AIGOM
ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

Congresso Nazionale sul carcinoma del polmone

CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2023?

9 OTTOBRE 2023
VERONA
Hotel Leon D'Oro

Responsabile scientifico
STEFANIA GORI

Immunoterapia
ruolo del rechallenge

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Definition of Rechallenge

- Rechallenge has been defined as «repeated treatment with the same therapeutic class in patients who had clinical benefit with prior treatment for unresectable or metastatic disease»

- Retreatment has been defined as «repeated treatment with the same therapeutic class after adjuvant treatment has ended»

- A consensus definition with practical clinical implications

International Journal of Biological Sciences, 19(8), 2428-2442, 2023

Current Guidance

- NCCN, ESMO and SIC recommend immunotherapy rechallenge for melanoma treatment, however they have no consensus for the timing.
- A few guidelines recommend immunotherapy rechallenge for renal cancer and head and neck squamous cell carcinoma, but the data were insufficient to support them.
- No guidelines have been published for lung cancer.
- BUT some patients with lung cancer benefited from ICI rechallenge

Differenti rechallenge

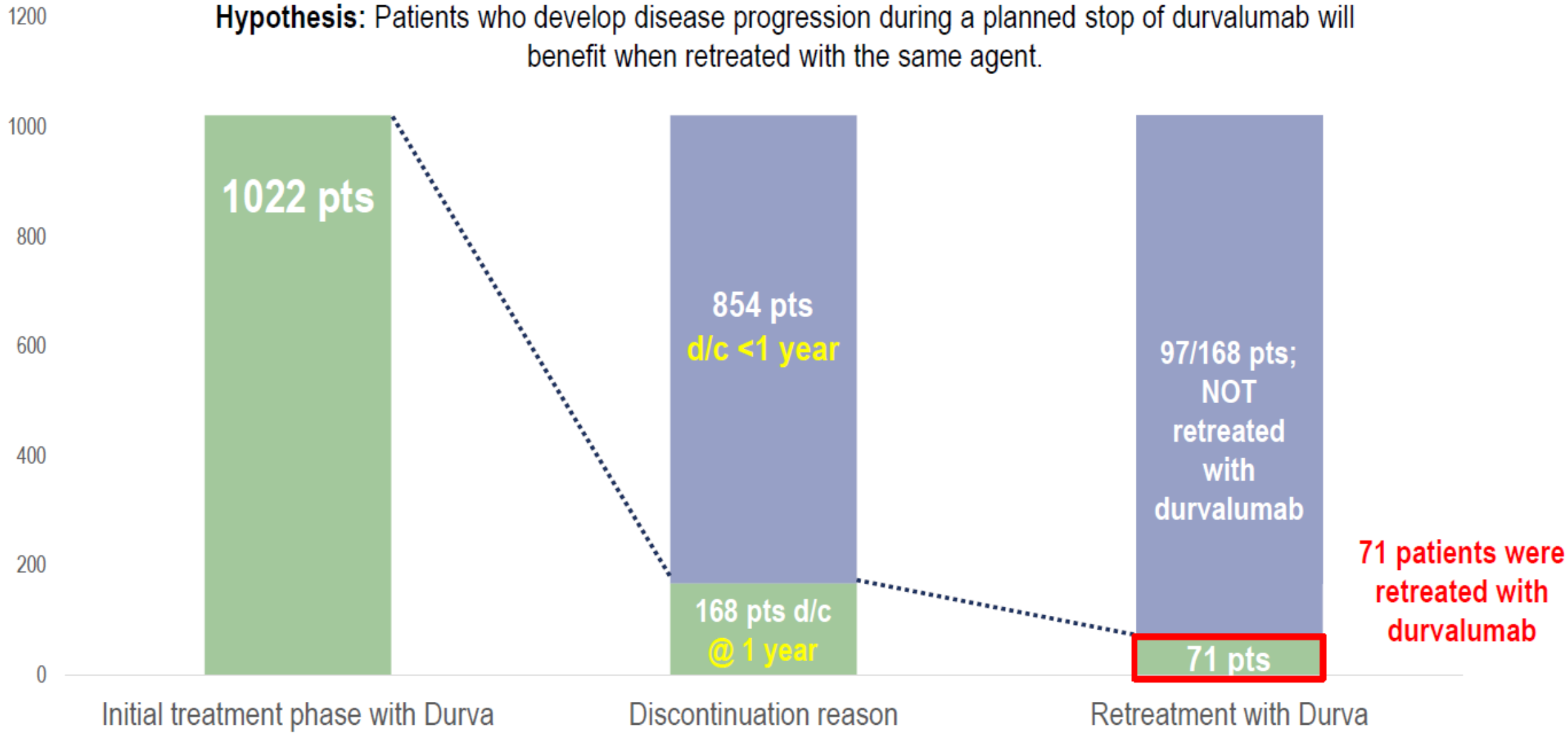
- Rechallenge dopo interruzione programmata
- Rechallenge dopo interruzione per progressione
- Rechallange dopo interruzione per tossicità immuno-correlata

Differenti rechallenge

- **Rechallenge dopo interruzione programmata**

RETROSPECTIVE ANALYSIS OF 71 PATIENTS WHO WERE RETREATED

Hypothesis: Patients who develop disease progression during a planned stop of durvalumab will benefit when retreated with the same agent.



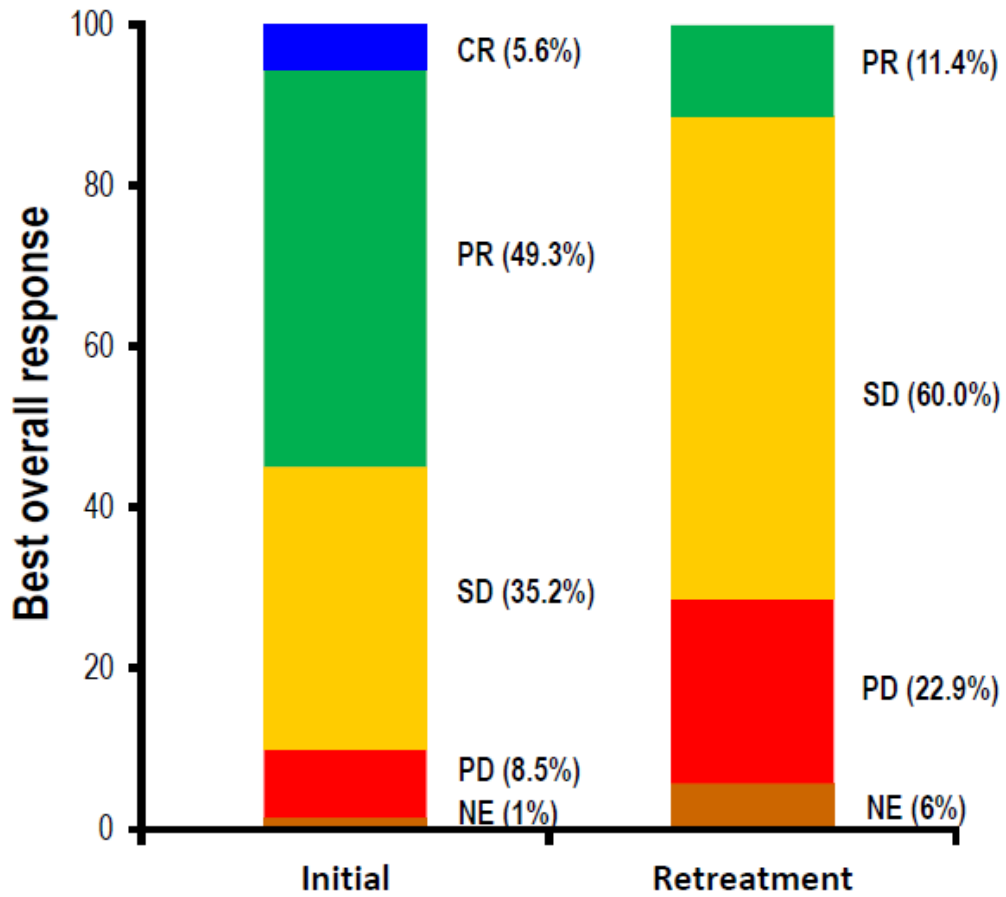
BARCELONA 2019 ESMO congress

Objectives: Characterize retreatment best overall response (BOR1) per RECIST v1.1, disease control rate (DCR1) at 24 weeks, progression free survival (PFS1) rate at 12 months, and median overall survival (OS)

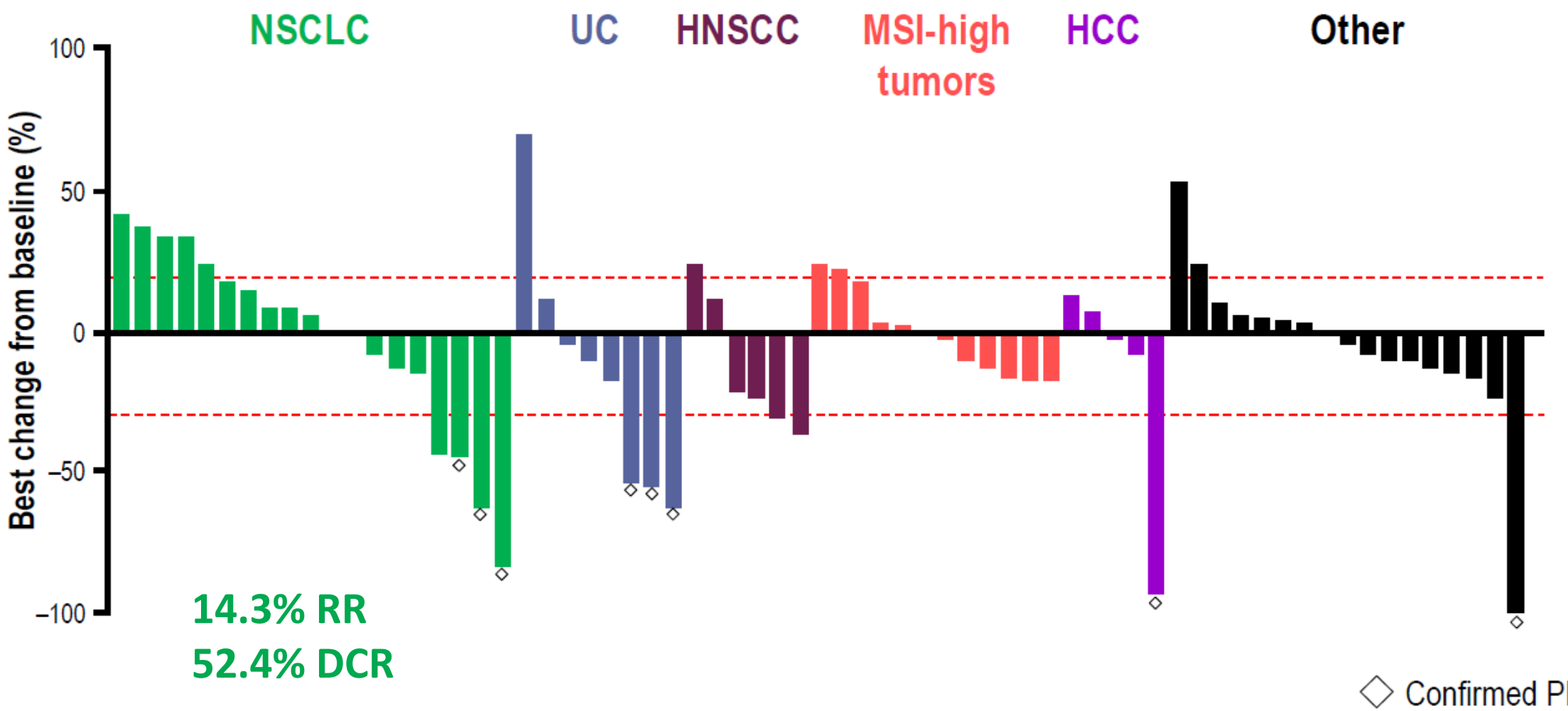
COMPARISON OF CLINICAL RESPONSES WITH INITIAL THERAPY AND AT RETREATMENT

- 6 patients with PD by RECIST → 4 pts had pseudoprogression, treated for 1 year; BOR was PR by iRECIST
- 1 glioblastoma patient was not RECIST evaluable and was excluded from retreatment analysis

Response	Initial (n=71)	Retreatment (n=70)
Best overall response, n (%)		
Complete response	4 (5.6)	0
Partial response	35 (49.3)	8 (11.4)
Stable disease	25 (35.2)	42 (60.0)
Unconfirmed partial response	*2 (2.8)*	*0 (0)*
Progressive disease	6 (8.5)	16 (22.9)
Non-evaluable	1 (1.4)	4 (5.7)
Median time to response, months	2.7	4.3
Median duration of response, months	14.8	16.5
DCR ≥24 weeks, %	81.7	47.1
PFS rate at 12 months, %	71.0	34.2
Median OS (months)	48.9	23.8

