ASCO 2023

Updates in Cutaneous Melanoma and Hepatocellular Carcinoma

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Disclosures:

- Consulting relationship with Replimune (2023)
- Consulting relationship with Immunocore (Ongoing)

Hepatocellular Carcinoma Updates

Advanced HCC management – Current Landscape

- Atezolizumab plus Bevacizumab [Child-Pugh Class A/B]
- Tremelimumab plus Durvalumab
- Lenvatinib [Child-Pugh Class A]
- Sorafenib [Child-Pugh Class A/B7]
- Single agent Durvalumab
- Single agent Pembrolizumab or Nivolumab

NCCN 2023

Efficacy, safety and patient reported outcomes (PROs) from the phase III **IMbrave050** trial of adjuvant atezolizumab (atezo) + bevacizumab (bev) vs active surveillance in patients with hepatocellular carcinoma (HCC) at high risk of disease recurrence following resection or ablation.

Abstract 4002
Presented by Dr. Masatoshi Kudo
Oral Abstract Session

- Currently, there is no standard of care for adjuvant systemic therapy in HCC, post surgery or ablation.
- The annual recurrence rate of HCC after surgical resection is ≥10% and reaches 70–80% after 5 years

Saito et al. Nature, Modern Pathology; 2020

IMbrave050 Study Design (Phase III)

HCC patients, s/p ablation or surgery
High-risk features
ECOG PS 0-1
CP Class A
Disease free
No extra-hepatic disease or macrovascular invasion

Randomized 1:1

Atezolizumab plus Bevacizumab for 17 cycles (12 months); N = 334

Active surveillance (SOC); N = 334

High Risk Features:
Tumor > 5 cm
>3 tumors
Microvascular invasion
Minor macrovascular invasion (Vp1/Vp2)
Grade 3 or higher histology

>87.87% of the study patients underwent hepatic resection

IMbrave050 Result Summary

	Atezo plus Bev (N=334)	Active surveillance (N=334)
12-month recurrence free-survival rate	78%	65%

Median follow-up of 17.4 months

Data also presented at AACR 2023 by Chow et al.

The patient reported outcomes (PRO) analysis showed that patients in both arms did not experience any clinically meaningful deterioration at any time in:

- Health-related QOL
- Physical Functioning
- Role functioning
- Emotional Functioning
- Social Functioning

Scores did not differ between (Atezo-Bev and Surveillance arms)

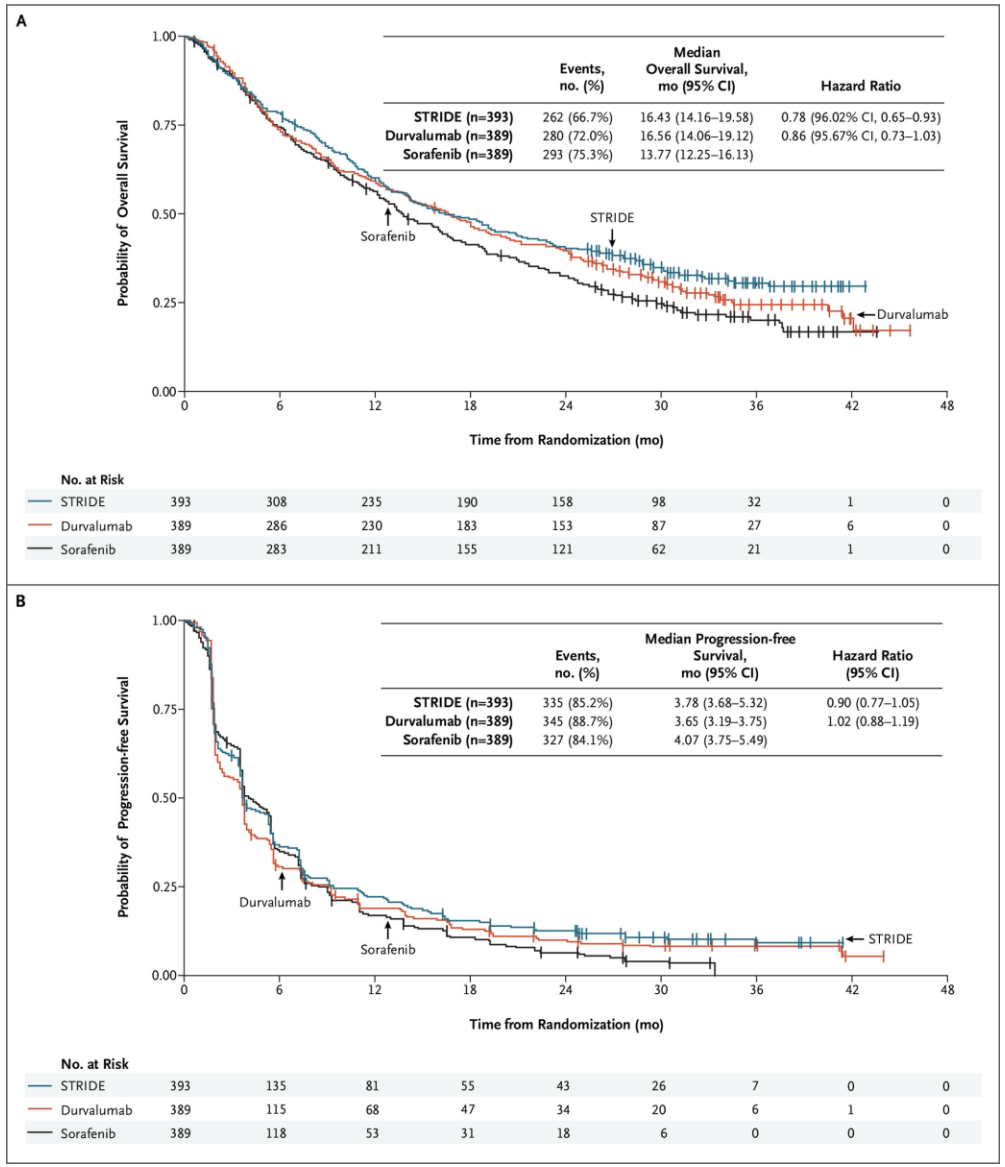
Questionnaire used: IL42–EORTC QLQ-C30 (reduced)

Temporal patterns of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC). Abstract 4073: George Lau, et al.

Background: In the Phase 3 HIMALAYA study in uHCC, STRIDE (Single T Regular Interval D) significantly improved OS vs. sorafenib (S) and had manageable safety.

STRIDE is FDA approved for uHCC in the US {front-line setting).

In this exploratory post hoc analysis, the authors assessed temporal patterns of imAEs for the STRIDE regimen in HIMALAYA.



(Abou-Alfa et al. *NEJM Evid* 2022)

Temporal patterns of immune-mediated adverse events (imAEs) with tremelimumab (T) plus durvalumab (D) in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma (uHCC). Abstract 4073: George Lau, et al.

Results: 388 (STRIDE) and 374 (S) pts were included in the safety analysis.

Any grade treatment-related AEs (TRAEs) and Grade 3 or 4 TRAEs were less frequent for STRIDE (75.8% and 25.8%, respectively) versus S (84.8% and 36.9%, respectively).

Any grade imAEs and Grade 3 or 4 imAEs occurred in 35.8% and 12.6% of pts, respectively for STRIDE. These were most likely to occur within the first 3 months after treatment.

