

2ND LINE TREATMENT FOR ADVANCED NSCLC

A moving field

Name

Martin Reck

Department of Thoracic Oncology

Airway Research Center North, German Center for Lung Research

LungenClinic, Germany



DECLARATION OF INTERESTS

Martin Reck

Honoraria for lectures and consultancies (self fee) from:

Amgen, AstraZeneca, Beigene, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Roche, Sanofi

Institutional Support for clinical trials from:

BMS, Boehringer-Ingelheim

Research funding for clinical trials paid to my institution by:

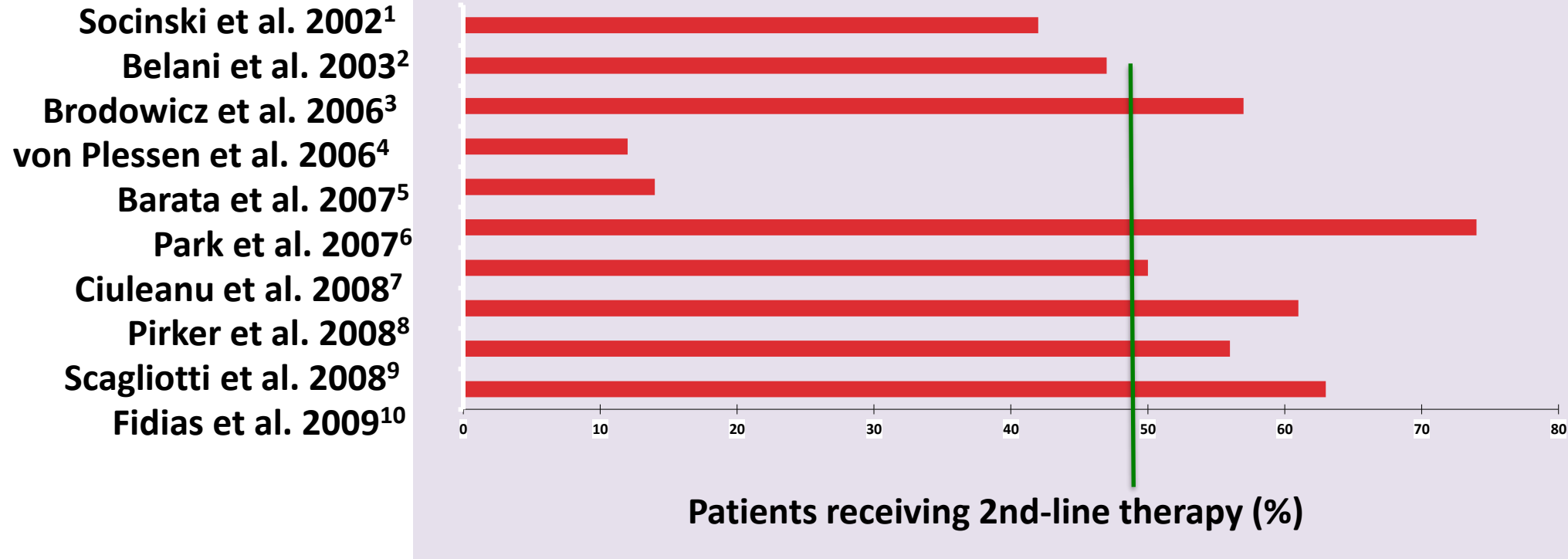
Amgen, AstraZeneca, Beigene, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Lilly, Merck, Mirati, MSD, Novartis, Pfizer, Roche, Gilead

CHALLENGES IN SECOND-LINE TREATMENT I



- Pretreated Patients
- Reduced performance status: Tolerability becomes more important.
- Low response rates: Tumor control becomes important.
- More symptomatic patients: Symptom control and symptom improvement become important .
- It is hard to show any improvement in efficacy...

SECOND-LINE TREATMENT – CHALLENGES II



In recent studies, approximately 50% of patients did not receive second-line therapy

¹J Clin Oncol 2002;20:1335–43; ²J Clin Oncol 2003;21:2933–39; ³Lung Cancer 2006;52:155–63; ⁴Br J Cancer 2006;95:966–73; ⁵J Thoracic Oncol 2007;2(Suppl. 4):S666 Abs. P2-235; ⁶J Clin Oncol 2007;25:5233–39; ⁷J Clin Oncol 2008;26(Suppl. 15S):426s Abs. 8011; ⁸J Clin Oncol 2008;26(Suppl. 15S):6s Abs. 3; ⁹J Clin Oncol 2008;26:3543–51; ¹⁰J Clin Oncol 2009;27:

THE THREE PERIODS OF SECOND-LINE TREATMENT



- Before Immunotherapy

SECOND LINE TREATMENT NSCLC – FIRST RESULTS



	Docetaxel	Pemetrexed	Erlotinib		
RR, %	5.0–12.0	7.1–11.8	7.9–9.0		
Median PFS, m	2.0–3.1	2.6–2.9	2.2–3.6		
Median OS, m	5.7–8.0	6.7–8.9	6.7–7.9		
1-year OS,%	28.7–37.0	29.7–38.5	31.0–35.7		

Shepherd, et al. JCO 2000; Fossella, et al. JCO 2000; Ramlau, et al. JCO 2006; Paz-Ares, et al. BJC 2008
 Kim, et al. Lancet 2008; Krzakowski, et al. JCO 2010; Hanna, et al. JCO 2004, Cullen, et al. Ann Oncol 2008
 Shepherd, et al. NEJM 2005; Vamvakas, et al. ASCO 2010; Ciuleanu, et al. IASLC Chicago 2010; Reck M , et al, Lancet Oncology 2014; Garon E et al, Lancet 2014; Soria JC, Lancet Oncology 2015

SECOND LINE TREATMENT NSCLC – UPDATED RESULTS



	Docetaxel	Pemetrexed	Erlotinib	Afatinib (SCC)	Docetaxel + Ramucirumab (NSCLC)	Docetaxel + Nintedanib (NSCLC)
RR, %	5.0–12.0	7.1–11.8	7.9–9.0	6	23	4.4 Central Review
Median PFS, m	2.0–3.1	2.6–2.9	2.2–3.6	2.4	4.5	3.4
Median OS, m	5.7–8.0	6.7–8.9	6.7–7.9	7.9	10.5	10.1
1-year OS,%	28.7–37.0	29.7–38.5	31.0–35.7	nr	nr	nr

Shepherd, et al. JCO 2000; Fossella, et al. JCO 2000; Ramlau, et al. JCO 2006; Paz-Ares, et al. BJC 2008
 Kim, et al. Lancet 2008; Krzakowski, et al. JCO 2010; Hanna, et al. JCO 2004, Cullen, et al. Ann Oncol 2008
 Shepherd, et al. NEJM 2005; Vamvakas, et al. ASCO 2010; Ciuleanu, et al. IASLC Chicago 2010; Reck M, et al, Lancet Oncology 2014; Garon E et al, Lancet 2014; Soria JC, Lancet
 Oncology 2015

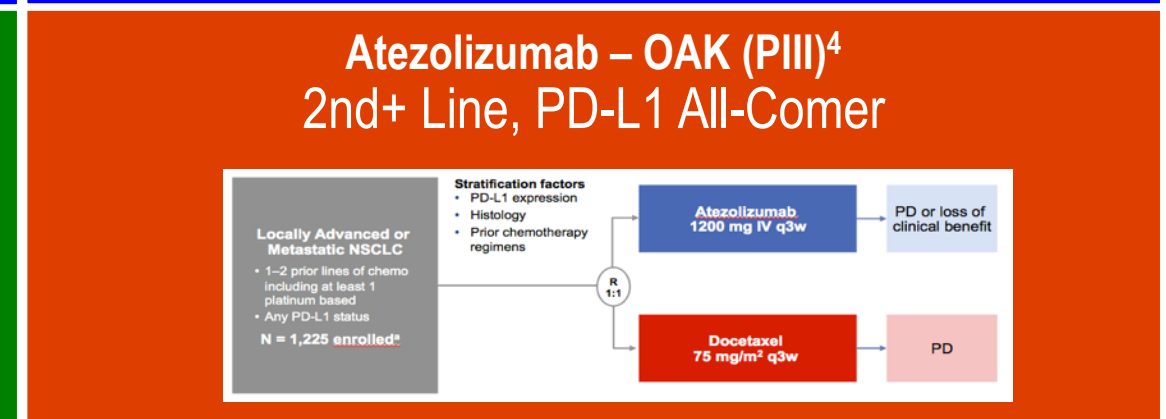
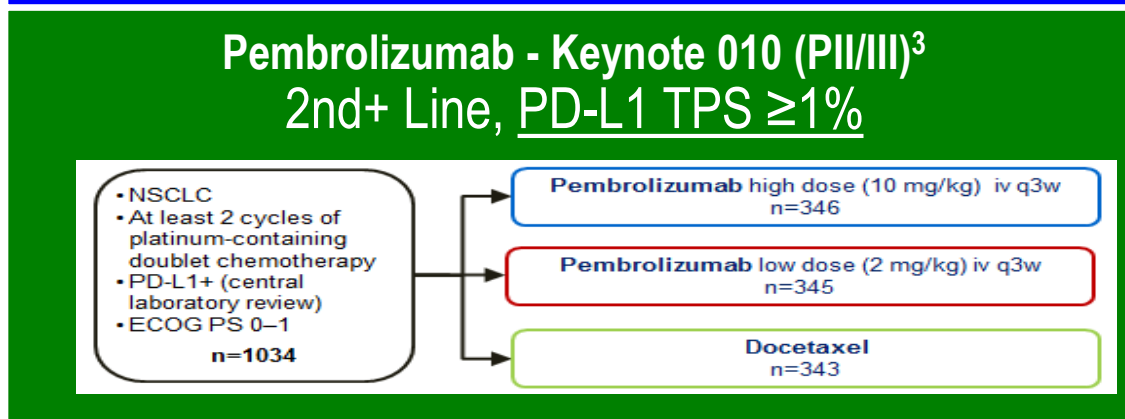
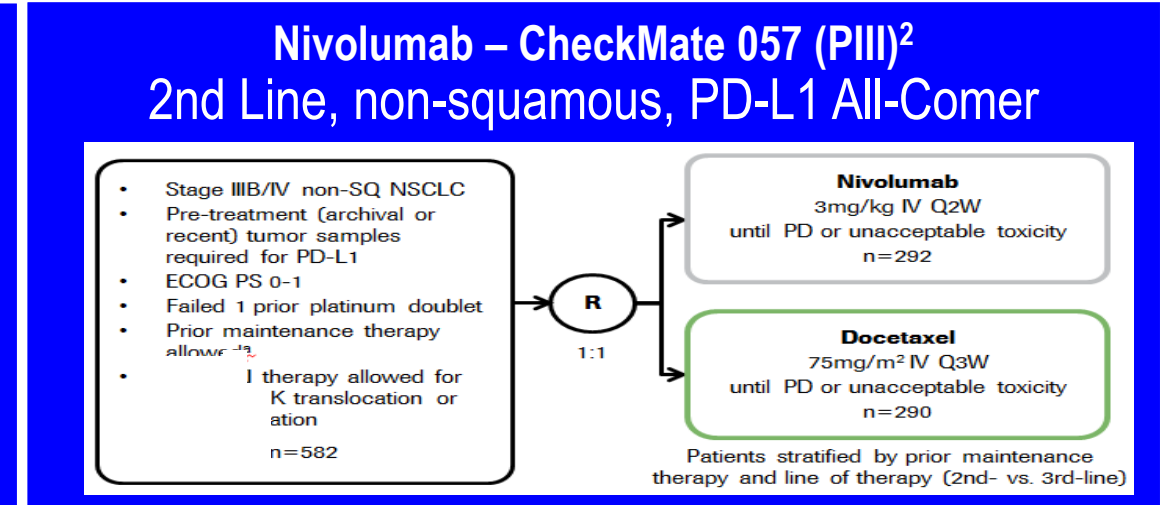
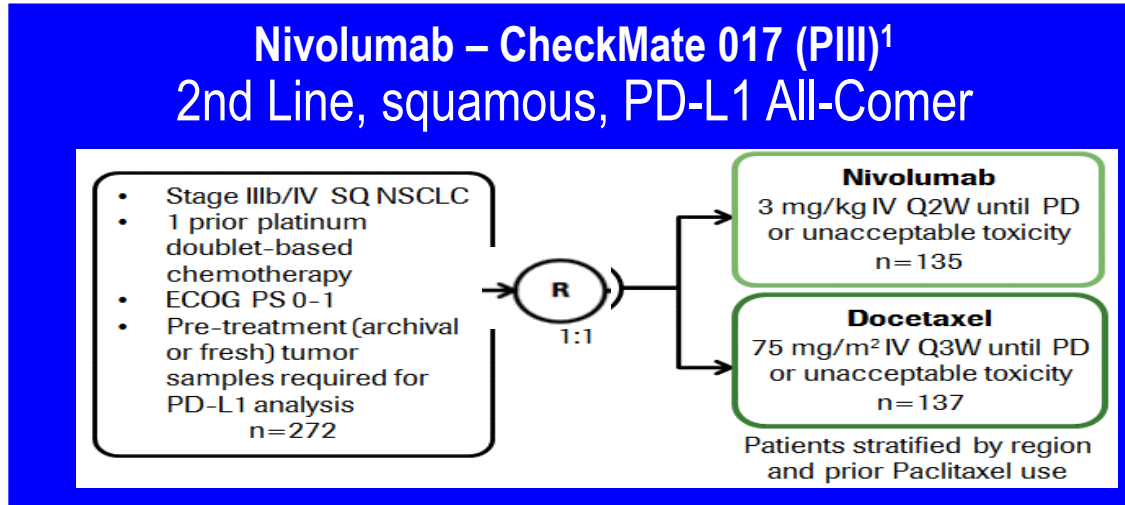


THE THREE PERIODS OF SECOND-LINE TREATMENT

- Before Immunotherapy
- During Immunotherapy

ANTI – PD-1 MONOTHERAPY IN PRETREATED PATIENTS

PRIMARY ENDPOINT: OS!

