Melanoma:
Novel Advances in Immunotherapy

Sanjiv S. Agarwala, MD

Overview

- Background and current options
- Advances in PD-1 refractory melanoma
- Advances in adjuvant therapy
- Neoadjuvant immunotherapy (ASCO plenary)

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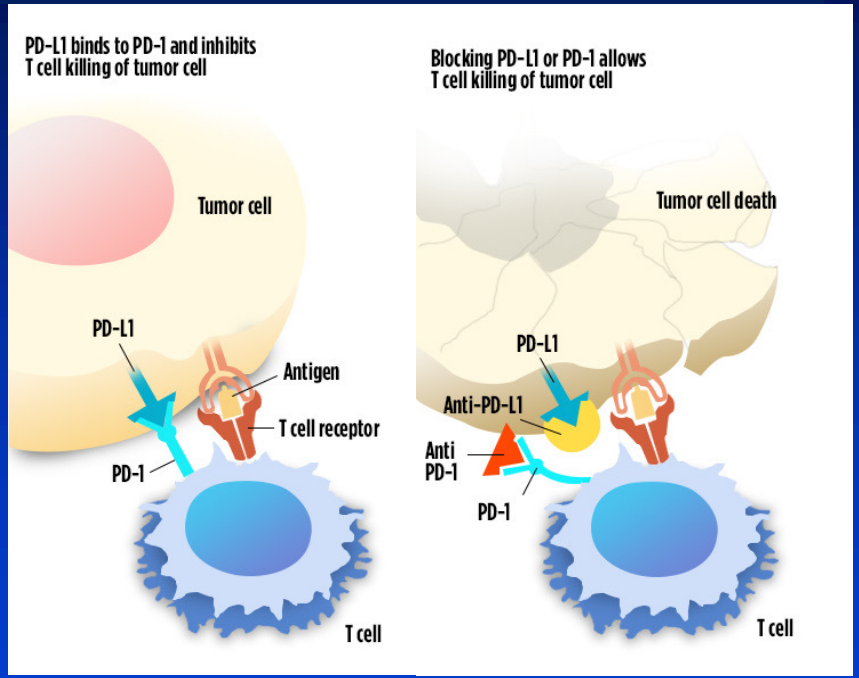
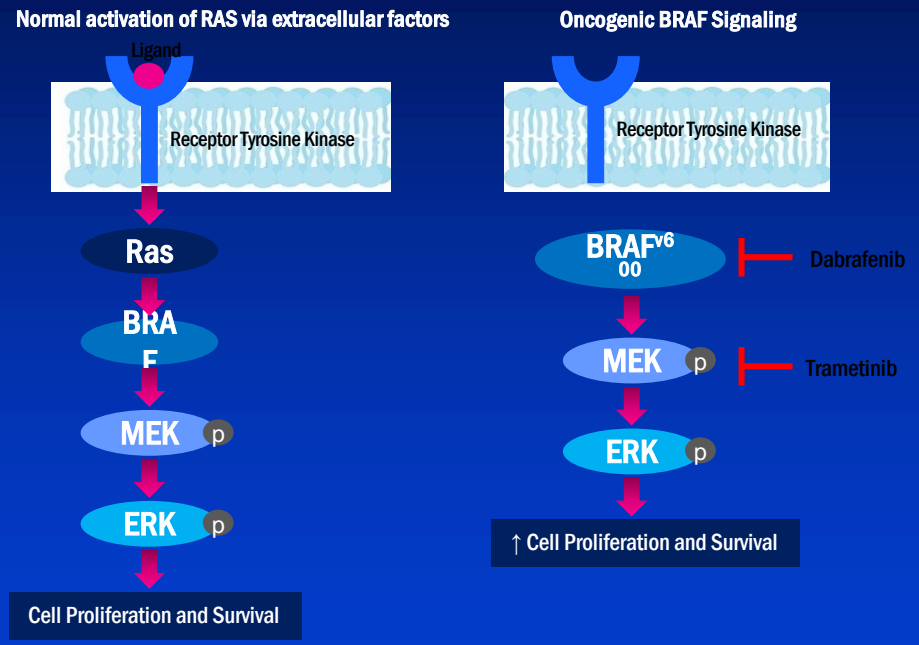
Two Modalities for Melanoma Treatment

Immuno-Oncology Agents



Targeted Agents

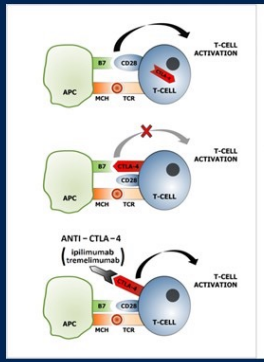


Adapted from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor; Ascierto PA, et al. *J Transl Med.* 2012; 10:85.

