Immunoterapia
ruolo del rechallenge

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Definition

Immunotherapy re-challenge refers to re-use of IO either as monotherapy or combined with other anti-neoplastic agents after previous interruption for one of the following reasons:

★ Scenario 1: Completion of 2 years of IO with excellent response

★ Scenario 2: Clinically significant (Grade 3-4) toxicity related to IO (irAEs)

★ Scenario 3: Acquired resistance to IO

These categories are biologically and Clinically distinct!!!!

Scenario 1

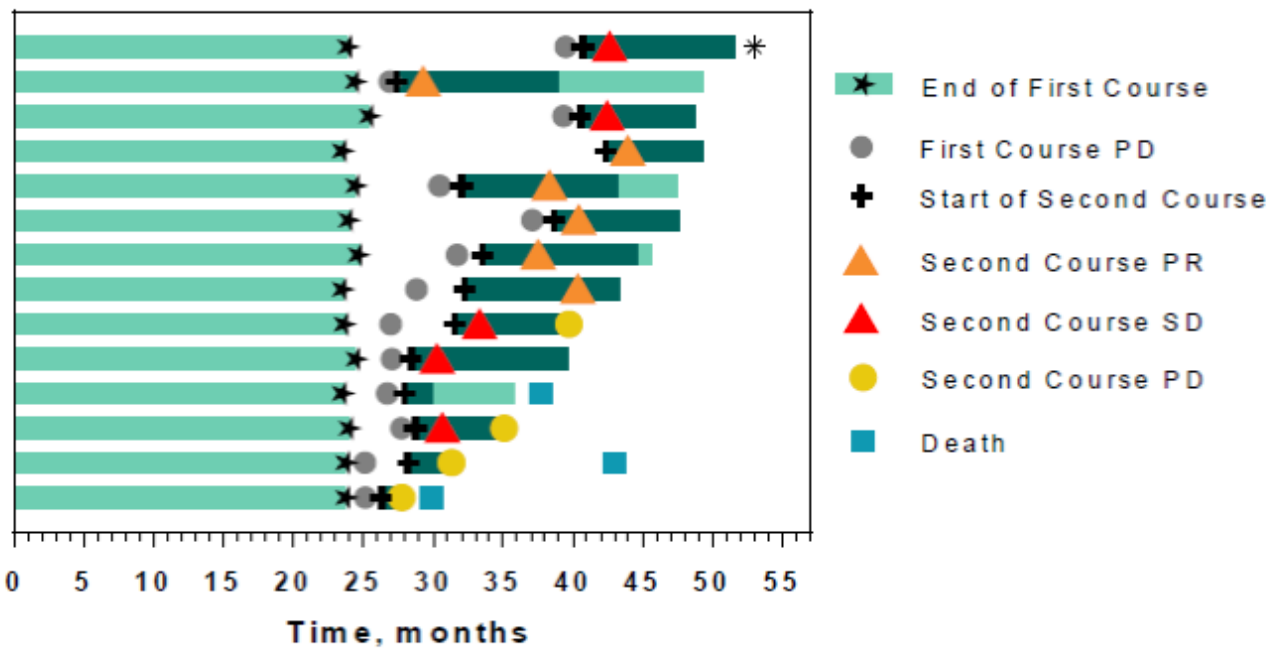
Long-Term Follow-Up in the KEYNOTE-010 Study of Pembrolizumab for Advanced NSCLC, Including in Patients Who Completed 2 Years of Pembrolizumab and Patients Who Received a Second Course of Pembrolizumab

Roy S. Herbst,[1] Edward B. Garon,[2] Dong-Wan Kim,[3] Byoung Chul Cho,[4] José Luis Pérez Gracia,[5] Ji-Youn Han,[6] Catherine Dubos Arvis,[7] Margarita Majem,[8] Martin Forster,[9] Isabella Monnet,[10] Silvia Novello,[11] Zsuzsanna Szalai,[12] Matthew A. Gubens,[13] Wu-Chou Su,[14] Giovanni Luca Ceresoli,[15] Ayman Samkari,[16] Erin Jensen,[16] Gregory M. Lubiniecki,[16] Paul Baas[17]

Herbst RS, et al. J Clin Oncol 2020

Treatment Duration and Time to Response

Patients Who Received Second-Course Treatment[a]



- 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.

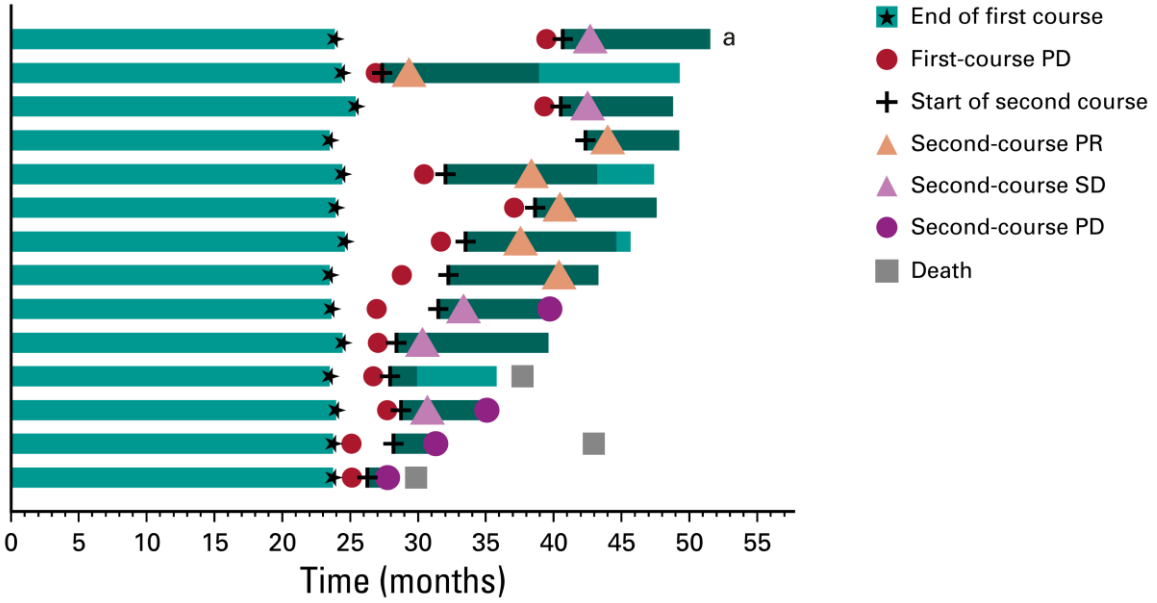
The data

LBA51 **KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%**

J.R. Brahmer[1], D. Rodriguez-Abreu[2], A.G. Robinson[3], R. Hui[3], T. Csőszi[4], A. Fülöp[5], M. Gottfried[6], N. Peled[7], A. Tafreshi[8], S. Cuffe[9], M. O'Brien[10], S. Rao[11], K. Hotta[12], T.A. Leal[13], J.W. Riess[14], E. Jensen[15], B. Zhao[15], M.C. Pietanza[15], M. Reck[16]

