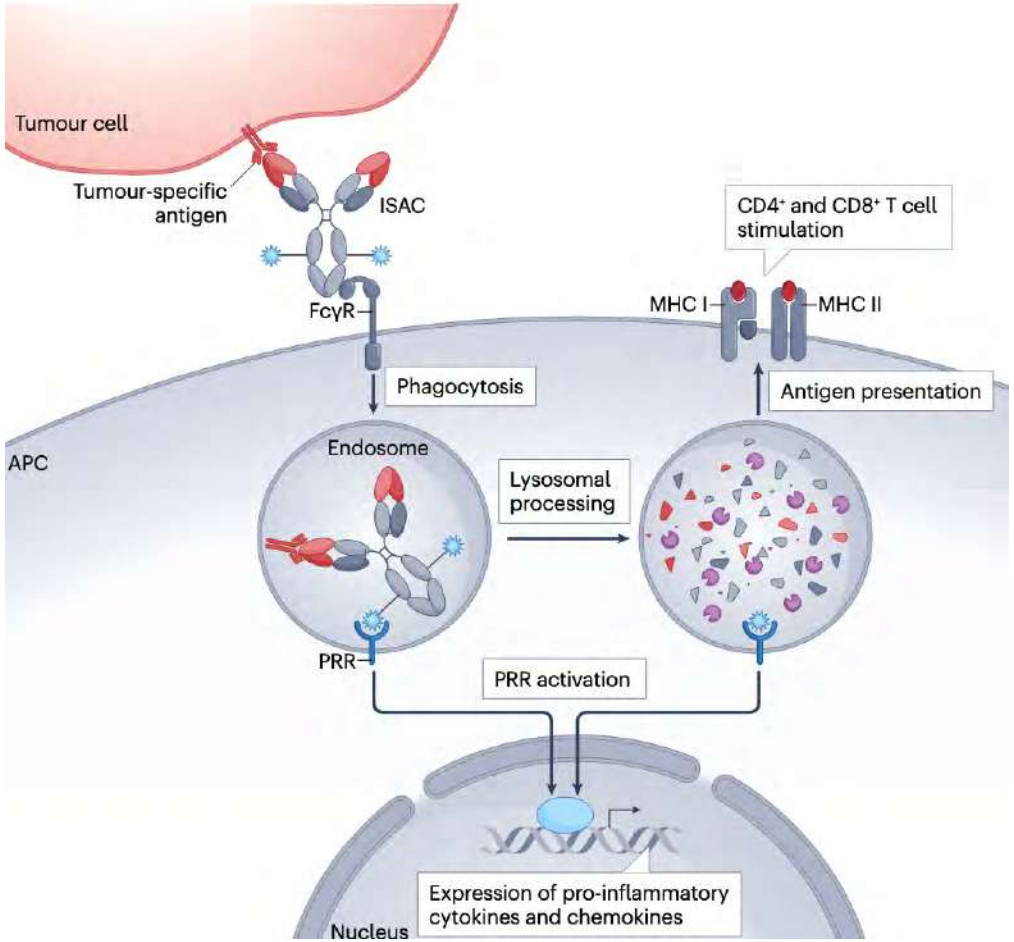


Conjugation methods
- Branched linker on a single site
- Linear linker on two or more sites

Payload combination
- MMAE–MMAF
- MMAE–SG3457
- MMAF–PNU-159682
- Hemiasterlin–TLR agonist

Journeaux. Nat. Chemistry 2024

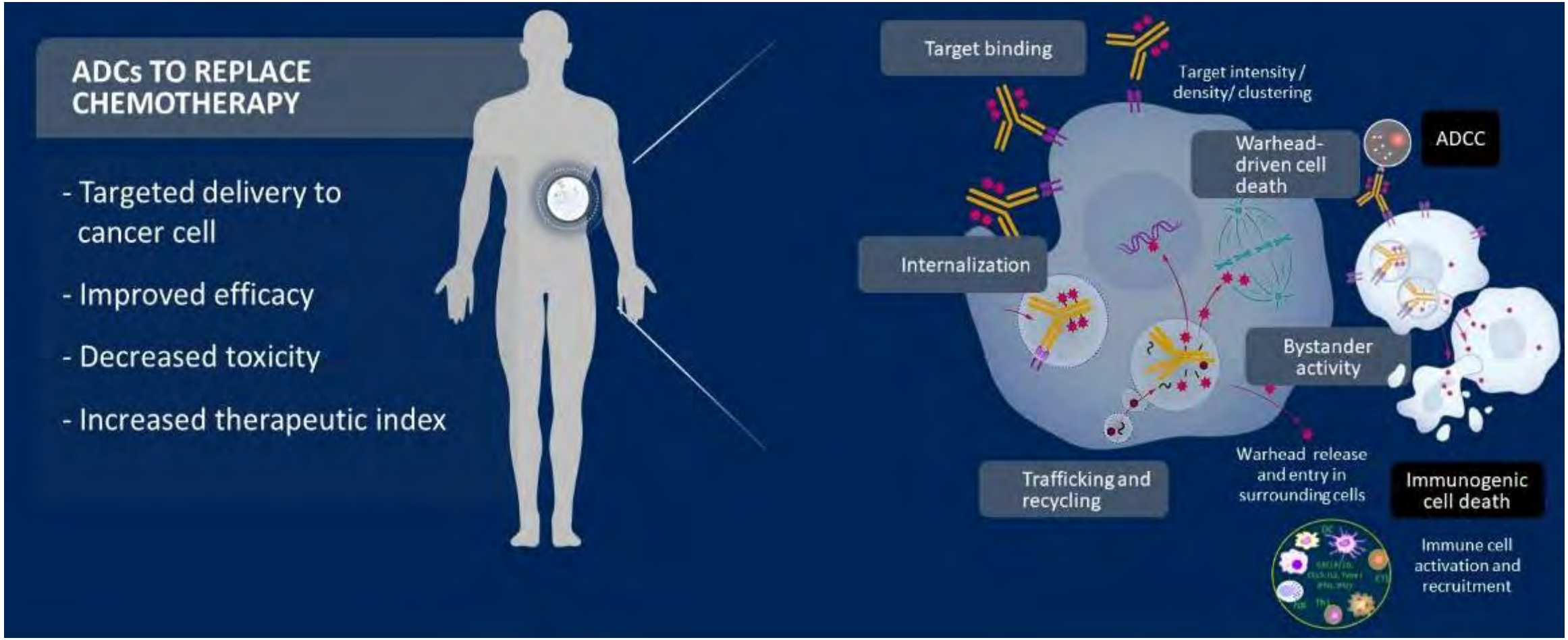
Considerations in ADC design: Immune stimulating payloads



- Toll like receptor 7,8,9
- STING
- PRR Activation
- Promote presentation of tumor associated DAMP's
- Activation of immune system

Tsuchikama. Nat. Rev. Clin. Oncol. 2024

What expectations of ADC's in the clinic?



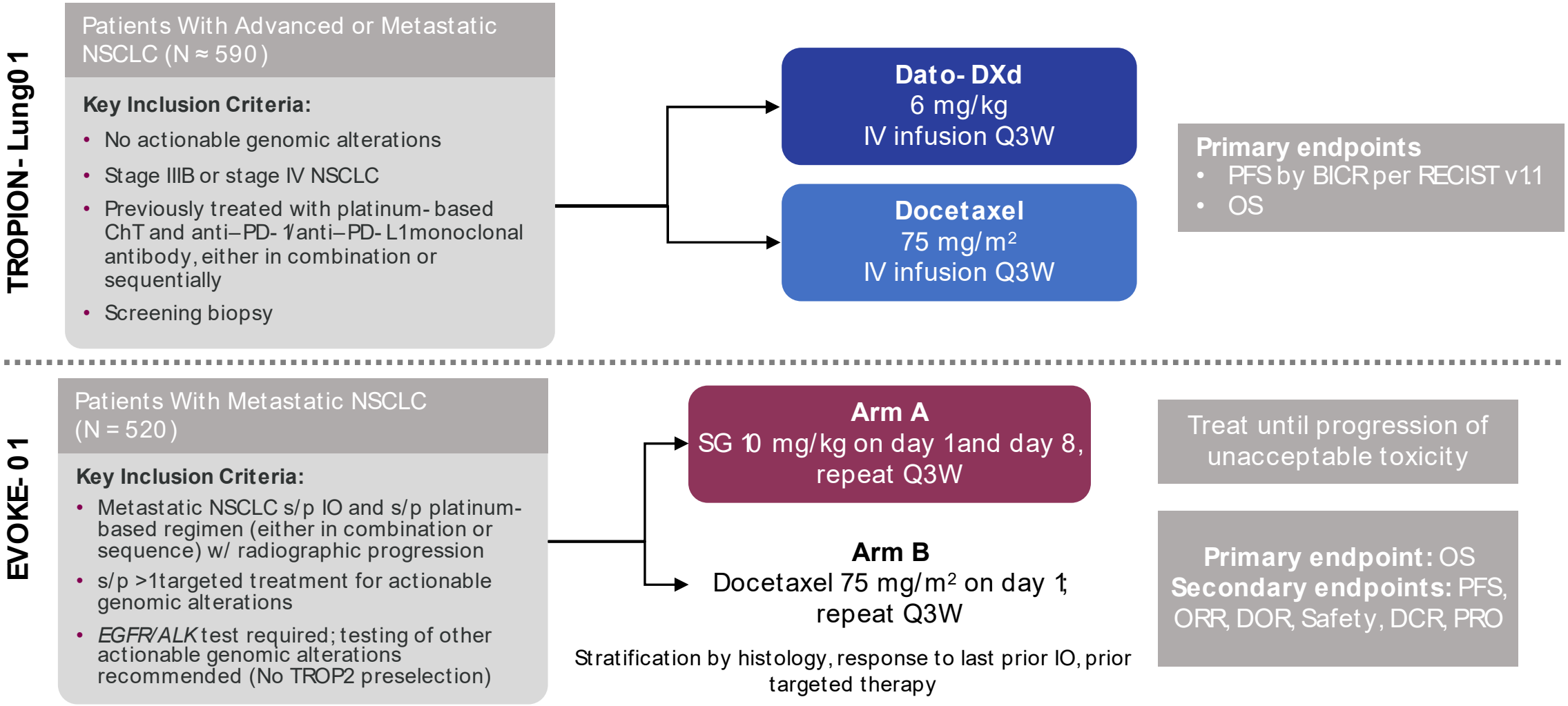
Mahtani RL. ASCO Annual Meeting 2022

A shortlist of ADC development in (N)SCLC

Drug		Target	Linker	Payload	DAR
Trastuzumab emtansine	**T-DM1**	HER2	Noncleavable	DM1	3.5
Trastuzumab deruxtecan	**T-DXd**	HER2	Cleavable	DXd	8
A166		HER2	Cleavable	Duostatin-5	-
Sacituzumab govitecan	**SG**	TROP 2	Cleavable	SN-38	7.6
Datopotamab-deruxtecan	**Dato-DXd**	TROP 2	Cleavable	DXd	4
Telisotuzumab vedotin	**Teliso-V**	MET	Cleavable	MMAE	3.1
Cofetuzumab pelidotin		PTK7	Cleavable	Aur0101	4
Anetumab ravtansine		Mesothelin	Cleavable	DM4	3.2
MGC018		B7-H3	Cleavable	Duocarmycin	2.7
Tisotumab vedotin		Tissue Factor	Cleavable	MMAE	4.1
Enapotamab vedotin	**EnaV**	AXL	Cleavable	MMAE	4
MRG003		EGFR	Cleavable	MMAE	-
Patritumab deruxtecan	**HER3-DXd**	HER3	Cleavable	DXd	8
XMT-1536		NaPi2B	Cleavable	AF-HPA	10-15
Tusamitamab ravtansine	**CEACAM5-DM4**	CEACAM5	Cleavable	MaytansinoidDM4	3.8

Courtesy T. Mok

Phase 3 Trials of Anti-TROP2 ADCs in Pretreated Patients

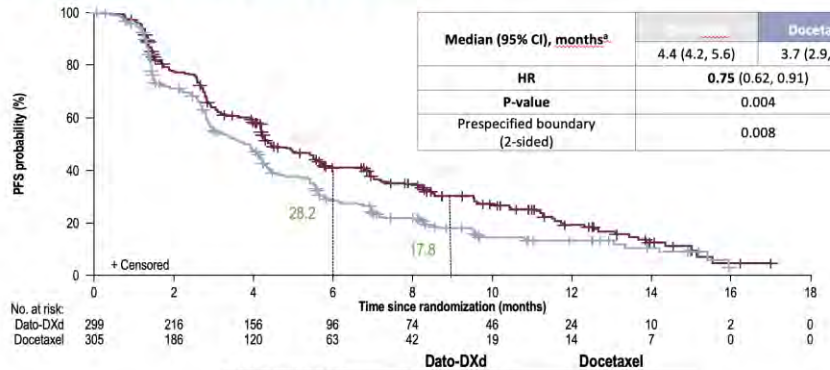


DCR: disease control rate; IO: immunotherapy; PRO: patient-reported outcomes; s/p: status post.

Ahn et al. ESMO 2023. Paz Ares et al ASCO 2024.