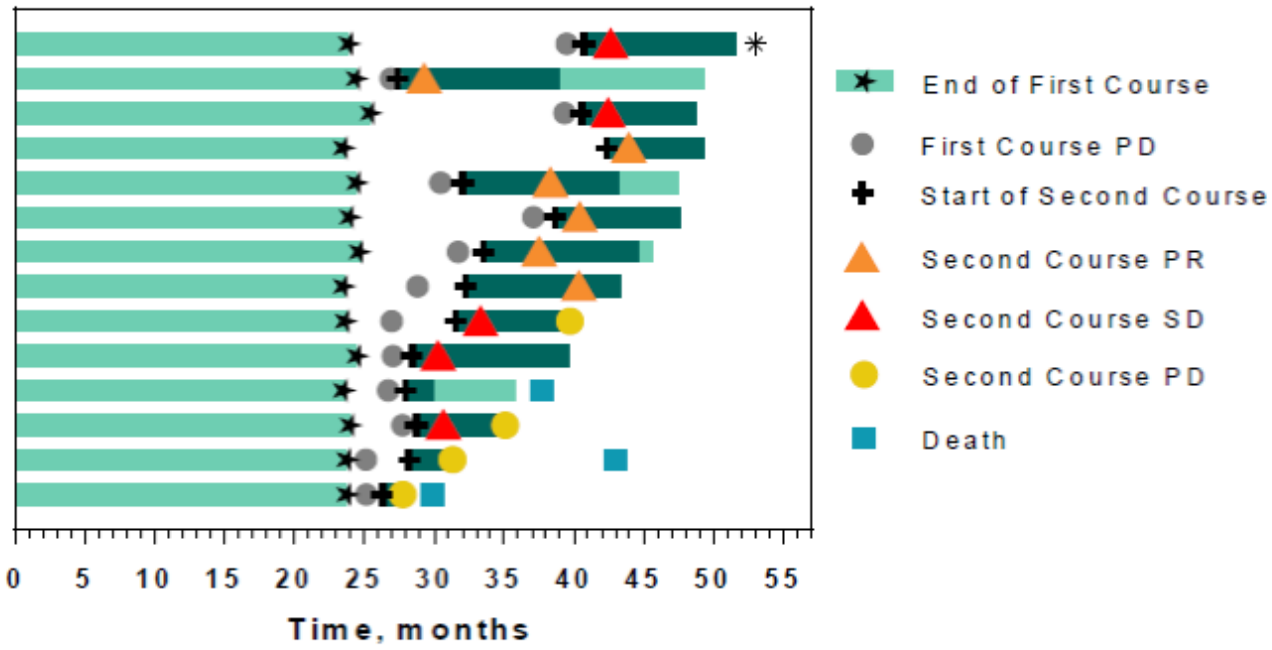


RETREATMENT RESULTED IN ANTITUMOR ACTIVITY ACROSS ALL TUMOR INDICATIONS



KEYNOTE-010

n=14



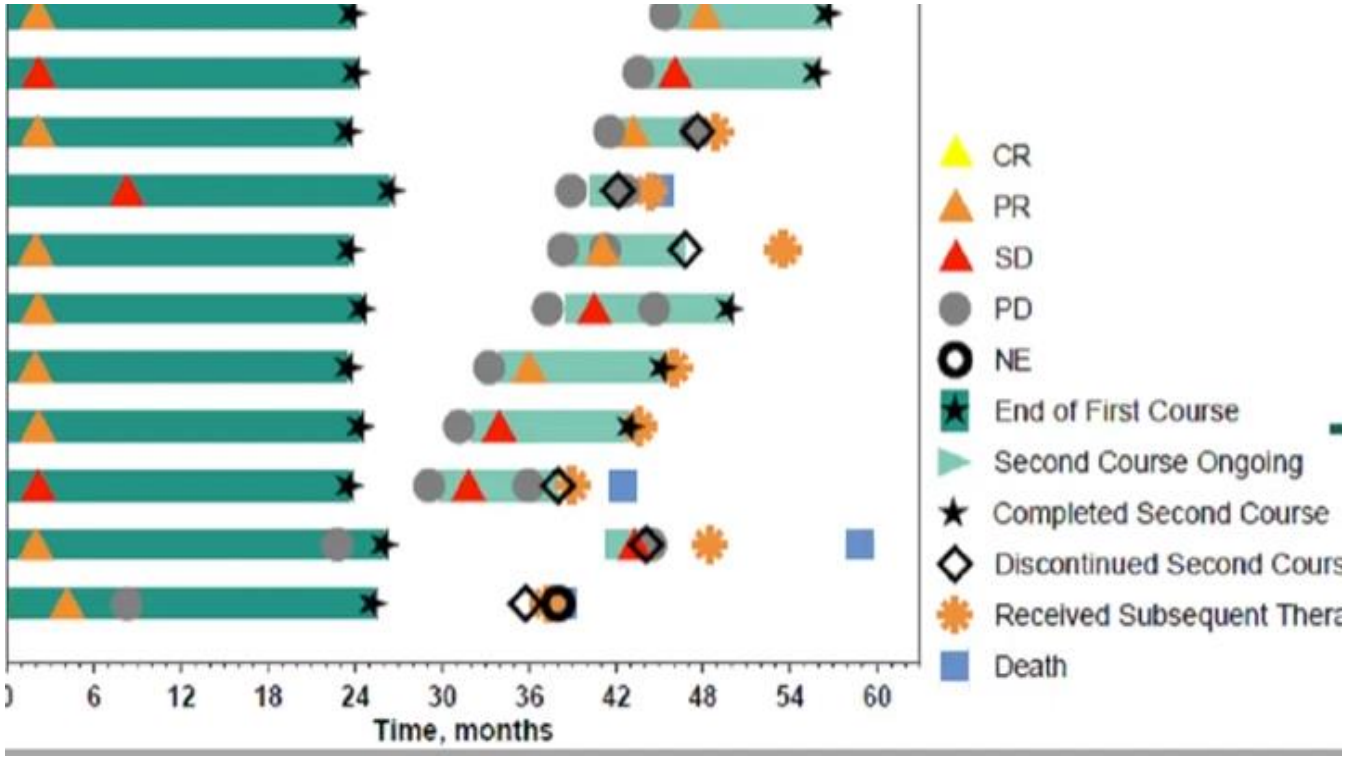
- In total, 14 patients started a second course of pembrolizumab after 35 cycles or 2 years of pembrolizumab treatment and subsequently having irPD per irRC by investigator review[b]
- Of these 14 patients, 6 (43%) had PR and 5 (36%) had SD during second course treatment per RECIST version 1.1 by independent central review
  - 5 patients (36%) completed 17 cycles
  - 11 patients (79%) remained alive

SD, stable disease.
[a]Bar lengths indicate duration of second course treatment (dark green) and months of second-course follow up (light green bar following dark green bar). Follow up was defined as the date of progression or last investigator assessment the patient was alive. CR and PR are per RECIST version 1.1 by independent central review; PD is per irRC by investigator review.
[b]One patient who received a second course of pembrolizumab did not meet eligibility criteria for having completed 35 cycles or 2 years of first course pembrolizumab (indicated with asterisk). One further patient had unconfirmed disease progression in first course. Data cutoff: March 16, 2018.

Herbst RS, et al. J Clin Oncol 2020

KEYNOTE-024

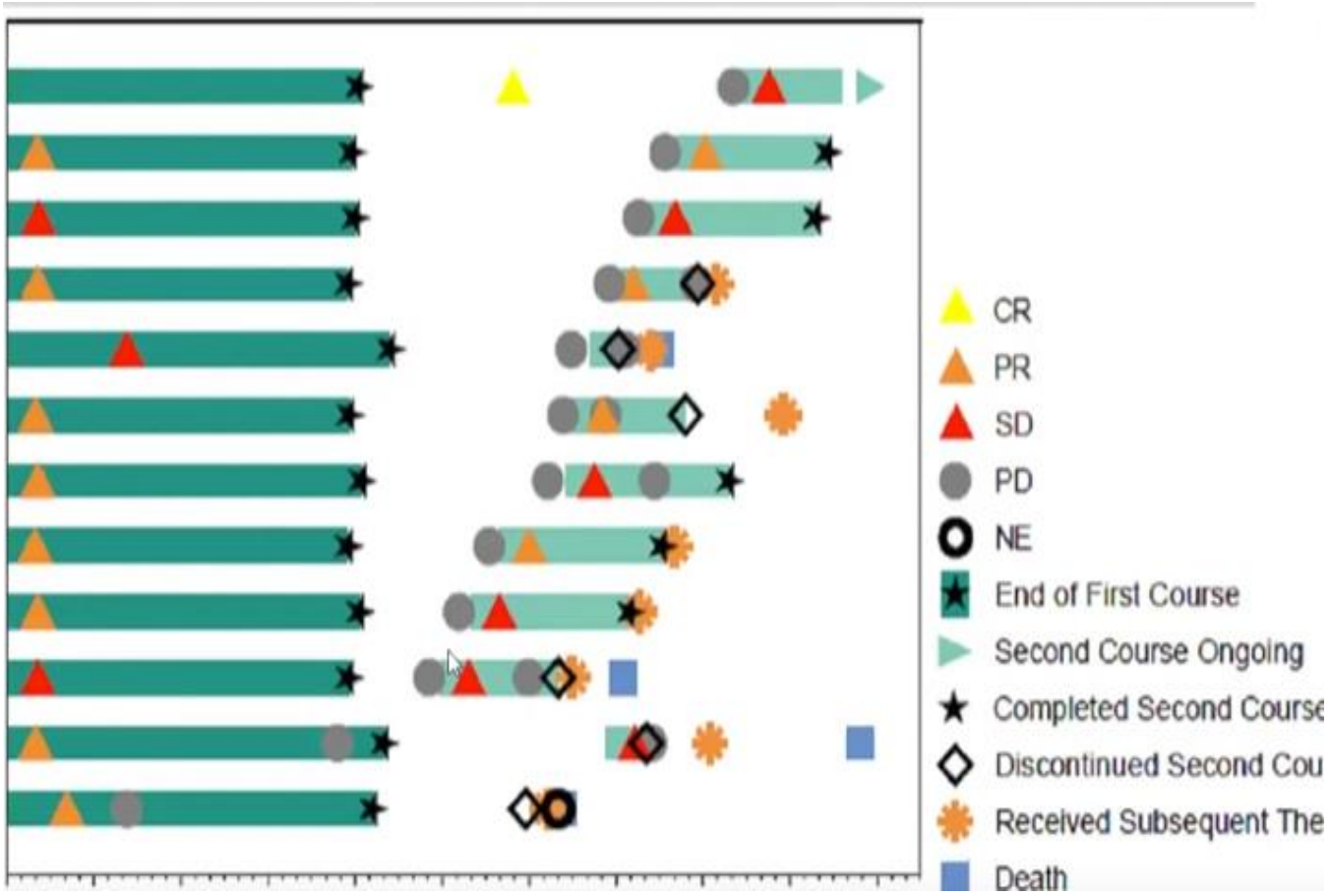
n=12



Characteristic	35 Cycles (2 Years) of Pembrolizumab N = 39[a]	Second Course of Pembrolizumab N = 12[b]
Age, y, median (range)	61.0 (43–80)	60.0 (43–77)
Male	25 (64.1)	8 (66.7)
ECOG PS 1	23 (59.0)	9 (75.0)
East Asian enrollment site	8 (20.5)	3 (25.0)
Squamous histology	2 (5.1)	1 (8.3)
Current/former smoker	37 (94.9)	12 (100.0)
Treated brain metastases	9 (23.1)	1 (8.3)
Prior neoadjuvant therapy	0	0
Prior adjuvant therapy	0	0

At data cutoff, 18/39 patients (46%) were alive without PD or subsequent therapy for NSCLC per investigator assessment

Brahmer et al. ESMO 2020



	N = 12[c]
Alive at data cutoff, n (%)	8 (67)
Objective response during second course, n (%)	4 (33)
Best objective response, n (%)	
Complete response	0
Partial response	4 (33)
Stable disease	6 (50)
Progressive disease	1 (8)

Brahmer et al. ESMO 2020

Outcomes in Patients Who Received Second-Course Pembrolizumab

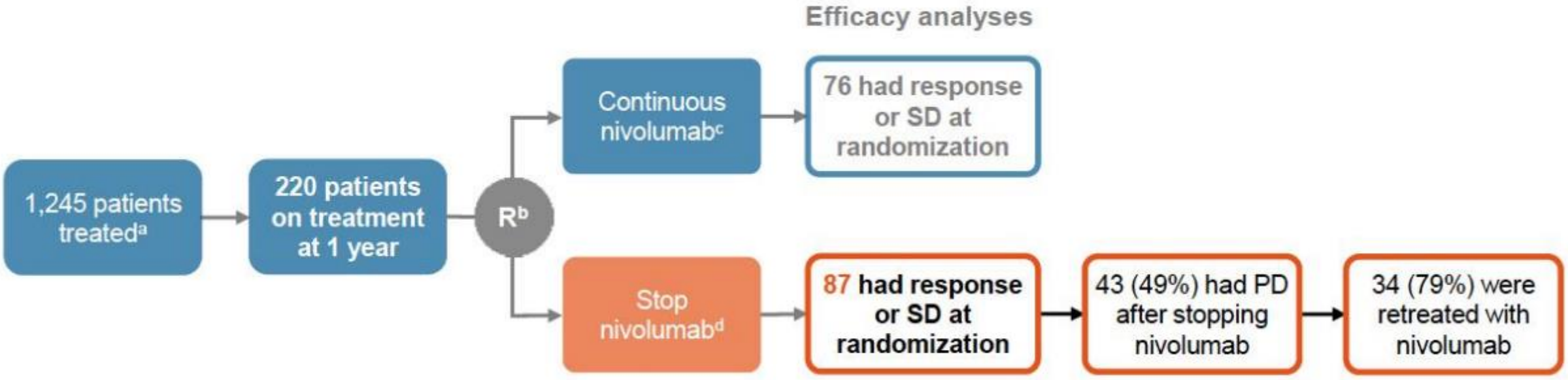
Upon assessment of PD, 33 eligible patients received second-course pembrolizumab (Data Supplement). Median time from random assignment to database cutoff was 63.7 (range, 52.0-75.2) months. Five patients (15.2%) had PR and 20 (60.6%) had SD, for a disease control rate of 75.8% (Data Supplement). At data cutoff, two patients (6.1%) were alive without PD and subsequent therapy.

KEYNOTE-042

DE CASRTO et al. Jco 2022

CheckMate 153: Continuous vs 1-Year Nivolumab

Retreatment in 1-Year Treatment Arm



Data at time of analysis (database lock May 15, 2017)

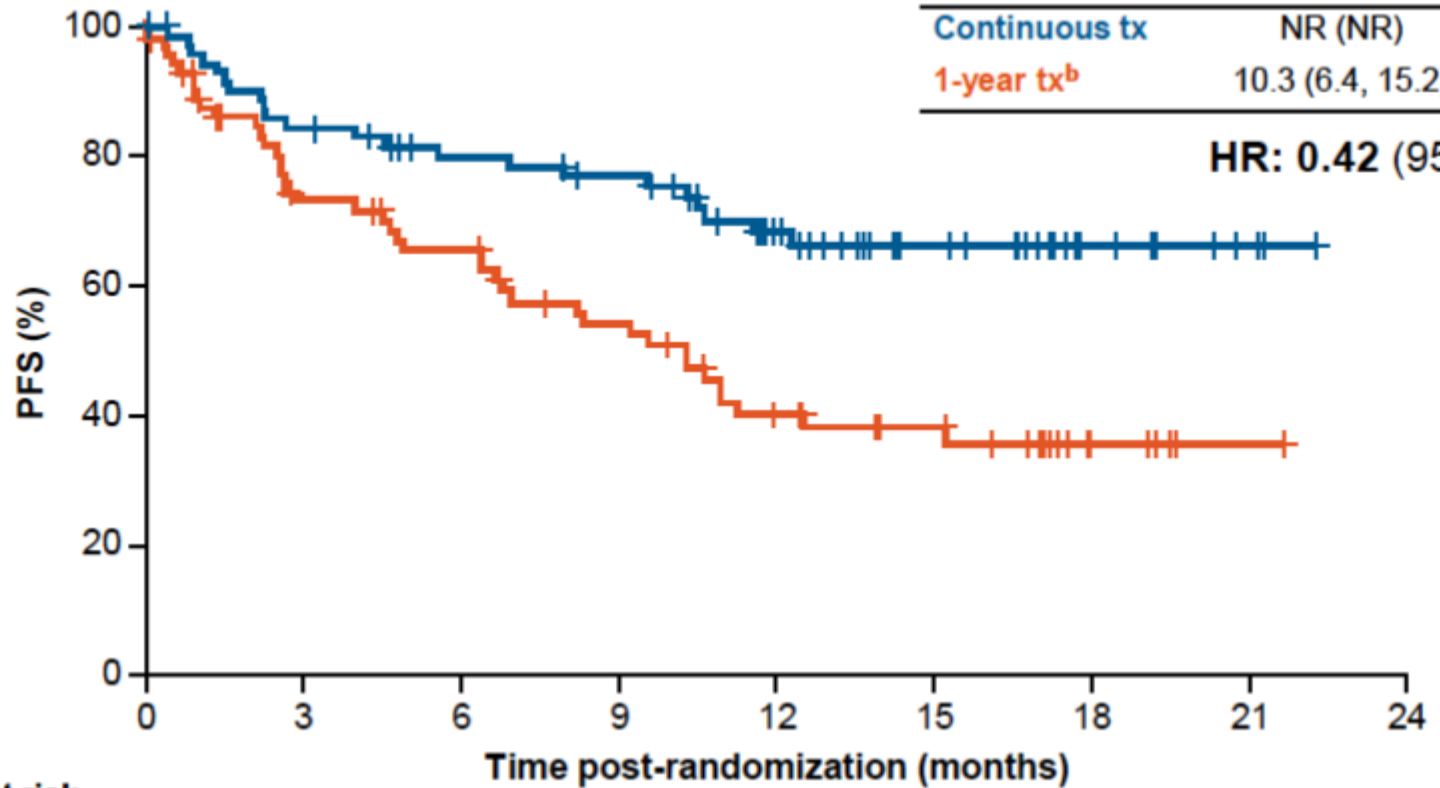
[a]Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons; [b]All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; [c]8 patients discontinued treatment due to patient request or withdrawal of consent; [d]12 patients discontinued treatment due to patient request or withdrawal of consent

CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization[a]