KN-010

n=14

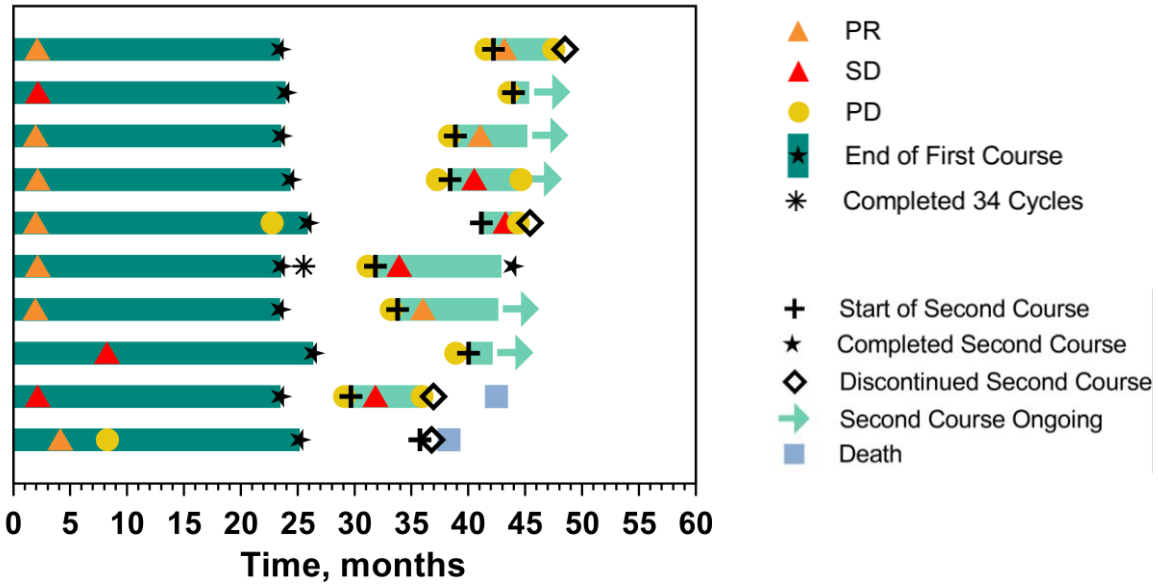


43% RR

79% DCR

KN-024

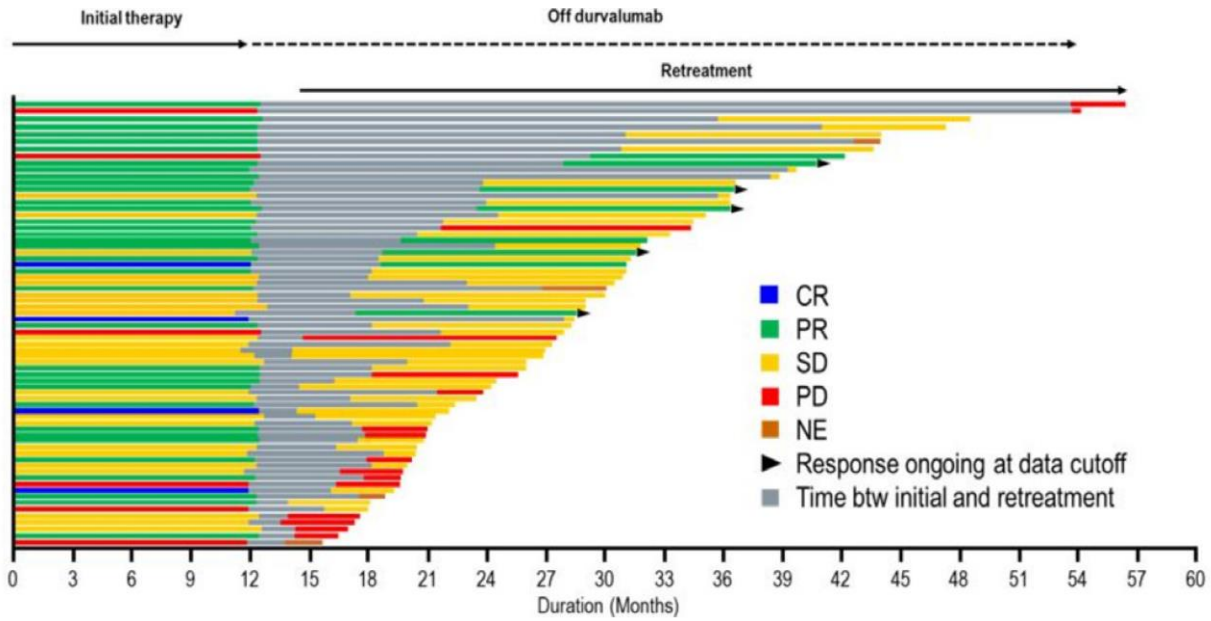
n=10

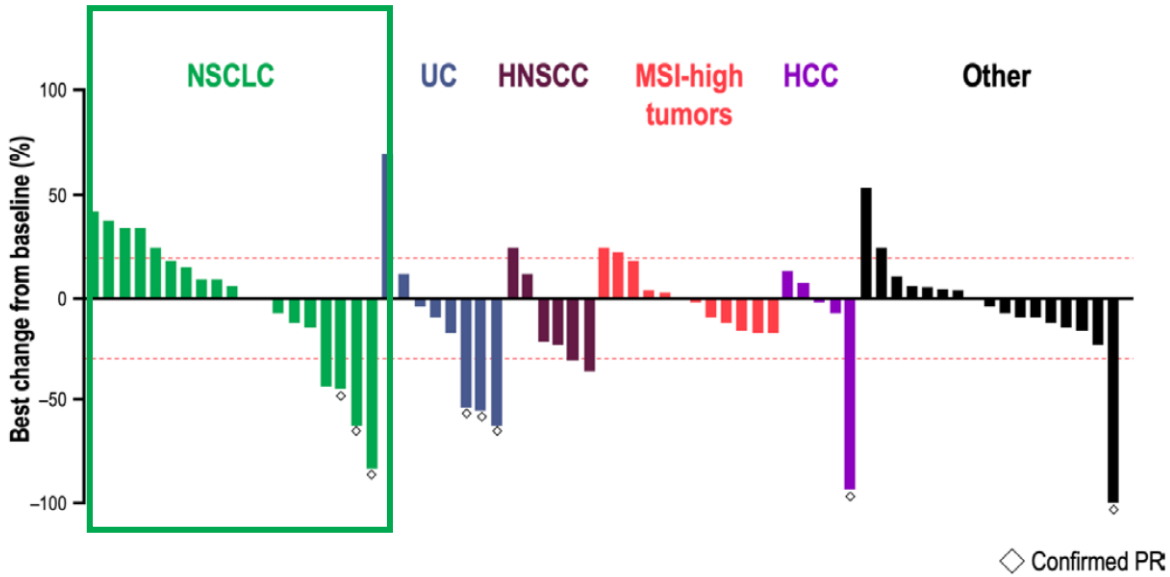


30% RR

70% DCR

Durvalumab activity in previously treated patients who stopped durvalumab without disease progression





Overall:

11.4% RR

71.4% DCR

NSCLC:

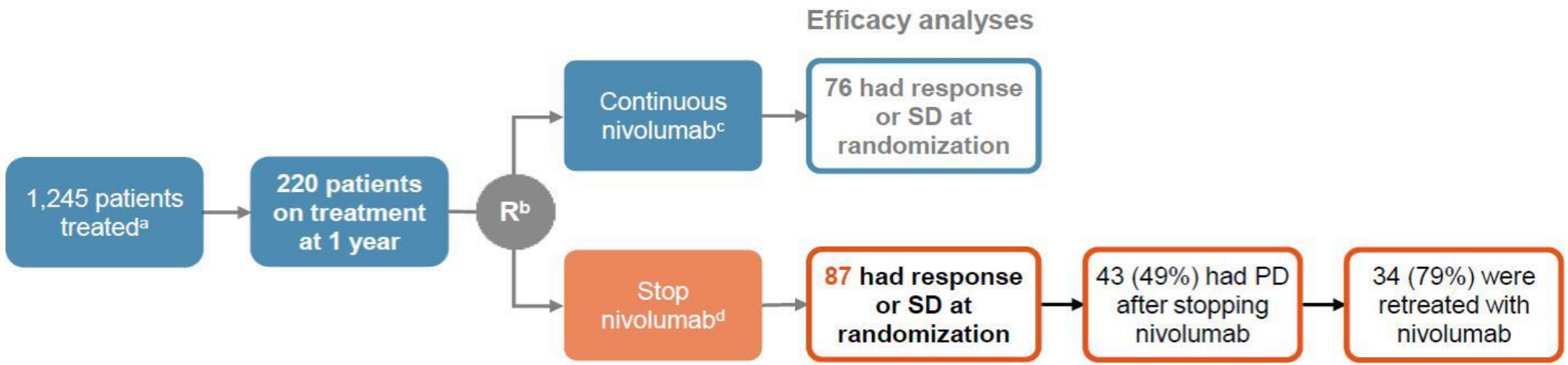
14.3% RR

52.4% DCR

Sheth S, et al. J Immunother Cancer 2020 ;8:e000650.

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

Lung Cancer 140 (2020) 99–106

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Lung Cancer

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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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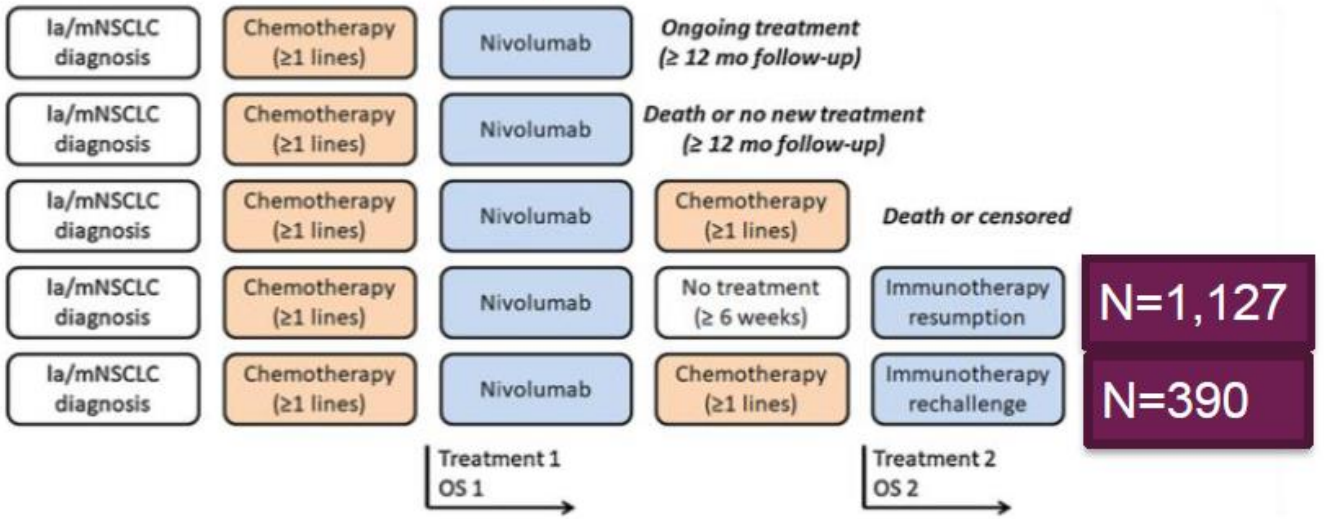
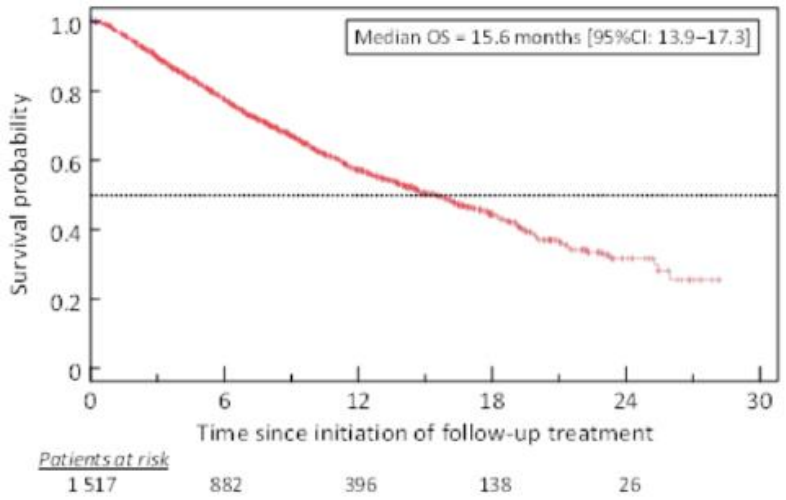
[d] CHU Rennes Hôpital Pontchaillou, Rennes, France
[e] Pharmacy Faculty Université Grenoble Alpes, Grenoble, France
[f] HEVA, Lyon, France
[g] GRC OncoThoParisEst, Service de Pneumologie, CHI Créteil, UPEC, Créteil, France
[h] Centre de Recherche des Cordeliers, Sorbonne Universités, Inserm, UMRS-1138, Paris, France