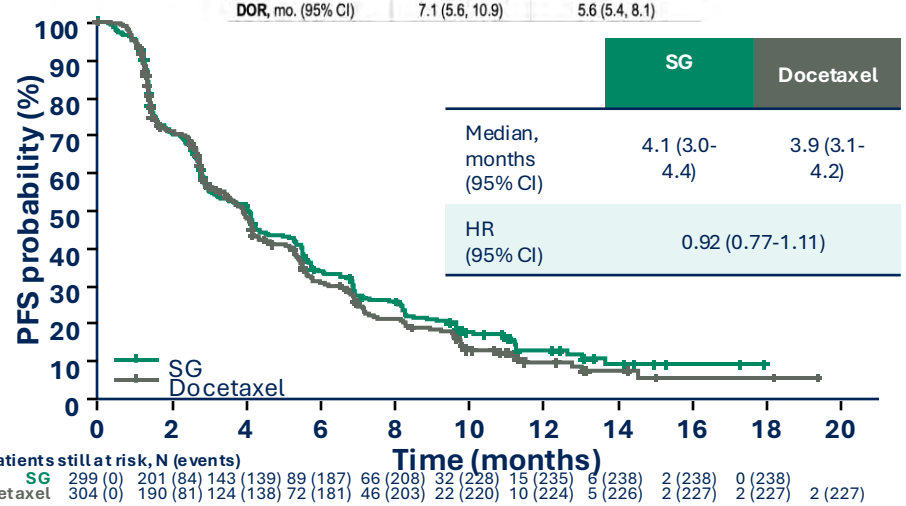
Similar Outcomes

Progression-Free Survival - ITT



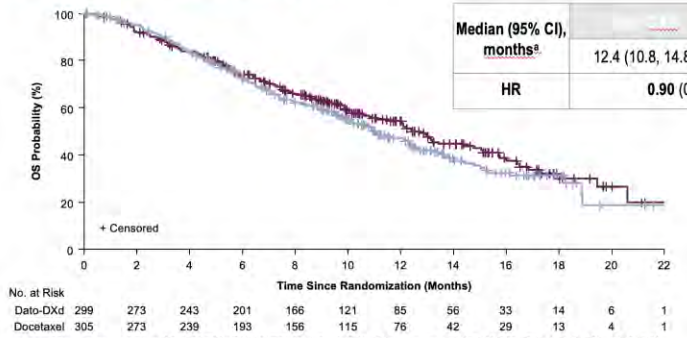
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2, 5.6)	3.7 (2.9, 4.2)
HR	0.75 (0.62, 0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

	Dato-DXd	Docetaxel
ORR, % (95% CI)[b]	26.4 (21.5, 31.8)	12.8 (9.3, 17.1)
DOR, mo. (95% CI)	7.1 (5.6, 10.9)	5.6 (5.4, 8.1)



	SG	Docetaxel
Median, months (95% CI)	4.1 (3.0-4.4)	3.9 (3.1-4.2)
HR (95% CI)	0.92 (0.77-1.11)	

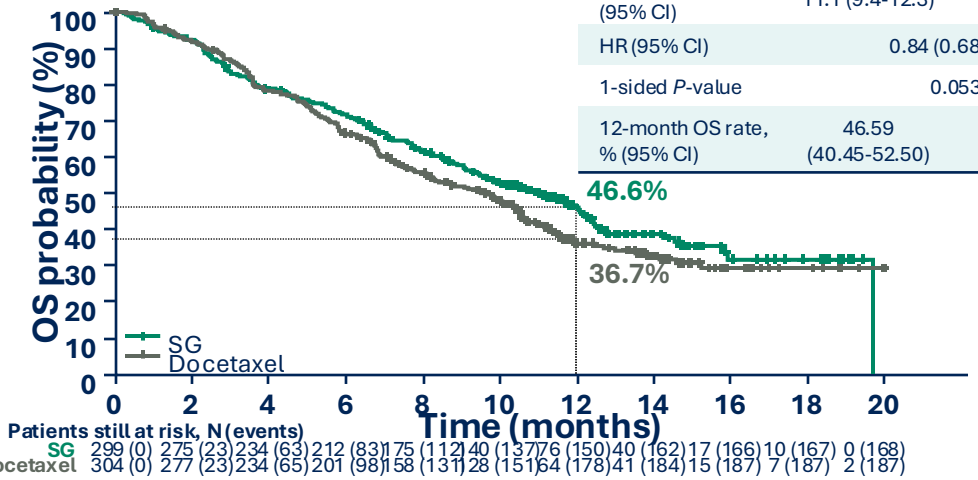
Interim Overall Survival - ITT



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8, 14.8)	11.0 (9.8, 12.5)
HR	0.90 (0.72, 1.13)	

Non-squamous HR (95% CI): **0.77** (0.59, 1.01); **Squamous HR** (95% CI): **1.32** (0.87, 2.00)

Trial is continuing until final OS analysis



	SG	Docetaxel
Median, months (95% CI)	11.1 (9.4-12.3)	9.8 (8.1-10.6)
HR (95% CI)	0.84 (0.68-1.04)	
1-sided *P*-value	0.0534	
12-month OS rate, % (95% CI)	46.59 (40.45-52.50)	36.72 (30.88-42.57)

Ahn. ESMO 2023, PazAres ASCO 2024

Similar outcomes

Trial		Docetaxel (mo)	ADC (mo)	HR
Tropion lung-01	PFS	3.7	4.4	0.75
EVOKE-01		3.9	4.1	0.92
Tropion lung-01	OS	11.0	12.4	0.90*
EVOKE-01		9.8	11.1	0.84

*survival analysis @ 74% maturity

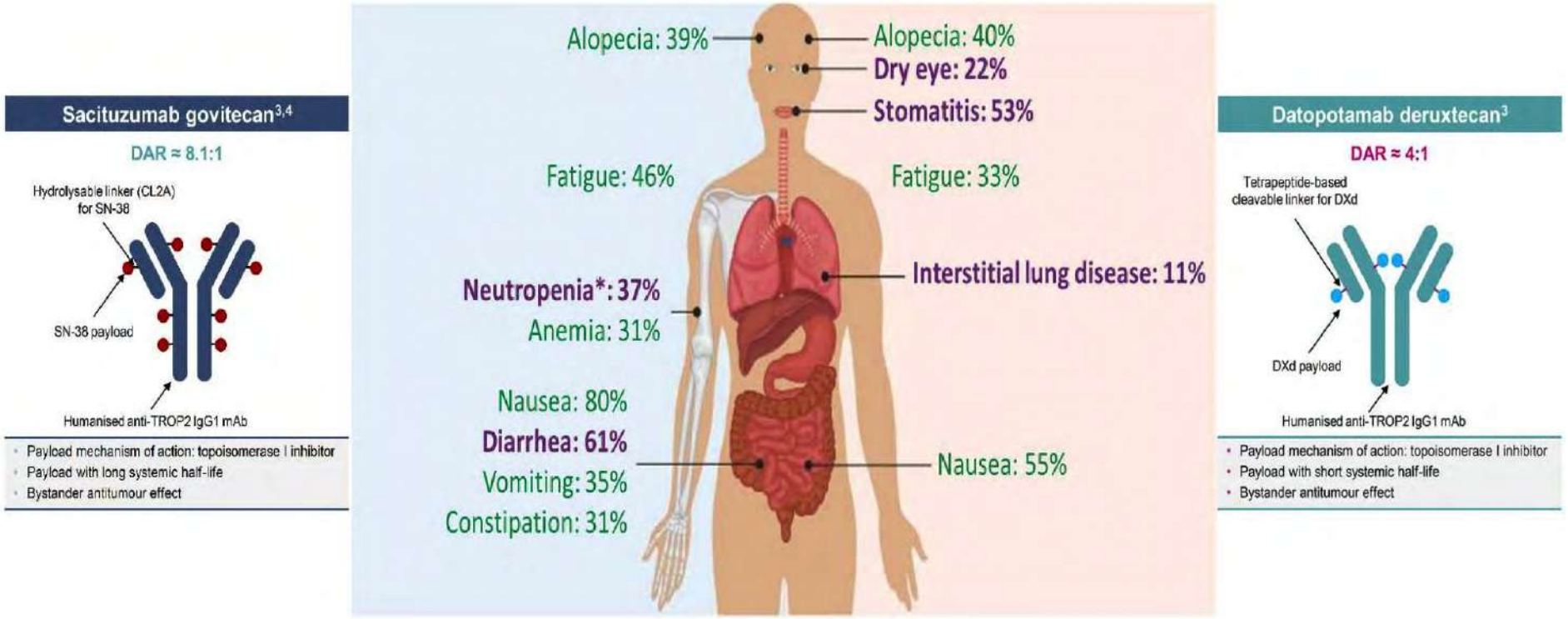
Some subtle differences

- Sacituzumab Govetican no differential activity against SC vs NSqC NSCLC

- Higher activity against patients with SD or PD as best response to prior IO
  - Not analysed in TROPION LUNG-01

- Different toxicities associated with treatment
  - On target/off cancer differences or off target only?

Understanding toxicities.
Same target, same class of payload, different toxicities



Heist. J. Clin. Oncol. 2017, Shimizu. J. Clin. Oncol. 2023

ADC – Designer Drugs?

- Antibody
  - Bispecific and Biparatopic antibodies
  - Probodies
- Linker
  - Conjugation
    - Modified and branched linkers
    - Homogeneous DAR
- Payload
  - Multi(dual) payload
  - Immune stimulating payload

Thank you for your attention

e.f.smit@lumc.nl

ESMO ON AIR

Targeting the microbiome

Bertrand Routy MD, PhD

Associate Professor Hemato-Oncology University of Montreal

co-director of the CHUM Microbiome Centre

ESMO EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

DECLARATION OF INTERESTS

Bertrand ROUTY, MD PhD

Research Support: AstraZeneca, Merck, Davolterra, BMS, Domains, Kanvas

Honoraria/Consultant: Merck, AstraZeneca, BMS, Bayer, DaVolterra, Pfizer, Vedanta, Illumina, Kaleido, Sanofi, Kanvas

Other: Patent EverImmune, Patent CRCHUM, co-founder Curebiota

Is the gut microbiome ready for prime time in thoracic oncology clinic ?

At your next clinic, 75 M, with advanced NSCLC you will request:

CBC, Electrolytes, LFT, EKG
Troponin, BNP, TSH, CK
HBsAg, Anti-HBs/c, Anti-HCV, Anti-HIV
CT/MRI brain
PET-scan
Biopsy + PD-L1 + mutational panel

?

Should you order microbiome profiling

“Doctor, should I take probiotics before starting my immunotherapy?”
“Doctor what should I eat to boost my immune system?”

ESMO ON AIR

The rapid evolution of the gut microbiome in oncology

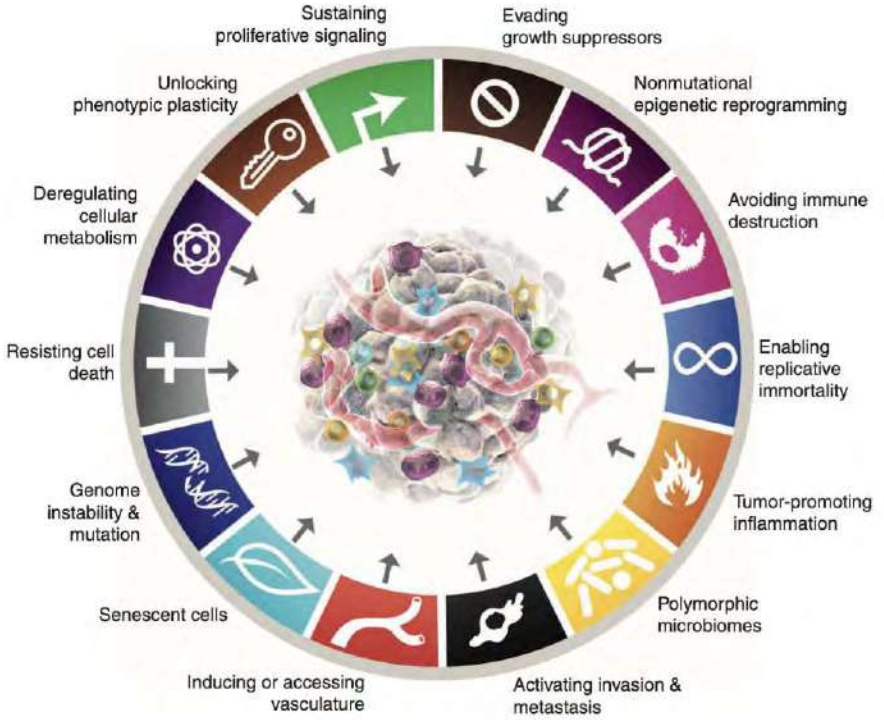
nature
International journal of science

Bertrand Routy earned a lamentable reputation with Parisian oncologists in 2015. A doctoral student at the nearby Gustave Roussy cancer centre, Routy had to go from hospital to hospital collecting stool samples from people who had undergone cancer treatments. The doctors were merciless. "They made fun of me," Routy says. "My nickname was Mr Caca."

But the taunting stopped after Routy and

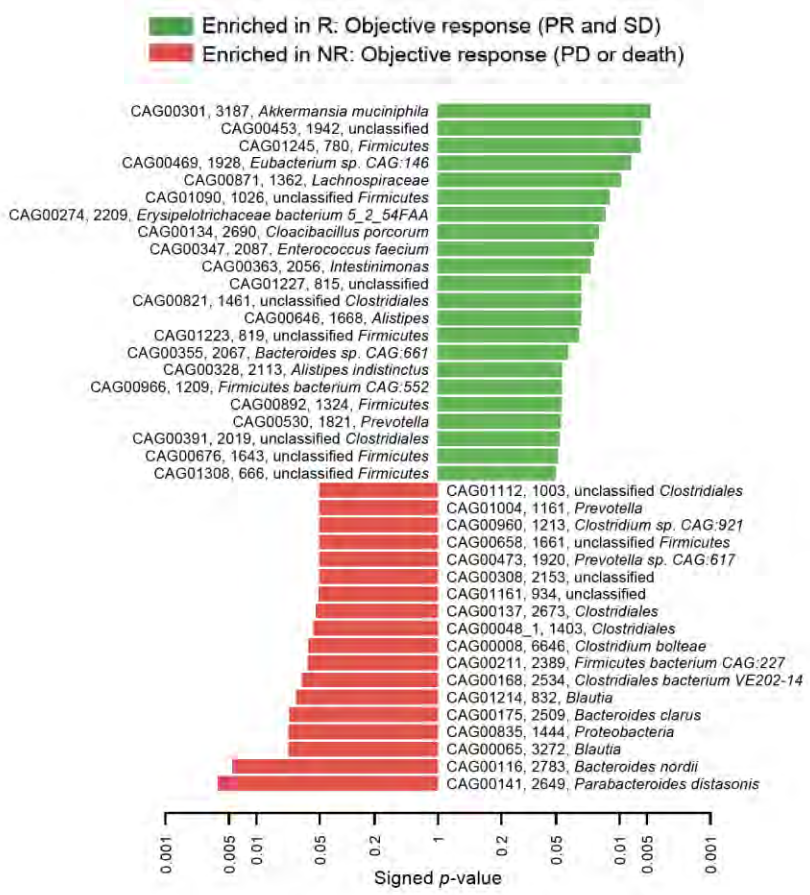
Nature 2018

Routy et al., Cancer Cell 2023



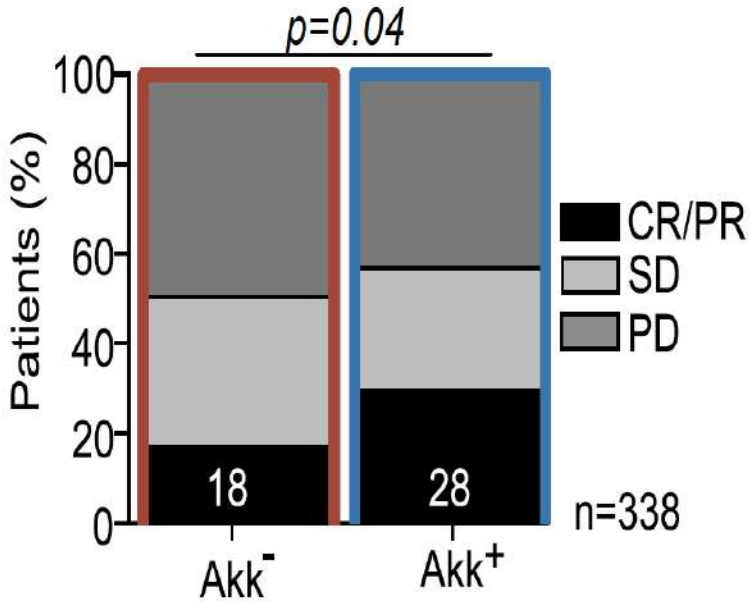
Hanahan et al., Cancer Discovery 2022

Akkermansia muciniphila bacteria: a new prognostic marker in patients with NSCLC amenable to anti-PD-1



Discovery cohort n =100 (NSCLC + RCC)