Current Immunotherapy Options

- Single agent
  - Anti-CTLA4 (ipilimumab)
  - Anti-PD1 (pembrolizumab or nivolumab)
- Combination
  - Anti-PD1/anti-CTLA4 (ipilimumab, nivolumab)
  - Anti-PD1/ anti-LAG3 (nivolumab, relatlimab)

Ipilimumab: the First Systemic Therapy Approved for Stage IV Melanoma Patients Demonstrating Survival Benefit

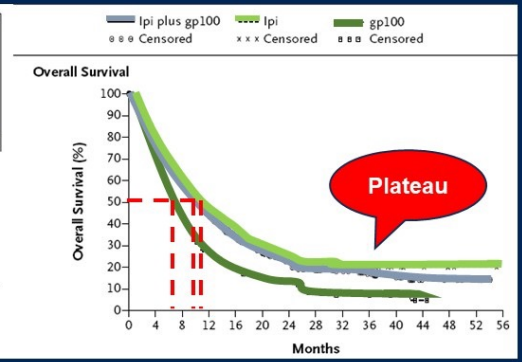


The NEW ENGLAND JOURNAL of MEDICINE

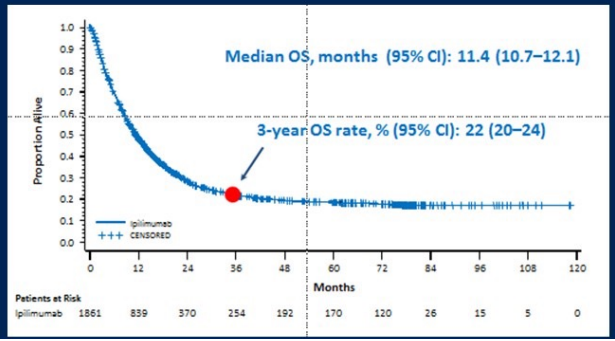
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

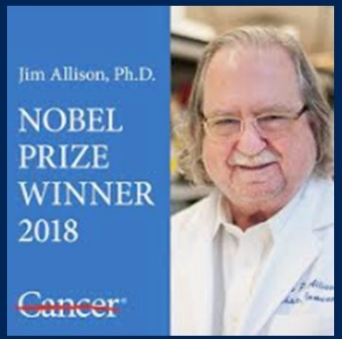
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

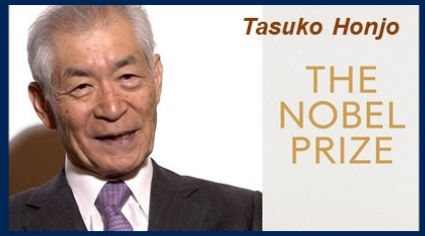


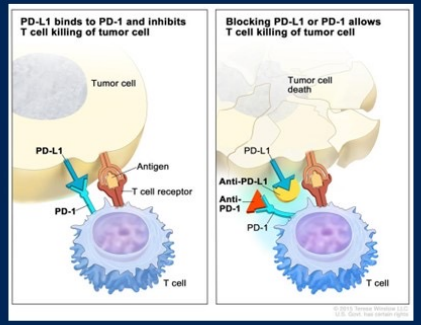
Schadendorf et al.
J Clin Oncol
2015;33:1889-1894