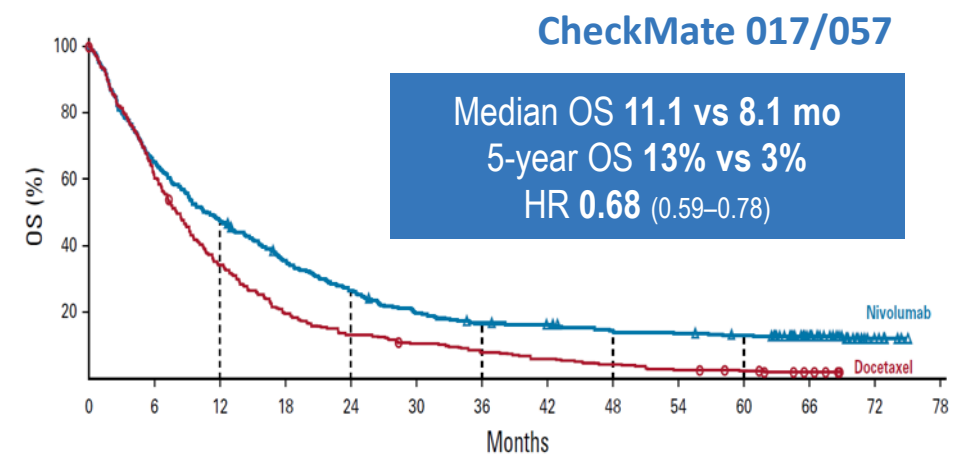
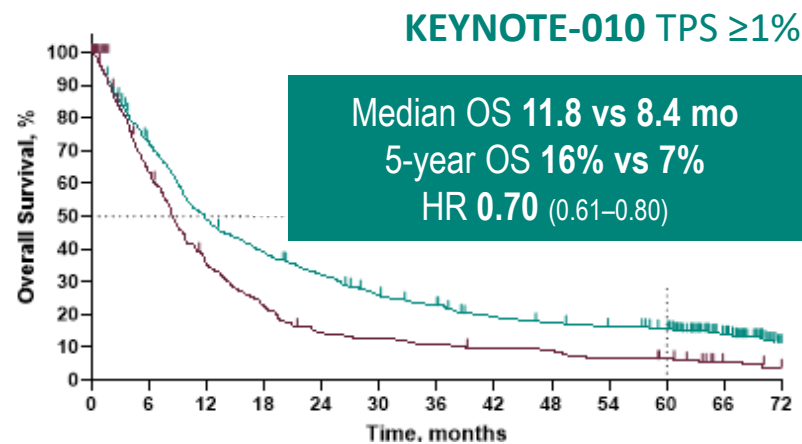
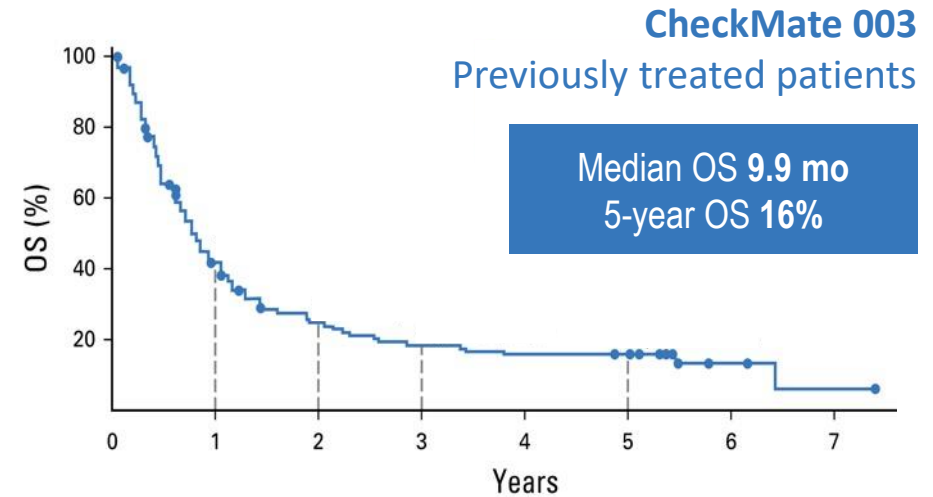
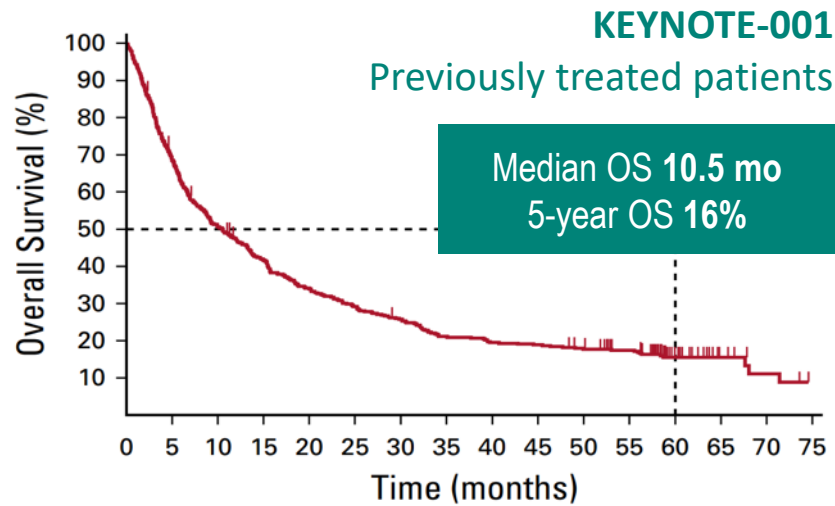


1. Borghaei H et al. Poster presentation at ASCO 2016. 9025. 2. Brahmer JR et al. Oral presentation at AACR 2017. CT077. 3. Herbst RS et al. Poster presentation at ASCO 9090. 4. Rittmeyer A et al. *Lancet*. 2017;389(10066):255-265.

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

IMMUNOTHERAPIES – 5-YEAR OS IN PHASE I–III TRIALS

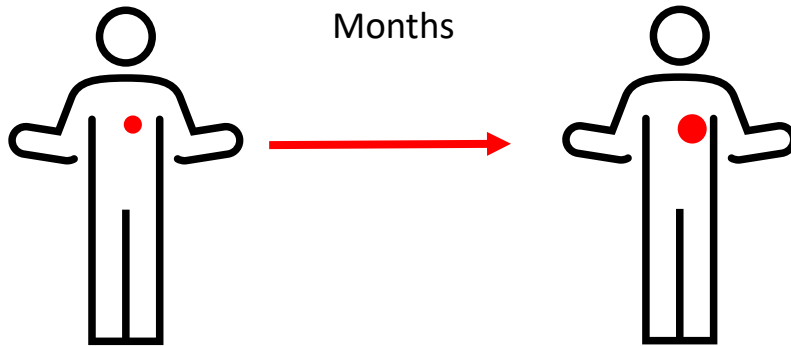
A 'TASTE' OF CHRONIC DISEASE



THE THREE PERIODS OF SECOND-LINE TREATMENT

- Before Immunotherapy
- During Immunotherapy
- After Immunotherapy (the reality of today!)

THE CLINICAL (PRAGMATIC) VIEW ON PD AFTER IO AND POTENTIAL TREATMENT IMPLICATIONS



Type 1:

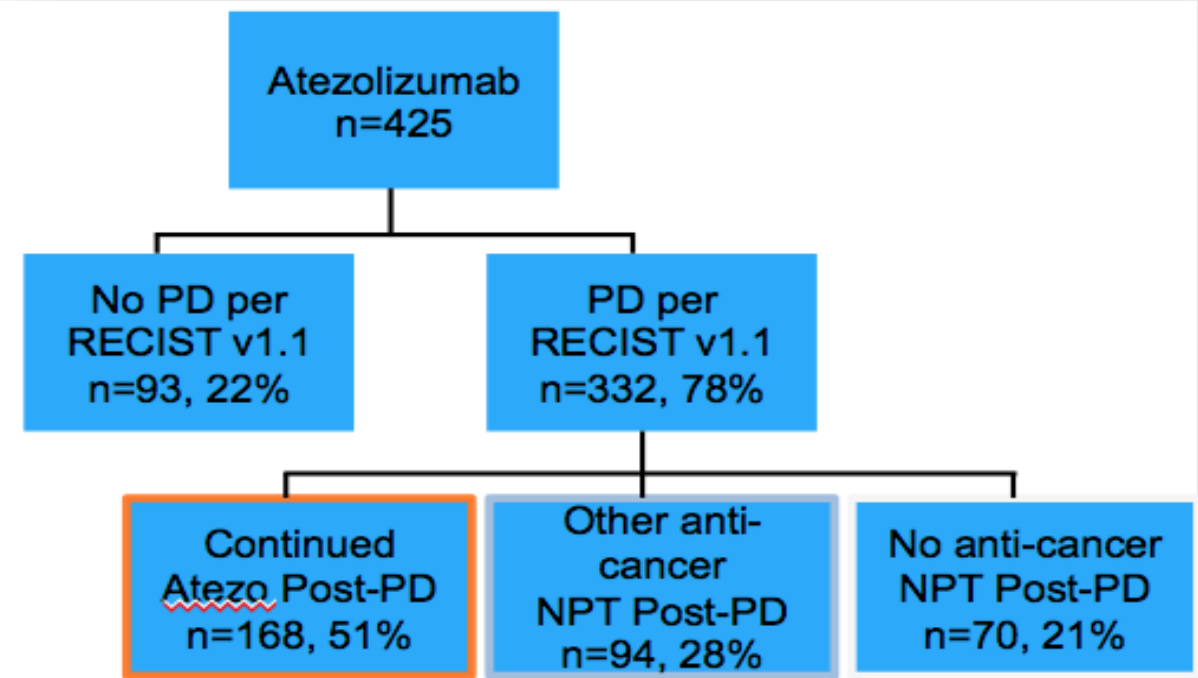
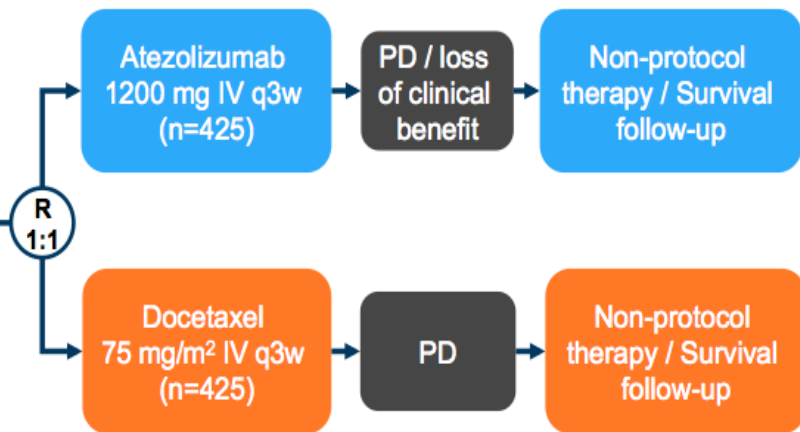
- Slow, asymptomatic PD
- No new tumor related symptoms
- Good tolerability of IO
- *Continuation of IO?*



Oak – Exploratory Analysis

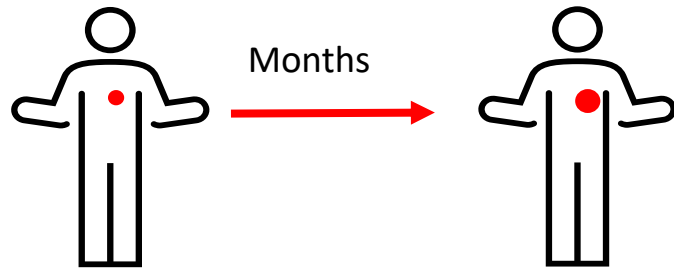
Key patient inclusion criteria

- Locally advanced or metastatic NSCLC
- 1–2 prior lines of chemotherapy including ≥ 1 platinum-based
- Any PD-L1 status (n=850)



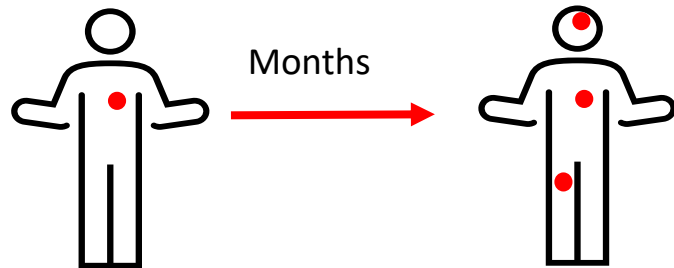
	Atezo Post-PD	Other Post PD	No Treatment Post PD
Number	168 (51%)	94 (28%)	70 (21%)
Median OS	12.7 m (9.3 ; 14.9)	8.8 m (6.0 ; 12.1)	2.2 m (1.9 ; 3.4)
18 m OS	37%	20%	9%

THE CLINICAL (PRAGMATIC) VIEW ON PD AFTER IO AND POTENTIAL TREATMENT IMPLICATIONS



Type 1 / Slow - PD:

- Slow, asymptomatic PD
- No new tumor related symptoms
- Good tolerability of IO
- *Continuation of IO?*

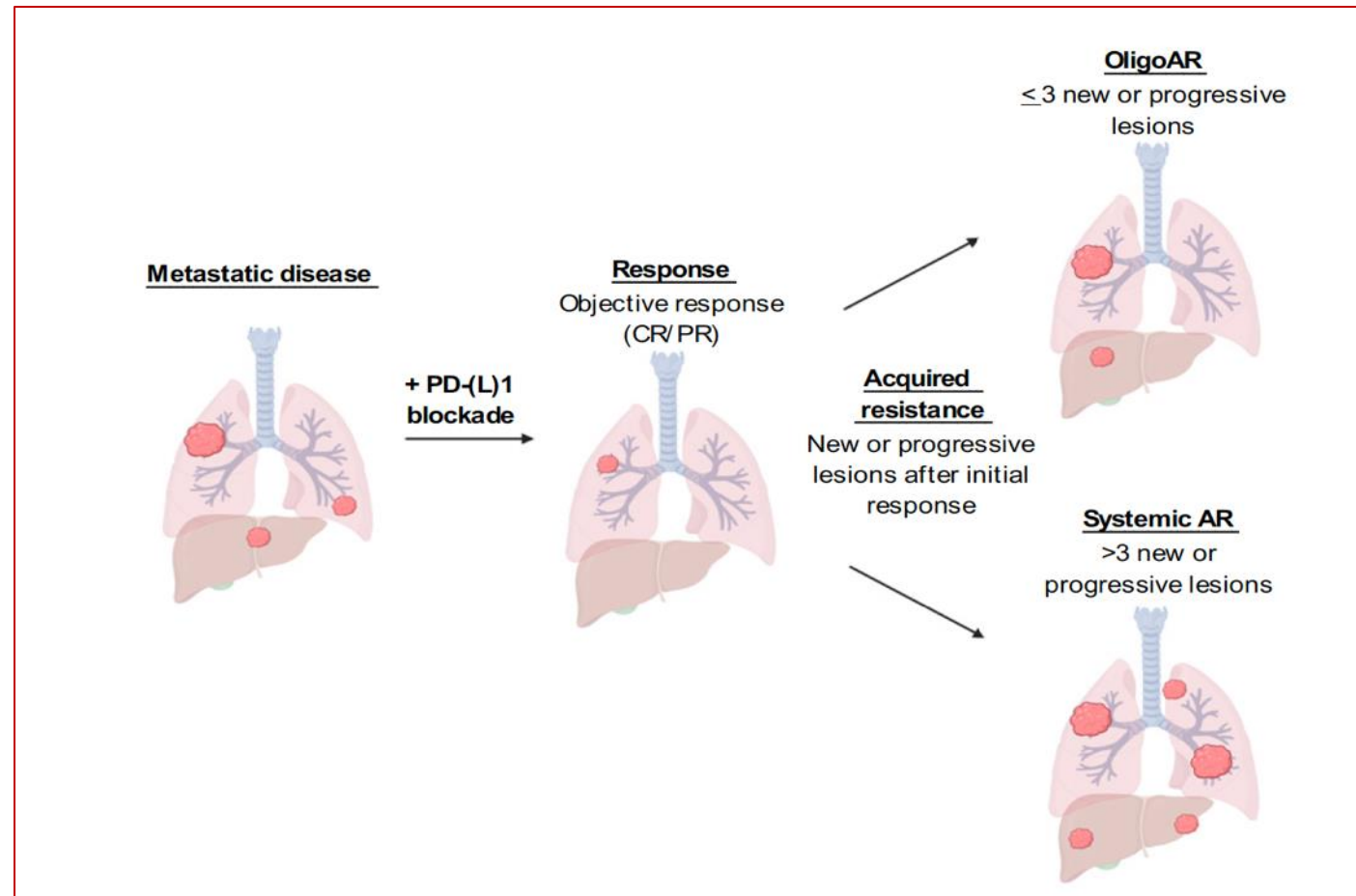


Type 2 / Oligo-PD:

- Stabilization/Response of primary tumor
- 1-2 new metastases
- Good tolerability of IO
- *Continuation of IO and local therapy?*

OLIGO PD / OLIGO RESISTANCE

1536 patients, 312 patients with initial response, 143 patients with acquired resistance