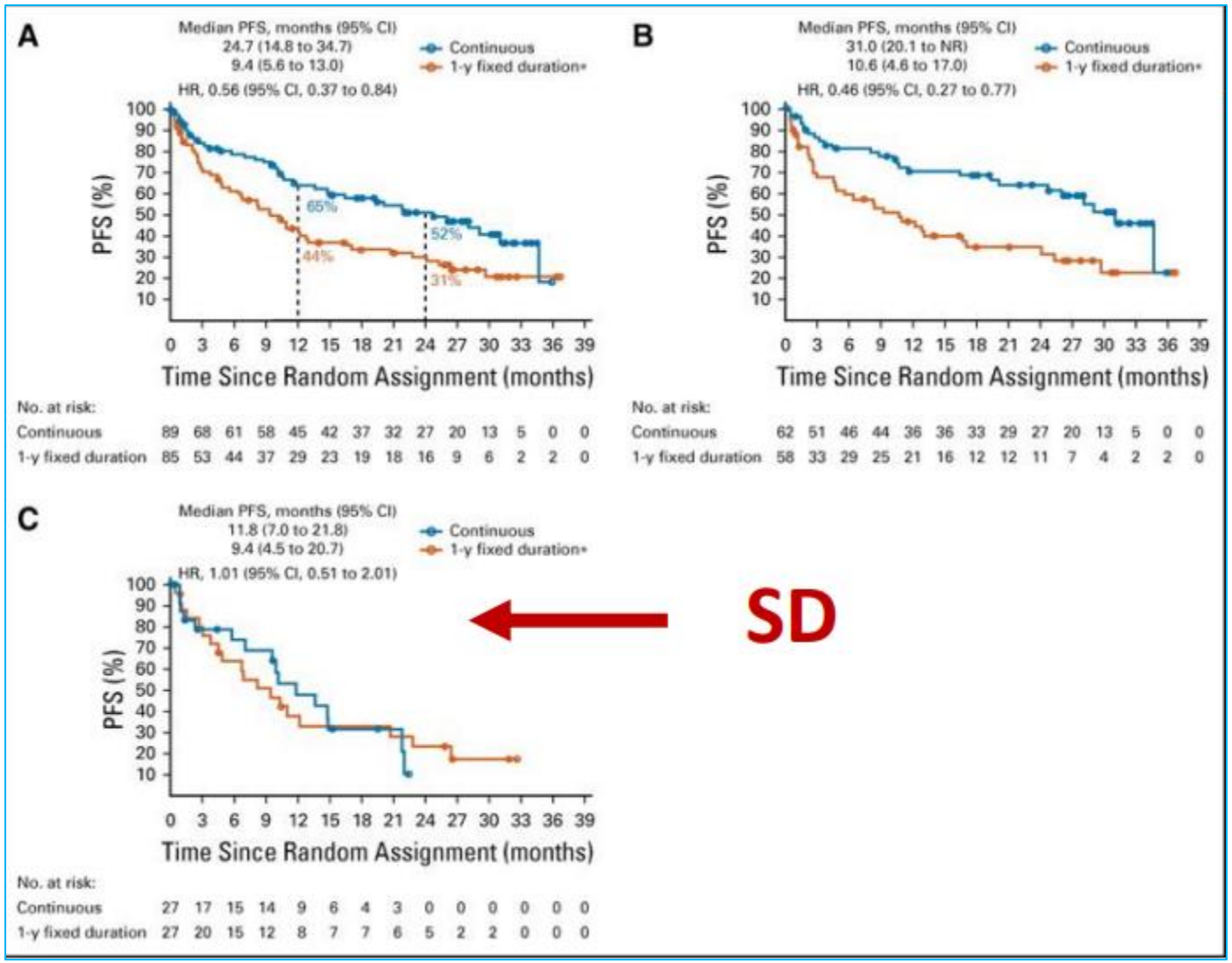
	Median, months (95% CI)	PFS rate, %	
		6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)



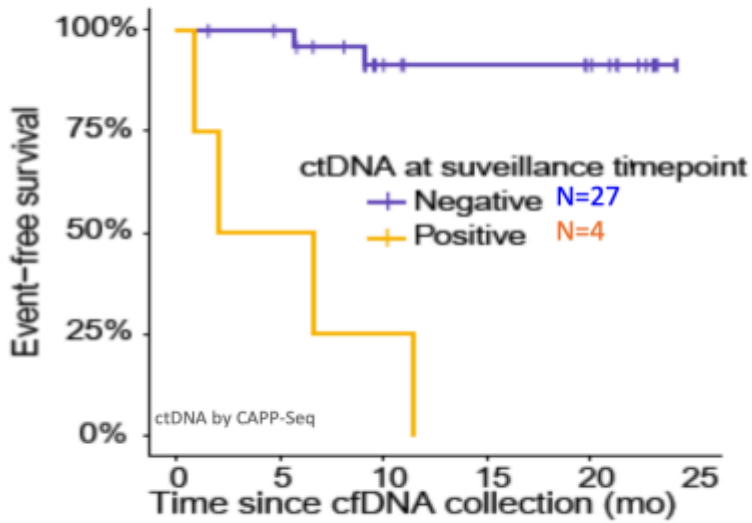
No. at risk									
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment



SD

31 NSCLC with sustained benefit ICI (PFS≥12 mo.)
ctDNA analysis at 26.7 mo. after ICI initiation



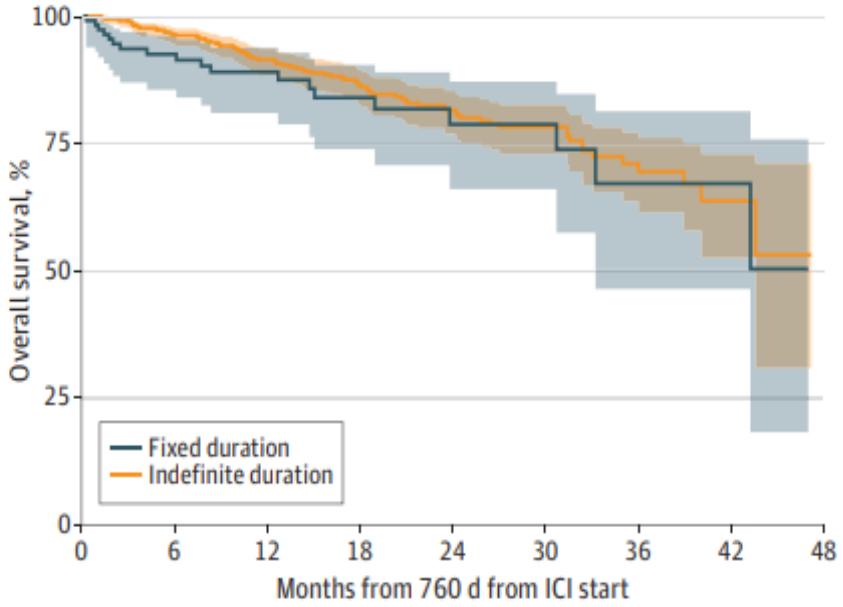
Undetectable ctDNA correlated with longer EFS

Research

JAMA Oncology | Original Investigation

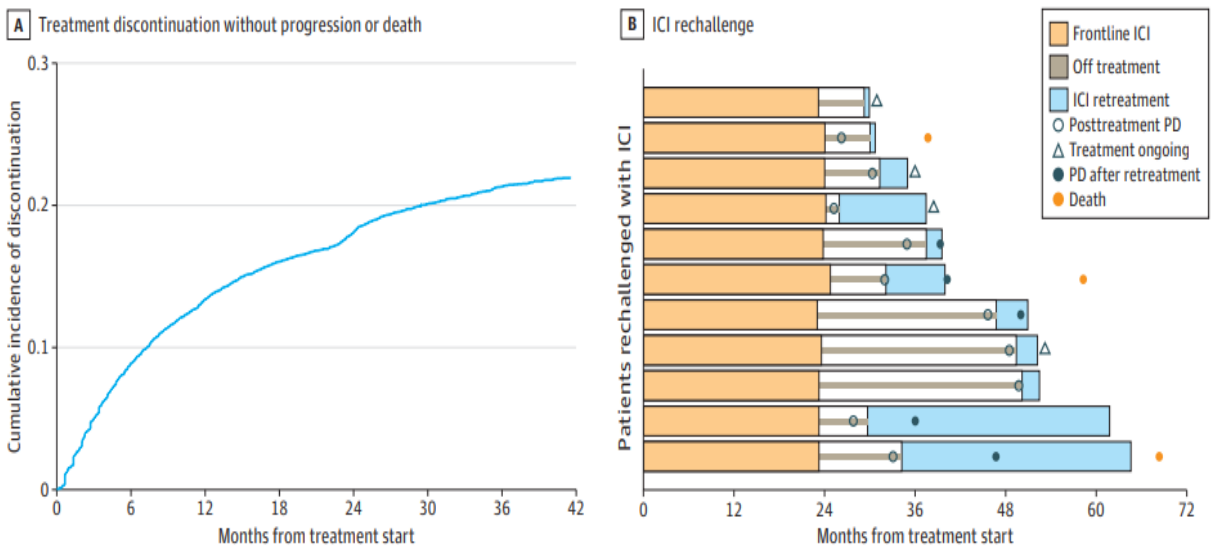
Association Between Duration of Immunotherapy and Overall Survival in Advanced Non–Small Cell Lung Cancer

Lova Sun, MD, MSCE; Benjamin Bleiberg, MD; Wei-Ting Hwang, PhD; Melina E. Marmarelis, MD, MSCE; Corey J. Langer, MD; Aditi Singh, MD; Roger B. Cohen, MD; Ronac Mamtani, MD, MSCE; Charu Aggarwal, MD, MPH



No. at risk

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



A, The cumulative incidence of treatment discontinuation in the absence of progression or death over time (in months) from treatment initiation. Patients with progression within 60 days of discontinuation or death within 6 months of discontinuation were classified as having a competing event for this analysis.

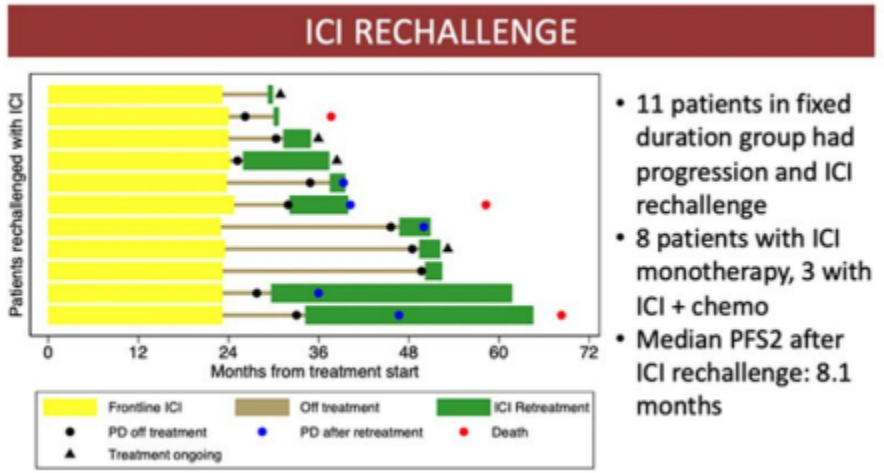
B, Swimmer plot with fixed-duration treatment group patients rechallenged with ICI-based therapy. Abbreviations: ICI, immune checkpoint inhibitor; PD, progressive disease.

Sun L: JAMA Oncology 2023 ; 9(8), 1075-1082

11/113 had PD and ICI rechallenge

Median time to restart 7.4 months

PFS2 8.1 months



- 11 patients in fixed duration group had progression and ICI rechallenge
- 8 patients with ICI monotherapy, 3 with ICI + chemo
- Median PFS2 after ICI rechallenge: 8.1 months

Sun L: JAMA Oncology 2023 ; 9(8), 1075-1082

editorials

To Continue or Not to Continue? That Is the Question

Marina Chiara Garassino, MD[1]; Benjamin Besse, MD, PhD[2]; and Valter Torri, MD[3]

ASCO

Journal of Clinical Oncology®

3830 Volume 38, Issue 33

Differenti rechallenge

- Rechallenge dopo interruzione programmata

- **Rechallenge dopo interruzione per progressione**

IO RESISTANCE

Definitions of primary and secondary resistance in advanced disease setting

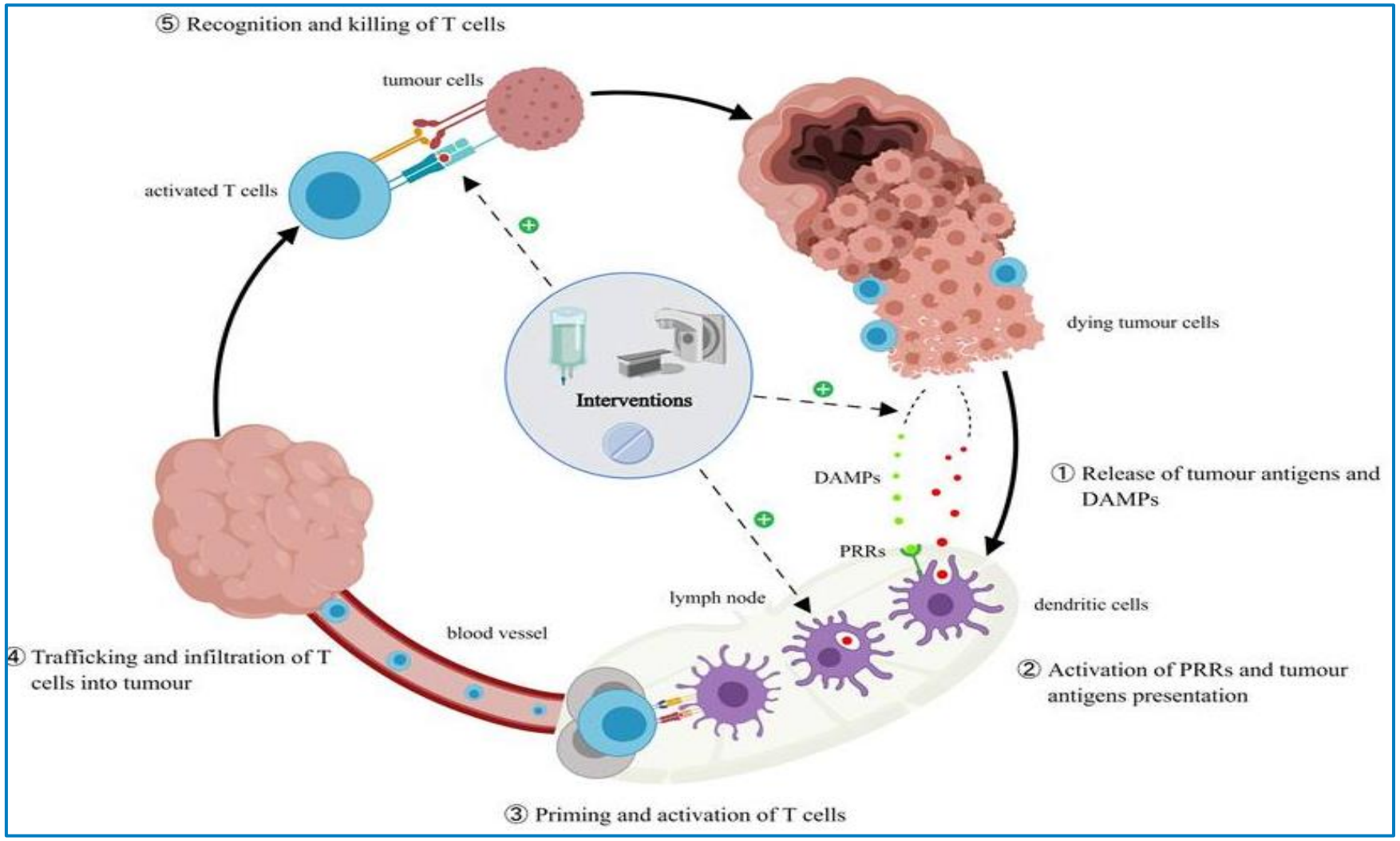
Resistance phenotype	Drug exposure requirement	Best response	Confirmatory scan for PD requirement	Confirmatory scan timeframe
Primary resistance	≥6 weeks	PD; SD for <6 months*	Yes†	At least 4 weeks after initial disease progression‡
Secondary resistance	≥6 months	CR, PR, SD for >6 months*	Yes†	At least 4 weeks after disease progression‡

Definitions of adjuvant therapy resistance

Adjuvant therapy	Timing of last dose prior to PD	Confirmatory biopsy requirement*
Primary resistance/early relapse	<12 weeks	Yes
Late Relapse	≥12 Weeks	Yes

Kluger HM, et al. J Immunother Cancer 2020;8:e000398

The cancer immunity cycle and the effects of interventions.