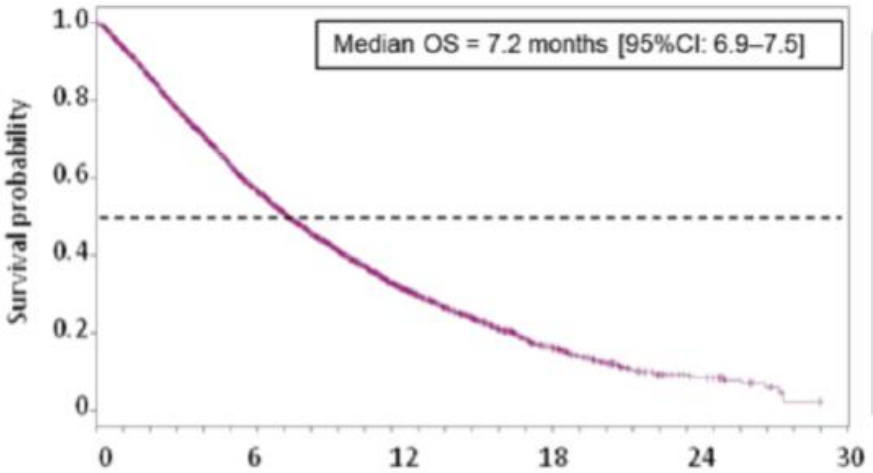
2nd line



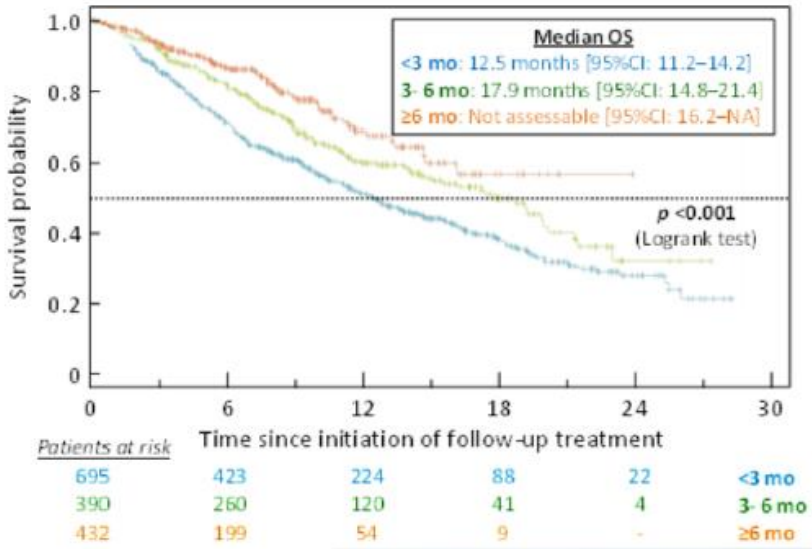
All retreated patients



In patients receiving only CT as subsequent therapy



According to initial treatment duration



Median OS after 2nd-line nivolumab discontinuation was :

- 15.6 months in all patients that received any ICI again
- 7.2 months in patients receiving only chemo as subsequent therapy
- 15.0 months [13.9–16.7] in the resumption group
- 18.4 months [14.8–21.9] in the re-challenge group (chemo intervened).

Median OS was significantly longer in patients with an initial nivolumab treatment duration ≥3 months.

Giaj Levra et al. Lung Cancer 2020

Scenario 2

	Santini	Simonaggio	Abu-Sbeih	Naidoo	Pollack	Delaunay
N	482	93	167 colitis	43 pneumonitis	80	64 ILD
tumor	NSCLC	Multiple (n=15 NSCLC)	Multiple (n= 27 NSCLC)	Multiple (n= 9 NSCLC)	Melanoma	Multiple (n=45 NSCLC)
irAEs	68 (14%)	93	167	43	80	64
Retreat.	38	40	167	12	80	10
New/Recurr.	52% (40% G≥3)	55% (60% G≥3)	34% (82% IS)	25% (0% G≥3)	18% (0% G≥3)	30% (0% G≥3)

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

IS: immunosuppressive therapy

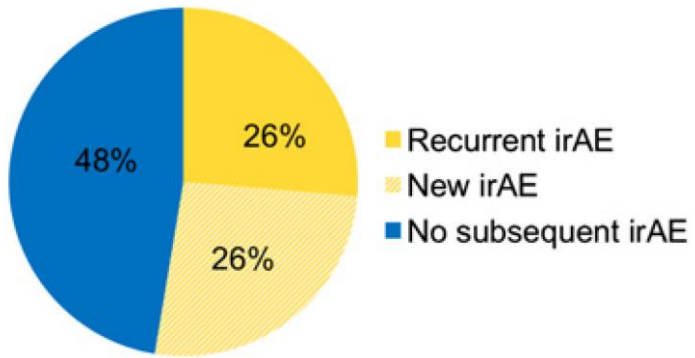
Santini FC, et al. Cancer Immunol Res 2018;6(9):1093-1099. Simonaggio A, et al. JAMA Oncol 2019;5(9):1310–7. Abu-Sbeih H, et al. J Clin Oncol 2019;37(30):2738-2745. Naidoo J, et al. J Clin Oncol 2017;35(7):709-717. Pollack MH, et al. Ann Oncol 2018;29(1):250-255. Delaunay M, et al. Eur Respir J 2017;50(2):1700050.

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*

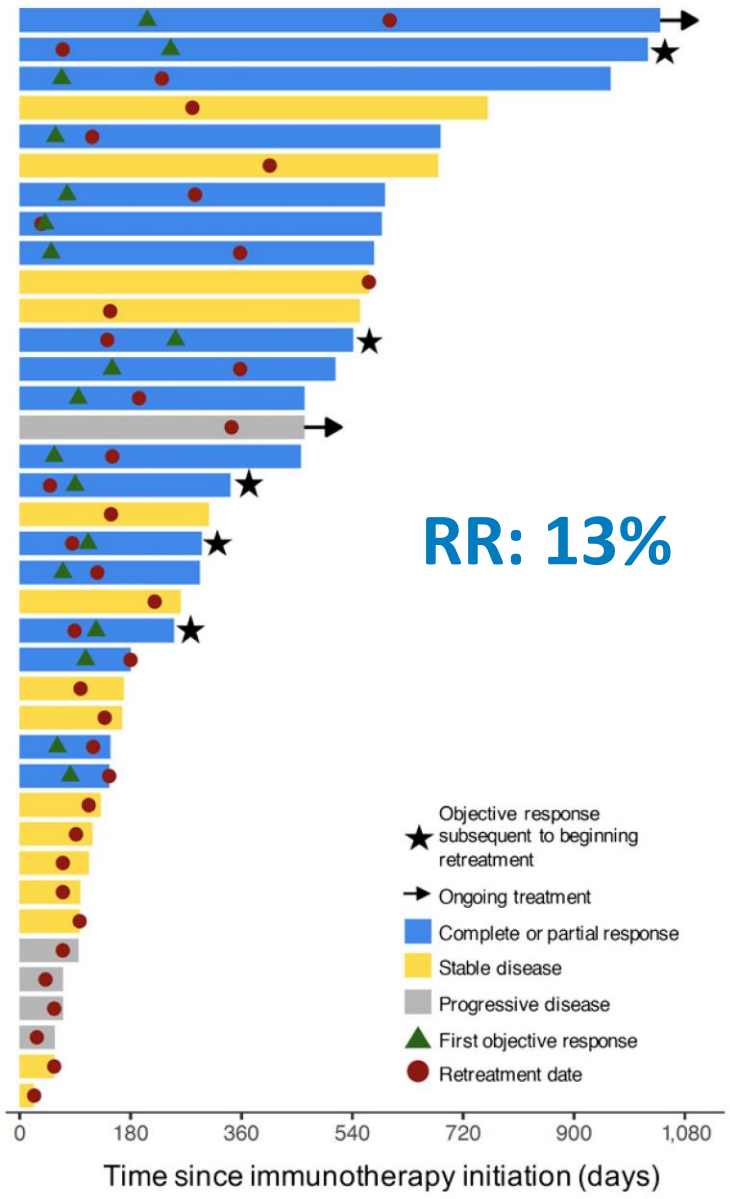
	Retreatment	Discontinuation	*P*
Grade of the first irAE, *N* (%)			0.01
Grades 1 and 2	25 (66)	10 (33)	
Grades 3 and 4	13 (34)	20 (67)	
Type of irAE; *N* (%)			0.62[a]
Pneumonitis	6 (16)	7 (23)	
Colitis	7 (18)	5 (17)	
Rash/pruritus	5 (13)	6 (20)	
ALT or AST increase	3 (8)	4 (13)	
Arthralgia/myalgia	5 (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