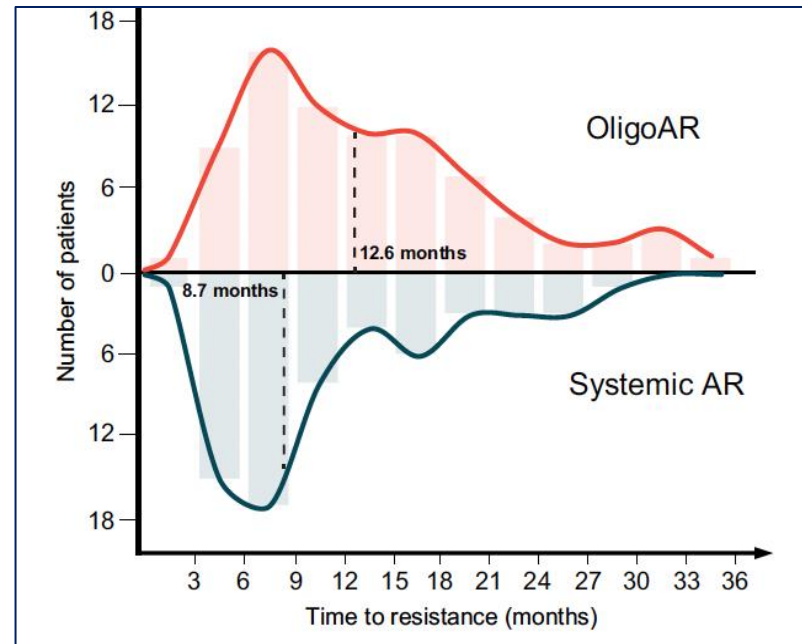
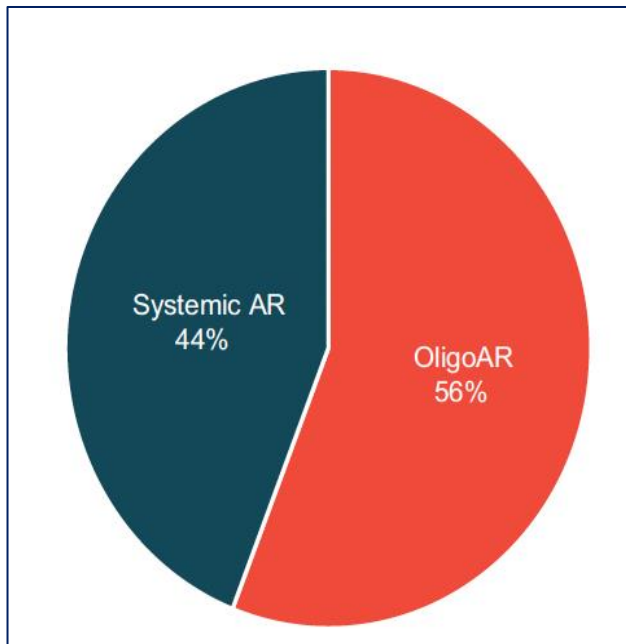
Schoenfeld A et al, *Clinical Cancer Research* 2022

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

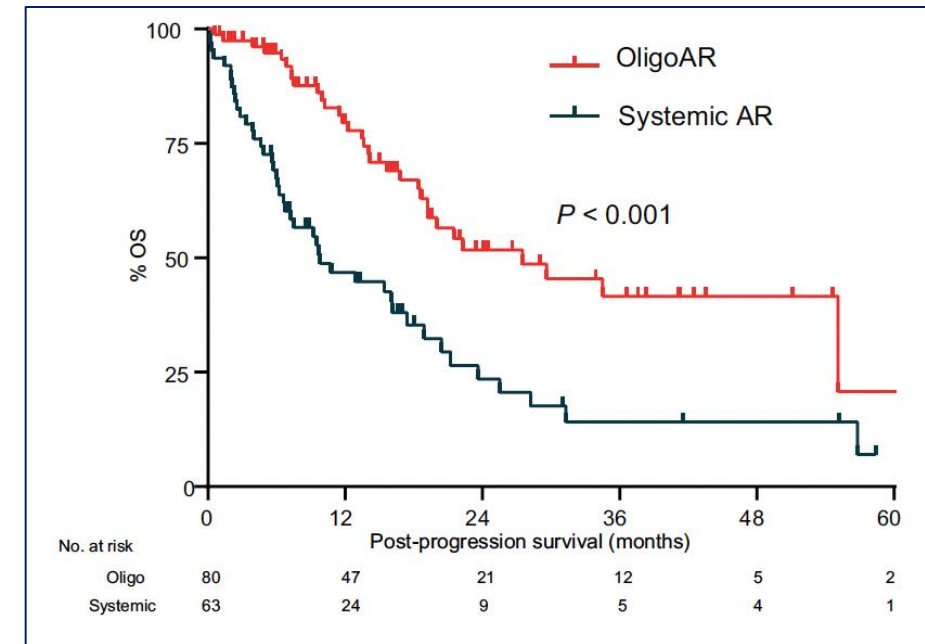


DIFFERENT CHARACTERISTICS OF OLIGO PD

Oligo PD: No difference in clinical characteristics or PD-L1 expression but higher TMB

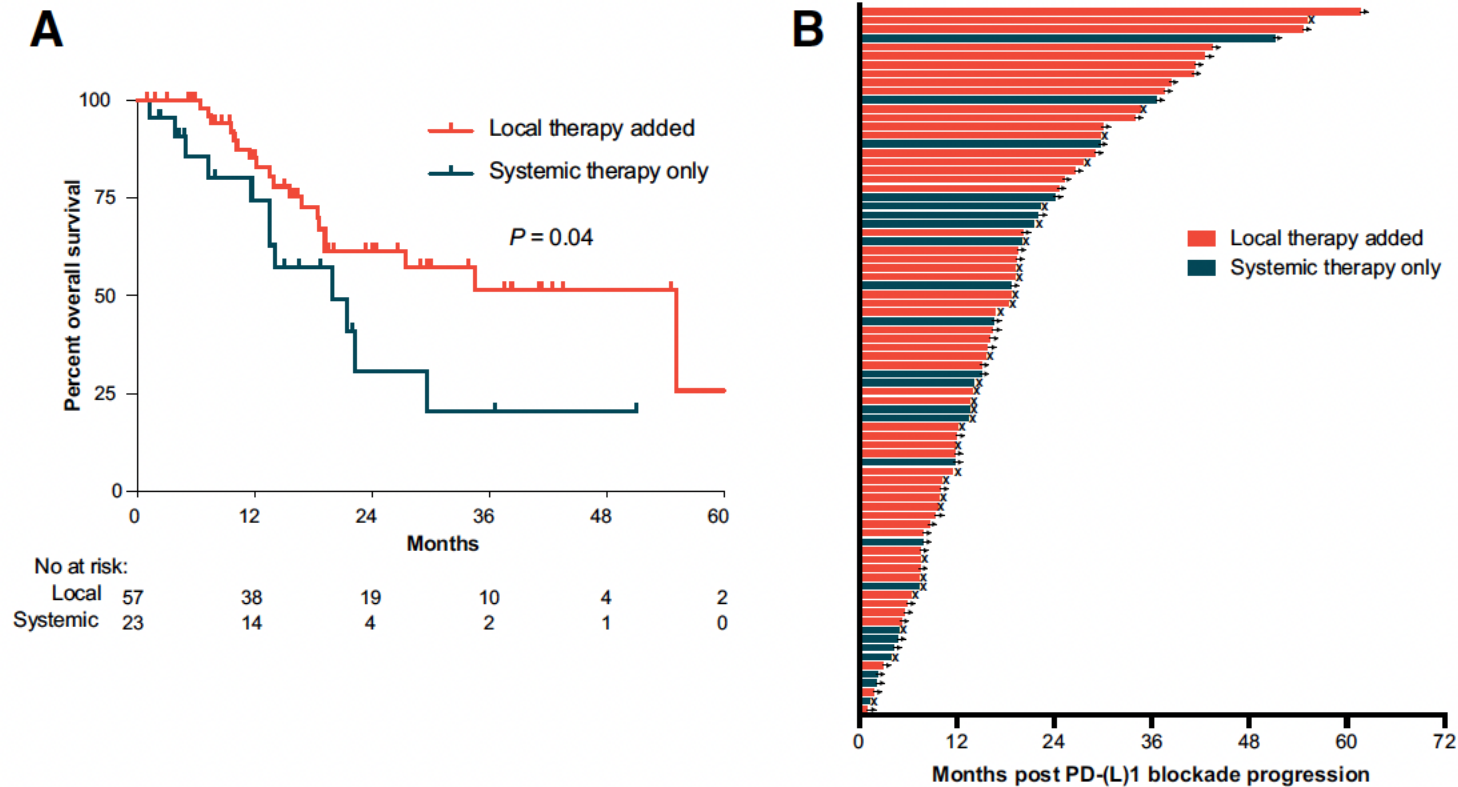


Median time to resistance 12.6 vs 8.7 m



Postprogression survival: 28 vs 10 m

IMPACT OF LOCAL TREATMENT IN OLIGO PD



THE CLINICAL (PRAGMATIC) VIEW ON PD AFTER IO AND POTENTIAL TREATMENT IMPLICATIONS



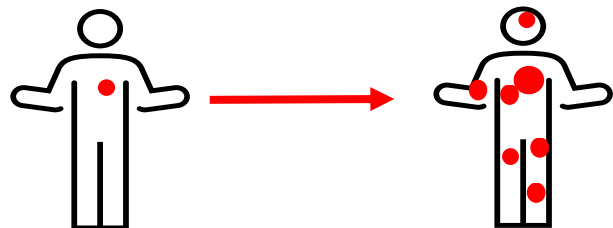
Type 1 / Slow - PD:

- Slow, asymptomatic PD
- No new tumor related symptoms
- Good tolerability of IO
- *Continuation of IO?*



Type 2 / Oligo-PD:

- Stabilization/Response of primary tumor
- 1-2 new metastases
- Good tolerability of IO
- *Continuation of IO and local therapy?*



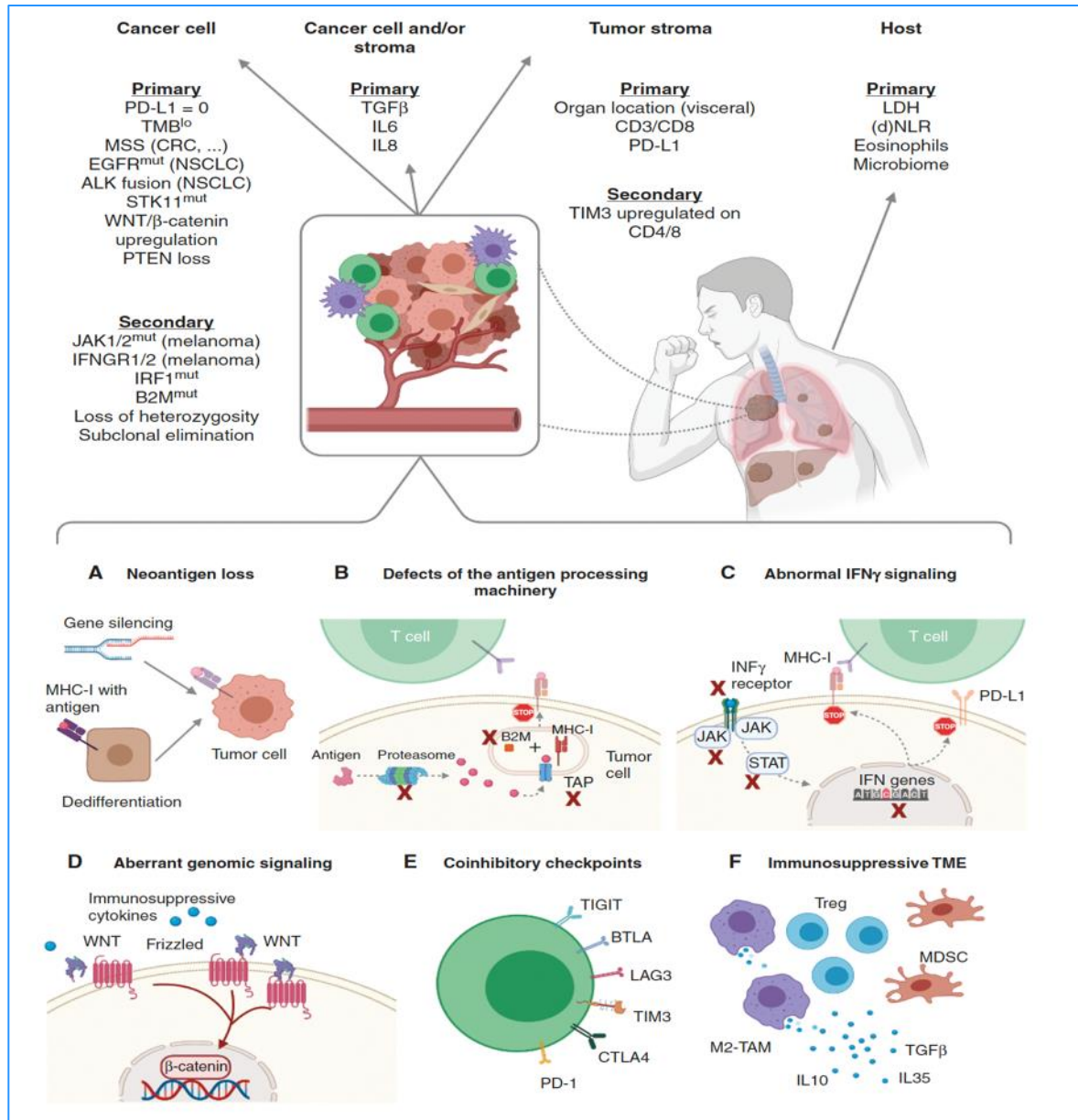
Type 3 / Systemic PD

- General PD
- Clinical Symptoms
- *Change of treatment?*



Do we have a standard of resistance?