Primary endpoint: objective response rate



Derosa, Routy et al., Nat Med 2022

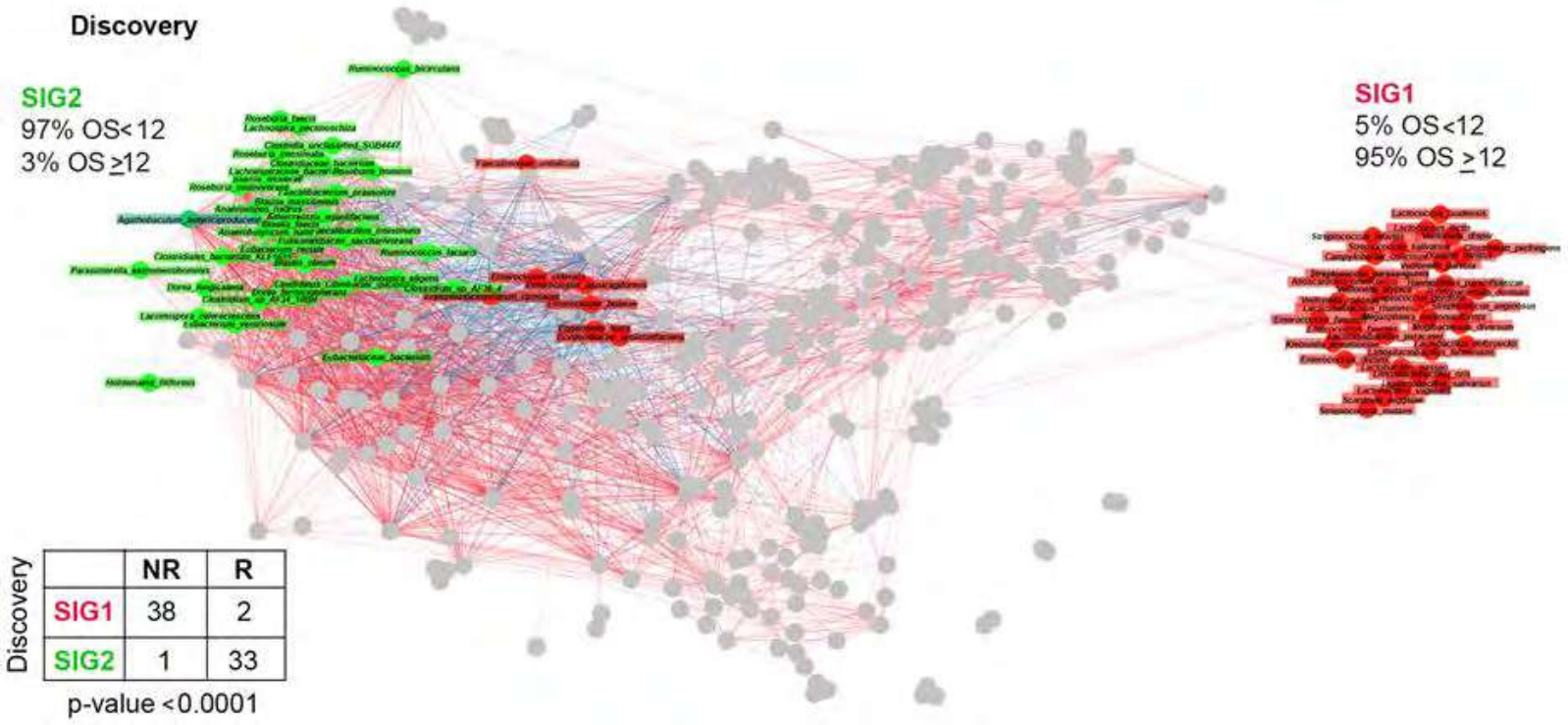
Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial

Tina Cascone, William N. William Jr, Annikka Weissferdt, Cheuk H. Leung, Heather Y. Lin, Apar

ESMO ON AIR

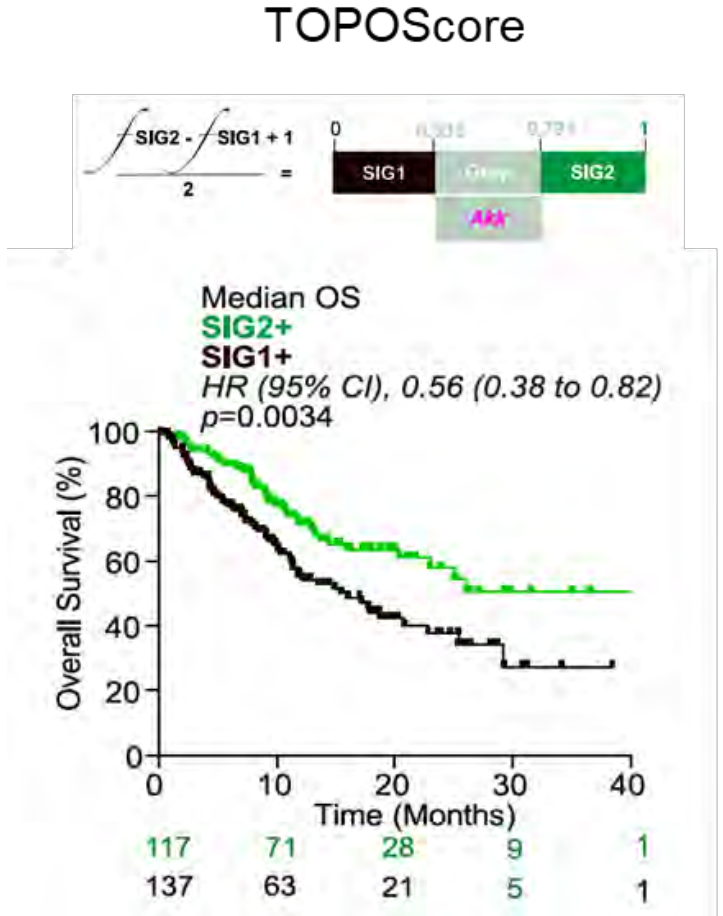
Routy et al. Science 2018

Representation of the microbiome composition using bacterial network (SIG = Species Interacting Groups) in NSCLC (n=254)



Discovery	NR	R
SIG1	38	2
SIG2	1	33

p-value <0.0001

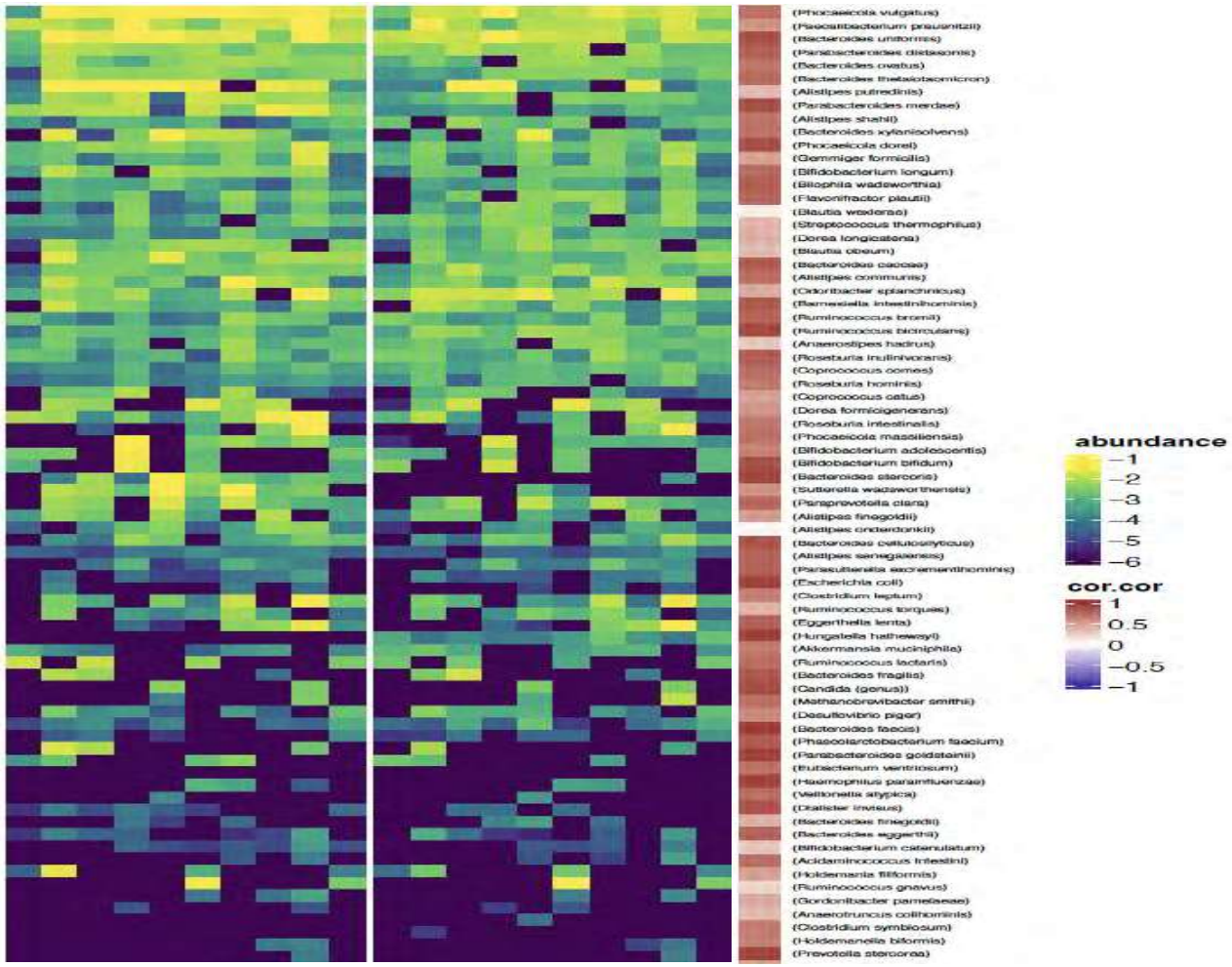


Dersosa et al., Cell 2024

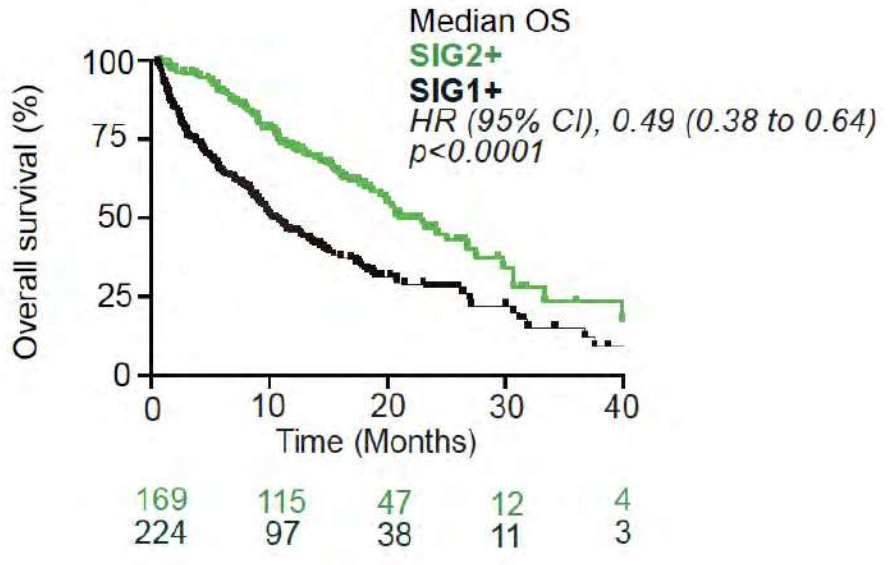
Rapid characterization of the microbiome composition for clinical use in less than 72 hrs using a bacteria PCR chip TOPOscore

Bio-Me
Microbiome Profiling

Metagenomics PCR



NSCLC, n=393
83 bacteria-based MGS TOPOSCORE



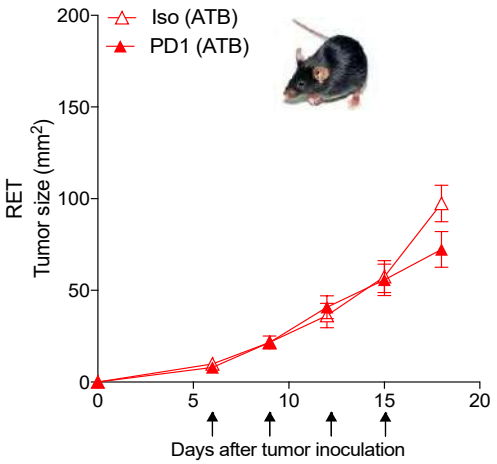
ESMO ON AIR

Messaoudene et al., Nat Com 2024

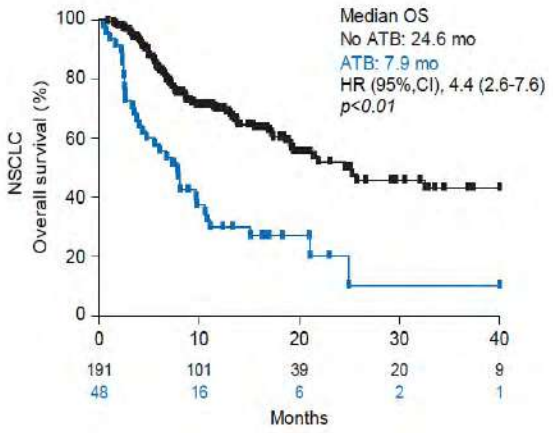
Dersosa et al., Cell 2024

ESMO

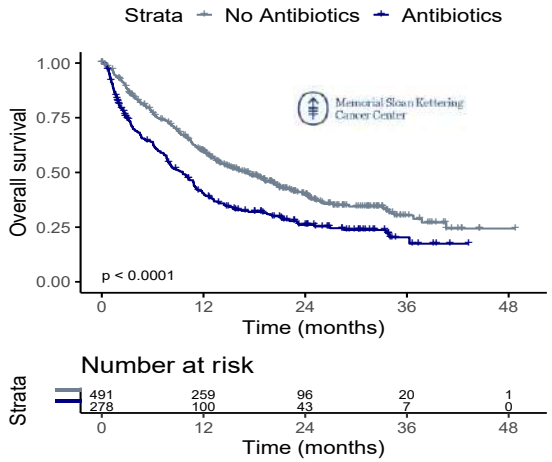
From mice to a meta-analysis in 46,000 patients confirms the negative role of antibiotics in patients with solid tumors treated with IO