International Journal of Biological Sciences, 19(8), 2428-2442, 2023

Lung Cancer 140 (2020) 99–106

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Data from Real-World Studies

Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis

Matteo Giaj Levra[a,b], François-Emery Cotté[c,*], Romain Corre[d], Christophe Calvet[c], Anne-Françoise Gaudin[c], John R. Penrod[c], Valentine Grumberg[e], Baptiste Jouaneton[f], Ronan Jolivel[f], Jean-Baptiste Assié[g,h], Christos Chouaïd[g]

[a] Thoracic Oncology Unit, Centre Hospitalier Universitaire Grenoble Alpes (CHUGA), Grenoble, France
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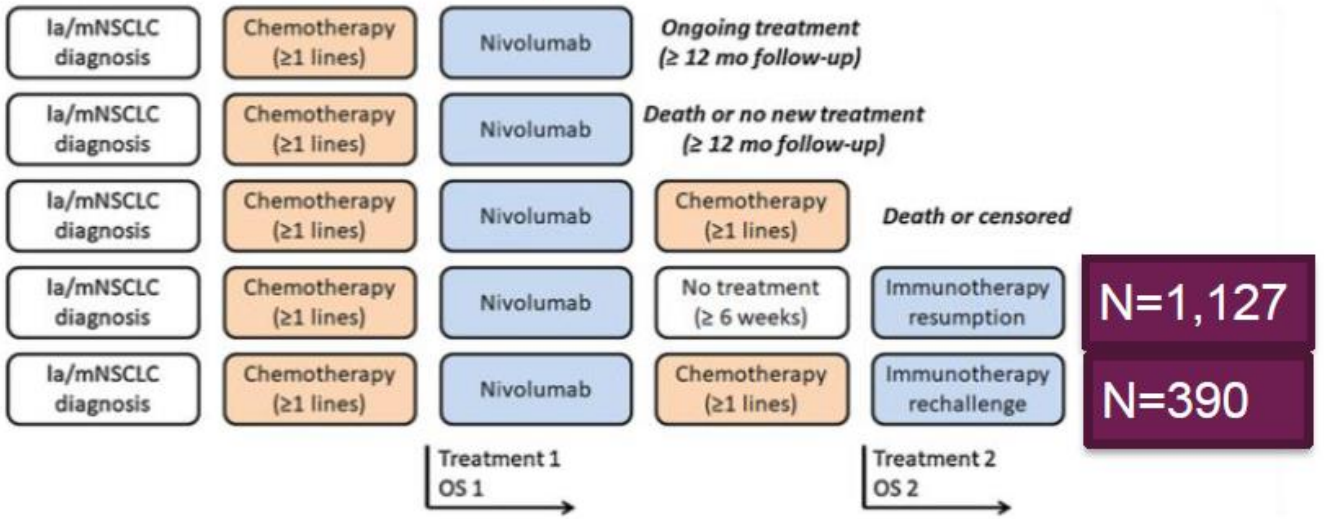
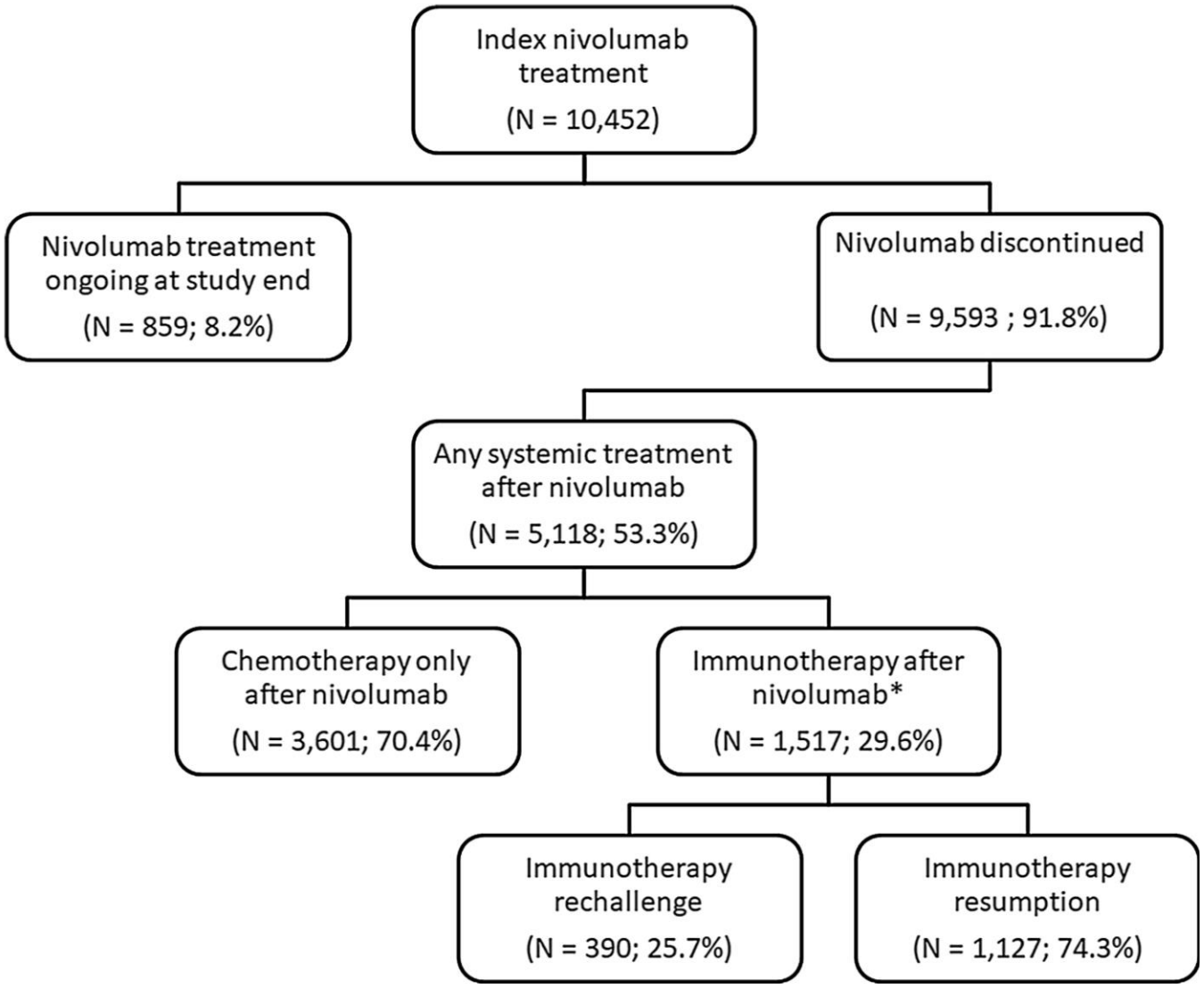
[h] Centre de Recherche des Cordeliers, Sorbonne Universités, Inserm, UMRS-1138, Paris, France

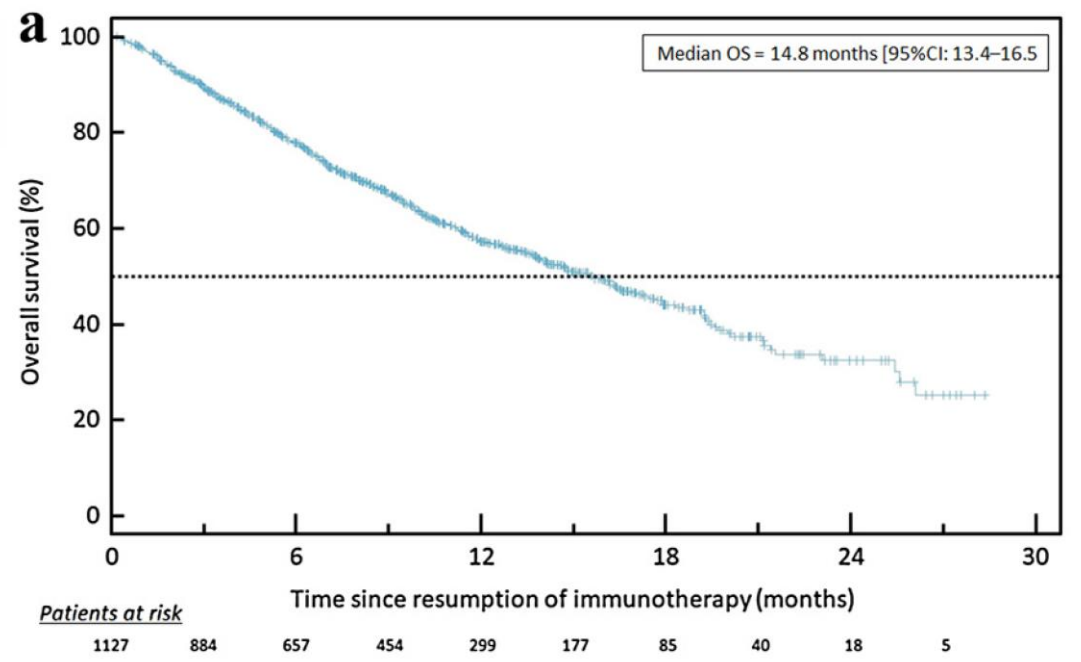
2nd line

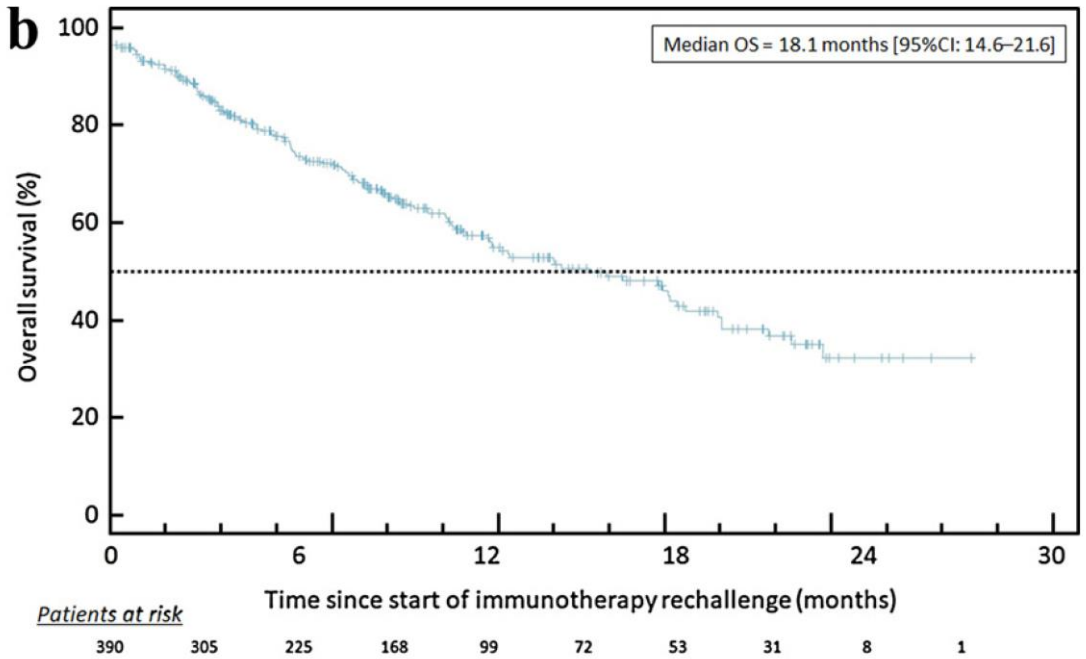


Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis



Percentages are calculated in each case with respect to the previous line.*Eighteen patients were prescribed pembrolizumab as immunotherapy after nivolumab (six as resumption and twelve as rechallenge), the remaining 1499 were prescribed a second course of nivolumab.

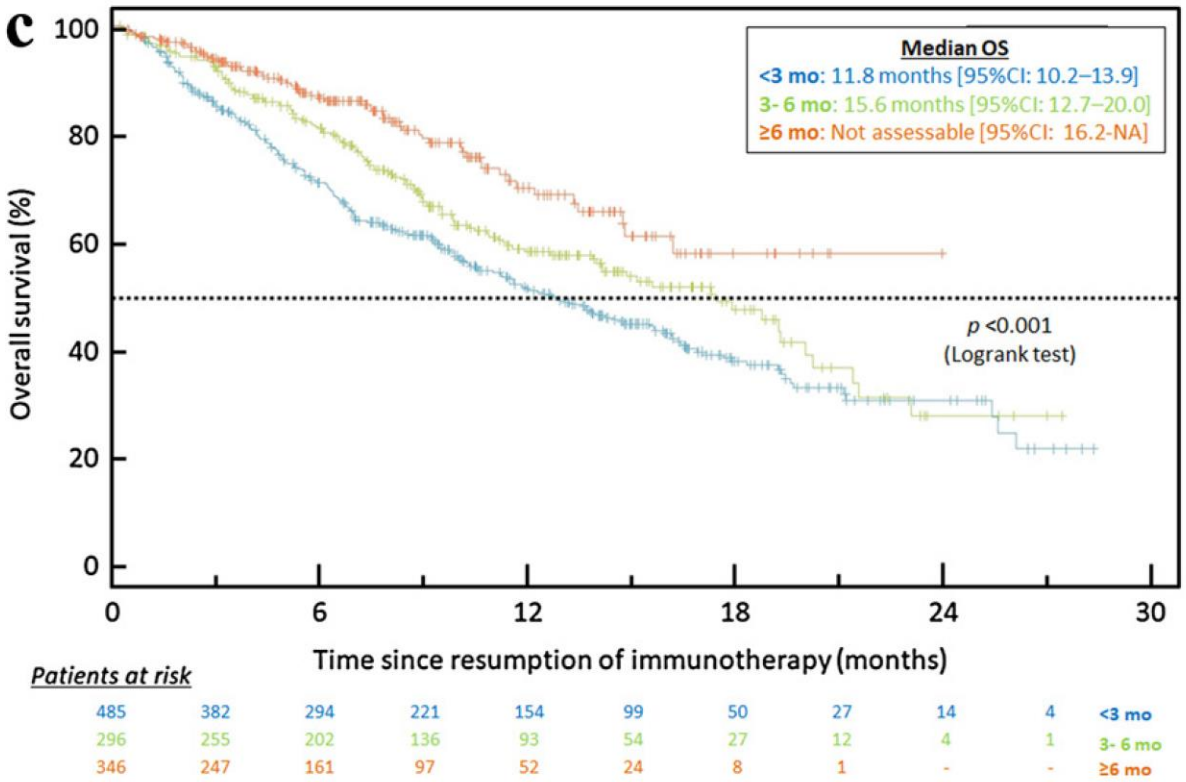




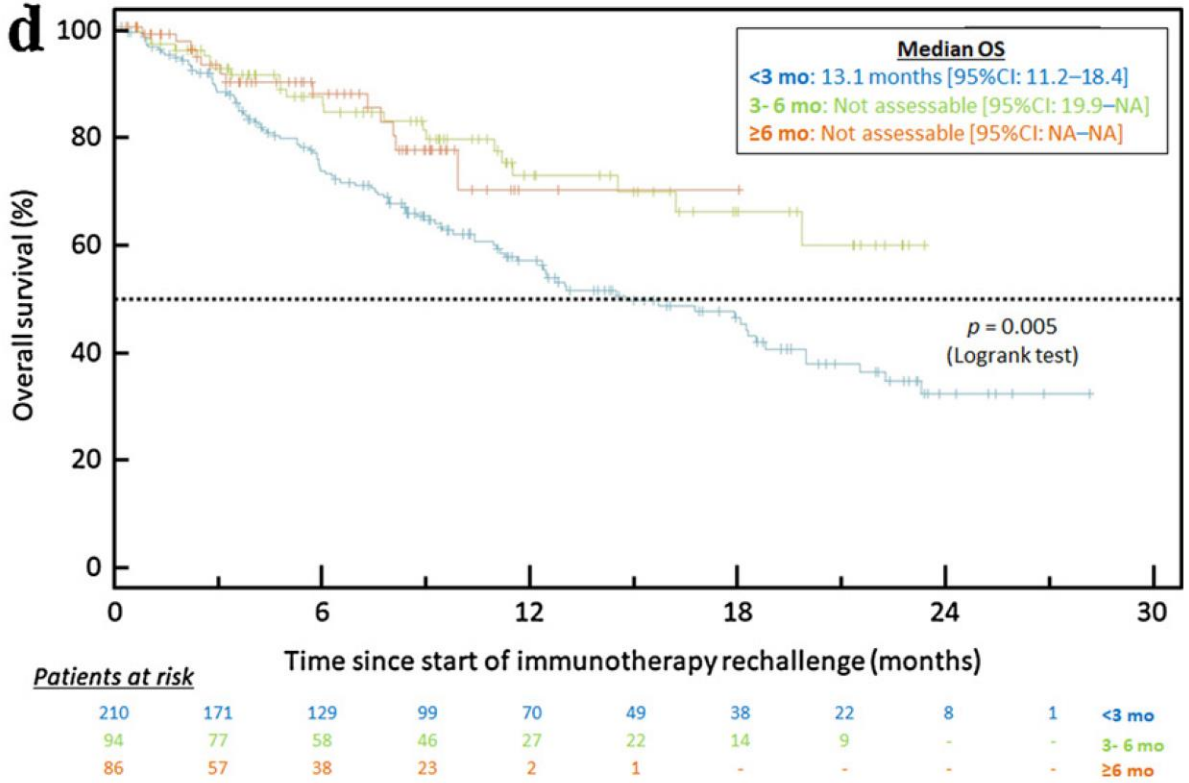
Giaj Levra M, et al. Lung Cancer. 2020;140:99-106.

Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis

Resumption cohort



Rechallenge cohort



Giaj Levra M, et al. Lung Cancer. 2020;140:99-106.

VIRTUAL 2020 ESMO congress

EMPOWER

EMPOWER-Lung 1 Study Design (NCT03088540)

Key Eligibility Criteria
- Treatment-naïve advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification Factors:
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

R 1:1

Arm A
Cemiplimab monotherapy IV
350 mg Q3W
Treat until PD or 108 weeks

PD → **Optional continuation of cemiplimab + 4 cycles of chemotherapy**

Arm B
4–6 cycles of investigator's choice chemotherapy

PD → **Optional crossover to cemiplimab monotherapy**

Follow-up

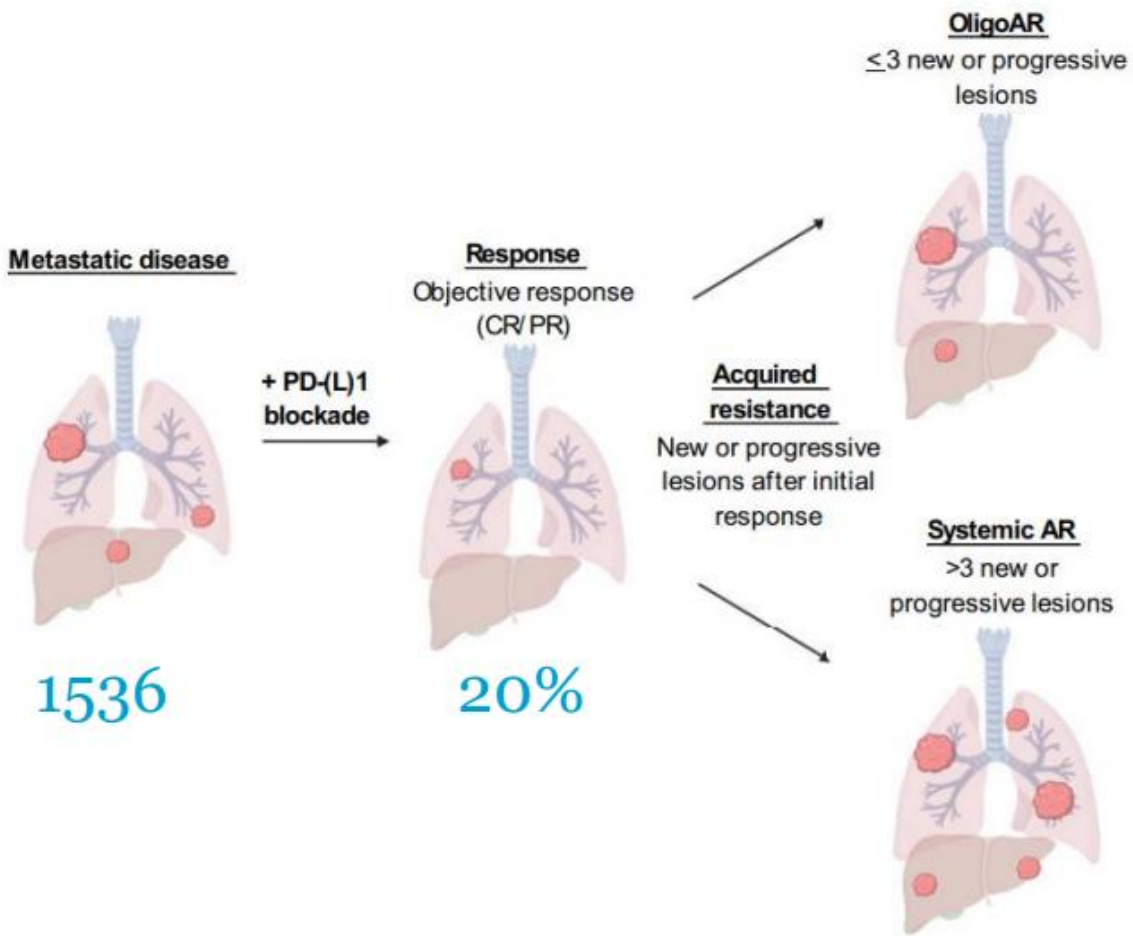
Endpoints:
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

N=710

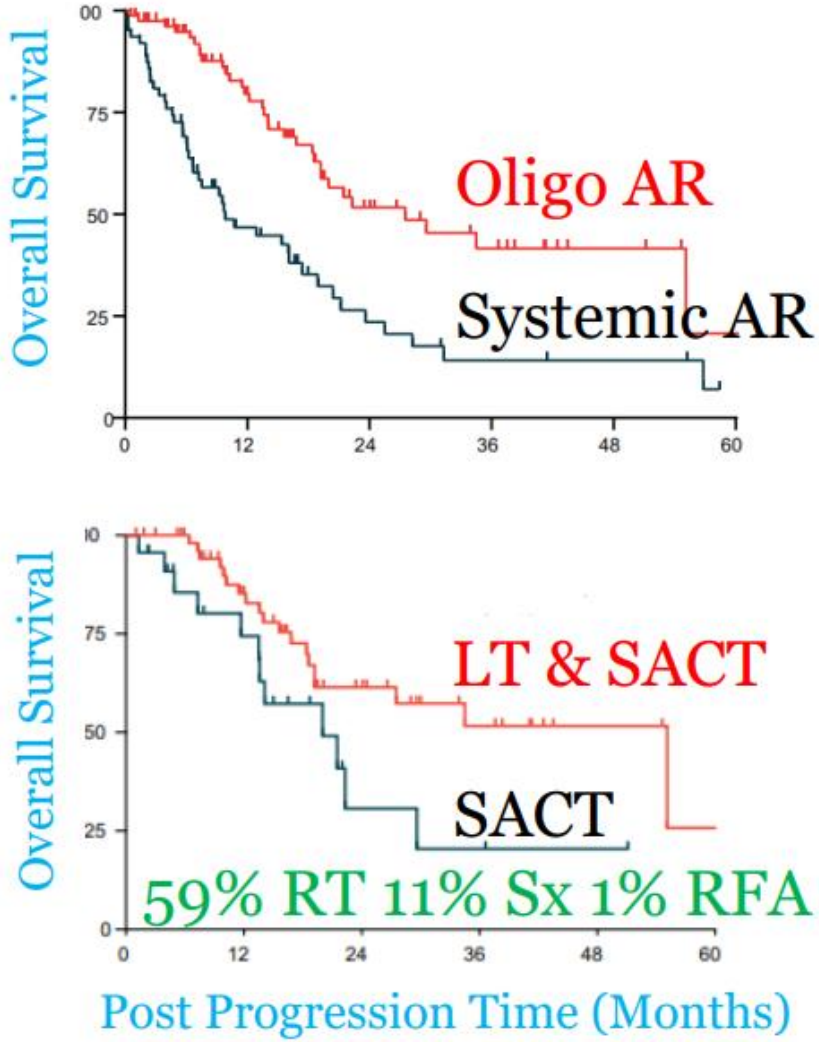
Five interim analyses were prespecified per protocol

Second interim analysis (1 March 2020) presented here

Oligo-Progression in NSCLC in Clinic: MSKCC



Acquired Resistance: RECIST
Response followed by Progression

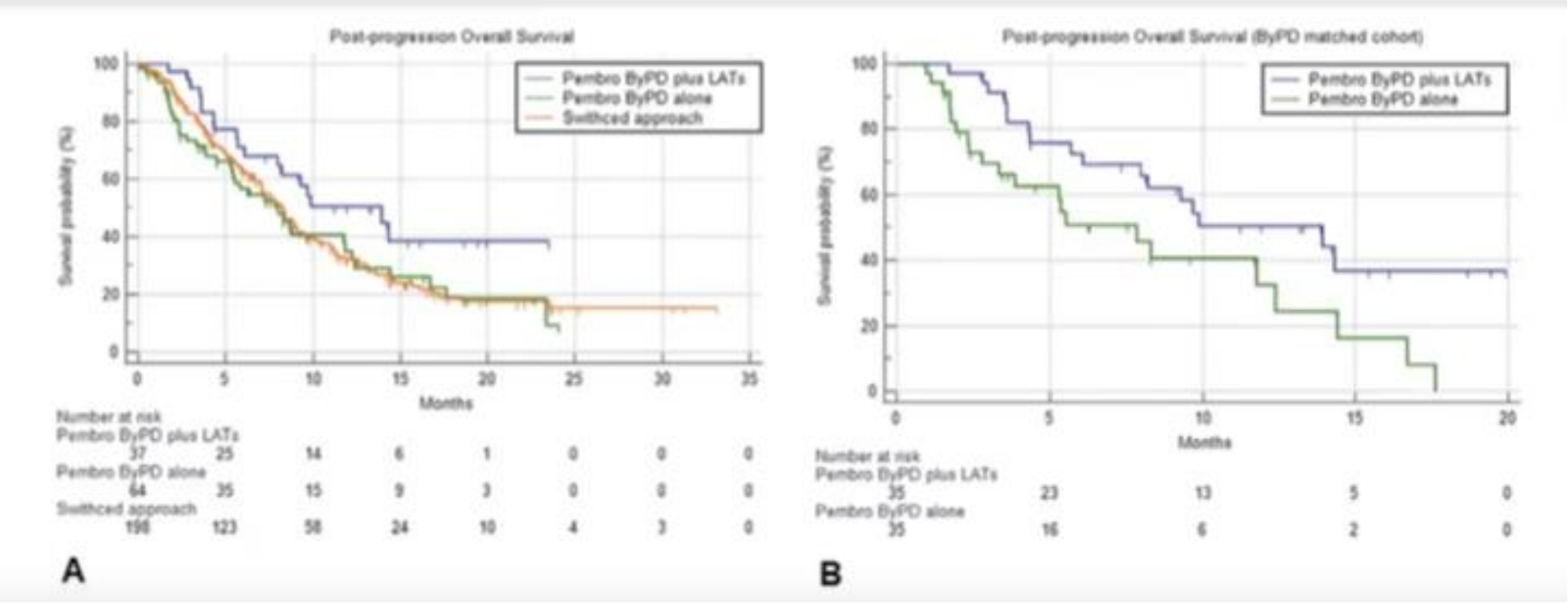


Schoenfeld et al Clin Can Res 2022;

974 pazienti trattati con Pembrolizumab in prima linea PDL1 superior al 50%

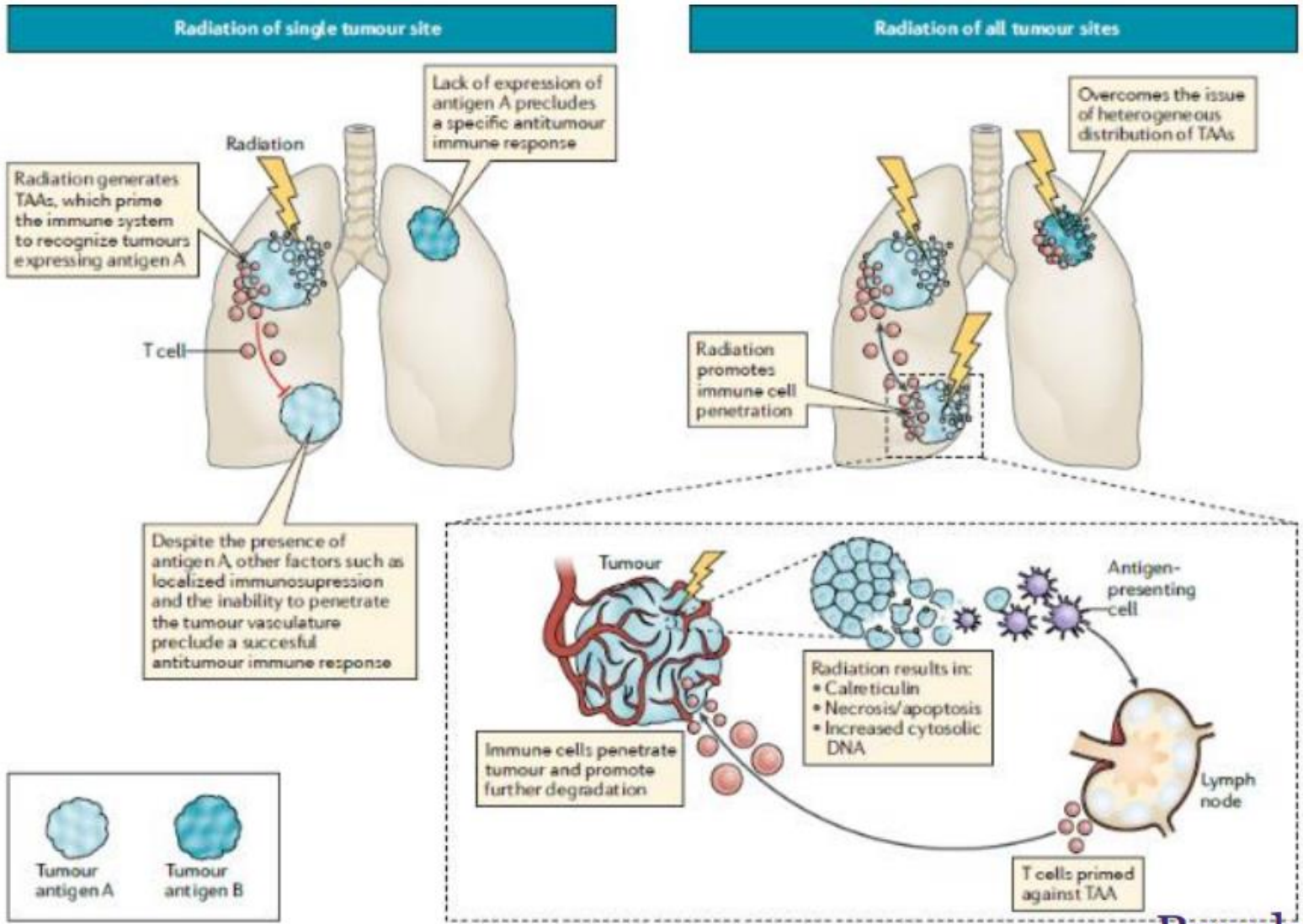
55.9% non hanno ricevuto alcun trattamento, 52.9% sono morti

198 switched approach, 101 Pembro alone, 64 Pembro + LAT



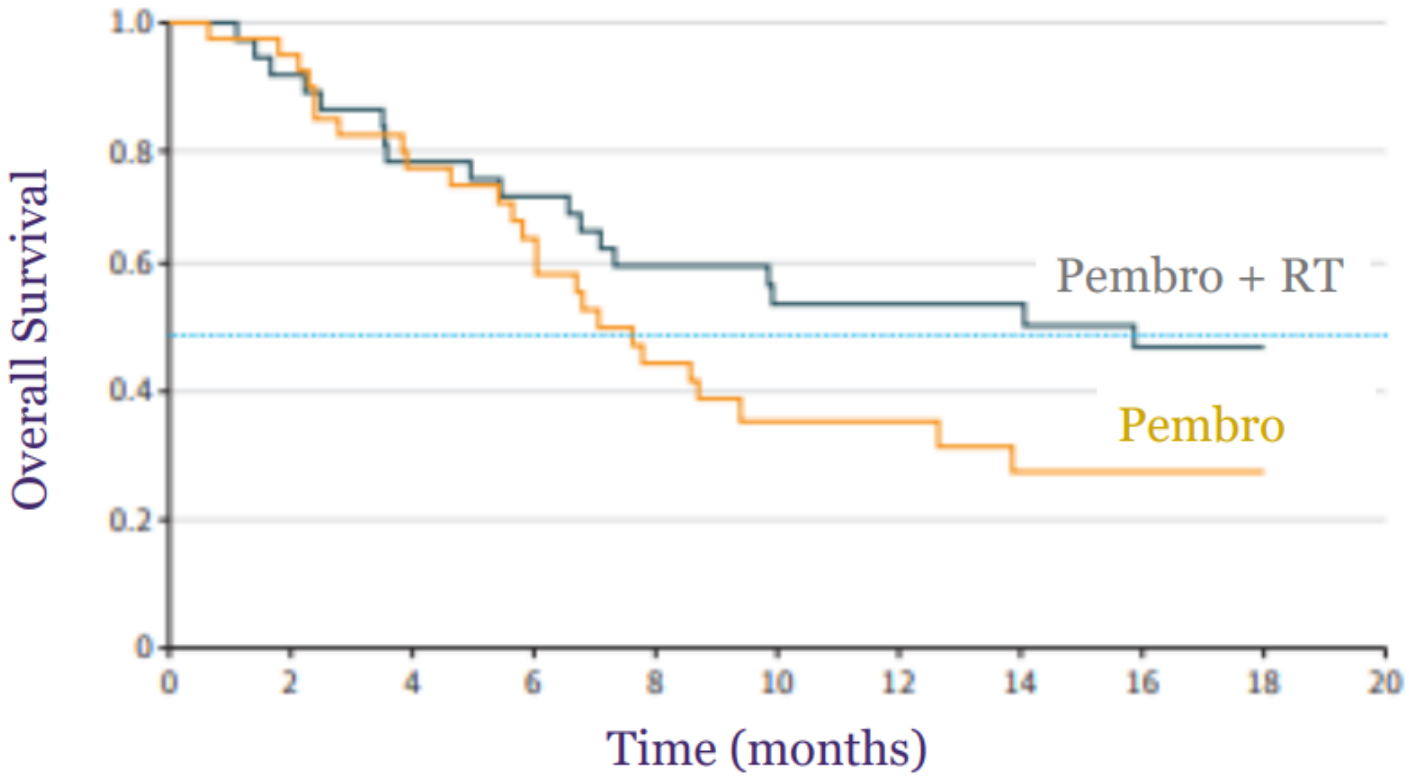
Cortellini, Europena Journal Cancer 2021

Widespread Disease: Irradiation of ≥1 Lesion?



