15th MADRID CONGRESS on Lung CANCER

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Duration of therapy and retreatment opportunities

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Thoracic Tumors Unit
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DISCLOSURES

Personal financial interests

- **Consulation Honoraria**: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, Lilly, MSD, Pfizer, Sanofi, Takeda, Pfizer
- **Speaker Honoraria**: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, MSD, Novartis, Pfizer, Takeda, Merck, Amgen, Pfizer

Institutional financial interests

- **Clinical Trials:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, DaiichiSankyo, F. Hoffmann-La Roche, GSK, Janssen, Lilly, Merck, Mirati Therapeutics, MSD, Novartis, Amgen, Pfizer
- **Research Grant**: BMS, F. Merck, Pfizer

TODAY´S TOPICS

- TREATMENT DURATION
- RECHALLENGE

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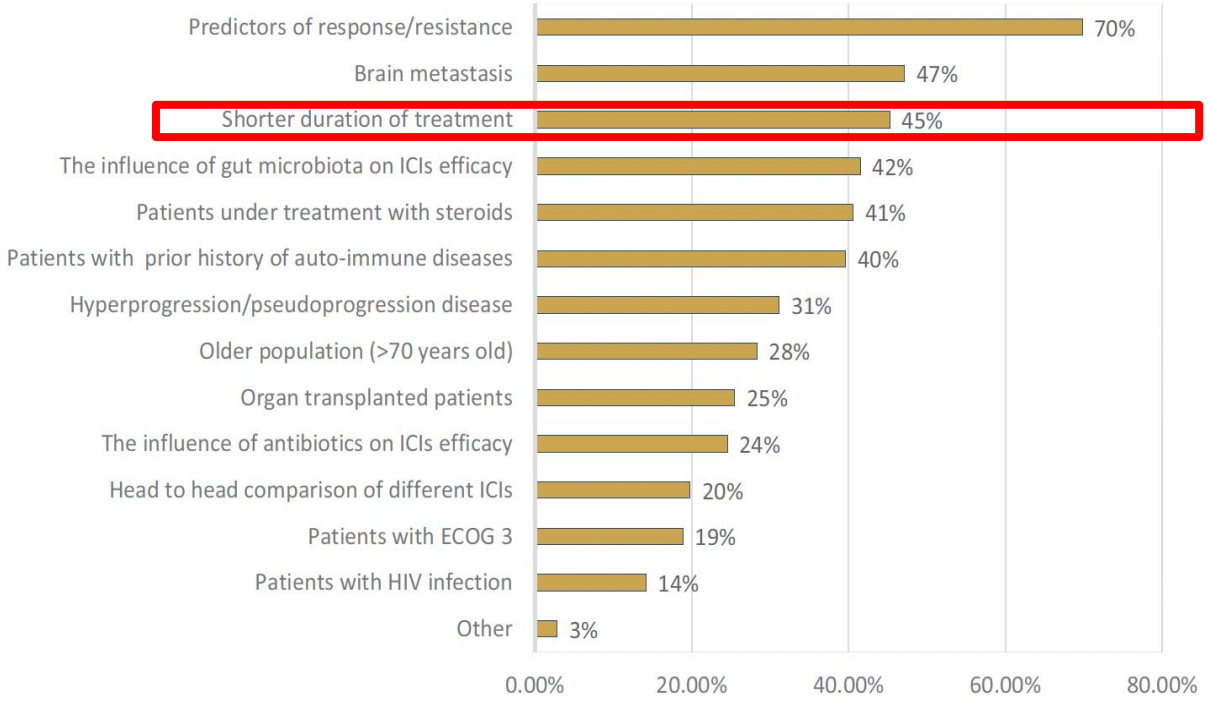
DURATION OF TREATMENT

C

Could you please choose, in your opinion, up to 5 (maximum) most important challenges for clinical practice with ICIs monotherapy in NSCLC to be addressed in further prospective clinical research?



Treatment outcomes

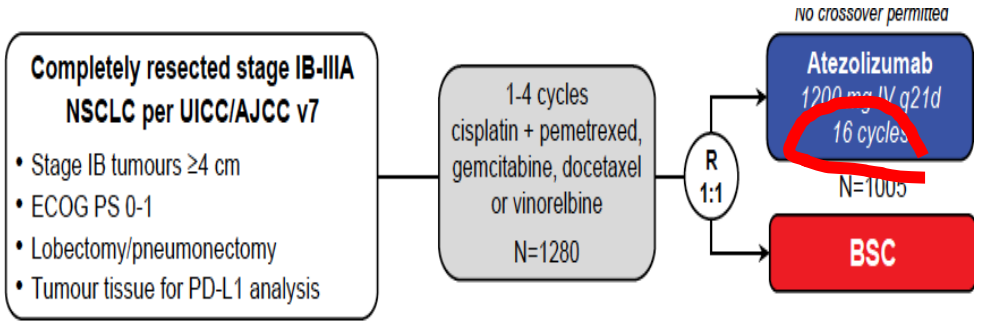
Challenges	Pseudoprogression disease	Hyperprogression disease	Predictors of response	Duration of treatment	Comparing anti-PD-1 versus anti-PD-L1
Completely disagree	3.77%	1.89%	0%	0%	3.77%
Disagree	12.26%	7.55%	0.94%	0.95%	20.75%
Neutral	23.58%	14.15%	9.43%	10.48%	26.42%
Agree	46.23%	52.83%	42.45%	39.05%	34.91%
Completely agree	14.15%	23.58%	47.17%	49.52%	14.15%

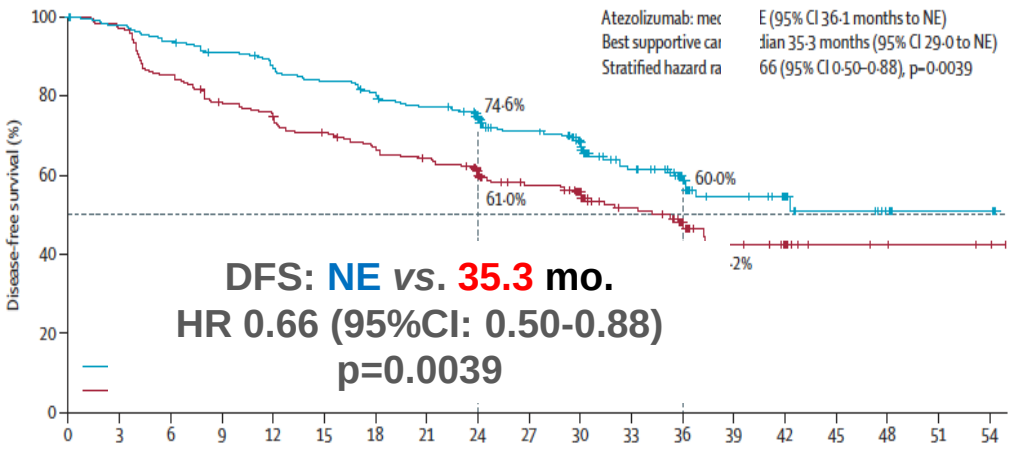
Castelo-Branco et al. ESMO Open 2023

IMpower 010 (DFS in II-IIIA, PD-L1≥1%)

PD-L1> 1% II-IIIA

PD-L1> 50% II-IIIA





PEARLS (DFS in Overall population)

IB-IIIA irrespective of PD-L1 expresión and stage

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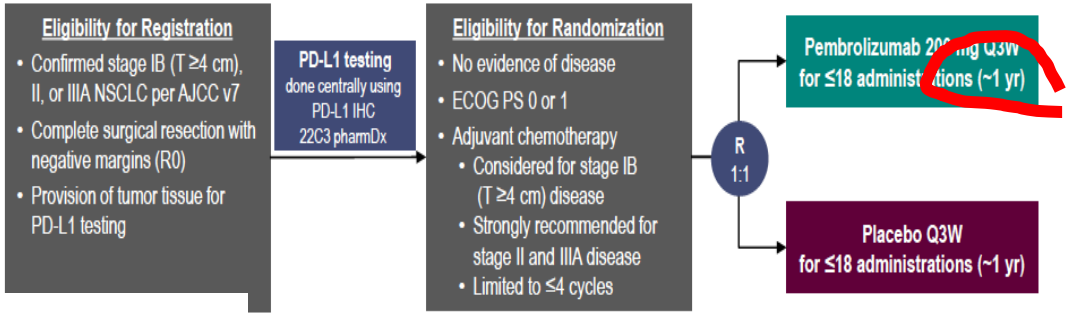

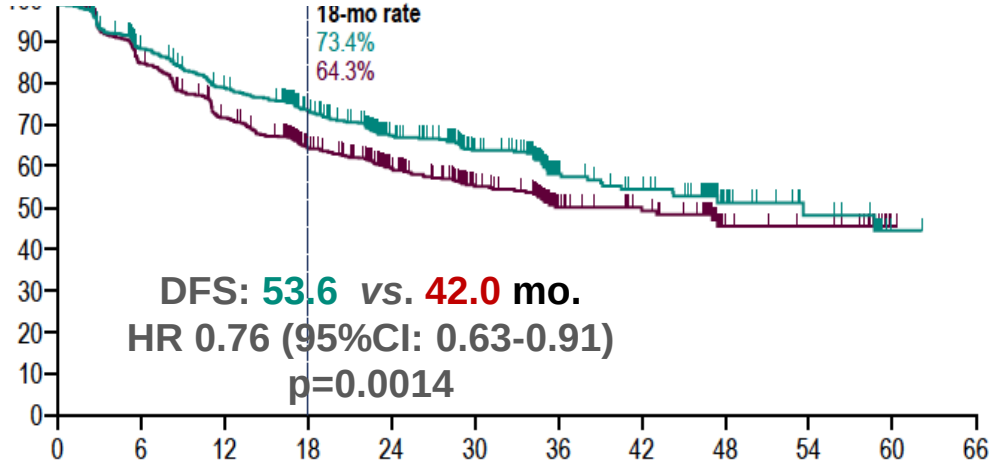

Felip Et, et al. Lancet Oncol 2022
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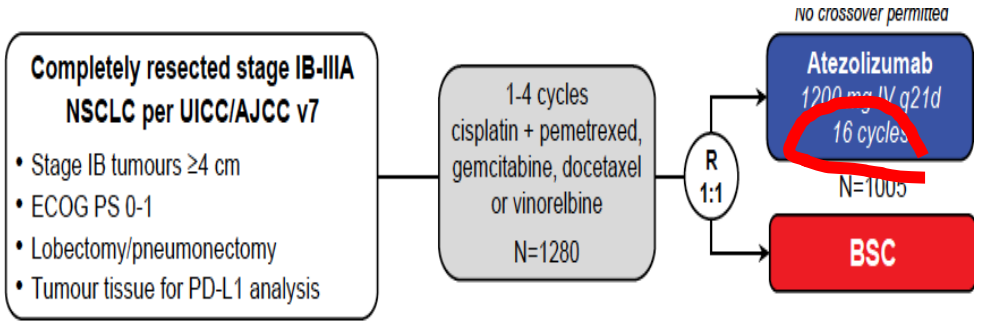

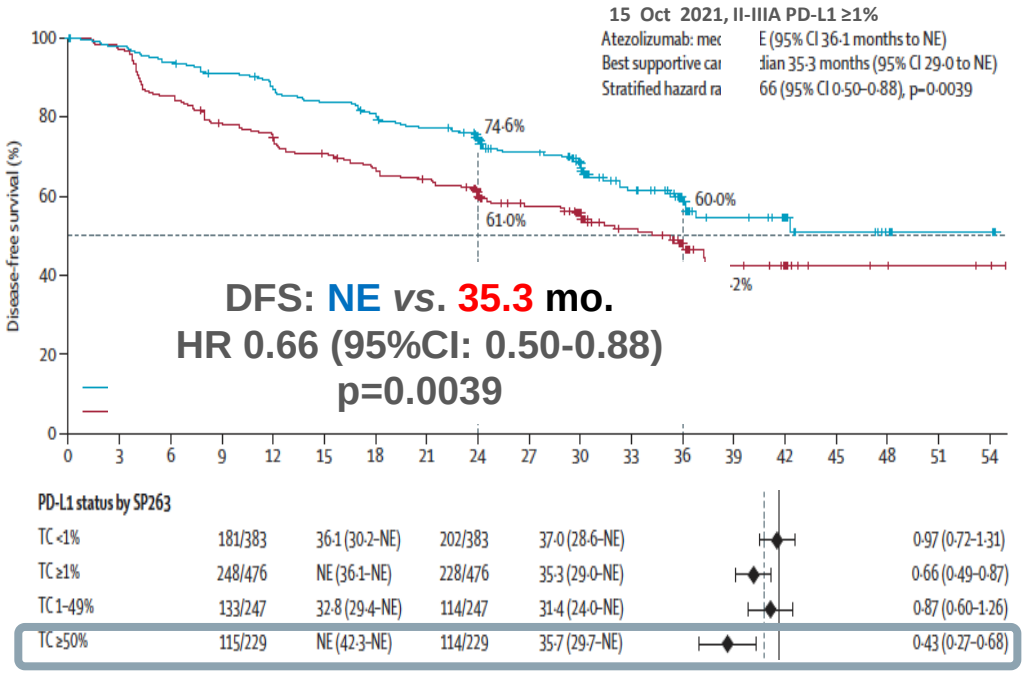

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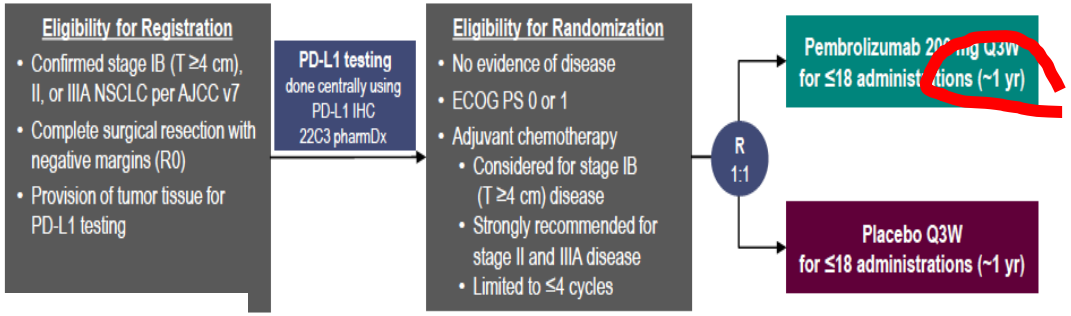

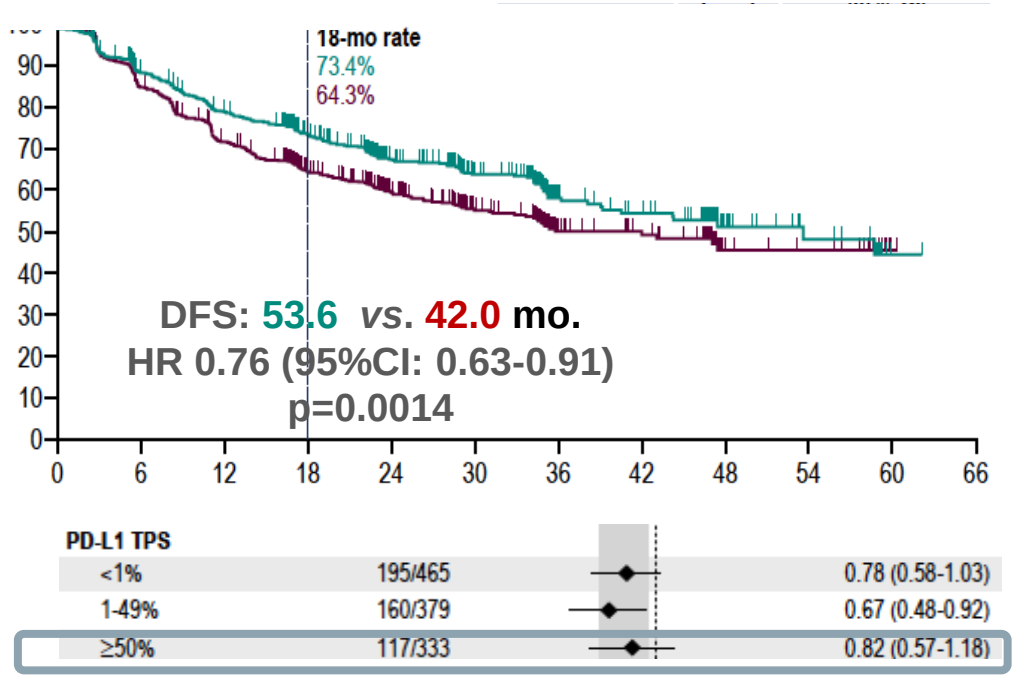

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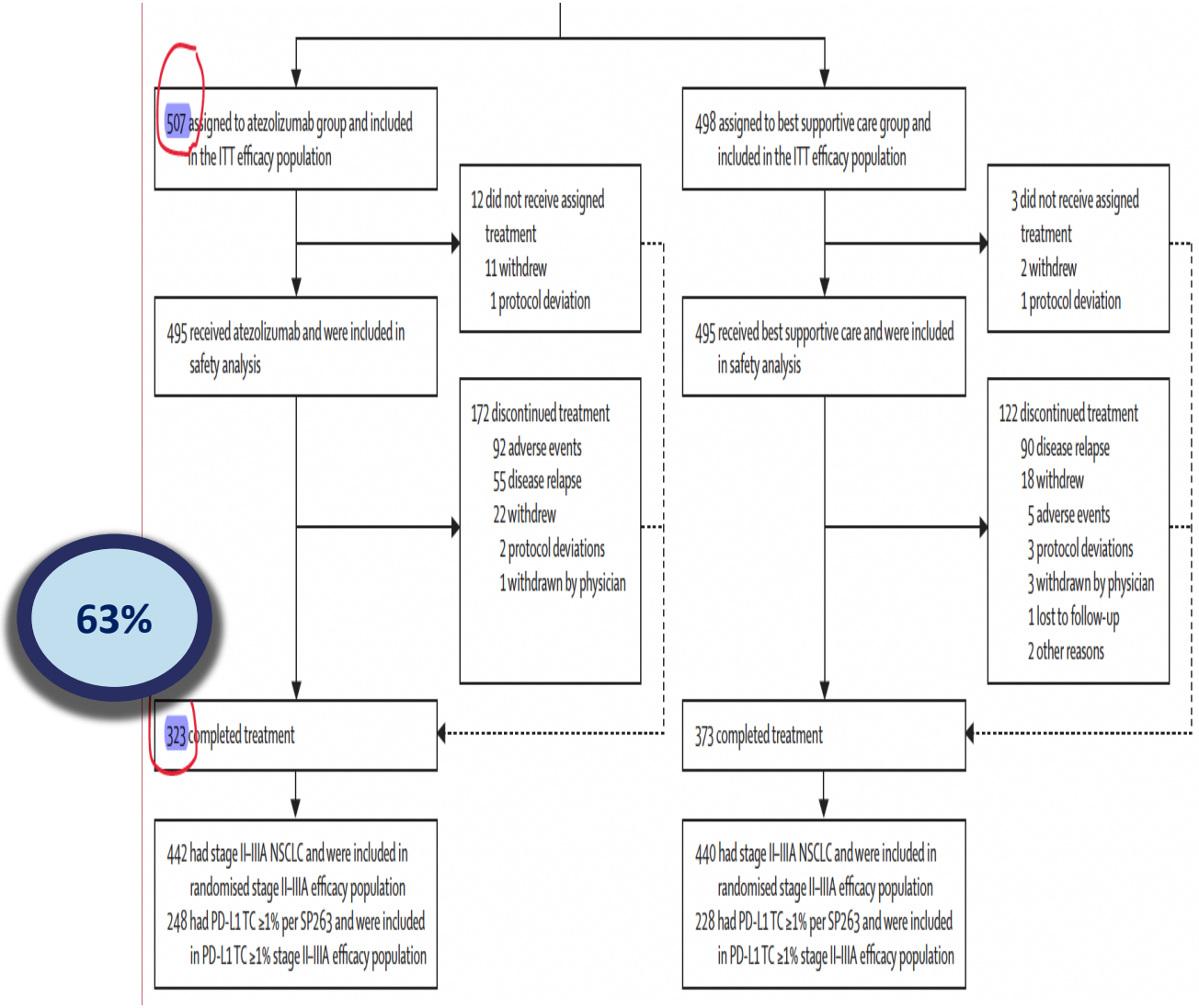

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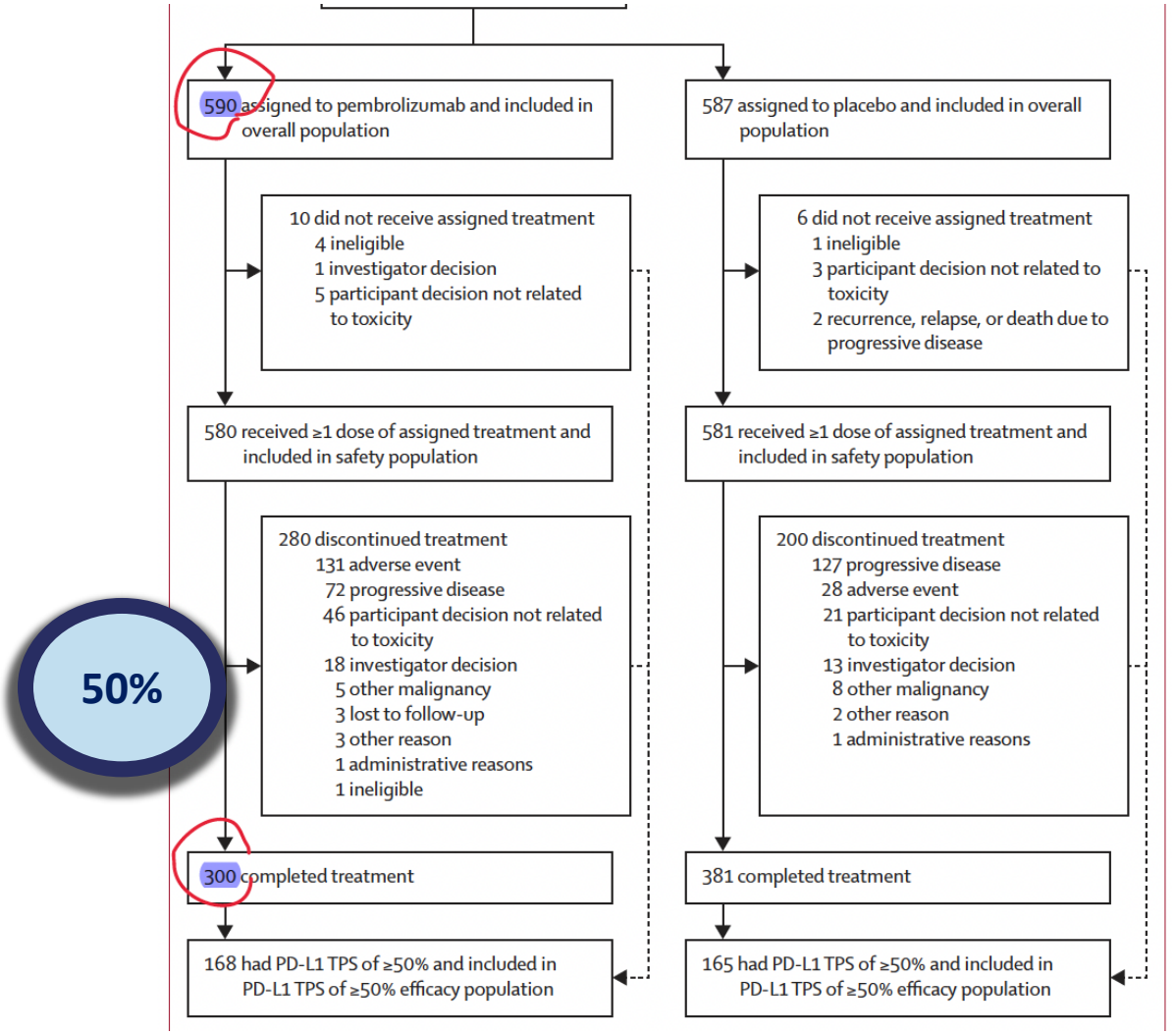

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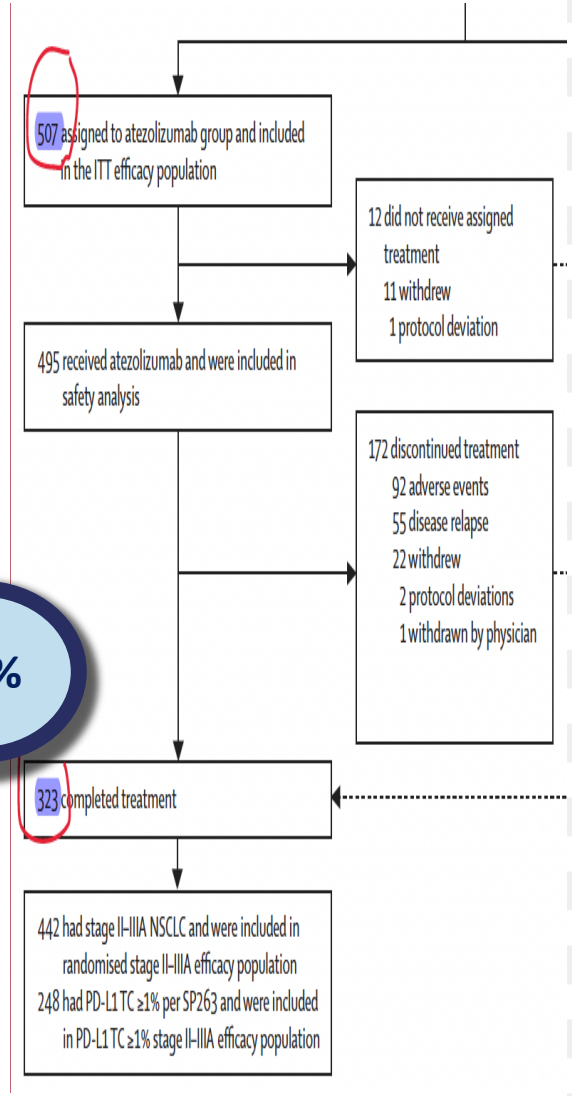