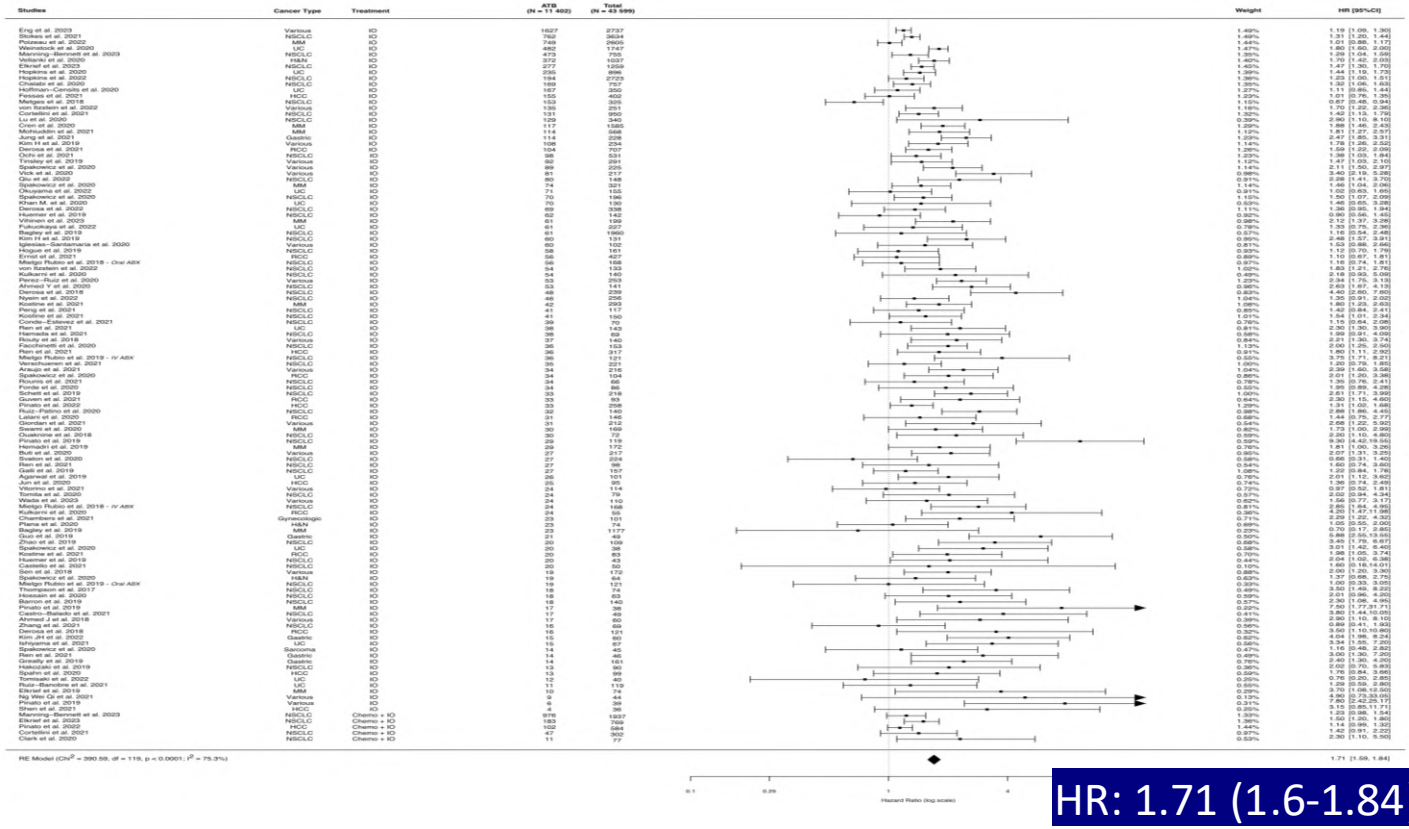


IO monotherapy



Chemo-IO

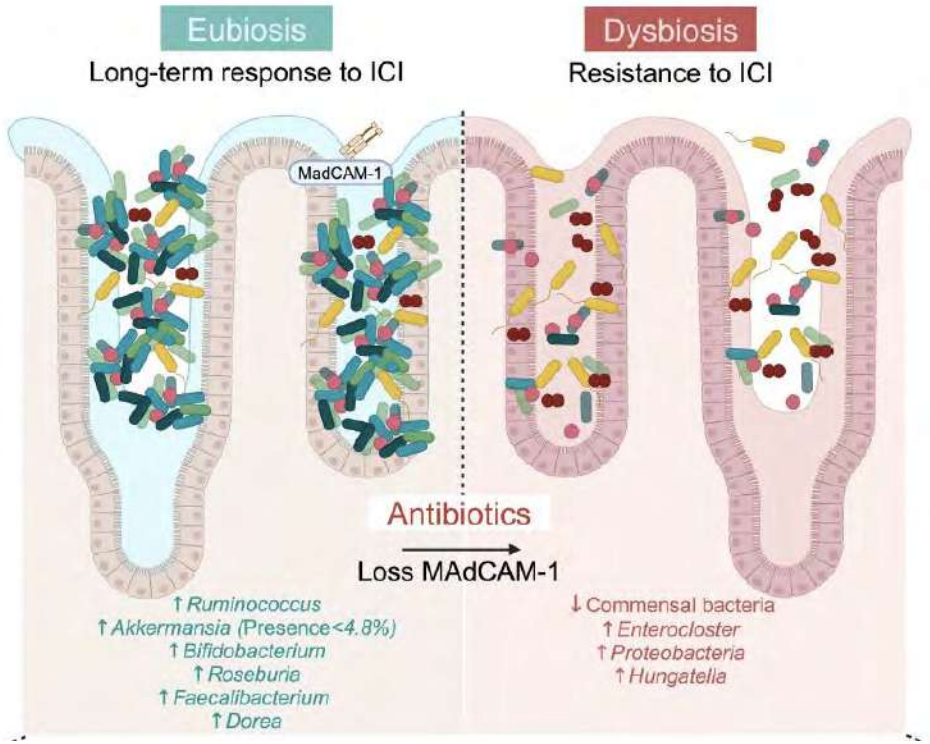


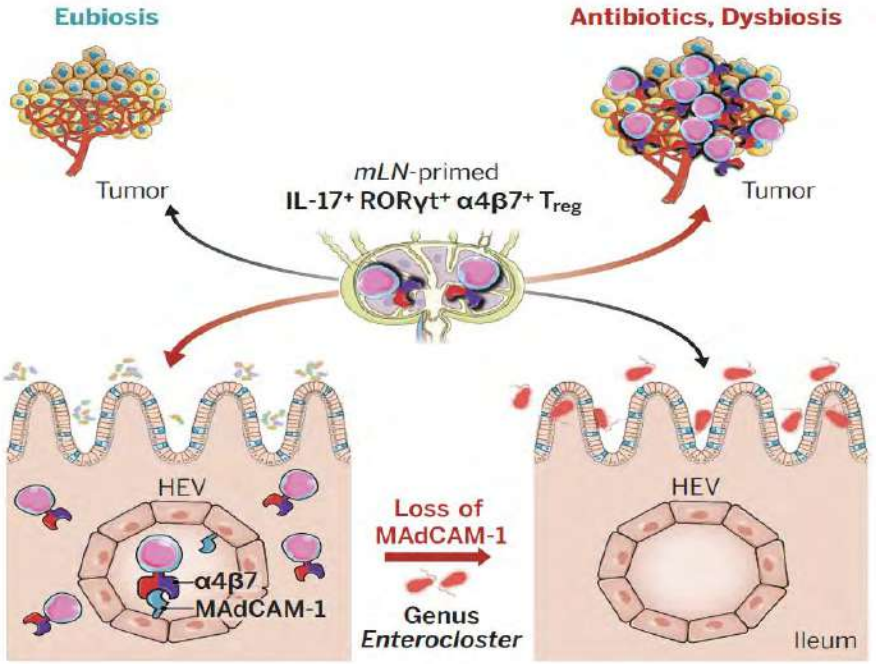


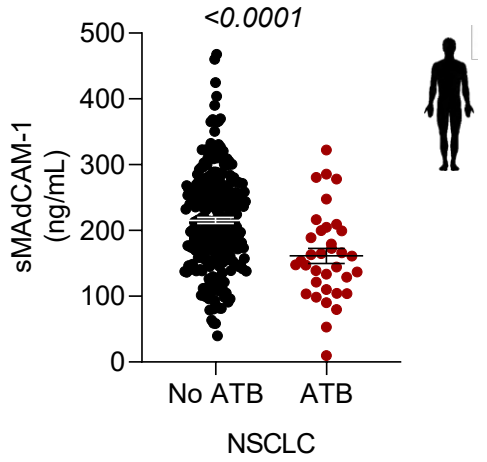
HR: 1.71 (1.6-1.84

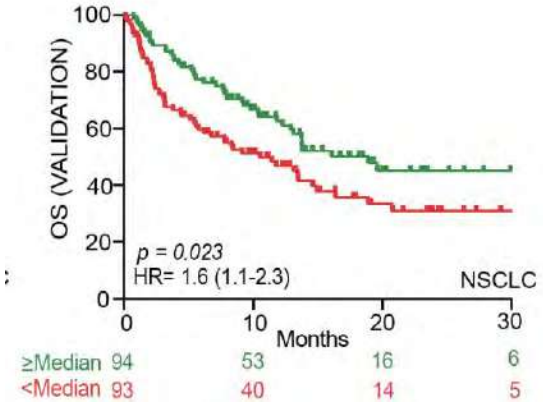
Routy et al., Science 2018/Derosa et al., Annals of Oncology 2018/ Elkrief et al., Nature Precision Oncol 2024

Mechanisms of ATB-related dysbiosis: elimination of beneficial bacteria and downregulation of gut checkpoint MAdCAM-1





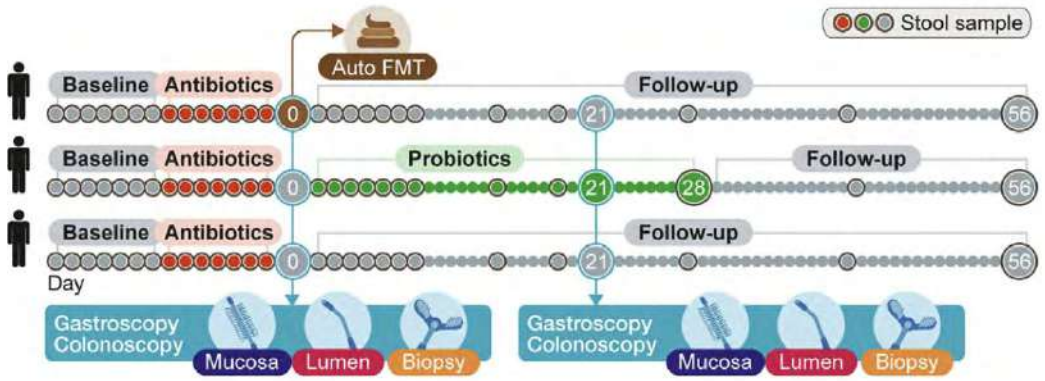


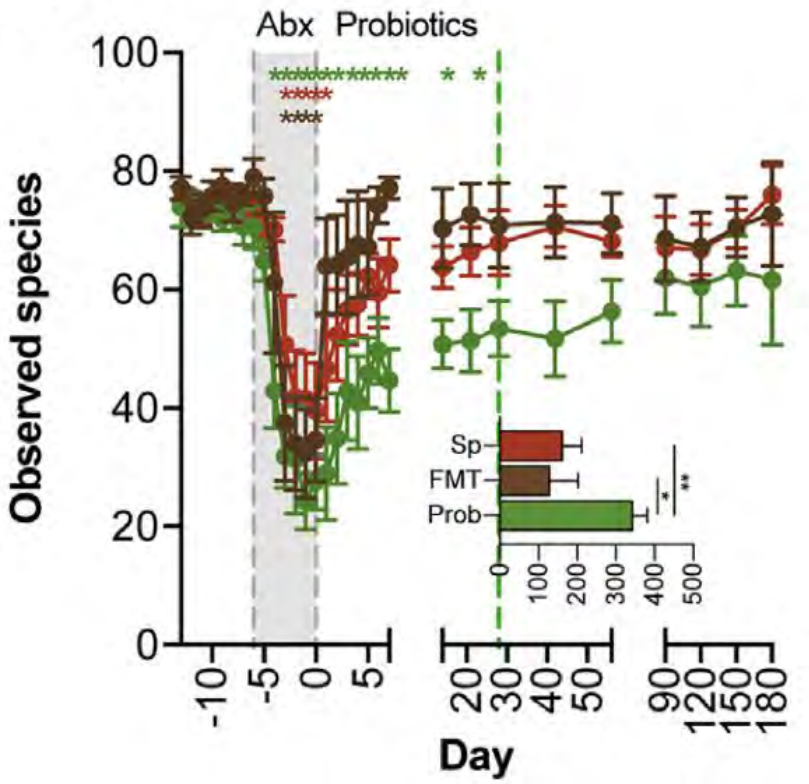


Elkrief et al., ASCO 2024 educational book

Fidelle et al., Science 2023

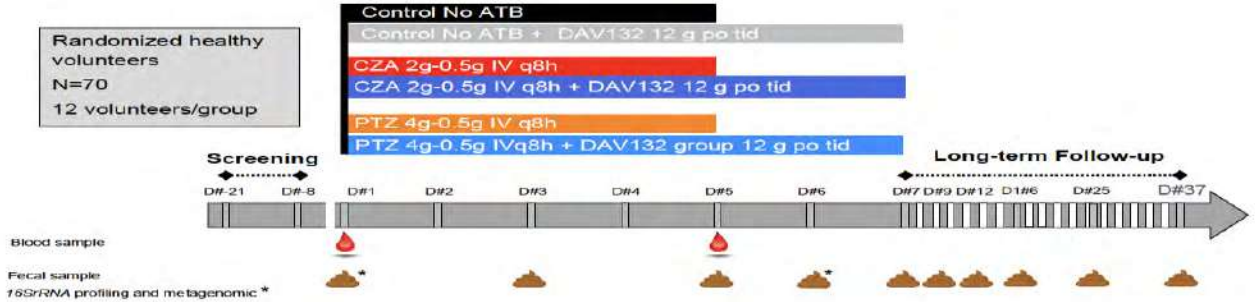
Overcoming ATB-related dysbiosis is more complicated than expected – no role of probiotics