Brooks & Chang 2018;

Pembro RT Ph II Trial



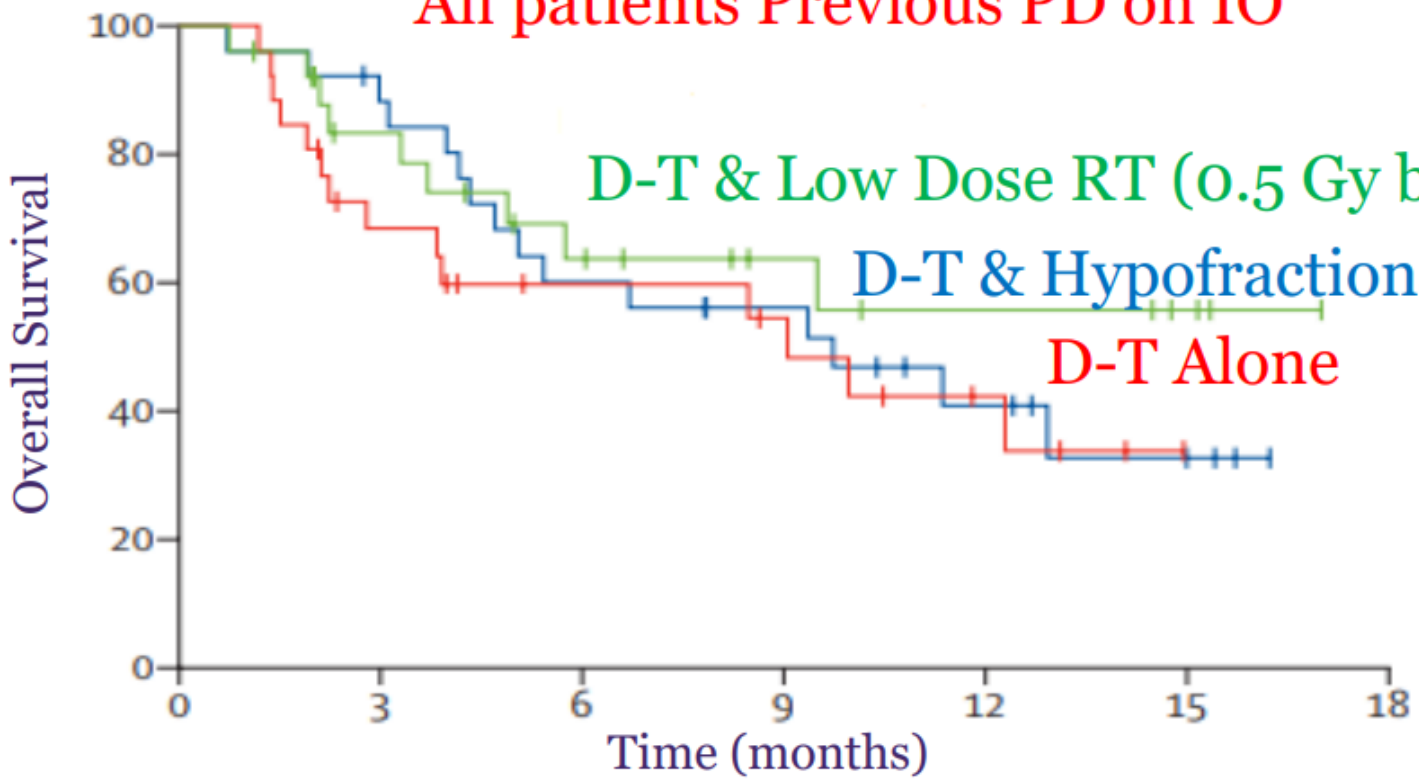
76 Patients

ORR at 12 weeks 18% vs 36% (p = 0.07)
mPFS 1.9 mths vs 6.6 mths (p = 0.19)
mOS 7.6 mths vs 15.9 mths (p = 0.16)

Theelan JAMA Oncol 2019;

Durvalumab & Tremelimumab/ RT Ph II Trial

All patients Previous PD on IO



D-T & Low Dose RT (0.5 Gy bd D1&2 for each of 4 cycles)

D-T & Hypofractionated RT (24 Gy 3# in cycle 1)

D-T Alone

RT commenced 1 wk after D-T commenced

RT targeted 1-2 metastases per patient

Schoenfeld et al Lancet Oncol 2022;

ANTIANGIOGENICS - S1800A phase 2 trial

A

Key eligibility criteria

- Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet, either sequentially or combined
- PD following treatment at least 84 days after initiation of ICI and platinum-based doublet therapy
- ECOG PS 0–1
- No contraindications to ramucirumab

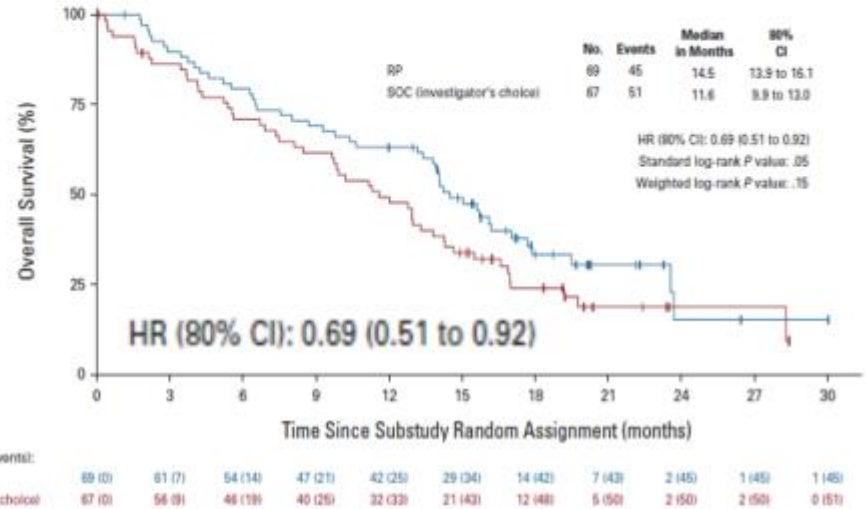
N=130
R 1:1

Pembrolizumab
200 mg, Q3W up to 35 cycles
+
Ramucirumab
10 mg/kg, Q3W

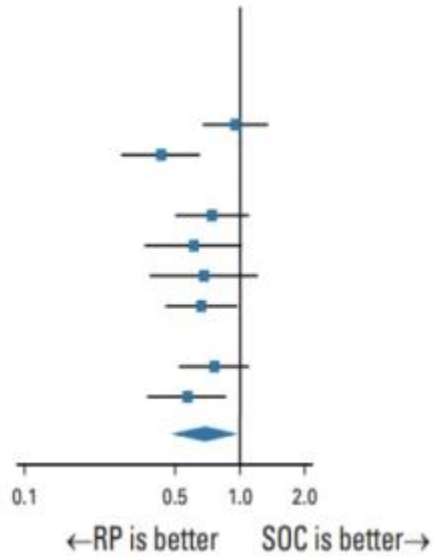
Investigator's choice SOC
Docetaxel + ramucirumab;
docetaxel + gemcitabine;
pemetrexed (non-squamous only)

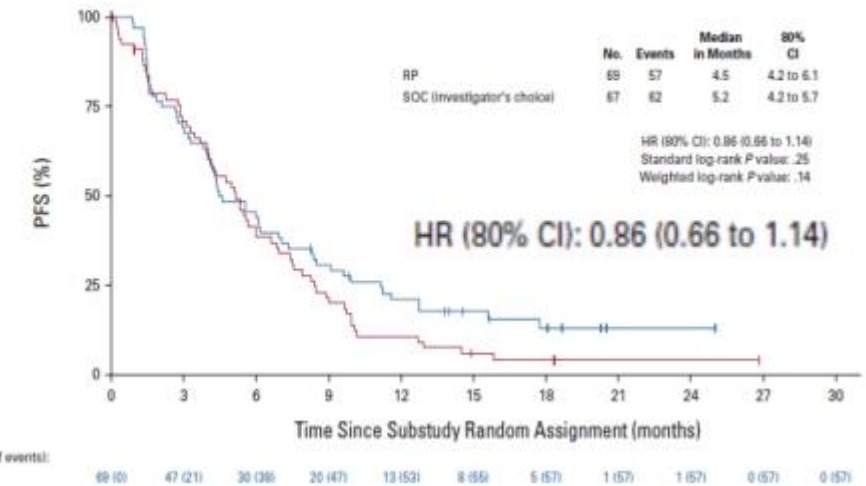
Primary endpoint
- OS

Secondary endpoints
- RR
- DCR
- DOR
- PFS
- Toxicities



	RP Events/n	SOC Events/n	HR (80% CI)	P
Histology				
Nonsquamous	27/40	27/39	0.95 (0.67 to 1.35)	.43
Squamous/mixed	18/29	24/28	0.43 (0.28 to 0.65)	.005
PD-L1				
0	21/29	21/26	0.74 (0.50 to 1.10)	.16
1-49	11/21	15/22	0.61 (0.36 to 1.02)	.11
≥ 50	8/12	12/16	0.68 (0.38 to 1.21)	.20
≥ 1	19/33	27/38	0.66 (0.45 to 0.97)	.08
TMB				
< 10	23/32	28/38	0.76 (0.52 to 1.10)	.17
≥ 10	18/33	20/25	0.57 (0.37 to 0.86)	.04
Overall	45/69	51/67	0.69 (0.51 to 0.92)	.05





Reckamp K et al. JCO 2022

ANTIANGIOGENICS/ MULTITARGETED TKIs

Trial	2nd/3rd line target population	Experimental arm	Control	N	Primary endpoint
LungMAP S1800A	All comers "Non-matched" NSCLC	Pembrolizumab + ramucirumab	Docetaxel± ramucirumab	166	OS 14.5 vs. 11.6; HR 0.69 (0.51, 0.92)
Sapphire NCT03906071	Non-squamous Prior PD-1/L1 therapy for ≥4 months	Sitravatinib + nivolumab	Docetaxel	532	OS
SAFFRON-301 NCT04921358	All comers	Sitravatinib + tislelizumab	Docetaxel	420	PFS and OS
Contact-01 NCT04471428	All comers	Cabozantinib + atezolizumab	Docetaxel	366	Did not meet OS primary endpoint ELCC 2023
LEAP-008 NCT03976375	All comers	Lenvatinib + pembrolizumab	Docetaxel	405	PFS and OS

Maurice Pérol. ELCC 2023

Differenti rechallenge

- Rechallenge dopo interruzione programmata
- Rechallenge dopo interruzione per progressione
- **Rechallange dopo interruzione per tossicità immuno-correlata**

Table. Studies Assessing Immune Checkpoint Inhibition Rechallenge After Immune-Related Adverse Events

Study	Tumor type	ICI type	Number of patients with initial irAE	Number of patients retreated	Grade of initial irAE	New or recurrent irAEs (%): total/new/recurrent	Grade of new or recurrent irAE
Santini et al[3]	NSCLC	Anti–PD-1/PD-L1 +/− anti–CTLA-4[b]	68	38 (56%)	1-2: 66% 3-4: 34%	52/26/26	1-2: 60% 3-4: 40%[a]
Simonaggio et al[8]	Melanoma (33%) Lung (16%) Lymphoma (9%) CRC (9%) Other (33%)[d]	Anti-PD-1/PD-L1	93	40 (43%)	2: 46% 3-4: 54%	55/12.5/42.5	2: 38% 3-4: 62%
Pollack et al[4]	Melanoma	Anti–PD-1/PD-L1 +/− anti–CTLA-4[e]	80	80 (100%)	2: 31% 3-4: 69%	50/32/18	Significant: 39%[f]
Abou Alaiwi et al[5]	RCC	Anti–PD-1/PD-L1 +/− other[g]	80	36 (45%)	1-2: 41% 3-4: 59%	50/33.3/16.7	1-2: 61% 3-4: 39%
Allouchery et al[7]	Melanoma (43.9%) Lung (41.1%) RCC (6.1%) Other (8.8%)[h]	Anti–PD-1/PD-L1 +/− anti–CTLA-4[e]	160	180 (100%)	2: 52% 3-4: 48%	39/27/12	≥ 2: 65%[i] 3-4: 35%

Abbreviations: CRC, colorectal cancer; ICI, immune checkpoint inhibition; irAE, immune-related adverse event; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma.

[a]Two patients ultimately progressed to grade 5 toxicity.

[b]Fourteen patients (37%) in the retreatment cohort were initially treated with combination PD-1/PD-L1 plus CTLA-4 inhibition; 8 (57%) resumed combination therapy; and 6 (43%) resumed single-agent PD-1 inhibition.