63%

1 year

Felip Et, et al. Lancet Oncol 2022
Paz-Ares L et al. ESMO plenary 2022; O´Brien Lancet 2022

NEOADJUVANT AND PERIOPERATIVE TRIALS

Trial	Schedule	Neoadj (Cycles)	Adjuvant (months)	MPR (%)	PCR (%)	EFS m HR	OS HR
CHECKMATE 816	Nivolumab + Chemotherapy	3 3 cy: 86%	0	37	24	21.1 vs NR (HR=0.68)	NR vs NR HR 0.62
NADIM-2	Nivolumab + Chemotherapy	3 3cy: 94%	6 66% compl	52	36	18.3 VS NR HR0.48	NR vs NR **HR 0.43***
AEGEAN	Durvalumab + Chemotherapy	4 4cy: 86%	12 24% compl 23% ongoing	33.3	17.2	25. vs NR HR=0.68	NA
NEOTORCH	Toripalimab + Chemotherapy	3@ 3cy: 87%	12 43% compl	48.5	24.8	15.5 vs NR HR=0.40	30.4 vs NR HR 0.62
KEYNOTE 671	Pembrolizumab + Chemotherapy	4 3cy: 87% 4cy: 76%	12 40% Compl	30	18	18.3 vs 47.2 HR 0.58	52.4 vs NR **HR 0.72***
CHECKMATE 77T	Nivolumab+ Chemotherapy	4 4cy 85%	12 60% compl	35.4	25.3	18.4 VS NR HR 0.58	NA
RATIONALE 315	Tislelizumab+ Chemotherapy	3-4 93.4%	12 ??	56.2	40.7	NA	NA

Neoadjuvant | Perioperative

Forde PM et al NEJM 2022; Girard et al ELCC 2023; Provencio et al NEJM 2023; Heymach J et al AACR 2023.
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EFS HR 0.5-0.6
OS HR 0.72*

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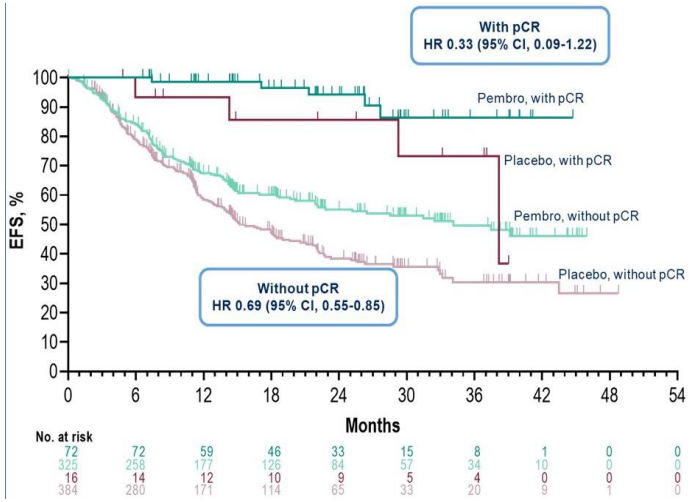
CM 671



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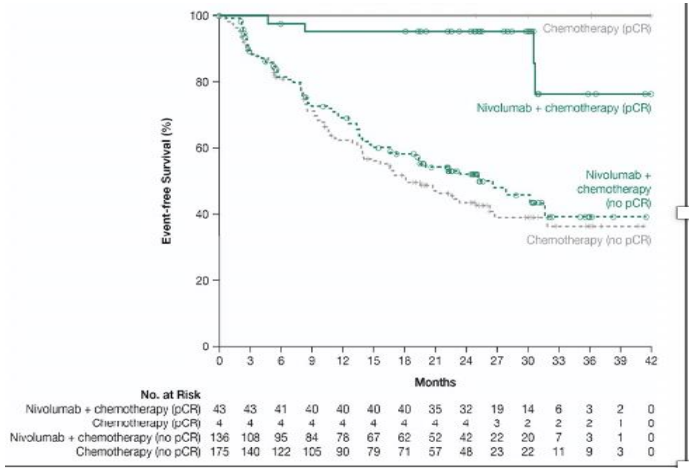

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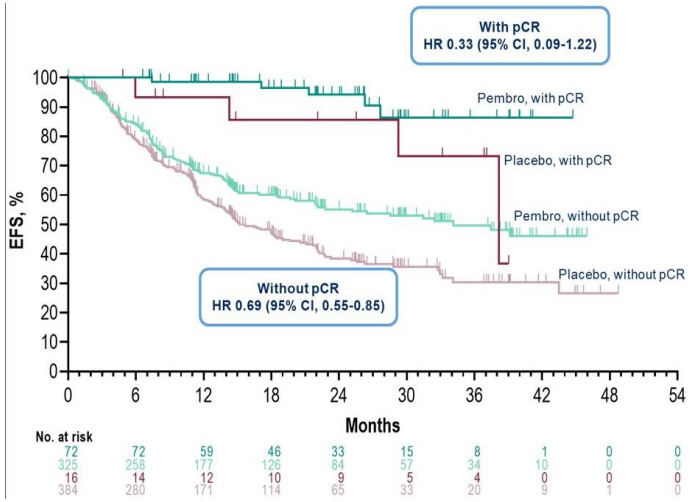

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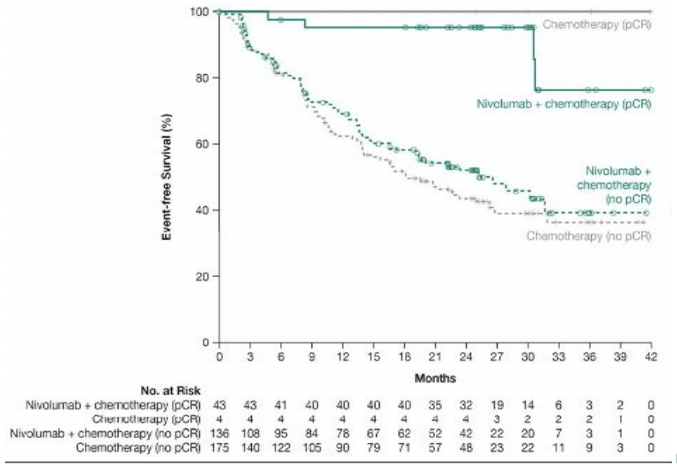

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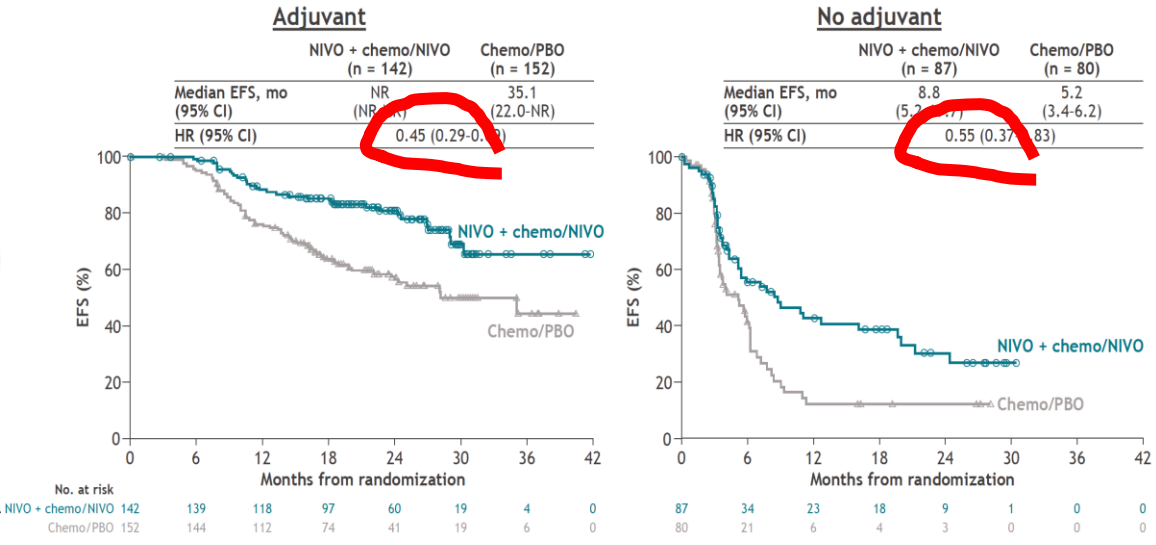

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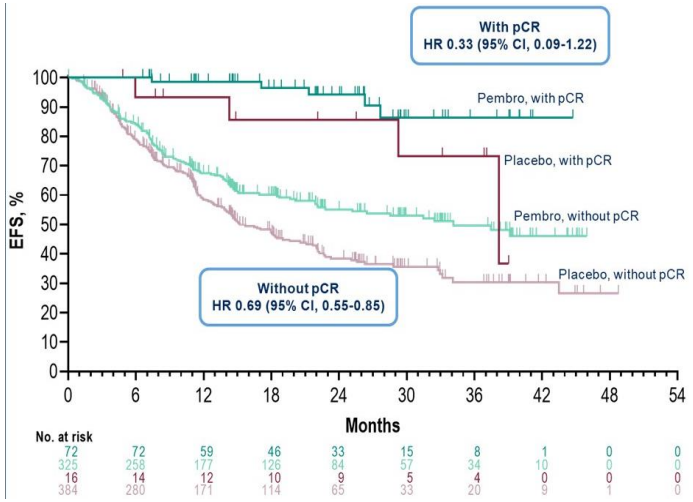

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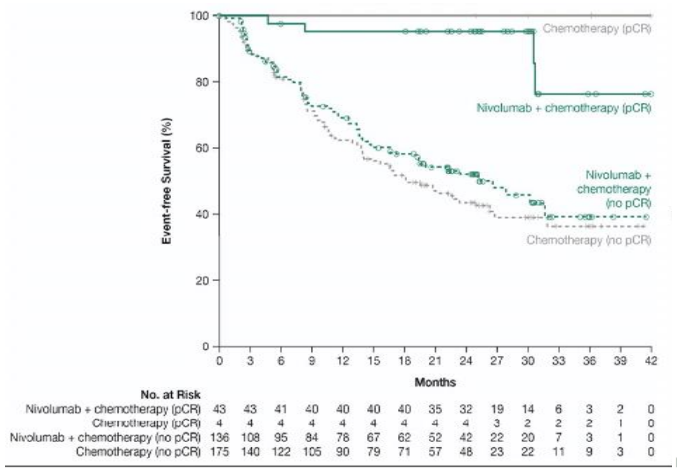

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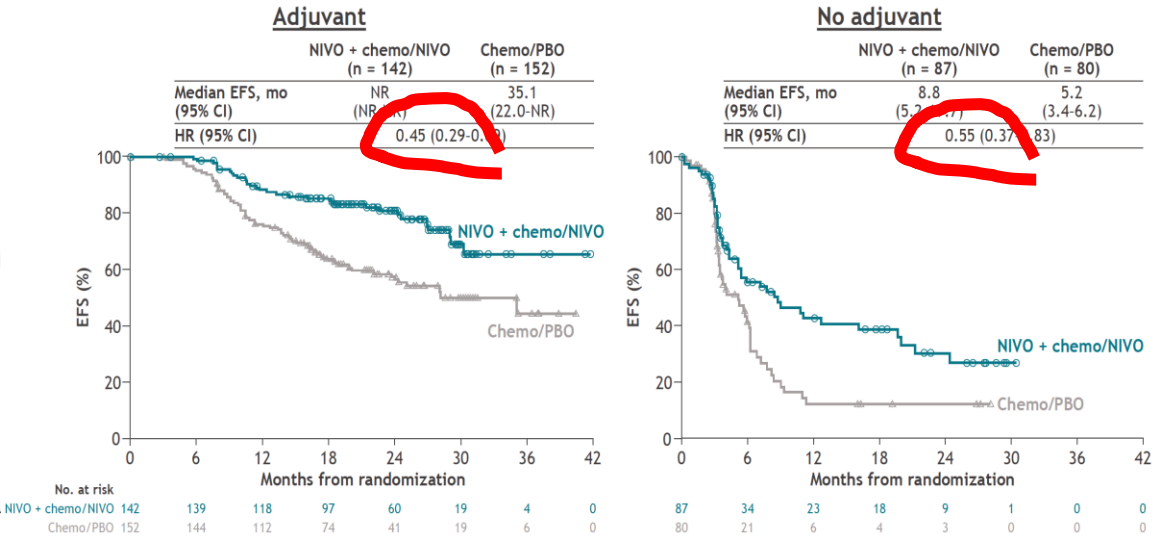

NADIM 2

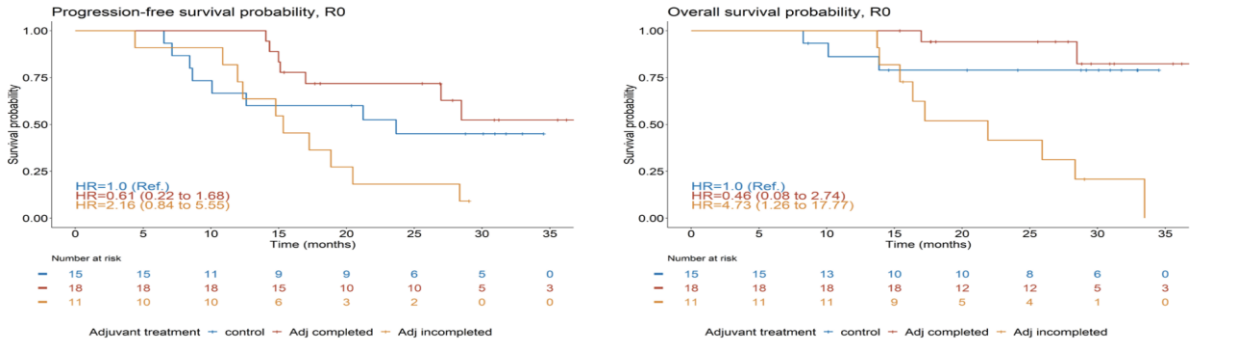

Figure S10. Progression-free survival (PFS) (left panel) and overall survival (OS) (right panel) in R0 according to adjuvant treatment in patients who did not achieve a pathological complete response. Control arm did not receive adjuvant treatment with nivolumab.

Among patients with R0 those who completed adjuvant treatment had better survival outcomes than those who did not complete adjuvant treatment

Forde PM et al NEJM 2022; Girard et al ELCC 2023; Spicer J, ESMO 2023, Cascone T ESMO 2023

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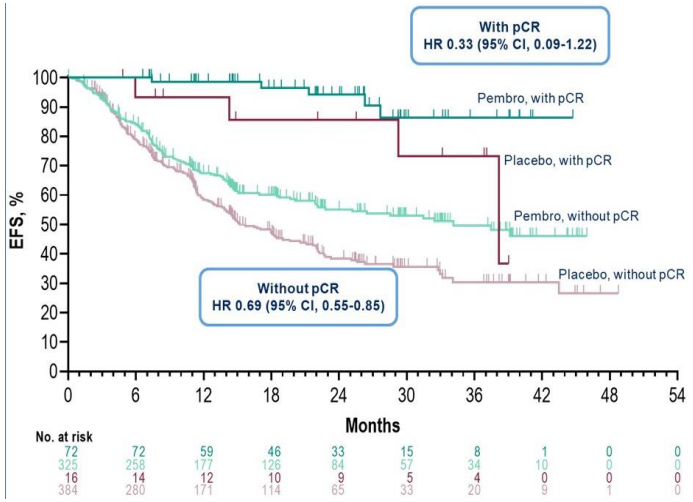

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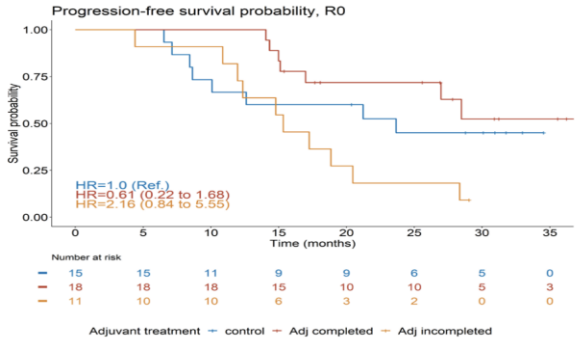

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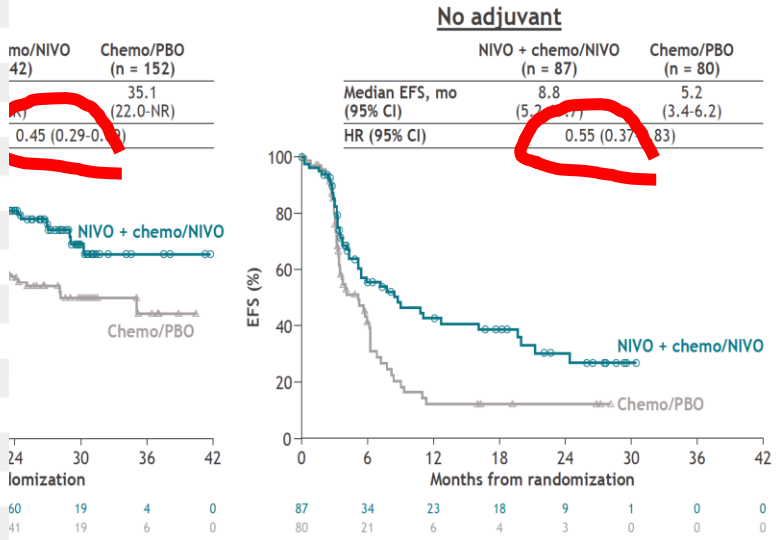
1 year

CM 77T



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PACIFIC

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT → R

Durvalumab 10 mg/kg q2w for up to 12 months

2:1 randomization, stratified by age, sex, and smoking history

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints
- PFS by BICR using RECIST v1.1†
- OS

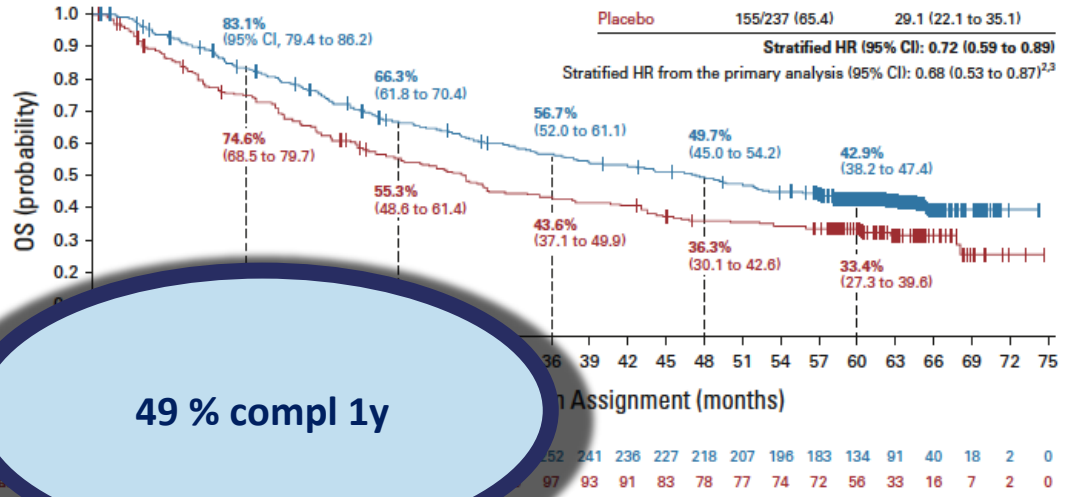
Key secondary endpoints
- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

*Using the Ventana SP263 immunohistochemistry assay

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

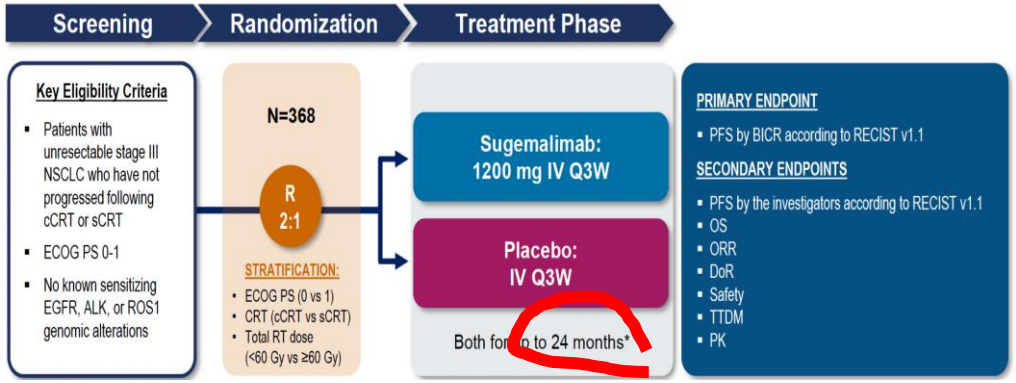
Stratified HR (95% CI): 0.72 (0.59 to 0.89)

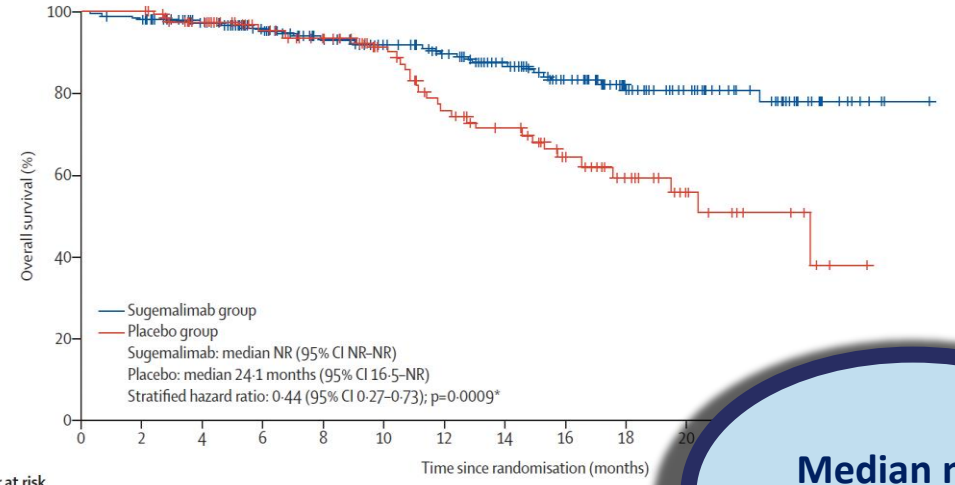
Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



49 % compl 1y

GEMSTONE-301





Number at risk (number censored)

Sugemalimab group	255 (0)	249 (1)	221 (27)	189 (56)	165 (75)	149 (88)	136 (98)	114 (117)	84 (142)	62 (163)	45 (
Placebo group	126 (0)	126 (0)	112 (11)	95 (26)	85 (34)	69 (48)	53 (53)	44 (59)	31 (68)	21 (76)	12 (8

Median nº of cycles: 9

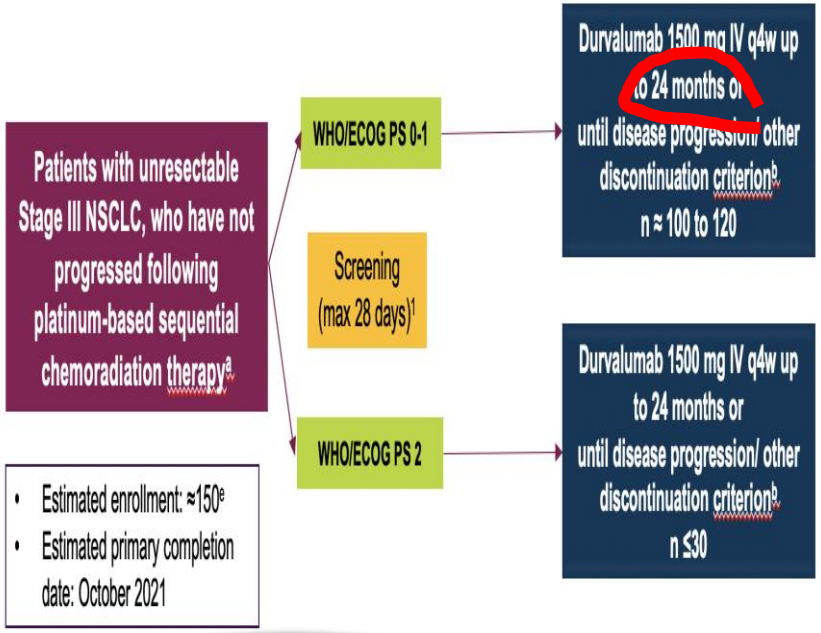
Spigel et al. J Clin Oncol 2022
Zhou et al. Lancet Oncol 2022

PACIFIC 6: Consolidation ICI after sCRT

Stage III unresectable NSCLC
Sequential CRT
No progression post sCRT

→ Durvalumab q4weekly x 2 years

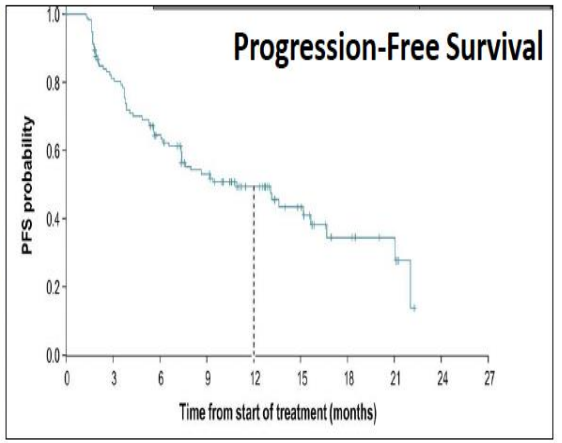
Primary Endpoint: g3+ TRAEs
Secondary Endpts: PFS, OS



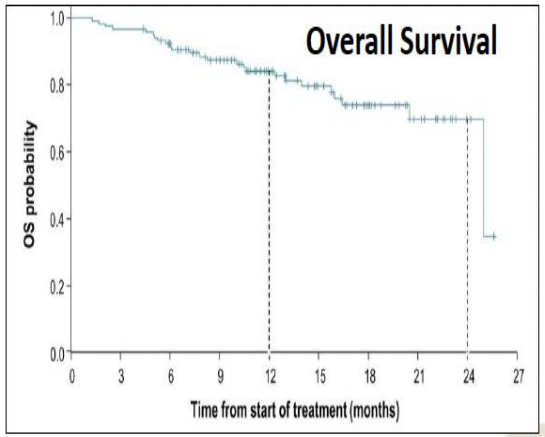
2.6 % compl 2y
Median nº of cycles: 8

Study Population:
117 pts
17.5% age >75yrs (20pts)
3pts ECOG PS2 (age <75yrs)

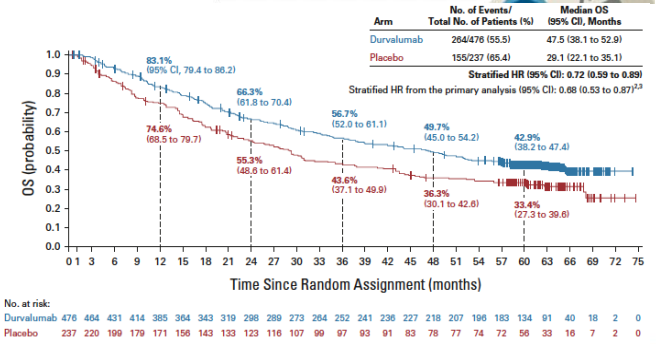
TRAEs:
18.8% g3+ TRAEs
5pts g3+ TRAEs in first 6m



mPFS: 10.9mos
2yr PFS rate: NR



mOS: 25mos
2yr OS rate: 69.8%



Garassino et al. J Thorac Oncol 2022
Spigel et al. JCO 2022

Length of immunotherapy in stage III

PACIFIC 2 (NCT03519971)

Phase III, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Patients with Stage III, locally advanced, unresectable NSCLC

18 years or older

ECOG PS score 0 or 1

Estimated life expectancy of ≥12 weeks

At least 1 lesion, not previously irradiated, that qualifies as a Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 target lesion at baseline.