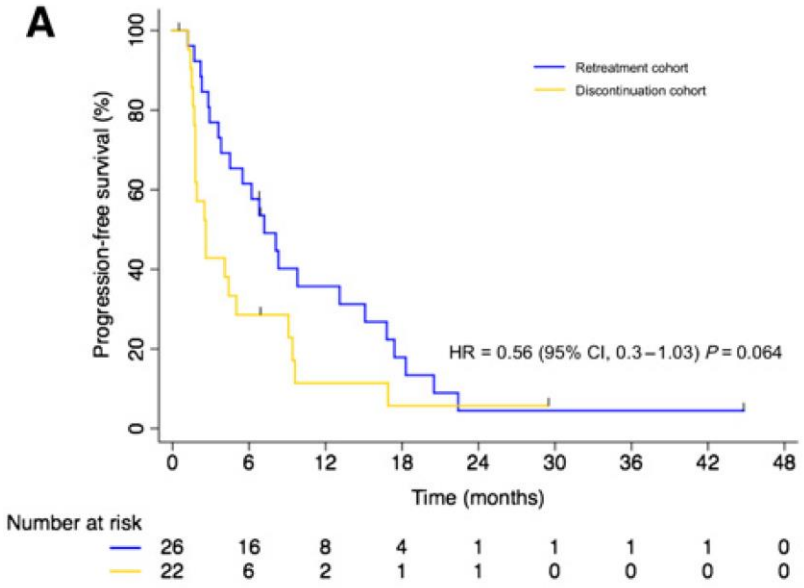


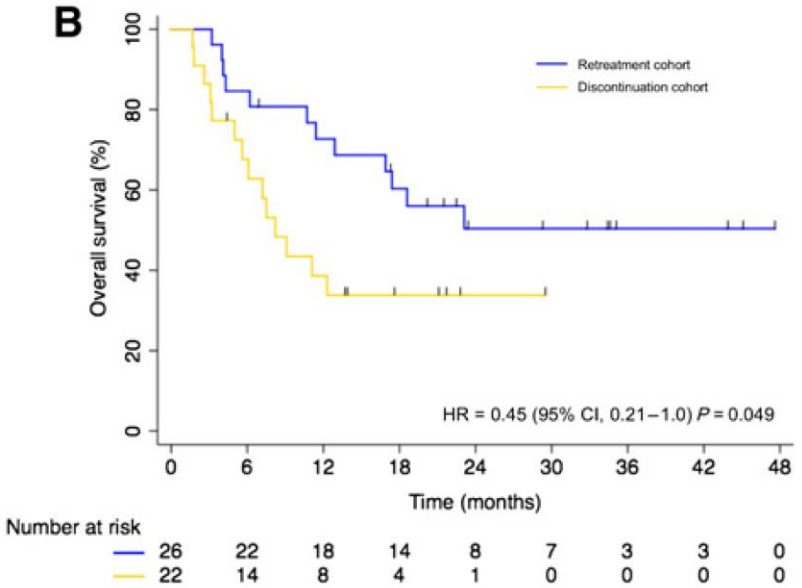
Recurrent irAE	Same irAE N (%)	New irAE N (%)
Total	10 (50)	10 (50)
Type irAE:		
Pneumonitis	1 (10)	2 (20)
Colitis	2 (20)	3 (30)
ALT/AST elevation	1 (10)	2 (20)
Arthralgia/Myalgia	3 (30)	1 (10)
Rash/Pruritus	1 (0)	1 (10)
Neuropathy	0 (0)	1 (10)
Ventricular arrhythmias	1 (10)	0 (0)
Nephritis	1 (10)	0 (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.

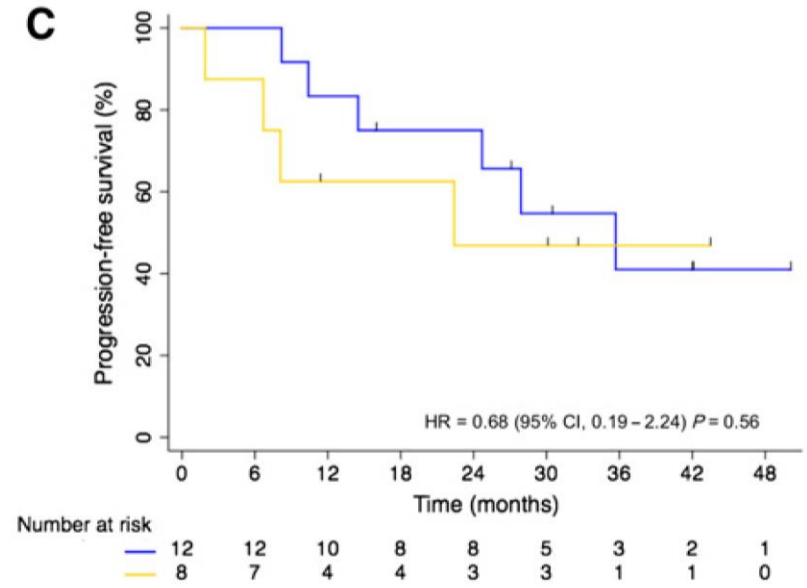


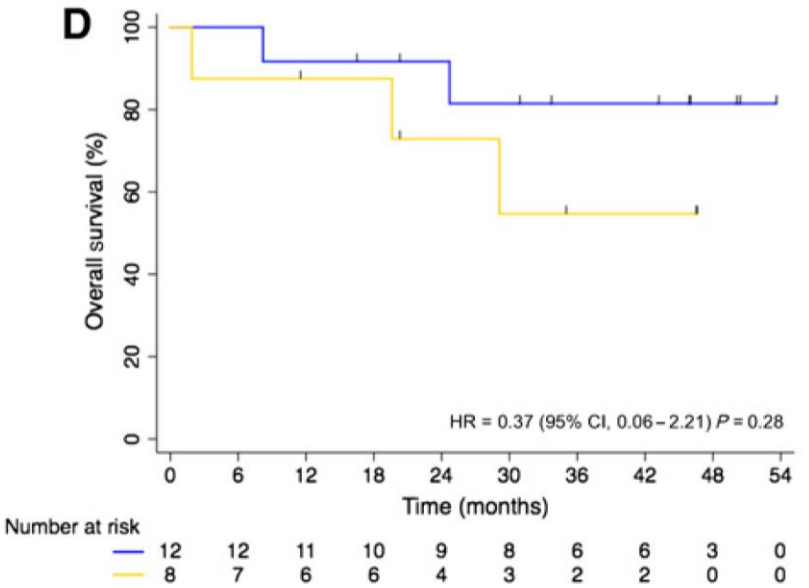
Pts without PR/CR before irAE





Pts with PR/CR before irAE





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

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

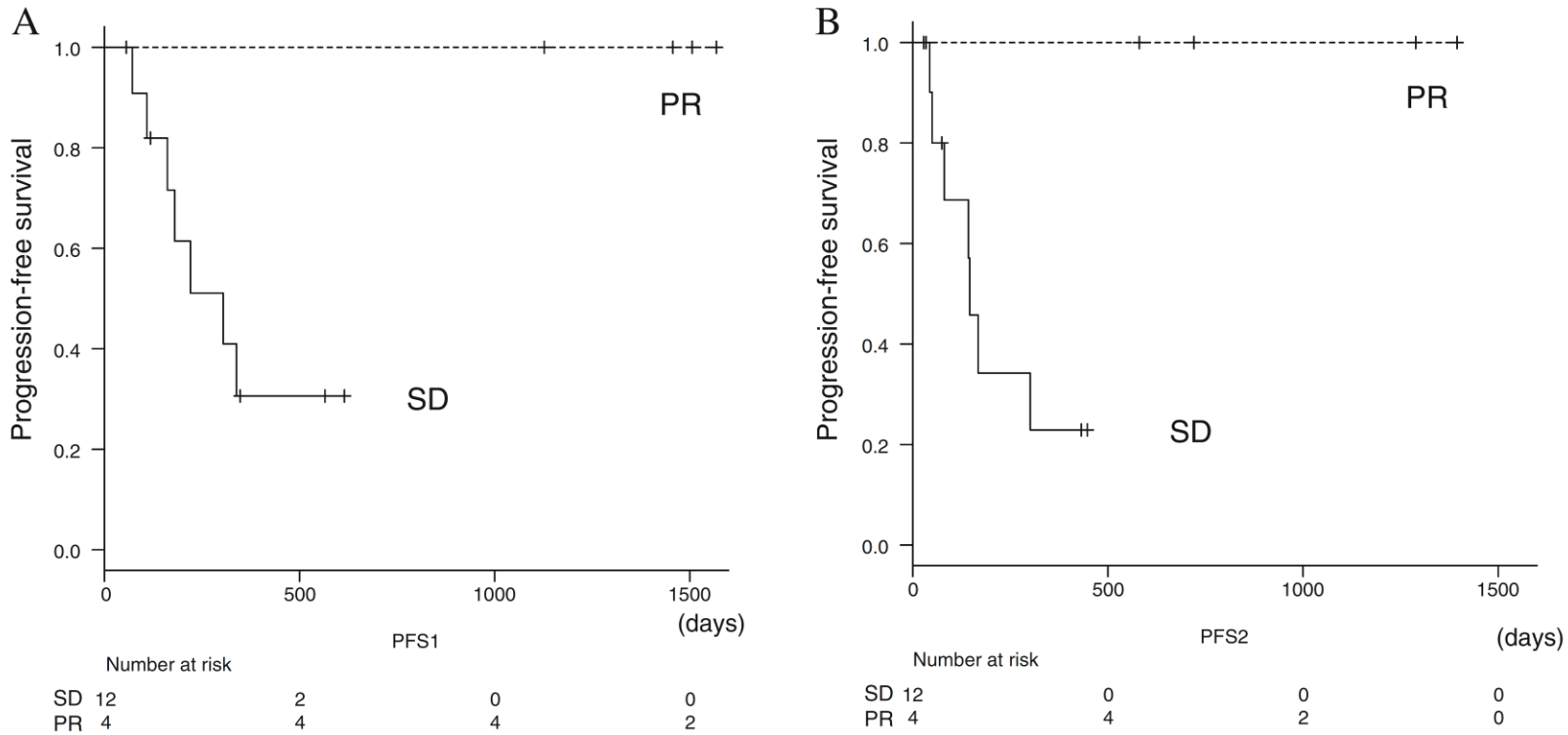


Fig. 3 Kaplan-Meier curves of PFS according to the confirmed response during treatment. **a** PFS from the treatment. **b** PFS from the discontinuation