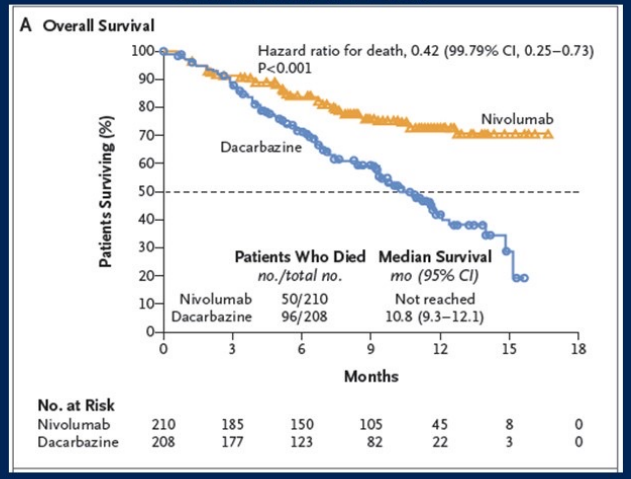


Anti-Programmed death 1 (PD1) Antibodies are More Active Than Ipilimumab



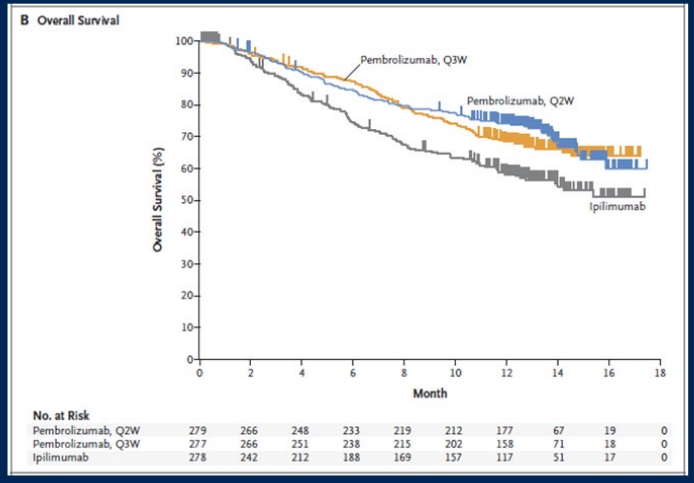


CHECKMATE 066[1]



	Nivo (n=210)	DTIC (n=208)
Median OS, months, (95% CI)	NR	10.8 (9.3-12.1)
1-year survival, %	72.9	42.1
HR (95% CI) p value	0.42 (0.25-0.73) p<0.001	

KEYNOTE-006[2]

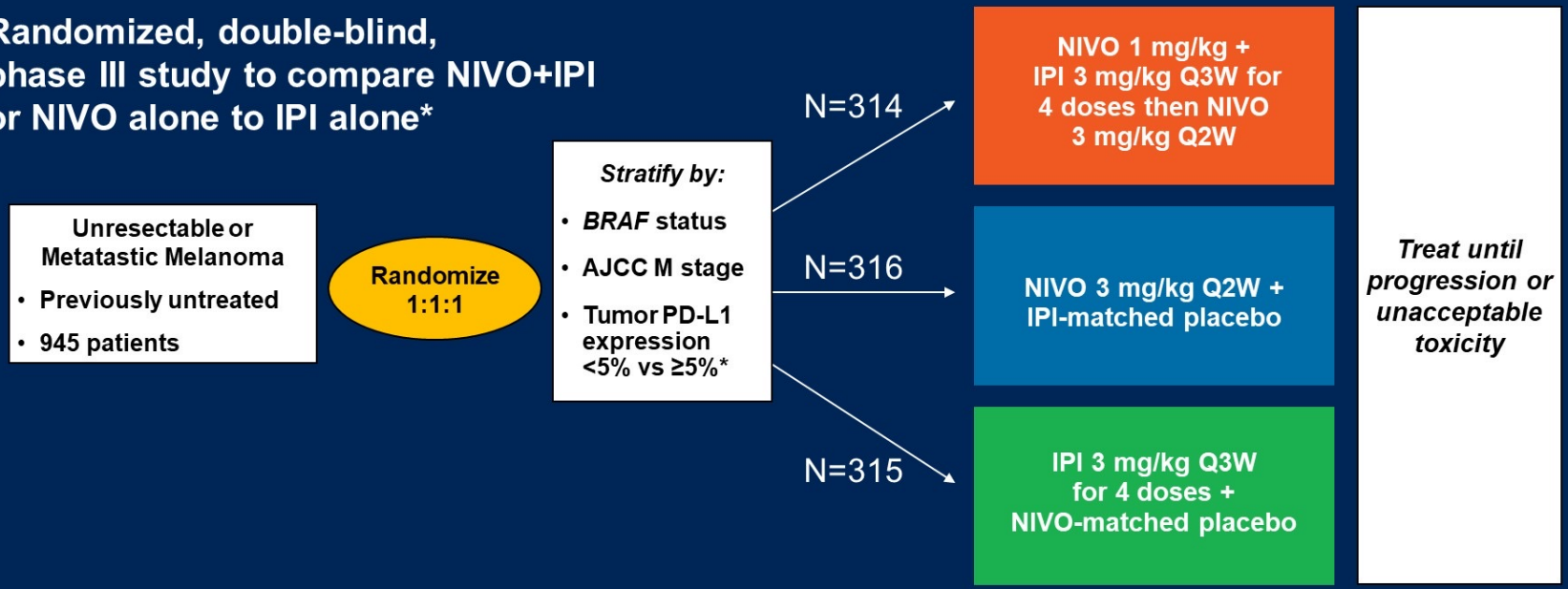


	Pembro Q2W (n=279)	Pembro Q3W (n=277)	Ipilimumab (n=278)
Median OS, months	NR	NR	NR
1-year survival, %	74.1	68.4	58.2
HR (95% CI) p value	0.63 (0.47–0.83) p<0.0005	0.69 (0.52–0.90) p=0.0036	