All-comers population

2:1

Stratification factors
1. Age at randomization
2. Disease stage (Stage IIIA versus IIIB-C)

CRT + Durvalumab IV 1500mg q4w up to until disease progression → Durvalumab 1500mg q4w until disease progression

CRT + placebo → Placebo

Patients with SD, PR, CR

Patients with SD, PR, CR

Co-PRIMARY ENDPOINT
- ORR and PFS using RECIST v1.1

SECONDARY ENDPOINTS
- OS
- OS 24
- DoR
- DCR
- TDDM
- Immunogenicity
- Safety/tolerability

1. In House Data, AstraZeneca Pharmaceuticals LP. CSP D933KC00001

CR = complete response; CRT = chemoradiation therapy; DCR = disease control rate; DoR = duration of response; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PS = performance status; q4w = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; TTDM = time to death or distant metastasis; WHO = World Health Organization.

PACIFIC 5

- Unresectable stage III NSCLC without progression following definitive concurrent/sequential chemoradiation
- WHO PS score 0 or 1
- Prospective EGFR/ALK testing not mandated, but known EGFR/ALK+ subjects are excluded
- ≤ 28 d from last radiation to first dose
- Mandatory tissue sample

Randomization 2:1

Durvalumab 1500mg Q4W (N=240)

Placebo (N=120)

- Treat to progression
- Fixed dosing with 1500 mg Q4W

Primary endpoint: PFS by BICR

Key secondary: OS

Stratification factors:
1. Prior therapy: (cCRT versus sCRT)
2. PD-L1 <1% v PD-L1>1%

Key Design features:
Sample size: N=360
- Recruitment split 50:50 between cCRT and sCRT

1. ClinicalTrials.gov. NCT03519971. Disponible en: https://clinicaltrials.gov/ct2/show/NCT03519971 [Último acceso: 11/11/2019]
2. ClinicalTrials.gov. NCT03706690. Disponible en: https://clinicaltrials.gov/ct2/show/NCT03706690 [Último acceso: 11/11/2019]

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All-comers population

NEGATIVE

2:1

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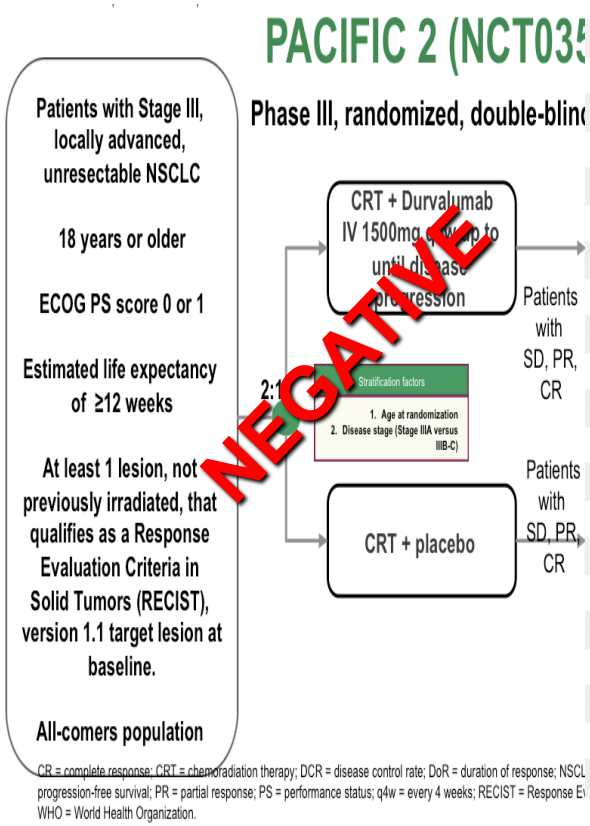
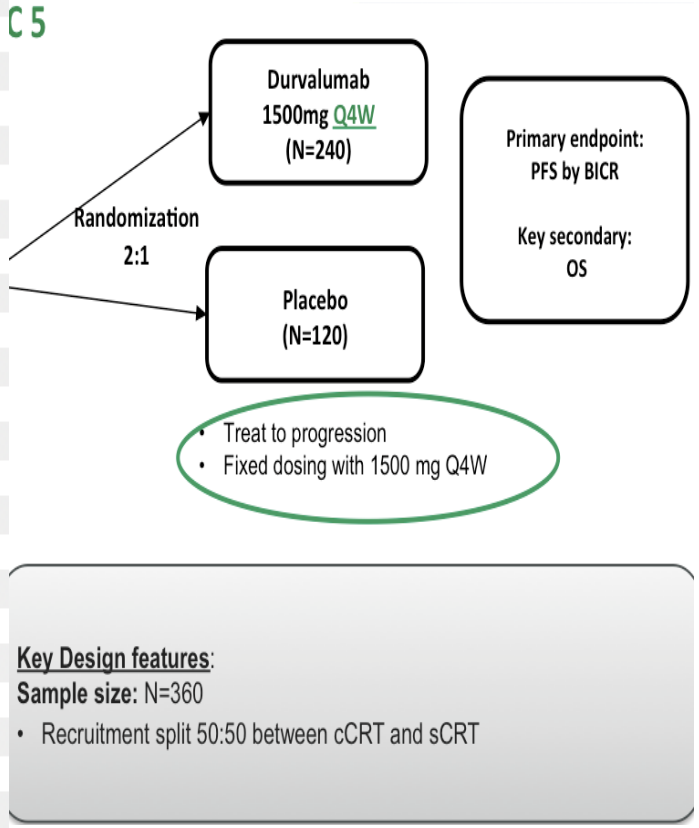
Length of immunotherapy in stage III





1. ClinicalTrials.gov. NCT03519971. Disponible en: https://clinicaltrials.gov/ct2/show/NCT03519971 [Ultimo acceso: 11/11/2019]
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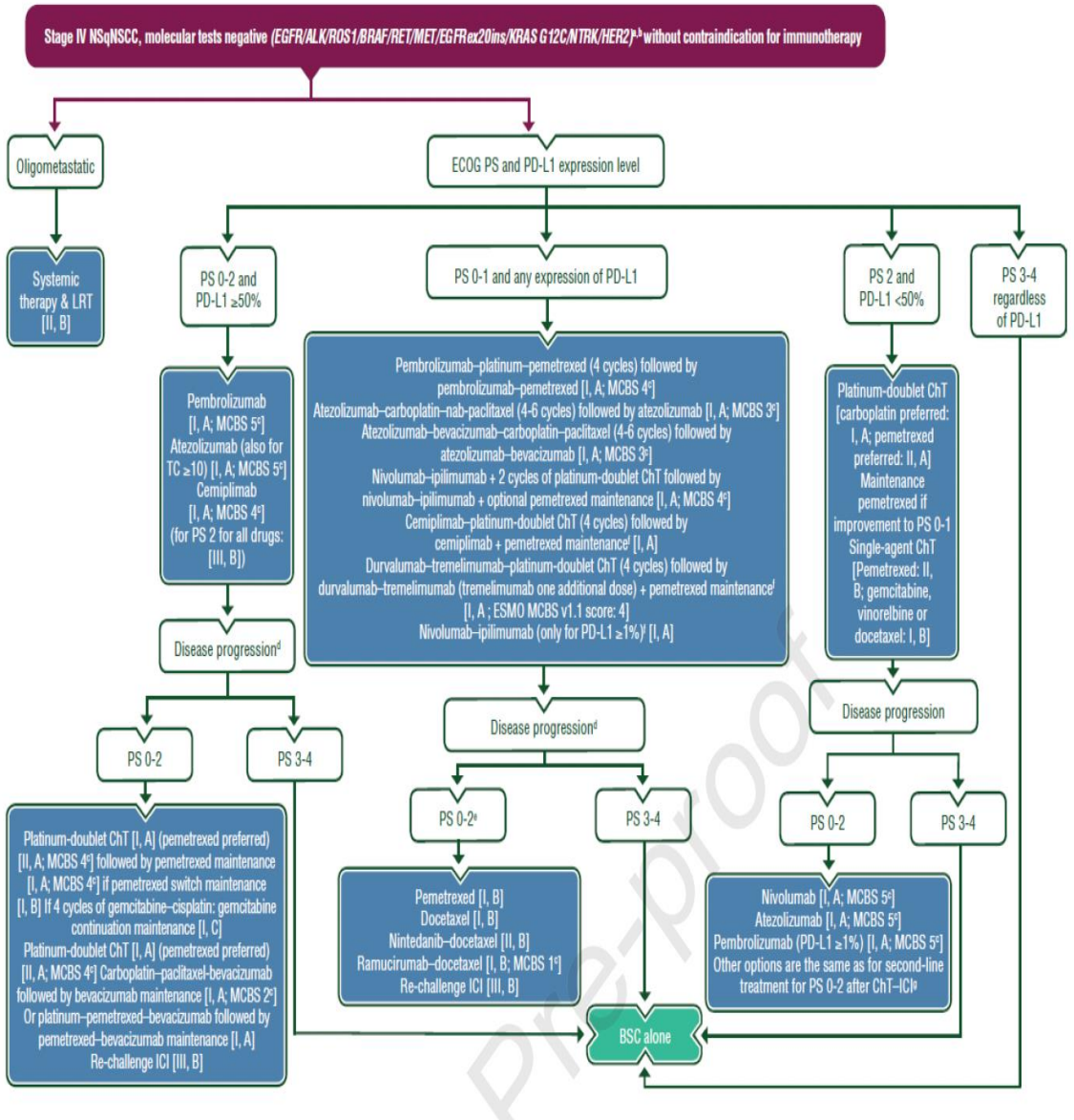
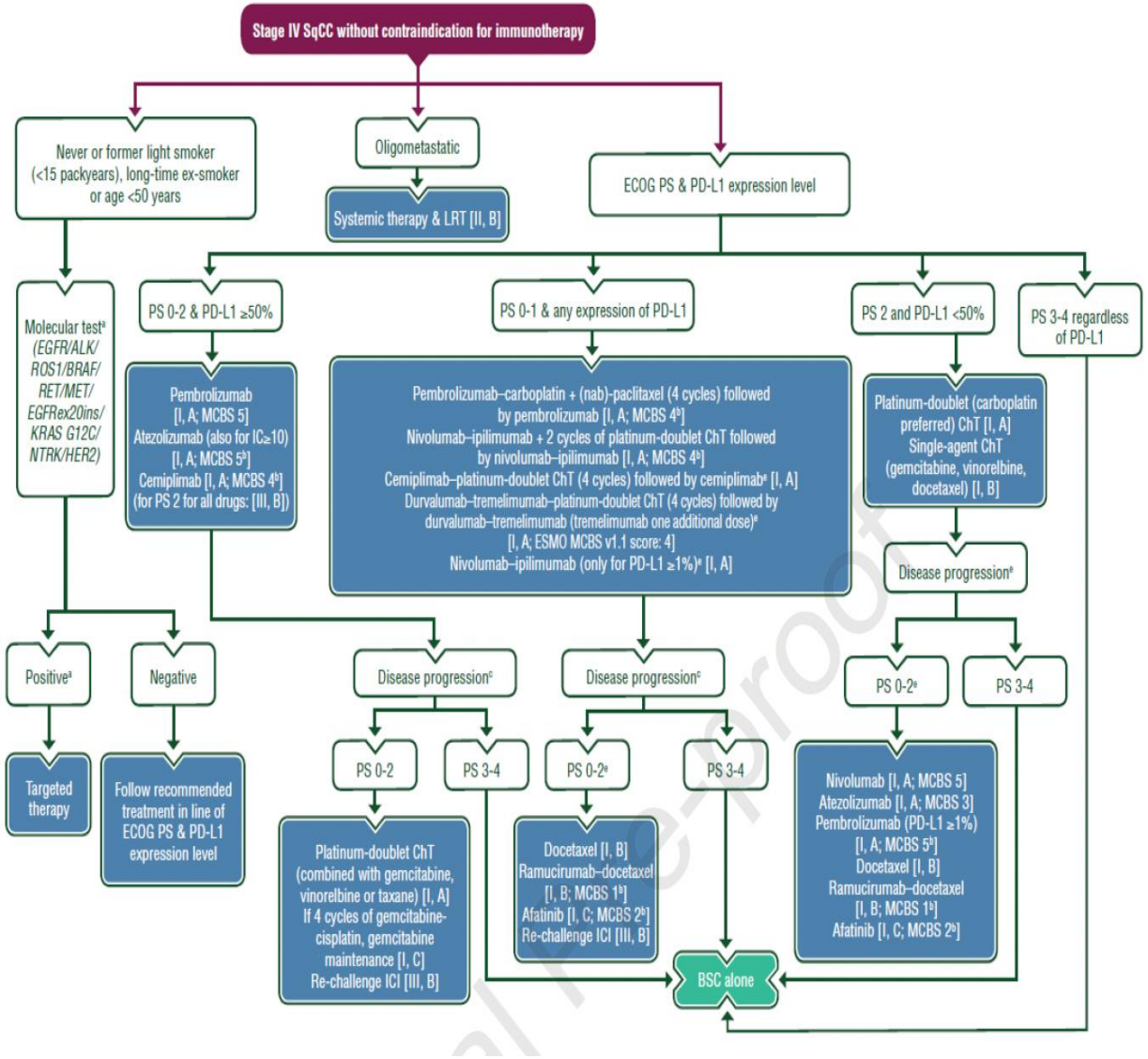
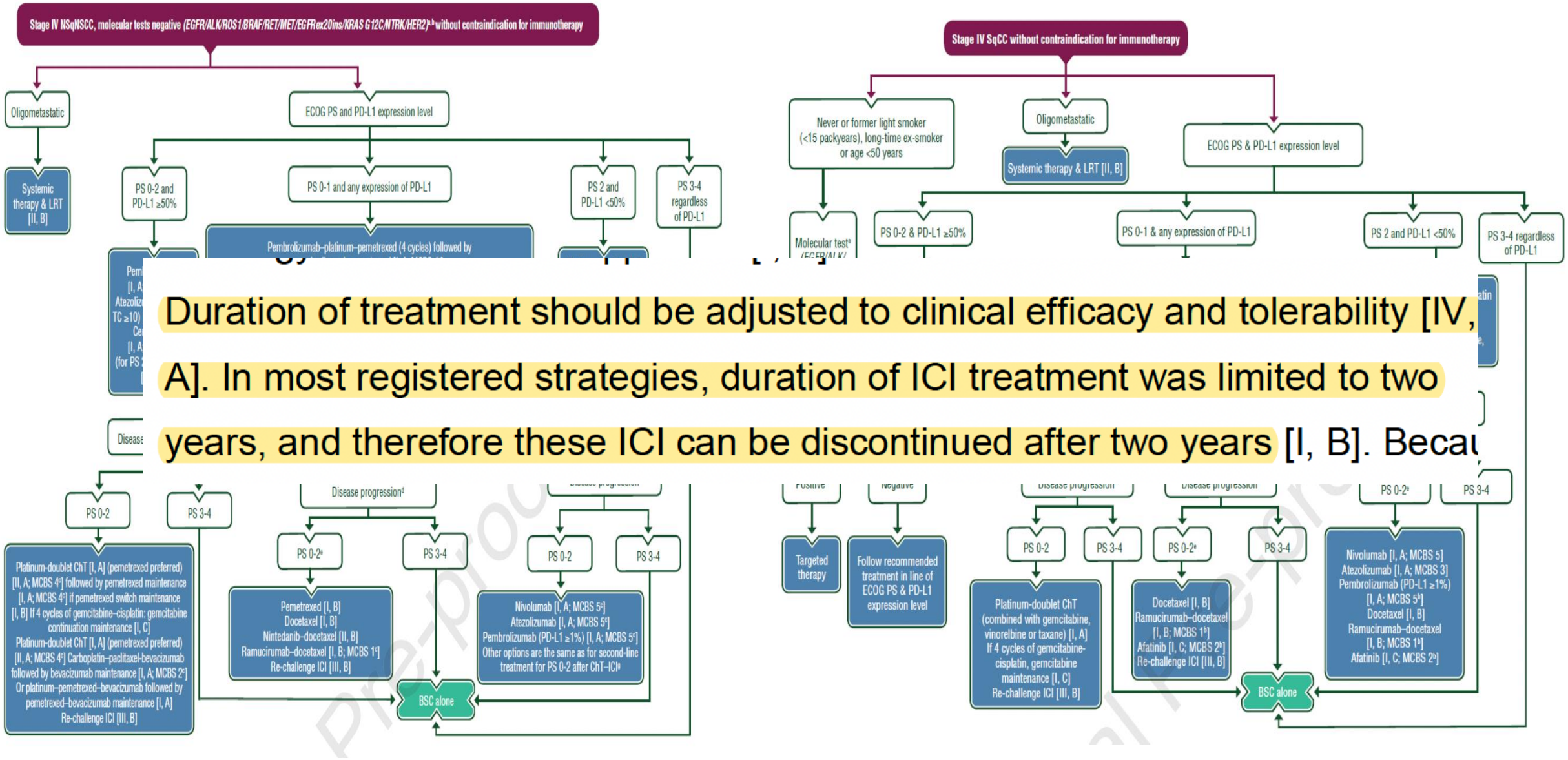




Hendriks LE, et al. Ann Oncol. 2023



Duration of treatment should be adjusted to clinical efficacy and tolerability [IV, A]. In most registered strategies, duration of ICI treatment was limited to two years, and therefore these ICI can be discontinued after two years [I, B]. Becau

Hendriks LE, et al. Ann Oncol. 2023

IO MONOTHERAPY IN UNPREVIOUSLY TREATED NSCLC, PD-L1 ≥50%

PD-1 inhibitor

KEYNOTE-024 Study Design (NCT02142738)

Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

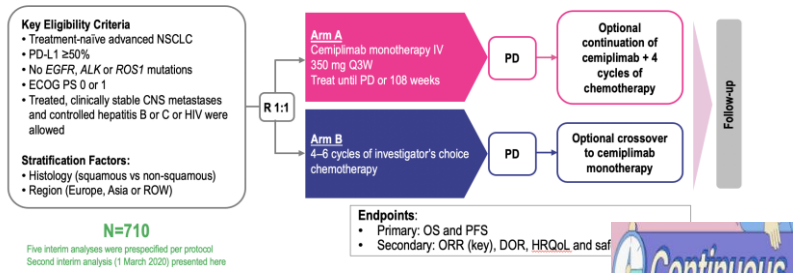
Secondary: OS, ORR, safety

Exploratory: DOR

2 YEARS

POSITIVE

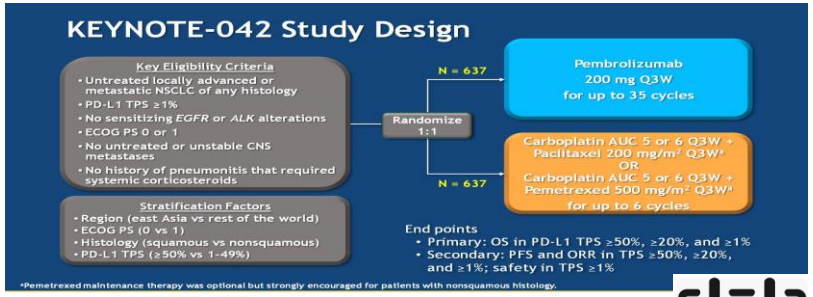
EMPOWER-Lung 1 Study Design (NCT03088540)



Continuous

POSITIVE

KEYNOTE-042 Study Design



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 PRESENTED BY: Gilberto Lopes

POSITIVE

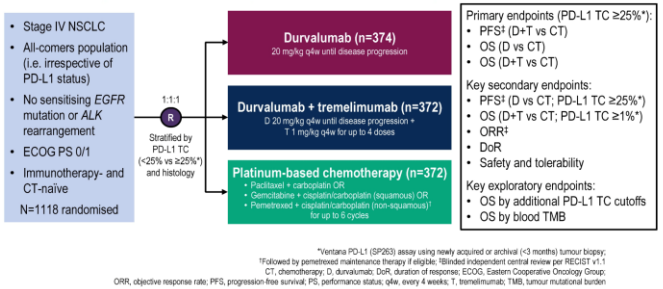
2 YEARS

Lopes G, et al. ASCO 2018.

PD-L1 inhibitor

MYSTIC: Study Design

Phase 3, global, randomised, open-label, multicentre study

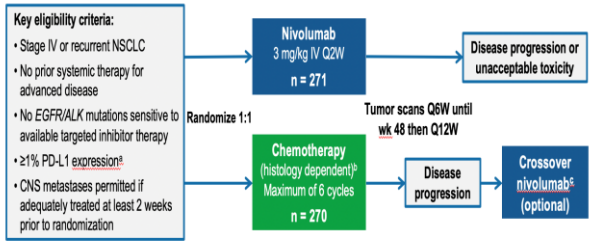


*Ventana PD-L1 (SP263) assay using newly acquired or archival (<3 months) tumour biopsy; †Followed by pemetrexed maintenance therapy if eligible; ‡Blinded independent central review per RECIST v1.1
CT, chemotherapy; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PFS, progression-free survival; PS, performance status; q4w, every 4 weeks; T, tremelimumab; TMB, tumour mutational burden

NEGATIVE

Continuous

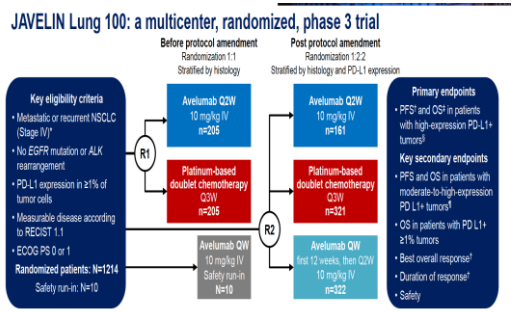
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



NEGATIVE

Continuous

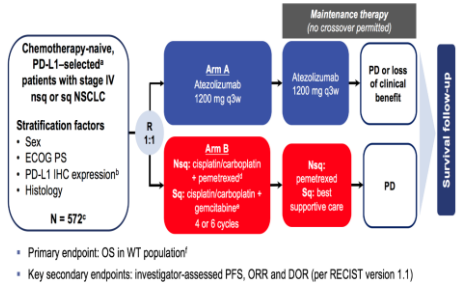
JAVELIN Lung 100: a multicenter, randomized, phase 3 trial



NEGATIVE

Continuous

IMpower110 Study Design



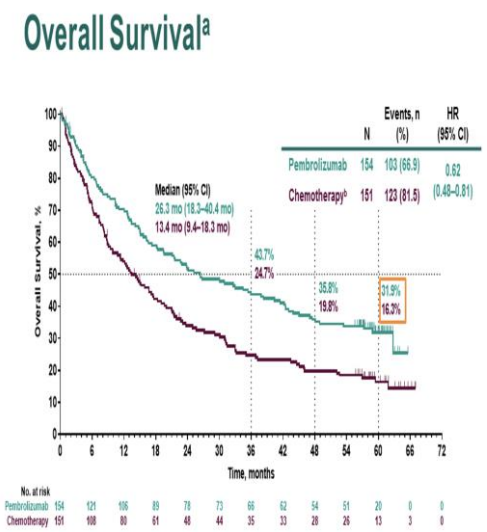
POSITIVE???