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

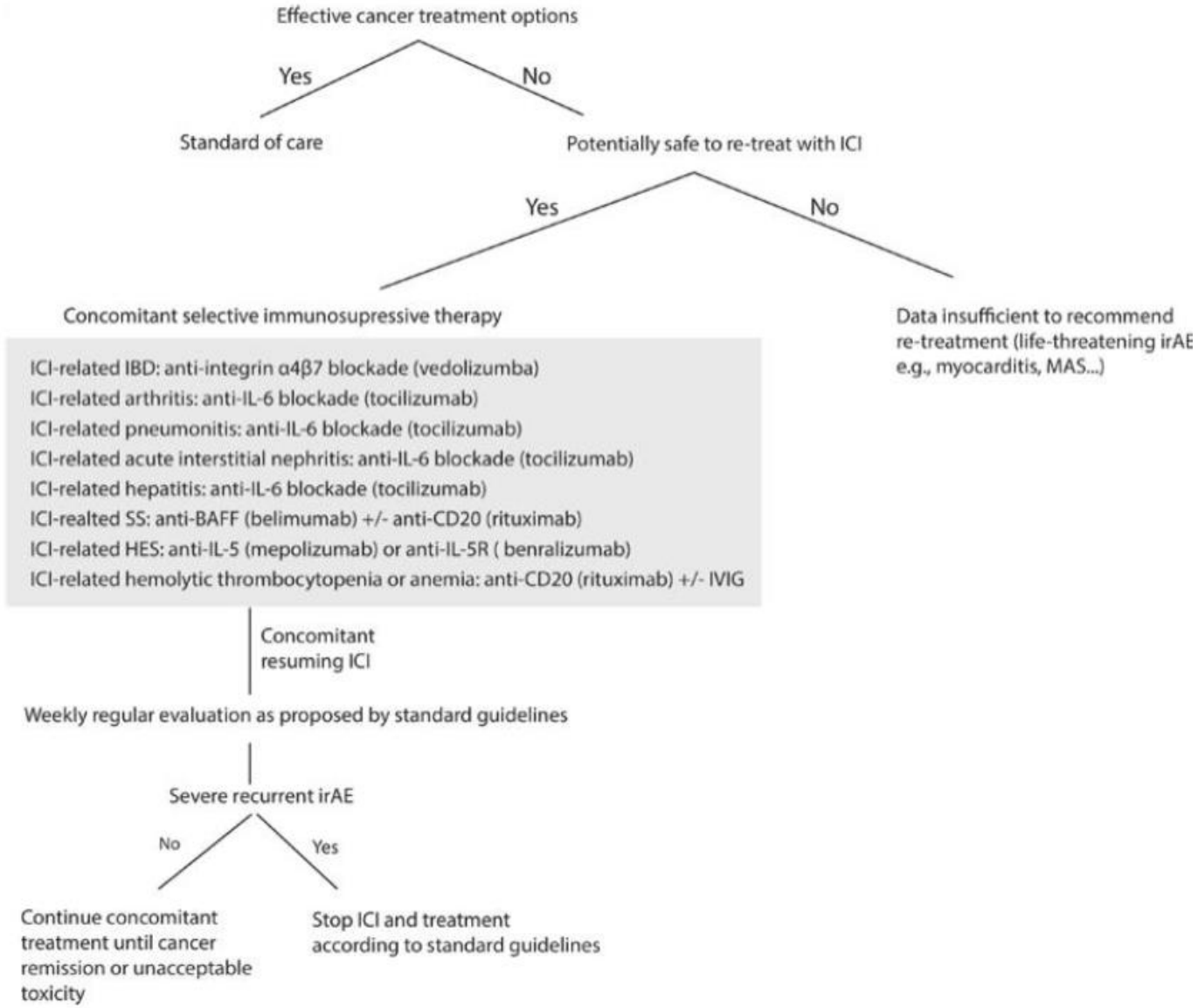
Open access Commentary

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

Scenario 3

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Clinical definition of acquired resistance to immunotherapy in patients with metastatic non-small-cell lung cancer

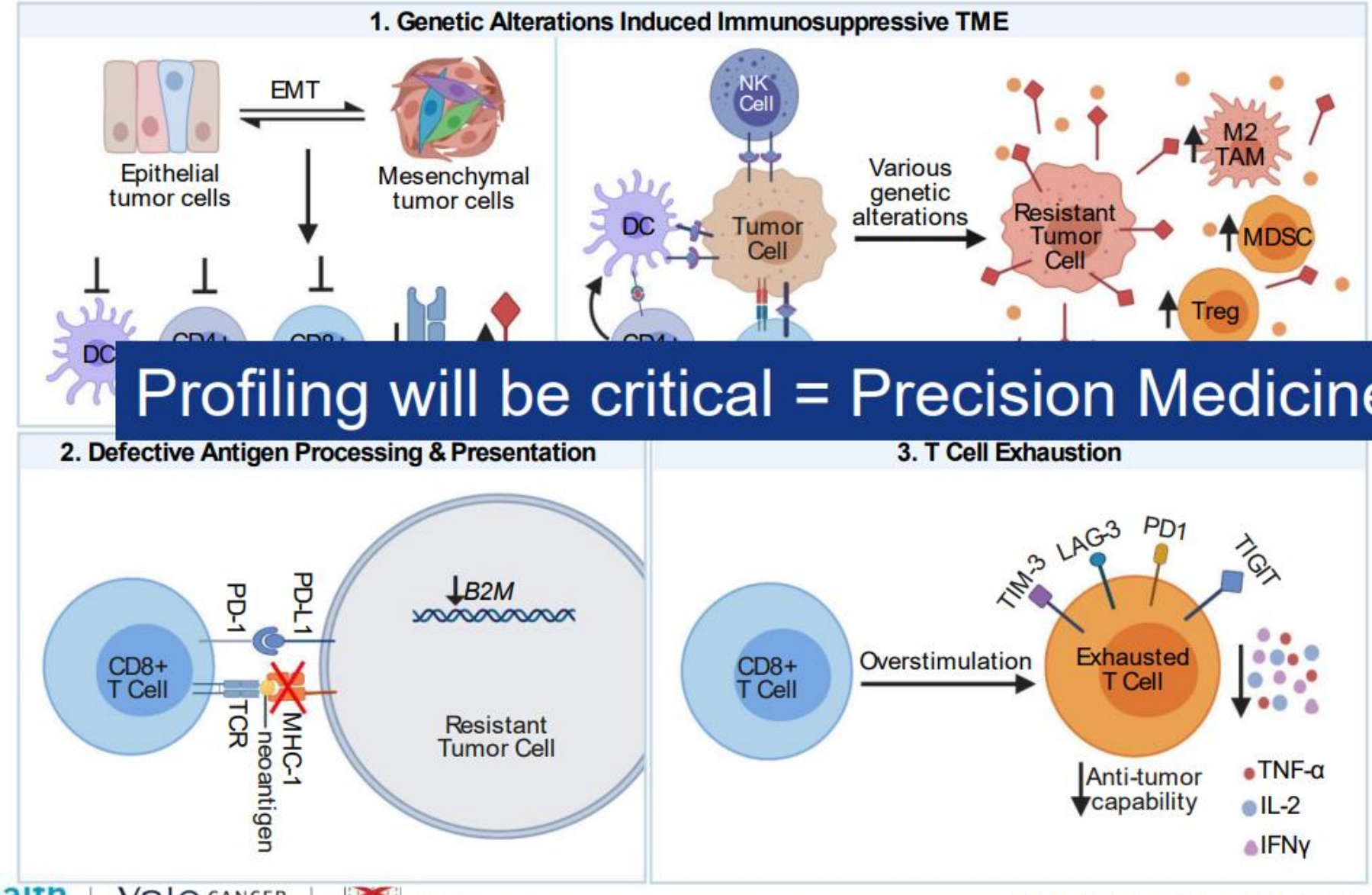
A. J. Schoenfeld[1,2], S. J. Antonia[3], M. M. Awad[4], E. Felip[5], J. Gainor[6,7], S. N. Gettinger[8], F. S. Hodi[4], M. L. Johnson[9], N. B. Leighl[10], C. M. Lovly[11], T. Mok[12], M. Perol[13], M. Reck[14], B. Solomon[15], J.-C. Soria[16], D. S. W. Tan[17], S. Peters[18†] & M. D. Hellmann[1*†]

Table 1. Criteria for acquired resistance to PD-(L)1 blockade in patients with NSCLC

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 et al. Ann of Oncol 2021

Defining Mechanisms of Resistance is Critical



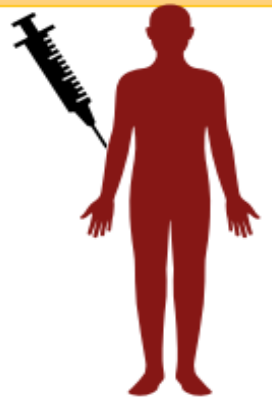
YaleNewHavenHealth Smilow Cancer Hospital | Yale CANCER CENTER A Comprehensive Cancer Center Designated by the National Cancer Institute | Yale SCHOOL OF MEDICINE

Wang, Herbst and Boshoff. Nature Medicine 2021

Potential Strategies to overcome acquired resistance to immunotherapy

A.

Acquired resistance to Immunotherapy



IO switch plus TKI

B.

Acquired resistance to Immunotherapy

Anti-PD1/PDL1 plus other IO

C.

Acquired resistance to Immunotherapy

local ablative therapy (SBRT) + anti-PD-(L)1

TABLE 1. Phase III Clinical Trials Investigating Strategies to Overcome ICI Resistance in Advanced-Stage Non–Small-Cell Lung Cancer

Trial Name (NCT identifier)	Setting	Target	Treatment Strategy	End Point
SKYSCRAPER-01 (NCT04294810)	1L, PD-L1 ≥ 50%	TIGIT	Atezolizumab plus tiragolumab or placebo	OS and PFS
MK-7684A-003 (NCT04738487)	1L, PD-L1 ≥ 1%	TIGIT	MK-7684A (*v* pembrolizumab)	OS and PFS
INTR@PID Lung 037 (NCT03631706)[a]	1L, PD-L1 ≥ 50%	TGF-β and PD-L1	Bintrafusp alfa (*v* pembrolizumab)	OS and PFS
LEAP-007 (NCT03829332)	1L, PD-L1 ≥ 1%	VEGF (RTKs)	Pembrolizumab plus lenvatinib/placebo	OS and PFS
LEAP-006 (NCT03829319)	1L (N-sq)	VEGF (RTKs)	Platinum-pemetrexed plus pembrolizumab plus lenvatinib or placebo	DLT, OS, and PFS
CANOPY-1 (NCT03631199)	1L	IL-1β	Platinum-doublet plus pembrolizumab plus canakinumab or placebo	OS and PFS
KEYLYNK-006 (NCT03976323)	1L, maintenance (N-sq)	PARP	Platinum-pemetrexed plus pembrolizumab → pembrolizumab plus olaparib (*v* pemetrexed)	OS and PFS
KEYLYNK-008 (NCT03976362)	1L, maintenance (Sq)	PARP	Platinum-(nab)paclitaxel plus pembrolizumab → pembrolizumab plus olaparib or placebo	OS and PFS
LEAP-008 (NCT03976375)	Post-CT and ICI	VEGF (RTKs)	Pembrolizumab plus lenvatinib (*v* docetaxel)	OS and PFS
SAPPHIRE (NCT03906071)	Post-CT and ICI	VEGF (RTKs)	Nivolumab plus sitravatinib (*v* docetaxel)	OS
CONTACT-01 (NCT04471428)	Post-CT and ICI	c-MET (RTKs)	Atezolizumab plus cabozantinib (*v* docetaxel)	OS
CANOPY-2 (NCT03626545)[b]	Post-CT and ICI	IL-1β	Docetaxel plus canakinumab or placebo	OS

Abbreviations: 1L, first line; c-MET, tyrosine-protein kinase MET or hepatocyte growth factor receptor; CT, chemotherapy; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; IL, interleukin; MK-7684A, pembrolizumab/vibostolimab coformulation; N-Sq, nonsquamous; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand-1; PFS, progression-free survival; RTKs, receptor tyrosine kinases; Sq, squamous; TGF-β, transforming growth factor-β; TIGIT, The T-cell immunoglobulin and ITIM domain; VEGF, vascular endothelial growth factor.

