Immunotherapy Updates in Melanoma

MLS Cleveland
April 13, 2024

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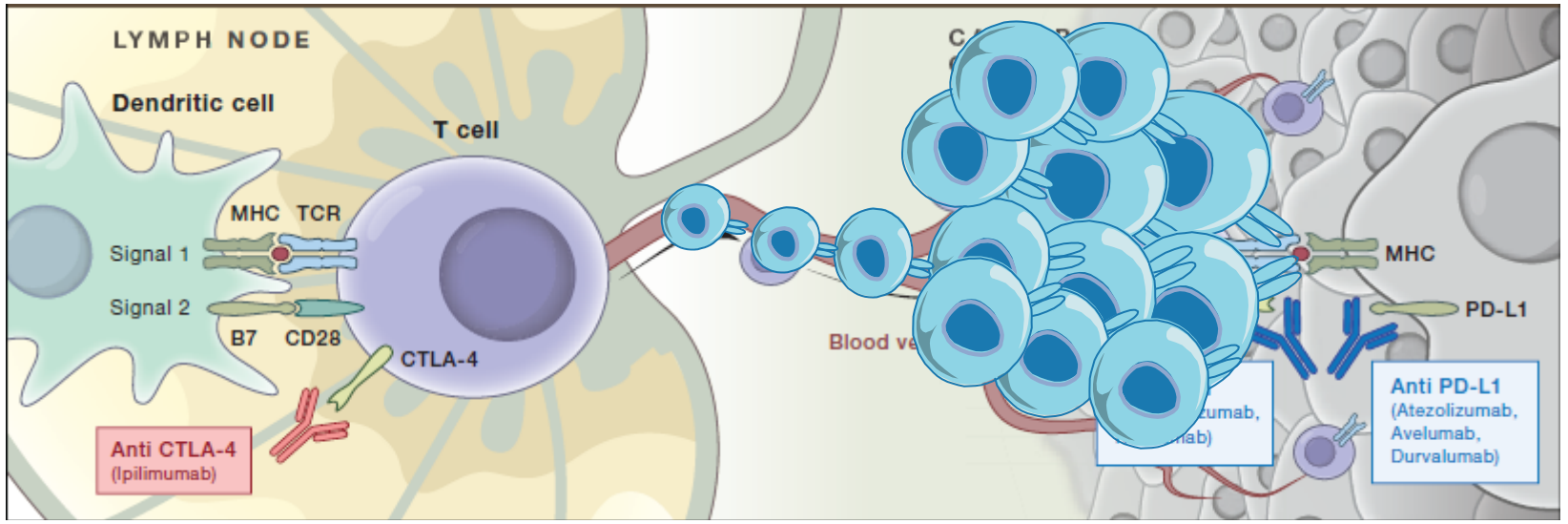
Immune-targeted strategies for metastatic cancer with checkpoint inhibitors

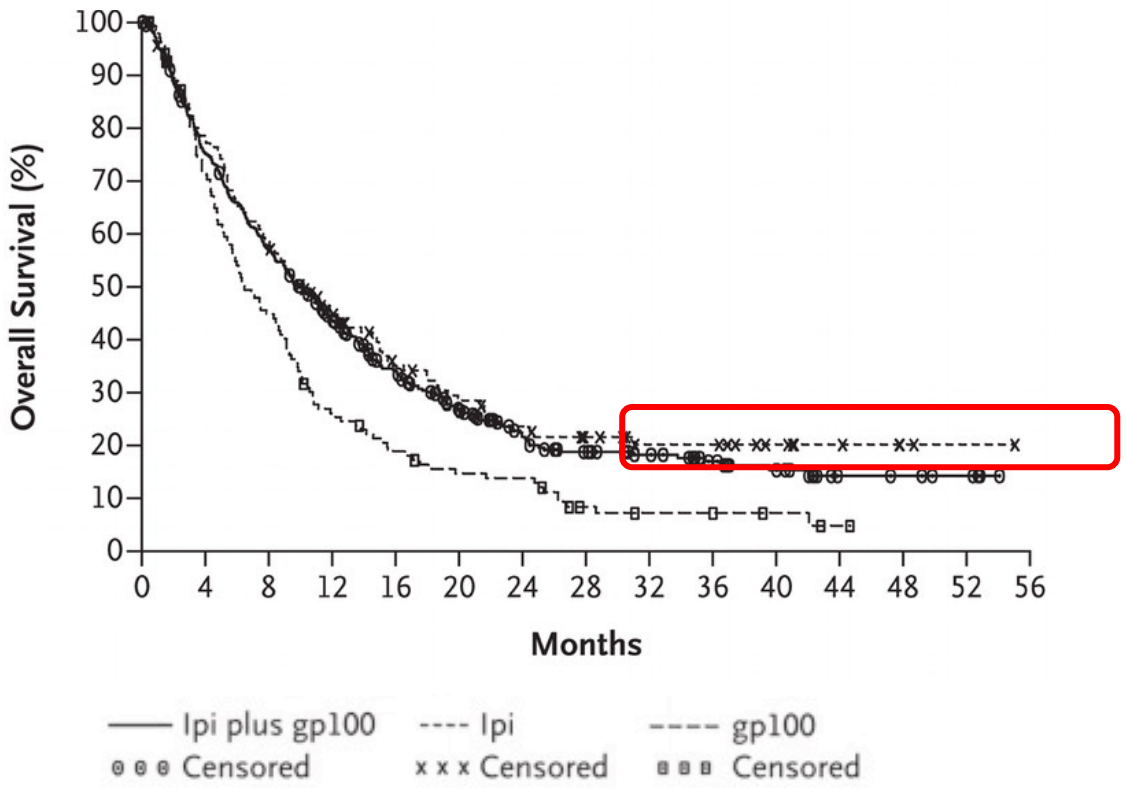


Taube… Topalian, Chen. *Sci Transl Med* 2012
Tumeh… Ribas, *Nature* 2014

Modified from Abril-Rodriguez and Ribas, Snapshot, *Cancer Cell* 2017, used with permission from A. Ribas

Updates in Advanced Melanoma

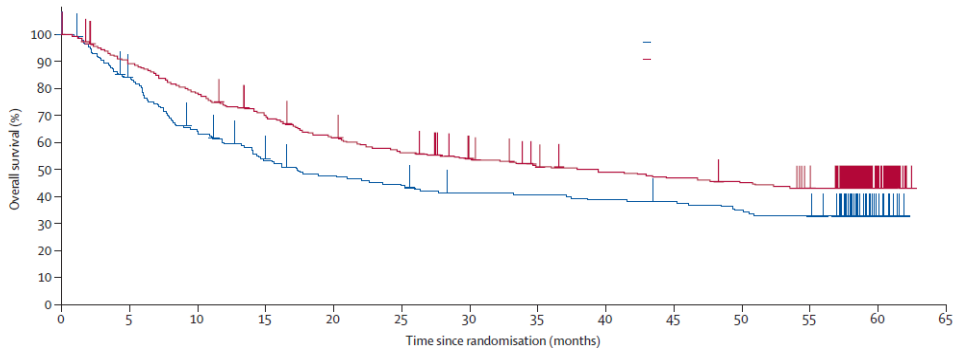
Approval of 1st checkpoint inhibitor therapy with anti-CTL4/ipilimumab in advanced unresectable melanoma



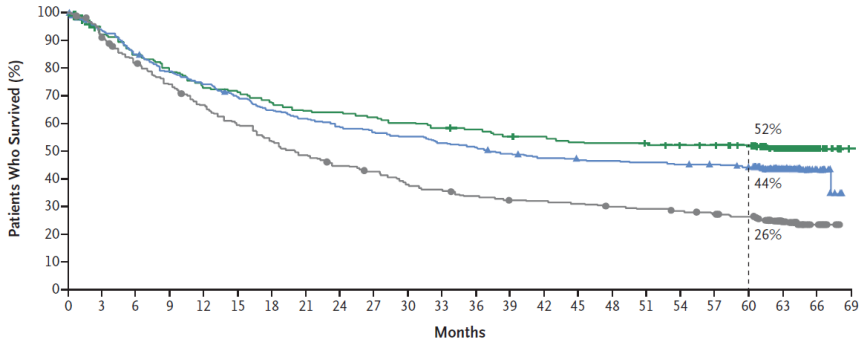
NEJM 2010; 363:711-723

Superior survival with anti-PD1 over anti-CTL4 alone

KN006



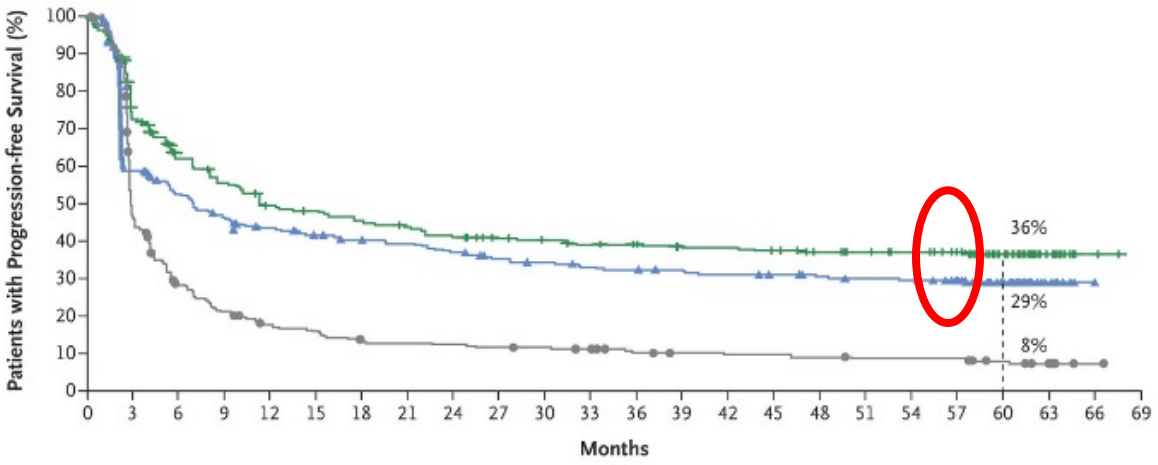
CM 067



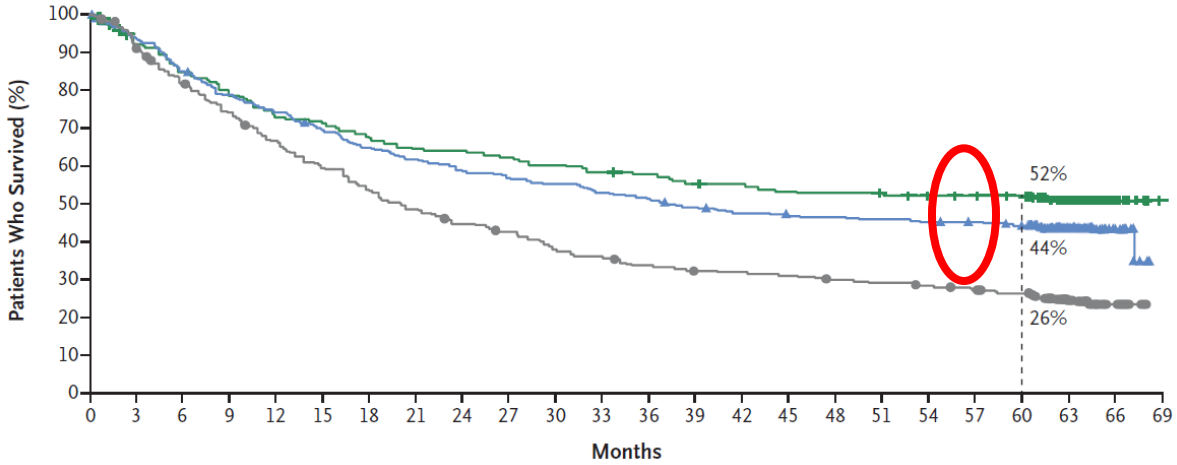
Lancet Onc 2019;20:1239-51; NEJM 2019; 381:1535-46

Combination anti-PD1/CTL4 blockade vs anti-PD1 alone

PFS



OS



Nivolumab plus Ipilimumab Nivolumab Ipilimumab

NEJM 2019; 381:1535-46

Response to treatment at 6.5 years

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53-64)	45 (39-51)	19 (15-24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
Median duration of response (95% CI), months	NR (61.9-NR)	NR (45.7-NR)	19.2 (8.8-47.4)

CI, confidence interval; NR, not yet reached.