Continuous

IO MONOTHERAPY IN UNPREVIOUSLY TREATED NSCLC, PD-L1 ≥50%

2 YEARS

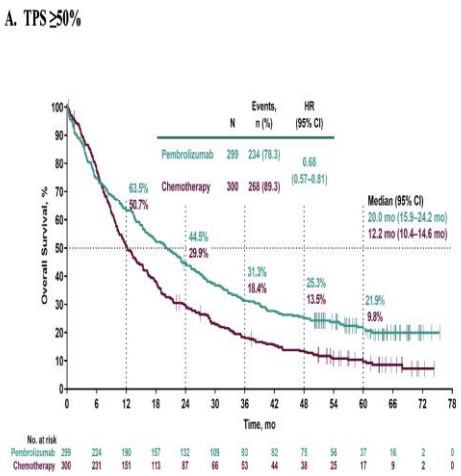
KEYNOTE 024, PD-L1 ≥50% (22C3)
Follow-up: 5-years



OS: 26.3 *vs.* 13.4 , HR 0.62

2 YEARS

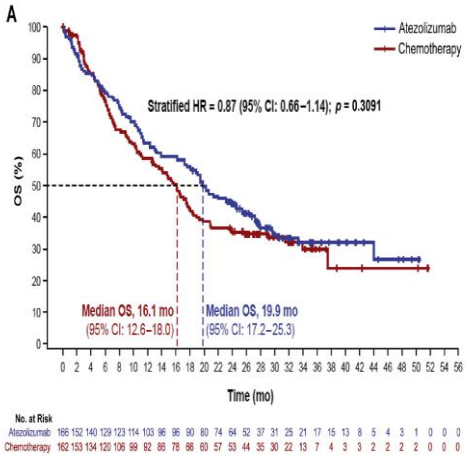
KEYNOTE 042, PD-L1 ≥50% (22C3)
Follow-up: 5 -years



OS: 20.0 *vs.* 12.2 , HR 0.68

Continuous

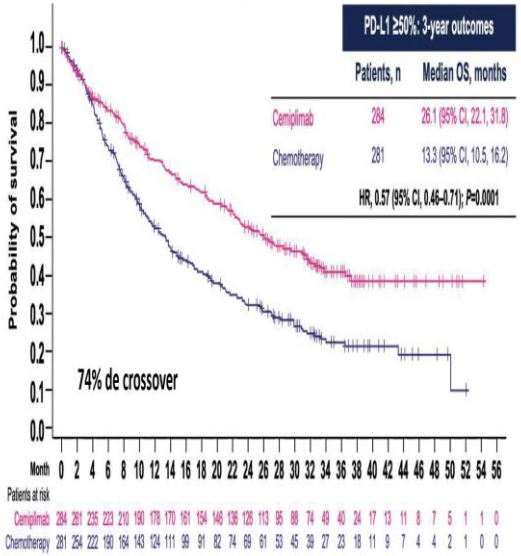
IMPOWER 110, PD-L1 TC3/IC3 (SP142)
Follow-up: 31 months



OS: 19.9 vs. 16.1 , HR 0.87

Continuous

EMPOWER LUNG 1 (22C3)
Follow-up: 37.1 months



OS: 26.1 vs. 13.3 , HR 0.57

Reck M, et al. J Clin Oncol 2021; de Castro G, et al J Clin Oncol 2022; Jaseem et al. J Thorac Oncol 2021; Reck M, et al WCLC 2022; Ozguroglu M, et al. Ann Oncol 2022

PD-1 inhibitor
PD-L1 inhibitor

IO MONOTHERAPY IN UNPREVIOUSLY TREATED NSCLC, PD-L1 ≥50%

2 YEARS

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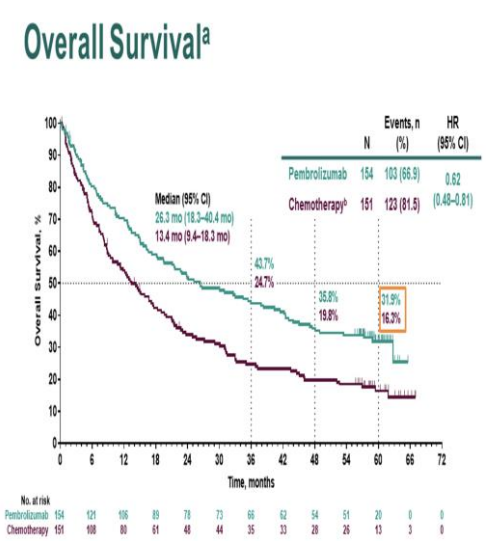
Follow-up: 5-years



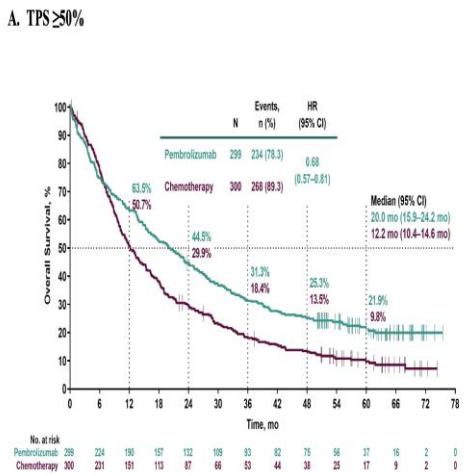
OS: 26.3 *vs.* 13.4 , HR 0.62

2 year completed

25.3%

2 YEARS

KEYNOTE 042, PD-L1 ≥50% (22C3)
Follow-up: 5 -years

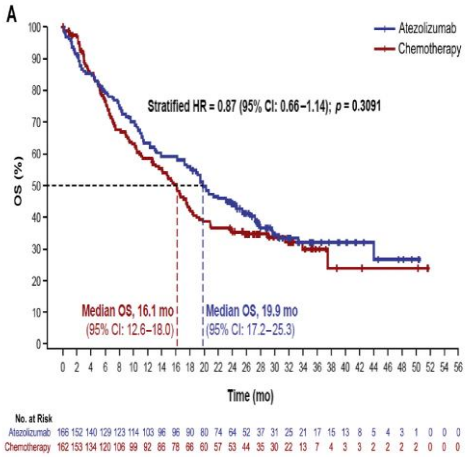


OS: 20.0 *vs.* 12.2 , HR 0.68

16%

Continuous

IMPOWER 110, PD-L1 TC3/IC3 (SP142)
Follow-up: 31 months

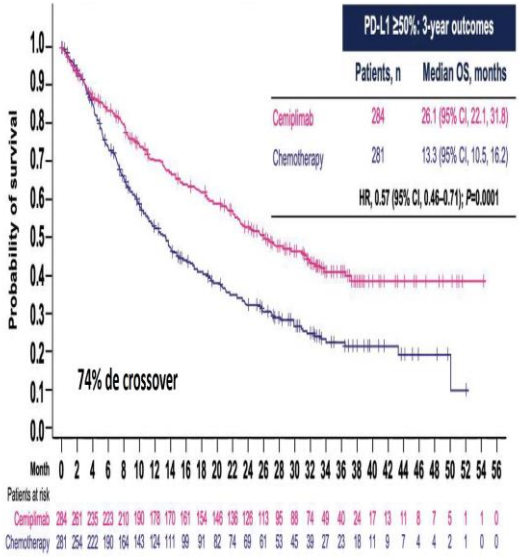


OS: 19.9 vs. 16.1 , HR 0.87

26%

Continuous

EMPOWER LUNG 1 (22C3)
Follow-up: 37.1 months



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PD-1 inhibitor
PD-L1 inhibitor

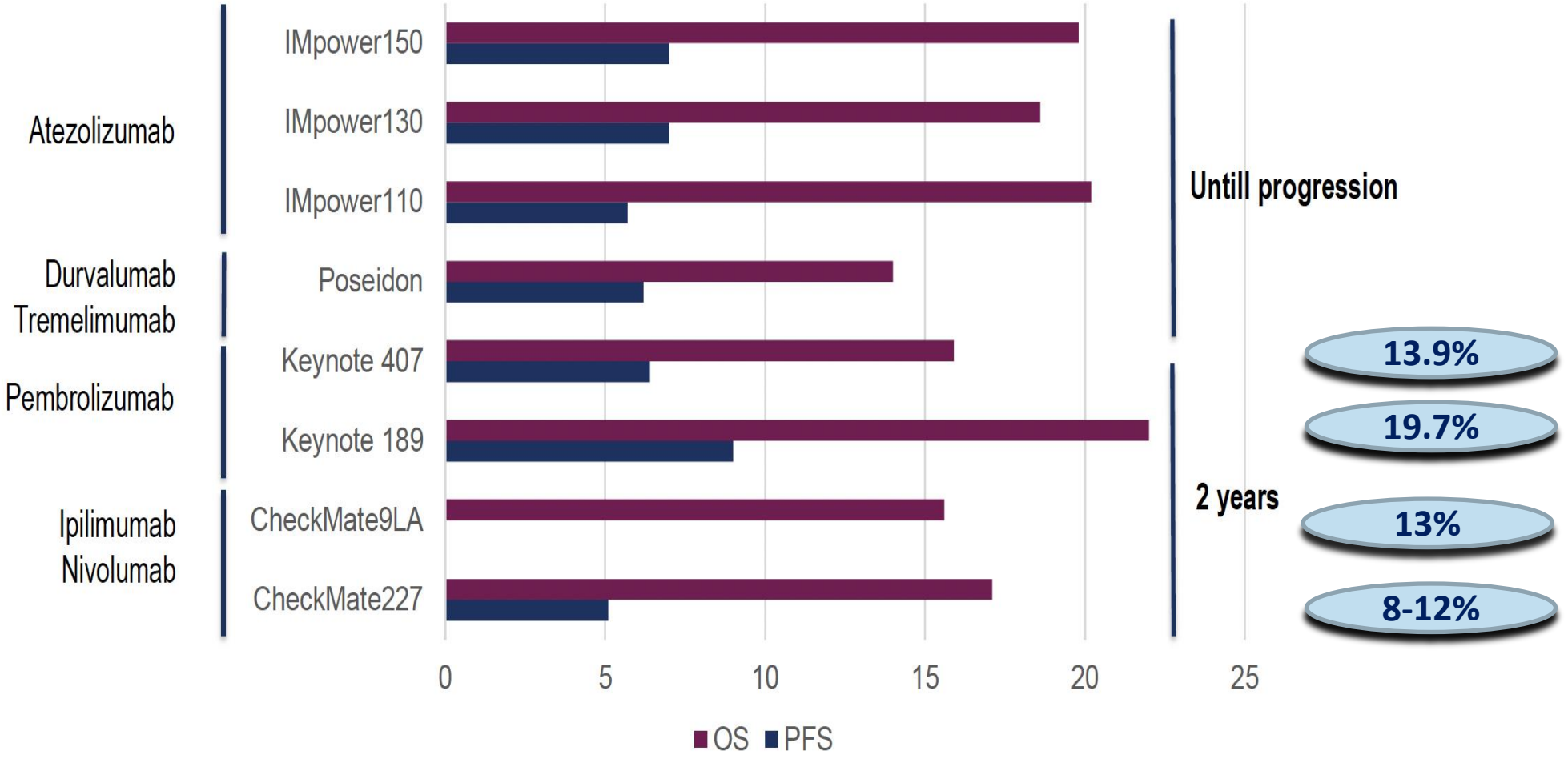
IO COMBOS IN UNPREVIOUSLY TREATED NSCLC

	Trial	Duration	PFS (HR)	OS (HR)
Non-Squamous	KEYNOTE 189	2 y	0.50	0.60
	IMpower 150 (ABCP arm)	Cont	0.57	0.80
	IMpower 132	Cont	0.60	0.86 (NS)
	IMpower 130	Cont	0.64	0.79
	ORIENT 11	2 y	0.48	0.61
	RATIONALE 304	Cont	0.65	Immature
	CAMEL	Cont	0.60	0.73
Squamous	KEYNOTE 407	2y	0.59	0.71
	IMpower 131	Cont	0.71	0.88 (NS)
	RATIONALE 307	Cont	0.52	Immature
	CAMEL-Sq	Cont	0.37	0.55
	ORIENT 12	2y	0.54	0.57
	CheckMate 227 (PD-L1 ≥1%)	2y	0.81	0.76
	CheckMate 9LA	2y	0.67	0.72
Both histologies	EMPOWER Lung03	Cont	0.56	0.71
	MYSTIC (D+T arm, PD-L1 ≥ 25%)	Cont	1.05	0.85 (NS)
	POSEIDON (D + CT arm)	Cont	0.74	0.86 (NS)
	GEMSTONE-302	2y	0.48	0.67
	CHOICE-01	Cont/ 2y	0.58	0.81

Gray – WCLC 2020 * Socinski – NEJM 2018 & JTO 2021 * Nishio – JTO 2020 * West – Lancet Oncol 2019 * Sugawara – Ann Oncol 2021 * Yang –JTO 2021 * Lu – JTO 2021 * Zhou – Lancet Resp Med 2020; Robinson – ELCC 2021 * Jotte – JTO 2020 * Wang – JAMA Oncol 2021 * Zhou – ELCC 2021 * Zhou - JTO 2021; Ramalingam – ASCO 2020 * Paz-Ares – ASCO 2021 * Reck – ASCO 2021 * Johnson –WCLC 2021 * Gogishvili –ESMO 2021 * Rizvi – JAMA Oncol 2020 * Zhou – ESMO Asia 2020 & WCLC 2021 * Wang – WCLC 2021 HR: Hazard Ratio. NS: Not significant.

Slide Courtesy and adapted from J. Remón

COMBO TRIALS

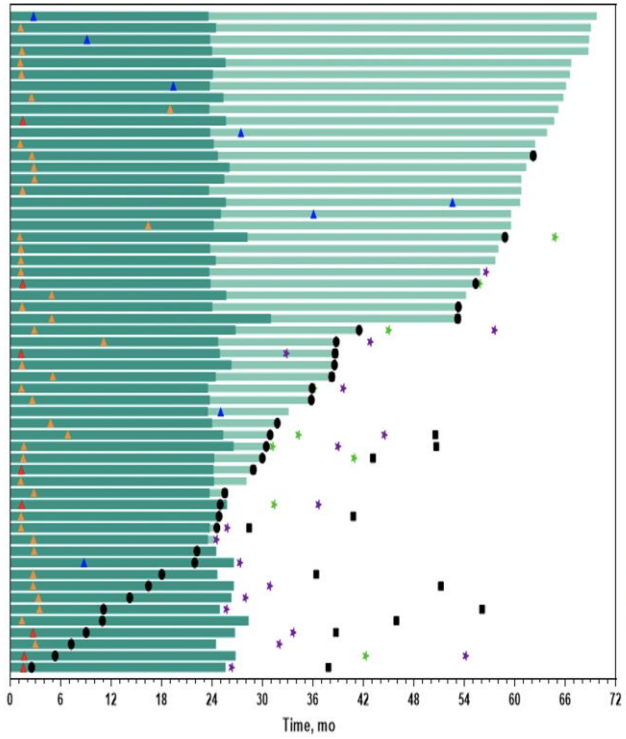


Yin et al. Front Immunol 2022

PATIENTS WHO COMPLETE TREATMENT DO WELL

KEYNOTE 189

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab

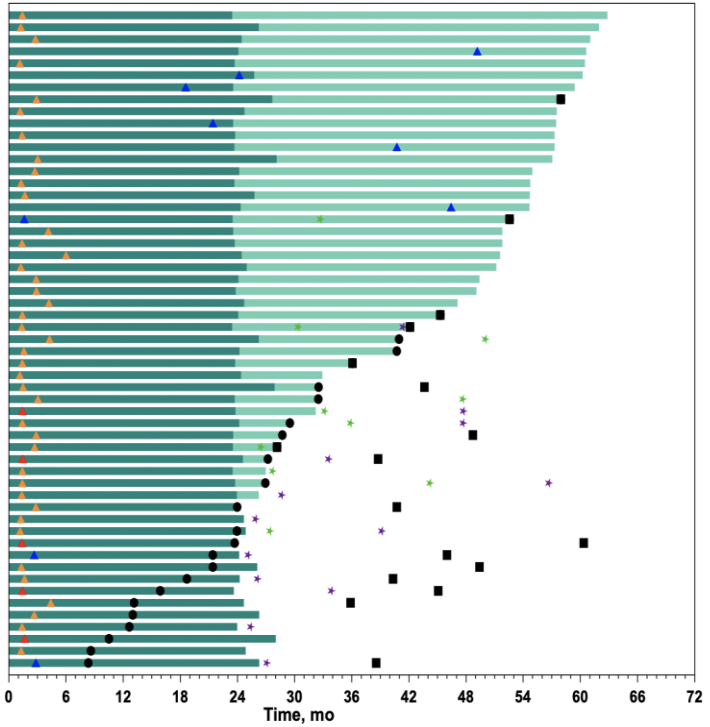


	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

CR
PR
SD
PD
Death
First course follow-up
First course treatment
Second-course pembrolizumab
Began subsequent therapy

KEYNOTE 407

Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



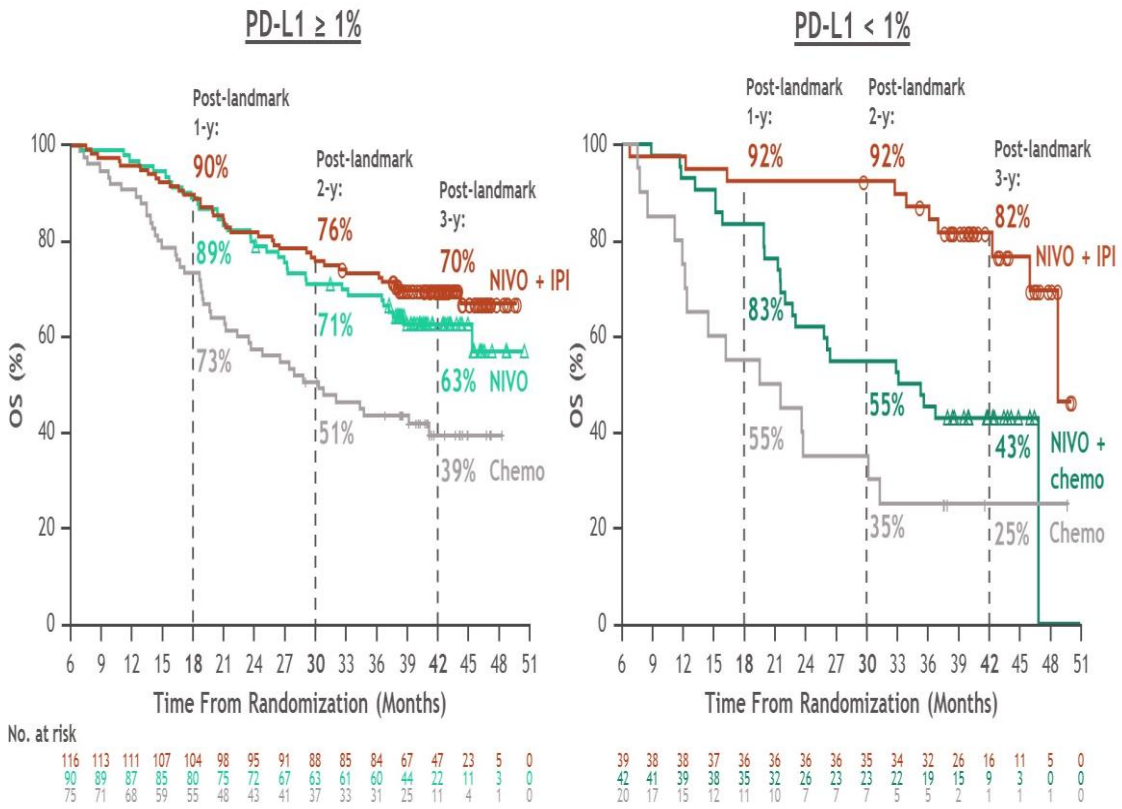
	n = 55
ORR (95% CI),[a] %	90.9 (80.0–97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] mo	NR (7.1 to 61.5+)
3-y OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

CR
PR
SD
PD
Death
First course follow-up
First course treatment
Second-course pembrolizumab
Began subsequent therapy

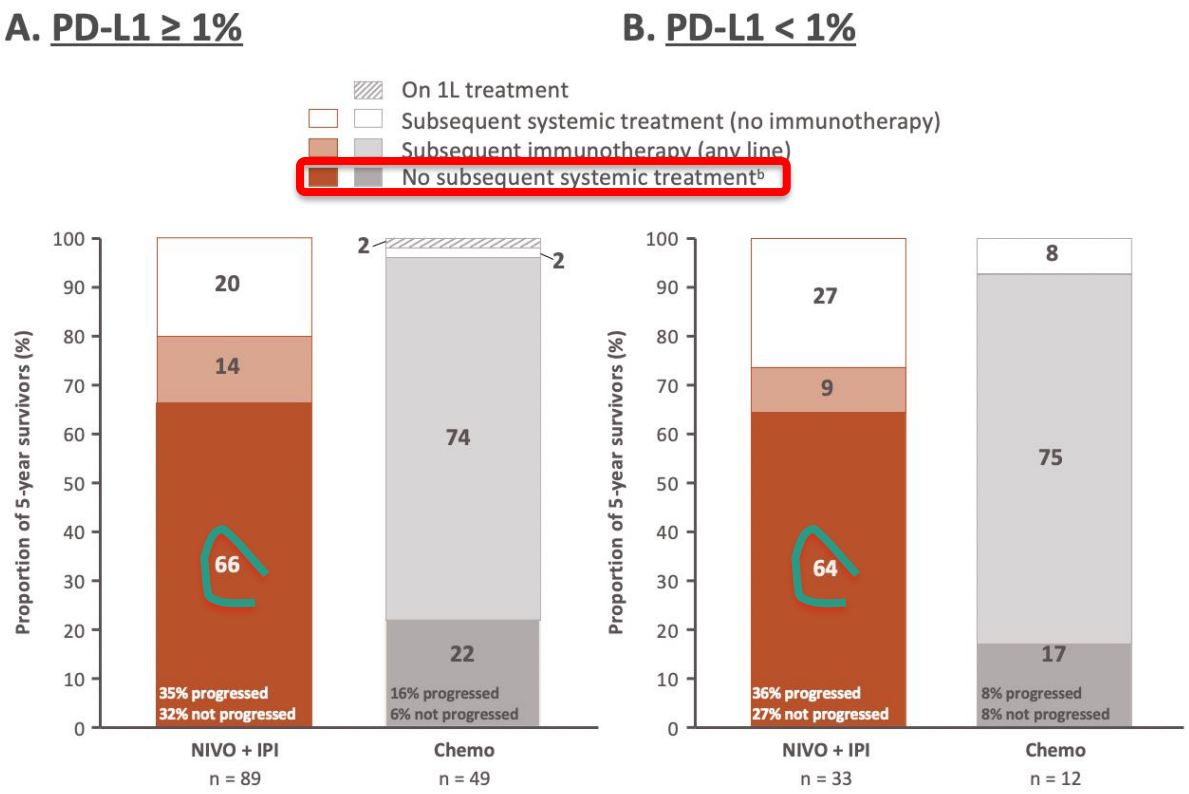
Garassino M, et al ESMO 2022; Novello S, et al. ESMO 2022

Reponse and long term activity

CM227: Post-landmark OS in CR/PR PD-L1≥ 1% and PD-L1< 1%



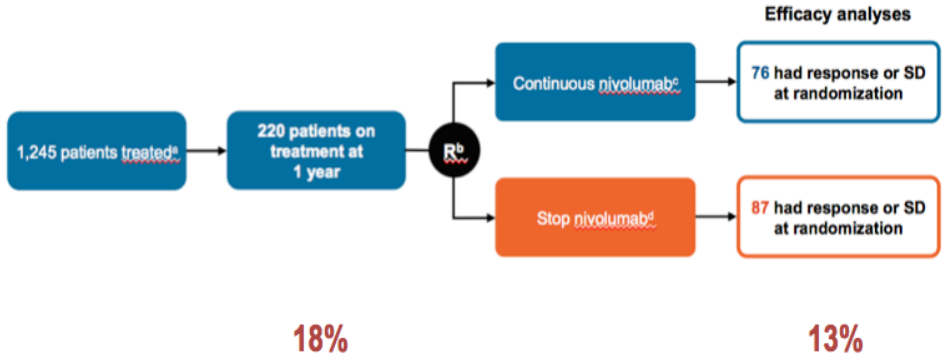
CM 227: Treatment status in 5-year survivors

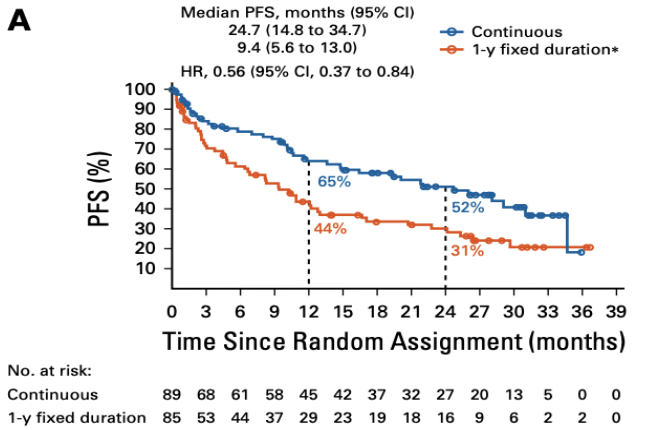


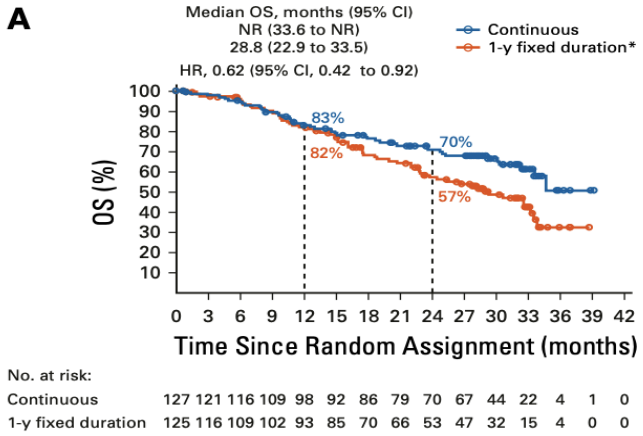
Ramalingam et al ASCO 2020; Brahmer J, et al. ASCO 2022

CheckMate 153: The Benefit of continuos administration related to Tumor Response

CheckMate 153: Continuous vs 1-Year Nivolumab
Patient Flow and Analysis Populations