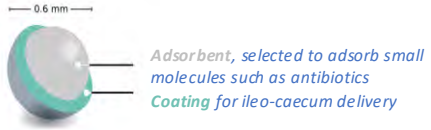


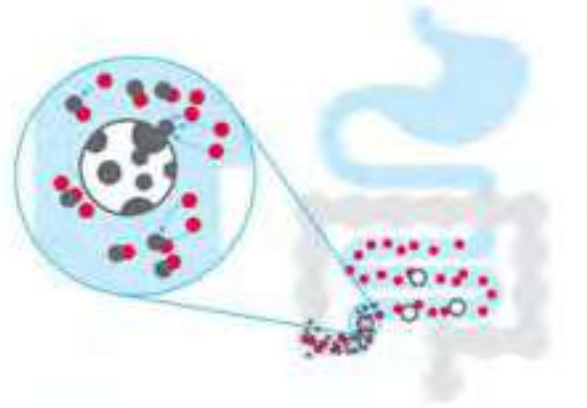


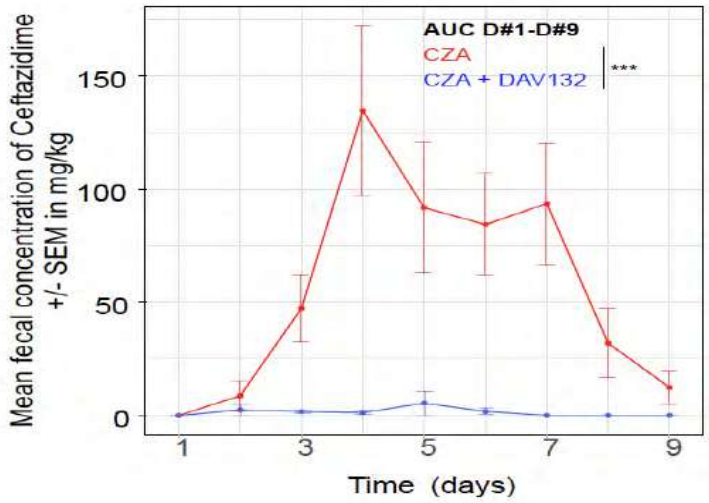
Suez et al., Cell 2018

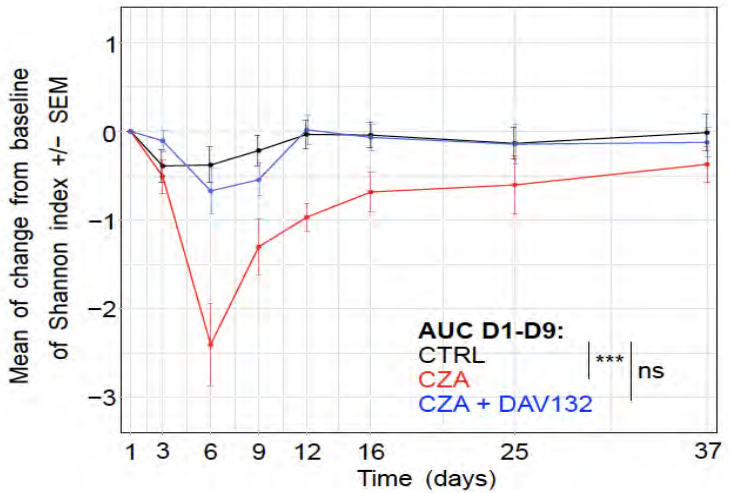
Absorbing ATB in the small intestine with a coated charcoal capsules – a potential future strategy to overcome ATB-related dysbiosis





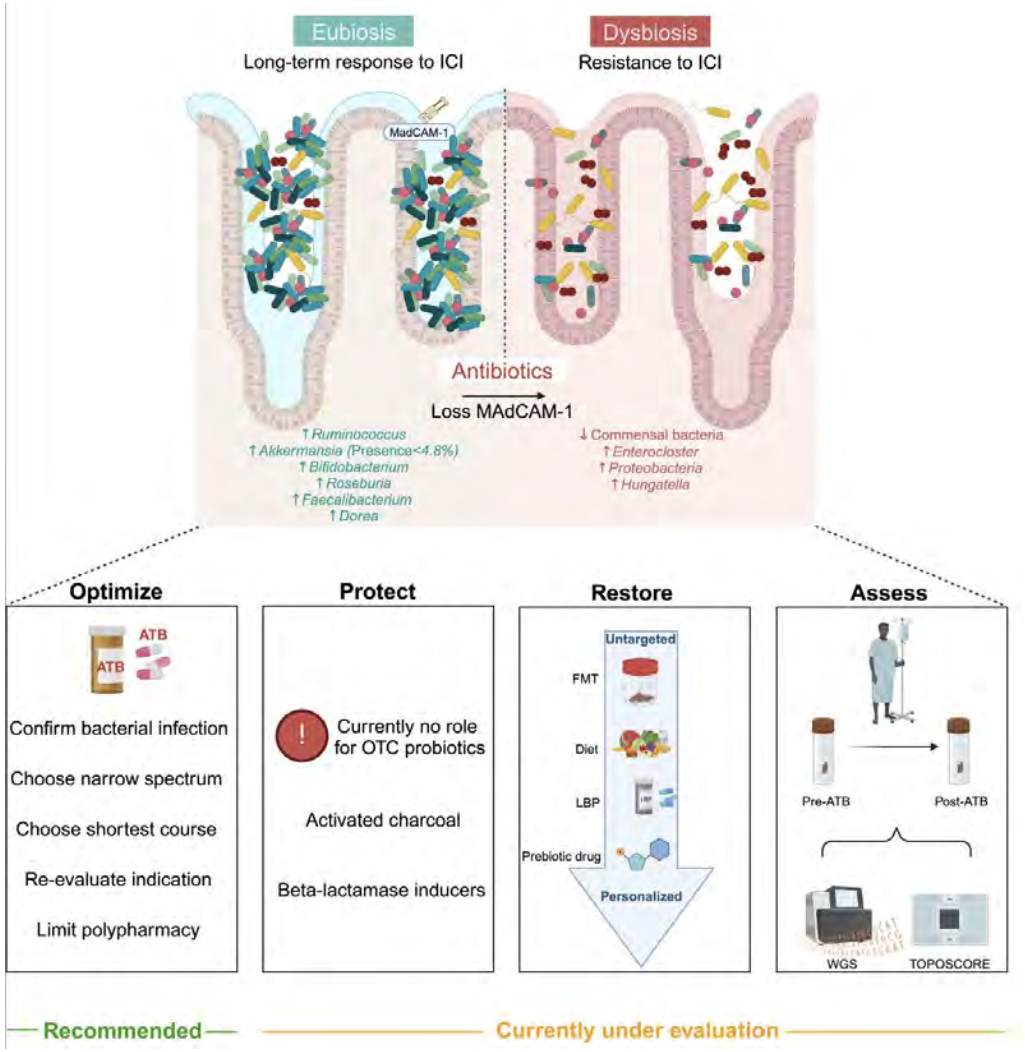






Messaoudene et al. Nat Med 2024

Implementation of judicious ATB stewardship decreased ATB prescriptions in one Canadian oncology centre



Elkrief et al., ASCO 2024 educational book

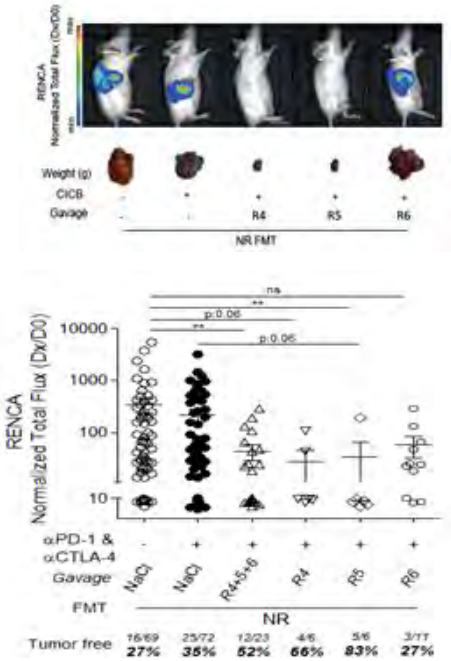
Study	N ATB	N Total	% ATB
Stokes et al. 2021	762	3634	21
Hopkins et al. 2022	194	2723	7
Cortellini et al. 2021	131	950	14
Lu et al. 2020	129	340	38
Jung M et al. 2021	114	228	50
Kim CG et al. 2023	67	152	44
Kim CG et al. 2023	57	123	46
Derosa et al. 2018	48	239	20
Pinato et al. 2019	29	119	24
Buti et al. 2020	27	217	12
Vitorino et al. 2021	24	114	21
Chambers et al. 2021	23	101	23
Sen et al. 2018	19	172	11
Pinato et al. 2019	17	38	45
Akashi et al. 2023	16	41	39
Derosa et al. 2018	16	121	13
Kim JH et al. 2022	15	60	25
Greally et al. 2019	14	161	9
Hakozaki et al. 2019	13	90	14
Ruiz-Banobre et al. 2021	11	119	9
Elkrief et al. 2019	10	74	14
Pinato et al. 2019	6	39	15
Shen et al. 2021	4	36	11
Cortellini et al. 2021	47	302	16
Clark et al. 2020	11	77	14
Total			22%

ATB exposure 1 month prior to ICI	
2018-2023 Meta-anlysis n=3634	**Local practice since 2018 n=417**
762 (22%)	40 (9.6%)

Elkrief et al., Revision Nature Precision Oncol 2024

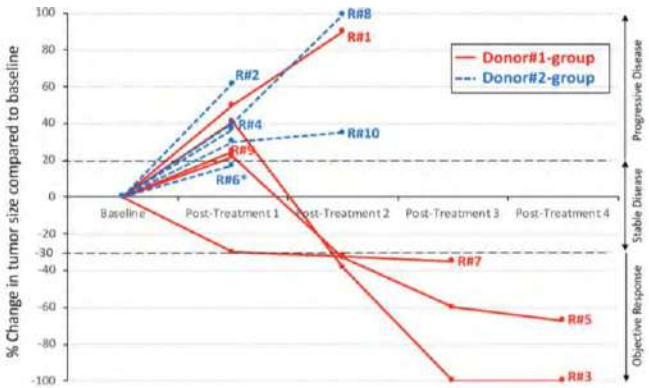
First-in-human studies demonstrate potential of FMT to reduce resistance to IO in melanoma

Pre-clinical model of FMT
Derosa, Routy Eur Urol 2020



Phase I: Baruch, Science 2021
2nd line FMT + single-agent anti-PD-1

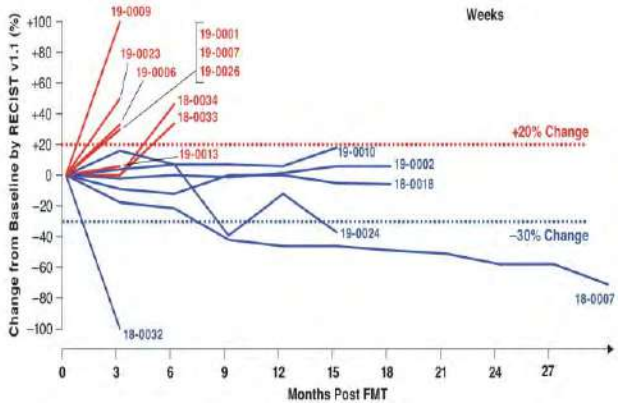
n=10 **ORR 30%**



2 donors with ICI-responsive melanoma
(2 CRs)

Phase I: Davar, Science 2021
2nd line FMT + single-agent anti-PD-1

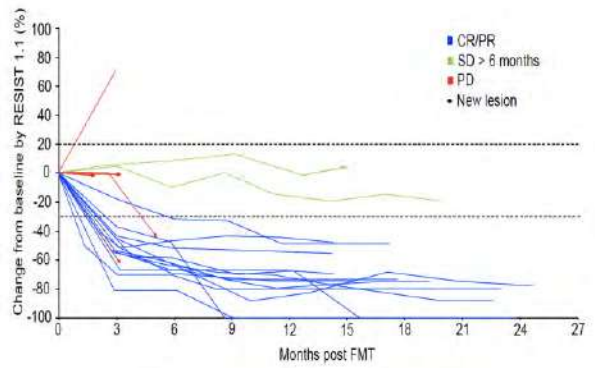
n=15 **ORR 20%**



7 donors with ICI-responsive melanoma,
4 in CR and 3 in PR

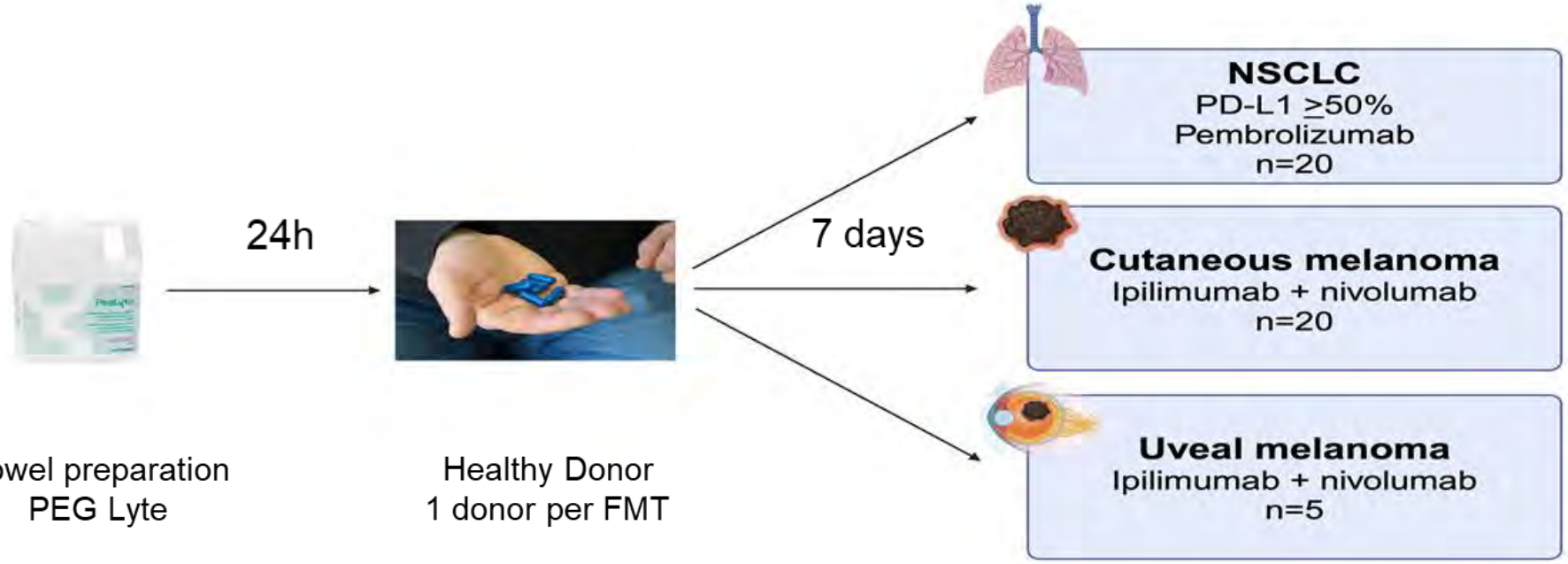
Phase I: MiMic, Routy, Nat Med 2023
1st line FMT + single-agent anti-PD1

n=20 **ORR 65%**



3 healthy volunteer donors

MT-LUMINate clinical trial design NCT04951583: FMT + IO in the first-line setting