Conclusion: Any grade TRAEs and Grade 3 or 4 TRAEs were less frequent for STRIDE versus S. Although imAEs with STRIDE could occur at any time, most were observed within the first three months after treatment.

Pts with event – n (%)	STRIDE (n=388)	STRIDE (n=388)
	Any grade	Max Grade 3 or 4
Time from first dose to imAE, months		
≤1	69 (17.8)	34 (8.8)
>1 to ≤2	43 (11.1)	6 (1.5)
>2 to ≤3	23 (5.9)	2 (0.5)
>3 to ≤6	23 (5.9)	2 (0.5)
>6	23 (5.9)	7 (1.8)

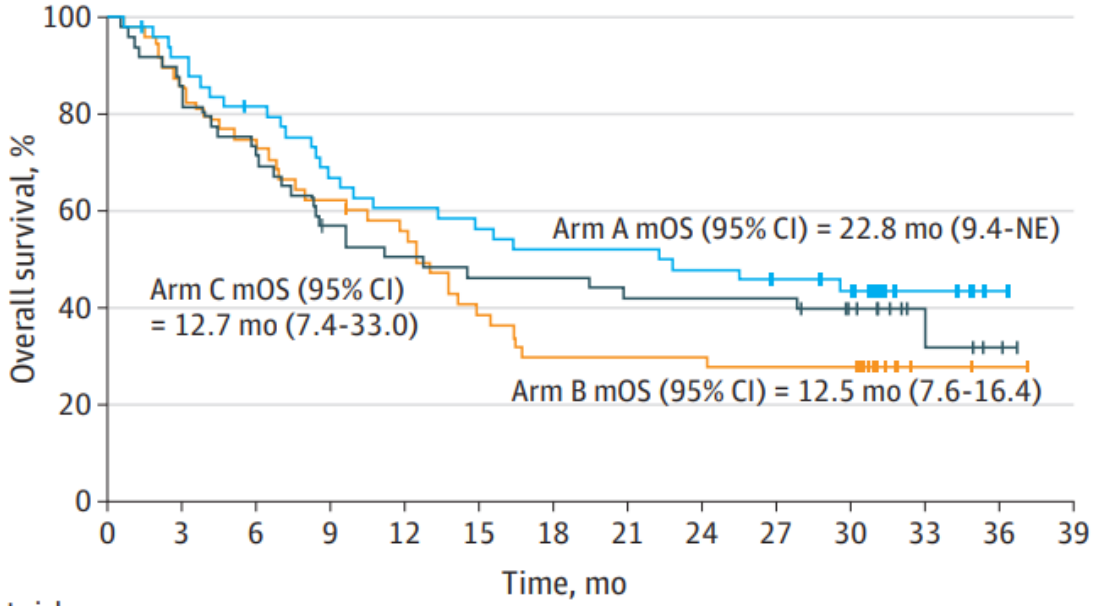
Salvage ipilimumab plus nivolumab in advanced hepatocellular carcinoma after prior anti-PD-(L)1 blockade. Abstract 4091; Stephanie Leigh Alden, MD

Background

JAMA Oncology | Original Investigation

Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib

The CheckMate 040 Randomized Clinical Trial



Phase 1-2 Study

N=148

Patients randomized 1:1:1

Study results led to accelerated FDA approval of Ipilimumab (3 mg/kg) plus Nivolumab (1 mg/kg) [x4] followed by Nivolumab 240 mg every 2 weeks [arm A regimen]

Yao et al. JAMA Oncology 2020

Salvage ipilimumab plus nivolumab in advanced hepatocellular carcinoma after prior anti-PD-(L)1 blockade. Abstract 4091; Stephanie Leigh Alden, MD

Methods: Multi-center retrospective review of HCC patients who had received at least one dose of anti-PD-(L)1 therapy prior to receiving ipilimumab plus nivolumab.

Results:

N=32 (Child-Pugh A 66%)

Prior anti-PD-(L)1 containing regimens included atezolizumab plus bevacizumab (50%, n = 16), other VEGF plus anti-PD-(L)1 combination (31%, n = 10), and anti-PD-(L)1 monotherapy (19%, n = 6).

The objective response rate (ORR) was 22% (1 CR, (3%), 6 PR (19%))
Additional responses: 8 SD (25%), 16 PD (50%), and 1 NE (3%).

Among patients who had an OR to Ipi-Nivo, none had an objective response to prior anti-PD-(L)1 treatments.

Conclusion: Ipi-Nivo has clinical activity in patients with advanced HCC who previously received anti-PD-(L)1 therapy, supporting this regimen as second line therapy in advanced HCC.

Updates in Cutaneous Melanoma

- RELATIVITY-047 Update
- KEYNOTE 716 Update
- New anti-LAG3 and anti-PD1 combination

Melanoma: Current Landscape of systemic immune therapy

Stage IV (front line)	Clinical Trial Ipilimumab plus Nivolumab Relatlimab plus Nivolumab (RELATIVITY-047) Nivolumab Pembrolizumab
Stage III (Adjuvant)	Nivolumab Pembrolizumab
Stage IIB-IIC (Adjuvant)	Pembrolizumab (KEYNOTE 716)