Resistance after Immunotherapy
A really complex event



MANAGEMENT - POTENTIAL STRATEGIES



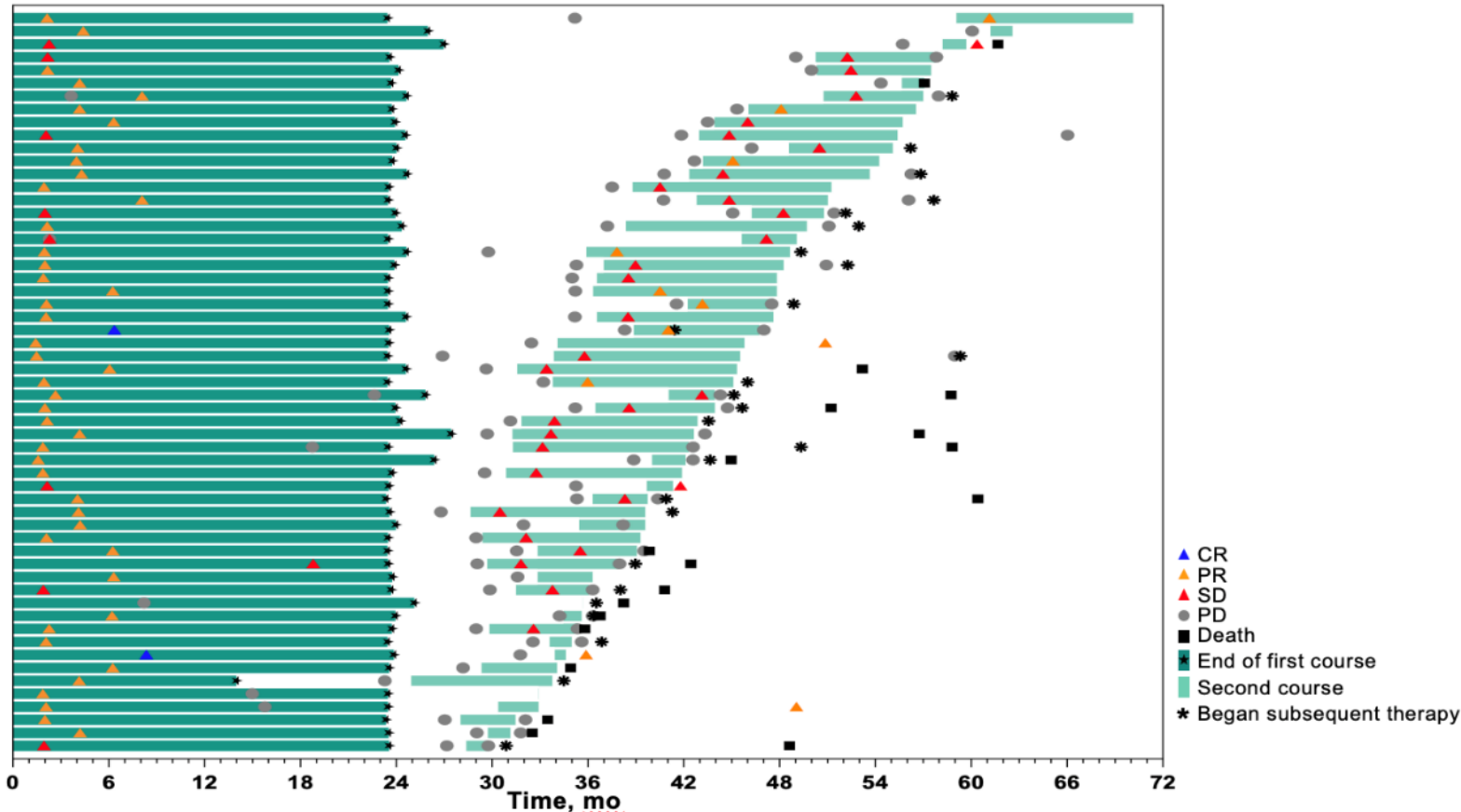
- . Re Challenge?

POOLED ANALYSIS REEXPOSITION PEMBROLIZUMAB KN 024, KN 042, KN 598, KN 189, KN 407



Rodriguez Abreu D, Reck M, WCLC 2022

Monotherapy Cohort



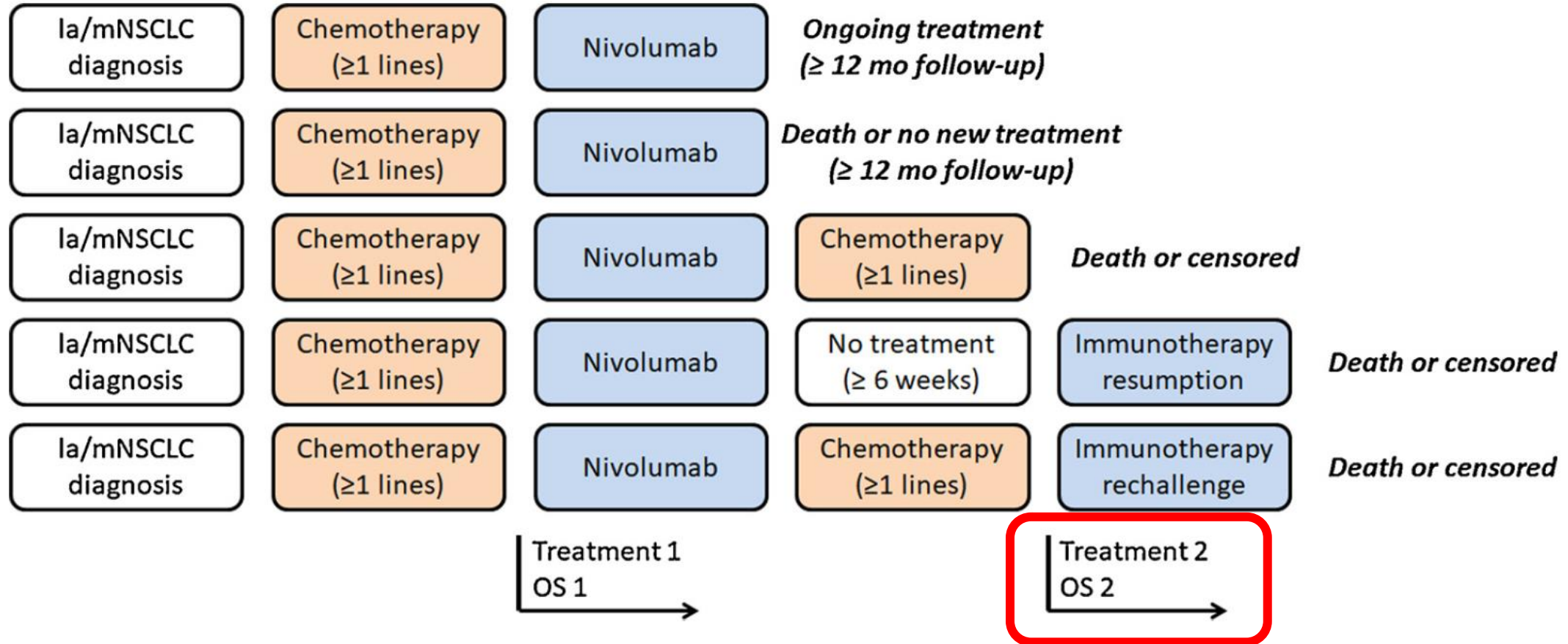
Time from stopping first course pembrolizumab to start of second course: **Median 12.0 m (3.8 - 35.6m)**

Time from starting second course pembrolizumab to cut off: **Median 21.5 m (0.6 - 46.5 m)**

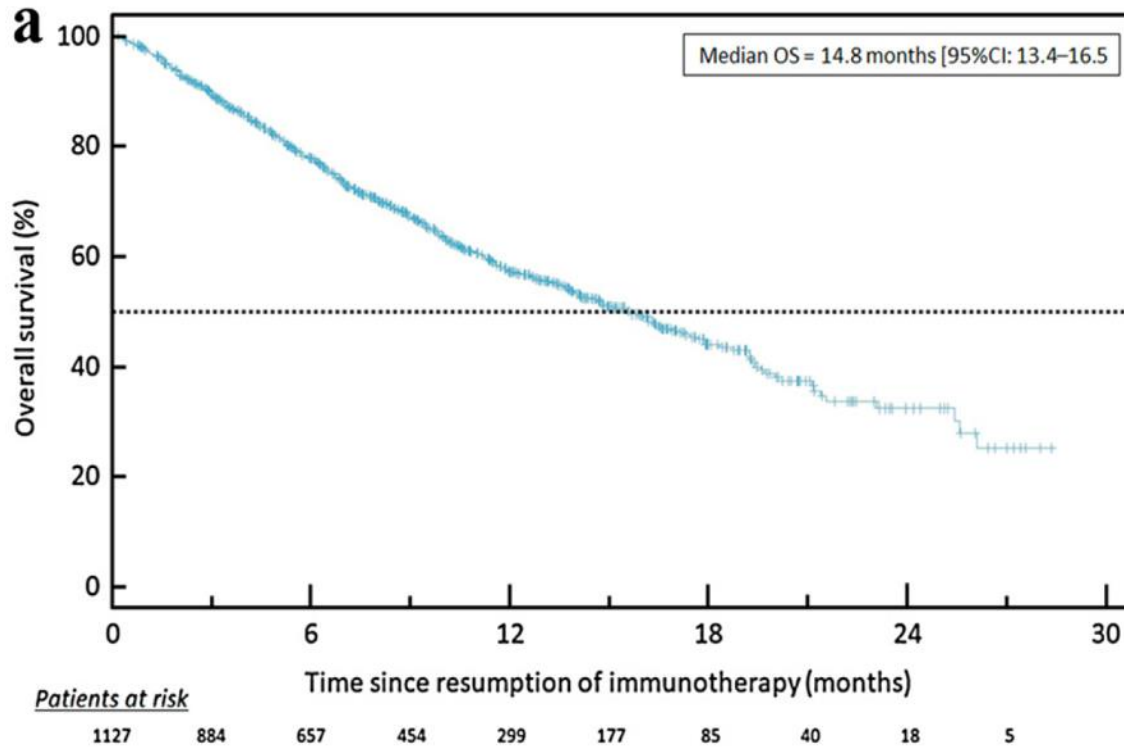
	Cohort 1 (pembro monotherapy) N = 57
ORR ^a (95% CI), %	19 (10–32)
DCR ^a (95% CI), %	74 (60–85)
Best overall response ^{a, n} (%)	
CR	0
PR	11 (19)
SD	31 (54)
PD	8 (14)
NA ^b	7 (12)
DOR ^{a, c} median (range), mo	NR (0.0+ to 20.0+)
DOR ≥6 mo, %	79
PFS ^{a, c} median (95% CI), mo	10.3 (5.6–14.0)
6-mo rate (95% CI), %	61 (46–73)
OS ^c median (95% CI), mo	27.5 (21.7–NR)
6-mo rate (95% CI), %	85 (72–92)

REEXPOSITION IN PRETREATED PATIENTS SOME INTERESTING DATA FROM FRANCE

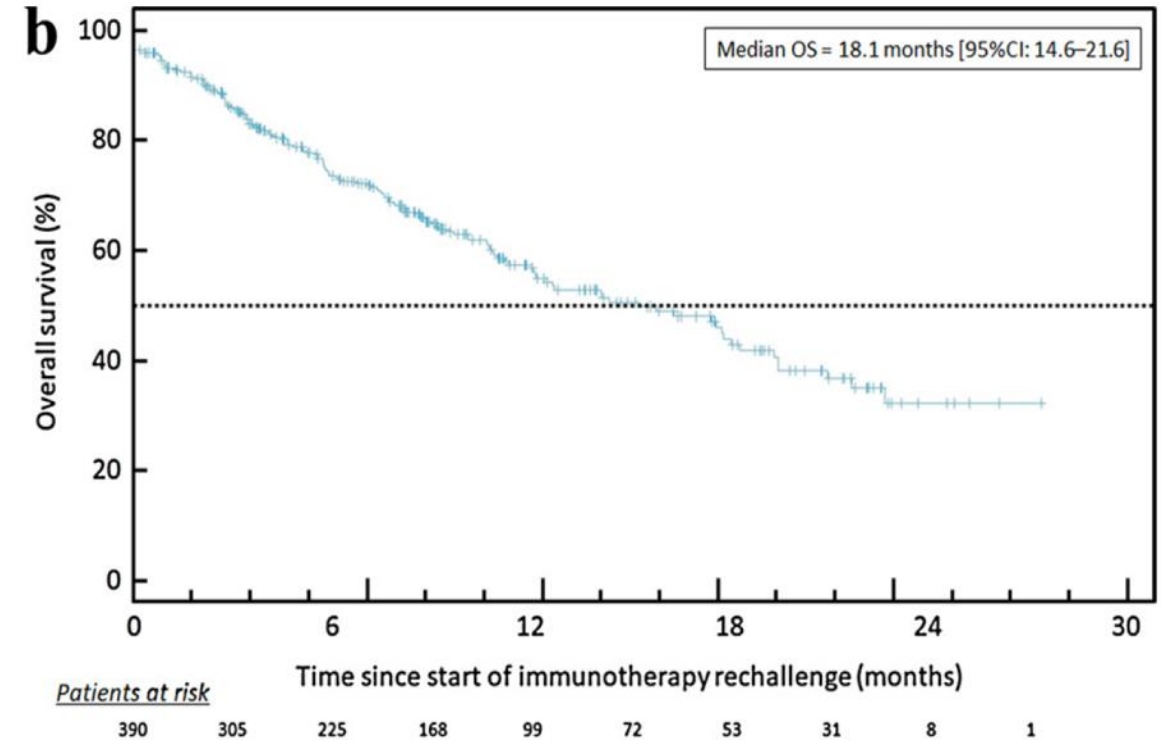
10.452 patients with advanced NSCLC



MEDIAN OS2 EVEN BETTER THAN OS1!



Median OS2 / Resumption: 14.8 m



Median OS2 / Rechallenge: 18.1m

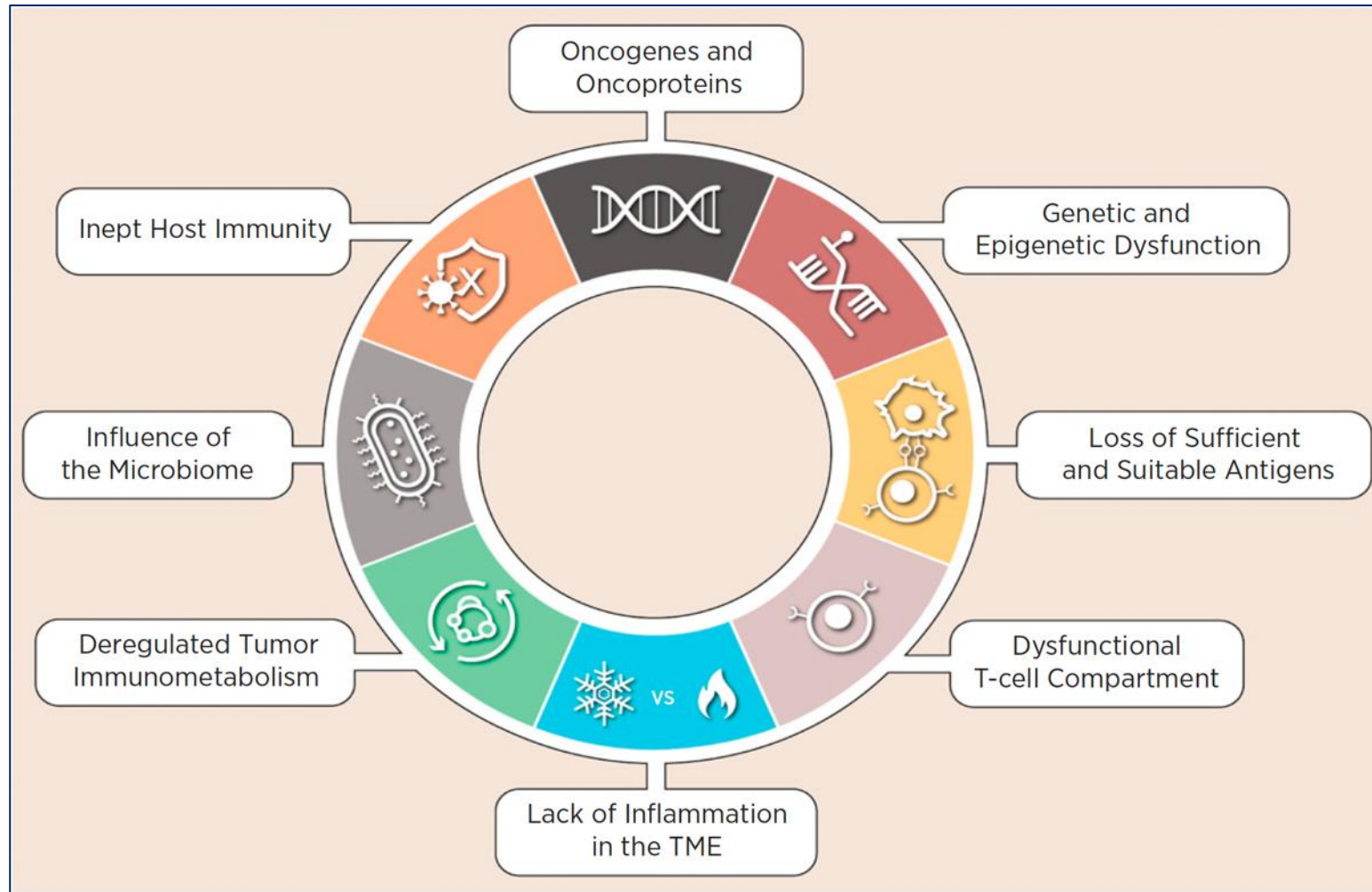
RELEVANT FACTORS DRIVING THE BENEFIT

Univariate and multivariate logistic regression analysis of factors of receiving a second PD-1 inhibitor.