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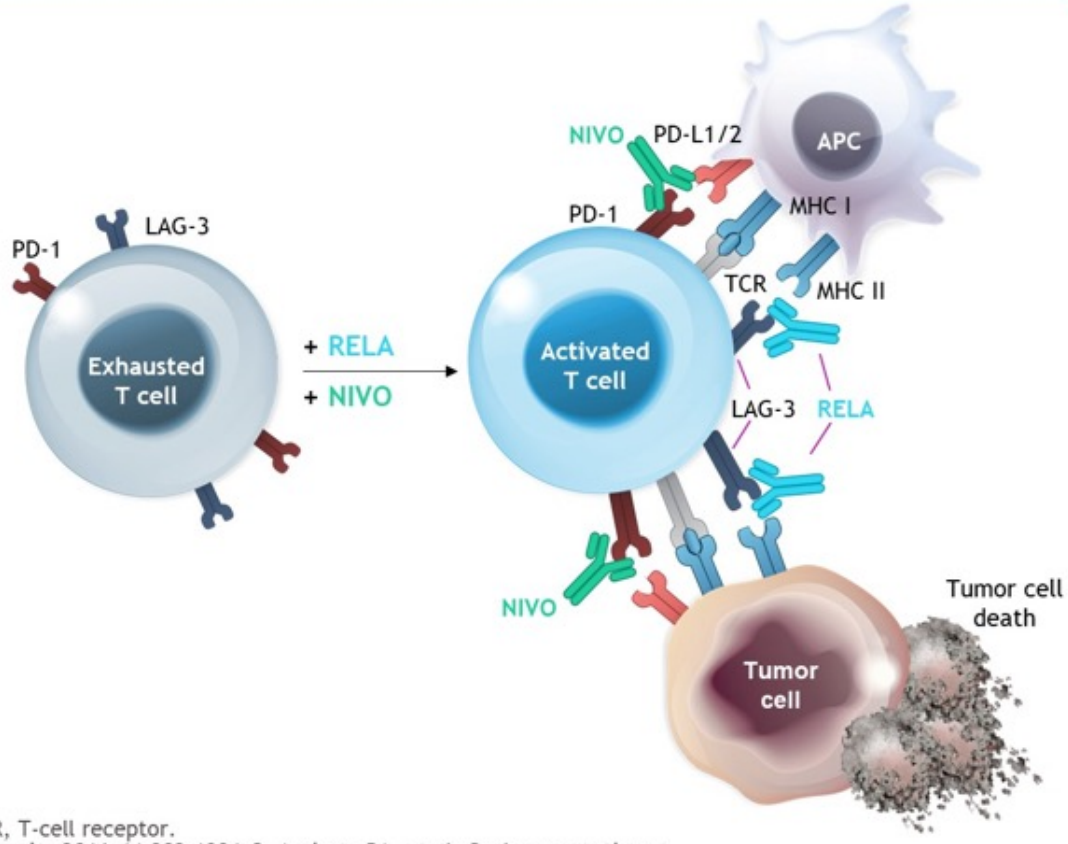
Rationale for RELA + NIVO

- LAG-3 and PD-1 are distinct immune checkpoints, often co-expressed on tumor-infiltrating lymphocytes, and contribute to tumor-mediated T-cell exhaustion[1,2]
- In preclinical models, LAG-3 and PD-1 blockade demonstrated synergistic antitumor activity[1]
- RELA + NIVO demonstrated clinically meaningful antitumor activity including durable objective responses and was well tolerated in patients with melanoma that was relapsed/refractory to anti-PD-1 therapy[3,4]



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Woo S-R, et al. *Cancer Res* 2012;72:917-927; 2. Anderson AC, et al. *Immunity* 2016;44:989-1004; 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract LBA18.

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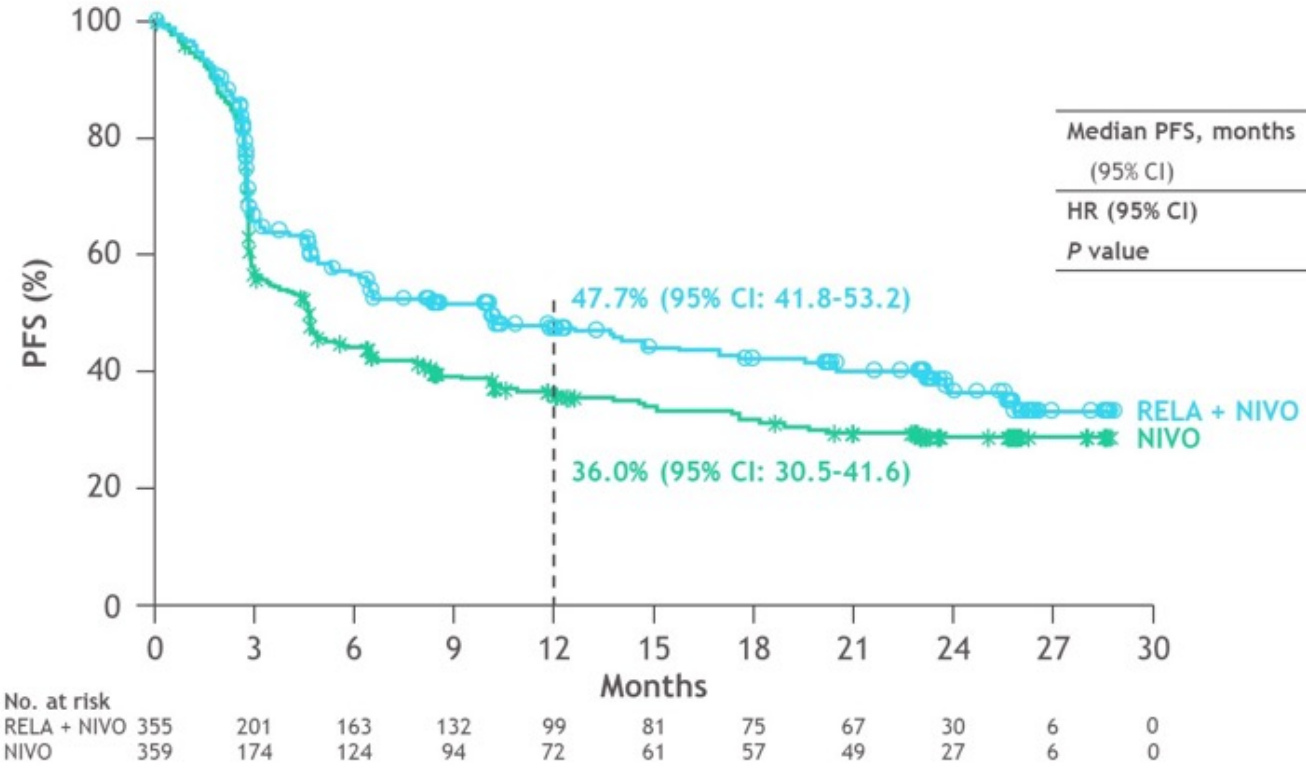
RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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Secondary endpoint: confirmed ORR by BICR

Overall response	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR, n (%)	153 (**43.1**)	117 (**32.6**)
95% CI	37.9-48.4	27.8-37.7
Difference of ORR, % (95% CI)	10.3 (3.4-17.3)	
Odds ratio, % (95% CI)	1.6 (1.2-2.2)	
Confirmed best overall response, n (%)		
Complete response	58 (16.3)	51 (14.2)
Partial response	95 (26.8)	66 (18.4)
Stable disease	61 (17.2)	59 (16.4)
Progressive disease	105 (29.6)	149 (41.5)
Unknown	27 (7.6)	28 (7.8)
DCR, n (%)	223 (62.8)	182 (50.7)
95% CI	57.6-67.9	45.4-56.0
Median DOR, months	NR	NR
95% CI	29.57-NR	29.93-NR

ORR could not be formally tested and was descriptively analyzed. Median follow-up, 19.3 months. Database lock date: October 28, 2021. Strata adjusted difference in ORR based on Cochran-Mantel-Haenszel method of weighting. Stratified by LAG-3, *BRAF*, AJCC M stage.

Safety summary

- RELA + NIVO FDC was associated with a manageable safety profile and without unexpected safety signals

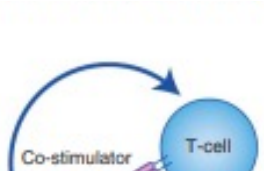
AE, n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
TRAE	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Leading to discontinuation	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
TRAE ≥ 10%				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0

- Treatment-related deaths: RELA + NIVO (n = 3) – hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis; NIVO (n = 2) – sepsis and myocarditis, and worsening pneumonia

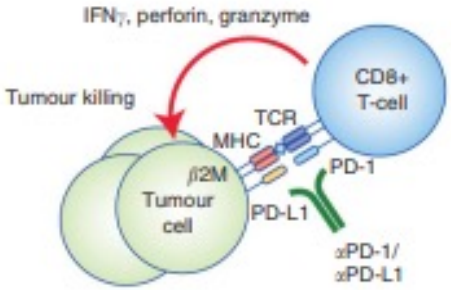
AE, adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Other grade 3/4 TRAEs that were associated with any grade TRAEs occurring in <10% of patients not shown.

Generation of an anti-tumor T cell response

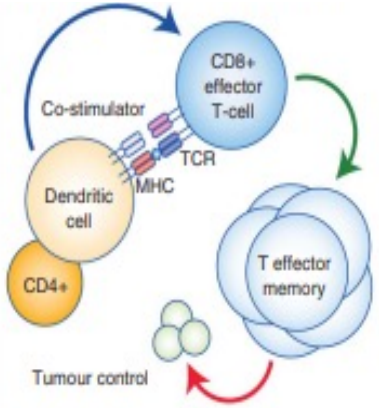
Formation of tumor reactive T cells



Activation of effector T-cell function

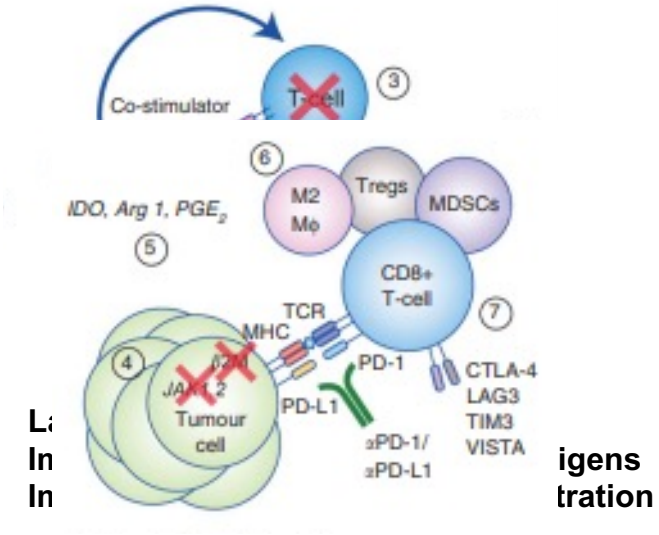


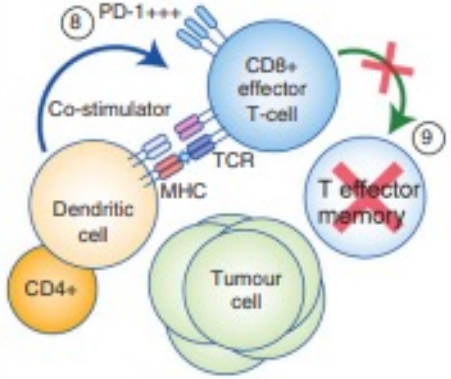
Formation of effector memory T-cells



Brit J Cancer 2018; 118: 9–16

Mechanisms of innate and acquired checkpoint inhibitor resistance





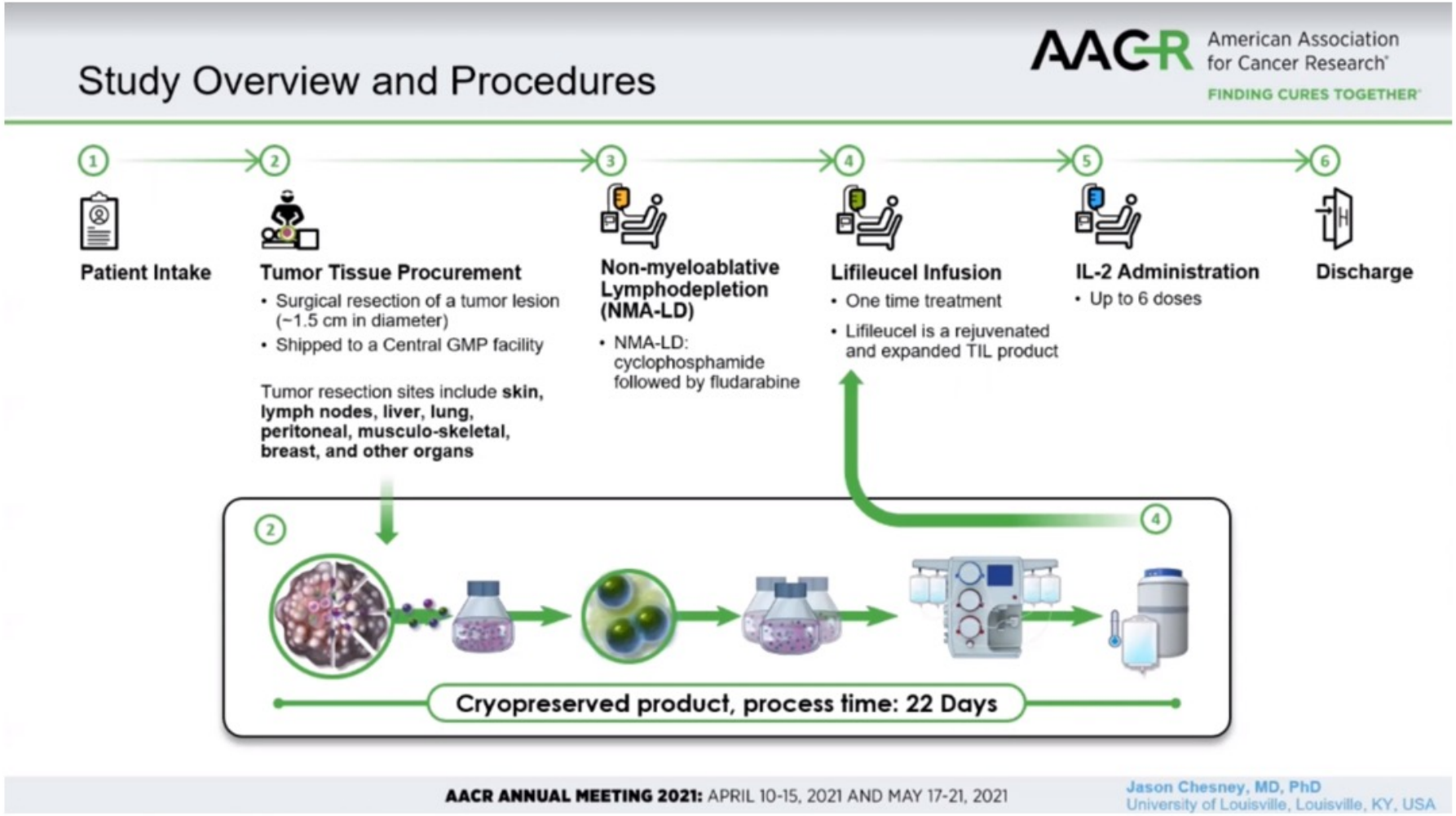
Severe T-cell exhaustion
T-cell epigenetic changes