1. Robert C, et al. N Engl J Med 2015; 372: 320-30.
2. Robert C, *et al*. N Engl J Med 2015; 372: 2521-32

CheckMate 067 Established Nivolumab + Ipilimumab as a New Standard of Care

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*

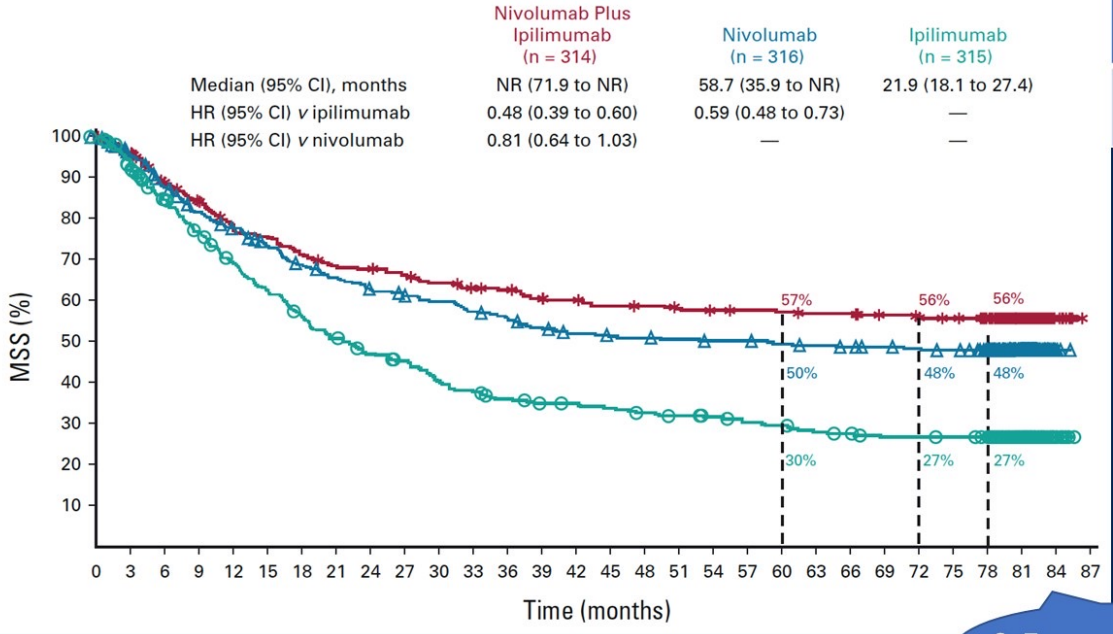


Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

Wolchock JD, et al. J Clin Oncol 2022; 40: 127-37

CHECKMATE 067 Trial Long Term Outcomes: NIVO+IPI Efficacy Must be Considered alongside Toxicity



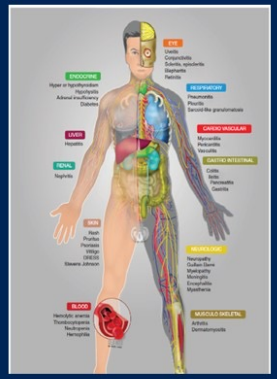
	Nivo+Ipi	Nivo	Ipi
Treatment-related AEs	96% Any 59% G3-4	86% Any 21% G3-4	86% Any 28% G3-4