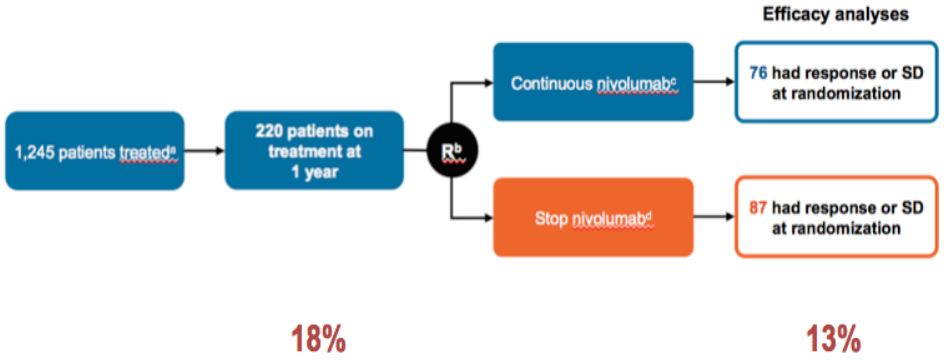


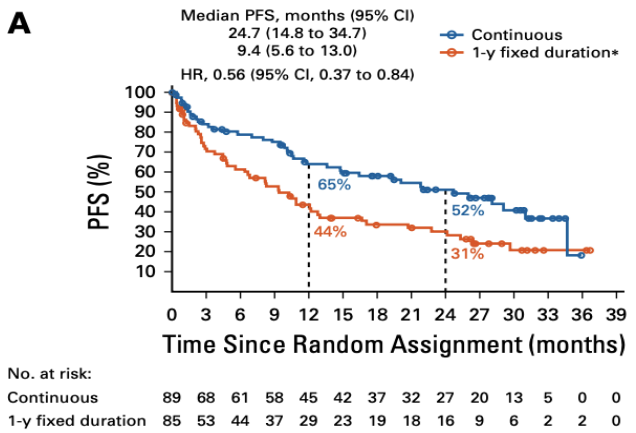


Waterhouse et al. J Clin Oncol 2020

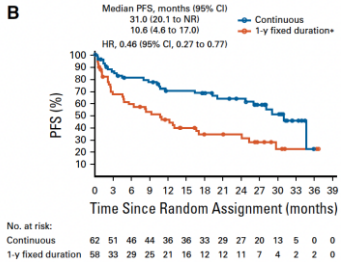
CheckMate 153: The Benefit of continuos administration related to Tumor Response

CheckMate 153: Continuous vs 1-Year Nivolumab
Patient Flow and Analysis Populations

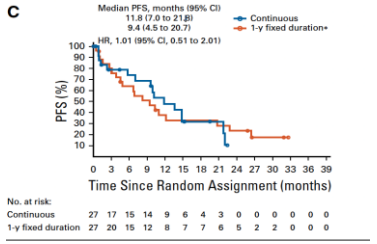


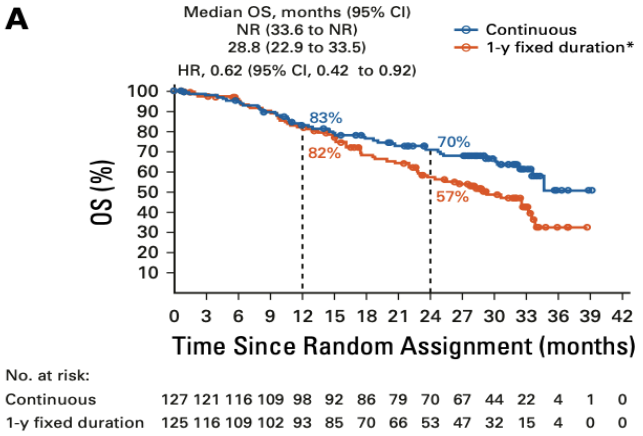


CR/PR

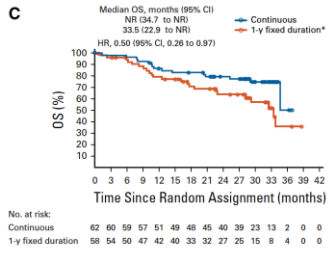


SD





CR/PR



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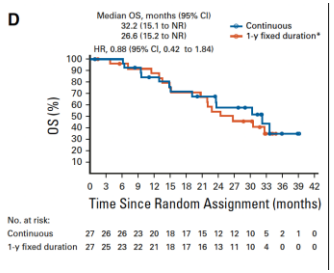


Waterhouse et al. J Clin Oncol 2020

TREATMENT DURATION

DICIPLE

Multicenter, non-inferiority, randomized phase III trial

Histogically-proven stage IV NSCLC:
- Measurable disease
- PS 0-1
- 18 – 75 years
- Any PDL1
- w/o EGFR/ALK alterations
- chemo & i.o naive

n = 1360

→ **Nivolumab** 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

→ **At 6 months patients with disease control Randomized 1:1**

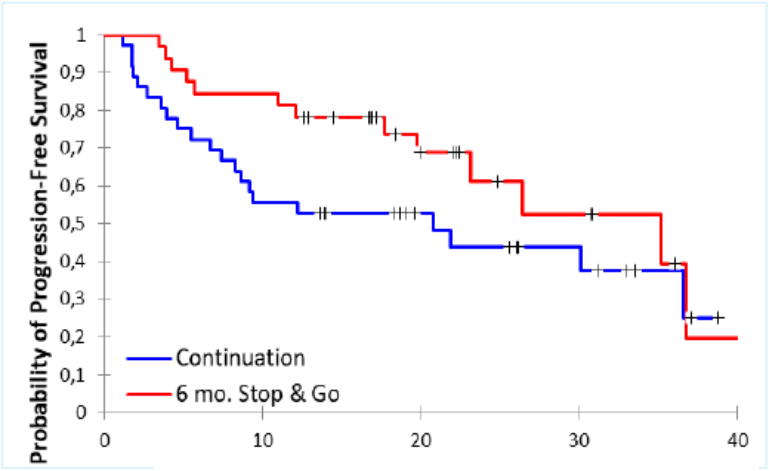
n = 868

Stratification factors:
- SCC/non-SCC
- PD-L1 (<1%, 1-49%, ≥50%)
- Ever smokers/never-smokers
- response: PR/SD
- PS = 0 *vs.* PS=1

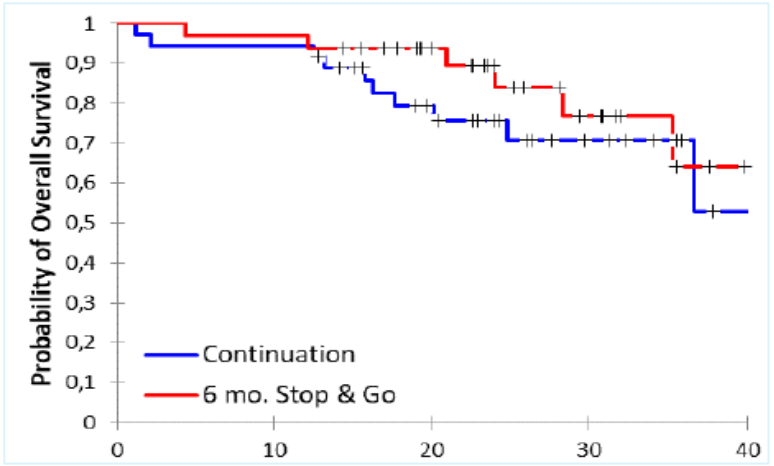
Arm A → **Nivolumab** 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w → *Prog* → **Platinum-based doublet recommended**

Arm B → **Observation** → *Prog* → **Nivolumab** 3mg /kg q2w + **Ipilimumab** 1 mg/kg q6w

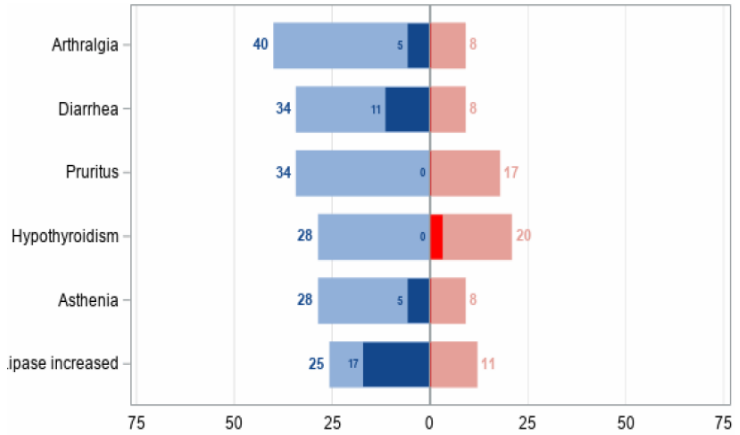
- Primary endpoint : **PFS from randomization**
- Secondary endpoints : safety and tolerance, overall survival, quality of life, PD-L1 tumour expression prognostic and predictive value
- CT-scan f.u q8 weeks for 1 year, then q12 weeks in both arms



mPFS: **35.2** *vs.* **20.8** mo., p=0.12



mOS: **NR** *vs.* **NR** mo., p=0.33

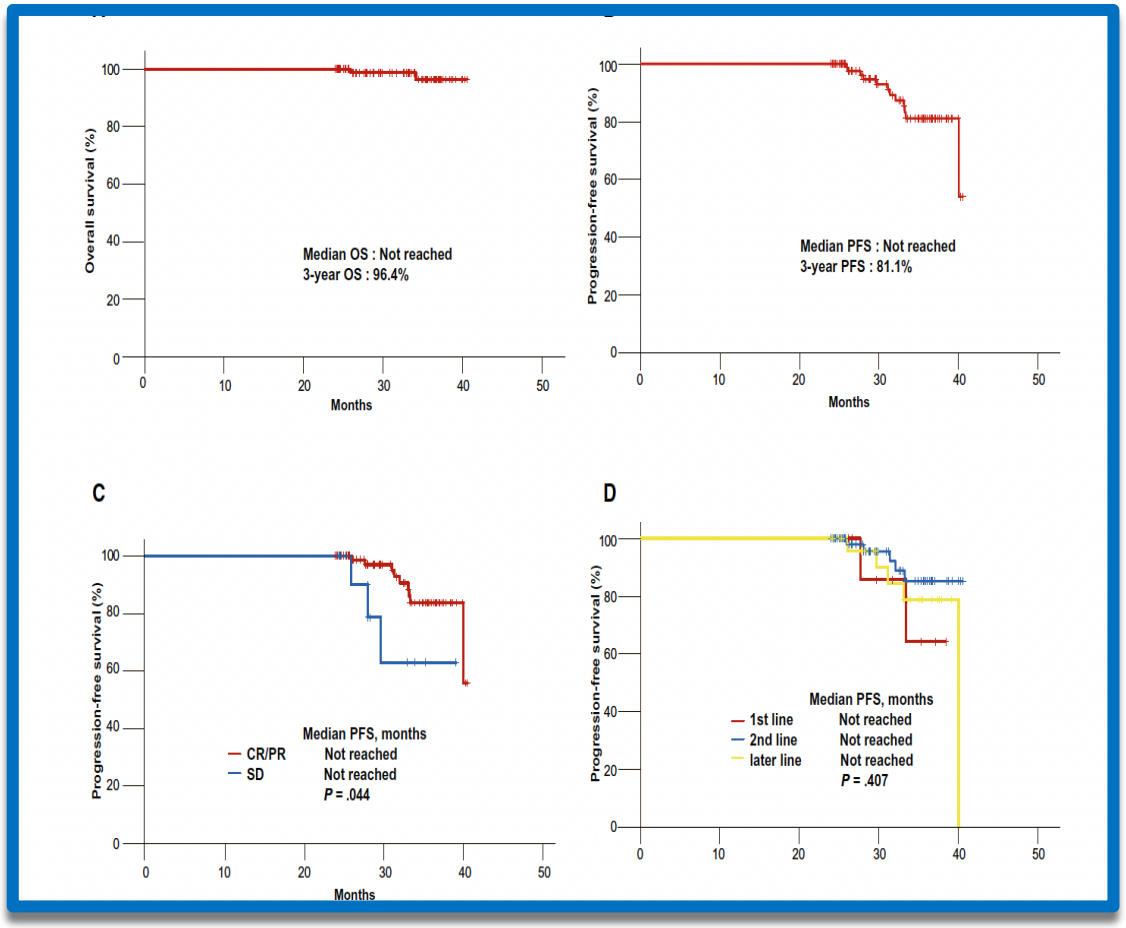


Lower G ≥3 ir-AEs with **stop** *vs.* **continue**

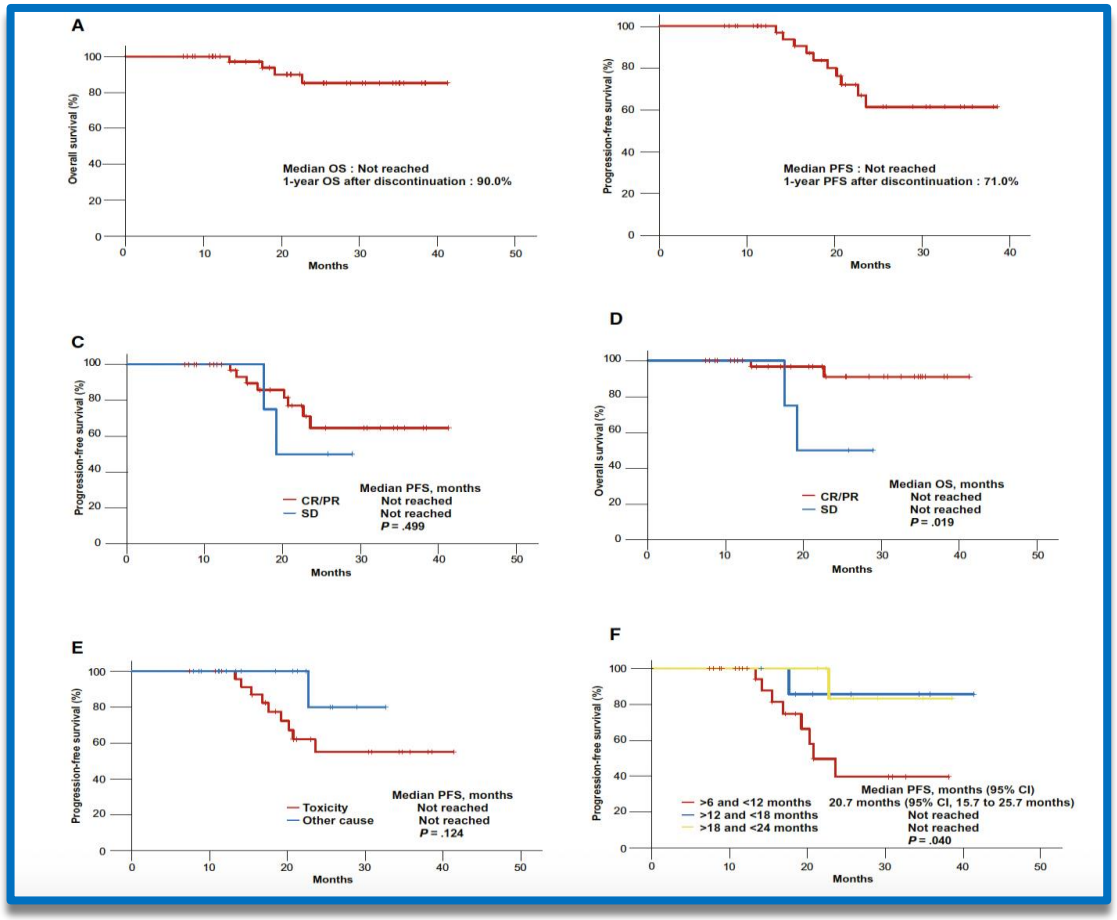
Zalcman et al. ESMO 2022

REAL-WORLD DATA (KCSG LU20-11)

COMPLETED 2 YEARS



DISCONTINUATION WITHOUT PD



Kim et al. Cancer 2022

BEYOND CLINICAL TRIALS
LARGE DATASETS

Figure 1. CONSORT Diagram

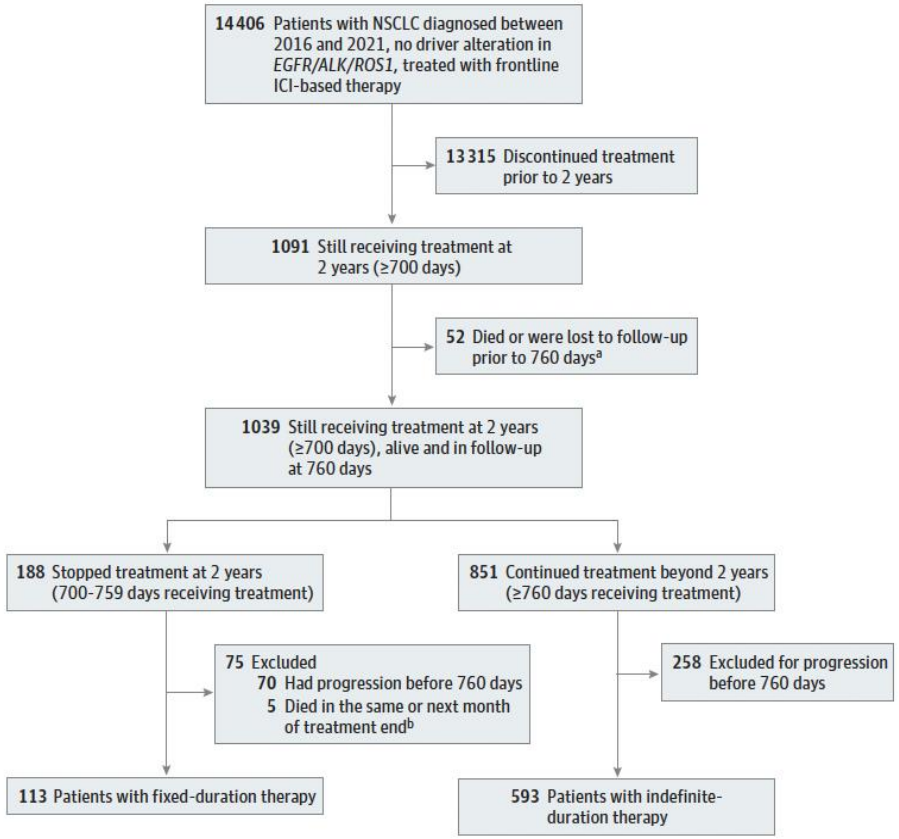
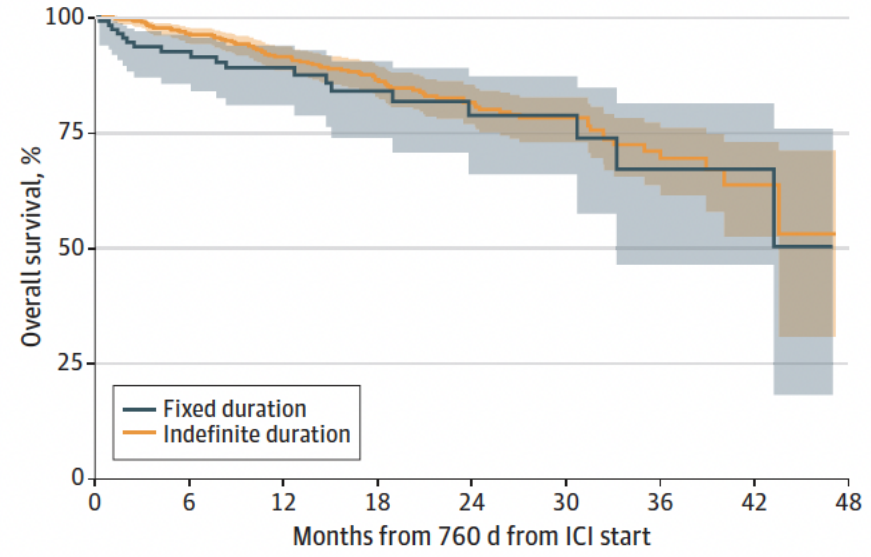


Figure 2. Overall Survival



No. at risk

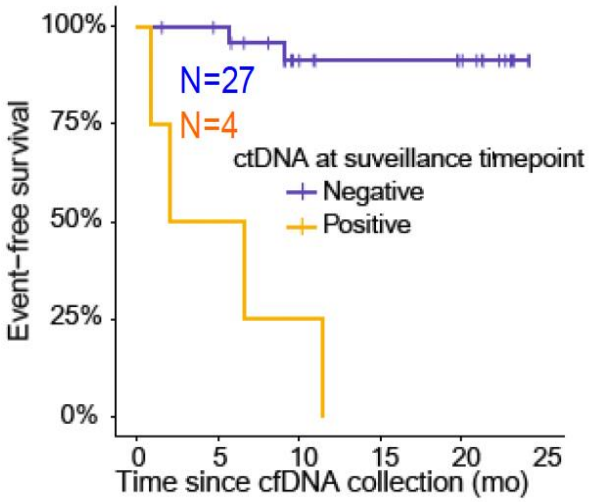
Fixed	113	81	62	39	25	17	7	4	1
Indefinite	593	458	340	244	167	96	46	11	1

Sun et al. JAMA Oncol 2023

THE POTENTIAL OF LIQUID BIOPSY

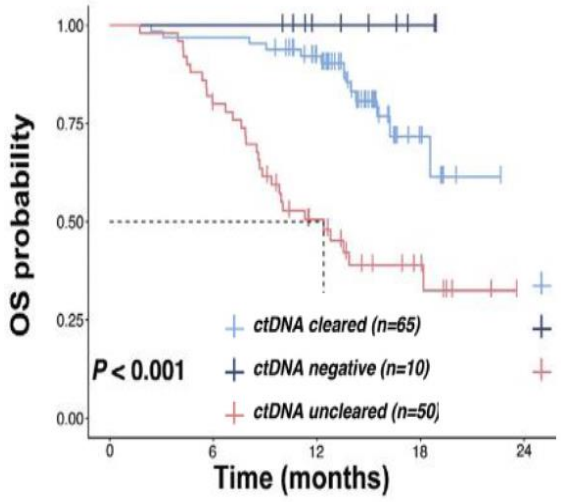
MSKCC cohort

ctDNA analysis at 26.7 mo.
after nivolumab initiation



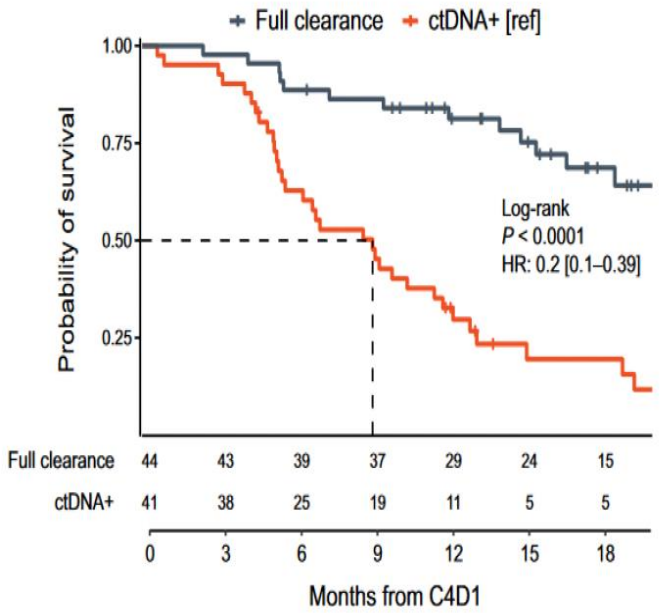
CameL-Sq

Camrelizumab + Carbo/Paclitaxel
ctDNA clearance C1-C3



IMpower131

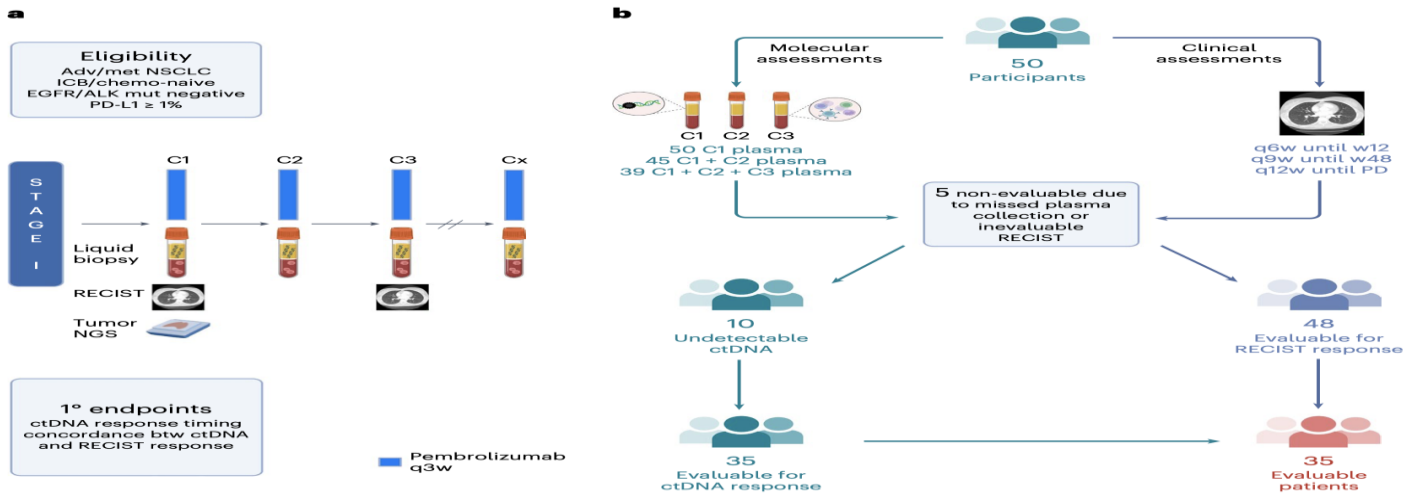
Atezolimab + Carbo/Nab-Paclitaxel
ctDNA clearance C1-C4

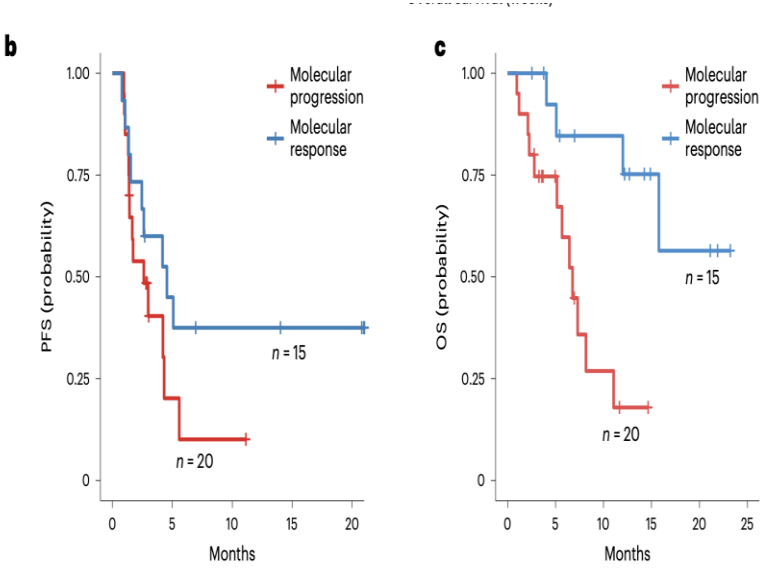


Overall survival (OS), complete response (CR), partial response, (PR), stable disease (SD), no evaluable disease (NE), Carboplatine (carbo) .