[a]Discontinued for futility.

[b]Negative trial.

TABLE 2. Novel Inhibitory and Stimulatory Targets to Prevent or Overcome ICI Resistance in Early Phase (I/II and II) Trials[a]

Molecular Target	Compound	Treatment Strategy	NCT Identifier	Setting
Inhibitory signals				
CTLA-4	Tremelimumab	Durvalumab plus tremelimumab	NCT03373760 (phase II)	Prior ICI
	Ipilimumab	Nivolumab plus ipilimumab plus guadecitabine	NCT04250246 (phase II)	Prior ICI
TIGIT	Vibostolimab	Pembrolizumab plus platinum-doublet plus vibostolimab	NCT02964013 (phase I)	ICI-naïve
	MK-7684A	MK-7684A with or without docetaxel (*v* docetaxel)	NCT04725188 (phase II)	Prior ICI
LAG-3	BI 754111	BI 754091 plus BI 754111	NCT03156114 (phase I)	Prior ICI
	XmAb22841 (LAG-3 and CTLA-4)	XmAb22841 with or without pembrolizumab	NCT03849469 (phase I)	Pretreated
	RO7247669 (LAG-3 and PD-1)	RO7247669 monotherapy	NCT04140500 (phase I)	Pretreated
	Eftilagimod alpha	Pembrolizumab plus eftilagimod alpha	NCT03625323 (phase II)	ICI-naïve and pretreated
TIM-3	TSR-022	TSR-022 plus nivolumab or TSR-042 or TSR-033	NCT02817633 (phase I)	Pretreated
		TSR-022 plus TSR-042 plus platinum-doublet	NCT03307785 (phase I)	Pretreated
	RO7121661 (TIM-3 and PD-1)	RO7121661 monotherapy	NCT03708328 (phase I)	Pretreated
	INCAGN02390	INCAGN02390 monotherapy	NCT03652077 (phase I)	Pretreated
S-15	NC318	NC318 monotherapy	NCT03665285 (phase I/II)	Pretreated
		NC318 plus chemotherapy	NCT04430933 (phase I/II)	Prior ICI

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Stimulatory signals

OX-40	PF-04518600	PF-04518600 with or without utomilumab	NCT02315066 (phase I)	Prior ICI
		PF-04518600 plus avelumab	NCT02554812 (phase II)	Pretreated
	INCAGN01949	INCAGN01949 plus nivolumab or ipilimumab or nivolumab-ipilimumab	NCT03241173 (phase I/II)	Pretreated
	INBRX-106 (OX40 and PD-1)	INBRX-106 with or without pembrolizumab	NCT04198766 (phase I)	Pretreated
CD40	APX005M	APX005M plus nivolumab	NCT03123783 (phase I/II)	ICI-naïve and pretreated
	SEA-CD40	SEA-CD40 with or without pembrolizumab	NCT02376699 (phase I)	Pretreated
ICOS	Vopratelimab	Vopratelimab plus ipilimumab	NCT03989362 (phase II)	Prior ICI
		Vopratelimab plus JTX-4014	NCT04549025 (phase II)	Pretreated
	GSK3359609	GSK3359609 plus tremelimumab	NCT03693612 (phase II)	Pretreated
		GSK3359609 plus docetaxel	NCT03739710 (phase II)	Pretreated
CD137	INBRX-105 (CD137 and PD-L1)	INBRX-105 monotherapy	NCT03809624 (phase I)	Prior ICI
GITR	INCAGN01876	INCAGN01876 plus nivolumab or ipilimumab or nivolumab-ipilimumab	NCT03126110 (phase I/II)	Pretreated

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2021 ESMO congress

#LBA47 Activity of OSE-2101 in HLA-A2+ non-small cell lung cancer (NSCLC) patients after failure to immune checkpoint inhibitors (IO): Final Results of Phase 3 Atalante-1 Randomised Trial

B. Besse, M.R. Garcia Campelo, M.A. Cobo Dols, E. Quoix, A. Madroszyk, E. Felip, F. Cappuzzo, F. Denis, W. Hilgers, G. Romano, D. Debieuvre, E. Baldini, D. Galetta, S. Viteri, M. Phan, W. Schuette, A. Zer, D. Costantini, R. Dziadziuszko, G. Giaccone

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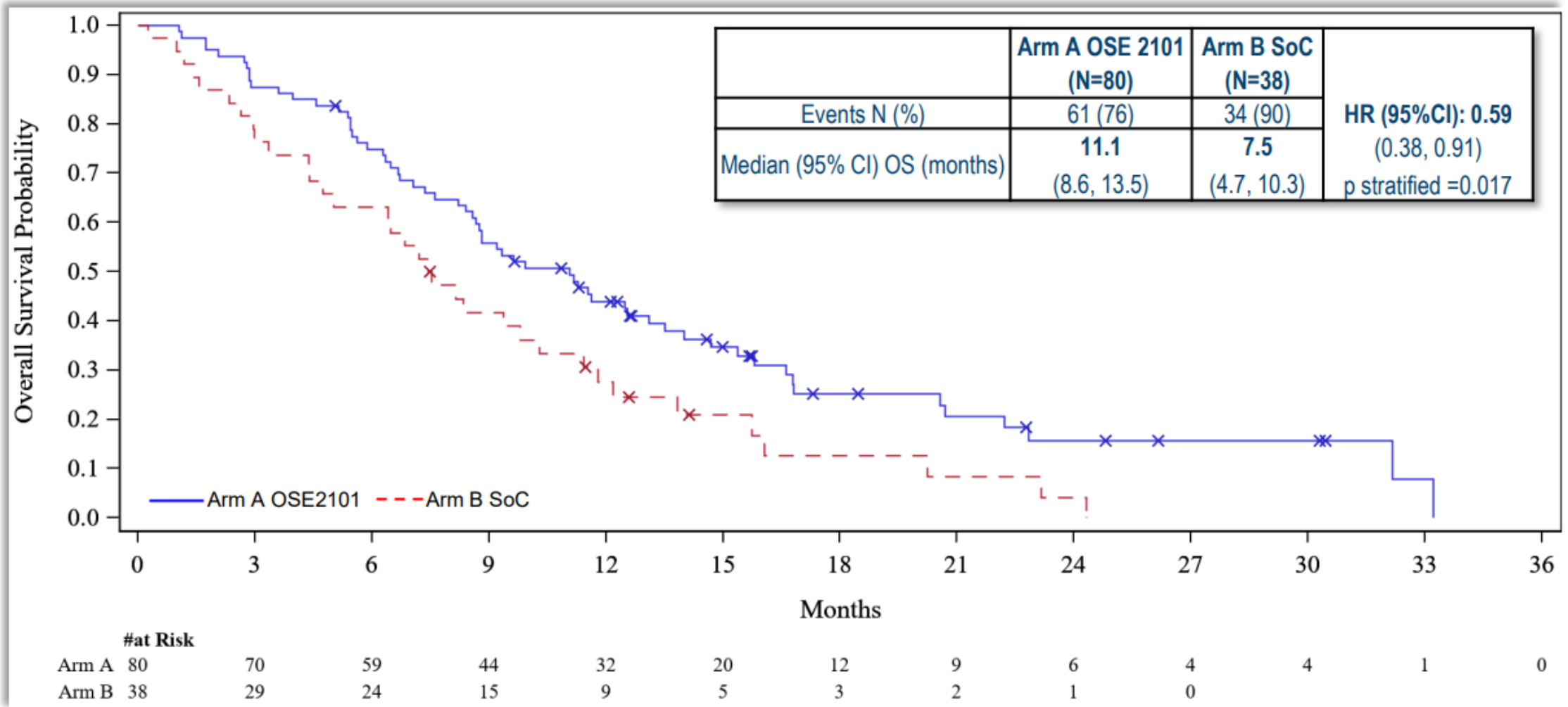
Overall Survival in PoI



	Arm A OSE 2101 (N=80)	Arm B SoC (N=38)	
Events N (%)	61 (76)	34 (90)	**HR (95%CI): 0.59** (0.38, 0.91) p stratified =0.017
Median (95% CI) OS (months)	**11.1** (8.6, 13.5)	**7.5** (4.7, 10.3)	

Cut-off 15JAN2021; median follow-up 25 months

PoI=Population of interest; SoC=Standard of care; OS=Overall survival; HR=Hazard ratio; CI=Confidence interval