La
In **igens**
In **tration**

Impaired IFN signalling
Metabolic/inflammatory mediators
Immune suppressive cells
Alternate immune checkpoints

Brit J Cancer 2018; 118: 9–16

Lifileucel: Tumor infiltrating lymphocyte therapy



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Iovance C-144-01 Study Design

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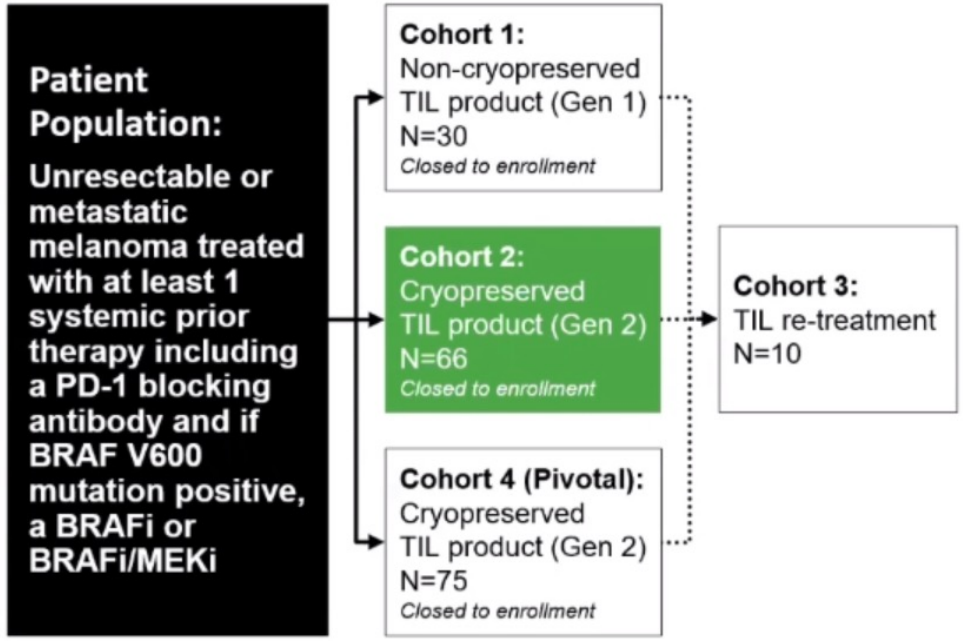
Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)



Cohort 2 Endpoints:

- Primary: Efficacy defined as investigator-assessed Objective Response Rate (ORR) following RECIST 1.1
- Secondary: Safety and additional parameters of Efficacy

Other Key Eligibility Criteria:

- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥ one tumor lesion as target for RECIST 1.1 assessment
- Age ≥ 18 years at the time of consent
- ECOG Performance Status of 0-1

Methods:

- Data Extract: 14 December 2020 for Cohort 2

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C-144-01 Cohort 2 Patient Characteristics

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CHARACTERISTICS	Cohort 2, N=66
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, Max	20, 79
Prior therapies, n (%)	
Mean # prior therapies	3.3
anti-PD-1 / anti-PD-L1	66 (100)
anti-CTLA-4	53 (80)
BRAFi/MEKi	15 (23)
Progressive Disease for at least 1 prior therapy, n (%)	
anti-PD-1 / anti-PD-L1	65 (99)
anti-CTLA-4	41 (77[(1)])
Baseline ECOG score, n (%)	
0	37 (56)
1	29 (44)

CHARACTERISTICS	Cohort 2, N=66
BRAF Status, n (%)	
Mutated V600E or V600K	17 (26)
Wild Type	45 (68)
Unknown	3 (5)
Other	1 (2)
Tumor PD-L1 expression, n (%)	
PD-L1 Positive (TPS ≥ 5%)	23 (35)
PD-L1 Negative (TPS < 5%)	26 (39)
Baseline LDH (U/L)	
Median	244
1-2 times ULN, n (%)	19 (29)
> 2 times ULN, n (%)	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, Max	11, 343
Number of Target and Non-Target Lesions (at Baseline)	
>3, n (%)	51 (77)
Mean (SD)	6 (2.7)
Liver and/or Brain Lesions, n (%)	28 (42)

Cohort 2 patients have:

- 3.3 mean prior therapies, ranging from 1-9
- High tumor burden at baseline

(1) % is calculated based on number of patients who received prior anti-CTLA-4

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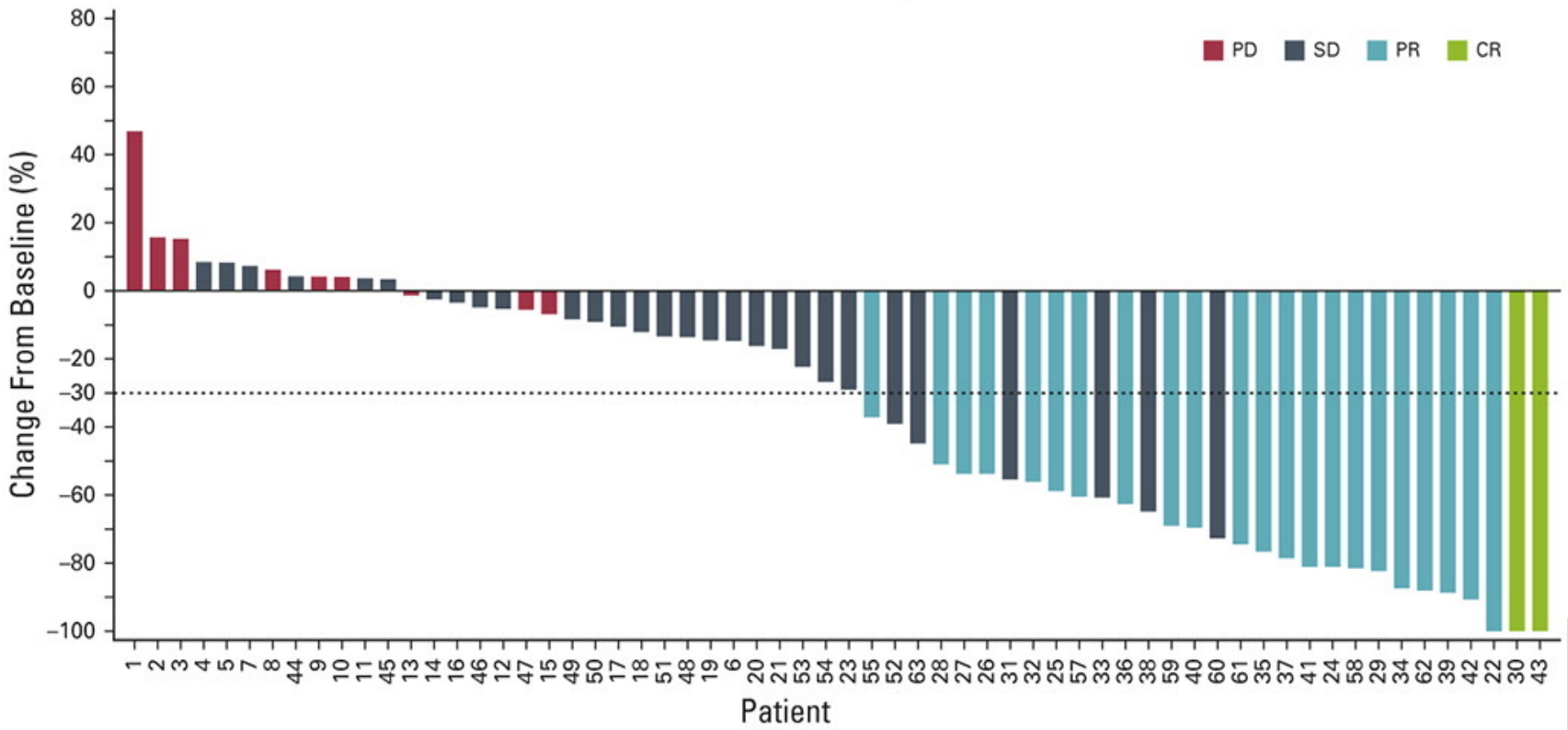
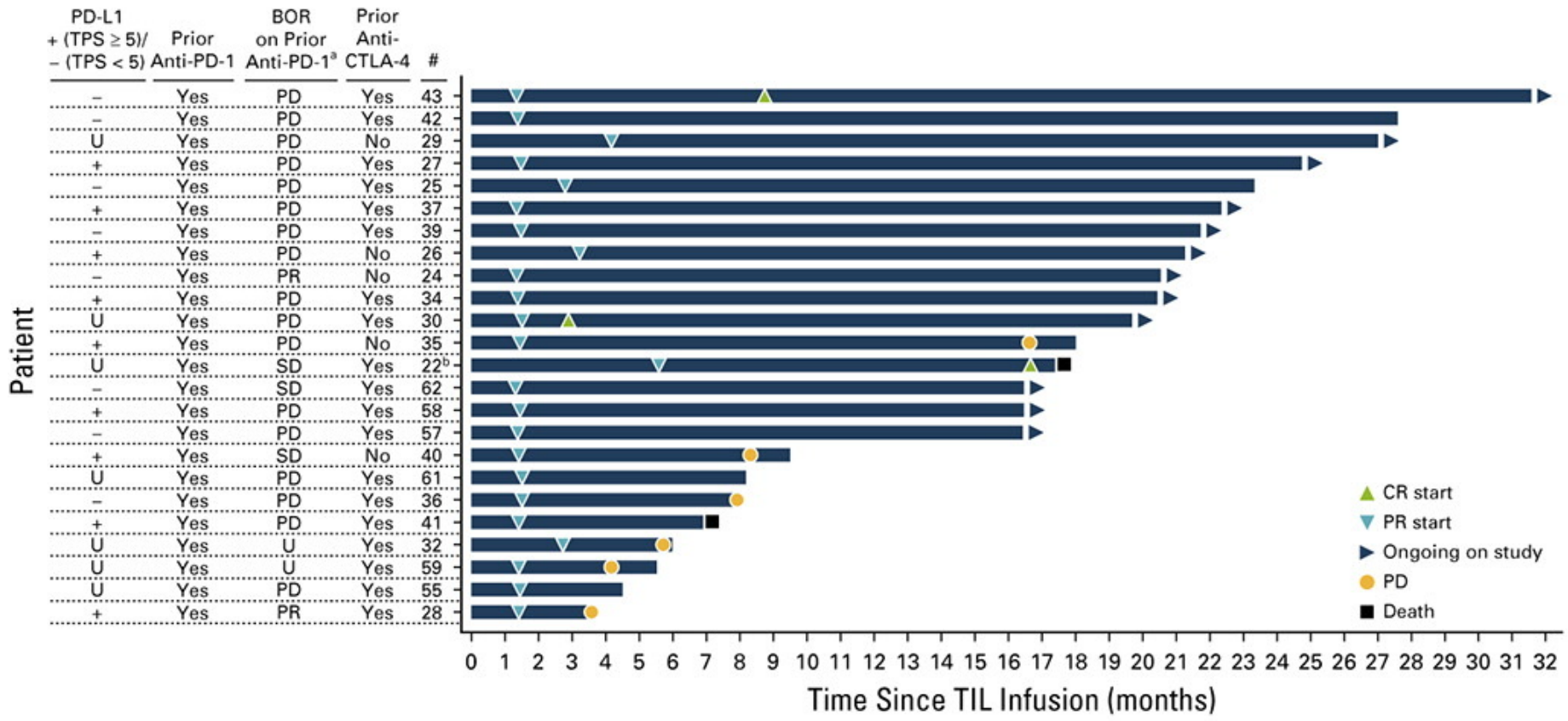
Best overall response



JCO 2021;39:2656-68

Time to response and duration for evaluable patients with PR or better



JCO 2021;39:2656-68

C-144-01 Cohort 2 Efficacy

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RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	3 (4.5)
Partial Response	21 (31.8)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable(1)	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 35.2+

- After a median study follow-up of 28.1 months, median DOR was still not reached (range 2.2, 35.2+)
- Mean number of TIL cells infused: 27.3×10^9
- Responses were demonstrated:
  - In patients who received prior anti-CTLA-4 or BRAF/MEK inhibitors
  - Regardless of BRAF mutational status
  - Regardless of Tumor PD-L1 expression
  - In patients with various LDH levels
  - In patients with various baseline tumor burden
  - In patients with liver and/or brain lesions
  - Regardless of time from stop of anti-PD-1/L1 to TIL infusion

(1) Not evaluable (NE) due to not reaching first assessment

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Iovance C-144-01 Cohort 2 Safety

Treatment Emergent Adverse Events (≥ 30%)

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	Cohort 2 (N=66)		
PREFERRED TERM	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE	66 (100)	64 (97.0)	2 (3.0)*
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

*One death was due to intra-abdominal hemorrhage considered possibly related to TIL, second was due to acute respiratory failure assessed as not related to TIL per Investigator assessment.
- Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term
- Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days