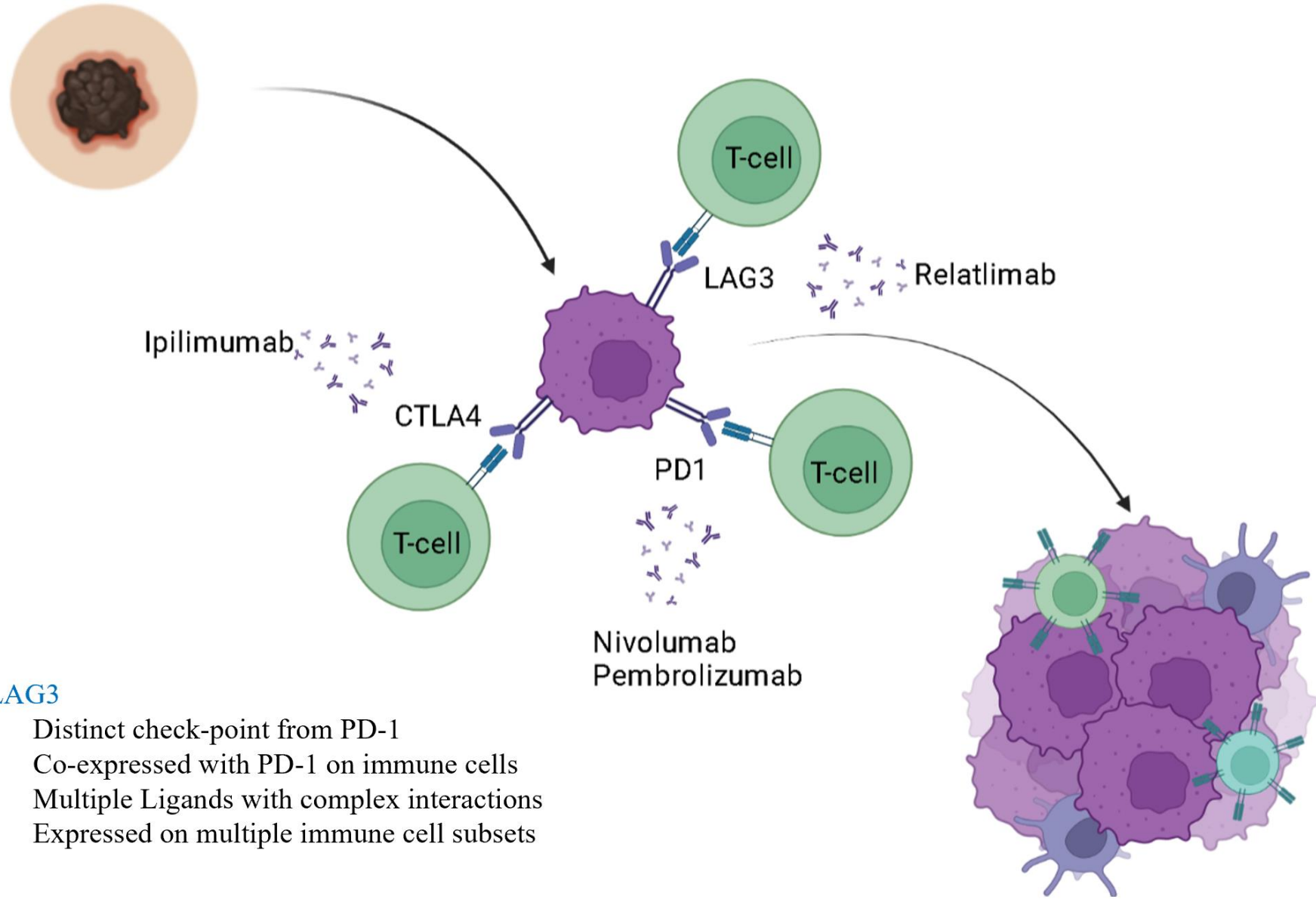
Abstract 9502 - Oral abstract Session

Presented by Dr. Hussein Tawbi

Nivolumab (NIVO) plus relatlimab (RELA) vs. NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047

In RELATIVITY-047, RELA plus NIVO demonstrated superior PFS as compared to NIVO, this led to FDA approval of Relatlimab plus Nivolumab in March 2022.

Tawbi et al. NEJM; 2022



LAG3

- Distinct check-point from PD-1
- Co-expressed with PD-1 on immune cells
- Multiple Ligands with complex interactions
- Expressed on multiple immune cell subsets

Study design

- RELATIVITY-047 is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated, unresectable, or metastatic melanoma
- ECOG PS 0–1

R 1:1

NIVO 480 mg + RELA 160 mg FDC IV Q4W

NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[a]

Secondary endpoints
- OS[b]
- ORR by BICR[c]

Stratified by: LAG-3,[d] PD-L1,[e] *BRAF*, and AJCC v8 M stage
Endpoints were tested in hierarchy: PFS → OS → ORR

Database lock	March 9, 2021	October 28, 2021	October 27, 2022
Min. follow-up[f]	1.3 months	8.7 months	21.0 months
Median follow-up	13.2 months	19.3 months	25.3 months
Endpoint(s)	PFS per BICR	OS, ORR per BICR, and updated PFS per BICR	Updated PFS per BICR, OS, and ORR per BICR

With permission, courtesy Dr. Tawbi

Baseline Characteristics

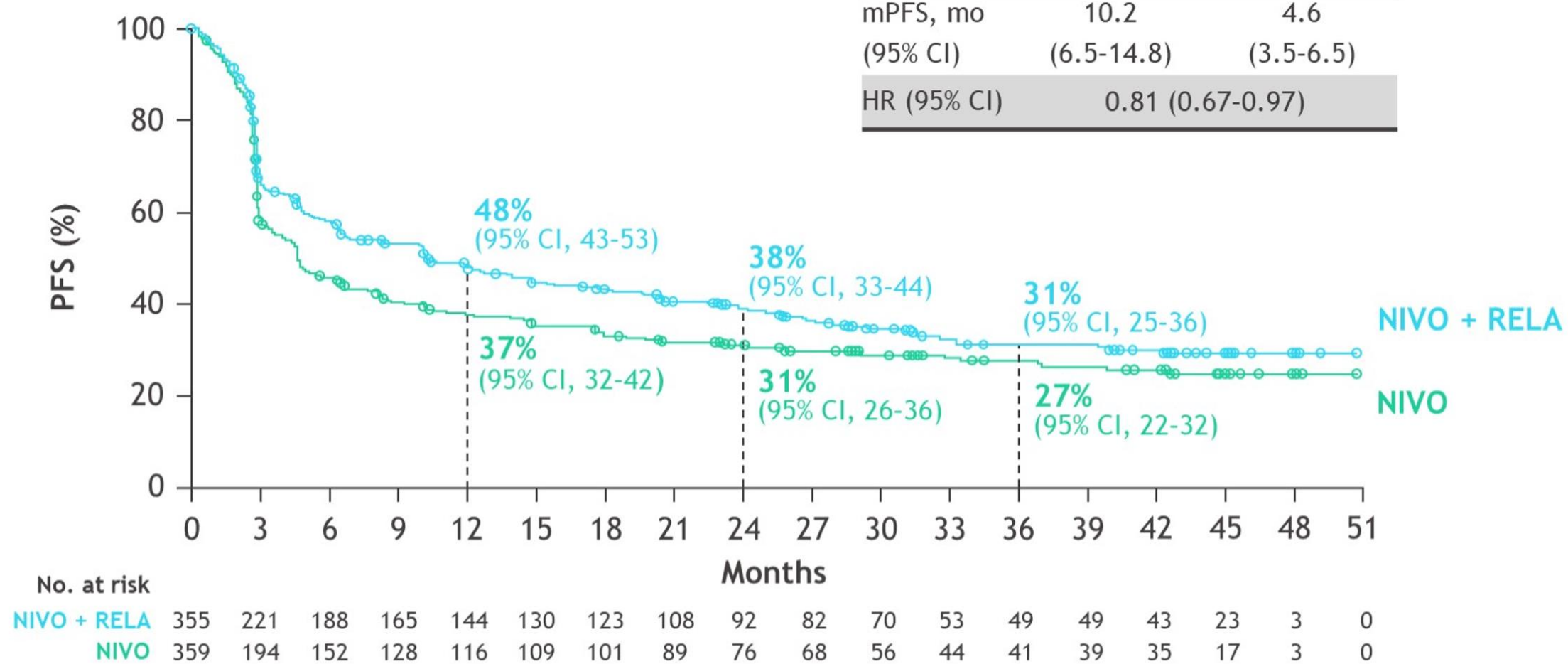
Table 1. Patient Demographics and Disease Characteristics at Baseline.*