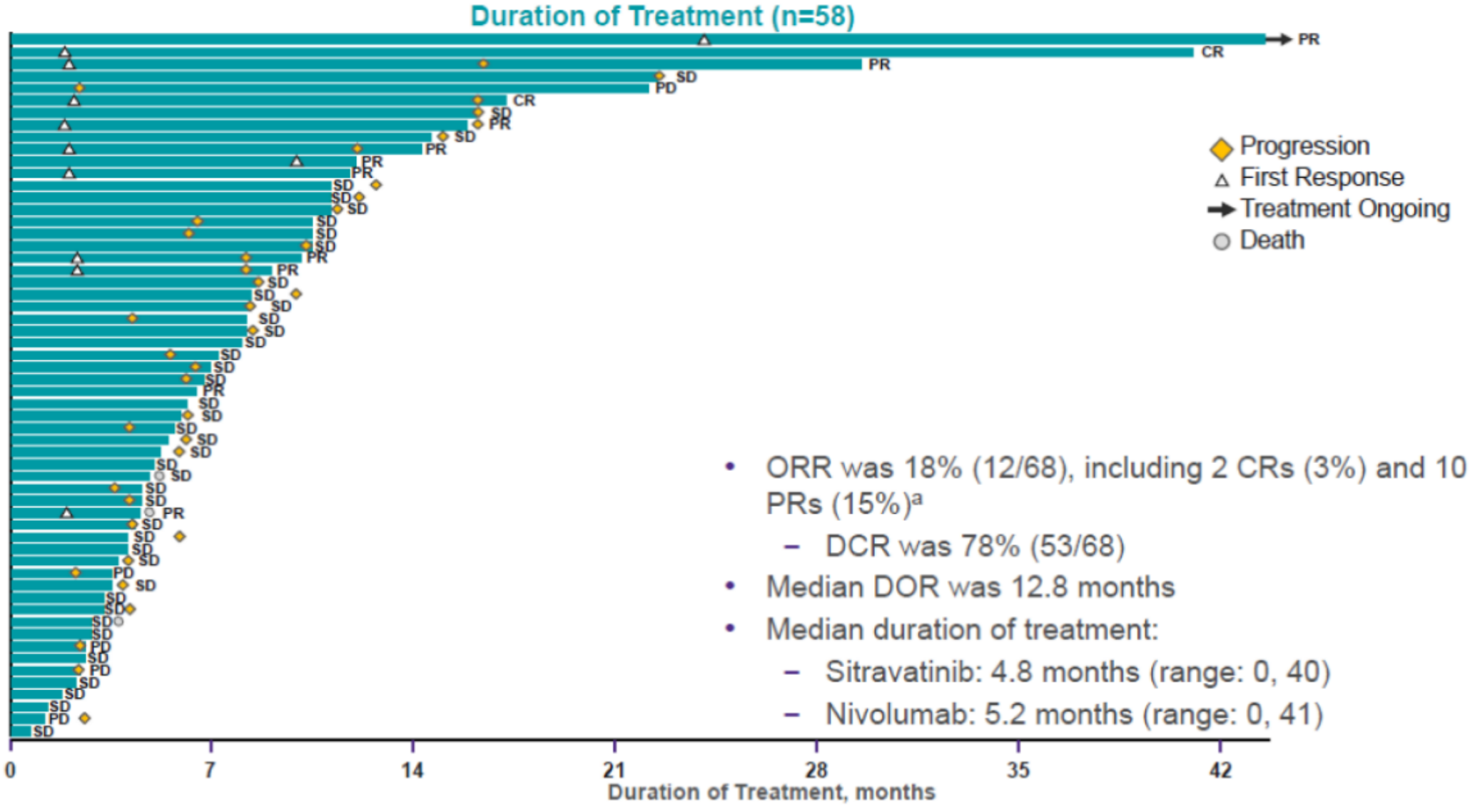
2021 ESMO congress

MRTX-500: Phase 2 Trial of Sitravatinib + Nivolumab in Patients With Nonsquamous Non–Small-Cell Lung Cancer Progressing on or After Prior Checkpoint Inhibitor Therapy

Ticiana A. Leal[1], David Berz[2], Igor I. Rybkin[3], Wade T. Iams[4], Debora S. Bruno[5], Collin M. Blakely[6], Alexander I. Spira[7], Manish R. Patel[8], David M. Waterhouse[9], Donald A. Richards[10], Anthony Pham[11], Robert Jotte[12], Edward B. Garon[13], David S. Hong[14], Ronald Shazer[15], Xiaohong Yan[15], Lisa Latven[15], Kai He[16]

[1]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; Emory University, Atlanta, GA,USA; [2]Department of Cellular Therapeutics, Beverly Hills Cancer Center, Beverly Hills, CA, USA; [3]Henry Ford Cancer Institute, Detroit, MI, USA; [4]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [5]University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH, USA; [6]Department of Medicine, University of California, San Francisco, and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [7]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; [8]Division of Hematology, Oncology and Transplantation, University of Minnesota Masonic Cancer Center, Minneapolis, MN, USA; [9]OHC, Cincinnati, OH, USA; Texas Oncology; [10]Texas Oncology Tyler, Tyler, TX, USA; US Oncology Research Network, The Woodlands, TX, USA; [11]Northwest Cancer Specialists, Tigard, OR, USA; [12]Rocky Mountain Cancer Centers, Denver, CO, USA; US Oncology Research, The Woodlands, TX, USA; [13]Department of Medicine, Division of Hematology/Oncology, David Geffen School of Medicine at the University of California, Los Angeles, CA, USA; [14]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Mirati Therapeutics, Inc., San Diego, CA, USA; [16]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA.

MRTX-500: PhII Sitravatinib + Nivo in Non-Sq NSCLC with prior ICI clinical benefit

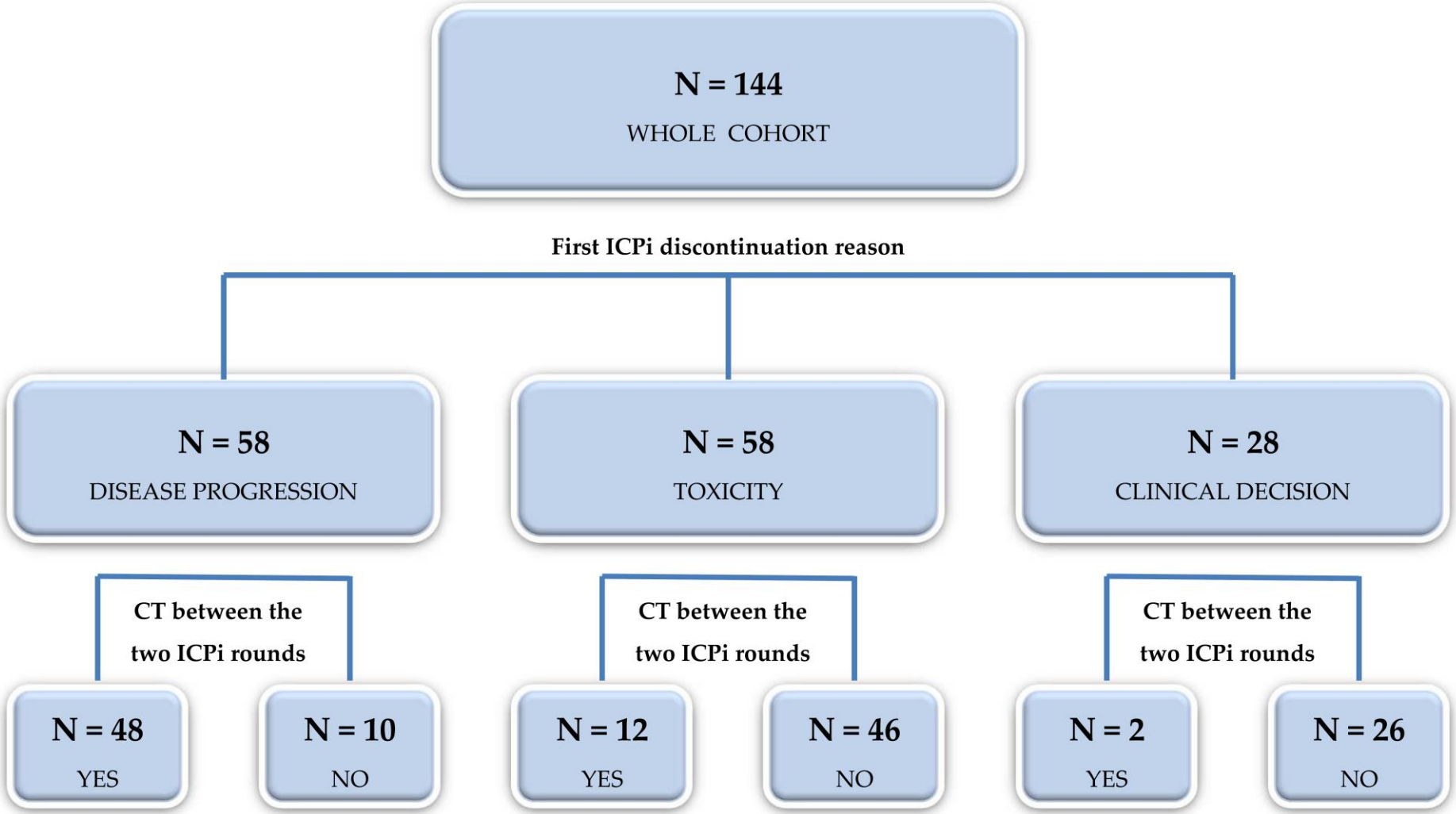


- ORR was 18% (12/68), including 2 CRs (3%) and 10 PRs (15%)[a]
  - DCR was 78% (53/68)
- Median DOR was 12.8 months
- Median duration of treatment:
  - Sitravatinib: 4.8 months (range: 0, 40)
  - Nivolumab: 5.2 months (range: 0, 41)

mPFS 5.7 mos (4.9-7.6); mOS 14.9 mos (9.3-21.1)