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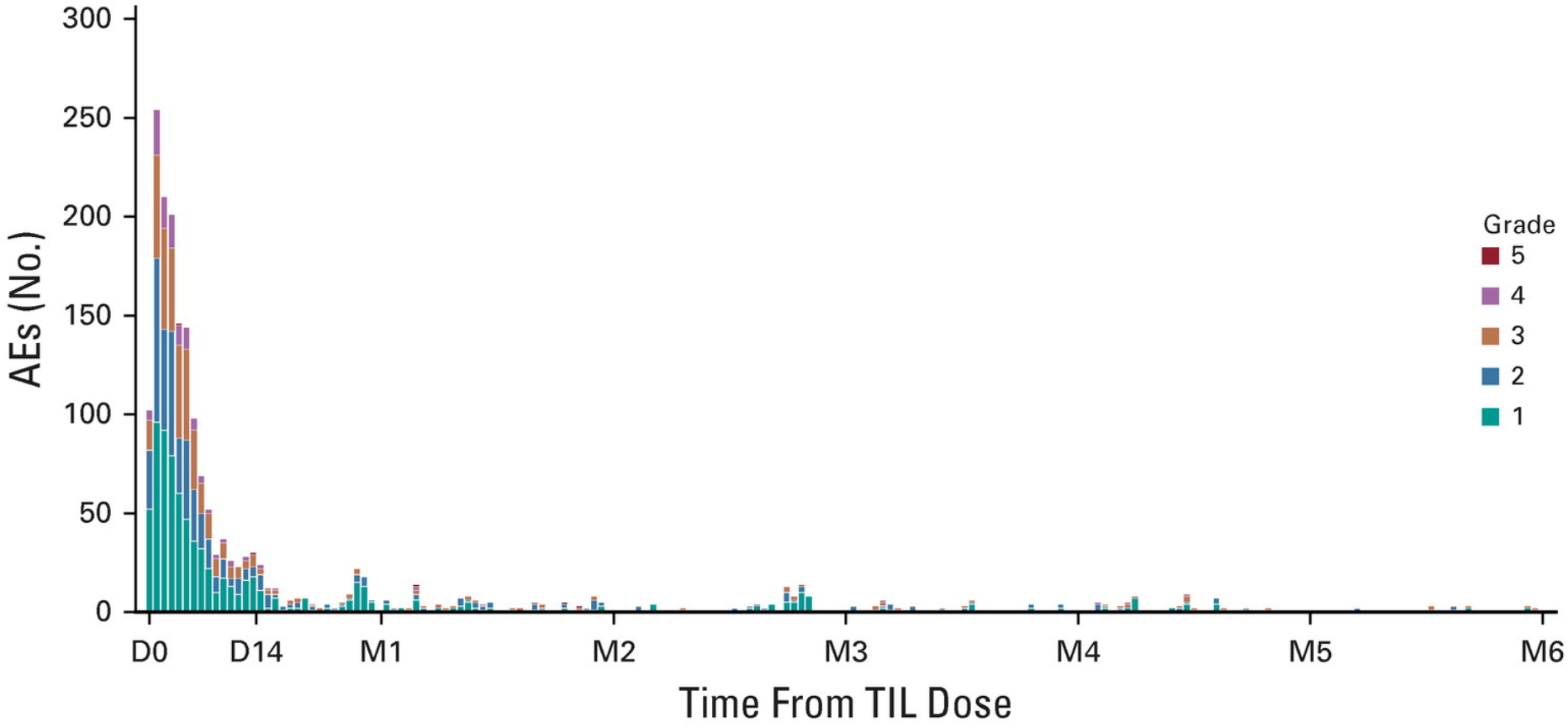
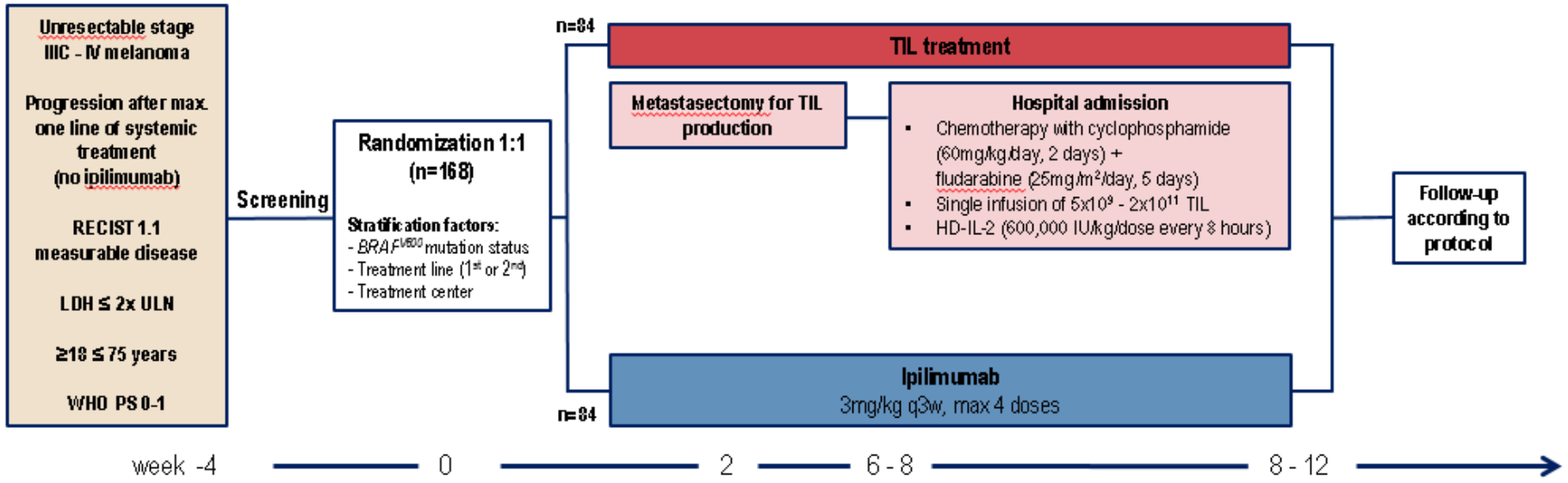
Adverse events over time



JCO 2021;39:2656-68

Trial design



Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

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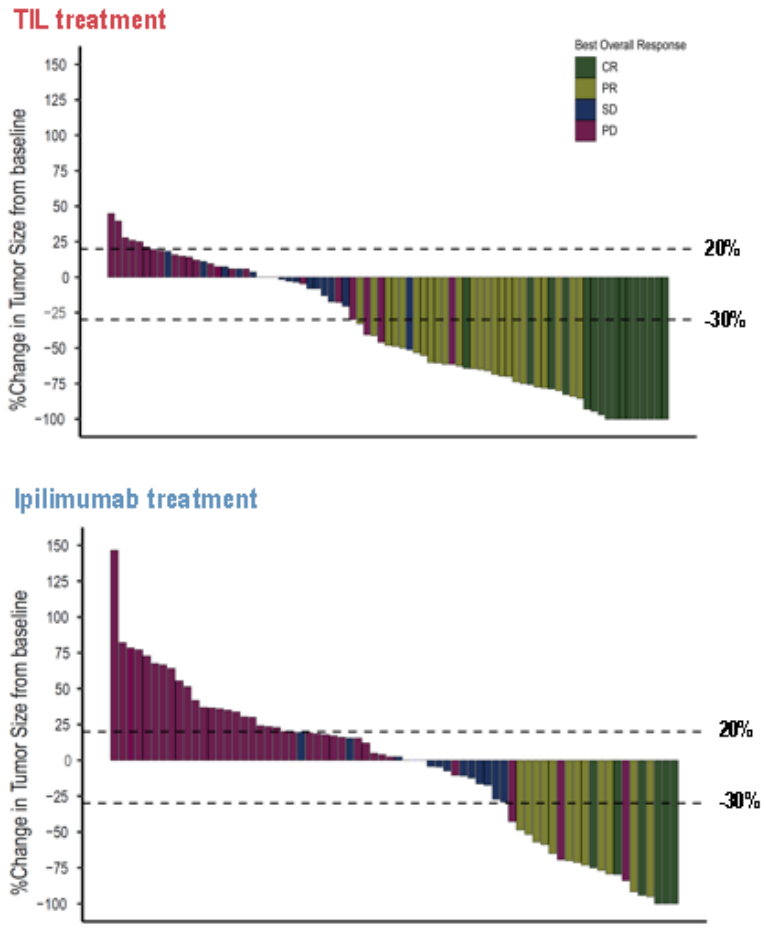
Results (3)

Best overall response according to RECIST 1.1*

	TIL (n=84)	Ipilimumab (n=84)
Best overall response	n (%)	n (%)
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done#	3 (3.6)	11 (13.1)
Overall response†	41 (48.8)	18 (21.4)
Clinical benefit‡	57 (67.9)	33 (39.3)

*In the intention-to-treat population. #In 3 (3.6%) and 11 (13.1%) of TIL and ipilimumab treated patients, respectively, best radiologic response could not be evaluated or was not done due to an event (death or need to start subsequent anticancer therapy) before the moment of first response evaluation or due to unevaluable target lesions in follow-up. †Defined as CR plus PR and ‡CR, PR plus SD according to RECIST 1.1.



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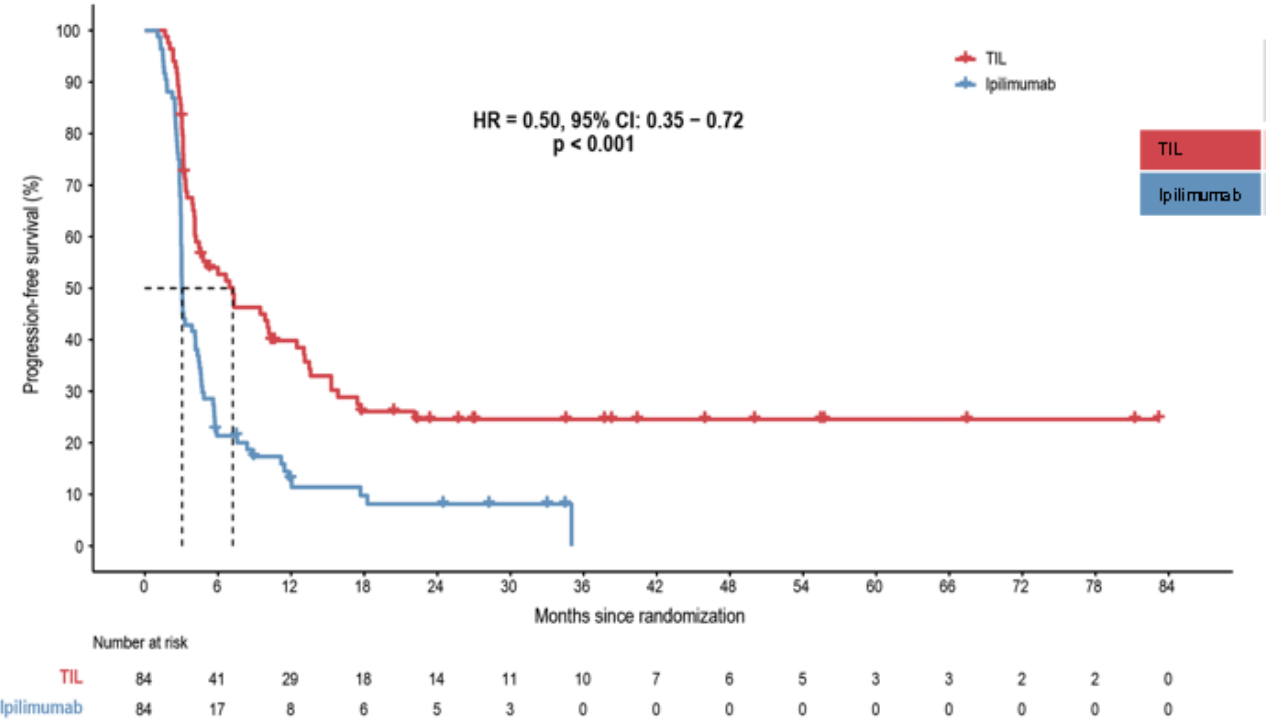
Results (1)

Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

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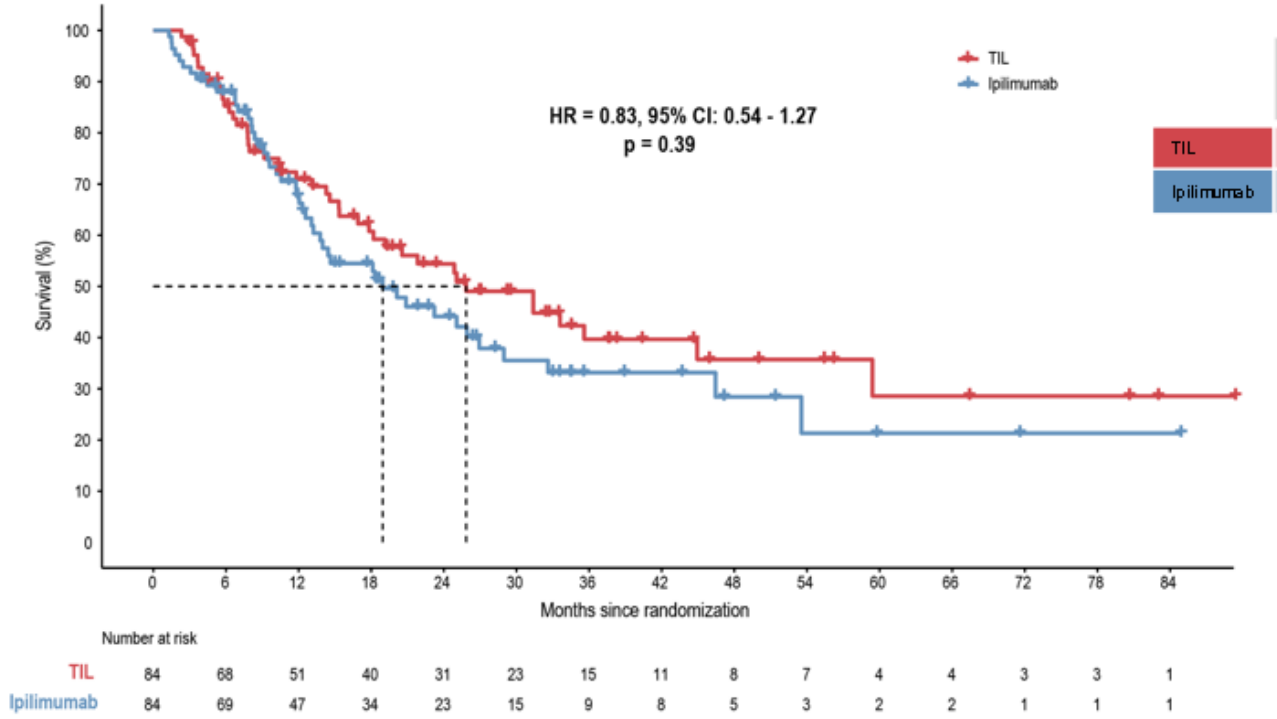
Results (4)