Characteristic	Relatlimab–Nivolumab (N=355)	Nivolumab (N=359)	Total (N=714)
Median age (range) — yr	63.0 (20–94)	62.0 (21–90)	63.0 (20–94)
Female sex — no. (%)	145 (40.8)	153 (42.6)	298 (41.7)
Previous systemic therapy — no. (%)			
Adjuvant	31 (8.7)	26 (7.2)	57 (8.0)
Neoadjuvant	2 (0.6)	1 (0.3)	3 (0.4)
Unknown or other	0	2 (0.6)	2 (0.3)
Metastasis stage — no. (%)†			
M0	35 (9.9)	23 (6.4)	58 (8.1)
M1a or b	162 (45.6)	195 (54.3)	357 (50.0)
M1c	151 (42.5)	127 (35.4)	278 (38.9)
M1d	6 (1.7)	11 (3.1)	17 (2.4)
Melanoma subtype classification — no. (%)			
Cutaneous acral	41 (11.5)	41 (11.4)	82 (11.5)
Cutaneous nonacral	249 (70.1)	254 (70.8)	503 (70.4)
Mucosal	23 (6.5)	28 (7.8)	51 (7.1)
Other	42 (11.8)	36 (10.0)	78 (10.9)
ECOG performance status — no. (%)‡			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
LDH level — no. (%)			
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
>2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Median tumor burden (range) — mm§	59.0 (10–317)	54.5 (10–548)	
Sites with ≥1 lesion — no. (%)¶			
1	127 (35.8)	158 (44.0)	285 (39.9)
2	111 (31.3)	102 (28.4)	213 (29.8)
≥3	112 (31.5)	87 (24.2)	199 (27.9)
Stratification factors — no. (%)			
LAG-3 expression			
≥1%	268 (75.5)	269 (74.9)	537 (75.2)
<1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression			
≥1%	146 (41.1)	147 (40.9)	293 (41.0)
<1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status			
Patients with *BRAF* mutations	136 (38.3)	139 (38.7)	275 (38.5)
Patients without *BRAF* mutations	219 (61.7)	220 (61.3)	439 (61.5)
Metastasis stage with LDH level			
M0, M1 and normal LDH level	232 (65.4)	237 (66.0)	469 (65.7)
M1 and elevated LDH level	123 (34.6)	122 (34.0)	245 (34.3)

Tawbi et al. NEJM; 2022

Updated primary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo	10.2	4.6
(95% CI)	(6.5-14.8)	(3.5-6.5)
HR (95% CI)	0.81 (0.67-0.97)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.

With permission, courtesy Dr. Tawbi

Safety summary

AE, n (%)	NIVO + RELA (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	352 (99)	161 (45)	344 (96)	139 (39)
TRAE	301 (85)	78 (22)	262 (73)	43 (12)
Leading to discontinuation	61 (17)	34 (10)	31 (9)	14 (4)
Treatment-related deaths[a]	4 (1)		2 (1)	

With permission, courtesy Dr. Tawbi

Table 2. Summary of Adverse Events.

Adverse Event	Relatlimab–Nivolumab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
	number of events (percent)			
Any adverse event	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
Treatment-related adverse event	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
Led to discontinuation of treatment	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
Treatment-related adverse event in ≥10% of patients in the relatlimab–nivolumab group				
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
Immune-mediated adverse event*				
Hypothyroidism or thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea or colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

RELA plus Nivo vs. Ipi plus Nivo: Toxicity Considerations

Immune Mediated AE (Any Grade)	RELA+NIVO (RELATIVTY) N=355	IPI + NIVO (Check Mate 067) N=313
Hypothyroidism	18% (including thyroiditis)	17%
Rash	9.3%	30% ↑
Diarrhea/colitis	6.8%	Diarrhea 45% Colitis: 13% ↑
Pneumonitis	3.7%	7% ↑
Hypophysitis	2.5%	8% ↑
Hepatitis	5.6%	17% (AST elevation) 19% (ALT elevation) ↑

Tawbi et al. NEJM; 2022

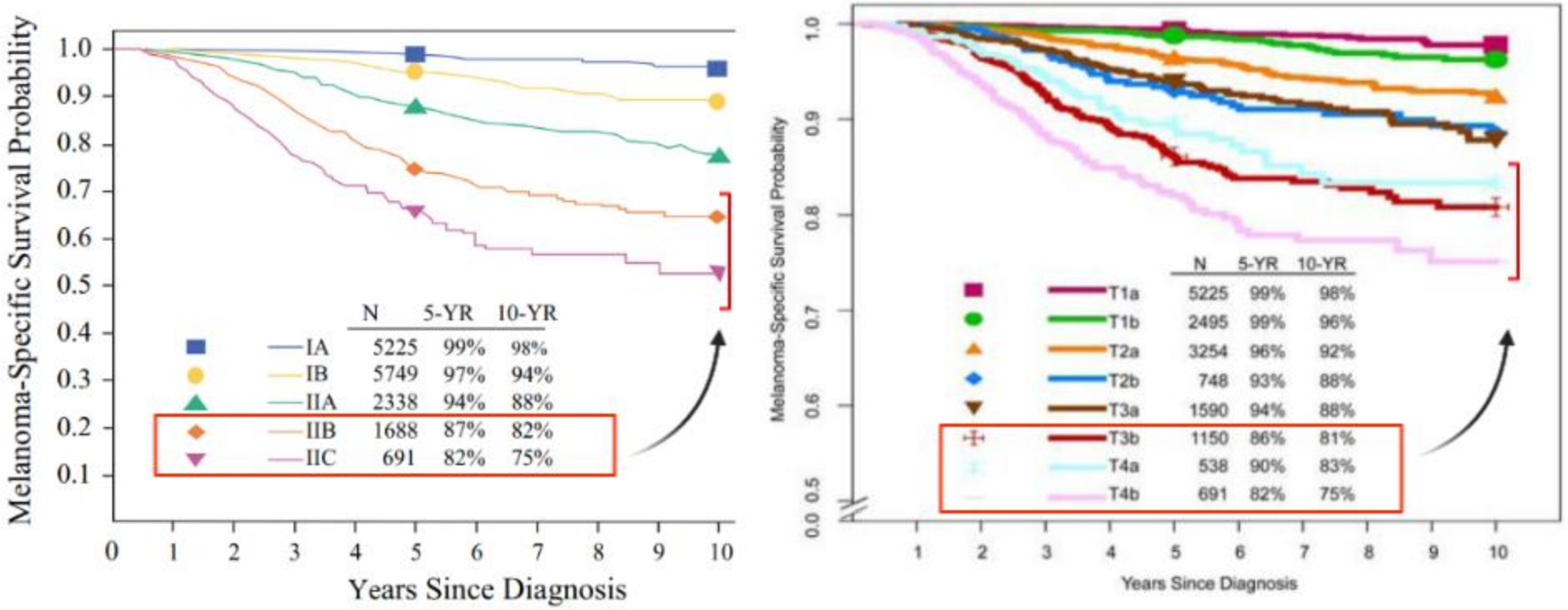
Update in Melanoma Adjuvant Therapy

Pembrolizumab vs. Placebo as Adjuvant Therapy in Stage IIB or IIC Melanoma: Final Distant Metastasis-Free Survival Analysis In the KEYNOTE-716 Study