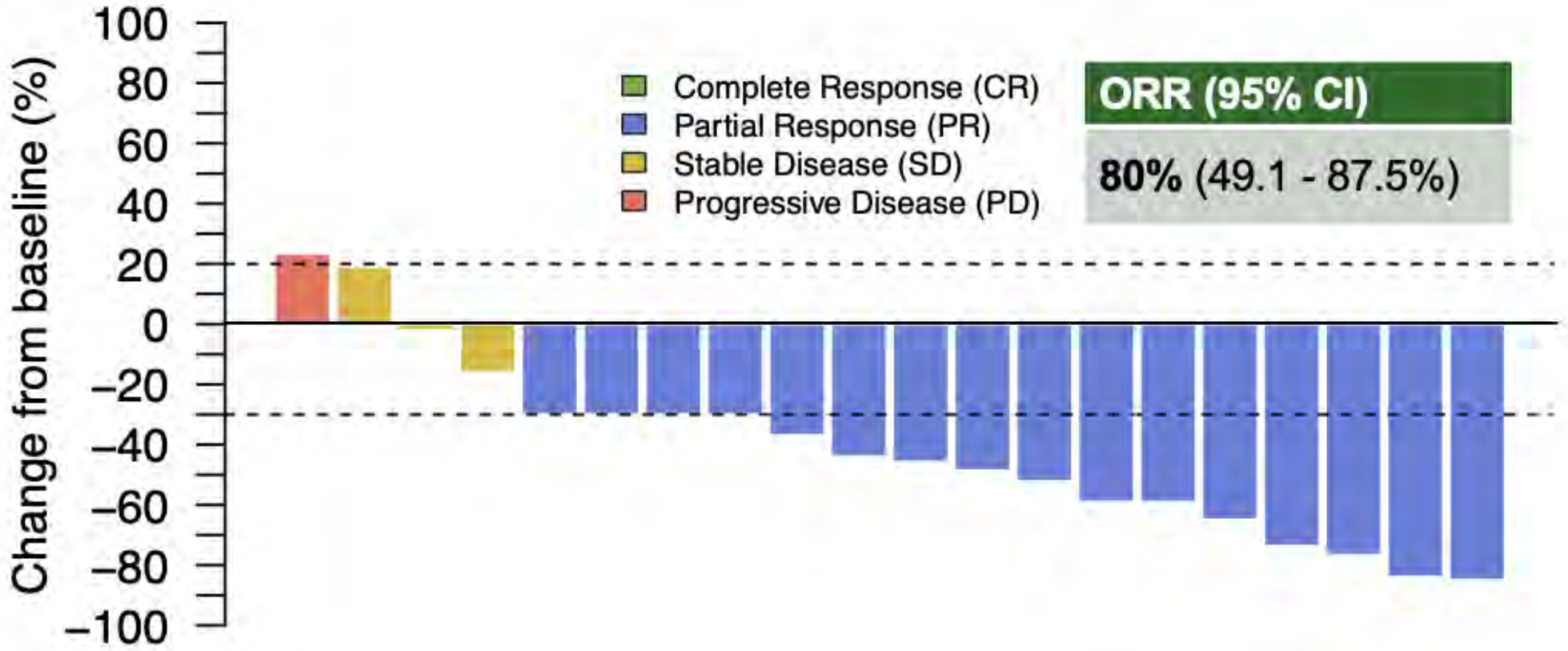
Primary objective: Objective response rate (ORR)

Secondary objective: Progression free survival , Overall Survival, Safety, Donor-host similarity

2024 World Conference on Lung Cancer

FMT-LUMINate NSCLC cohort meets primary endpoint

Pre-specified primary endpoint for positive study ORR 64%



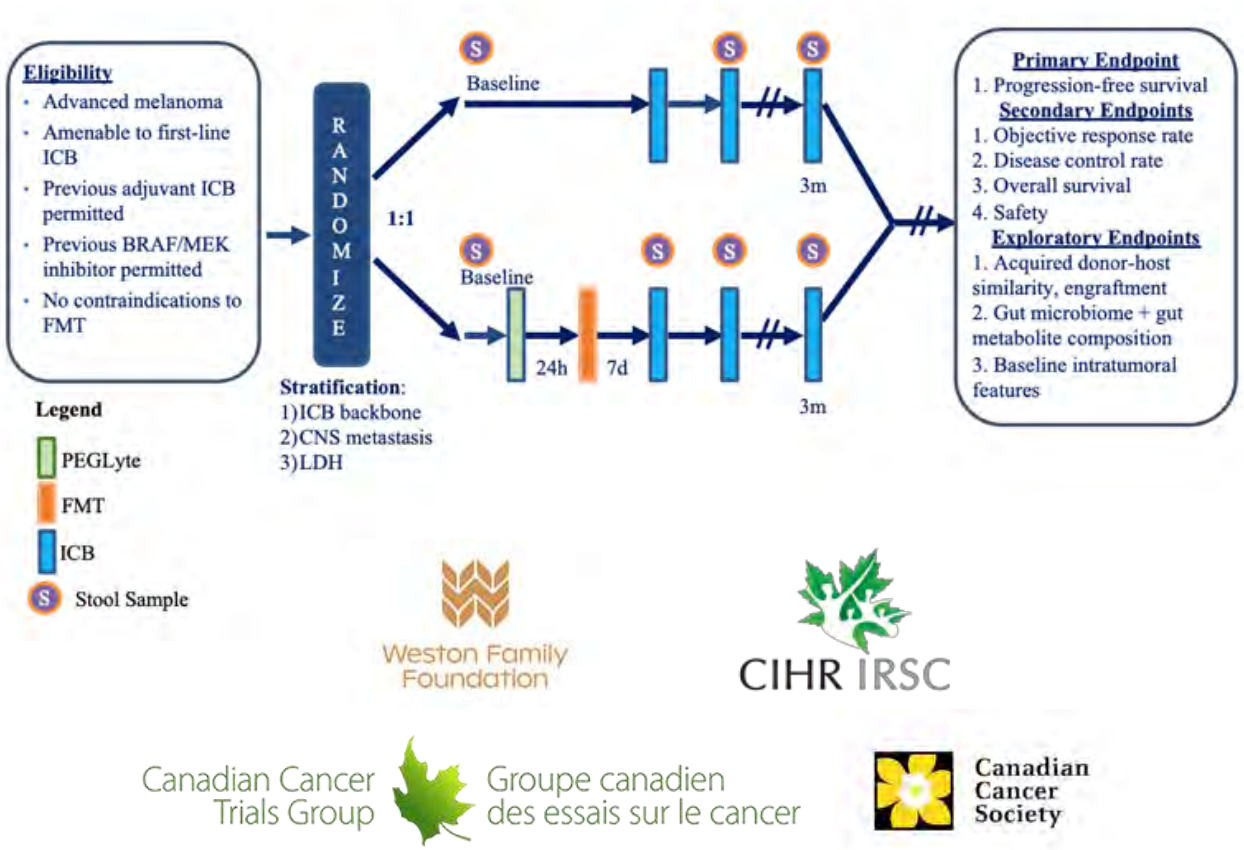
No grade 3 toxicities in NSCLC cohort, expect ~20% with single-agent anti-PD-1

ADVERSE EVENT	Any grade	Grade 1	Grade 2	Grade 3-4
Any AE	15 (78.9%)	13 (68.4%)	6 (31.6%)	0 (0.0%)
Abdominal pain	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
ALT increased	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Alopecia	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Anemia	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Arthritis	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Bullous dermatitis	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Changes in stool appearance	3 (15.8%)	3 (15.8%)	0 (0.0%)	0 (0.0%)
Diarrhea	3 (15.8%)	3 (15.8%)	0 (0.0%)	0 (0.0%)
Edema	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Eosinophilia	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Esophageal pain	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Fatigue	5 (26.3%)	4 (21.1%)	1 (5.3%)	0 (0.0%)
Hypothyroidism	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Myalgia	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Nausea	2 (10.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
Pain	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Pneumonitis	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)
Pruritus	2 (10.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
Rash acneiform	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Rash maculopapular	4 (21.1%)	4 (21.1%)	0 (0.0%)	0 (0.0%)
Rash pustular	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Vomiting	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)

FMT represents the first success in microbiome interventions in the field of oncology; stay tuned for more results (ASCO, AACR, ESMO 2025)

NCT	Cancer + Type of IO	Bowel preparation	FMT administration	Source of capsules	N=	Primary outcome	Status/Country
NCT04951583	Advanced cutaneous and uveal melanoma (1L) Anti-PD-1 + Anti-CTLA-4	Polyethylene glycol	Oral capsules	Healthy volunteer	25	Objective response rate	Recruiting Canada
NCT04988841	Melanoma (1L) Anti-PD-1 + Anti-CTLA-4	Enema (MoviPrep and Normacol)	Enema (performed every 3 weeks after every 4 weeks. Total=7)	MaaT013 vs Placebo	60	The safety during 23wks with MaaT013	Recruiting France
NCT03353402	Melanoma (2L) Anti-PD-1	N/A	Colonoscopy + oral capsules	Patients with metastatic melanoma who responded to ICI	40	Incidence of FMT-related Adverse Events	Closed Israel
NCT03817125	Metastatic melanoma Anti-PD-1	N/A	Oral capsules	N/A	14	Incidence of irAEs	Completed United States
NCT04577729	Melanoma stage III and IV Anti-PD-1	N/A	N/A	Patients responding to ICI and autologous FMT	60	Progression-free survival	Recruiting Austria
NCT05251389	Melanoma Stage III and IV Anti-PD-1	N/A	Esophagogastroduodenoscopy	Patients responding to ICI x non-responding to ICI	24	Efficacy FMT, defined as clinical benefit	Recruiting Netherlands
NCT05286294	Melanoma stage IV + CSCC + RCC	N/A	N/A	Patients responding to ICI	20	Safety evaluation of FMT	Recruiting Norway
NCT04951583	Lung (1L)- NSCLC Anti-PD-1	Polyethylene glycol	Oral capsules	Healthy volunteer	70	Objective response rate	Recruiting Canada
NCT04924374	Lung (1L and refract.) Anti-PD-1	None	Oral capsules	Healthy volunteer	20	Safety	Recruiting Spain
NCT05502913	Lung metastatic (1L) Anti-PD-1	N/A	Oral capsules (10)	Patients responding to ICI	80	Progression-free Survival	Not yet Recruiting Israel
NCT04729322	Colorectal cancer (2L) Anti-PD-1	Flagyl, Vancomycin, Neomycin	Colonoscopy + oral capsules	Responding patients to ICI	15	Efficacy of ICI with FMT	Recruiting United States
NCT04130763	GI (2L) Anti-PD-1	N/A	Oral capsules (3 days/ once every 2 weeks for up to 6 times)	Healthy volunteer	10	Objective Response Rate	Unknown China
NCT04975217	Resectable pancreatic ductal ADC	Colonoscopy	Oral capsules during Colonoscopy	N/A	10	Incidence of irAEs	Recruiting United States
NCT04758507	Renal cell carcinoma (1L) Anti-PD-1 + Anti-CTLA-4	N/A	Colonoscopy + oral capsules (8) 3-6 months after first FMT	Donors who are responding to ICI or Placebo	50	Patients in complete response	Recruiting Italy
NCT04163289	Renal cell carcinoma (1L) Anti-PD-1 + Anti-CTLA-4	Polyethylene glycol	Oral capsules (1 day every month for 3 months)	Healthy volunteer	20	Occurrence of immune-related-colitis associated with ICI treatment	Recruiting Canada
NCT04264975	Solid Carcinoma	N/A	Solution fecal into the intestinal tract	N/A	60	Overall response rate	Recruiting Korea
NCT04116775	Prostate 1/ metastatic Anti-PD-1 +Enzalutamide	N/A	Endoscopy	Patients responding to ICI	32	Cancer activity of FMT from R to NR	Recruiting United States
NCT05273255	Cancers stage IV + IO specific	N/A	Colonoscopy	Patients responding to ICI	30	Change in the intestinal microbiome community	Recruiting Switzerland
NCT04056026	Mesothelioma Anti-PD-1	N/A	Colonoscopy (600cc)	Healthy family donor	1	Progression free survival	Completed United States

CSCC: Cutaneous Squamous Cell carcinoma; **CTLA-4**: cytotoxic T-lymphocyte-associated antigen 4; **ICI**: Immune-checkpoint inhibitors; **irAEs**: immune-Related Adverse Events; **MaaT013**: a microbiome restoration biotherapeutic, produced by MaaT Pharma, and composed of pooled-donor, full-ecosystem intestinal microbiome; **PD-1**: programmed cell death protein; **RCC**: Renal cell carcinoma



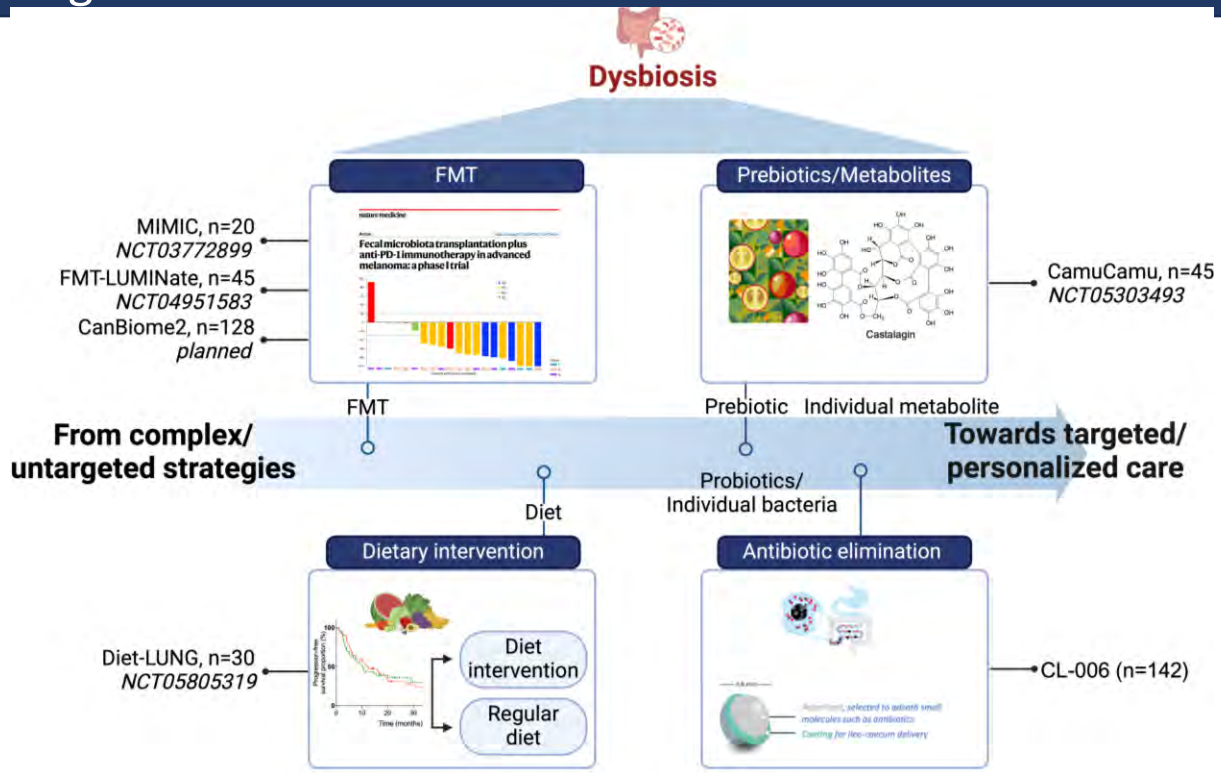
Jamal et al., Semin Immunol 2023

However FMT as several limitations:

1. Mechanism and bacterial compatibility between donor-recipient
2. Scalability
3. Source of donors
4. Risk for pathogens infections