Overall survival in the ITT population



	Median overall survival (months)	95% CI	2 year overall survival (%)	95% CI
TIL	25.8	18.2 – NR	54.3	43.9 – 67.2
Ipilimumab	18.9	13.8 – 32.6	44.1	33.6 – 57.8

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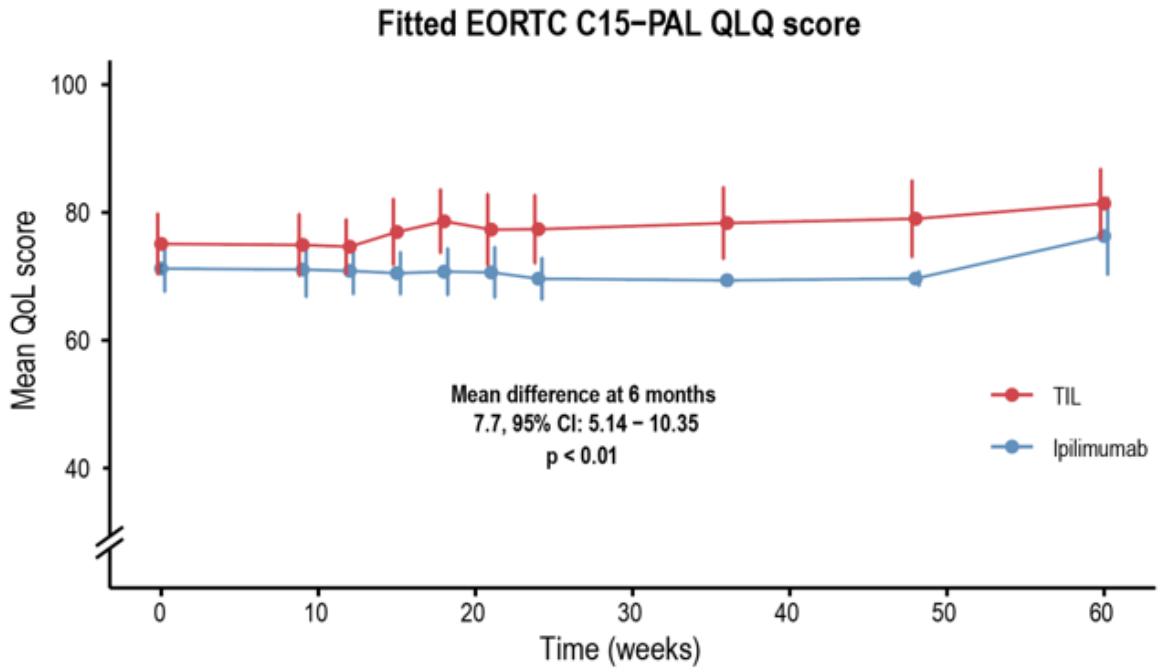
Results (6)

Overall Health-related Quality of Life



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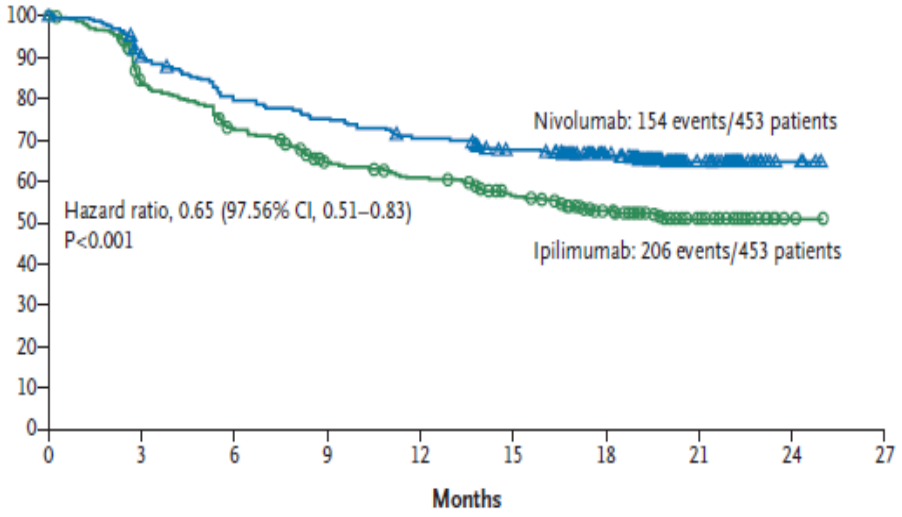
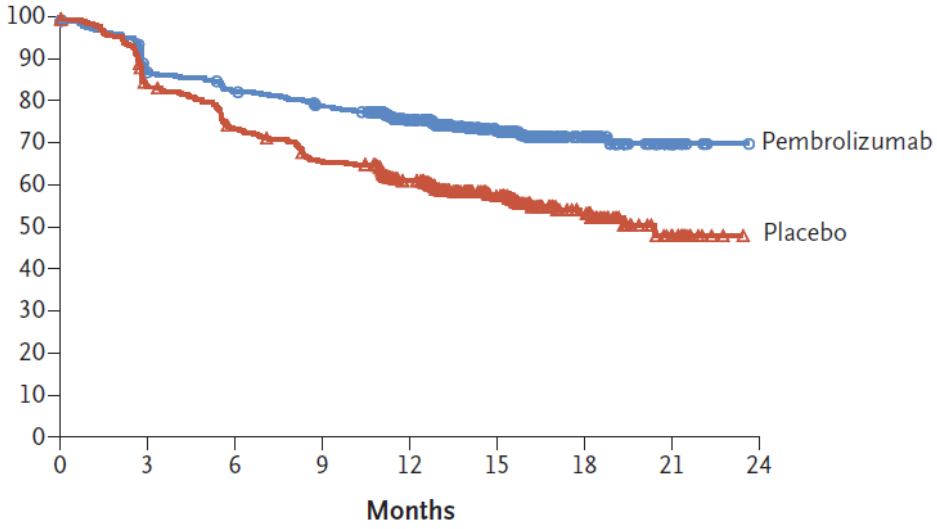
Updates in Resectable Melanoma

Improved recurrence free survival w adjuvant anti-PD1 for high-risk stage III melanoma



CheckMate 238--NIVO

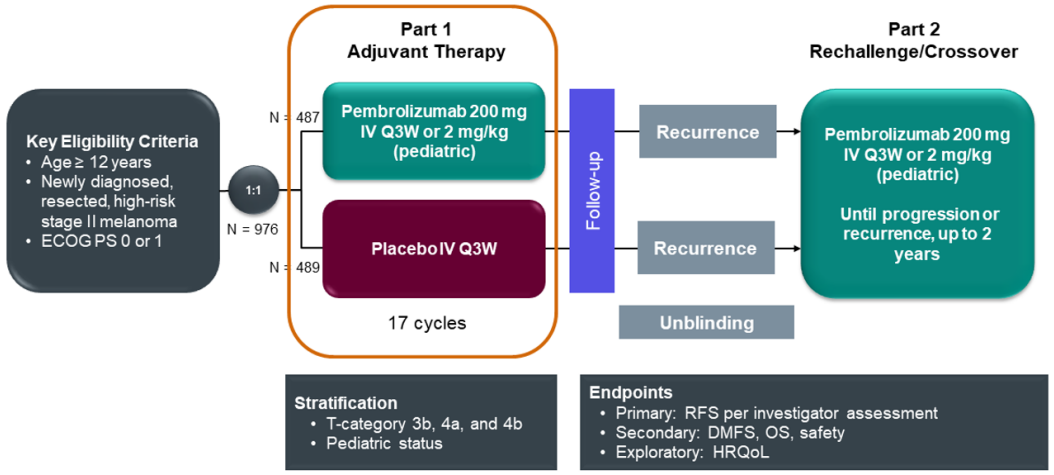


EORTC 1025/KN 054--Pembro

NEJM 2017; 377:1824-1835, NEJM 2018; 378:1789-801

Adjuvant IO for node-negative melanoma, stage IIB/C

KEYNOTE-716 Study Design
(NCT03553836)



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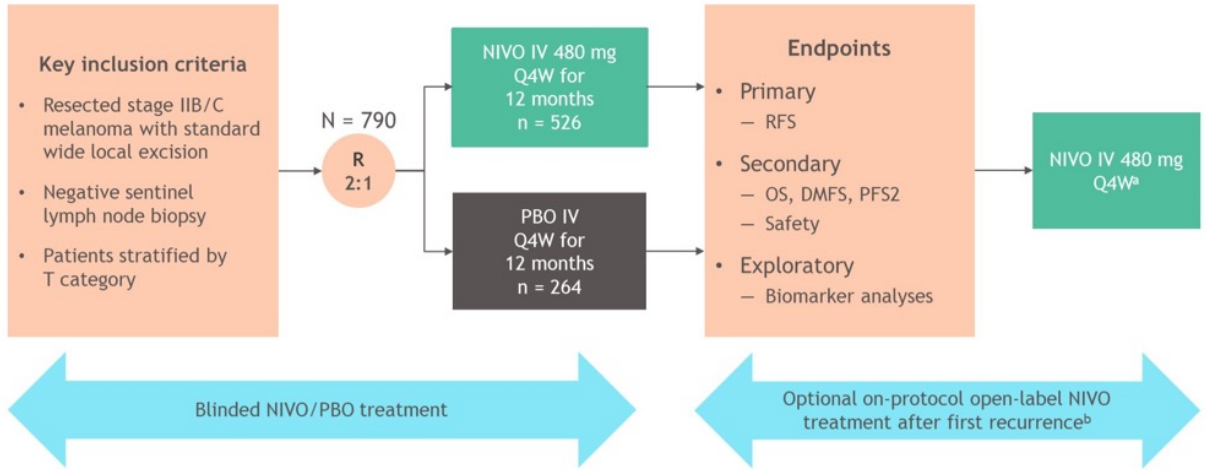
CheckMate 76K study design[1,2]



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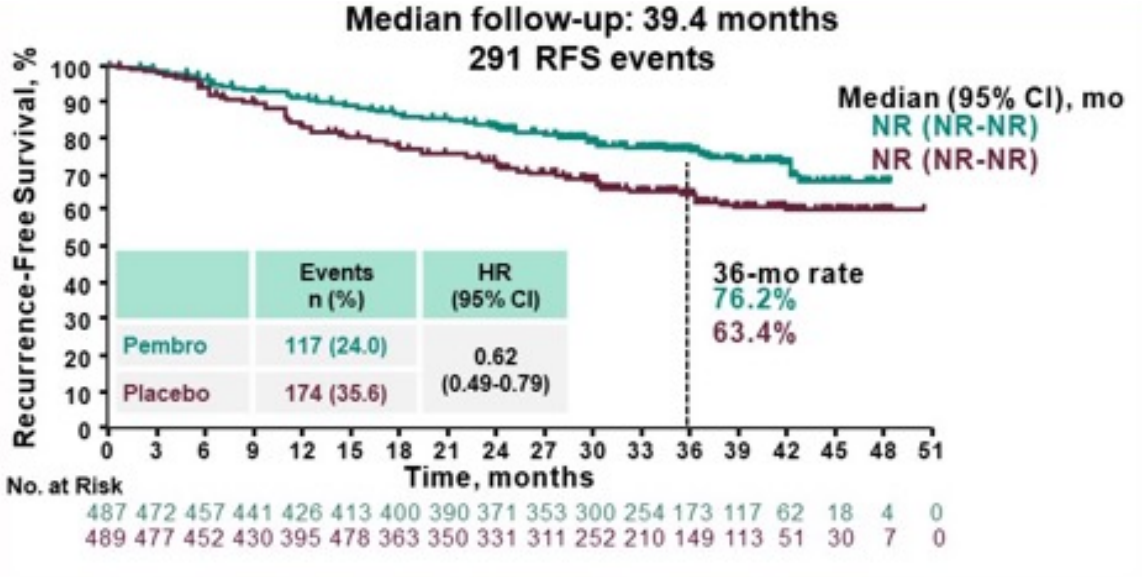
Improved RFS also in resected high-risk node-negative melanoma



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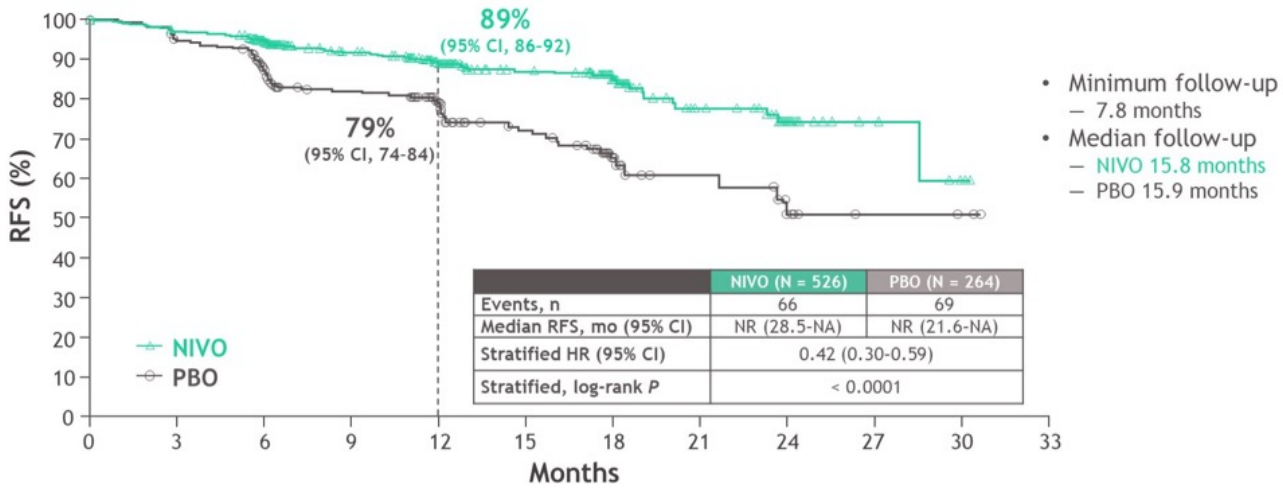