AE= side effect
G3= severe
G4= life threatening

Nivo+ipi

Nivolumab

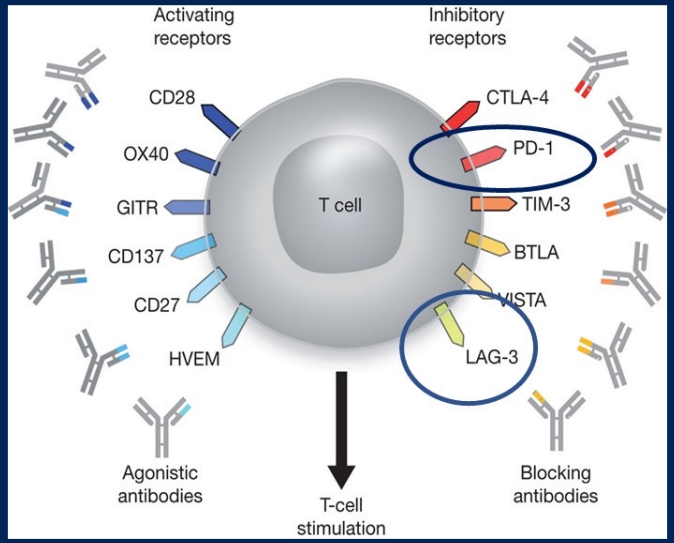
Ipilimumab

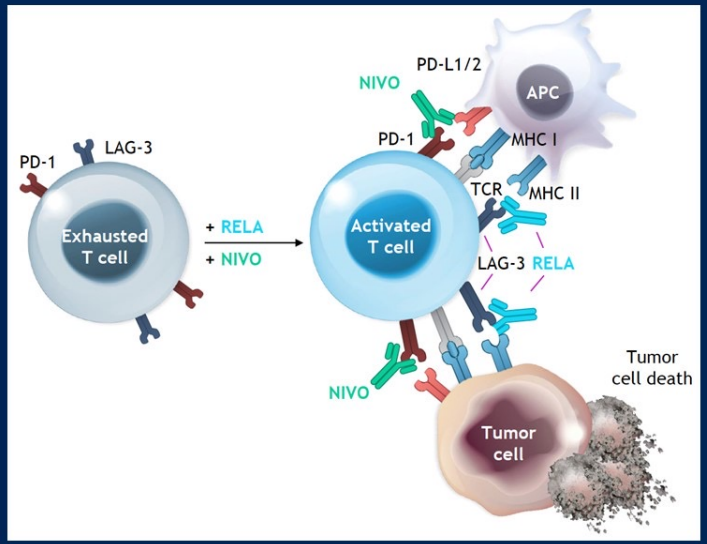


6.5 years = cure?

Wolchock JD, et al. NEJM 2017; 377: 1345-56; J Clin Oncol 2022; 40: 127-37

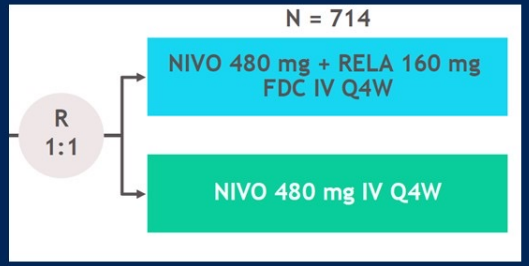
Can we Improve Outcomes by Targeting other Immune Checkpoints?



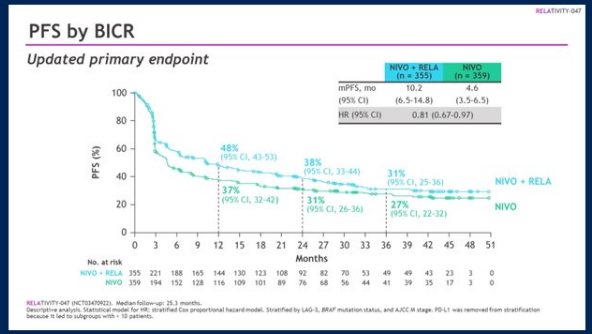


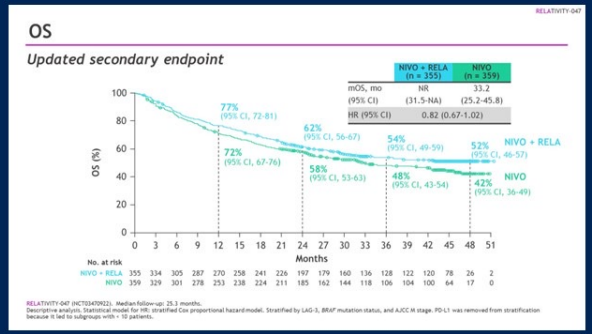
Relatlimab Blocks LAG-3 and Restores T cell Function

RELATIVITY 047: Nivolumab + Relatlimab Improves Relapse-Free Survival and Maintains Quality of Life Compared with Nivolumab alone



	Nivo+Rela	Nivo
Treatment-related AEs	84% Any 21% G3-4	72% Any 11% G3-4



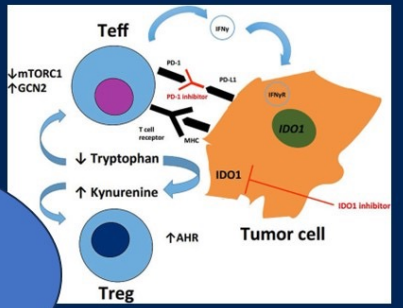


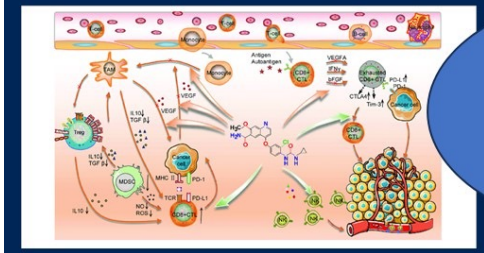
Tawbi H, et al. NEJM 2022; 386: 24-34; Schadendorf D, et al. EJC 2023; 187: 164-173

What Strategies Haven't Worked?