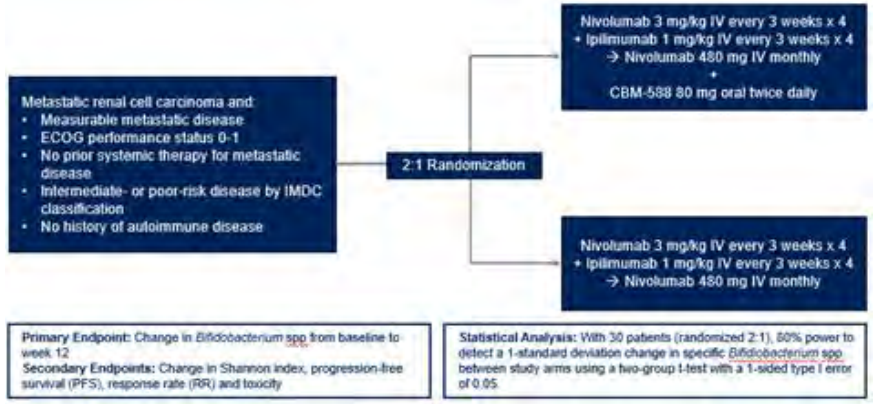
Dec 2024- FDA only allowed FMT use in the context of clinical trials

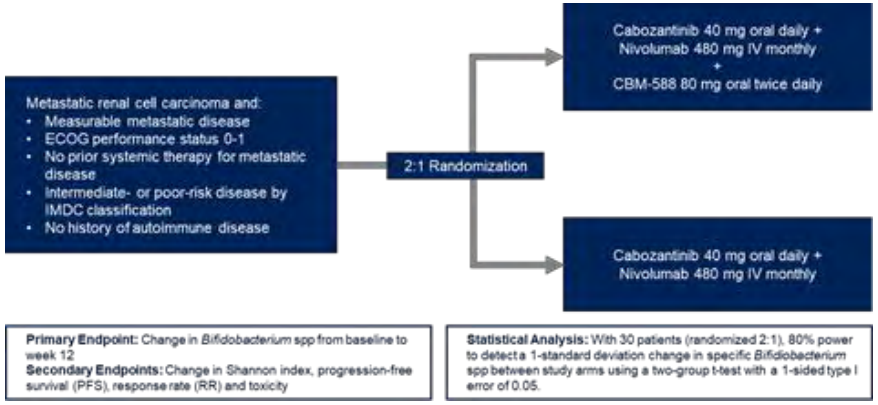
Second generation and tailored microbiome interventions are required

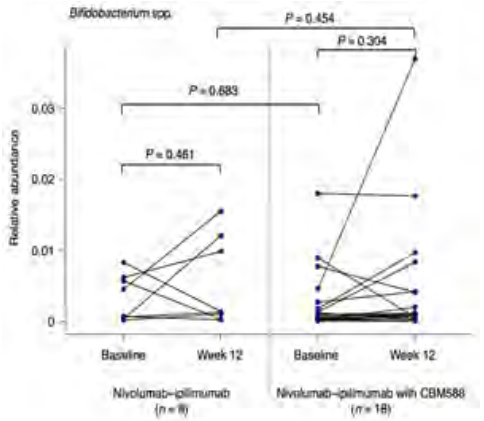


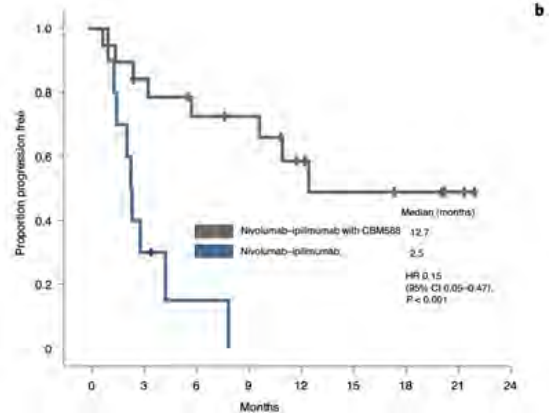
Zitvogel et al., Nat Med: in press

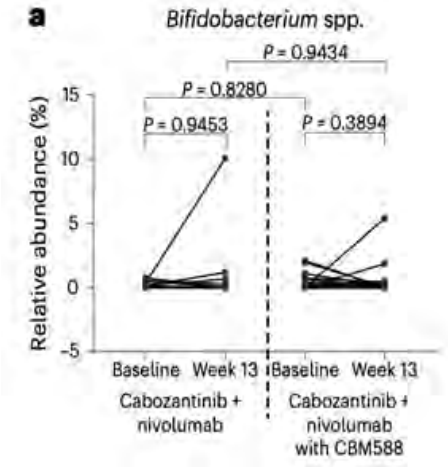
Probiotic intervention in combination with IO; first success with Clostridium Butyricum-588 in renal cell carcinoma

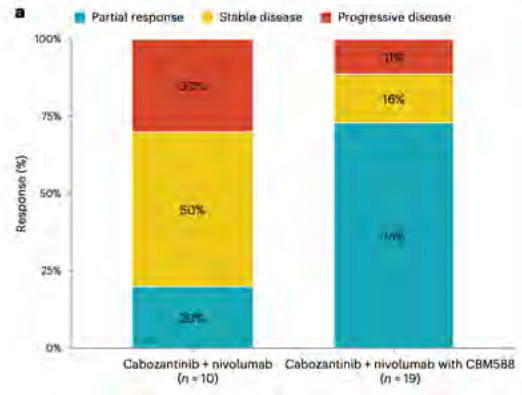










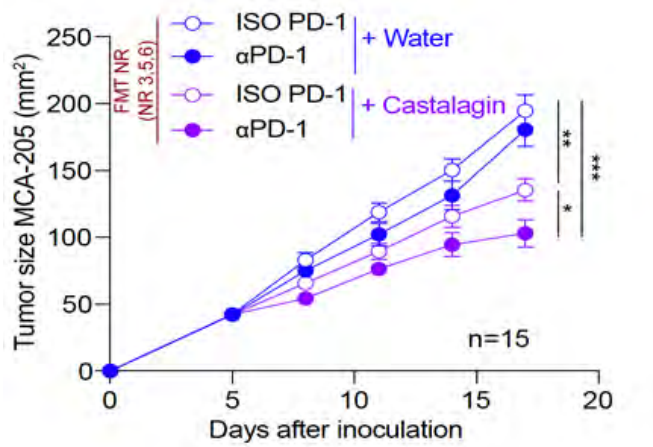


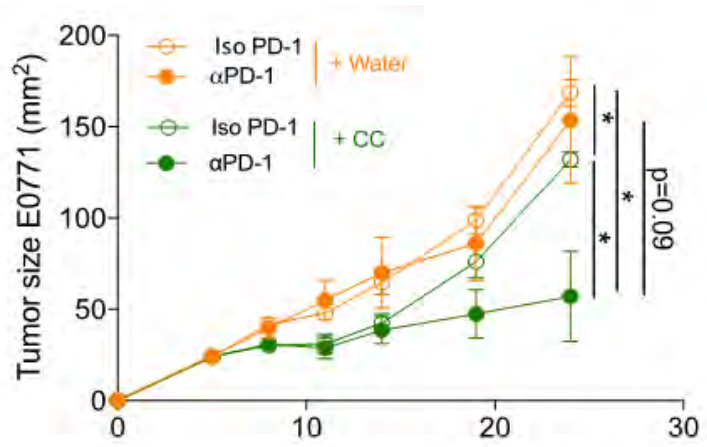
Dizman et al., Nat Med 2022 /Ebrahimi et al., Nat Med 2024

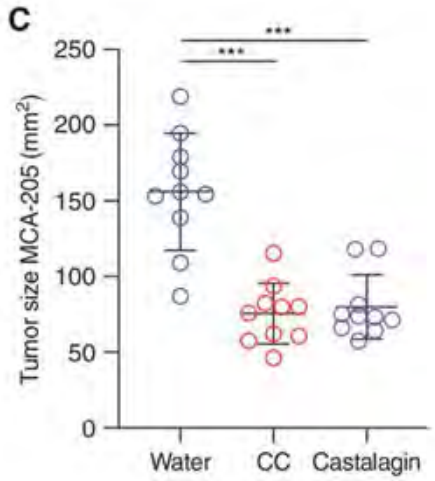
SWOG trial Phase III assessing CBM588 will open soon

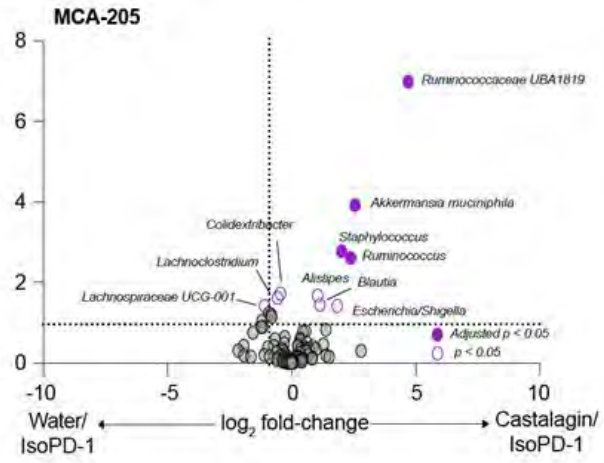
ESMO ON AIR

Castalagin polyphenol extracted from Camu-Camu berry provides an additive effect to anti-PD-1 activity and beneficially shifts microbiome composition





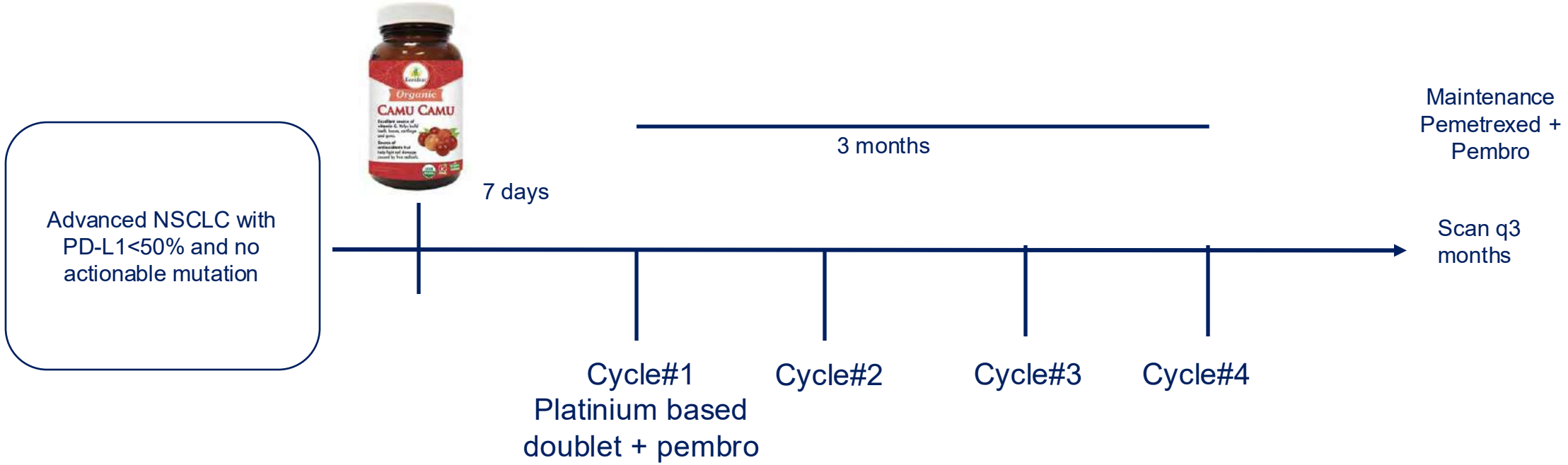




ESMO ON AIR

Messaoudene et al., Can Disco 2022

Phase I trial of Camu-Camu plus platinum-based chemo-immunotherapy in NSCLC (NCT05303493) - completed



Efficacy data: AACR 2025
Outcome: ESMO 2025

ESMO ON AIR

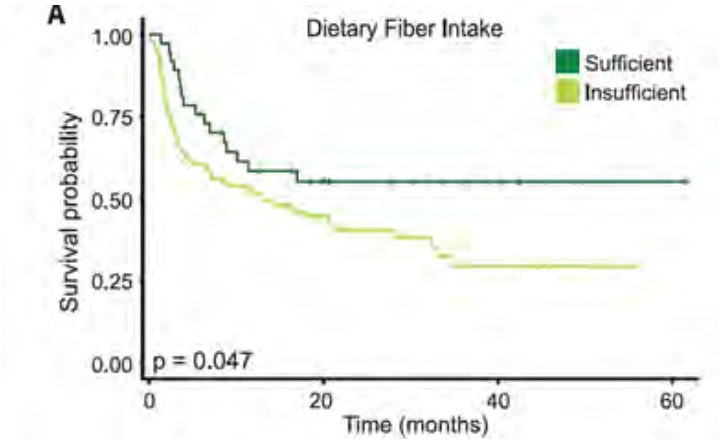
Randomize trial completed in RCC
ESMO 2025

City of Hope

ESMO

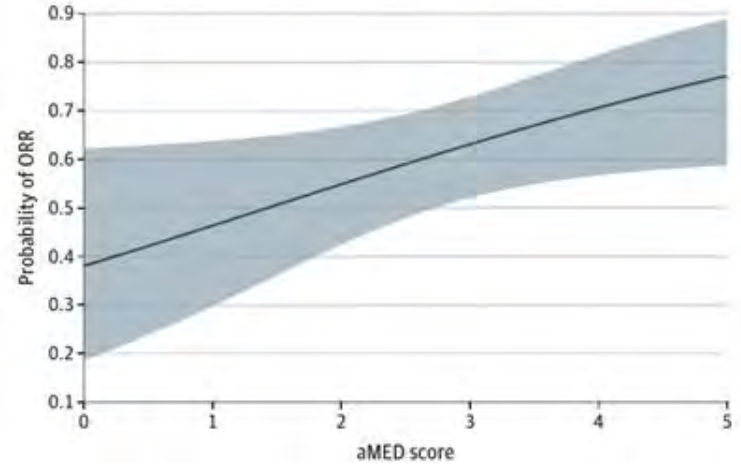
Correlation between diets (fiber vs Mediterranean) and outcomes in melanoma and NSCLC treated with IO