Patients' characteristics	All patients with 2 nd PD-1 inhibitor course (N = 1517)	All patients with post-nivolumab chemotherapy only (N = 3601)	Univariate analysis		Multivariate analysis	
			OR (95 % CI)	P value	OR (95 % CI)	P value
Age (mean ± SD; years)	63.5 ± 9.7	63.4 ± 9.4	1.00 (0.99–1.01)	0.634	–	–
Gender (men: n, %)	1057 (69.7 %)	2526 (70.2 %)	1.02 (0.90–1.17)	0.737	–	–
Histology (non-squamous; n, %)	810 (53.4 %)	2047 (56.9 %)	1.15 (1.02–1.30)	0.023	NS	NS
Cancer duration						
Less than 1 year	689 (45.4 %)	1729 (48.0 %)	Reference		–	–
1 to 5 years	741 (48.9 %)	1678 (46.6 %)	1.11 (0.98–1.25)	0.103	–	–
5 years and more	87 (5.7 %)	194 (5.4 %)	1.13 (0.86–1.47)	0.388	–	–
Cerebral metastases	254 (16.7 %)	562 (15.6 %)	1.09 (0.93–1.28)	0.310	–	–
Duration of initial nivolumab course						
< 3 months	695 (45.8 %)	1888 (52.4 %)	Reference		Reference	
3 – 6 months	390 (25.7 %)	912 (25.3 %)	1.16 (1.00–1.35)	0.046	1.17 (1.01–1.36)	0.035
≥6 months	432 (28.5 %)	801 (22.2 %)	1.47 (1.27–1.70)	< 0.001	1.48 (1.28–1.71)	< 0.001
Comorbidities (yes vs. no)						
Hypertension	297 (19.6 %)	592 (16.4 %)	1.24 (1.06–1.44)	0.007	1.21 (1.03–1.42)	0.019
Diabetes	138 (9.1 %)	289 (8 %)	1.15 (0.93–1.42)	0.206	–	–
Renal failure	68 (4.5 %)	147 (4.1 %)	1.10 (0.82–1.48)	0.515	–	–
COPD	222 (14.6 %)	425 (11.8 %)	1.28 (1.08–1.53)	0.005	1.24 (1.03–1.48)	0.021
Pulmonary insufficiency	24 (1.6 %)	42 (1.2 %)	1.36 (0.82–2.26)	0.230	–	–
Other chronic pulmonary disease	147 (9.7 %)	274 (7.6 %)	1.30 (1.06–1.61)	0.014	NS	NS

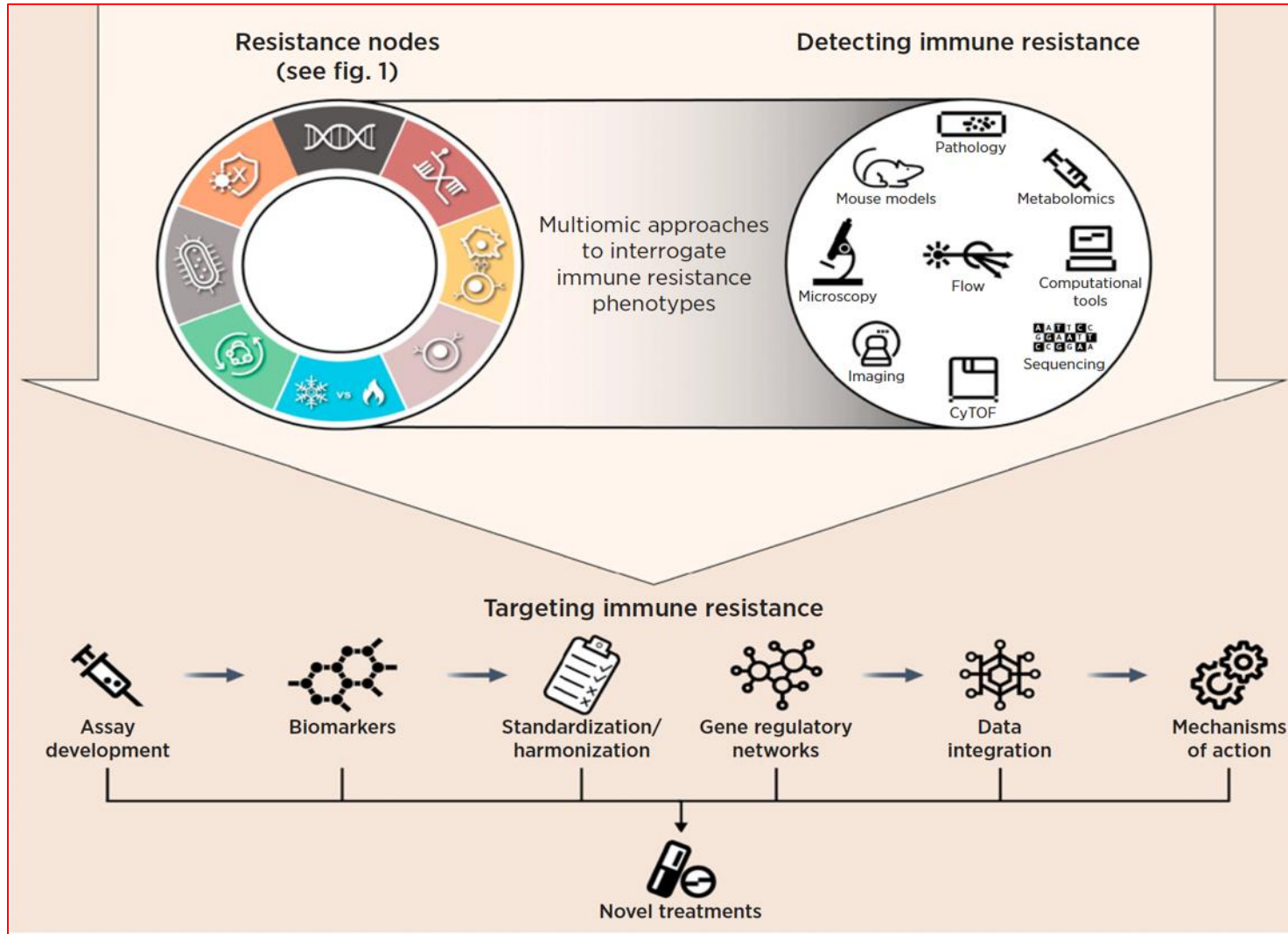
Levra MG et al, Lung Cancer 2020

MULTIPLE HALLMARKS OF RESISTANCE TO IMMUNOTHERAPY



Karasarides M et al, Cancer Immunol Res 2022

CHALLENGES IN DIAGNOSIS AND THERAPY



Karasarides M et al, Cancer Immunol Res 2022

POTENTIAL APPROACHES

- . ADCs - the new weapon for everything?
- . Antiangiogenic compounds?
- . Different approaches?
- . Vaccines?
- . Cellular therapies? (will be covered later)

TROPION LUNG 01 TRIAL

SECOND-LINE TREATMENT AFTER FAILURE OF CT AND CIT



Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
 - ECOG PS of 0 or 1
 - No prior docetaxel
- Without actionable genomic alterations^a**
- 1 or 2 prior lines, including platinum CT and anti-PD-(L)1 mAb therapy
- With actionable genomic alterations**
- 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

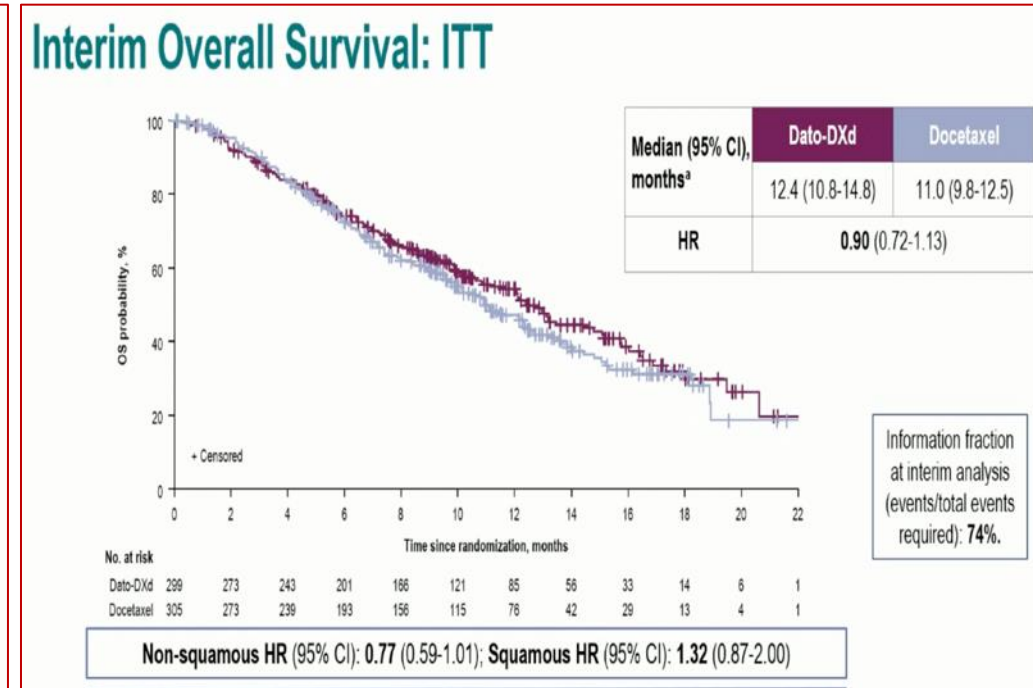
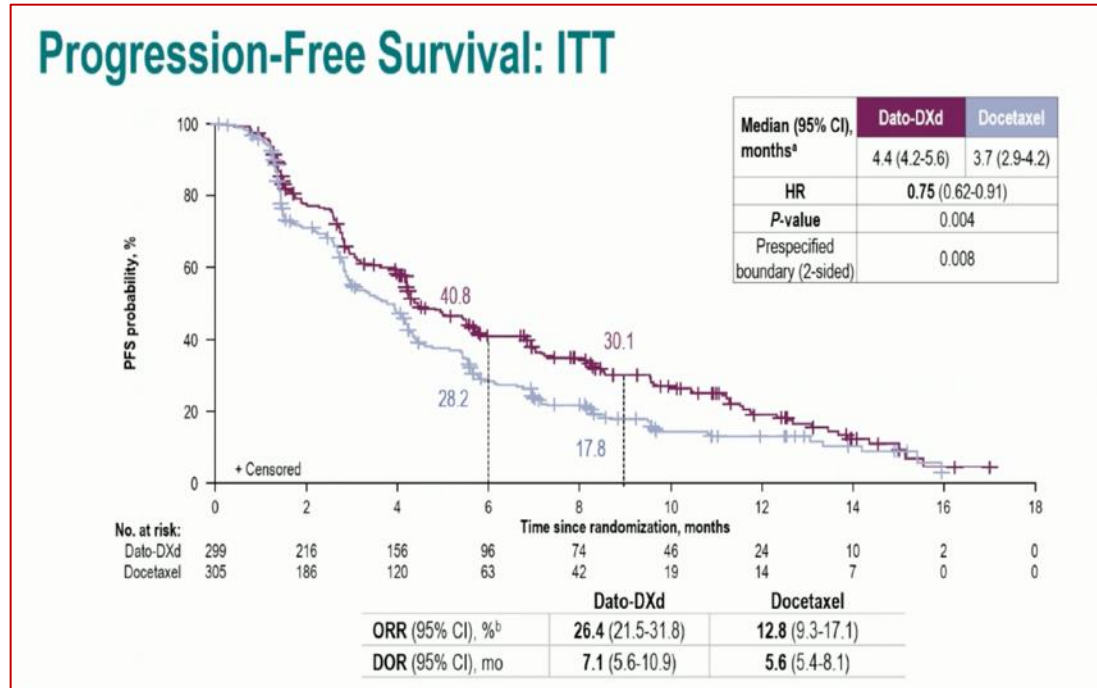
Dato-DXd
6 mg/kg Q3W
(N=299)

Docetaxel
75 mg/m² Q3W
(N=305)

Prim EP: PFS & OS
Results of Interim Analysis

Lisberg A et al, LBA12, ESMO 2023

TROPION LUNG 01 - RESULTS



- Med PFS: 4.4 vs 3.7 M (HR 0.75, p 0.004)
- PFS Squamous: HR 1.38, Non Squamous: HR 0.63
- RR: 26.4 vs 12.8%

- OS data not mature

Lisberg A et al, LBA12, ESMO 2023

TROPION LUNG 01 - ADVERSE EVENTS



TRAEs Occurring in $\geq 10\%$ of Patients

System organ class Preferred term, n (%)	Dato-DXd N=297		Docetaxel N=290	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Blood and lymphatic system				
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia ^a	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
Nausea	100 (34)	7 (2)	48 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
General				
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and subcutaneous				
Alopecia	95 (32)	0	101 (35)	1 (0.3) ^b
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

Characteristic AEs:

- Mucositis
- Stomatitis
- Pneumonitis / ILD
- Skin toxicity
- Eye Toxicity

Lisberg A et al, LBA12, ESMO 2023

NEGATIVE TRIALS

EVOKE-01

Sacituzumab Govitecan vs Docetaxel

January 22, 2024

Gilead Provides Update on Phase 3 EVOKE-01 Study

FOSTER CITY, Calif.--(BUSINESS WIRE)-- Gilead Sciences, Inc. (Nasdaq: GILD) today announced that the Phase 3 EVOKE-01 study did not meet its primary endpoint of overall survival (OS) in previously treated metastatic non-small cell lung cancer (NSCLC). EVOKE-01 is evaluating Trodelvy® (sacituzumab govitecan-hziy; SG) vs. docetaxel in patients with metastatic or advanced NSCLC that had progressed on or after platinum-based chemotherapy and checkpoint inhibitor therapy.

CARMEN-LC03

Tusamitamab Ravtansine vs Docetaxel

Press Release



Sanofi announces end of program evaluating tusamitamab ravtansine after a 2L NSCLC Phase 3 trial did not meet a primary endpoint

- CARMEN-LC03 trial did not meet dual primary endpoint of improving progression-free survival; tusamitamab ravtansine clinical development program will be discontinued
- Sanofi reinforces commitment to broader oncology development program including CEACAM5-directed antibody drug conjugates (ADC) with additional anticipated trials

PARIS, December 21, 2023. Sanofi is discontinuing the global clinical development program of tusamitamab ravtansine. The decision is based on the outcome of a prespecified interim analysis of the Phase 3 CARMEN-LC03 trial evaluating tusamitamab ravtansine as monotherapy compared to docetaxel in previously treated patients with metastatic non-squamous (NSq) non-small cell lung cancer (NSCLC) whose tumors express high levels of carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5).