Presented by Dr. Jason Luke

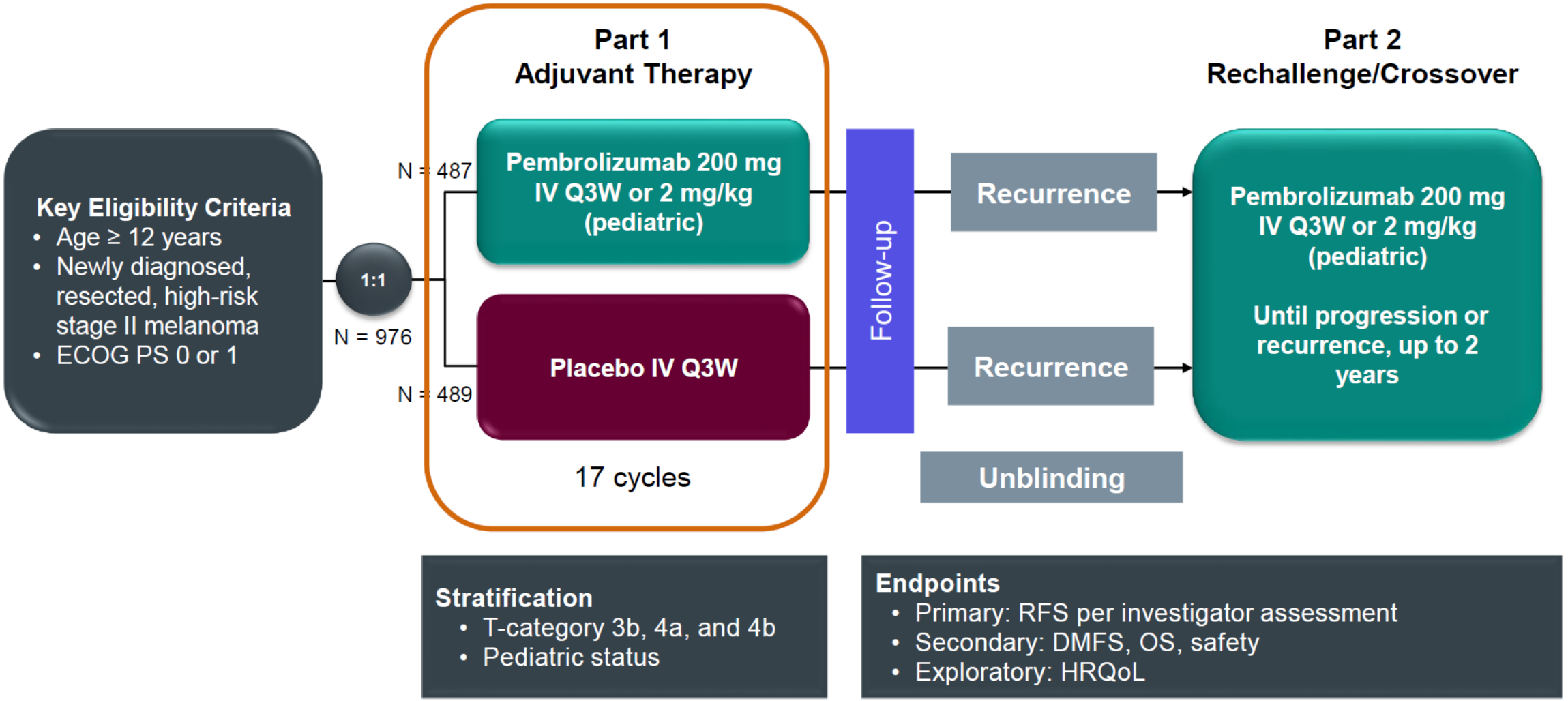
Rationale for using adjuvant therapy in High-risk Stage II Melanoma

AJCC 8th Ed. Stage			
Stage IIB	T3b (>2-4 mm + ulceration)	N0	M0
	T4a (>4mm w/o ulceration)	N0	M0
Stage IIC	T4b (>4mm + ulceration)	N0	M0



Gershenwald et al. CA Cancer J Clin. 2017; 67(6): 472–492
Gershenwald and Scolyer. Ann Surg Oncol (2018) 25:2105–2110

KEYNOTE-716 Study Design
(NCT03553836)



With Permission, courtesy, Dr. Jason Luke

Relevant Baseline Characteristics:

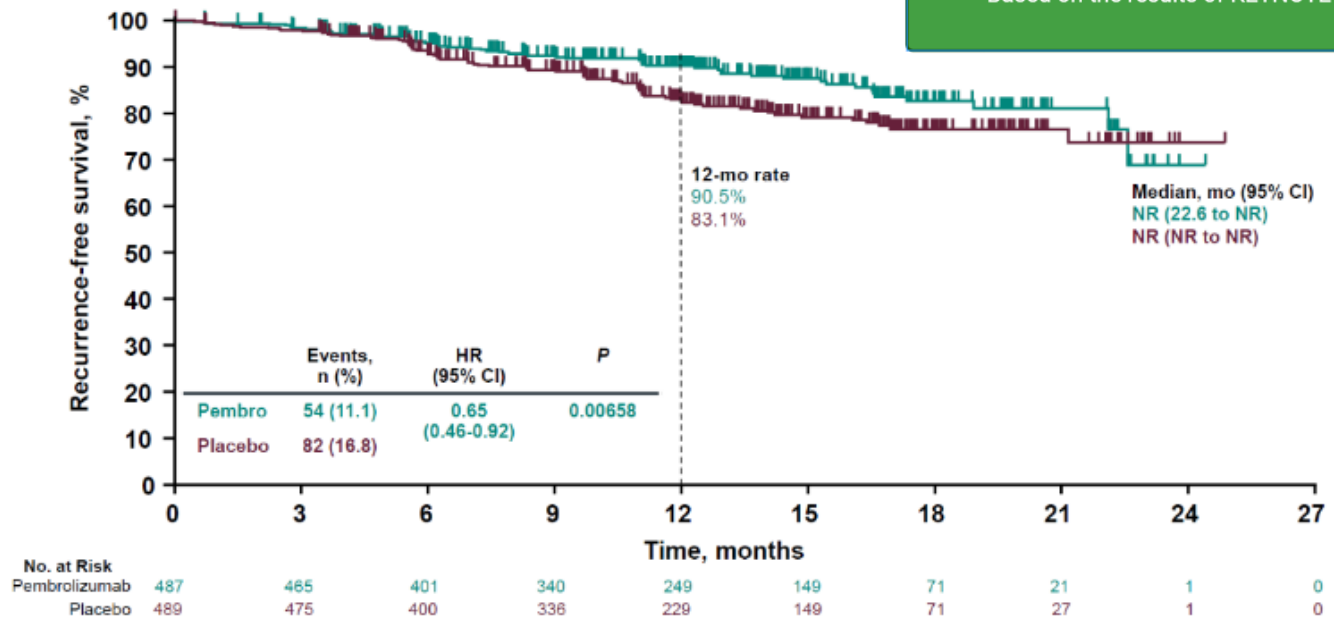
	Pembrolizumab N =487	Placebo N = 489
T Category		
T3b	200 (41.1)	201 (41.1)
T4a	113 (23.2)	116 (23.7)
T4b	172 (35.3)	172 (35.2)
Disease Stage		
IIB	309 (63.4)	316 (64.6)
IIC	171 (35.1)	169 (34.6)

Approximately one third of the patients had T4b disease or stage IIC disease

Recurrence-Free Survival (Primary Endpoint)