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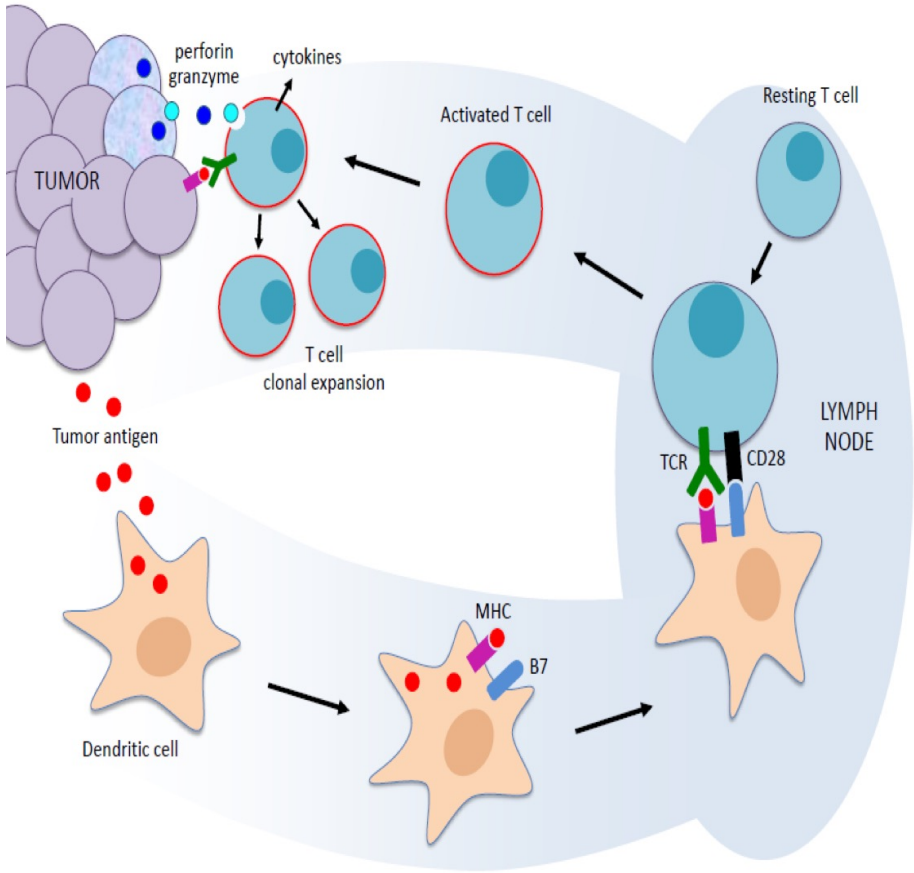
When is the best time to give peri-operative immunotherapy?

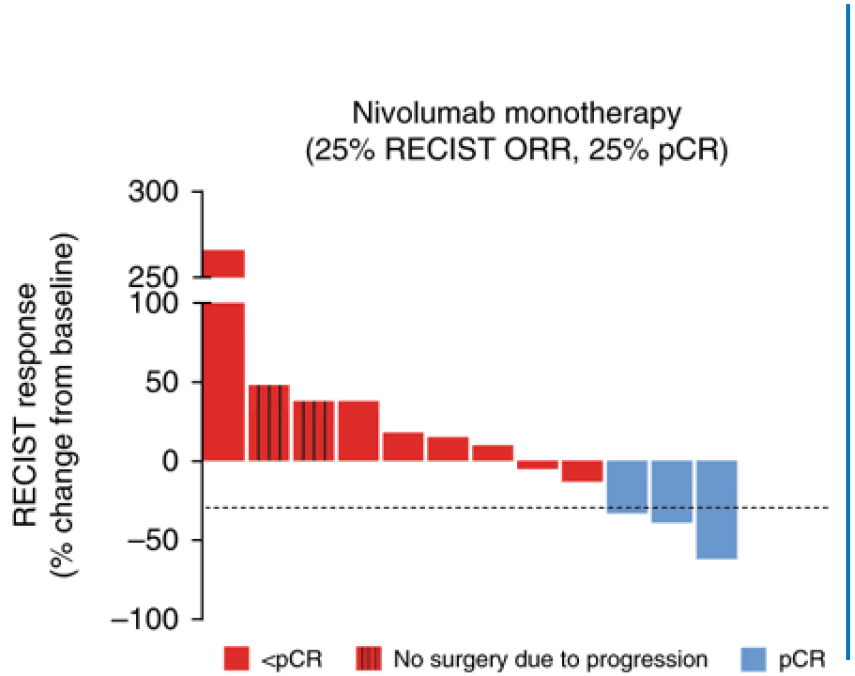
- Systemic therapy before definitive surgery may
  - Improve surgical outcomes
  - Reduce distant metastasis events by giving therapy sooner
  - Improve overall survival

- Beneficial mechanisms of neoadjuvant therapy for immunotherapy
  - Priming of resident tumor infiltrating lymphocytes → expansion

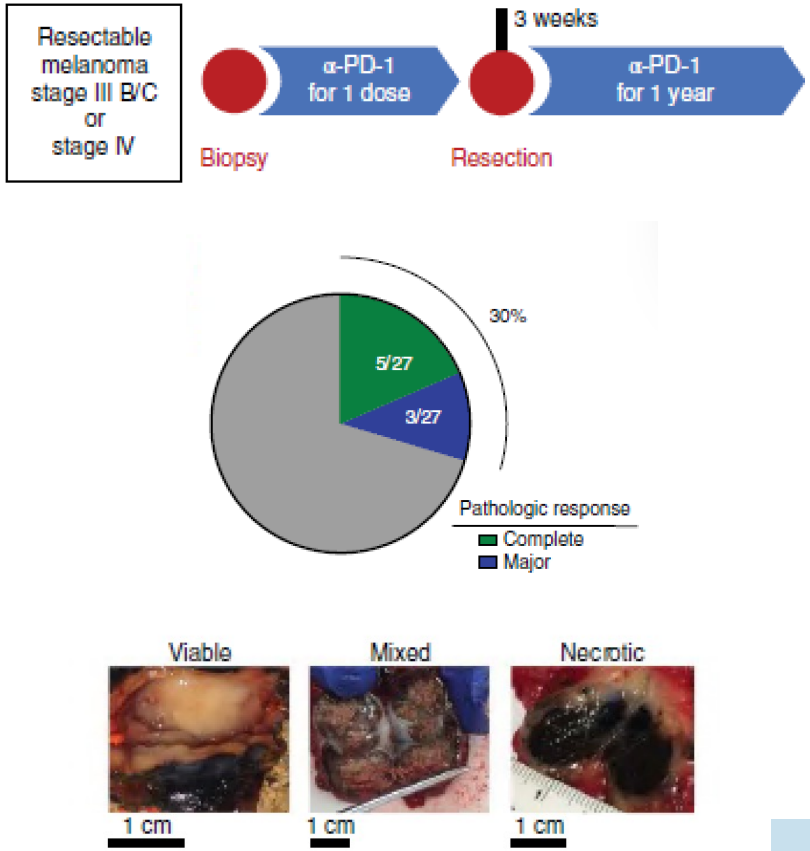


Nat Med 2019; 25:454–61

Higher response rates noted with anti-PD1 therapy prior to surgery



Amaria RN et al., *Nature Med* 2018.



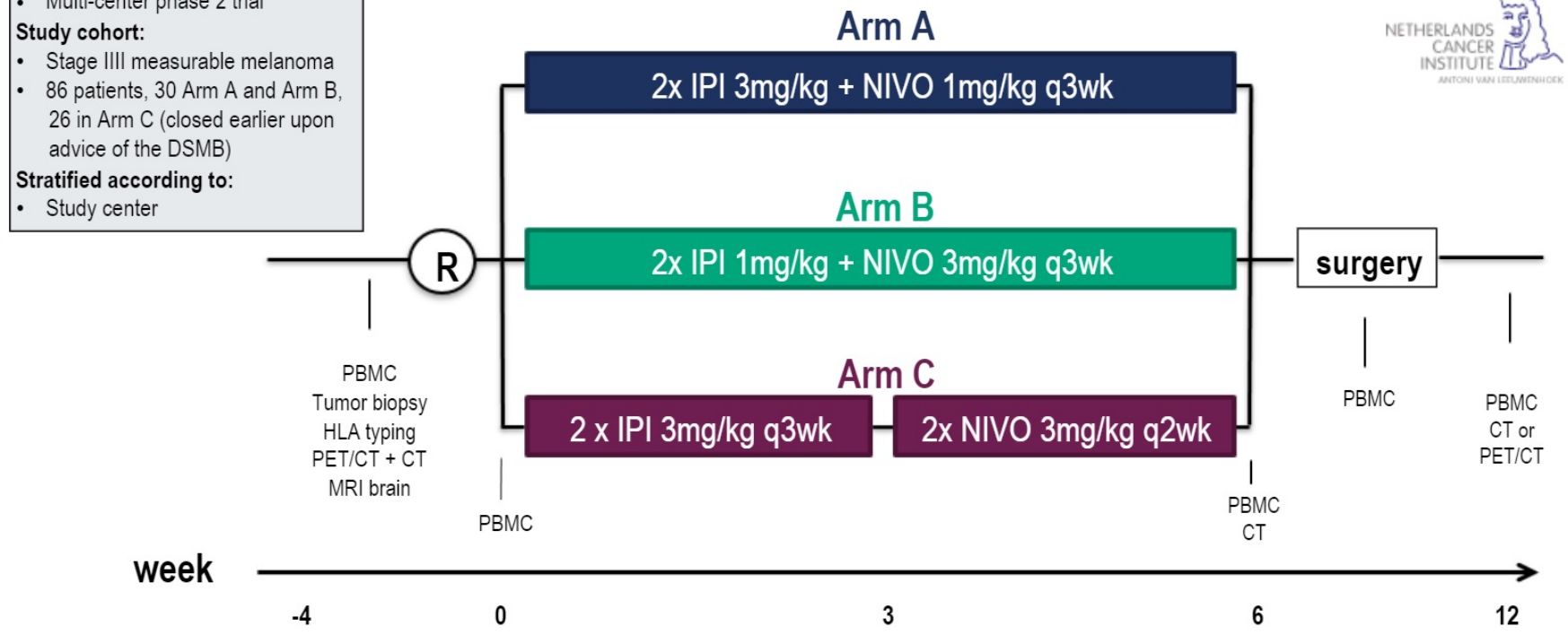
Mitchell TC et al., *Nature Med* 2019.

OPACIN-NEO: STUDY DESIGN

Study design:
- Multi-center phase 2 trial

Study cohort:
- Stage IIII measurable melanoma
- 86 patients, 30 Arm A and Arm B, 26 in Arm C (closed earlier upon advice of the DSMB)

Stratified according to:
- Study center



Dosing in Arm A, B, and C based on data from Blank, Rozeman, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink, Rozeman, et al. Ann Oncol 2017

Data lock: 28 Sep 2018
Median follow-up 8.3 months

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PATHOLOGIC RESPONSE – CENTRAL REVISION

	Treatment arm		
	A: 2xI3+N1 (n=30)	B: 2xI1+N3 (n=30)	C: 2xI3-2xN3 (n=26)
pRR	24 (80)	23 (77)	17 (65)
pCR	14 (47)	17 (57)	6 (23)
near pCR	7 (23)	2 (7)	6 (23)
pPR	3 (10)	4 (13)	5 (19)
pNR	6 (20)	7 (23)[a]	8 (31)
Not evaluable	-	-	1 (4)[b]

MUNICH 2018 ESMO congress

[a] One patient had only palliative resection of largest lymph node, [b] Surgery was not performed because of toxicity, this patient had a radiologic CR
Data are presented as n, (%).