VEGF ACTS AS A KEY MEDIATOR OF AN IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT (TME)

VEGF creates an immunosuppressive (pro-tumour) microenvironment¹

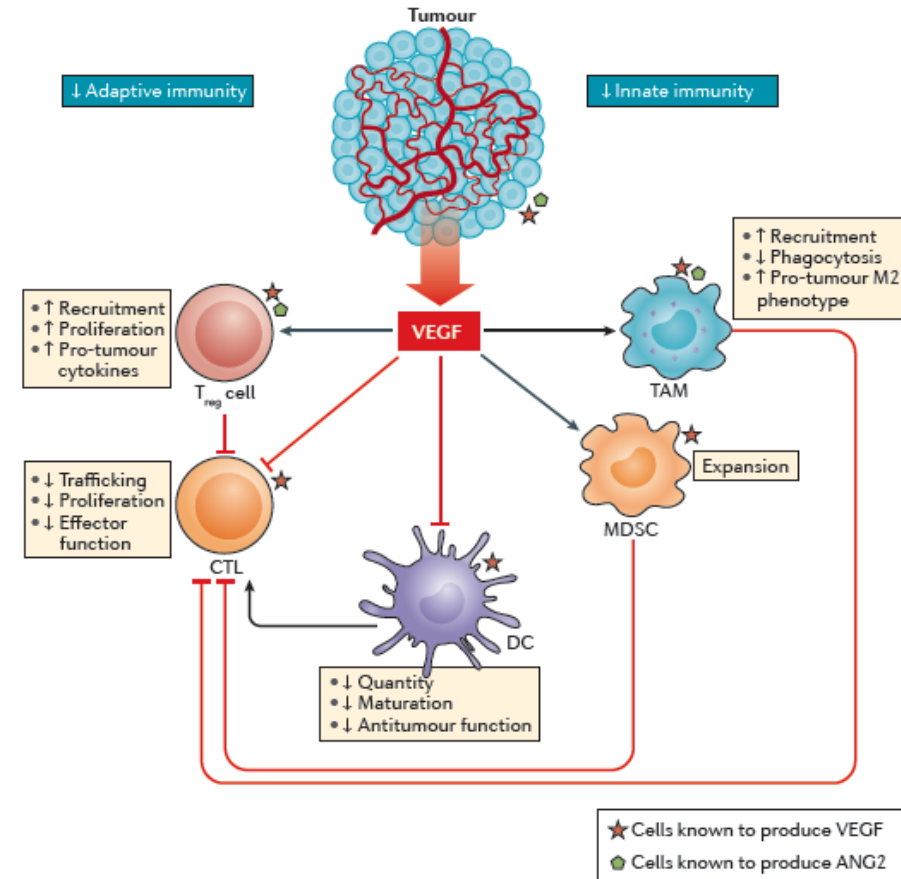
Upregulation of immunosuppressive cells:

- Regulatory T-cells (T-regs)
- Myeloid-Derived Suppressor Cells (MDSCs)

Impaired antigen presentation:

- Suppression of dendritic cell (DC) maturation, macrophages (TAMs)
- Impaired T-cell function (CTLs)

Direct effects of angiogenic factors on immune cells¹



1. Fukumura D et al. *Nat Rev Clin Oncol.* 2018;15(5):325-340

COMBINATION TRIALS - MISSING CONFIRMATION IN PHASE III TRIALS



	COSMIC-021 Cohort 7	LUNG-MAP S1800A	MRTX-500	Phase II	Retrospective	Phase I
Schedule	Cabozantinib Atezolizumab	Ramucirumab Pembrolizumab	Sitravatinib Nivolumab	Bevacizumab Atezolizumab	Ramucirumab Atezolizumab	Lenvatinib Pembrolizumab
N	80	69	68	24	21	21
ORR (%)	19*	22	18	13	4.8	33**
PFS (mo.)	4.5*	4.5	5.7	5.6	3.4	NR
OS (mo.)	13.8*	14.5	14.9	14.0	16.5	NR
G≥3 TRAE (%)	53	42	66	4.2	43	42
Phase III	CONTACTT	Pragmatica-lung	SAPPHIRE			LEAP-007

*RR: PD-L1<1%: 11% ; PD-L1≥1%: 20%. PFS: PD-L1<1%: 4.7; PD-L1≥1%: 5.4. OS: PD-L1<1%: 10.4 ; PD-L1≥1%: 17.8

** Includes treatment naïve population.

Slide courtesy J Remon, Hendricks L adapted

Neal - ASCO 2022 * Reckamp –JCO 2022 * Leal –ESMO 2021 * Lee –JTO 2022 * Herzog –Lung Cancer 2022* Brose – ASCO 2019 * Taylor –JCO 2020 *Borghaei Ann Oncol 2023 *Neal ELCC 2023

(There is no intention of cross trial comparison) Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.



SELECTED POTENTIAL CONCEPTS

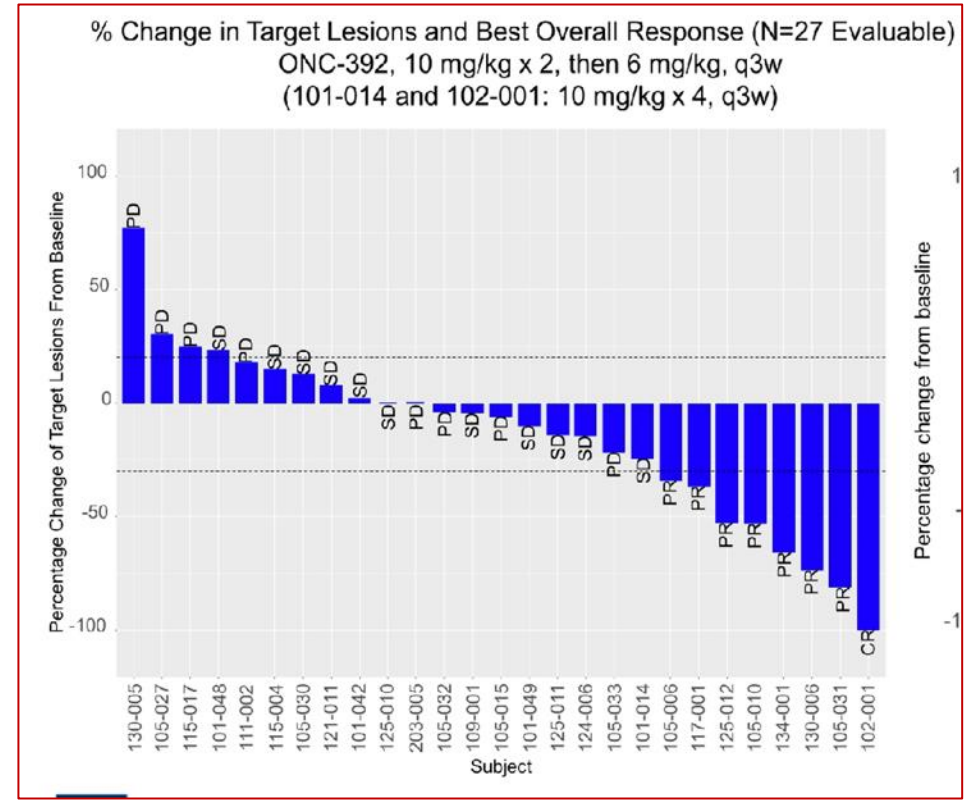
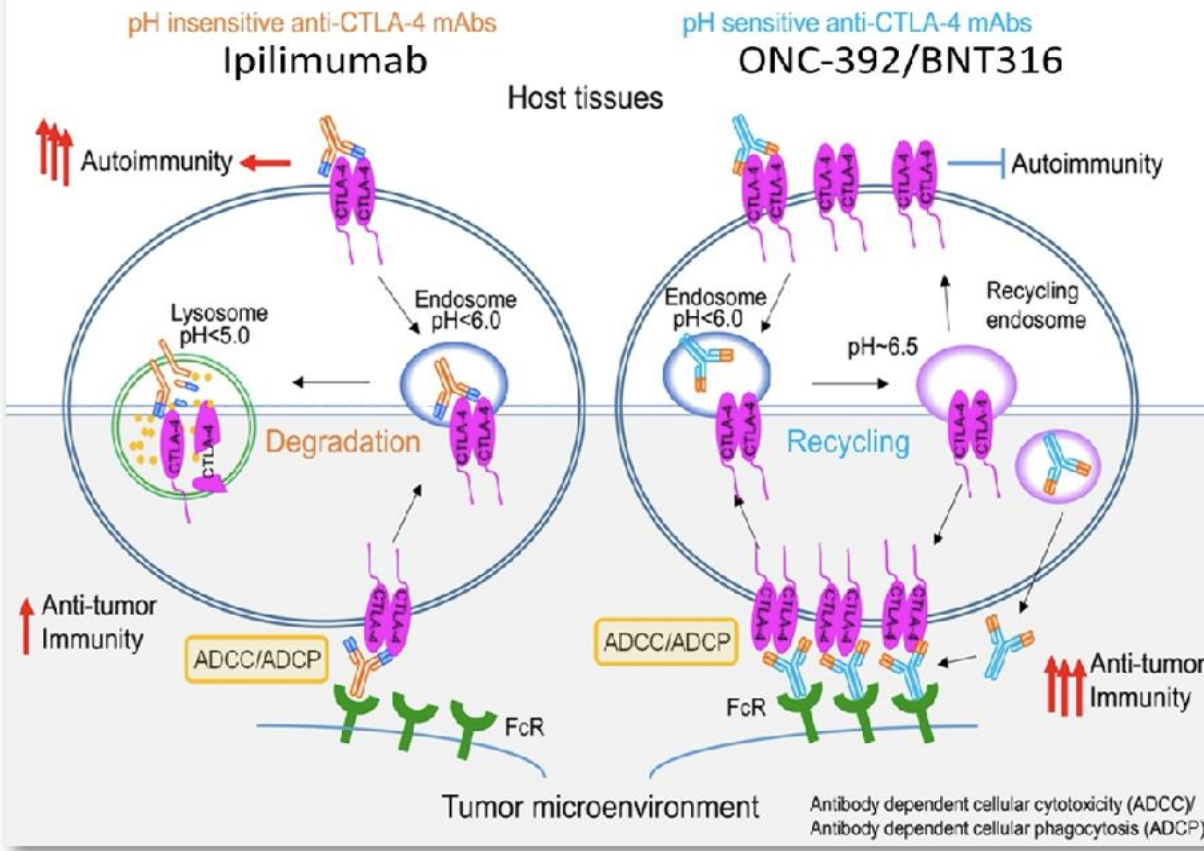
ONC-392/BNT316



He K et al, abstract 9024, ASCO 2023

Mechanism of action

Avoiding lysosomal degradation of CTLA-4 in regulatory T cells for safer and more effective immunotherapy



- Long treatment duration despite extensive first-line immunotherapy in some patients
- GI Tox CTC Grade 3/4: 43%, irAE CTC Grade 3/4: 34%
- Moving to phase III trial

Liu Y, Zheng P. Preserving the CTLA-4 Checkpoint for Safer and More Effective Cancer Immunotherapy. *Trends Pharmacol Sci.* 2020;41(1):4-12. doi:10.1016/j.tips.2019.11.003

If this presentation is copyright and responsibility of the author. Permission is required for re-use.

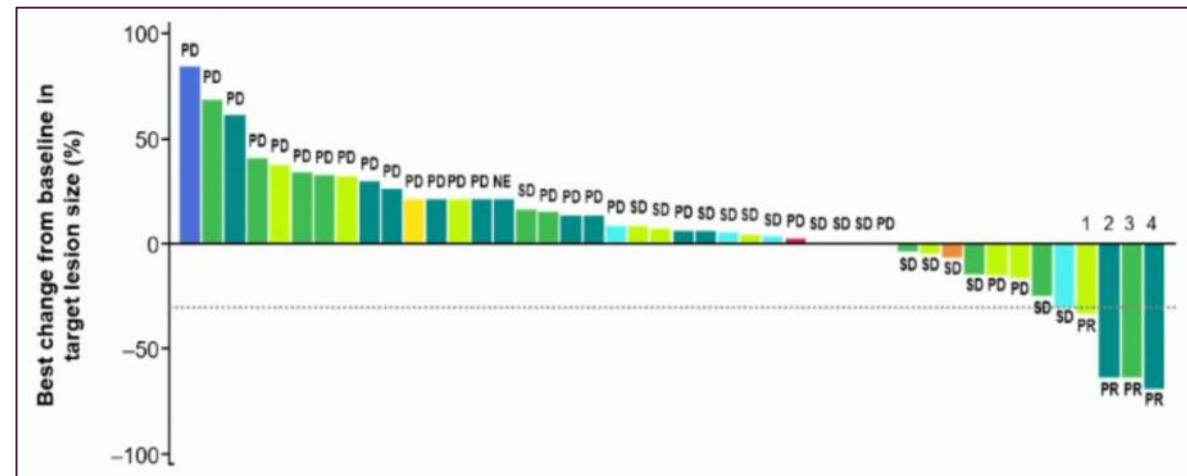
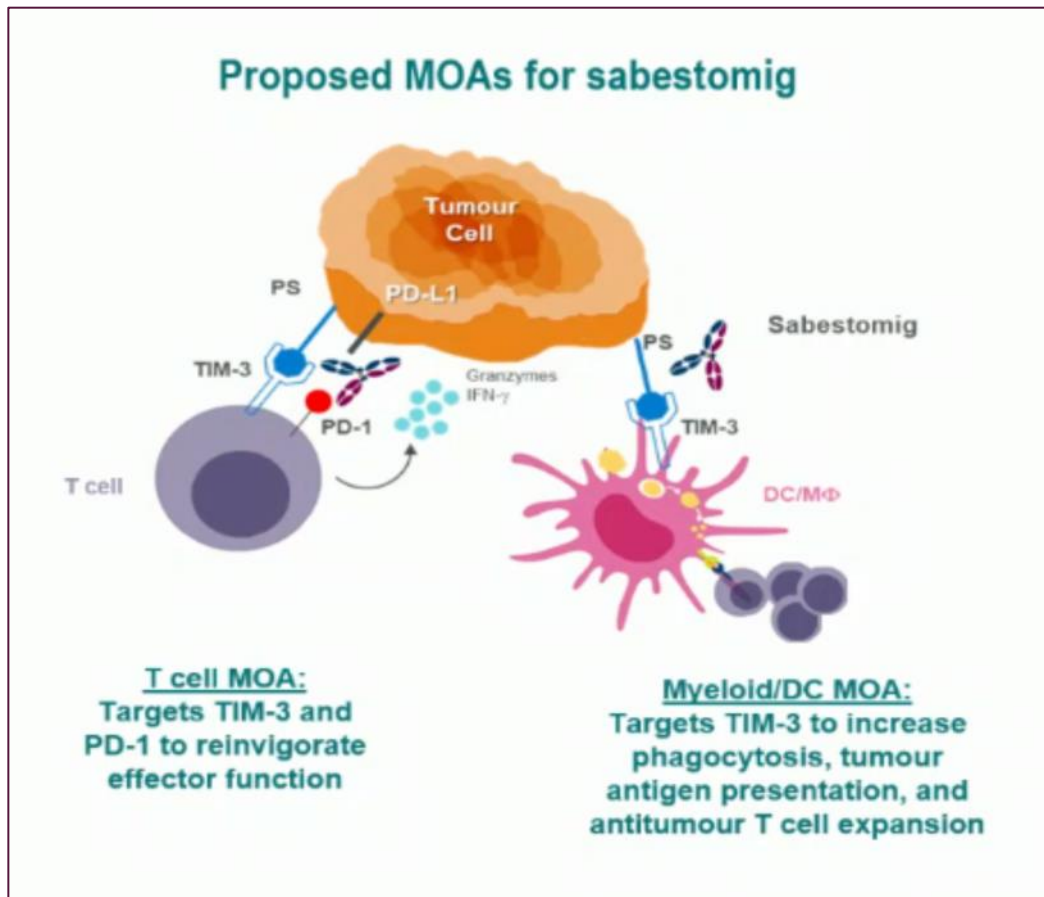