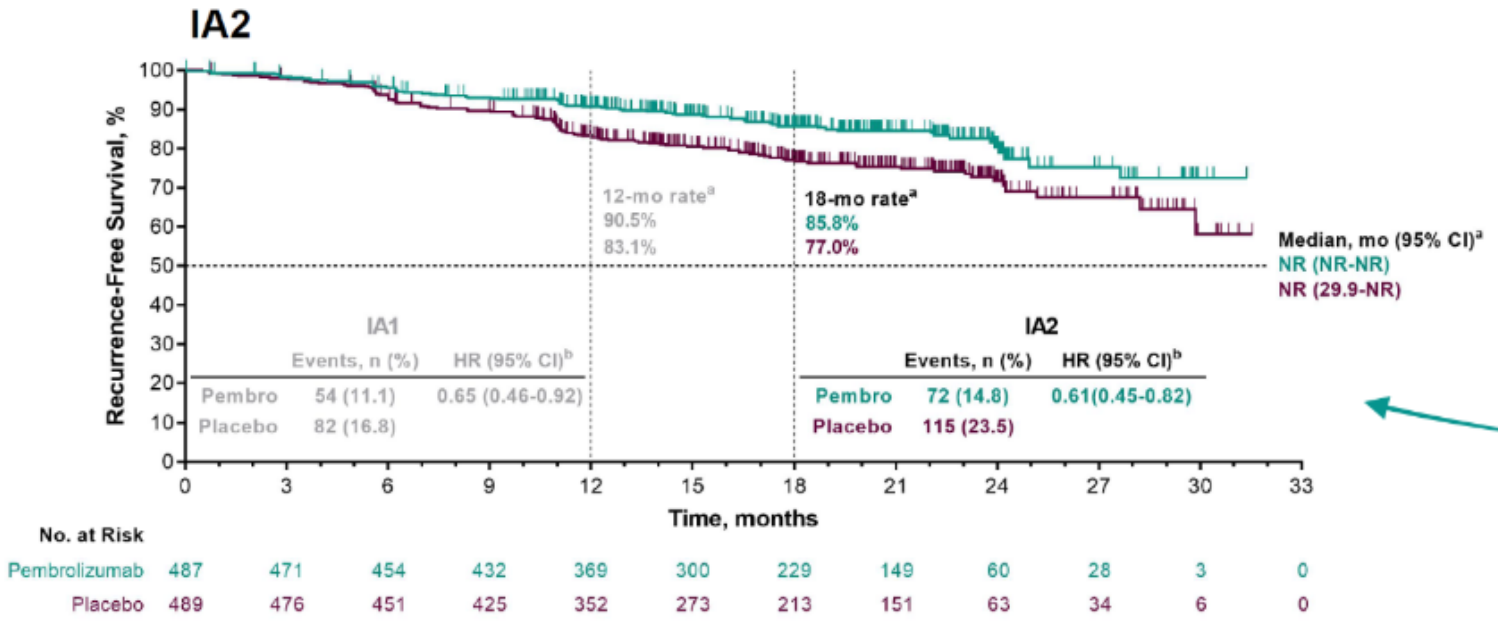
December 3rd 2021
Based on the results of KEYNOTE-716 (NCT03553836) FDA approved pembrolizumab for adjuvant treatment of Stage IIB or IIC melanoma