Triplet Therapy:
KEYNOTE-022[1]
IMspire150[2]
COMBI-I[3]

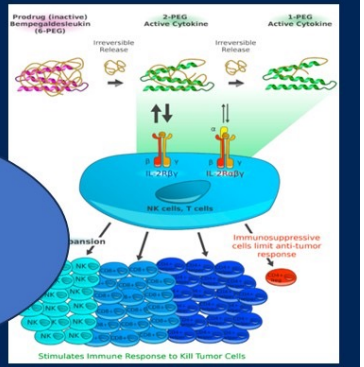
KEYNOTE-252[4]
Epacadostat+
pembrolizumab





LEAP-004[6]
Lenvatinib+
pembrolizumab

PIVOT IO 001[5]
Bempegaldesleukin
+nivolumab



1. Ascierto PA et al, 2019; 2. Gutzmer R et al, 2020; 3. Dummer R et al, 2022; 4. Long GV et al, 2019; 5. Diab A et al, 2023; 6. Arance A et al, 2023

Overview

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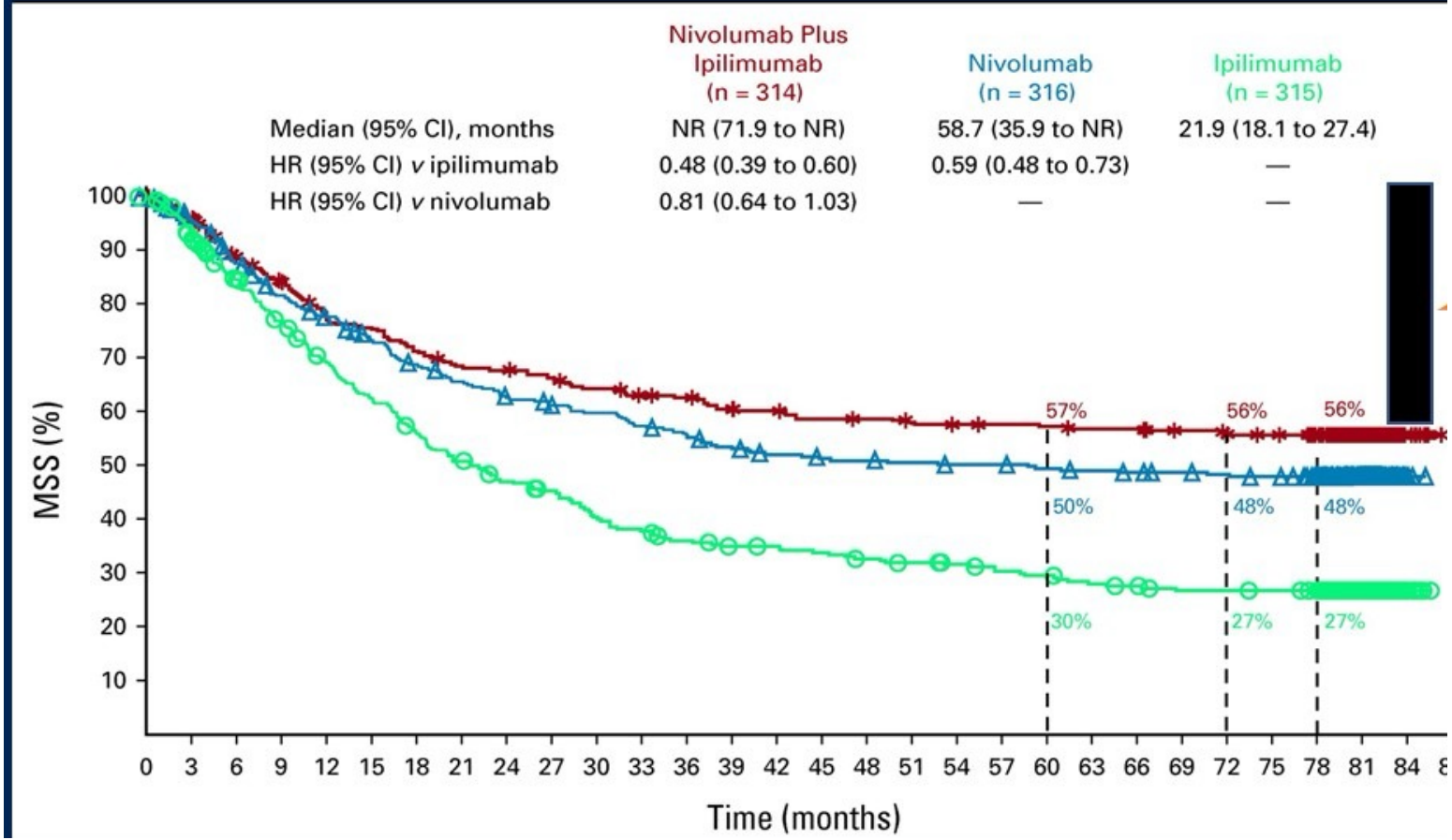
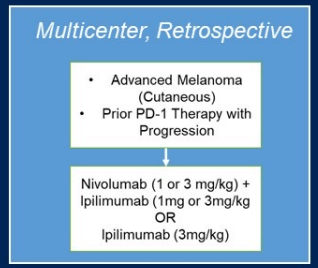
- Advances in adjuvant therapy
- Neoadjuvant immunotherapy (ASCO plenary)