SELECTED POTENTIAL CONCEPTS

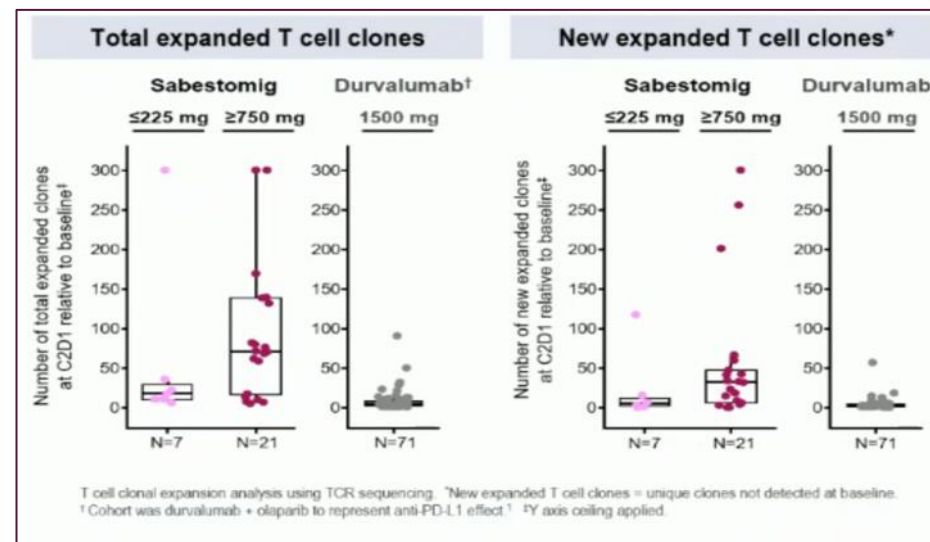
SABESTOMIG - AZD7789 (ANTI PD-1 & ANTI TIM)



Besse B et al, ESMO 2023



Response: 4/36 (11%) (Dose \geq 750 mg)



45 patients, prior treatment with anti PD(L)-1
Median 2 lines of prior therapy (1-6)

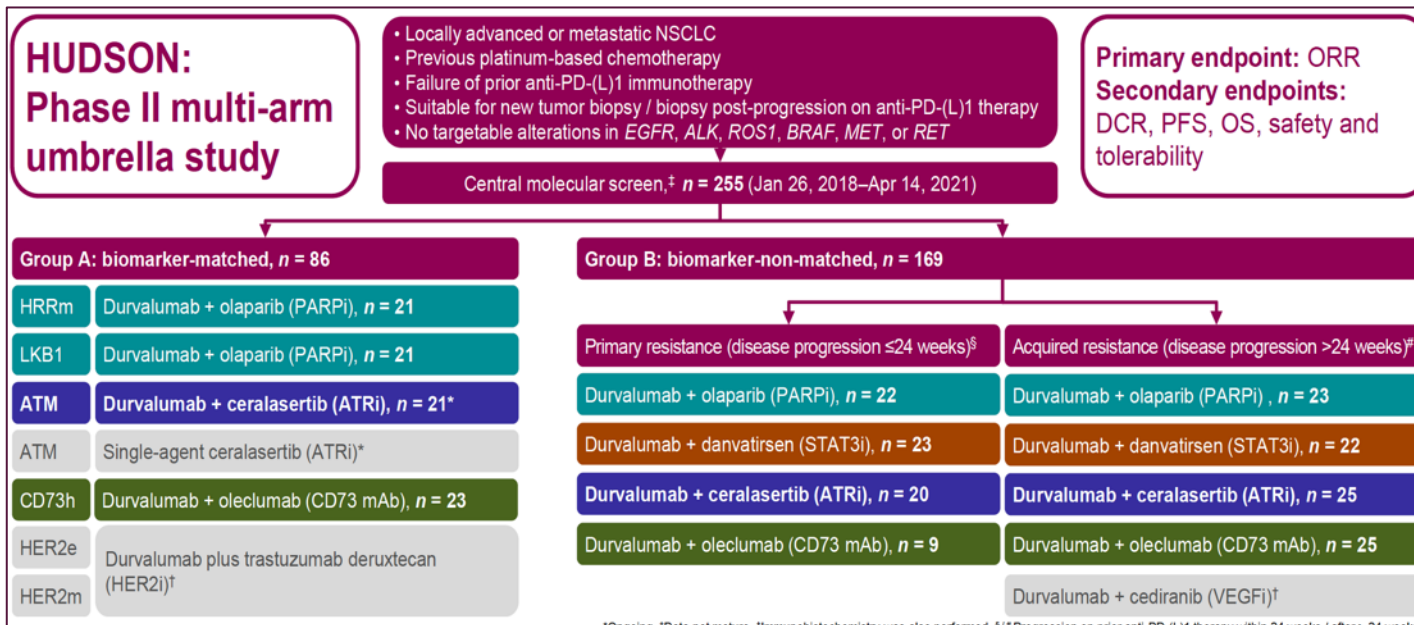
Martin Reck

required for re-use.

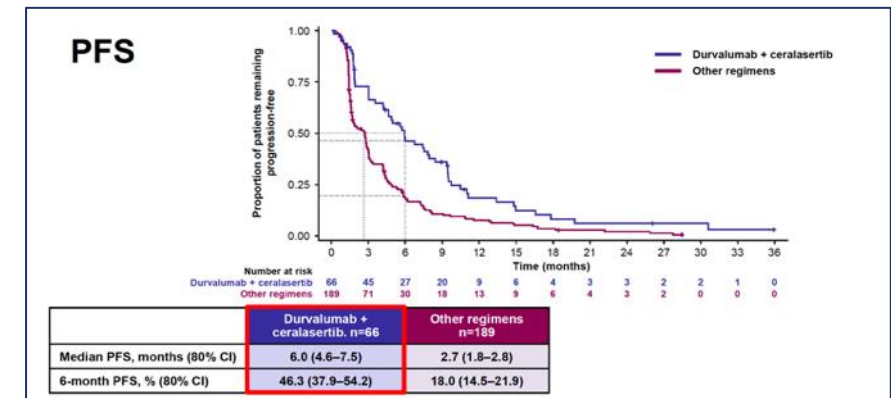
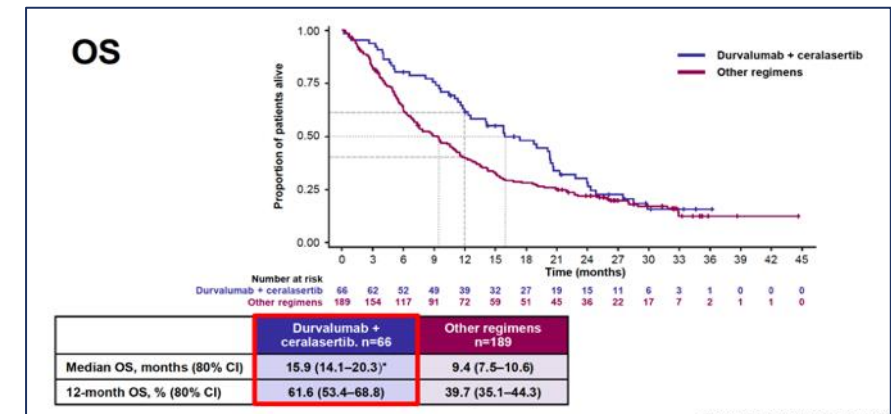


SELECTED POTENTIAL CONCEPTS HUDSON - PLATFORM STUDY

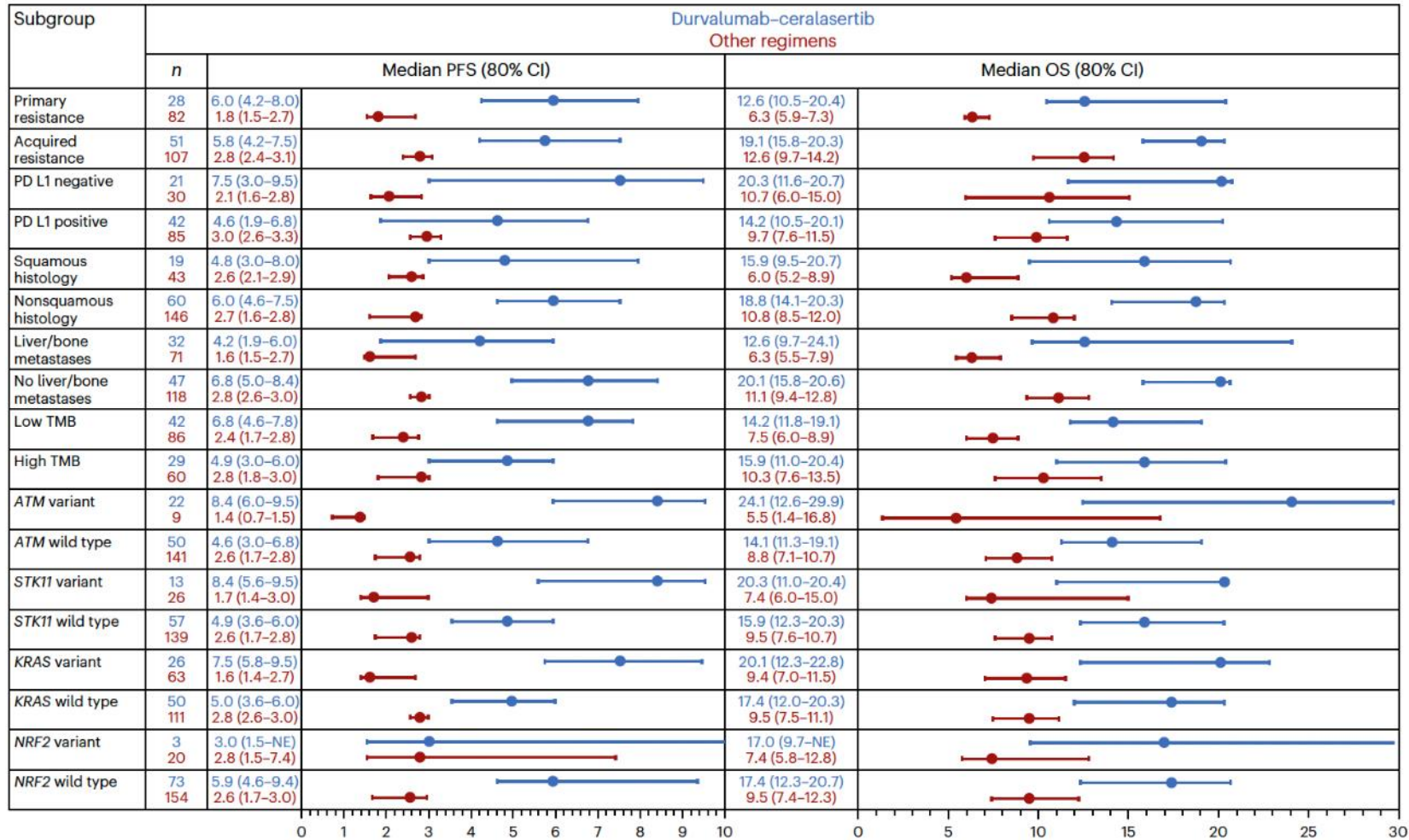
Besse B et al, WCLC 2022



Ceralasertib + Durvalumab

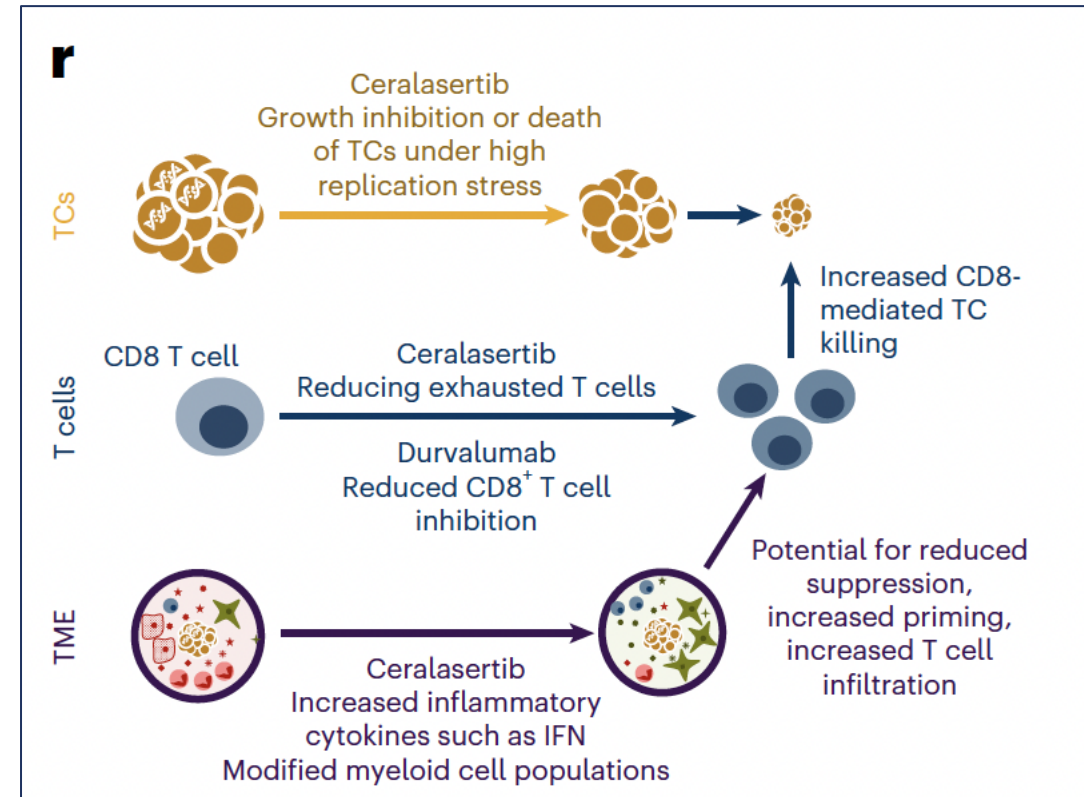
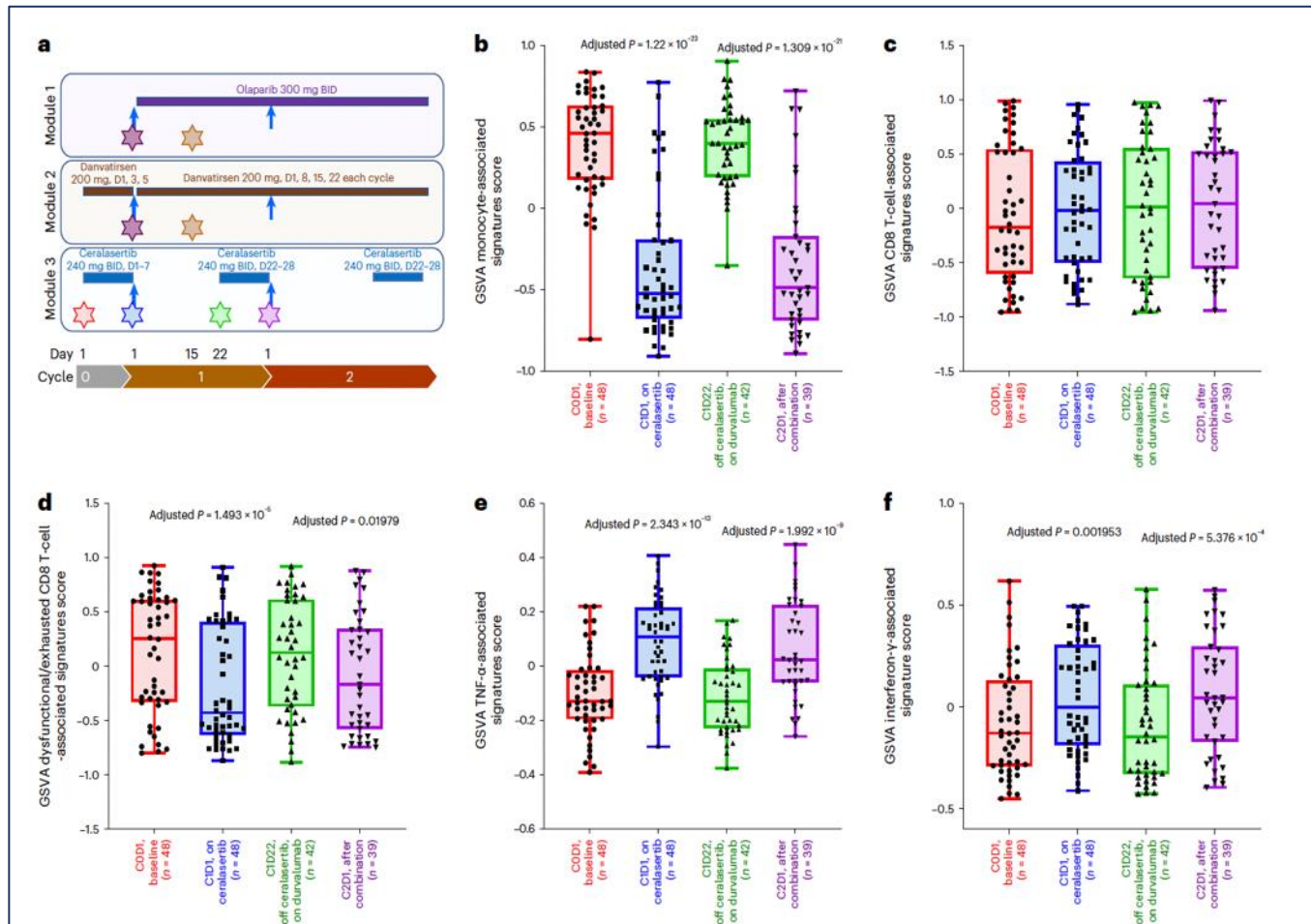