Results



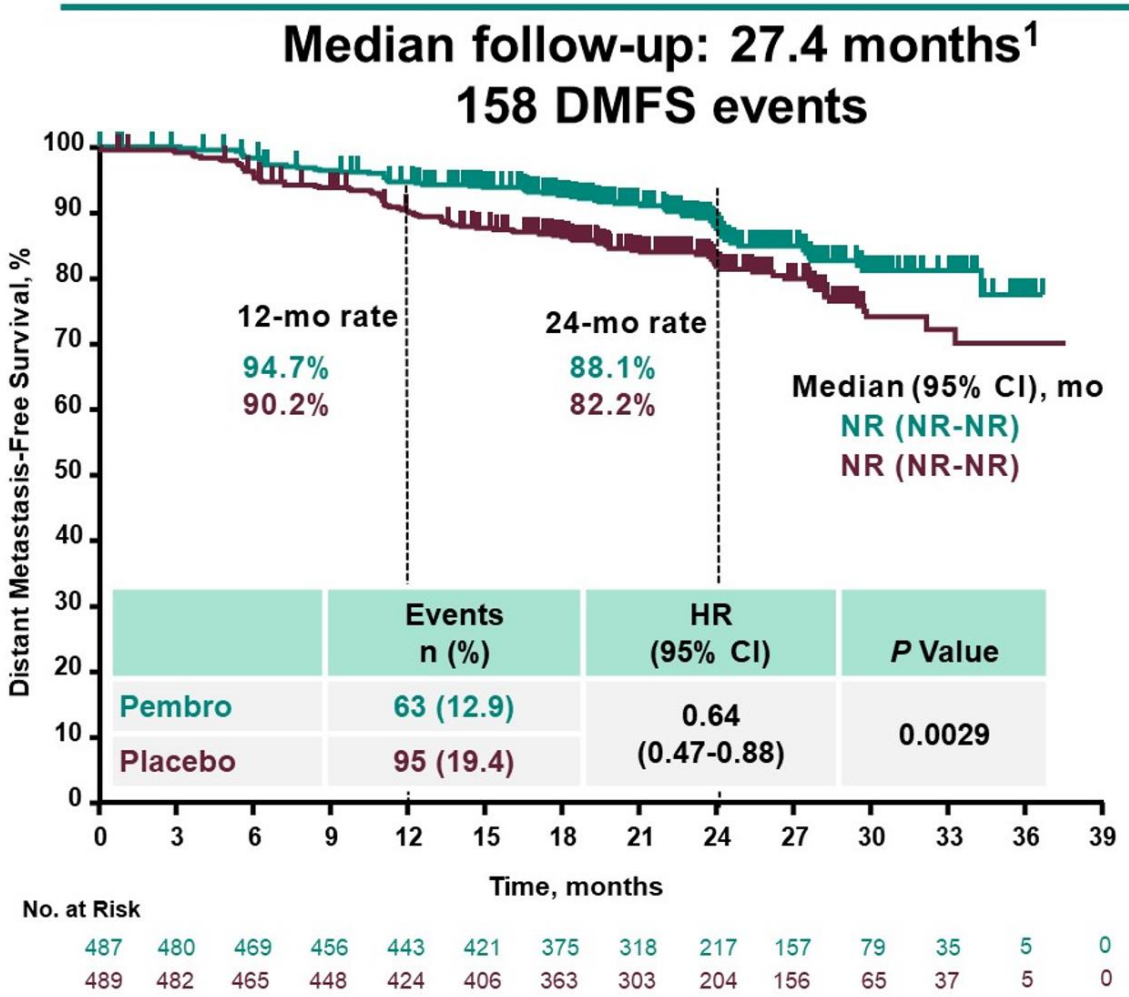
12-month data at ESMO September 2021

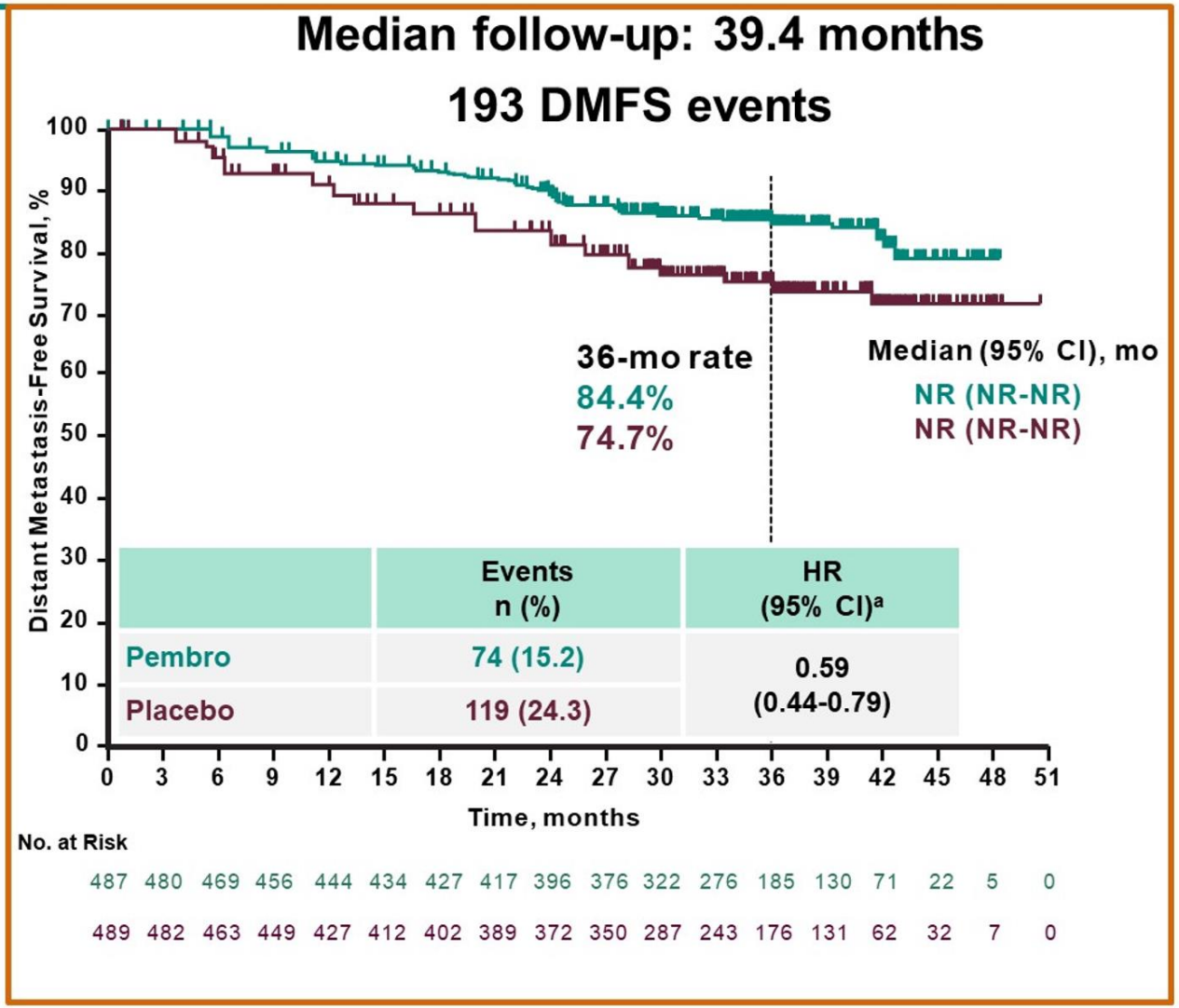
18-month follow-up data at SMR, October 2021



Jason J. Luke et al. Presented at ESMO September 2021
Updated data from SMR 2021, courtesy Dr. JJ Luke.