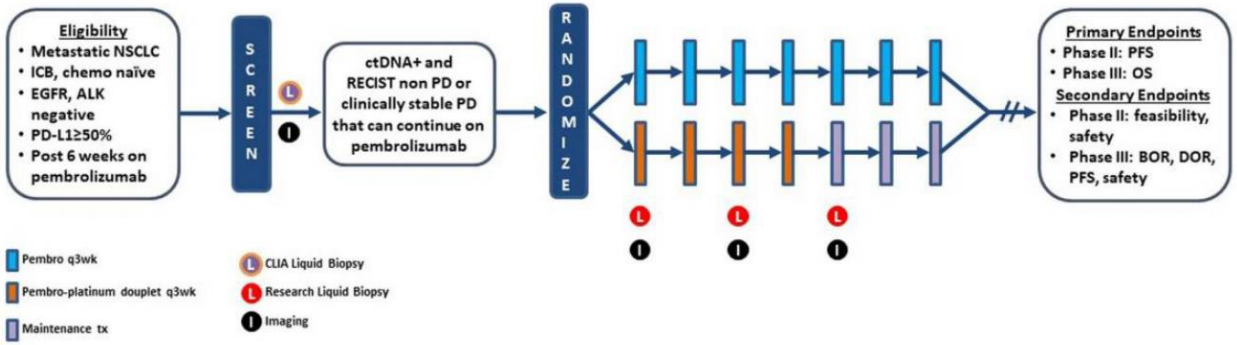
Hellman CCR 2020, Ren JTO 2022, Pellini CCR 2023

THE POTENTIAL OF LIQUID BIOPSY





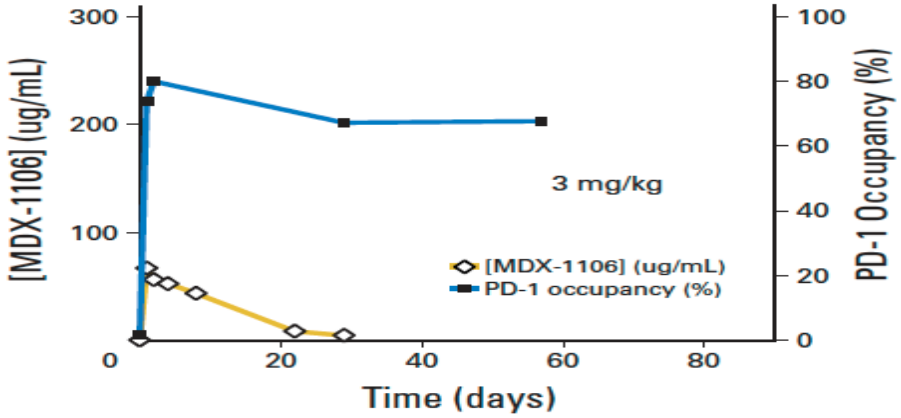
BR.36
Step 2



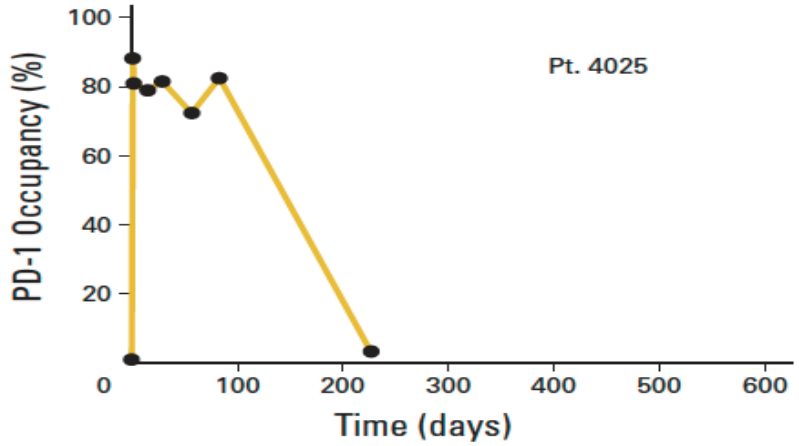
Anagnostou et al. Nat Med 2023

Treatment schedule

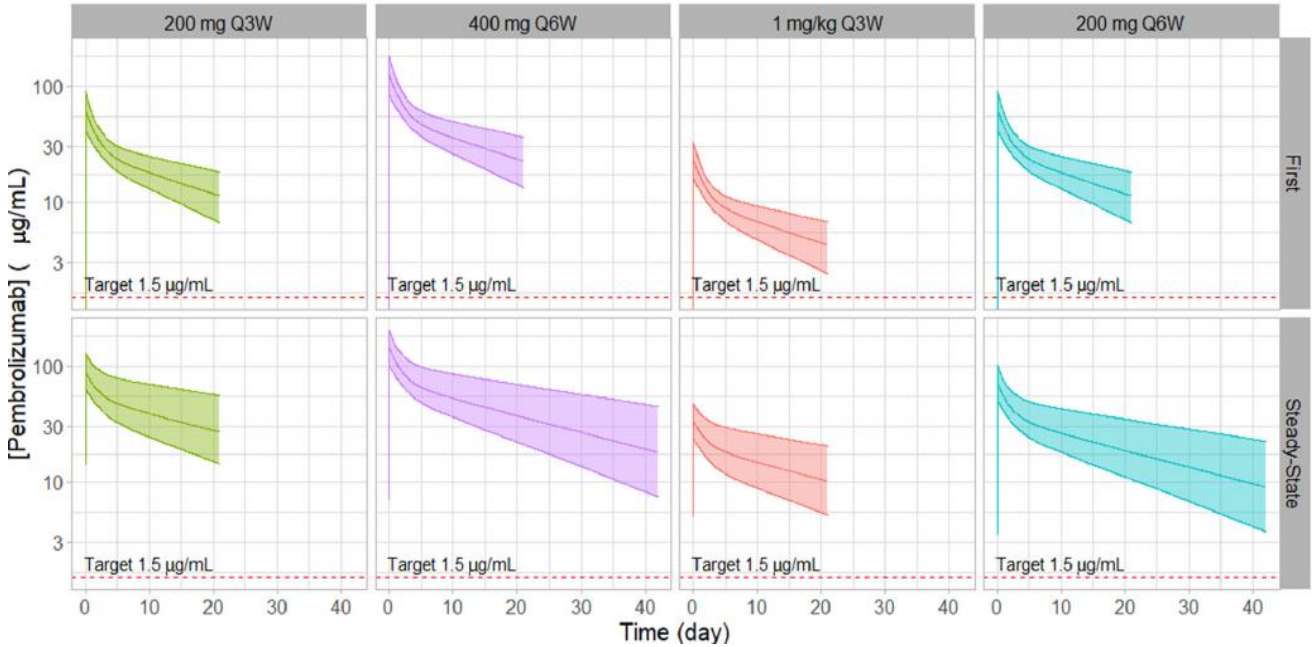
Pharmacodynamic PD-1 occupancy on



Long-term PD-1 occupancy analysis after receiving one doce af 10 mg/kg



Do we need IO every 2 or 3 weeks?
Is it necessary to increase the dose?
Financial toxicity / higher risk of chronic ir-AEs

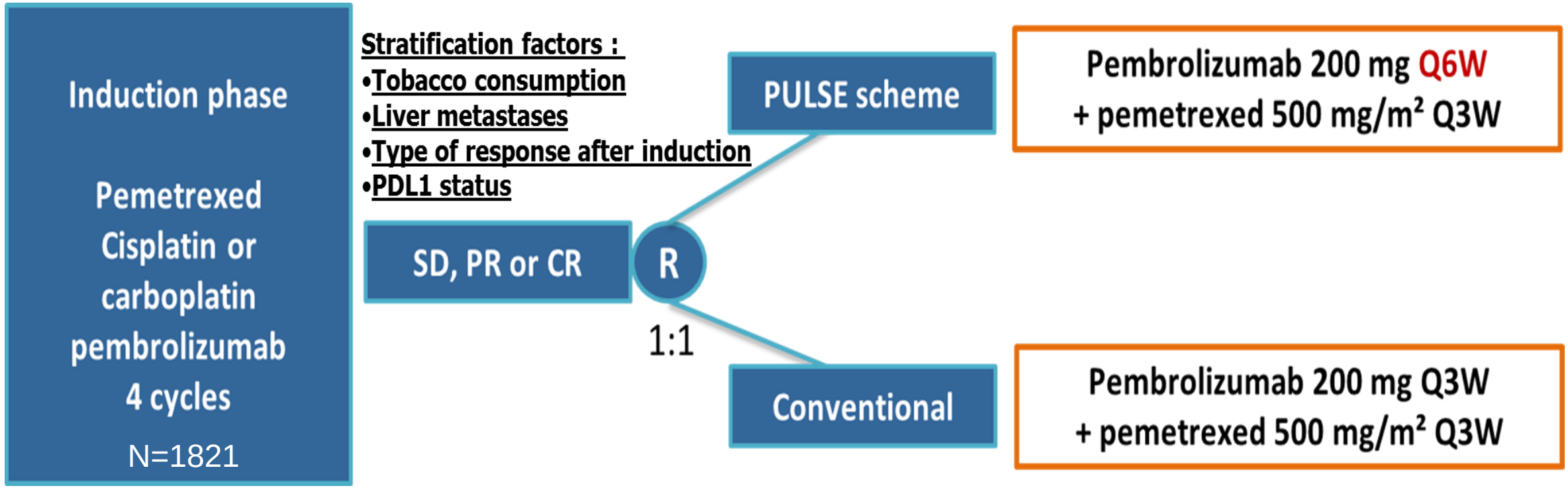


Extended dosing regimens of nivolumab 240 mg Q4W and 480 mg Q8W along with **pembrolizumab 200 mg Q6W** were simulated, showing that >95% of patients maintained the minimum effective concentration or greater.

Slide courtesy Dr Remón

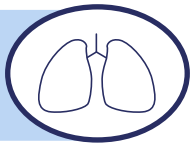
Peer et al J of Clinical Pharmacol 2022; Higashiyama et al; JTO 2022

Treatment schedule: PULSE TRIAL



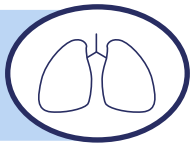
Primary endpoint: Overall survival
Secondary endpoint: PFS, RR, QoL, **economic impact**, target saturation, pharmacokinetic.

RECHALLENGE
THE MOST FREQUENT SITUATIONS

- AFTER ICI HELD FOR irAE 
- AFTER ICI TREATMENT COMPLETION 
- AFTER PD DURING ICI 

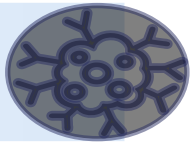
RECHALLENGE
THE MOST FREQUENT SITUATIONS

AFTER ICI HELD FOR irAE



AFTER ICI TREATMENT COMPLETION

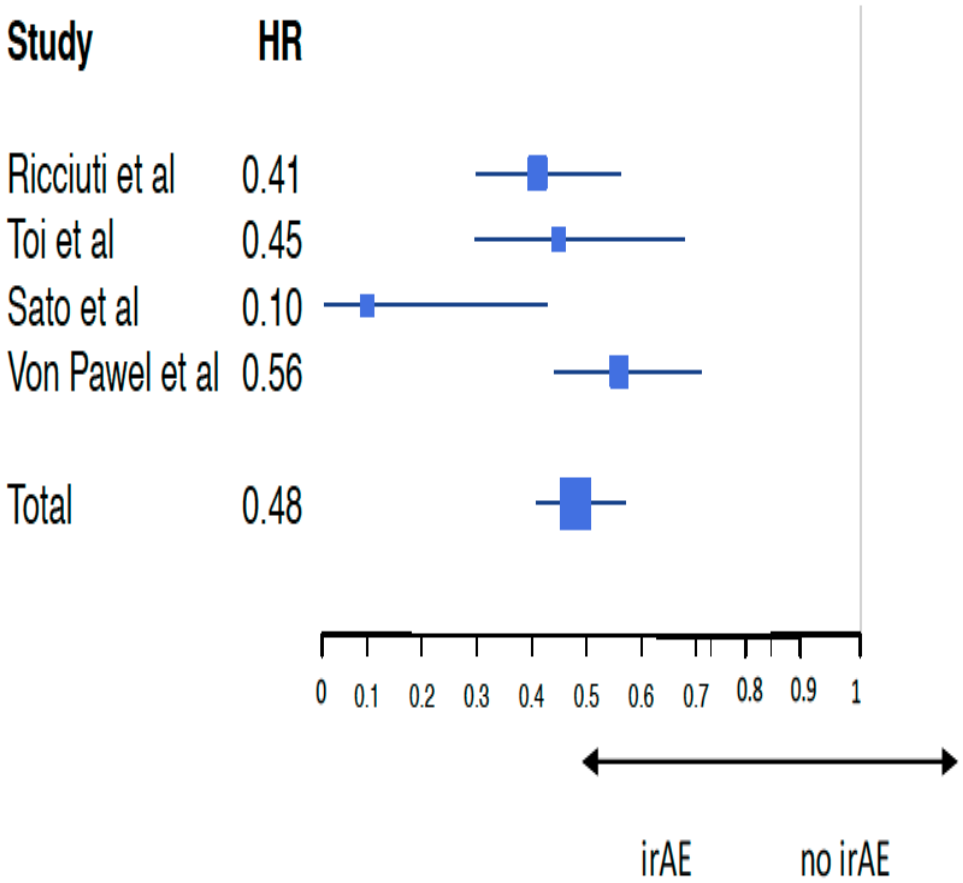
AFTER PD DURING ICI



irAEs and outcome in NSCLC

Author	ICI	N	Grade ≥ 3 irAE's (%)	RR (%)		PFS (mo.)		OS (mo.)	
				irAE's	No-irAE's	irAE's	No-irAE's	irAE's	No-irAE's
Ricciuti [12]	Nivolumab	195	7.6	43.5	10.0	5.7	2.0	17.8	4.0
Moor [13]	Nivolumab	196	13.2	NR	NR	5.9	2.5	23.8	6.4
Toi [14]	Nivolumab	70	NR	57	12	12	3.6	NR	NR
Haratani [15]	Nivolumab	134	9	52	28	9.2	4.8	Not R	11.1
Teraoka** [16]	Nivolumab	43	0	37	17	6.4	1.5	NR	NR
Sato [17]	Nivolumab	38	NR	64	7.4	Not R	1.6	NR	NR
Lisberg[18]	Pembrolizumab*	97	3.1	39.5	8.9	8.2	2	16.4	4.8
Von Pawel* * [19]	Atezolizumab	823	6.0	22.3	9.9	5.4	2.3	20.7	10.6
Kfoury [20]	Anti-PD(L)1	618 @	Grade ≥ 2 28.3%@	NR	NR	14.2	13.4	23.7	16.2
Toi [21]	Anti-PD1	137	NR&	52	13	10.3	3.4	Not R	11.4
Shafqat[33]	Anti-PD(L)1	157X	11.4	NR	NR	24.4	4.2	NR	NR

PFS

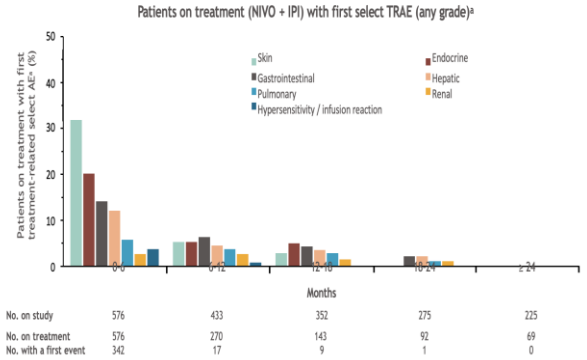


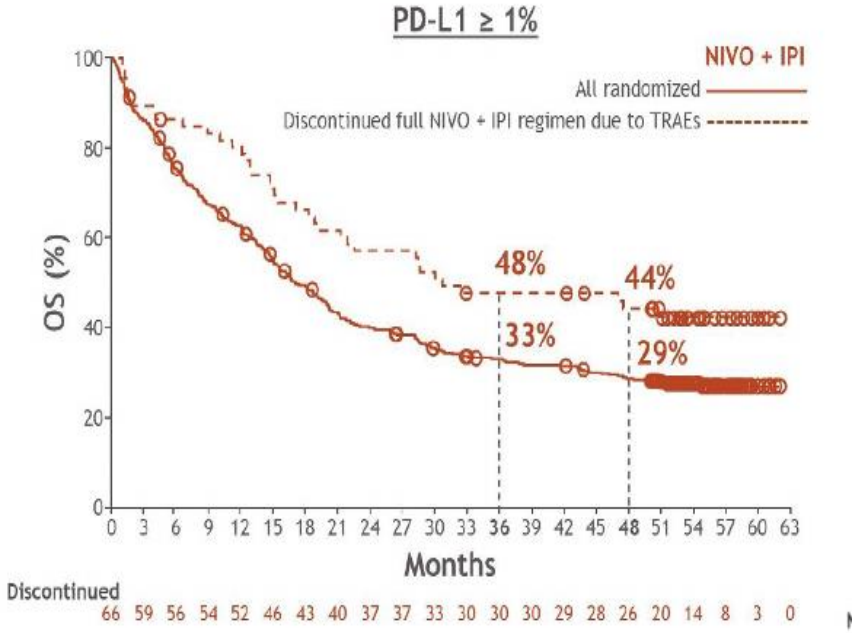
Specially if ≥ 2 irAEs and some specific irAEs (thyroid, skin)

Remon et al JTO 2019

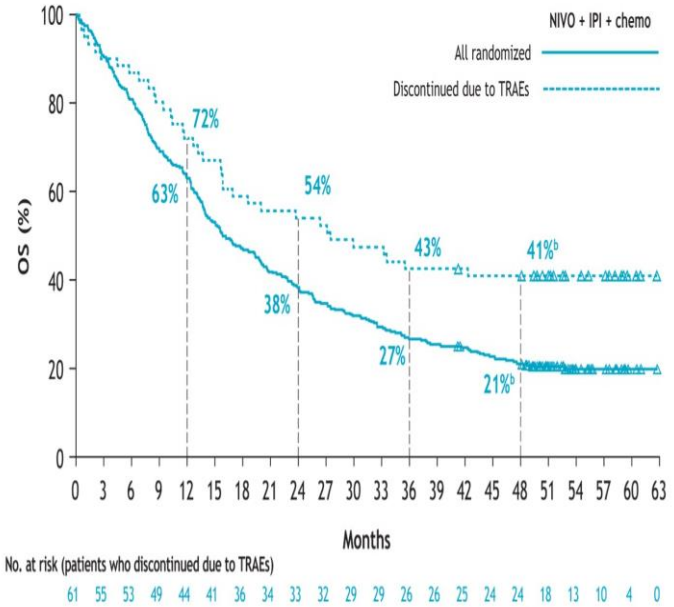
EFFICACY IN PATIENTS WHO DISCONTINUE IO DUE TO TRAEs

CHECKMATE 227





CHECKMATE 9LA



Ramalingam et al. ASCO 2020;Carbone D et al. ASCO 2023

Rechallenge: is it safe?

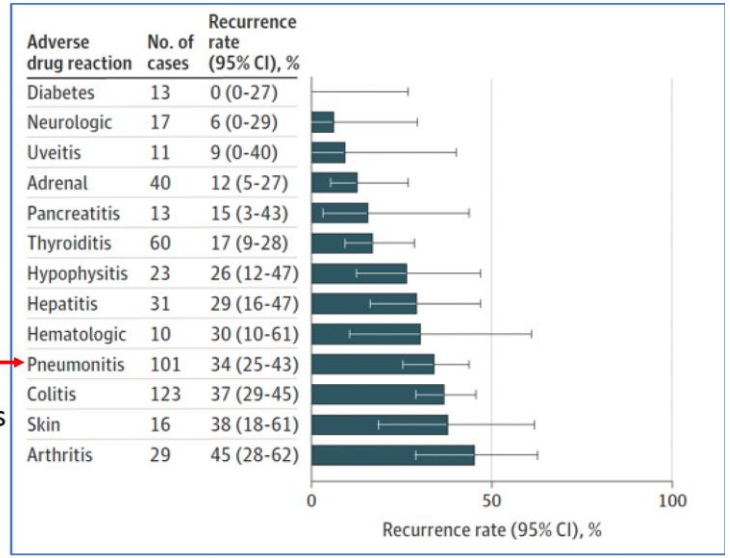
N=482 pts NSCLC anti-PD(L)-1 +/- antiCTLA-4

14,7% irAEs

45% permanently discontinued
54% retreated 50% irAEs (early onset)
5% mortality (colitis, neumonitis)
8% ORR
No OS differences

Real world data from WHO Drug Monitoring Program

- WHO VigiBase
- 24,079 cases with irAEs from >130 countries
- 25% had ICI rechallenge
- 29% recurrence of same irAE
- 4% had different irAE
- Higher rates for colitis, pneumonitis

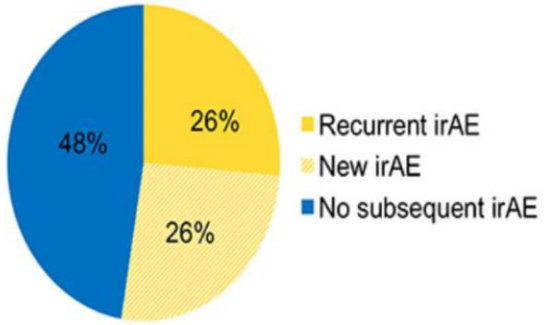


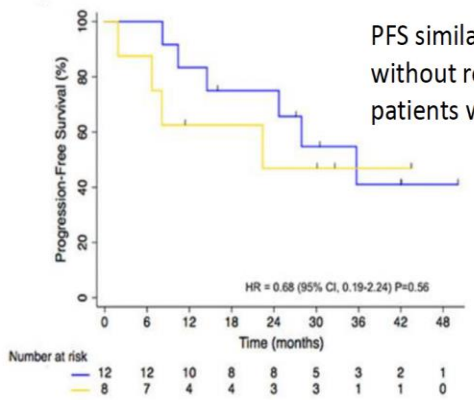
Menzies AM, et al. Ann Oncol 2017, Schadendorf D, et al. JCO 2017, Doladille et al JAMA Oncol 2020

Rechallenge: is it needed?

Rechallenge after irAE (without disease progression)

- N=68/482 NSCLC patients experienced irAE → 38 retreated

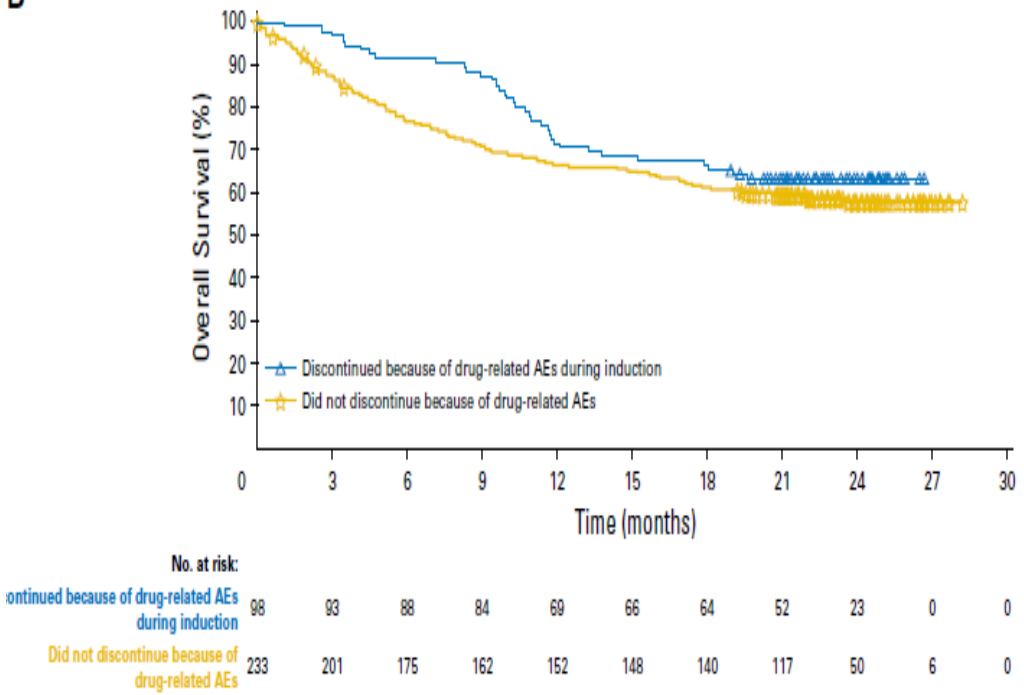




PFS similar with or without rechallenge in patients with CR/PR

- 2 treatment related deaths (5%)
- Recurrent/new irAE more likely if initial irAE required hospitalization
- Grade of irAE, time off ICI before rechallenge, other factors did not impact

B



Santini et al. Cancer Immunol Res 2018

Guidelines recommend restarting I-O therapy in certain circumstances after IMAR resolution, acknowledging that the decision is complex and multifactorial

ESMO guidelines state whether to retreat/rechallenge with the same or a different ICI class involves a challenging balance of clinical benefit and treatment-related toxicities, the decision being dependent on multiple factors and requiring discussion in MDTs and on a case-by-case basis[1]

The guidelines include that patients who have previously developed grade 3 or 4 IMARs are at risk of redeveloping severe toxicities on ICI rechallenge[1]

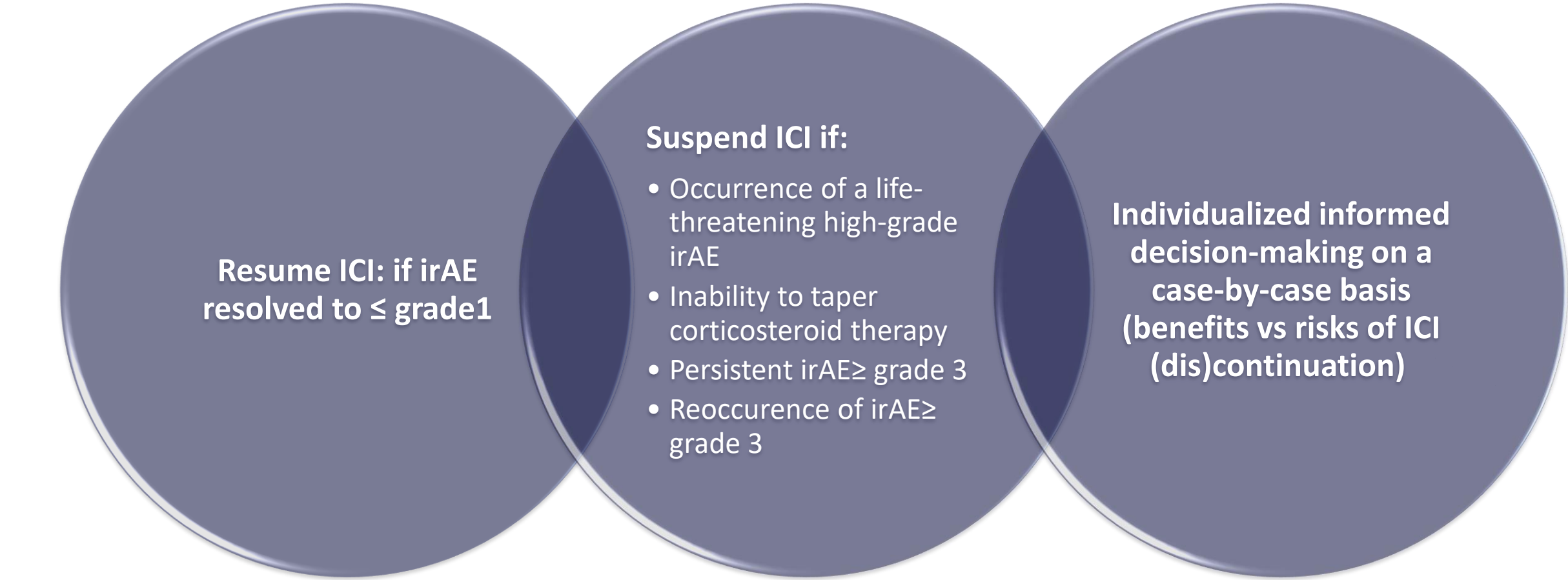
ASCO assert the decision to retreat/rechallenge with an ICI is challenging, involving consideration of factors including previous tumor response, duration of treatment, type and severity of the toxicity, time to toxicity resolution, availability of alternate therapies, and patient performance status[2]

SITC recommends the decision to rechallenge a patient after grade 3 or 4 IMARs should be risk-adjusted based on anticipated benefit with therapy vs the potential for toxicity (Level 3 evidence[a])[3]

NCCN recommends permanent ICI discontinuation for grade 3 or 4 IMARs; for most grade 2 IMARs, ICI resumption can be considered after resolution to ≤ grade 1 with the risks/benefits being discussed with the patient, and exercising caution with close follow-up for recurrent symptoms[4]

- 1. Haanen 2022. 2. Schneider 2021. 3. Brahmer 2021. 4. NCCN 2022.