HUDSON - EFFICACY ACROSS SUBGROUPS



Besse B et al, Nature Medicine 2024

HUDSON - CHANGES IN TME AND CLONALITY

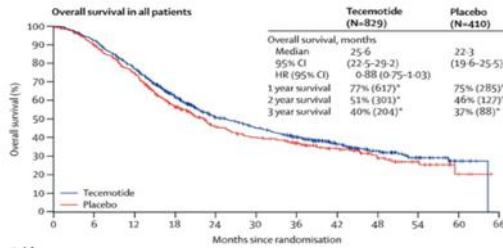


VACCINATION IN NSCLC - SO FAR NOT A SUCCESS STORY



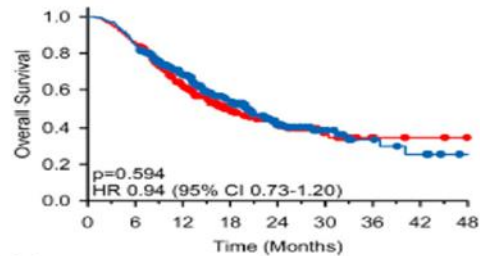
Relevant steps in optimization

Tecemotide (L-BLP25) MUC 1 peptide



Butts, Lancet Onc, 2013

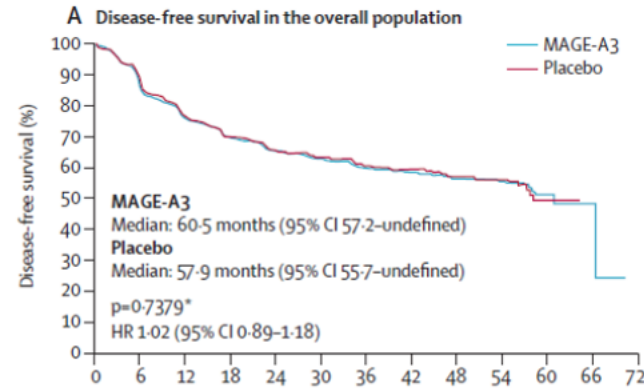
Belagenpumacel-L Whole cell vaccine



Giaccone, European Journal of cancer_2015

Martin Reck

(MAGE-A3) peptide



Vansteenkiste JF, et al.
Lancet Oncol 2016

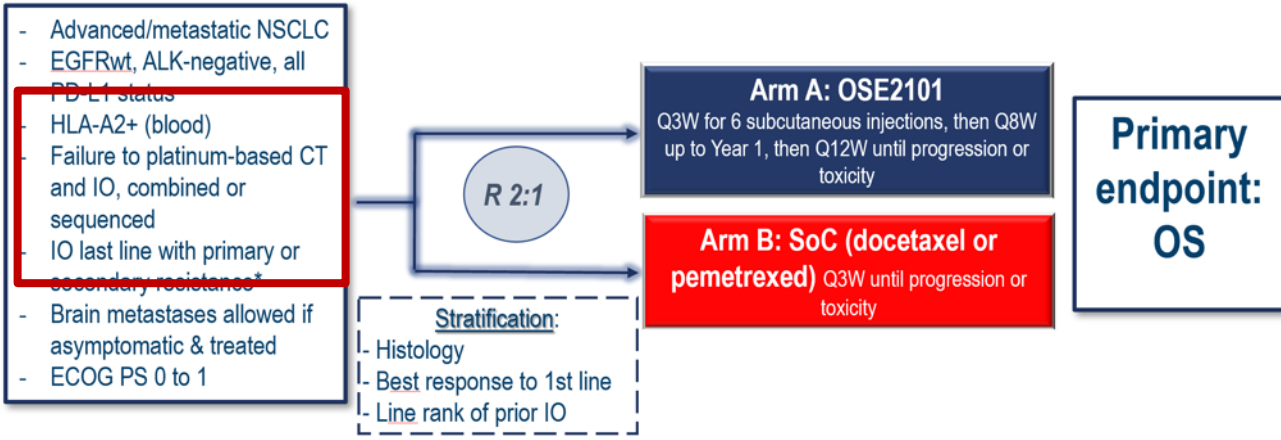
Right antigen

Right delivery

Right adjuvant

Right combination

VACCINES – PH III ATALANTE TRIAL



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%

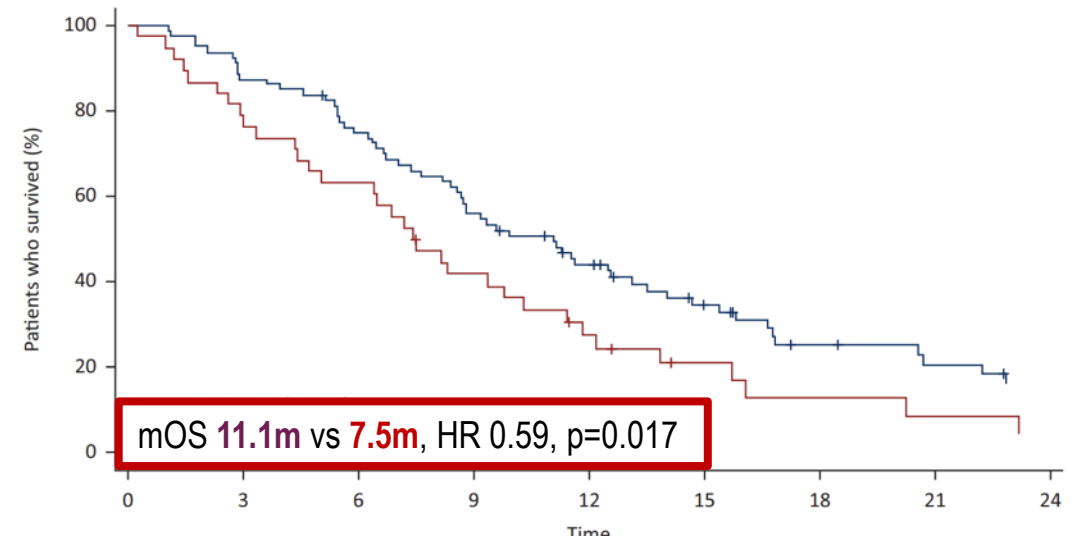
9 EPITOPES (TAA PEPTIDES) TARGETING 5 TAAS FREQUENTLY OVEREXPRESSED IN MANY CANCERS:

TAAs	Wild-type and neo-epitopes
CEA	1 heterocyclic*
	1 heterocyclic
p53	1 heterocyclic
	1 fixed-anchor**
HER-2	1 fixed-anchor
	1 fixed-anchor
MAGE-2	1 wild-type***
	1 wild-type
MAGE-3	1 heterocyclic
	1 heterocyclic

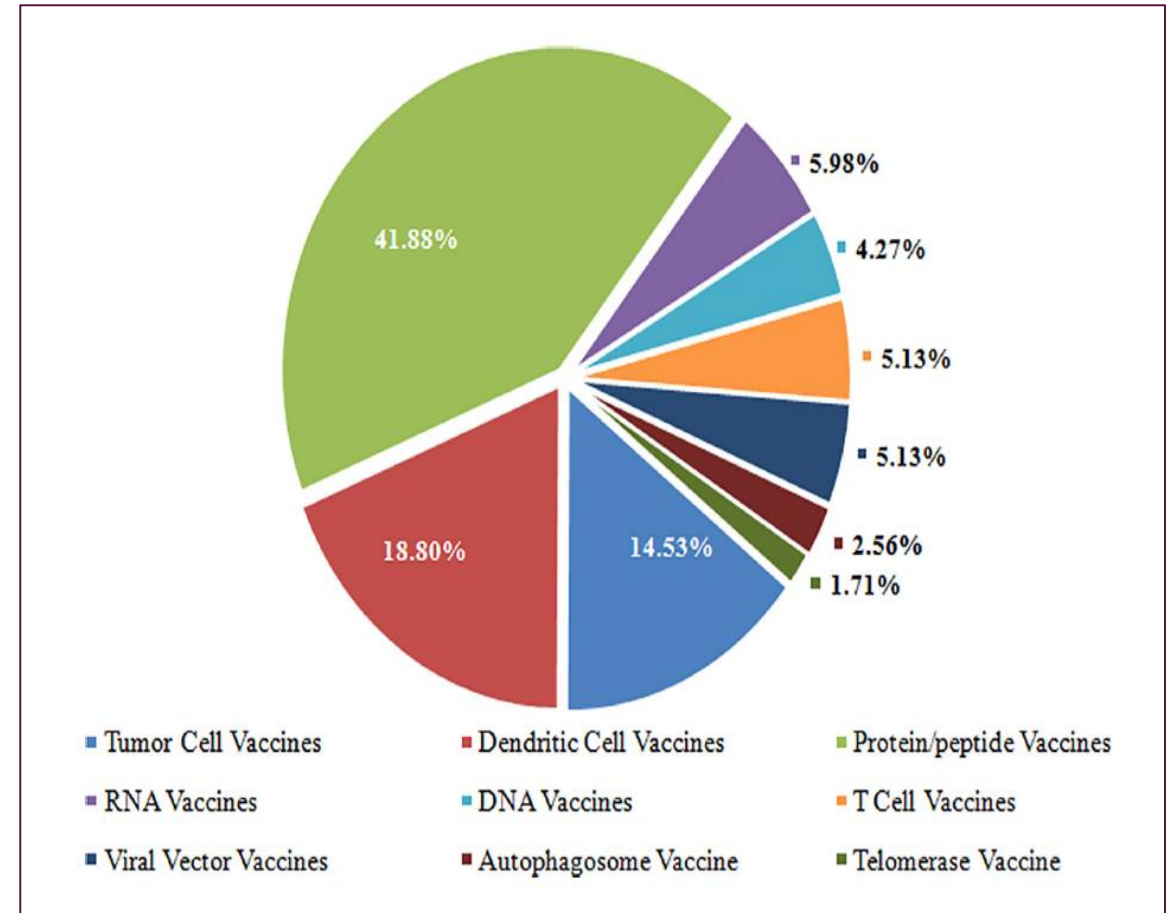
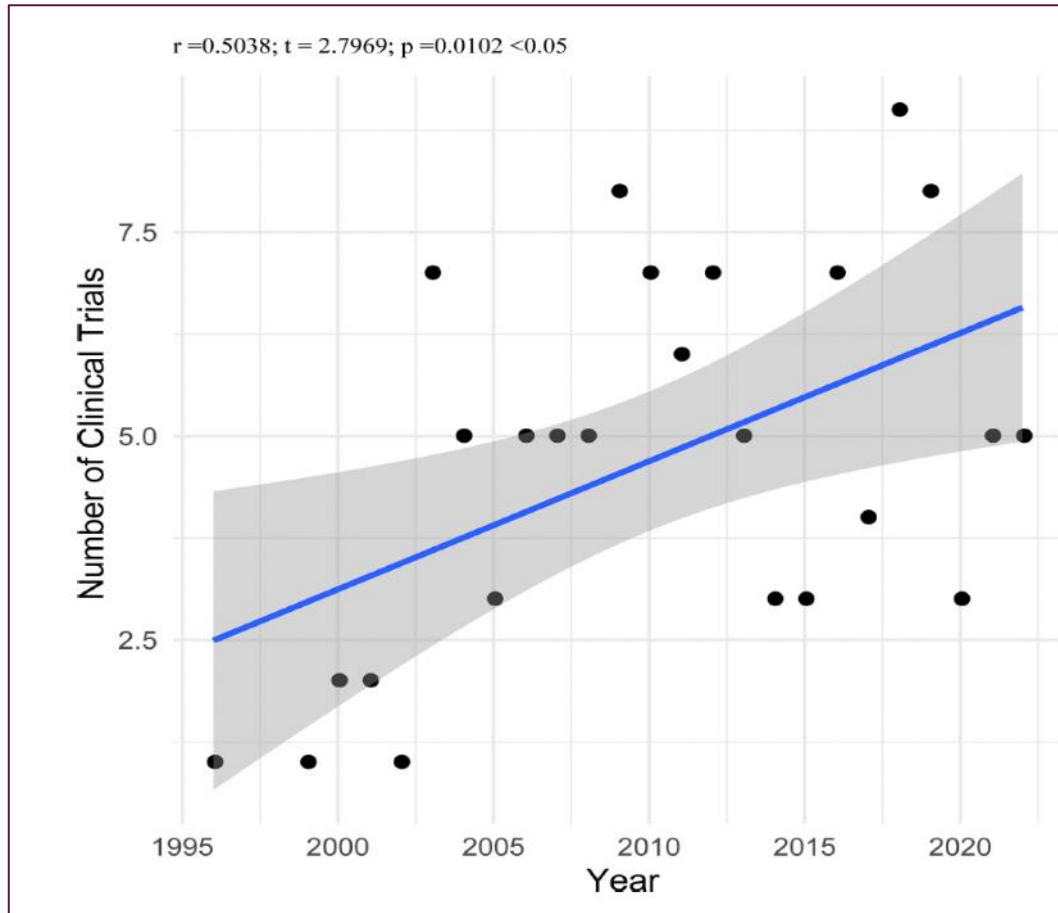
+ 1 Pan DR T Helper cell epitope (PADRE)

Emulsified in mineral oil adjuvant.

* Heterocyclic analogs have an increased TCR affinity**.
** Anchor analogs have an increased affinity to HLA binding**.
*** Wild-type epitopes with a high HLA-A2 binding.



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



CONCLUSIONS

- Second Line Treatment represents an effective and important part of lung cancer treatment
- Second Line Treatment should be offered to all eligible patients (we should be able to beat the 50%)
- Second Line Treatment has undergone significant changes with the implementation of immunotherapies
- Second Line Treatment will have to undergo significant changes with the introduction of immunotherapies in first-line treatment

Thank you!

Martin Reck, m.reck@lungenclinic.de
Twitter: @MartinReck2

Contacts ESMO

European Society for Medical Oncology
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org