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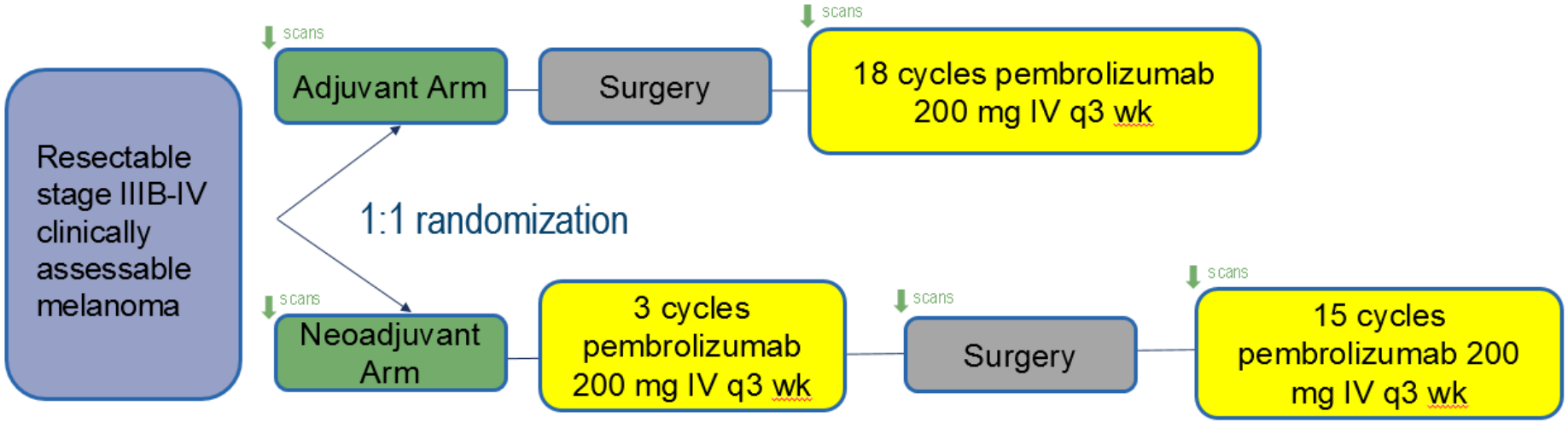
S1801 Study Schema

Primary endpoint: Event-free survival



⬇radiographic assessment (scans)

Additional criteria: strata included AJCC 8th ed. stage and LDH, adjuvant radiation allowed, concomitant radiation & pembrolizumab was not allowed, brain metastasis excluded, uveal melanoma excluded

Surgery type and extent was required to be pre-specified and carried out regardless of radiologic response to therapy

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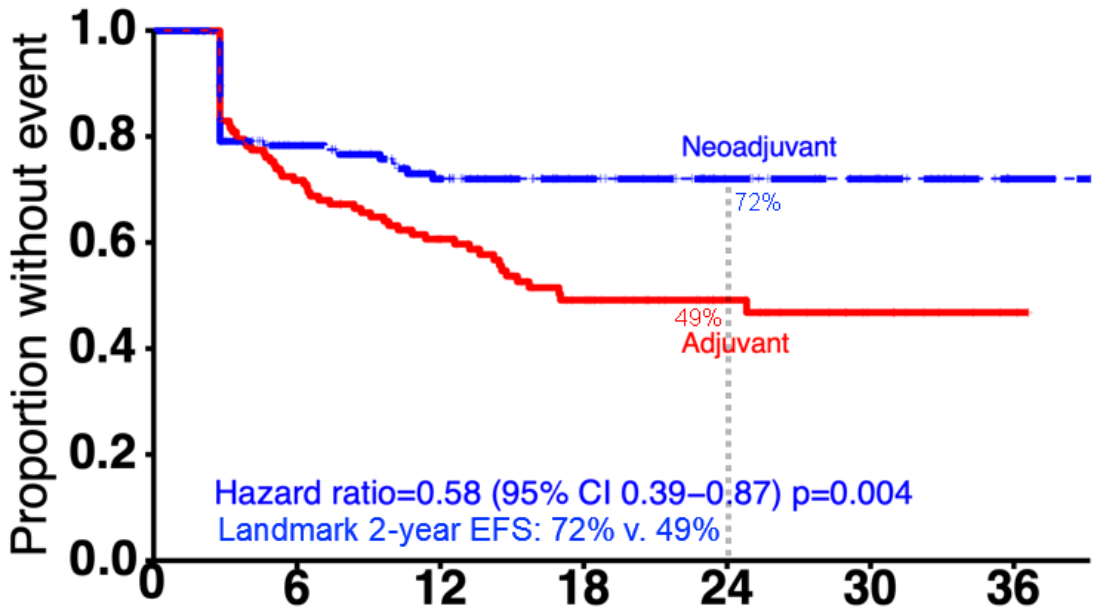
S1801 primary endpoint: Event-free survival



No. at Risk							
159	98	67	40	22	10	2	Adjuvant
154	96	69	46	25	17	1	Neoadjuvant

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S1801 Pathologic Response and Recurrence-Free Survival (RFS)

Pathologic response by blinded independent central review in submitted specimens

	n (%)	12-month RFS (95% CI)	24-month RFS (95% CI)
pCR	40 (38%)	92% (84-100)	89% (80-100)
pnCR	16 (15%)	87% (71-100)	87% (71-100)
pPR	27 (26%)	93% (83-100)	88% (77-100)
pNR	22 (21%)	76% (60-97)	70% (53-94)
MPR	56 (53%)	91% (83-99)	88% (80-98)
No MPR	49 (47%)	85% (75-96)	80% (70-93)

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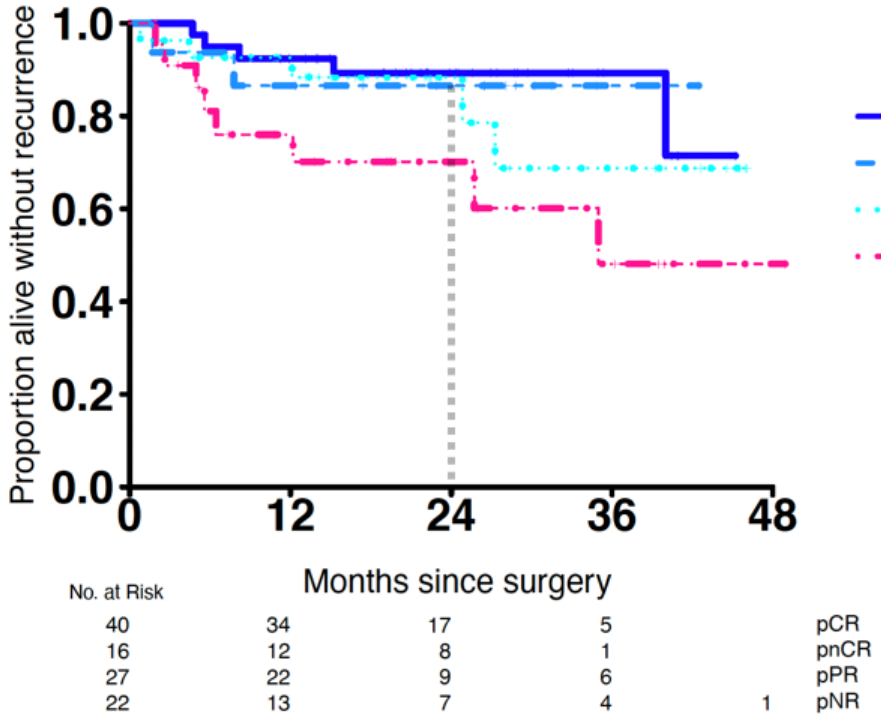
S1801 Recurrence-free survival (RFS) by pathologic response



Response	24-month RFS (95% CI)
pCR	89% (80-100)
pnCR	87% (71-100)
pPR	88% (77-100)
pNR	70% (53-94)

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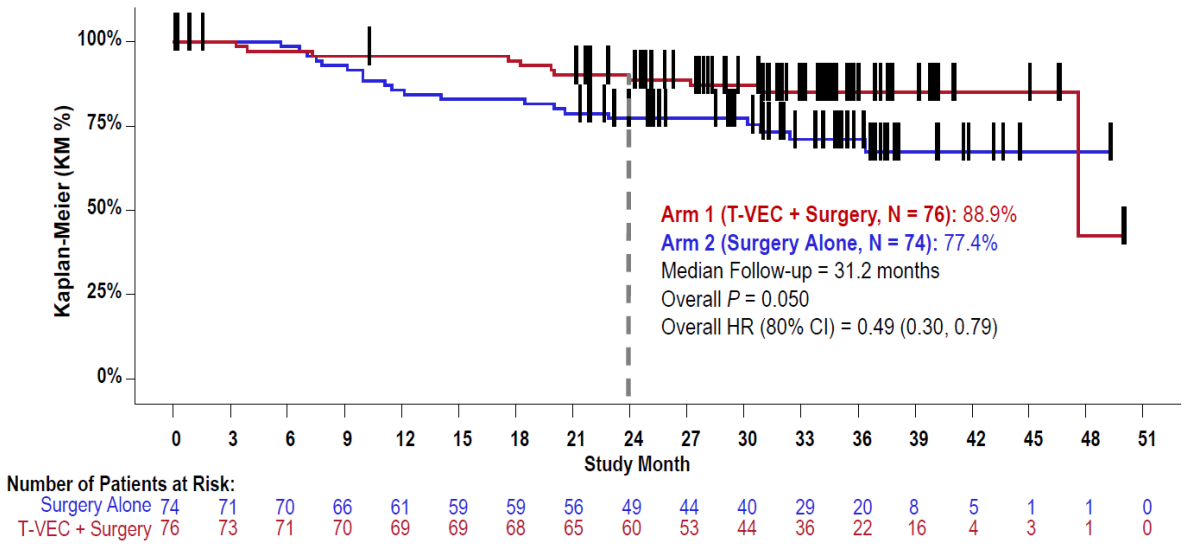
Other neoadjuvant strategies

Improved 2-Year OS With Neoadjuvant T-VEC



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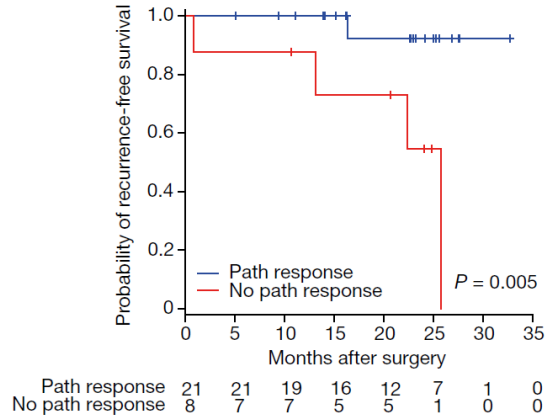
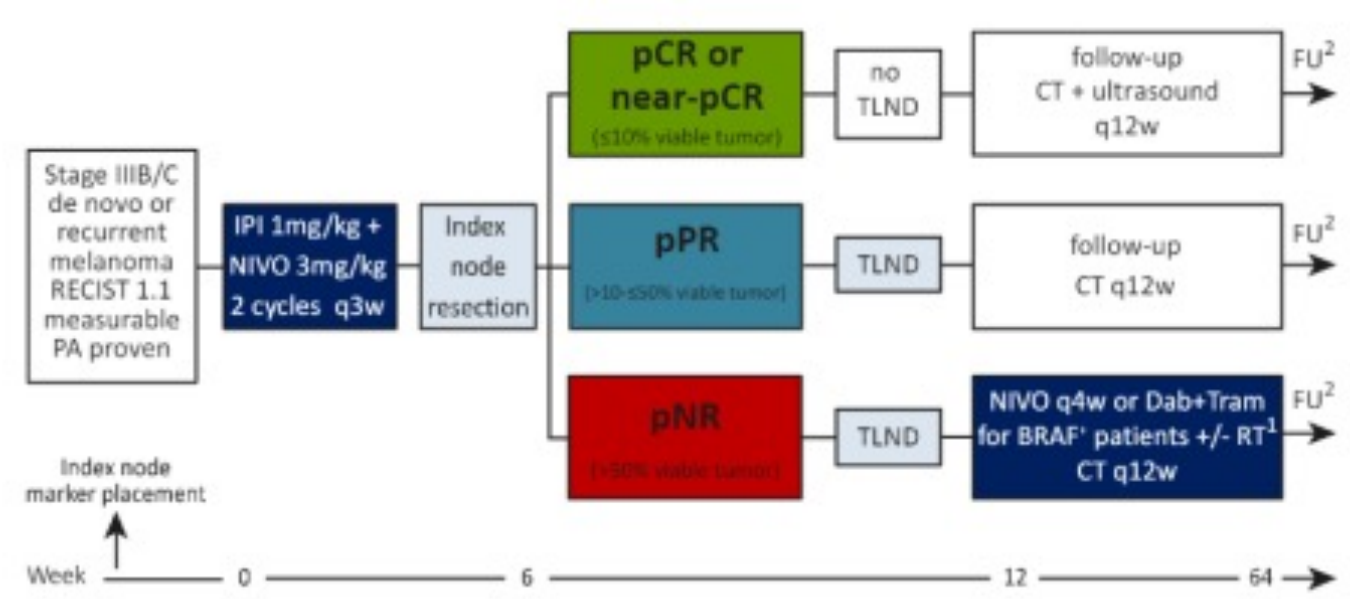
Improved RFS with neoadjuvant nivolumab/relatlimab



Amaria et al Nature 2022

What is the role of surgery, if a durable long-term anti-tumor immune response can be achieved with systemic therapy?

Prado Trial



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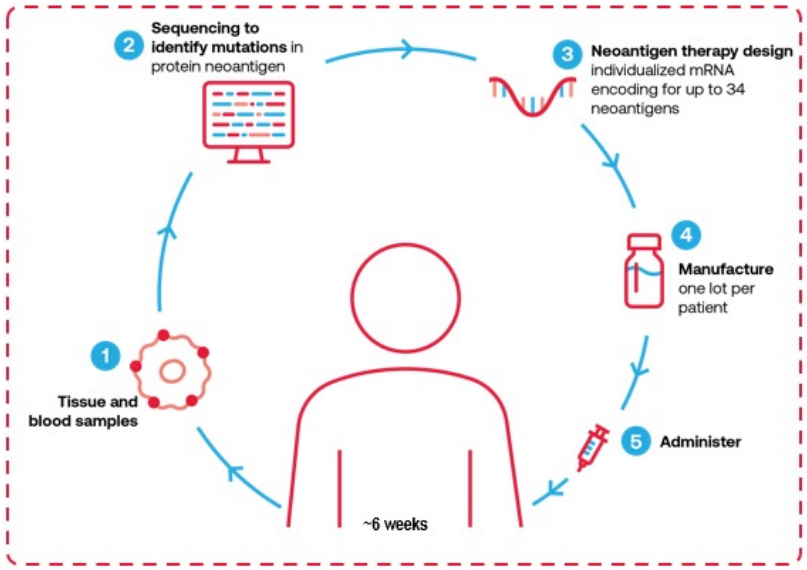
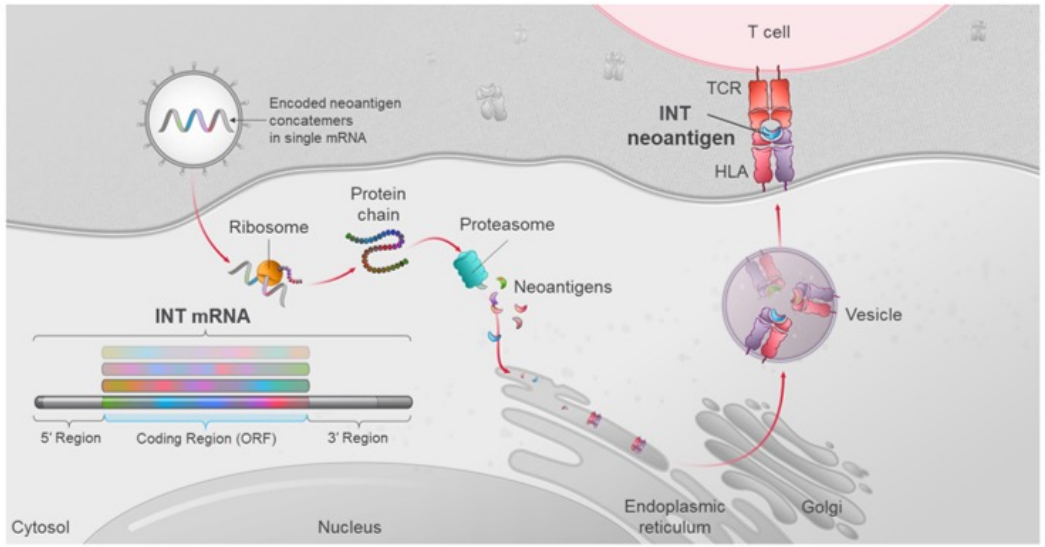
mRNA-4157 (V940): An individualized neoantigen therapy (INT) mechanism of action