CRITERIA TO RESUME/ SUSPEND ICI



RECHALLENGE
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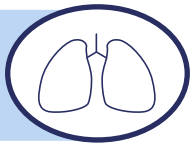
- AFTER ICI HELD FOR irAE 
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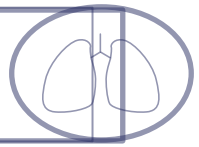
RECHALLENGE
THE MOST FREQUENT SITUATIONS

AFTER ICI HELD FOR irAE

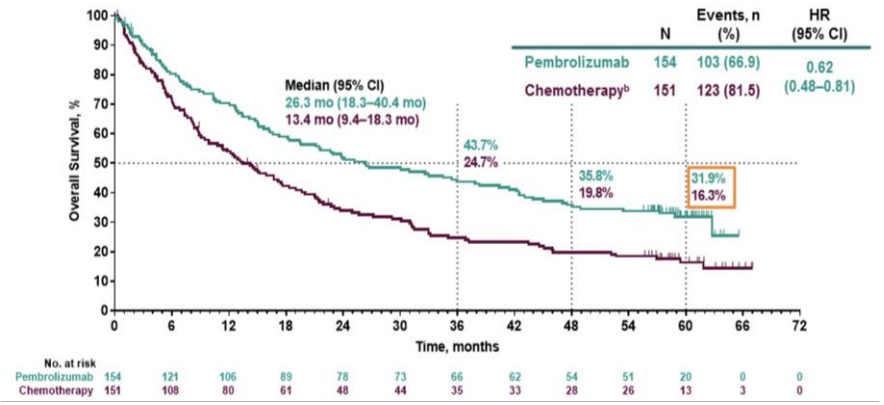


AFTER ICI TREATMENT COMPLETION

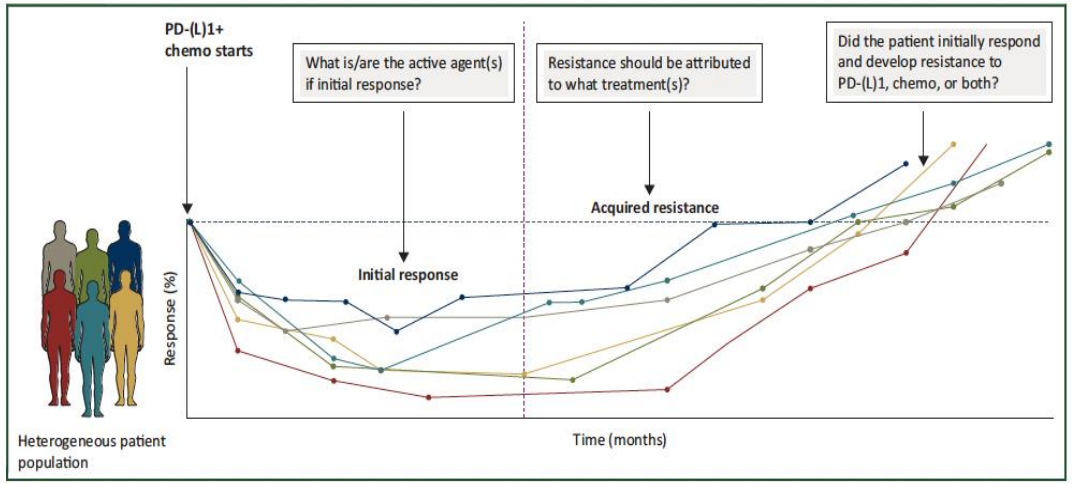
AFTER PD DURING ICI

UNDERSTANDING RESISTANCE…

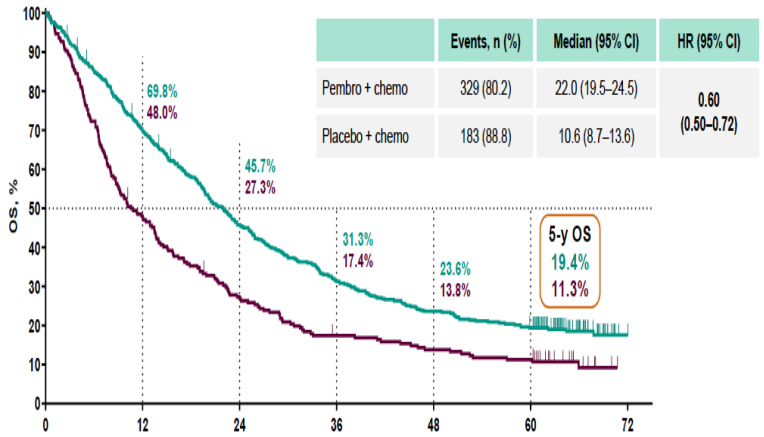
KEYNOTE 024



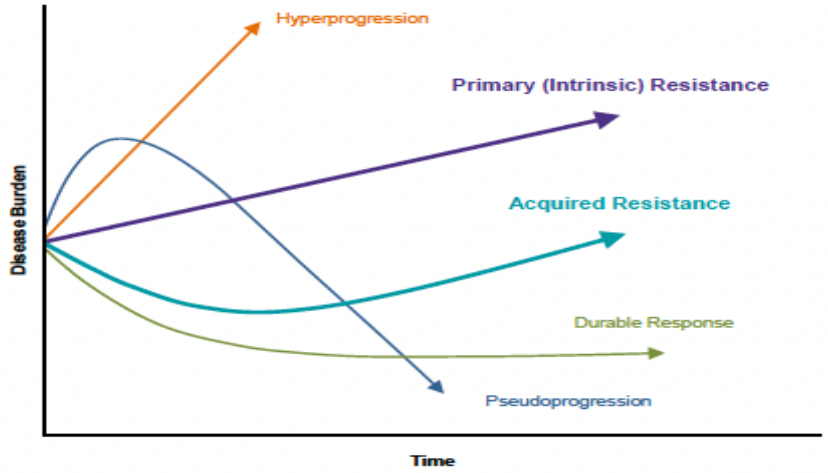
5-y OS: 32%



KEYNOTE

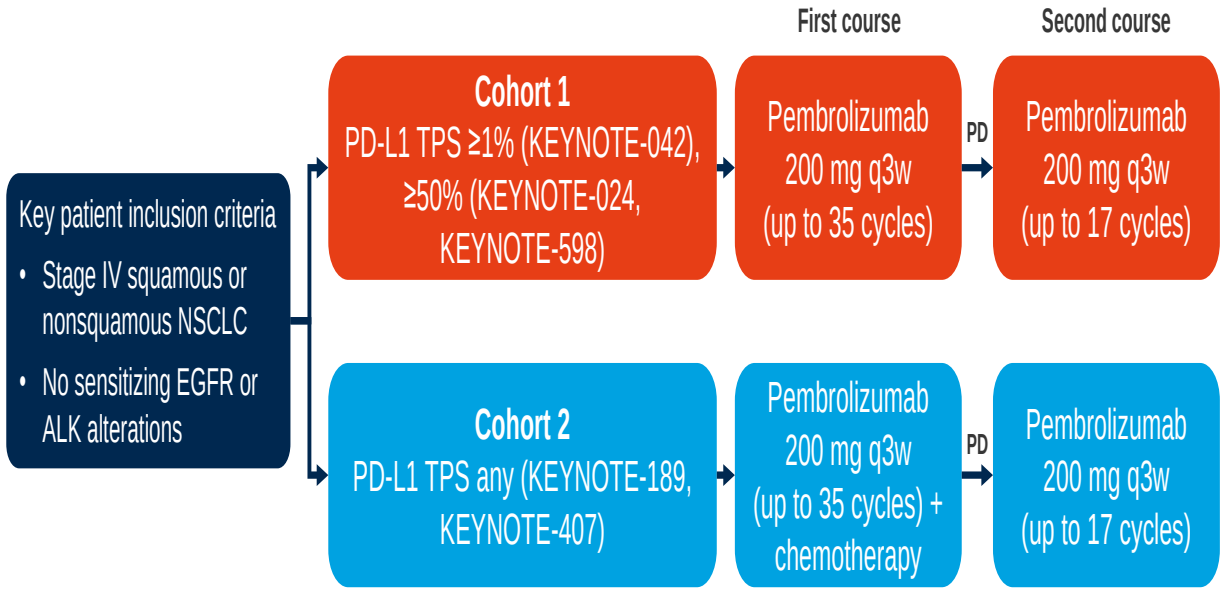


5-y OS: 19.4%



Reck M, et al. J Clin Oncol 2021; Gadgeel S, et al. J Clin Oncol 2020; Garassino ESMO 2022; Schoenfeld et al. Ann Oncol 2021; Schoenfeld et al. Cancer Cell 2020; Sharma et al. Cancer Disc 2021

After ICI completion: Rechallenge



Endpoints

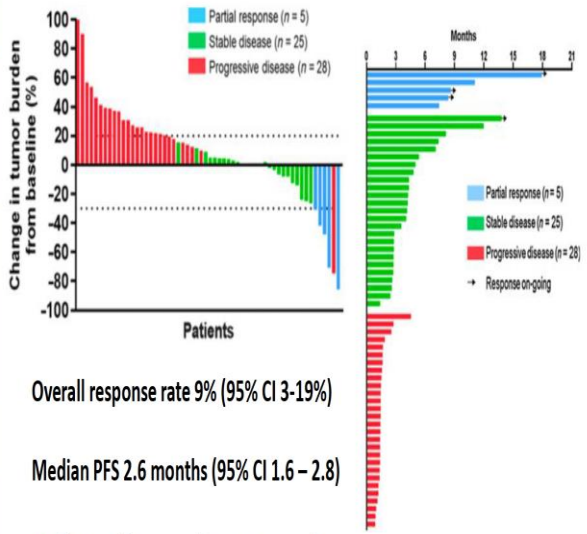
- ORR, DCR, DoR, OS, PFS, safety

	Cohort 1 (pembrolizumab) (n=57)	Cohort 2 (pembrolizumab + chemo) (n=14)
ORR, % (95%CI)	19.3 (10.0, 31.9)	0 (0, 23.2)
DCR, % (95%CI)	73.7 (60.3, 84.5)	50.0 (23.0, 77.0)
BOR, n (%)		
CR	0	0
PR	11 (19.3)	0
SD	31 (54.4)	7 (50.0)
PD	8 (14.0)	2 (14.3)
NA	7 (12.3)	5 (35.7)
mDoR, mo (range)	NR (0.0+ to 20.0+)	–
DoR ≥6 mo, %	78.8	–
mOS, mo (95%CI)	27.5 (21.7, NR)	NR (NR, NR)
6-mo OS, % rate (95%CI)	85.1 (72.4, 92.3)	85.1 (52.3, 96.1)
mPFS, mo (95%CI)	10.3 (5.6 ,14.0)	7.7 (1.8, NR)
6-mo PFS rate, % (95%CI)	60.8 (46.0, 72.7)	54.5 (22.9, 78.0)

Rodríguez Abreu D, et al. WCLC 2022; Haanen J, et al. JITC 2021

WJOG9616L: Phase II study of Nivolumab retreatment in patients iwth advanced NSCLC that previously responded to ICI and had and ICI-free interval

	N=59
PD-L1 score	
<50%	34%
>=50%	29%
unknown	37%
Prior ICI alone	92%
Prior ICI + chemotherapy	8%
Best response to prior ICI	
CR/PR	69%
SD>=6 months	31%
Median duration prior ICI, m (range)	8.1 (1-37)
Median ICI-free interval, m (range)	9.2 (2-29)
irAE → ICI discontinuation	34%



Overall response rate 9% (95% CI 3-19%)

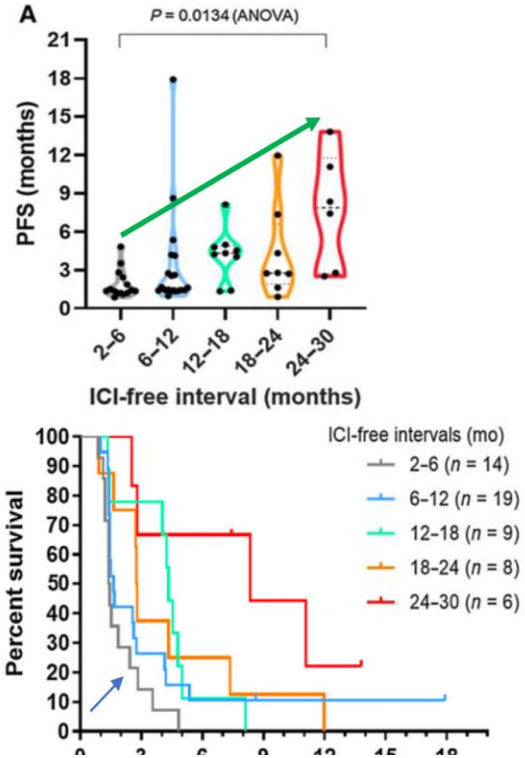
Median PFS 2.6 months (95% CI 1.6 – 2.8)

Median PFS in responders: 11.1 months

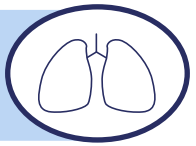
WJOG9616L: ICI-free interval associated with Benefit with Retreatment

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age (≤70/>70)	1.10 (0.64-1.87)	0.73		
Sex (male/female)	1.25 (0.69-2.29)	0.47		
Smoking history (yes/no)	1.55 (0.75-3.18)	0.23		
ECOG PS (0/1)	0.73 (0.42-1.28)	0.28		
Histology (non-Sq/Sq)	0.45 (0.25-0.81)	0.01	0.57 (0.31-1.05)	0.07
Stage (III, IV/recurrence)	1.35 (0.72-2.53)	0.35		
PD-L1 expression at diagnosis (<50%/≥50%)	1.24 (0.89-1.70)	0.59		
Response with prior ICI (CR, PR/SD ≥ 6 months)	0.85 (0.48-1.49)	0.56		
Duration of prior ICI (<8.1 months/>8.1 months)	1.83 (1.02-3.30)	0.04	1.27 (0.68-2.38)	0.46
ICI-free interval (≤9.2 months/>9.2 months)	2.61 (1.47-4.64)	0.001	2.02 (1.10-3.73)	0.02
History of irAE with prior ICI (yes/no)	0.51 (0.28-0.91)	0.02	0.69 (0.37-1.29)	0.24

Abbreviations: Non-Sq, non-squamous; PS, performance status; Sq, squamous.



RECHALLENGE
THE MOST FREQUENT SITUATIONS

- AFTER ICI HELD FOR irAE 
- AFTER ICI TREATMENT COMPLETION 
- AFTER PD DURING ICI 

RECHALLENGE
THE MOST FREQUENT SITUATIONS

AFTER ICI HELD FOR irAE

AFTER ICI TREATMENT COMPLETION

AFTER PD DURING ICI

IO RESISTANCE *Definition*

- **Concepts of innate and secondary resistance to IO have been translated from advanced NSCLC treated under CT +/- TKIs**
- **A clear consensus is lacking: SITC vs ESMO**

1. Type of treatment:
   - Prior treatment with PD-(L)1 blockade is required. IO–IO combinations are allowed.
2. Depth of response:
   - Patients experience objective response on PD-(L)1 blockade. Stable disease is excluded.
3. Timing of progression:
   - No duration of response threshold is required. Confirmatory scans of progression after prior response are not required.
4. Continuity of treatment:
   - Progression occurs within 6 months of last PD-(L)1 blockade treatment. In patients with progression occurring >6 months since last treatment, PD-(L)1 blockade retreatment is required.

Schoenfeld AJ, et al. Ann Oncol 2021; Kluger HM, et al. J Immunother Cancer 2020

Treatment beyond PD

ORIGINAL ARTICLE

IASLC

Atezolizumab Treatment Beyond Progression in Advanced NSCLC: Results From the Randomized, Phase III OAK Study

David R. Gandara, MD,[a,*] Joachim von Pawel, MD,[b] Julien Mazieres, MD, PhD,[c]

Continued cemiplimab with addition of chemotherapy beyond progression appears superior to historical data for chemotherapy in the 2nd line setting where median OS is 8.4 months (range: 5.6 - 11.2) (Bersanelli et al., Lung Cancer, 2020)

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Prolonged Survival in the 2nd Line Setting
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	Cemiplimab Beyond Progression N=64	
OS	Period 1+2 Randomization to Death	Period 2 Day 1 of Continued Treatment to Death
Median (95% CI, months)	27.4 (23.0, 31.8)*	15.1 (11.3, 18.7)
Estimated Survival Probability, % (95% CI)		
6 months	100 (NE, NE)	91.9 (81.6, 96.5)

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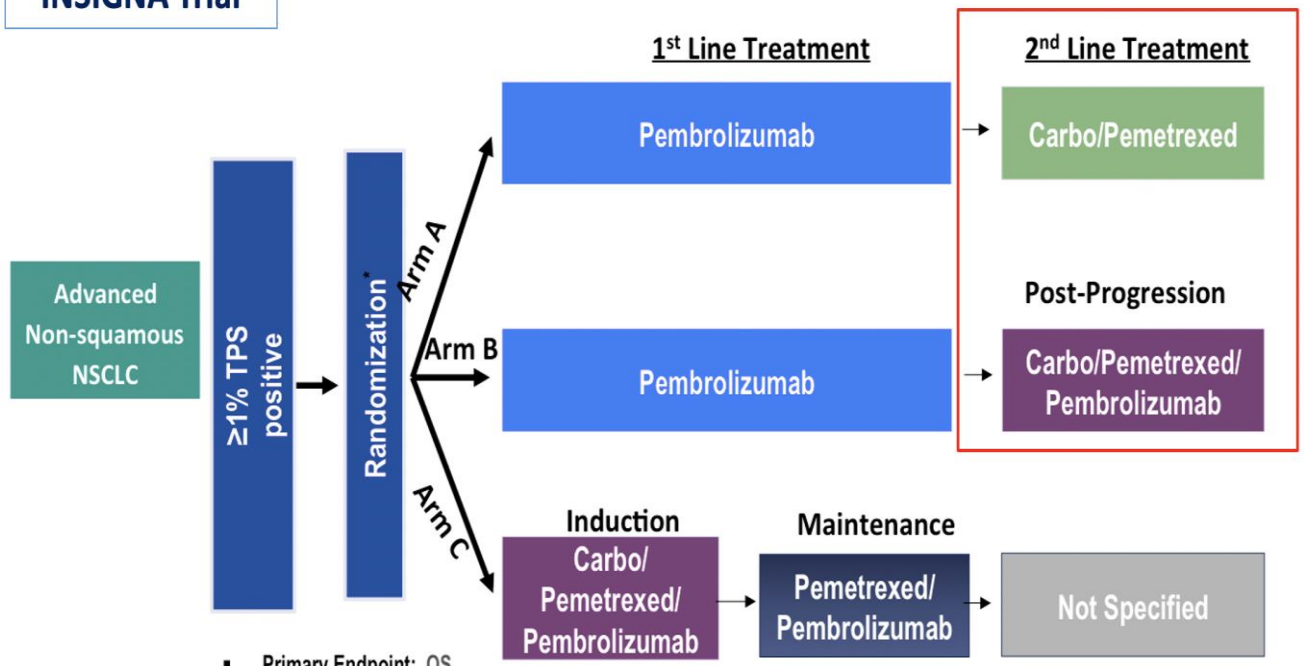
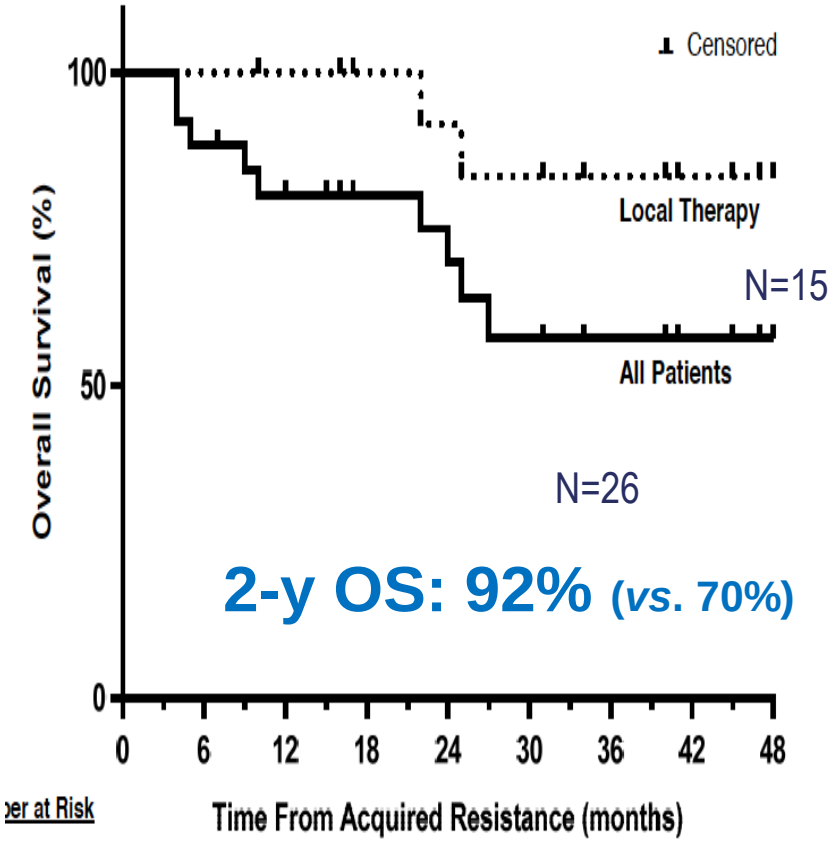
INSIGNA Trial

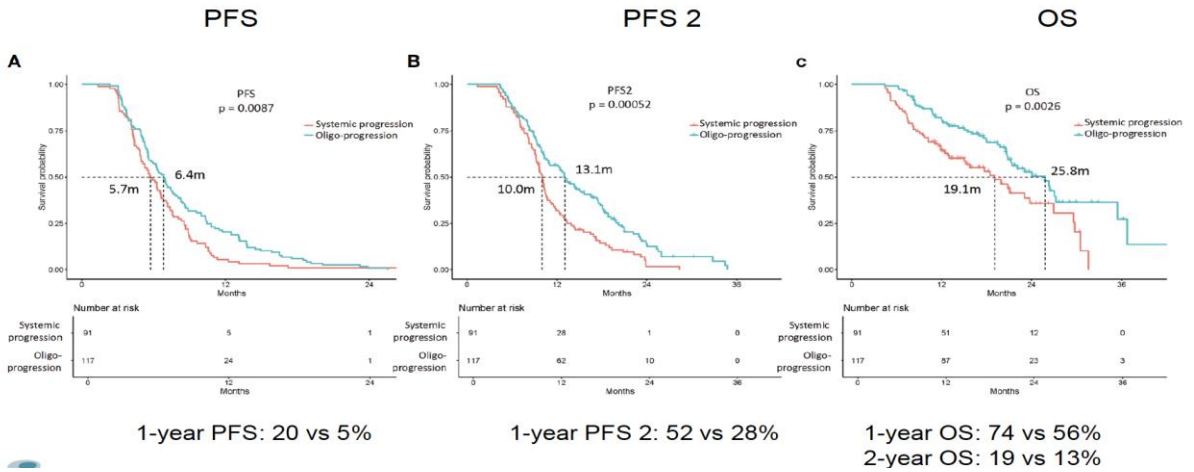


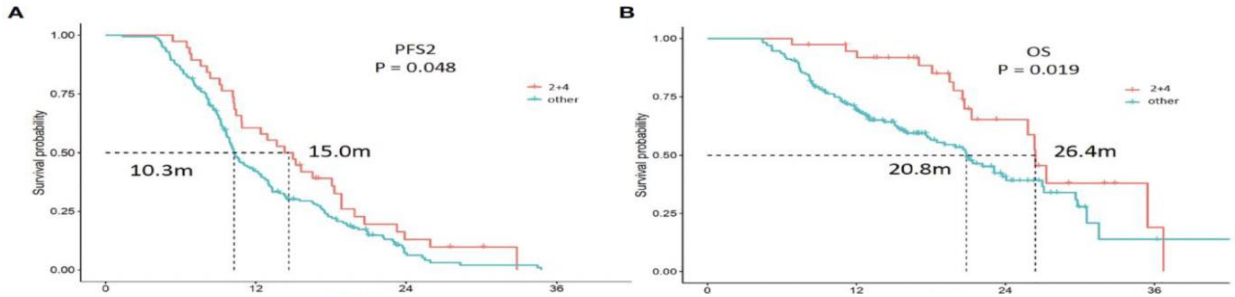
- **Primary Endpoint:** OS
- **Overall Objective:** Determine which approach is of greatest benefit in 1st line therapy of Non-Squamous NSCLC

Gandara D, et al. J Thorac Oncol 2018; Ozguroglu M, et al. ESMO 2022

A place for local treatment (Oligo-PD)?