Melanoma : Fiber



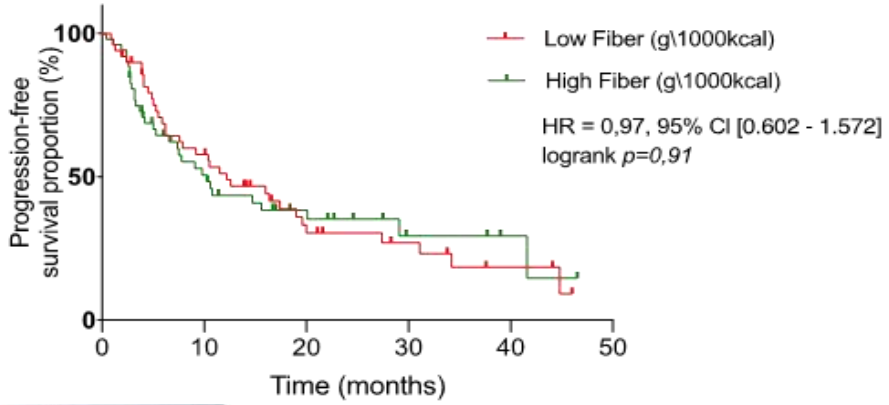
Spencer et al., Science 2022

Melanoma: Mediterranean diet

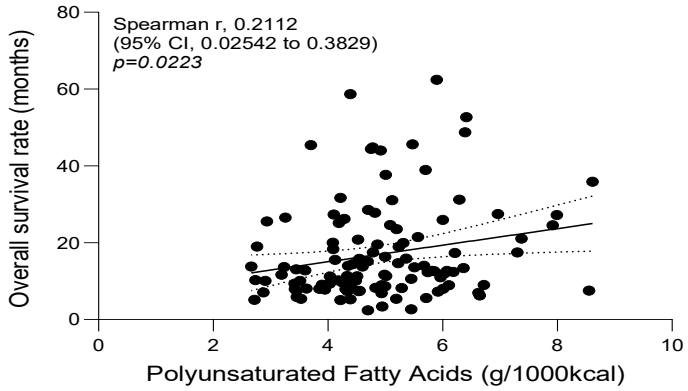


Bolte et al., Jama Onc 2023

NSCLC =104 patients: Fiber



NSCLC =104 patients: Mediterranean diet



ESMO ON AIR

NSCLC results will be updated ASCO with matching metagenomics

CONQUER CANCER® MERIT AWARD RECIPIENT

ESMO

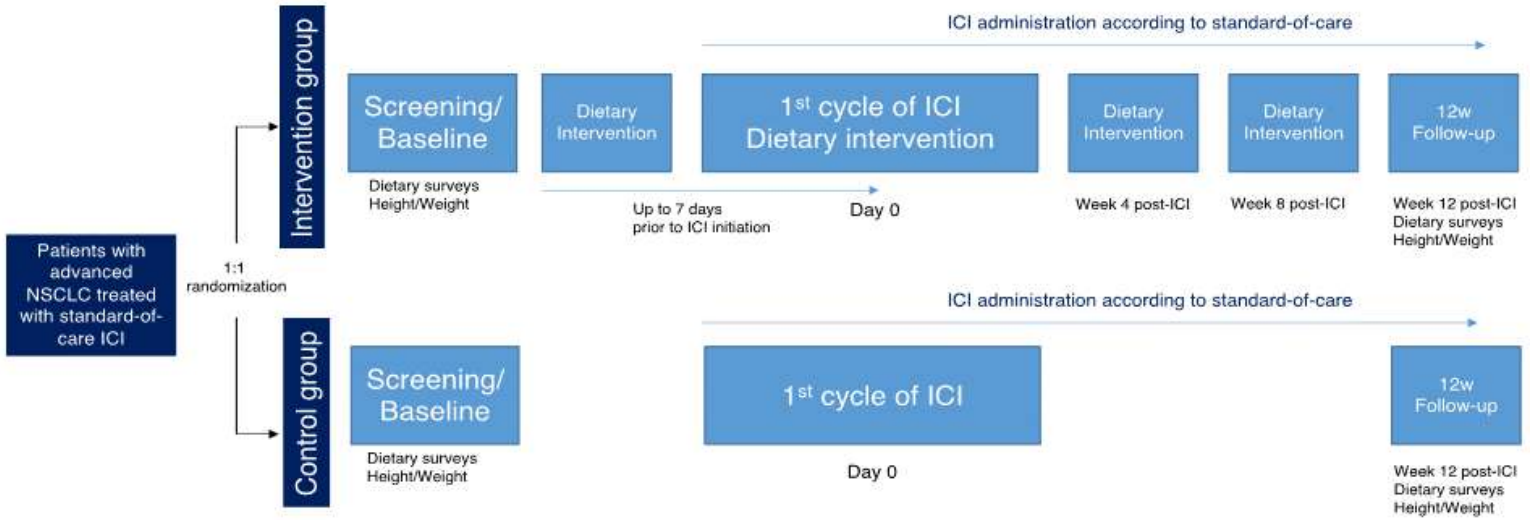
In absence of recommendations we launched a randomized trial evaluating dietary intervention

Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline

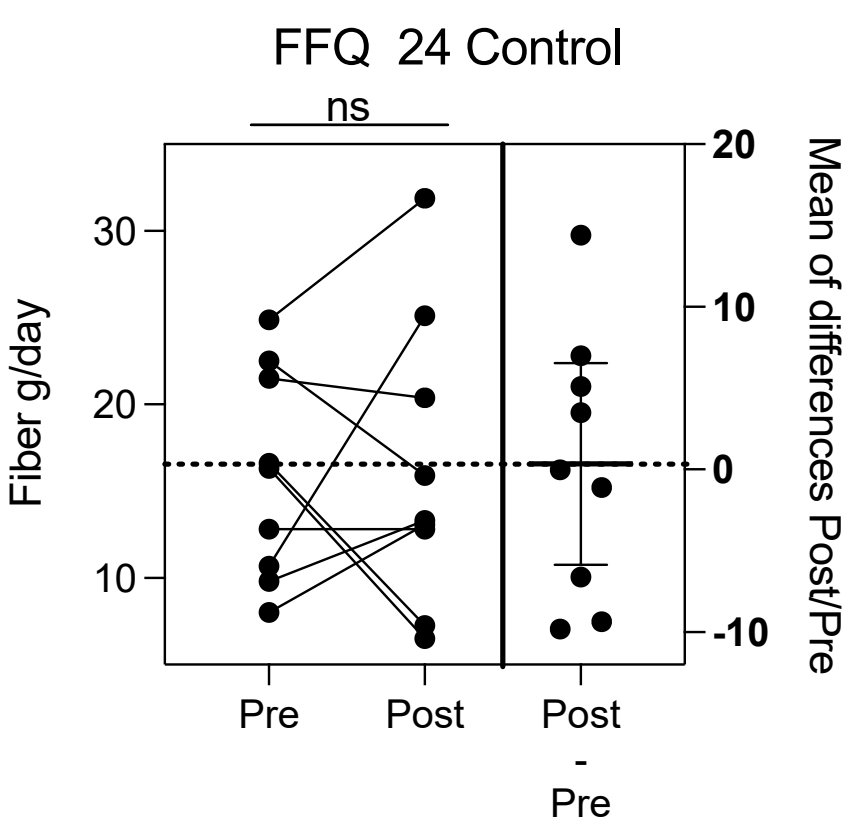
Jennifer A. Ligibel, MD[1]; Kari Bohlke, ScD[2]; Anne M. May, PhD[3]; Steven K. Clinton, MD, PhD[4]; Wendy Demark-Wahnefried, PhD, RD[5]; Susan C. Gilchrist, MD, MS[6]; Melinda L. Irwin, PhD, MPH[7]; Michele Late[8]; Sami Mansfield, BA[9]; Timothy F. Marshall, PhD, MS[10]; Jeffrey A. Meyerhardt, MD, MPH[1]; Cynthia A. Thomson, PhD, RD[11]; William A. Wood, MD, MPH[12]; and Catherine M. Alfano, PhD[13]

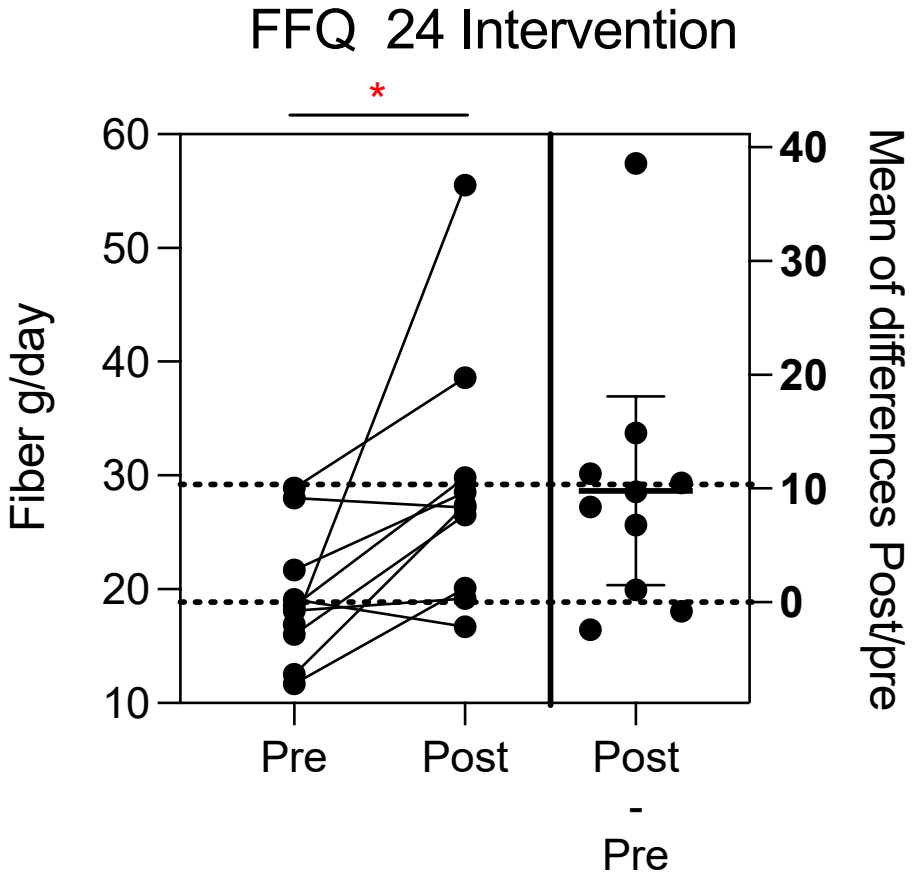
Recommendation 2.1. There is currently insufficient evidence to recommend for or against dietary interventions such as ketogenic or low-carbohydrate diets, low-fat diets, functional foods, or fasting to improve outcomes related to QoL, treatment toxicity, or cancer control.

Recommendation 2.2. Neutropenic diets (specifically diets that exclude raw fruits and vegetables) are not recommended to prevent infection in patients with cancer during active treatment (Type: evidence based, harms likely to outweigh benefits; Evidence quality: low; Strength of recommendation: weak).



Preliminary analysis: dietary intervention successfully increase fiber intake





Conclusions

- The gut microbiome represents a biomarker of response to immunotherapy for patients with NSCLC. However, still not ready for routine oncology practice because metagenomics is limited by long turnaround time. Therefore need for more rapid tools in the clinic (qPCR) and validation of signature such as TOPOscore

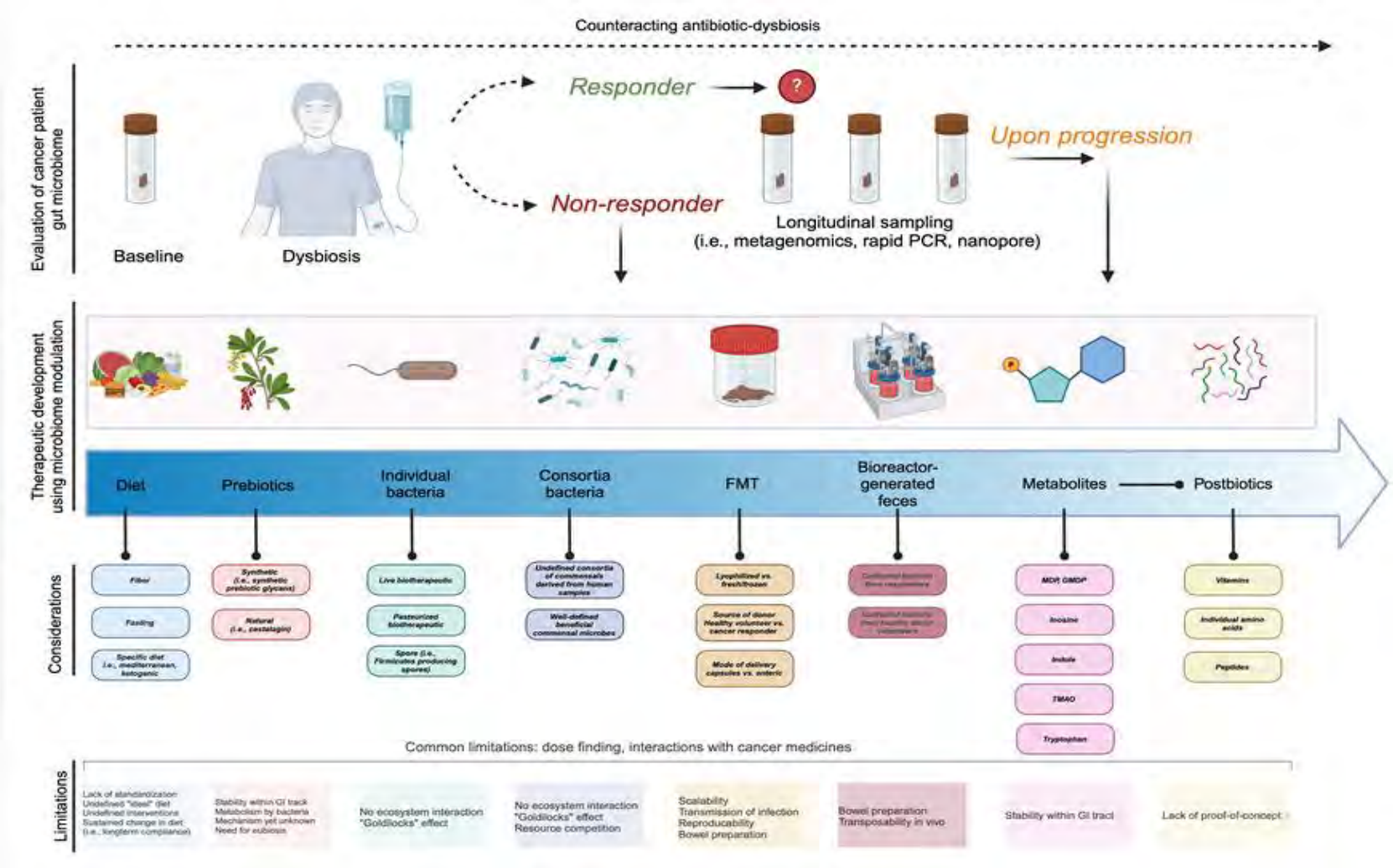
- The microbiome needs to be implemented in routine oncology practice with the judicious use of antibiotics

- FMT represents the first proof-of-concept that the microbiome can improve IO response in melanoma and now NSCLC

- Several personalized strategies are currently under evaluation (probiotics, prebiotics, diet)

- Time for patient stratification and tailor-made microbiome interventions

Road map towards more personalized approaches in microbiome interventions



Elkrief and Routy et al., Nature Review Drug Discovery: In press

Acknowledgements

Routy Lab
Meriem Messaoudene
Sreya Duttagupta
Wiam Belkaid
Mayra Ponce
Katerina Prifti
Julie Malo
Souad Maatouk
Jade Maillou
Yongjia Hu
Afnan Al-Saleh
Babacar Mbaye
Myriam Benlaifaoui
Antoine Desilets
Catherine Lehoux
Marjorie Drolet
Xiaojing Dong
Souad Mattouk

Elkrief Lab
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Michal Punčochář

CIHR IRSC
Canadian Cancer Society
INSTITUT DU CANCER DE MONTRÉAL
Weston Family Foundation
ONCOBIOME Microbiota against cancer International research program
Fonds de recherche Santé Québec
THE TERRY FOX FOUNDATION
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