CheckMate 067: Melanoma Specific Survival



PD-1 Refractory Melanoma: anti CTLA-4/PD-1

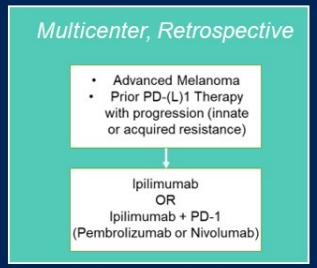
Ipilimumab +/- Nivolumab



- Ipilimumab + Nivolumab
  - ORR 23%
- Ipilimumab
  - ORR 17%

Zimmer et al, EJCA 2017

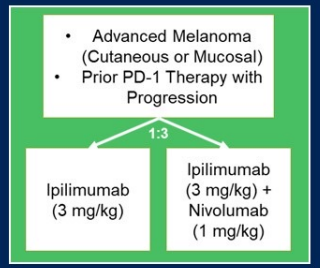
Ipilimumab +/- anti-PD-1



- Ipilimumab + PD-1
  - ORR 31%
- Ipilimumab
  - ORR 13%

Pires da Silva et al, Lancet Oncol 2021

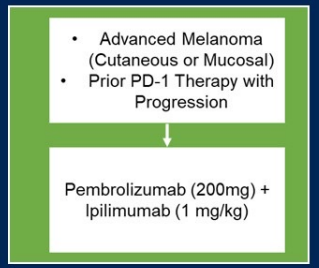
Ipilimumab +/- Nivolumab



- Ipilimumab + Nivolumab
  - ORR 28%
- Ipilimumab
  - ORR 9%

VanderWalde et al, Nat Med. 2023

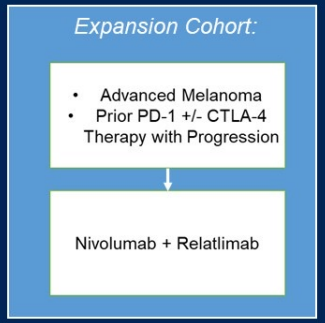
Ipilimumab +/- Pembrolizumab



- Ipilimumab + Pembrolizumab
  - ORR 29%