Local T+ICI vs Others:
mPFS 15m vs 10.3m
mOS 26.4m vs 20.8m
1 year OS 89% vs 61%

Gettinger et al. J Thoracic Oncol 2018
Xu Y et al. Frontiers in Oncol 2021

IT IS DIFFICULT TO IMPROVE OUTCOMES POST CHEMO-ICI RESISTANCE

SAPPHIRE phase III RCT

Key Eligibility Criteria

- Unresectable, locally advanced, or metastatic NSQ NSCLC
- No EGFR, ROS1, or ALK alterations
- One or two prior regimens with most recent including CPI (≥4 months) with or after PBC
- Discontinuation of prior CPI <90 days prior to randomization
- ECOG PS 0 or 1
- No active brain metastases[a]

R 1:1

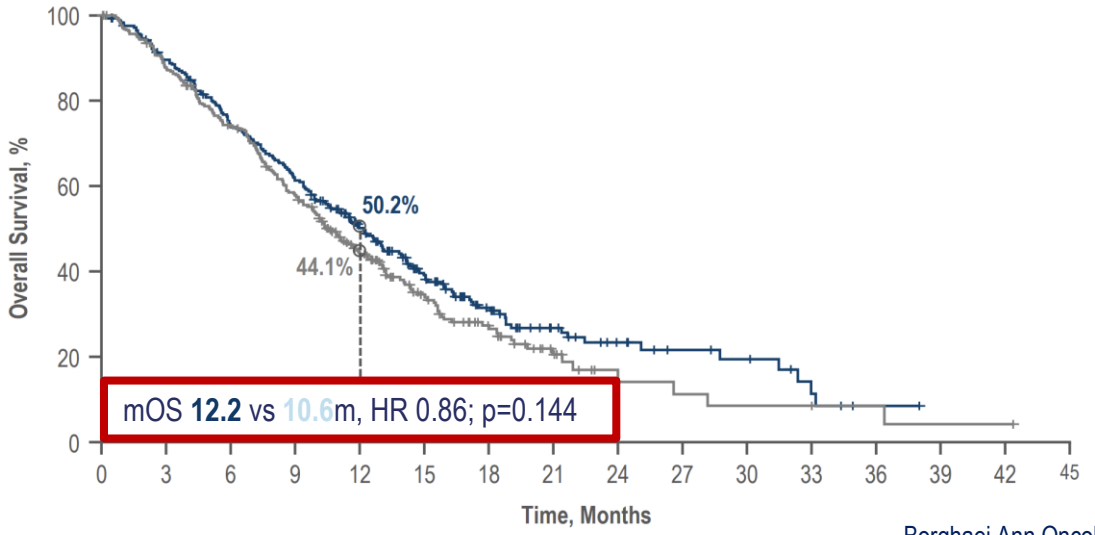
- **Sitravatinib (100 mg QD) + Nivolumab (240 mg Q2W or 480 mg Q4W) n=284[b]**
- **Docetaxel (75 mg/m² Q3W) n=293[b]**

Stratification Factors

- Prior treatment regimens in the advanced setting: 1 vs 2
- Baseline ECOG PS: 0 vs 1
- Treated and/or stable brain metastases at baseline: presence vs absence

Study Objectives

- Primary endpoint: OS
- Secondary endpoints[c]: ORR (RECIST v1.1), CBR, DOR, PFS, and safety
- Median follow-up: 17.1 months



CONTACT phase III RCT

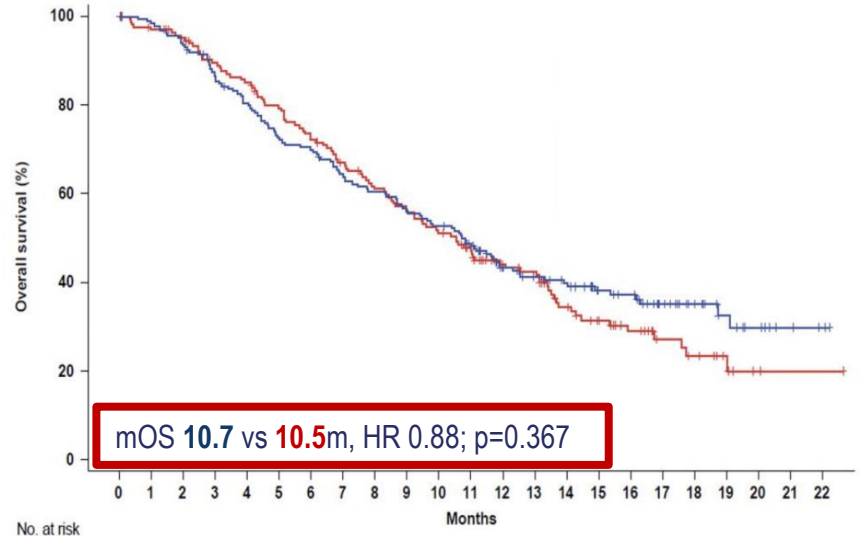
- Histologically or cytologically confirmed NSCLC (nonsquamous and squamous)
- ECOG PS 0-1
- Progression on or after immune checkpoint inhibitor and platinum-based chemotherapy
- Any PD-L1 status[a]
- Absence of sensitizing *EGFR* mutation or *ALK* fusion oncogene

N=366

R 1:1

- **Atezolizumab** 1200 mg Q3W + **Cabozantinib** 40 mg QD → PD or loss of clinical benefit
- **Docetaxel** (75 mg/m² Q3W) → PD

No crossover allowed



Borghaei Ann Oncol 2023; Neal ELCC 2023

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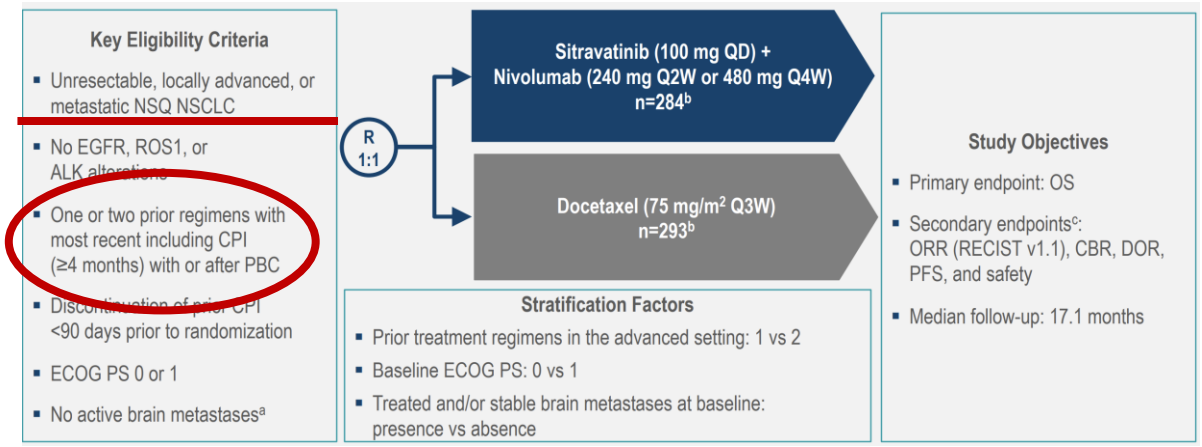
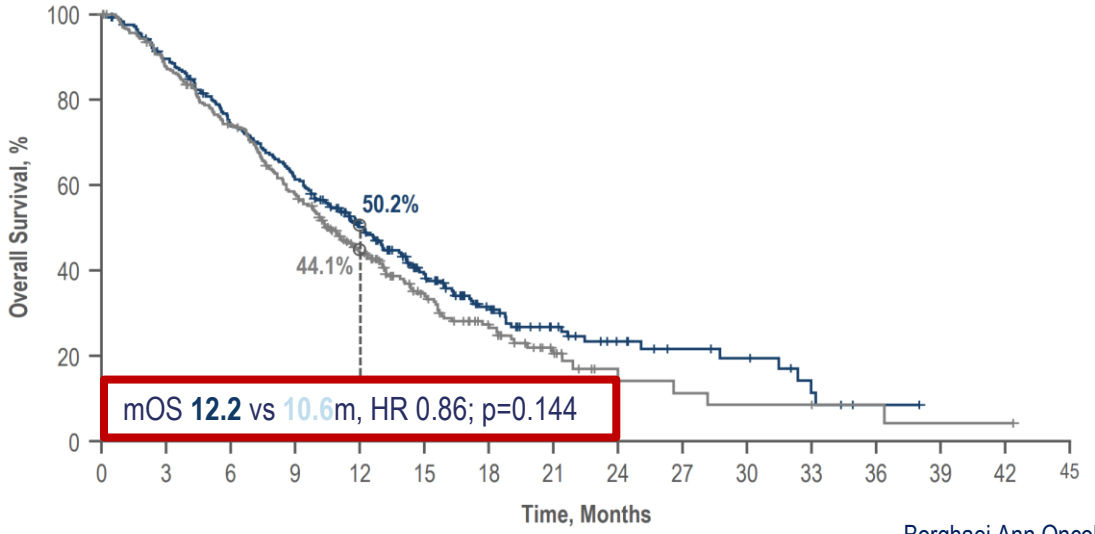
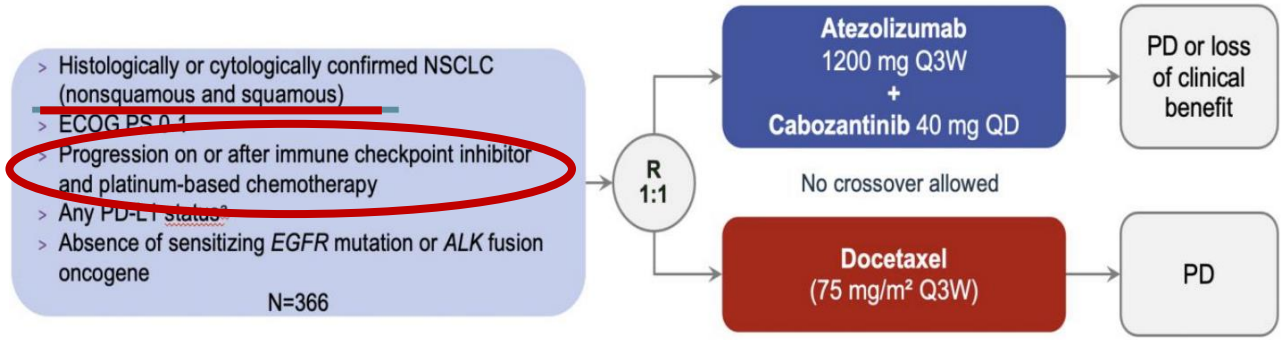
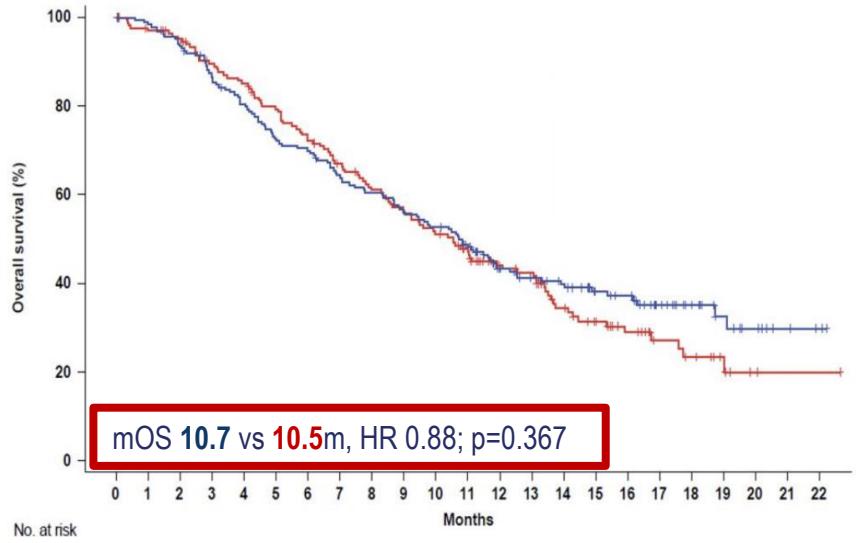
SAPPHIRE phase III RCT





CONTACT phase III RCT





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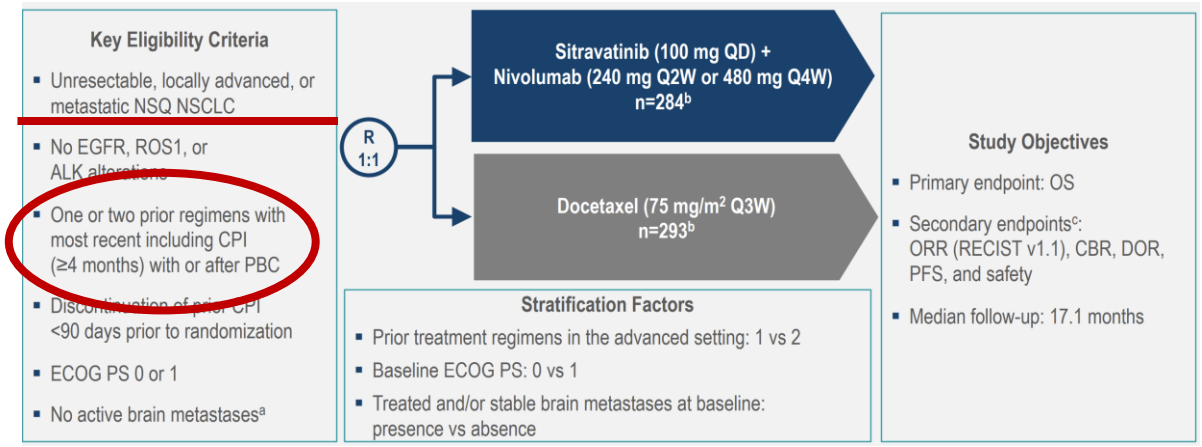
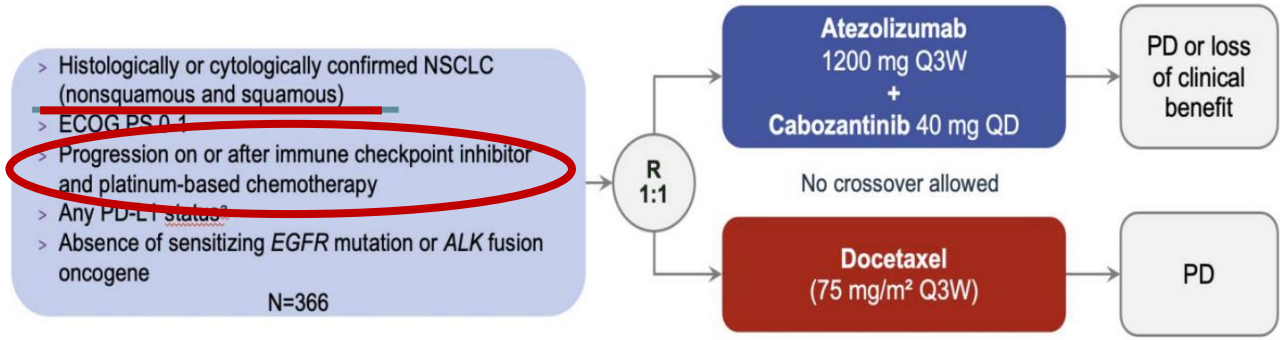
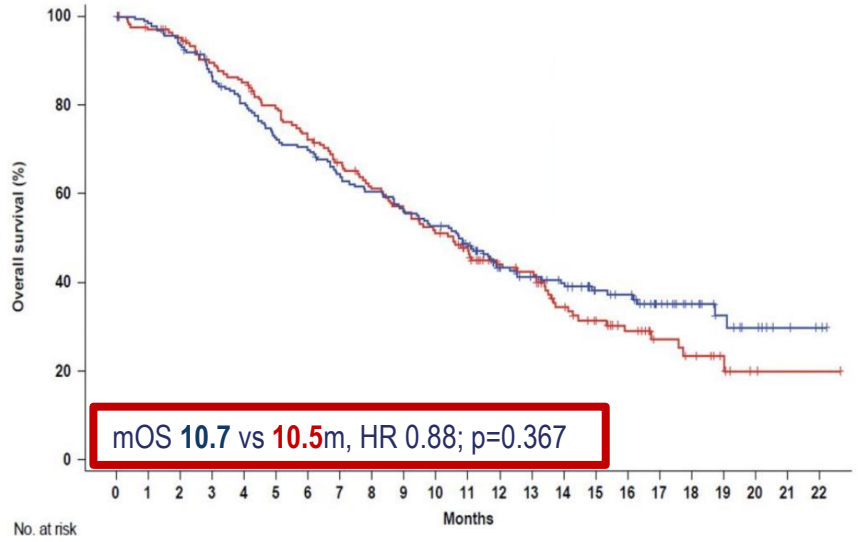


		mOS	OS HR (95% CI)
Prior NSCLC treatment	Platinum + anti-PD(L)1	9.8 vs 9.5	0.90
	Platinum then anti-PD(L)1	12.6 vs 10.5	0.80
	Anti-PD(L)1 then platinum	9.8 vs 11.9	1.26
Duration of prior CPI to PD	<6 months		1.06
	≥6 months		0.78

CONTACT phase III RCT





Borghaei Ann Oncol 2023; Neal ELCC 2023

Minimal impact of anti PD-L1 rechallange after ICI discontinuation for Progressive Disease

Paper	N	PR	PR + SD	Median PFS (months)
Fujita et al 2018	12	1	4	3.1
Niki et al 2018**	5*	0	1	1.6
Watanabe et al 2019	14	1	3	1.6
Fujita et al 2019	18	0	7	2.9 m
Fujita et al 2020	15	0	4	2.4
Katayama et al 2020**	35	1	14	2.7
Kitigawa et al 2021	10*	0	6	4.2
Furuya et al 2021	38	1	13	1.9
Total	**147**	**4 (2.7%)**	**52 (35%)**	**2.5*** **

* Patients with immune related adverse events during initial treatment excluded

** Patients received intervening chemotherapy and/or radiation

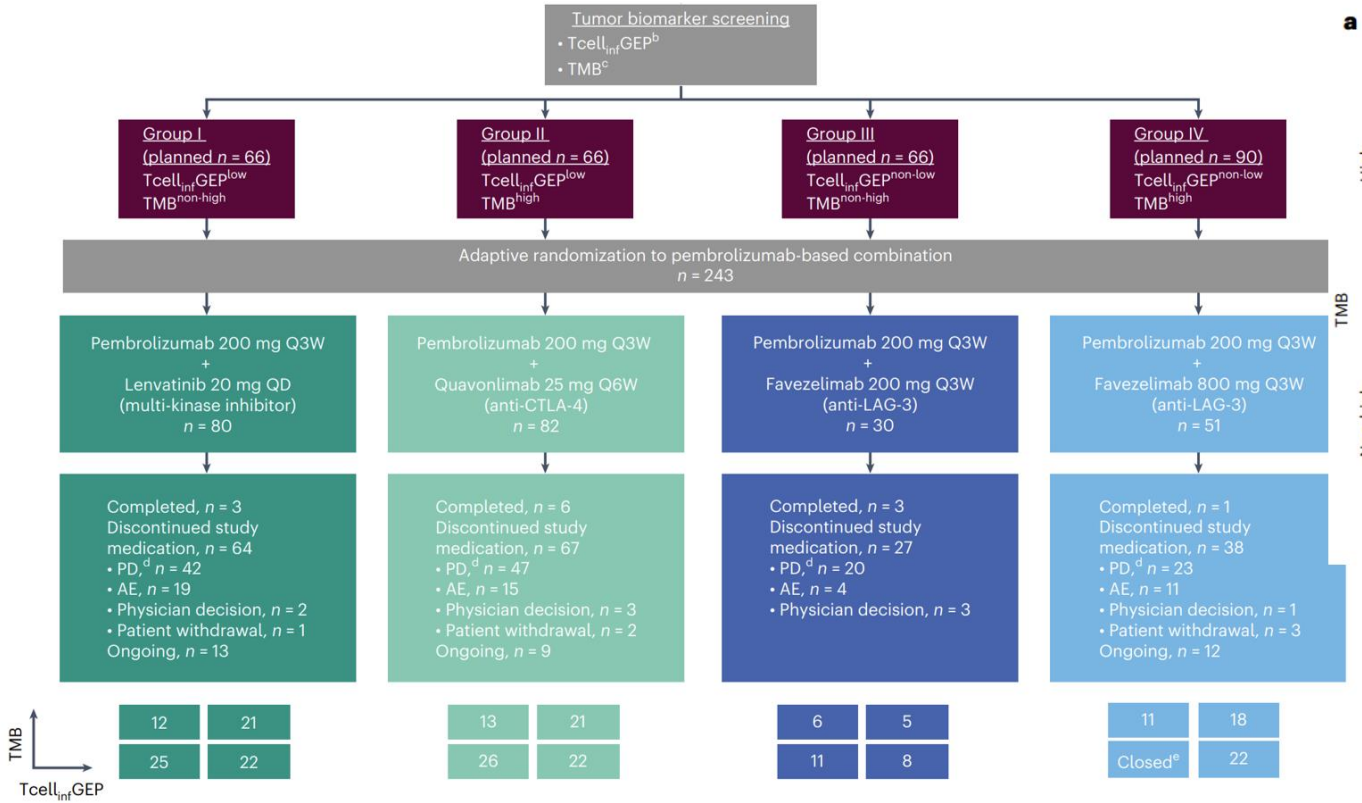
Guideline	I-O retreatment/rechallenge/escalation guidance provided
NCCN	**Not supported - *setting of recommendation unclear*** An anti-PD-1/PD-L1 is not recommended for patients who have PD on anti-PD-1/PD-L1 therapy (unclear if statement applies for non-met→1L mNSCLC vs 1L→2L+ mNSCLC)
ESMO	**Only consider for patients NOT discontinuing due to PD** Consider anti-PD-(L)1 rechallenge if the patient previously obtained a substantial clinical benefit from ICI (if the ICI was discontinued previously, but not for PD)

[1]NCCN NSCLC V1.2023; [2]Hendriks Ann Oncol 2023

We need to move away from "one-size-fits-all"

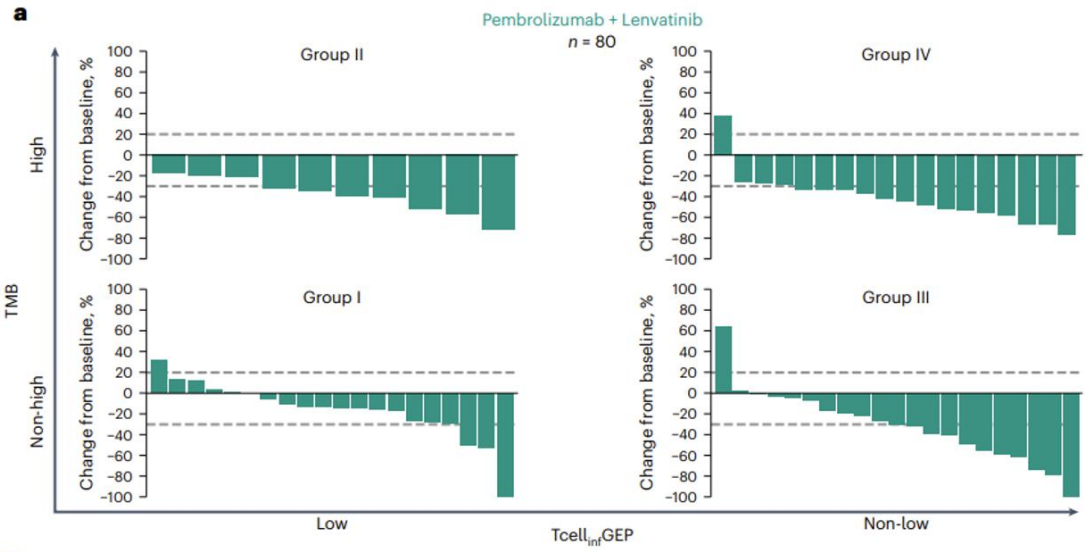
1st line KEYNOTE-495/KeyImPaCT phase II: randomization based on T cell inflamed gene expression profile & TMB

Primary endpoint RECIST 1.1 ORR
Pre- specified efficacy tresholds for each biomarker defined group



Threshold ORR: >5% >20% >20% >45%

Pembro + lenvatinib group III met primary endpoint



Still phase III RCT needed!
And are these tresholds enough in 1st line?

Gutierrez Nat Med 2023

THE MOST FREQUENT SITUATIONS

AFTER ICI HELD FOR irAE

Decision depends on:

Severity of irAE
Type of toxicity
P. with increased risk of irAEs: caution
Alternative therapies
Status of the cancer

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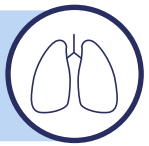
AFTER ICI HELD FOR irAE



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AFTER ICI TREATMENT COMPLETION

Decision depends on:

Interval free
Previous response
Available options

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AFTER PD DURING ICI


15th
MADRID
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Muchas Gracias