- mRNA-4157 (V940) is a **customizable,** individualized neoantigen therapy encoding up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]



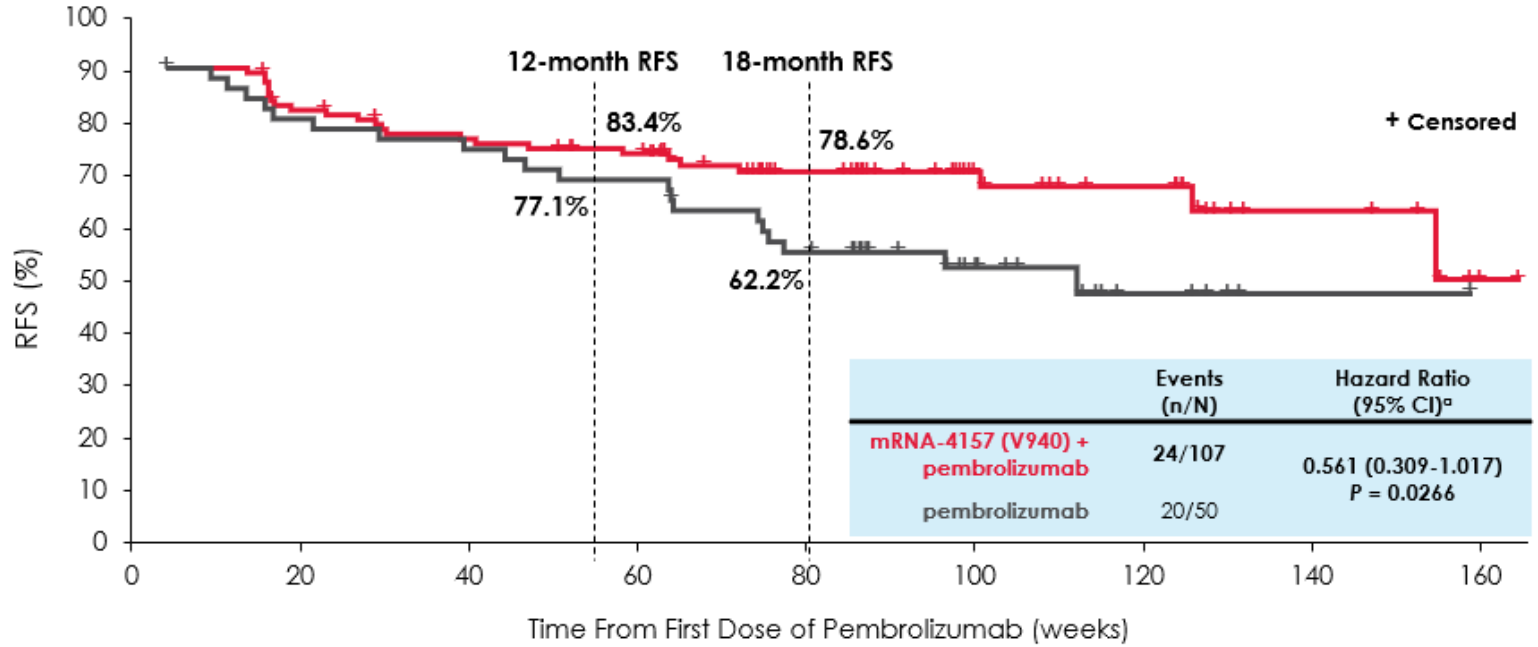


HLA, human leukocyte antigen; INT, individualized neoantigen therapy; mRNA, messenger RNA; ORF, open-reading frame; TCR, T-cell receptor.

1. Burris HA, et al. *J Clin Oncol* 2019;37(suppl 15). Abstract 2523. 2. Zhong S, et al. *Cancer Res* 80(suppl 16). Abstract 6539. 3. Wirth TC, Kühnel F. *Front Immunol* 2017;8:1848. 4. Ott PA, et al. *Nature* 2017;547:217–221. 5. Hu Z, et al. *Nat Med* 2021;27:515–525. 6. Ott PA, et al. *Cell* 2020;183:347-362. 7. Palmer CD, et al. *Nat Med* 2022;28:1619–1629.
Khattak A, et al. Presented at the American Association for Cancer Research® (AACR) Annual Meeting; April 14–19, 2023; Orlando, FL, USA. Oral presentation CT001. Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

Presented by Jeffrey Weber at ESMO 2023, used with permission

mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in recurrence-free survival (RFS) vs pembrolizumab



	Events (n/N)	Hazard Ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	24/107	0.561 (0.309-1.017) *P* = 0.0266
pembrolizumab	20/50	

Number at Risk

mRNA-4157 (V940) + pembrolizumab	107	92	85	73	49	24	20	8	1
pembrolizumab	50	42	40	37	28	13	6	1	0

CI, confidence interval; mRNA, messenger RNA; RFS, recurrence-free survival.
[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization. The *P* value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization.

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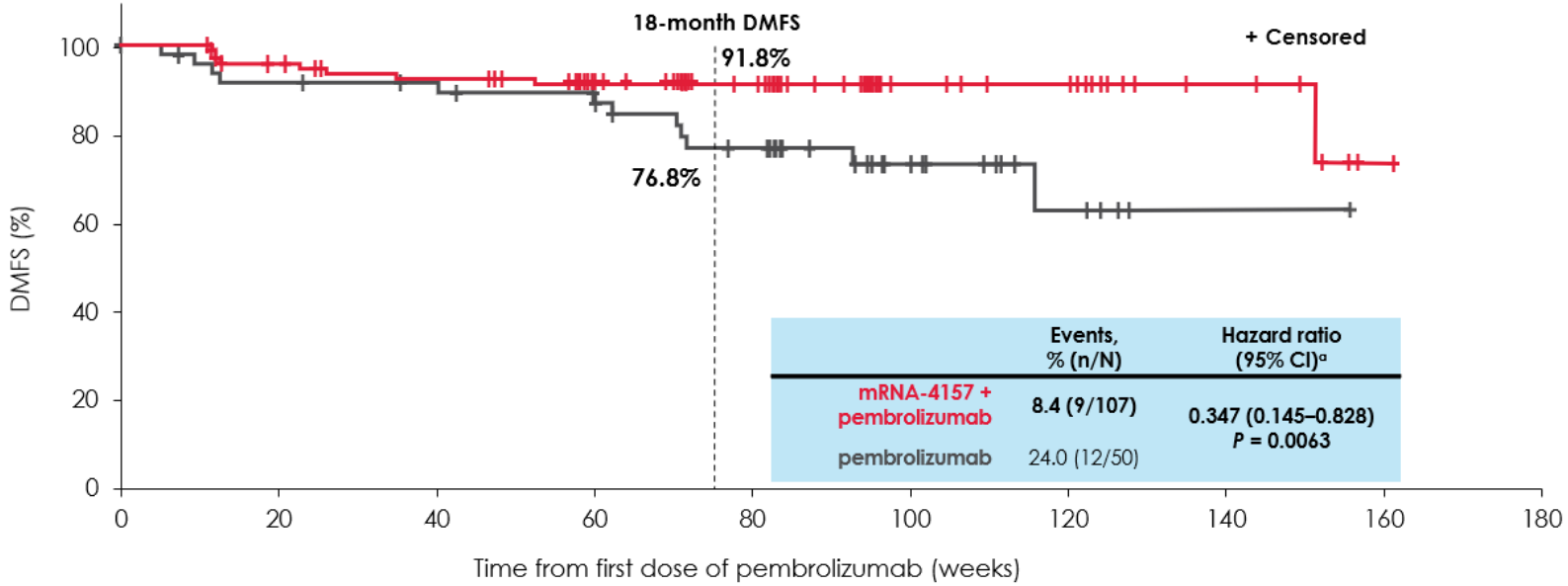
mRNA-4157 (V940) and pembrolizumab demonstrated an improvement in DMFS versus pembrolizumab monotherapy



Number at risk

mRNA-4157 + pembrolizumab	107	94	86	73	49	23	20	8	1
pembrolizumab	50	43	41	39	29	14	6	1	0

ITT population.
[a]The HR and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab is estimated using a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID versus stage IV) used for randomization. The p-value is based on a 1-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID versus stage IV) used for randomization.
CI, confidence interval; DMFS, distant metastasis-free survival; ITT, intent to treat; mRNA, messenger RNA.
Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

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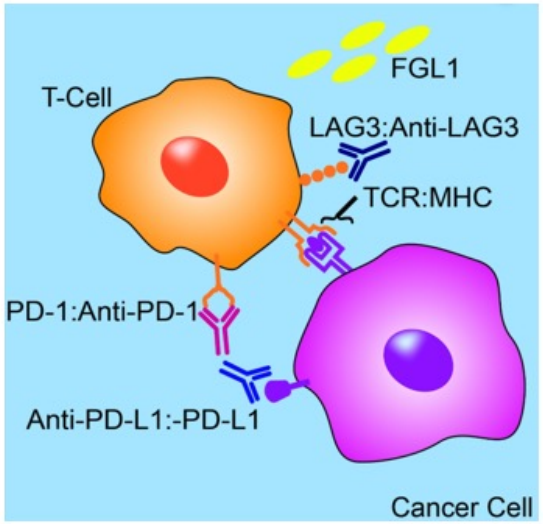
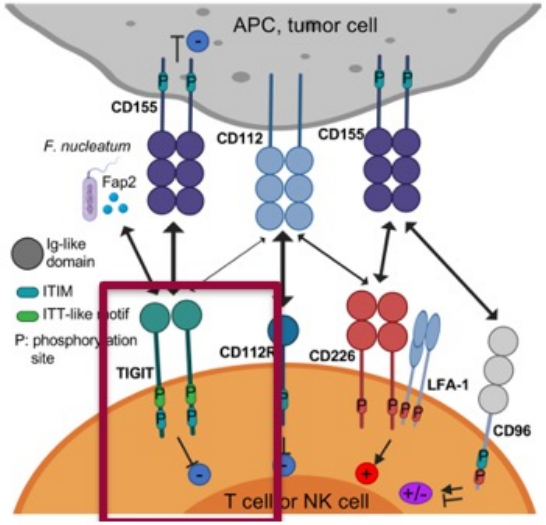
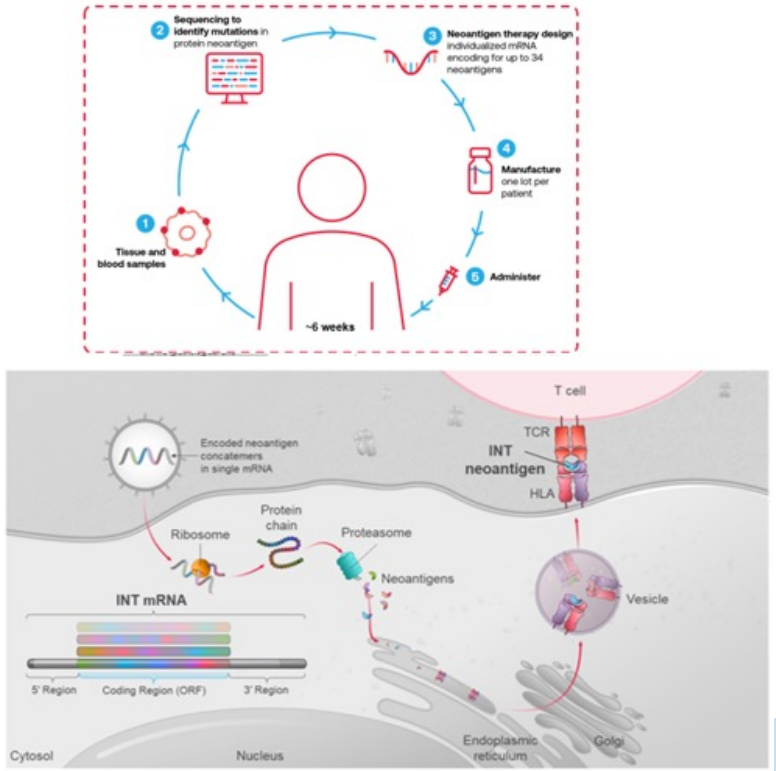
Adjuvant therapy in development



RELATIVITY-098 (stage III-IV):
Nivolumab + Relatlimab
R3767-ONC-2055 (stage IIC-IV):
Cemiplimab + Fianlimab



KEYVIBE-010 (stage IIB-IV):
Pembrolizumab + Vibostolimab



KEYNOTE-V940 (stage IIB-IV):
Pembrolizumab + V940 (mRNA-4157)

Schalper *et al. Cancer Cell*. 2019; Luke *et al. Clin Cancer Res*. 2012; Dummer *et al*. AACR. 2022; Kattak *et al*. ASCO. 2022

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Questions?

Thank you!

Cleveland Clinic

Every life deserves world class care.