DMFS: ITT Population

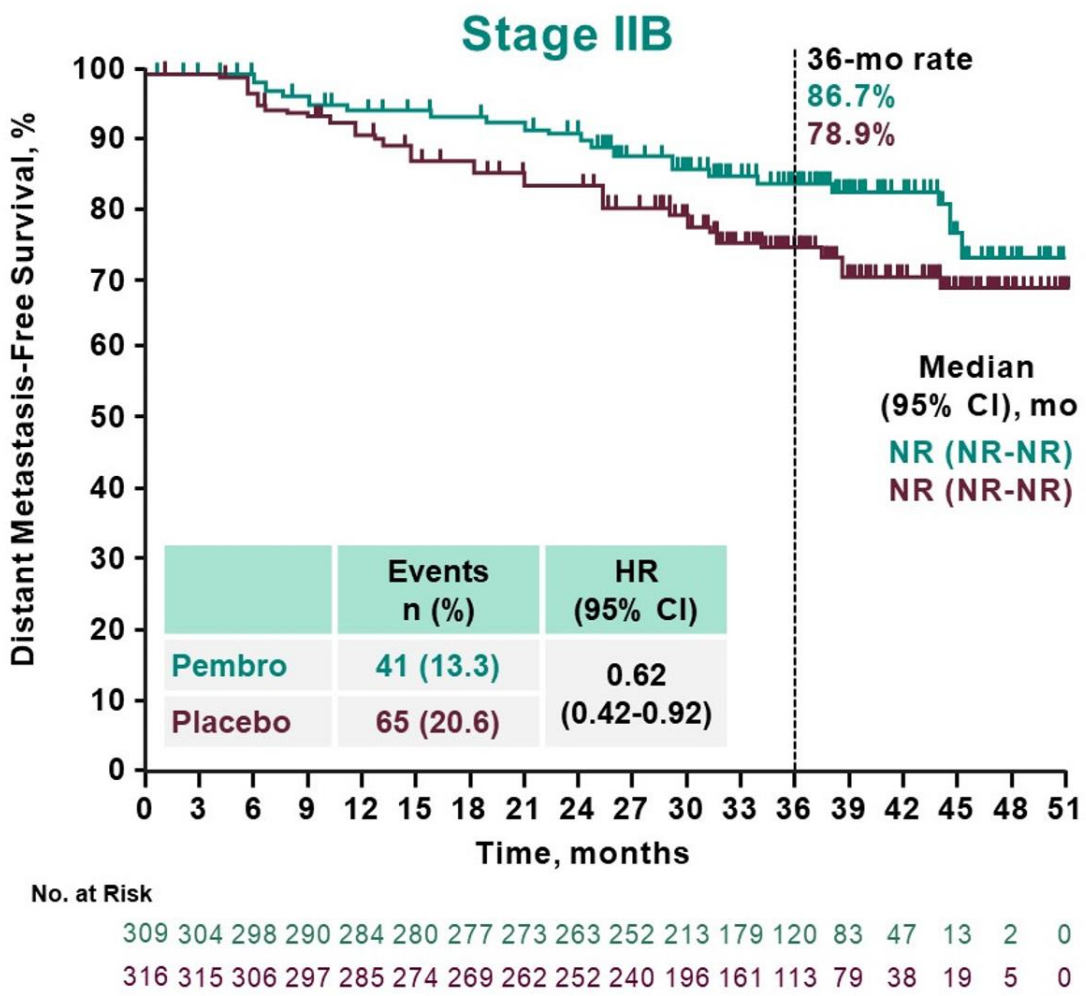


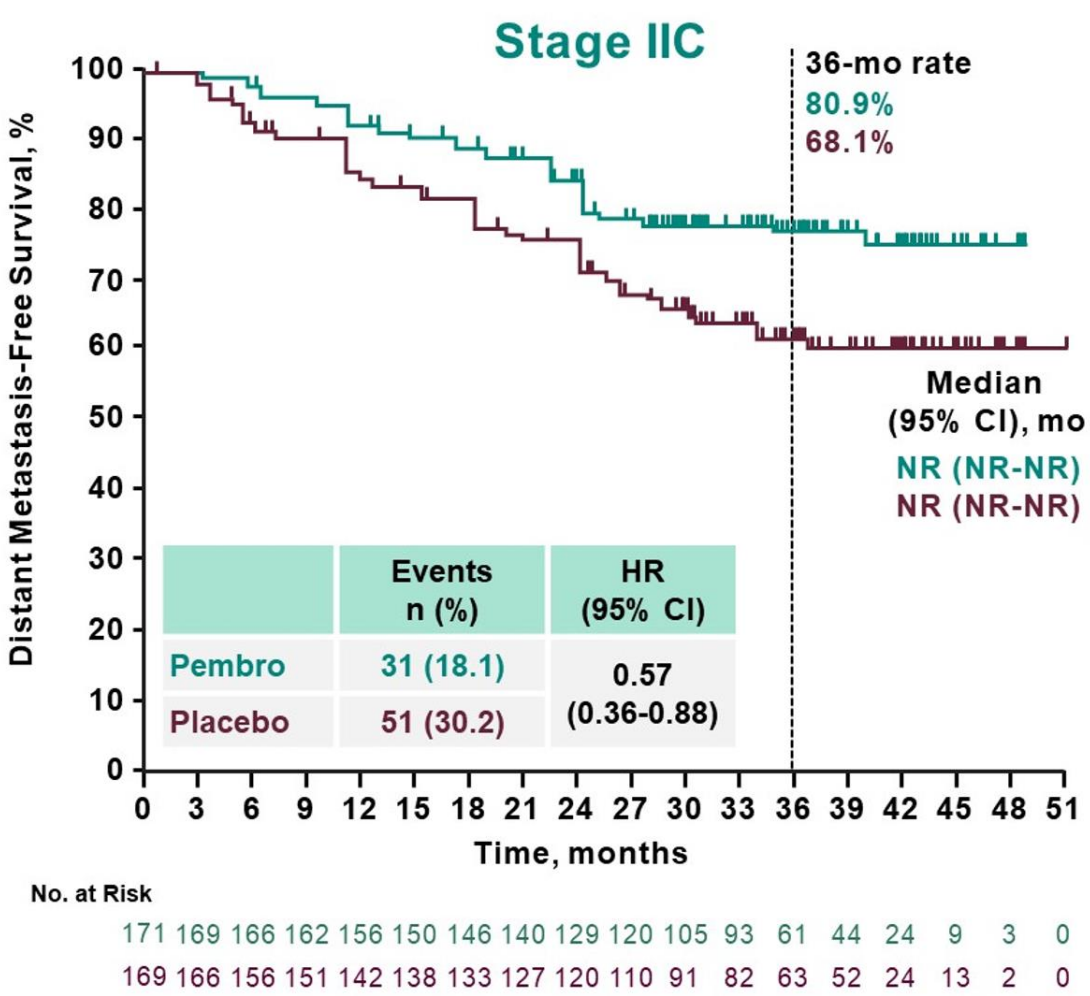


Long GV et al. *Lancet Oncol.* 2022;23(11):1378-1388.

With Permission, courtesy, Dr. Jason Luke

DMFS by Stage





With Permission, courtesy, Dr. Jason Luke

Significant durable response with Fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: Post adjuvant PD-1 analysis.

Abstract 9501

Oral Abstract presented by Dr. Omid Hamid, MD

The benefit the fianlimab + cemiplimab combination in pts exposed to prior anti-PD-1 therapy as adjuvant therapy is unknown.

Current study was a phase 1 trial, including advanced melanoma patients (including those who received prior adjuvant systemic therapy)

Patients were enrolled into 3 expansion cohorts. All received fianlimab 1600 mg + cemiplimab 350 mg IV Q3W for 12 months.

Abstract 9501

N=98

23.5% had received prior systemic therapy in the adjuvant/neo-adjuvant setting (13.3% received nivolumab or pembrolizumab).

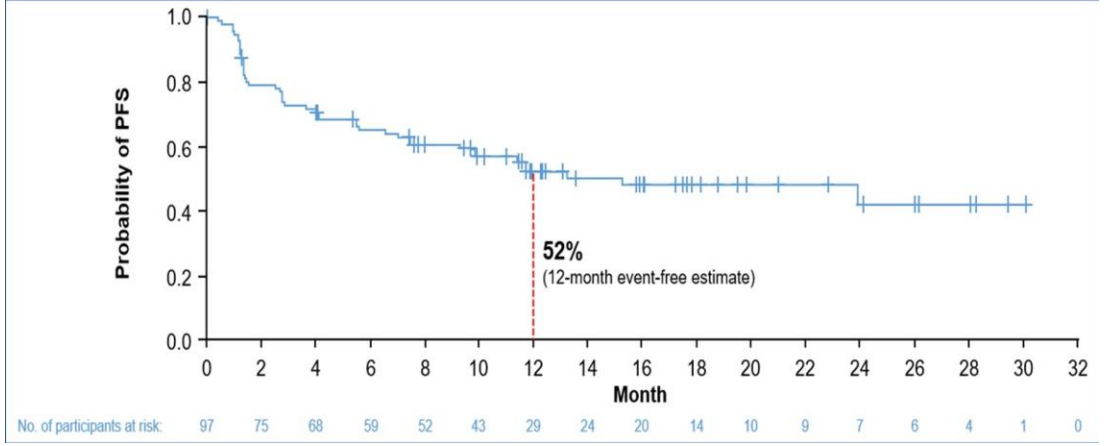
Median follow up was 12.6 m.

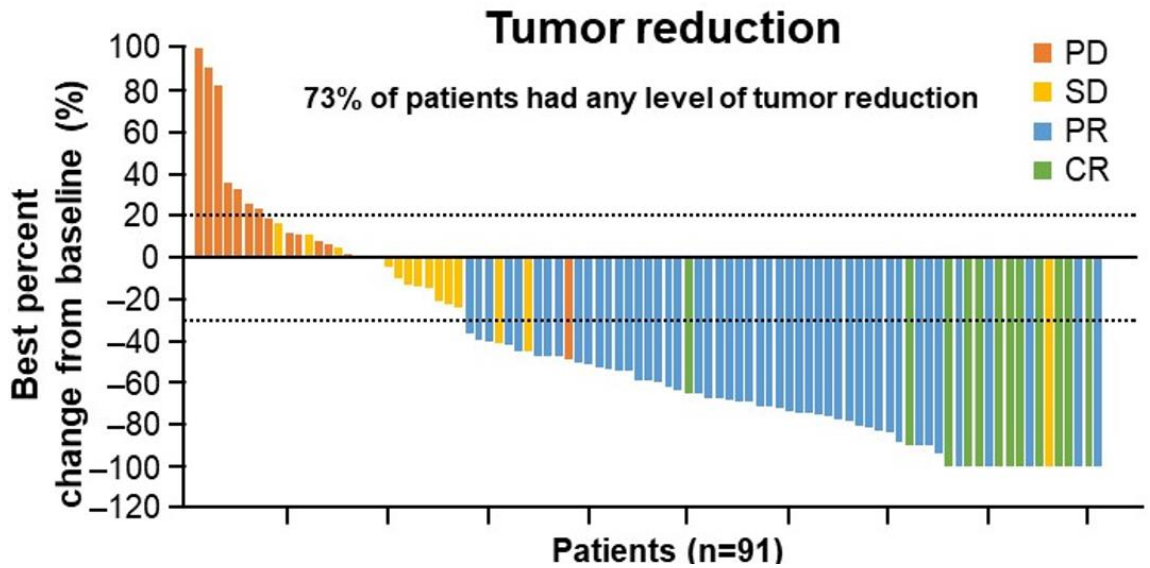
RECIST 1.1-based investigator-assessed overall ORR was 61.2% (12 complete responses; 48 partial responses).

KM estimation of median PFS (mPFS) was 15.3 (95% CI: 9.4–NE) mo.

In pts with prior anti-PD-1 adj Tx, ORR, mDOR, and mPFS was 61.5% (8/13), NR, and 11.8 mos, respectively.

	Cohorts MM1# + MM2# + MM3# Advanced melanoma (N=98)
KM-estimated PFS, median (95% CI), months	15 (9–NE)
Estimated event-free probability at 12 months, (95% CI)	52% (41–62)





Courtesy, Dr. Omid Hamid

Thank you!