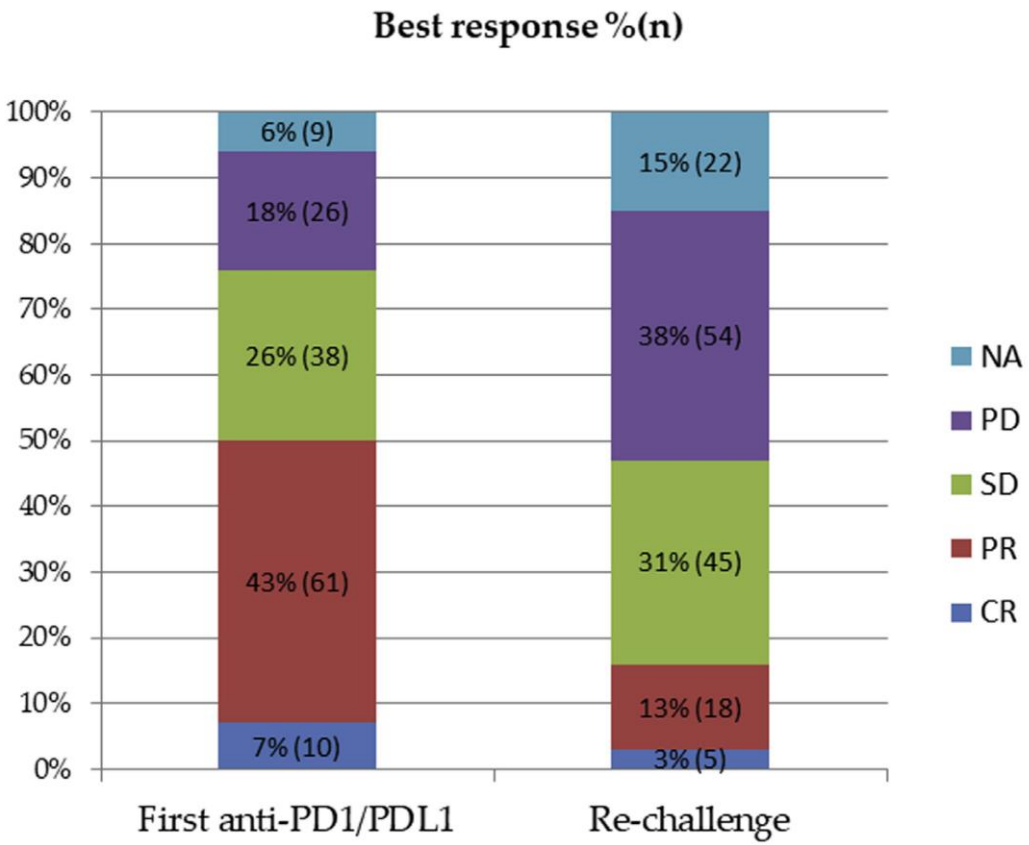
Leal TA, et al. ESMO 2021

Immune Checkpoint Inhibitors Rechallenge Efficacy in Non–Small-Cell Lung Cancer Patients



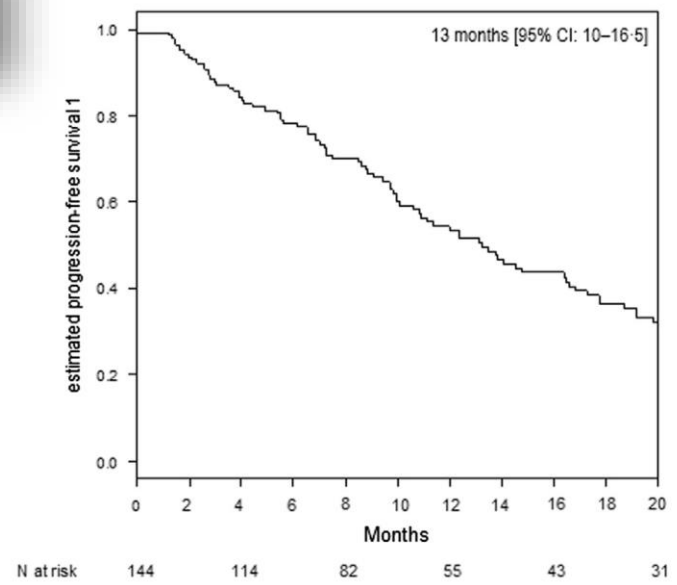
Gobbini E, et al. Clin Lung Cancer 2020;21(5):e497-e510.

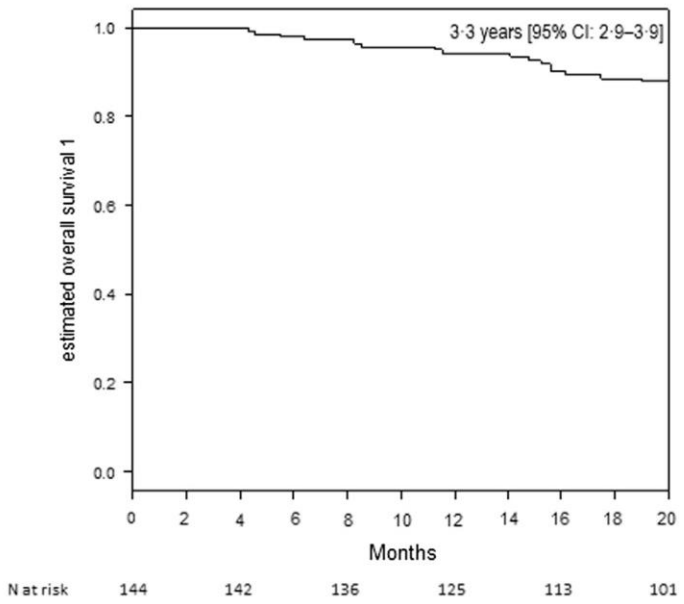
Immune Checkpoint Inhibitors Rechallenge Efficacy in Non–Small-Cell Lung Cancer Patients



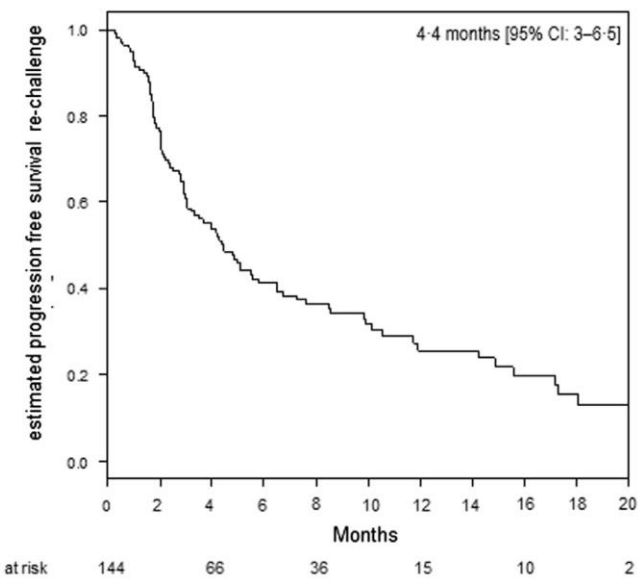
50% **16%**

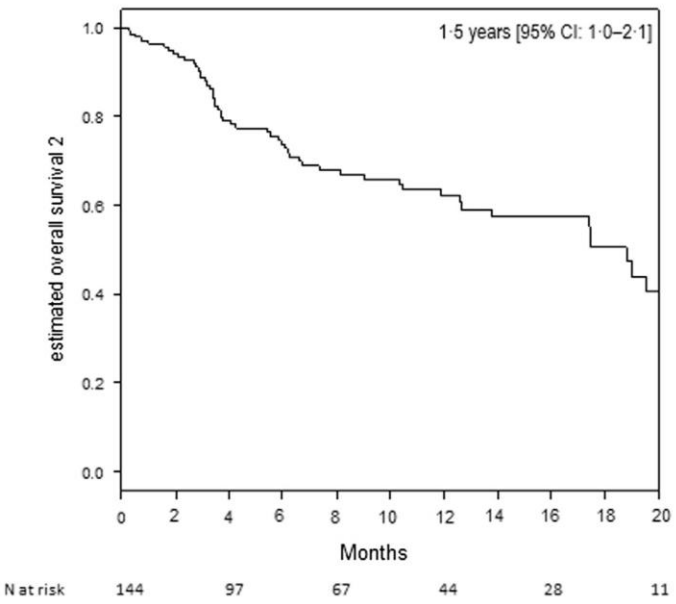
First anti-PD1/PDL1





Rechallenge





Gobbini E, et al. Clin Lung Cancer 2020;21(5):e497-e510.

Immune Checkpoint Inhibitors Rechallenge Efficacy in Non–Small-Cell Lung Cancer Patients

Table 3 Univariate and Multivariate Analysis Regarding Progression-Free Survival at Rechallenge

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Discontinuation reason		2.10^{-2}		
Disease progression	1			
Toxicity	0.54 (0.33-0.86)			
Clinical decision	0.63 (0.37-1.07)			
Chemotherapy between 2 ICPi rounds		4.10^{-2}		
No	1			
Yes	1.81 (1.21-2.72)			
ECOG PS at rechallenge		6.10^{-3}		6.10^{-3}
0	1		1	
1	2.12 (1.25-3.60)		2.12 (1.25-3.60)	
2-3	2.74 (1.42-5.26)		2.74 (1.42-5.26)	
Treatment line at rechallenge		9.10^{-2}		
First or second	1			
Third	1.17 (0.61-2.27)			
Further	1.74 (0.97-3.14)			
Bone metastasis		1.10^{-1}		
No	1			
Yes	0.67 (0.41-1.09)			
Brain metastasis		1.10^{-1}		
No	1			
Yes	1.46 (0.92-2.31)			
No. of metastasis sites		2.10^{-1}		
0	1			
1	0.79 (0.48-1.29)			
≥2	1.27 (0.78-2.06)			

Table 4 Univariate and Multivariate Analysis Regarding Overall Survival From Rechallenge

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Discontinuation reason		3.10^{-2}		
Disease progression	1			
Toxicity	0.44 (0.23-0.82)			
Clinical decision	0.61 (0.23-0.82)			
Chemotherapy between 2 ICPi rounds		1.10^{-1}		
No	1			
Yes	1.52 (0.90-2.60)			
ECOG PS at rechallenge		1.10^{-2}		1.10^{-2}
0	1		1	
1	2.98 (1.32-6.75)		2.98 (1.32-6.75)	
2-3	3.97 (1.60-9.87)		3.97 (1.60-9.87)	

mOS:

Toxicity	**2.1 years**
Clinical decision	**1.6 years**
Disease progression	**1.0 years**

Gobbini E, et al. Clin Lung Cancer 2020;21(5):e497-e510.

Rechallenge: *Le conclusioni*

- Dopo **interruzione programmata** (o decisione clinica) è fattibile ed attivo
- Dopo **interruzione per irAEs** andrebbe considerato caso per caso, valutando il rapporto rischio/beneficio nel singolo paziente tenendo conto delle opzioni terapeutiche alternative, dell'evento che ha determinato l'interruzione, e dello stato di malattia (riposta/stabilità)
- Dopo **progressione di malattia** rappresenta un approccio sperimentale

Grazie per l’attenzione!

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