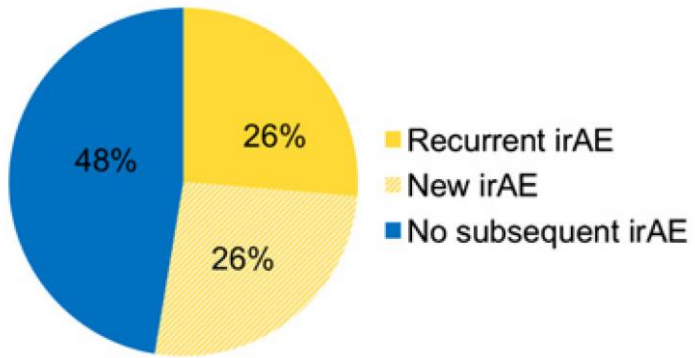
≈30-50% New/Recurrent irAEs. ≈50% G≥3 IrAEs

Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC

Table 2. Characteristics of initial irAEs *N=38* *N=30*

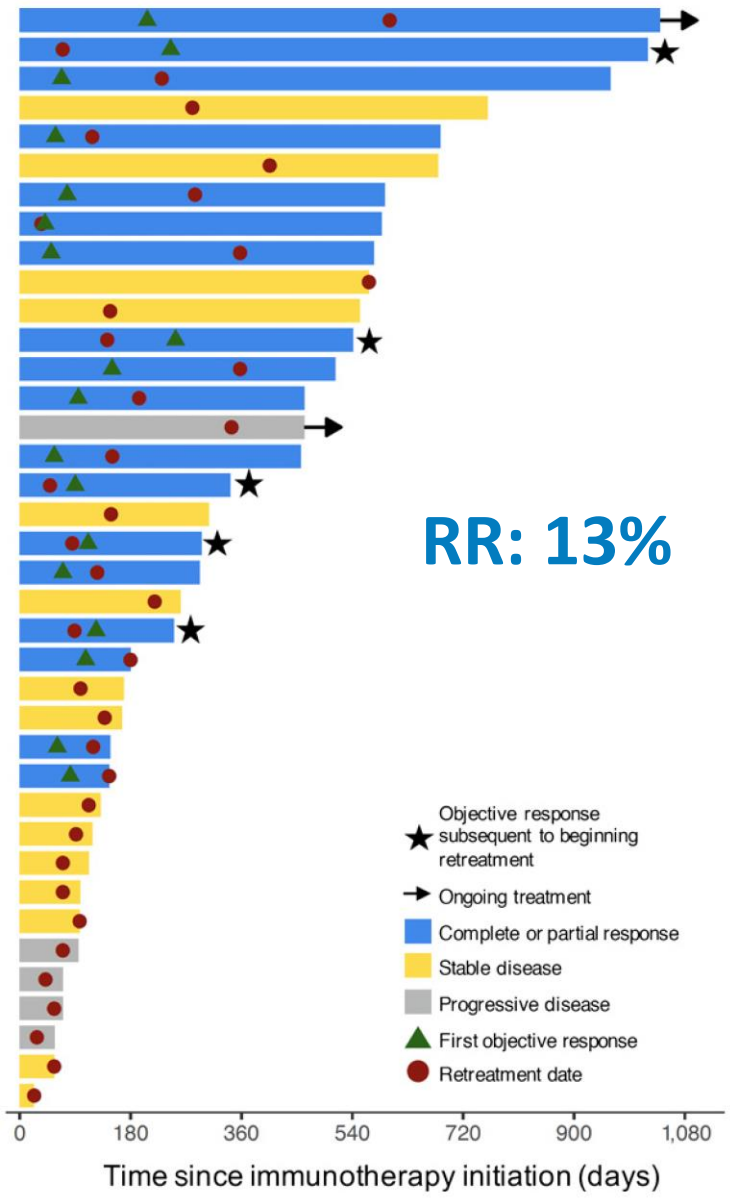
	Retreatment	Discontinuation	*P*
Grade of the first irAE, *N* (%)			0.01
Grades 1 and 2	25 (66)	10 (33)	
Grades 3 and 4	13 (34)	20 (67)	
Type of irAE; *N* (%)			0.62[a]
Pneumonitis	6 (16)	7 (23)	
Colitis	7 (18)	5 (17)	
Rash/pruritus	5 (13)	6 (20)	
ALT or AST increase	3 (8)	4 (13)	
Arthralgia/myalgia	5 (13)	1 (3)	
Nephritis	2 (5)	2 (7)	
Pancreatic enzymes elevation	4 (11)	0 (0)	
Meningitis/headache	2 (5)	1 (3)	
Endocrine disorders[b]	2 (5)	1 (3)	
Ventricular arrhythmias	1 (3)	0 (0)	
Fatigue	1 (2)	0 (0)	
ITP	0 (0)	1 (3)	
Other	0 (0)	2 (7)	
Hospitalizations, *N* (%)	8 (21)	16 (53)	0.01
Time interval to irAE:			
Days, median (range)	69 (14–577)	73 (2–452)	0.77
No. infusions before the irAE:			
No., median (range)	4.5 (1–42)	5.5 (1–27)	0.51
Corticosteroid used, *N* (%)	29 (76)	29 (97)	0.03
Intravenous	3 (10)	12 (40)	
Oral	23 (80)	16 (53)	
Other[c]	3 (10)	2 (6)	
Steroids > 4 weeks, *N* (%)	10 (34)	15 (65)[d]	0.04
Anti-TNF used in the first toxicity, *N* (%)	0 (0)	3 (9)	0.05
irAE resolved to, *N* (%)			0.03
Grades 0 and 1	37 (97)	23 (79)	
Grade > 2	1 (3)	6 (21)	
Death related to irAE; *N* (%)	0	2	

A

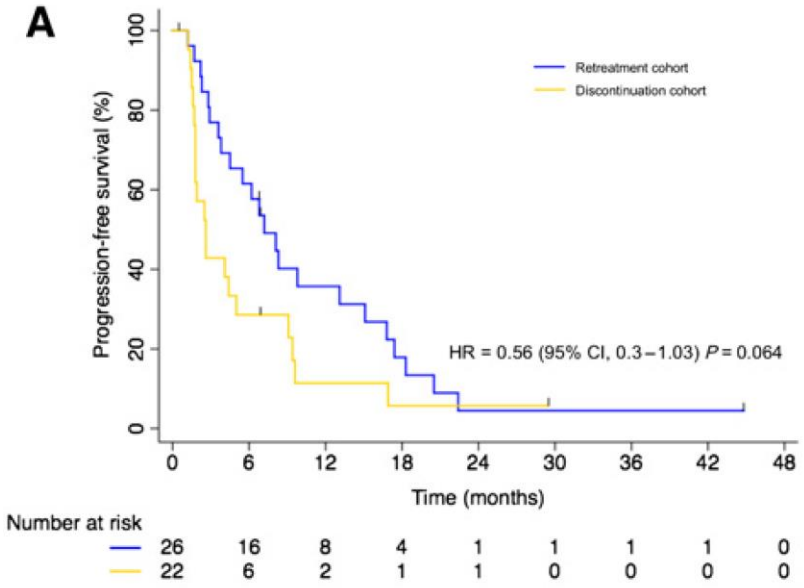


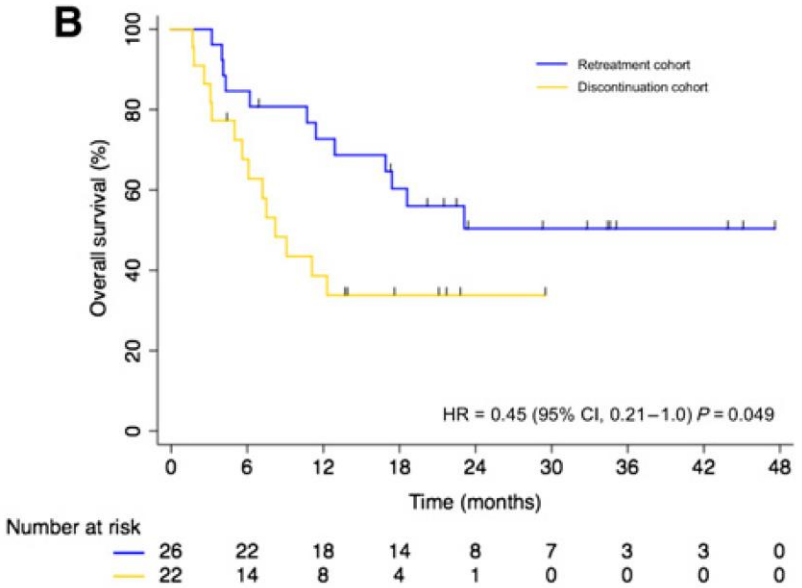
Recurrent irAE	Same irAE N (%)	New irAE N (%)
Total	10 (50)	10 (50)
Type irAE:		
Pneumonitis	1 (10)	2 (20)
Colitis	2 (20)	3 (30)
ALT/AST elevation	1 (10)	2 (20)
Arthralgia/Myalgia	3 (30)	1 (10)
Rash/Pruritus	1 (0)	1 (10)
Neuropathy	0 (0)	1 (10)
Ventricular arrhythmias	1 (10)	0 (0)
Nephritis	1 (10)	0 (0)
Grades of the recurrent irAE		
Grade 1 and 2	4 (40)	8 (80)
Grade 3 and 4	6 (60)	2 (20)
Corticosteroid		
Oral	7 (70)	4 (40)
Intravenous	2 (20)	2 (20)
Steroids > 4 weeks	5/9 (55)	5/6 (83)
Anti-TNF	0 (0)	2 (20)
irAEs resolved to:		
Grades 0 and 1	9 (90)	8 (80)
Grades >= 2	1 (10)	2 (20)
Deaths related to irAE	0 (0)	2 (20) Pneumonitis Colitis

Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099.

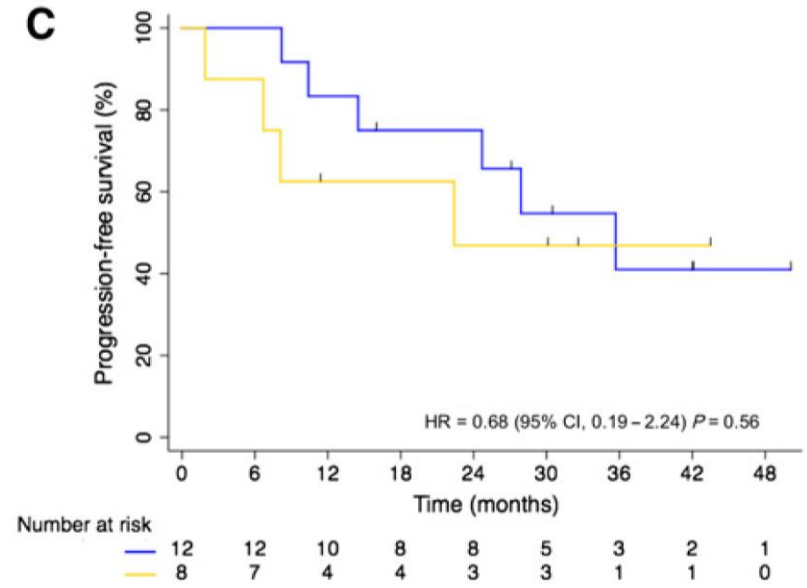


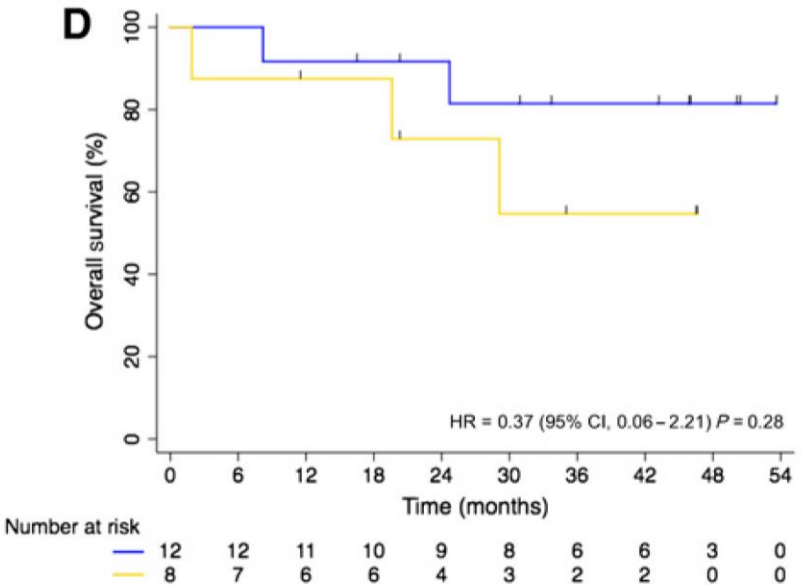
Pts without PR/CR before irAE





Pts with PR/CR before irAE





Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099.

Database Farmacoviglianza

3964 casi

180 pazienti con AE superiore a 2 e riitrattati con immunoterapia

Table 2 Characteristics of the immune-related adverse events

irAEs (n°)	Initial irAE(s)† (n=191) Initial irAEs (%)	Grade 2	Grade 3/4	Systemic corticosteroids	Second irAEs after ICI rechallenge‡ (n=77) Second irAEs (%)	Grade 2	Grade 3/4	Systemic corticosteroids
Gastrointestinal disorders (71)	**24.6**	**17**	**30**	**35§**	**31.2**	**15**	**9**	**20¶**
Colitis (57)	19.4	13	24	30	26.0	12	8	17
Pancreatic disorders (13)	4.7	3	6	5	5.2	3	1	3
Gastritis (1)	0.5	1	–	–	–	–	–	–
Endocrine disorders (41)	**17.8**	**23**	**11**	**4**	**9.1**	**4**	**3**	**1**
Hyperthyroidism (13)	6.3	10	2	4	1.3	1	–	1
Hypophysitis (10)	4.7	5	4	–	1.3	1	–	–
Diabetes (8)	2.1	2	2	–	5.2	1	3	–
Hypothyroidism (5)	2.6	4	1	–	1.3	–	–	–
Adrenal insufficiency (5)	2.1	2	2	–	1.3	1	–	–
Hepatitis (39)	**16.2**	**12**	**19**	**17§**	**10.4**	**2**	**6**	**7**
Respiratory disorders (28)	**11.0**	**15**	**6**	**15**	**9.1**	**5**	**2**	**4**
Pneumonitis (24)	9.4	12	6	15	7.8	4	2	4
Pulmonary sarcoidosis (2)	1.0	2	–	–	–	–	–	–
Pulmonary embolism (2)	0.5	1	–	–	1.3	1	–	–
Skin disorders (28)	**9.4**	**9**	**9**	**8§**	**13.0**	**6**	**4**	**6**
Musculoskeletal disorders (17)	**5.8**	**8**	**3**	**11§**	**7.8**	**5**	**1**	**3¶**
Arthritis/arthralgia (14)	4.7	6	3	9	6.5	5	–	2
Myositis (3)	1.0	2	–	2	1.3	–	1	1
Renal and urinary disorders (16)	**5.2**	**6**	**4**	**5**	**7.8**	**6**	–	**6**
Neurological disorders (8)	**3.1**	**4**	**2**	**5**	**2.6**	**1**	**1**	**1**
Hematological disorders (8)	**3.1**	**2**	**4**	**4**	**2.6**	**2**	–	–
Ocular disorders (7)	**2.6**	**3**	**2**	**1**	**2.6**	**2**	–	**2**
Cardiac disorders (5)	**1.0**	–	**2**	–	**3.9**	**2**	**1**	**2**
Total (268)	**100.0**	**99**	**92**	**105****	**100.0**	**50**	**27**	**52††**

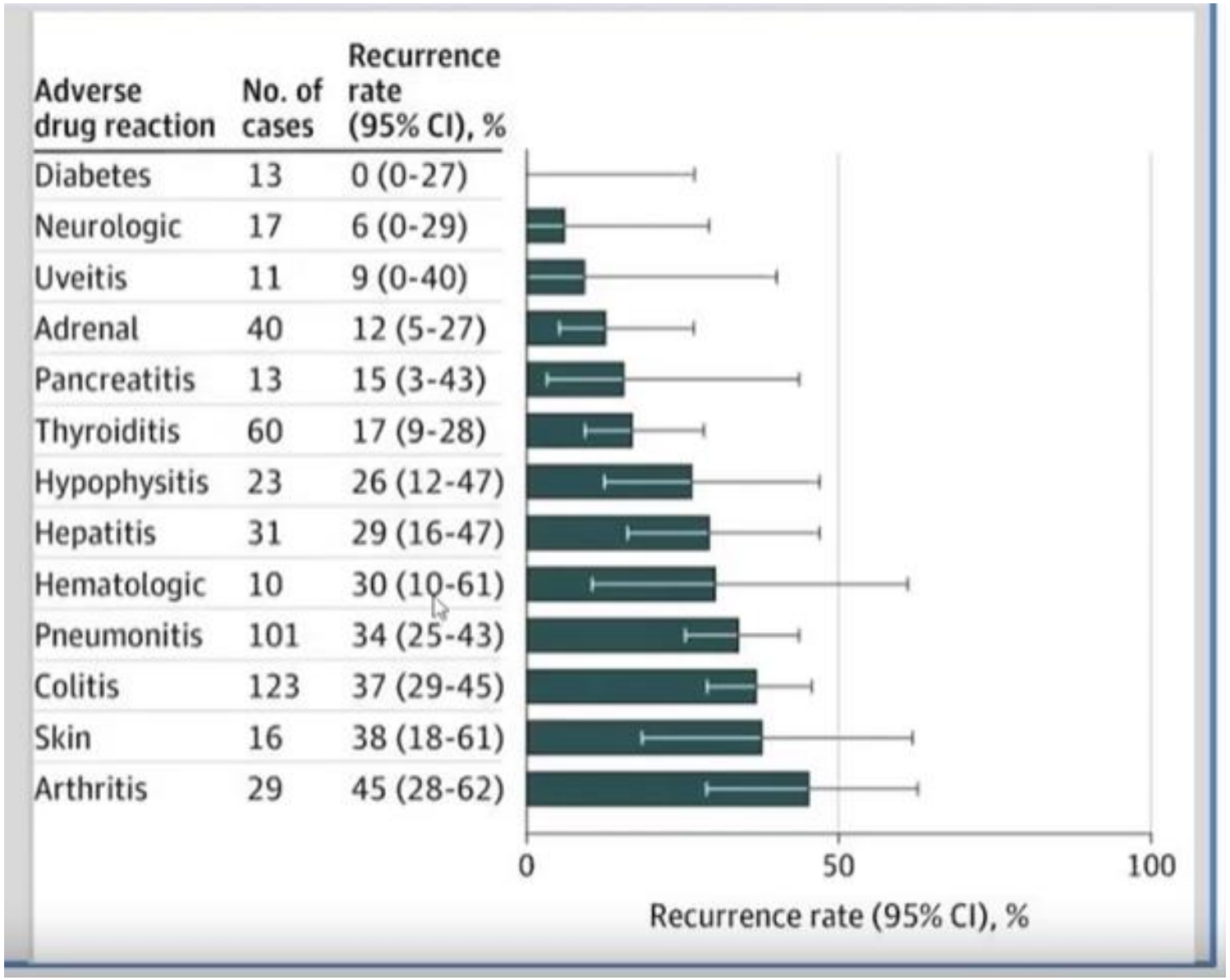
M Allouchery, J Immun Cancer 2020

WHO database VIGIBASE 09/2019

24079 IrAE riportati

6123 casi di pazienti sottoposti a rechallenge (25.4%)

452 casi con informazioni relative al rechallenge



Dolladile et al , JAMA 2020

[Back]

Table 2. . Factors Associated With the Recurrence of the Same Immune-Related Adverse Event

Initial irAE	No. (%)		Reporting OR (95% CI)	
	Recurrence after ICI rechallenge (n = 130)	No recurrence after ICI rechallenge (n = 322)	Univariate analysis	Multivariate analysis
ICI				
Anti–PD-1 or anti–PD-L1 alone	105 (80.8)	265 (82.3)	0.9 (0.54-1.52)	NA
Anti–CTLA-4 alone	7 (5.4)	15 (4.7)	1.16 (0.46-2.93)	3.5 (1.05-11.64)
Combination therapy	18 (13.8)	42 (13.0)	1.07 (0.59-1.94)	NA
Type of initial irAE[a]				
Adrenal	5 (3.8)	35 (10.9)	0.33 (0.13-0.86)	NA
Arthritis	13 (10.0)	16 (5.0)	2.12 (0.99-4.55)	NA
Colitis	47 (36.2)	78 (24.2)	1.77 (1.14-2.75)	2.99 (1.60-5.59)
Diabetes	0	13 (4.0)	NA	NA
Hematological	3 (2.3)	7 (2.2)	1.06 (0.27-4.18)	NA
Hepatitis	11 (8.5)	22 (6.8)	1.26 (0.59-2.68)	3.38 (1.31-8.74)
Hypophysitis	6 (4.6)	17 (5.3)	0.87 (0.33-2.25)	NA
Mucositis	2 (1.5)	3 (0.9)	1.66 (0.27-10.06)	NA
Myocarditis	0	3 (0.9)	NA	
Myositis	2 (1.5)	7 (2.2)	0.7 (0.14-3.43)	NA
Nephritis	4 (3.1)	4 (1.2)	2.52 (0.62-10.25)	4.92 (0.94-25.64)
Neurological	3 (2.3)	16 (5.0)	0.45 (0.13-1.58)	NA
Pancreatitis	3 (2.3)	11 (3.4)	0.67 (0.18-2.43)	NA
Pneumonitis	36 (27.7)	67 (20.8)	1.46 (0.91-2.33)	2.26 (1.18-4.32)
Skin	6 (4.6)	10 (3.1)	1.51 (0.54-4.24)	3.21 (0.81-12.75)

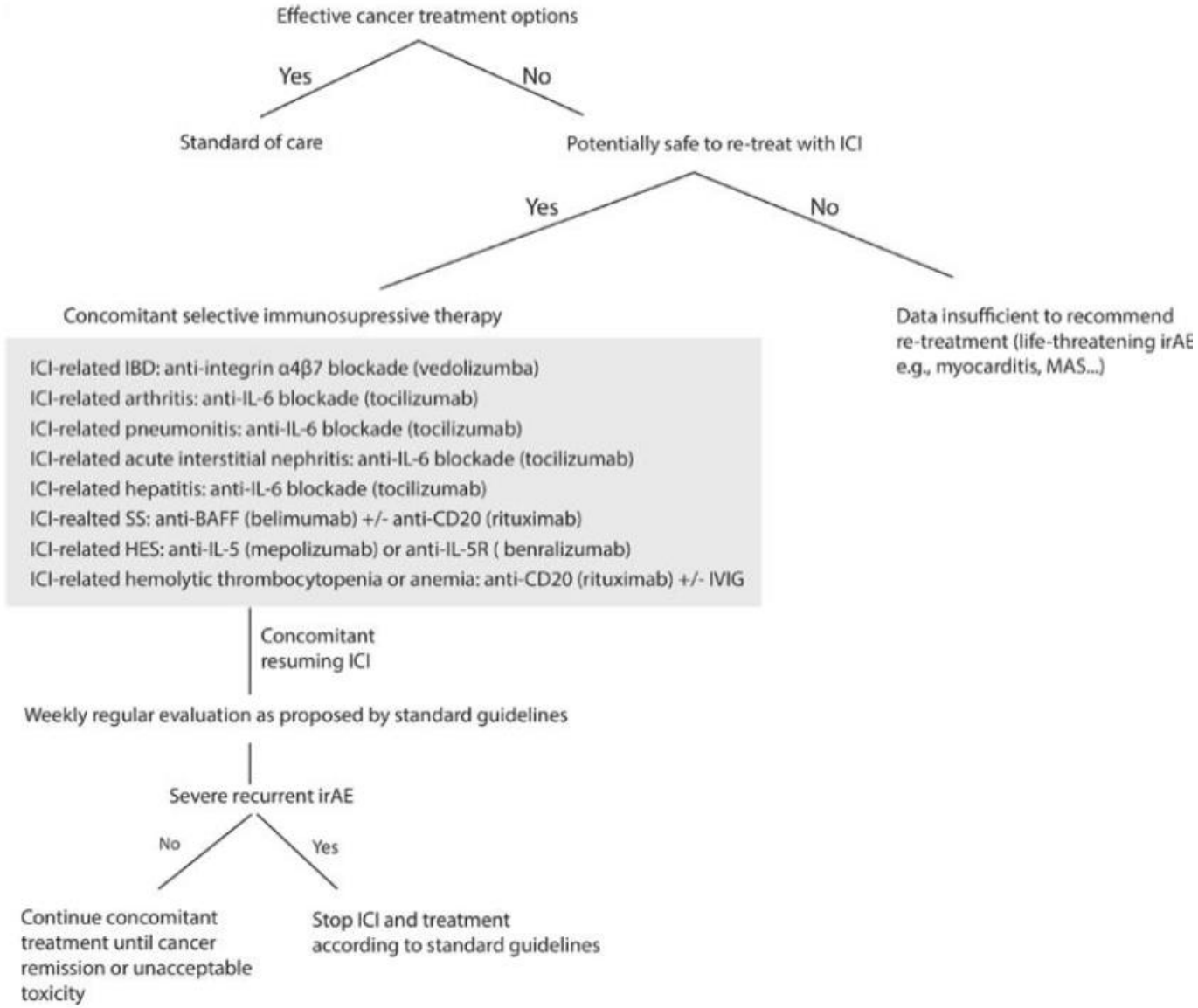
Open access Commentary

Journal for ImmunoTherapy of Cancer

Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy

John Haanen,[1] Marc Ernstoff,[2] Yinghong Wang ,[3] Alexander Menzies,[4,5] Igor Puzanov,[2] Petros Grivas,[6] James Larkin,[7] Solange Peters,[8] John Thompson,[6] Michel Obeid[9,10]

- Patients who developed severe, grade 3 or 4 immune-related adverse events (irAEs) during therapy with immune checkpoint inhibitors are at risk for developing severe toxicities again on re-challenge with checkpoint inhibitors
- Concomitant selective immunosuppressive therapy should be available depending on the nature of the previous irAE



Haanen et al. JITC 2021

Efficacy of anti-PD-1/PD-L1 antibodies after discontinuation due to adverse events in non-small cell lung cancer patients (HANSHIN 0316)

Table 2 Efficacy of PD-1/PD-L1 inhibitors

	n = 19
median number of Cycle (range)	7 (1–70)
Duration of treatment	2.8 months (1 day-32.9 months)
Best response during administration[a]	PR 4, SD 12, PD 1, NE 2
Best response including after discontinuation[a]	CR 1, PR 5, SD 11, PD 2 (PR → CR 1, SD → PR 2, NE → SD, PD1)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated
[a]According to RECIST 1.1; Confirmed by a later scan performed at least 4 weeks after initial response was observed

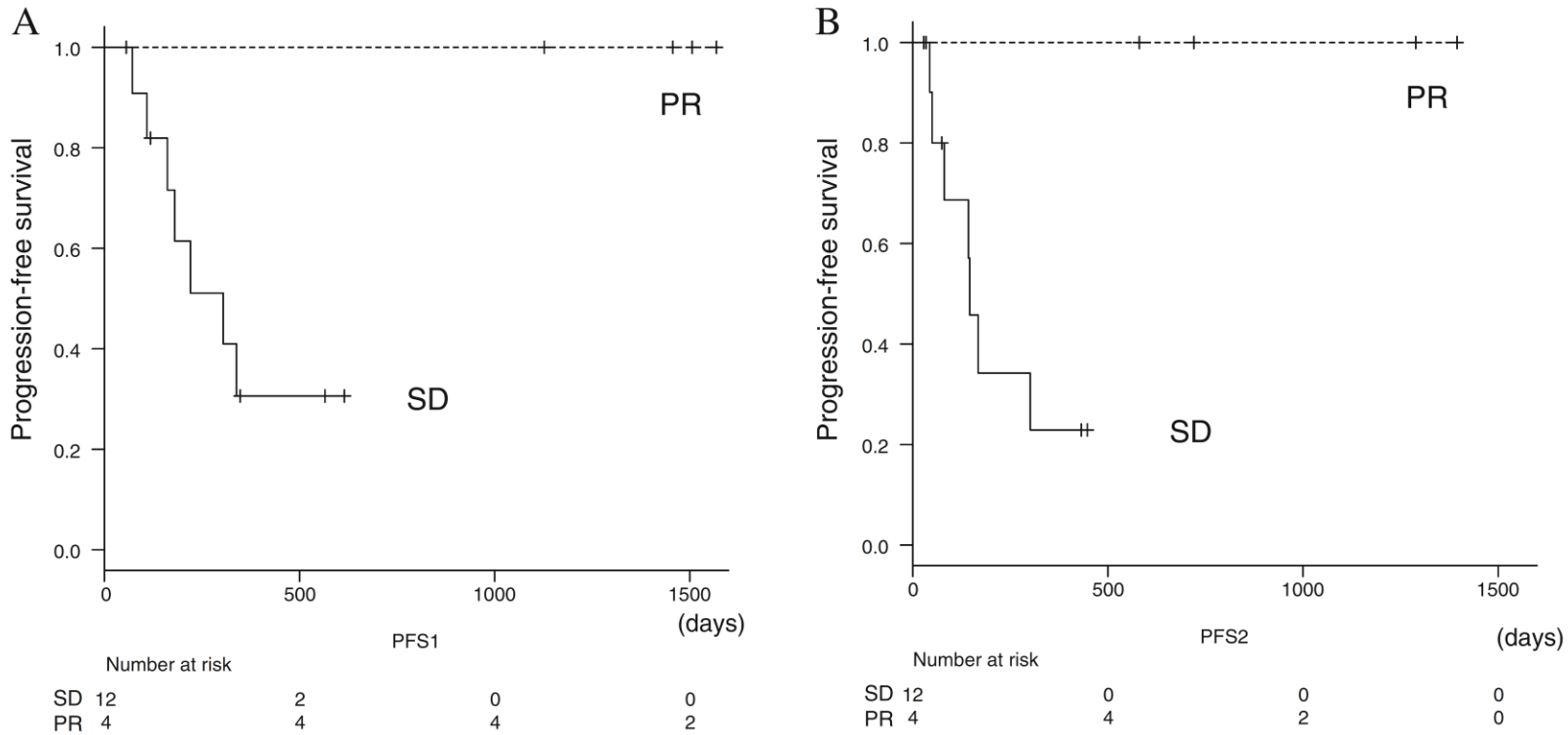


Fig. 3 Kaplan-Meier curves of PFS according to the confirmed response during treatment. **a** PFS from the treatment. **b** PFS from the discontinuation

Tachihara M, et al. BMC Cancer 2018;18(1):946.

Lots to Learn & More Trials Needed .....

Table 1. Ongoing ICI rechallenge clinical trials related to lung cancer

Cancer type	Prior ICI	Rechallenge regimen	Endpoints	Phase	Trial
NSCLC	Nivolumab+Ipilimumab	Nivolumab+Ipilimumab	PFS	III	NCT03469960
NSCLC	ICI	Nivolumab+Anlotinib	ORR	Ib/IIa	NCT04507906
NSCLC	Anti-PD-1	Atezolizumab+platinum doublet chemotherapy	ORR	II	NCT03977467
NSCLC	ICI	Atezolizumab+Tocilizumab	ORR	Ib/II	NCT04691817
NSCLC	ICI	Atezolizumab+Ramucirumab	ORR	II	NCT03689855
NSCLC	Anti-PD-(L)1	Camrelizumab+Apatinib	PFS	II	NCT04670913
NSCLC	Anti-PD-(L)1	Camrelizumab+famitinib	OS	III	NCT05106335
NSCLC	Anti-PD-(L)1	Pembrolizumab	ORR	II	NCT03526887
NSCLC	Anti-PD-(L)1	Pembrolizumab+Docetaxel/Pemetrexed/Gemcitabine	PFS	II	NCT03083808
NSCLC	Anti-PD-(L)1	Durvalumab	ORR	II	NCT03334617
SCLC	Anti-PD-(L)1	Durvalumab+Topotecan hydrochloride	OS	II	NCT04607954

Table 2. Ongoing ICI rechallenge clinical trials related to other cancers

Cancer type	Prior ICI	Rechallenge regimen	Endpoints	Phase	Trial
Melanoma	Anti-PD-(L)1	Pembrolizumab+Ipilimumab	ORR	II	NCT02743819
Melanoma	Anti-PD-1±Ipilimumab	Pembrolizumab+4SC-202	safety	Ib/II	NCT03278665
HCC	ICI	Camrelizumab+Apatinib	ORR	II	NCT04826406
HCC	ICI	Sintilimab+Lenvatinib	ORR	II	NCT05010681
HCC	Anti-PD-(L)1	Pembrolizumab+Regorafenib	ORR	II	NCT04696055
GC/CRC	Anti-PD-(L)1	Tislelizumab+Anlotinib	ORR	II	NCT04777162
UC	ICI	Same ICI	Efficiency	II	NCT04322643
UC	Anti-PD-(L)1	Atezolizumab+Carboplatin+Gemcitabine	PFS	II	NCT03737123
TCC	ICI	Pembrolizumab+Ramucirumab	ORR	II	NCT04179110
NPC	Anti-PD-(L)1	Sintilimab+IBI310	ORR	Ib/II	NCT04945421
RCC	Nivolumab	Nivolumab+Ipilimumab	ORR	II	NCT03177239
RCC	Nivolumab+Ipilimumab	Nivolumab+Ipilimumab	ORR	II	NCT03126331
RCC	Nivolumab+Ipilimumab	Nivolumab+Ipilimumab	DCR	II	NCT04088500
RCC	Anti-PD-(L)1	Atezolizumab+Cabozantinib	PFS/OS	III	NCT04338269
SCCHN	Anti-PD-1	Pembrolizumab+Radiation	ORR	II	NCT03085719
Solid tumor	Durvalumab	Durvalumab	safety	II	NCT03847649
Solid tumor	Anti-PD-(L)1	Pembrolizumab+BI 1206	safety	I/IIa	NCT04219254

Table 1 and Table 2 NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; CRC, colorectal cancer; UC, urothelial carcinoma; TCC, transitional cell carcinoma; NPC, nasopharyngeal carcinoma; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; ICI, immune checkpoint inhibitor; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival.

International Journal of Biological Sciences, 19(8), 2428-2442, 2023

Take Home Messages

- GUIDELINES ARE A USEFUL FRAMEWORK
- RECHALLENGE DATA ARE LIMITED AND WE NEED MORE!!!
- SISTEMIC TREATMENT LANDSCAPE CONTINUE TO EVOLVE RAPIDLY
- MDT DISCUSSIONS REMAIN PARAMOUNT

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