Olson et al, JCO 2021

PD-1 Refractory Melanoma: LAG-3/PD-1



RELATIVITY-020: Nivolumab + Relatlimab

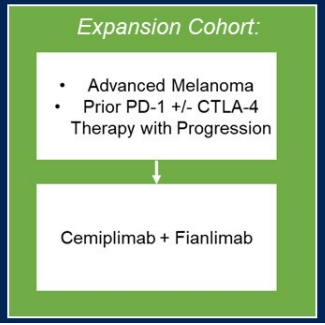
- ORR 9.2-12%

Ascierto et al, JCO 2023

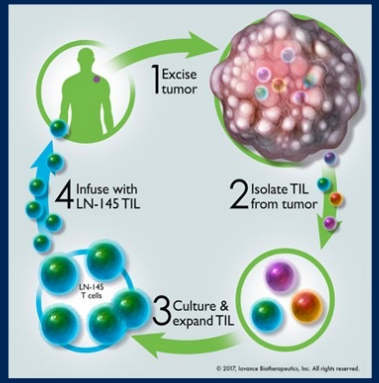
Cemiplimab + Fianlimab

- ORR 13.3%

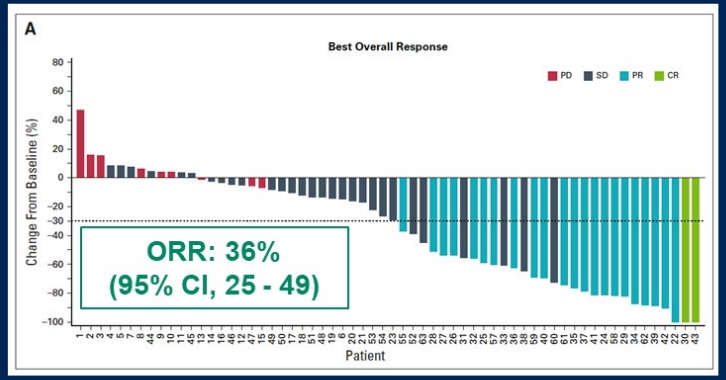
Hamid et al, ESMO 2022

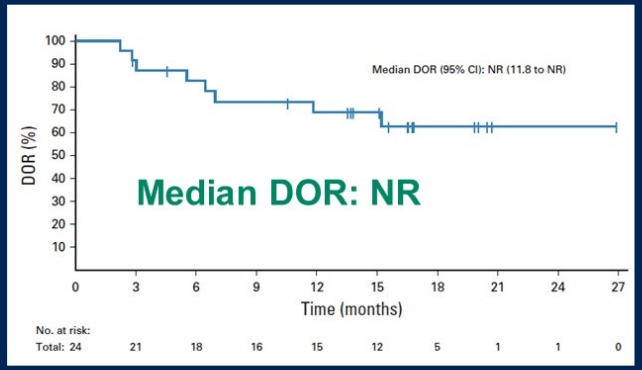


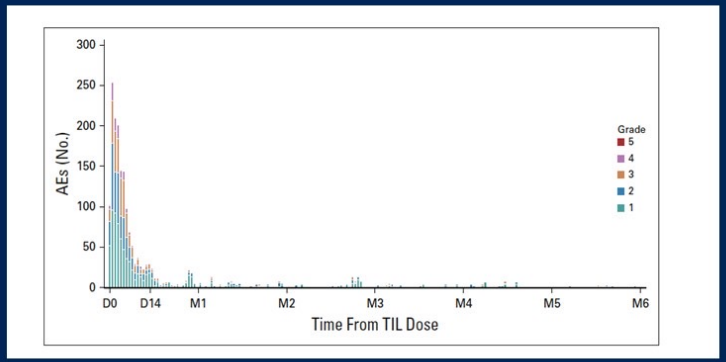
C-144-01 Phase II Trial: Tumour Infiltrating Lymphocytes (TILs) Generated Durable Responses in Heavily Pretreated Melanoma Patients

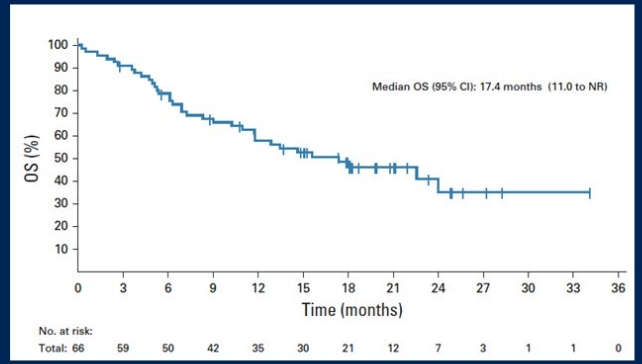


Sarnaik AA, et al. J Clin Oncol 2021; 39: 2656-65)

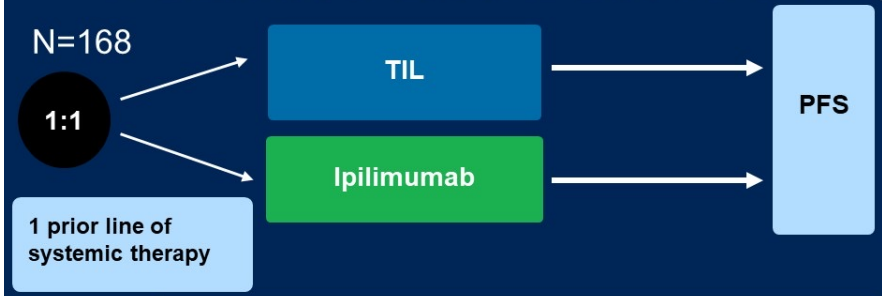


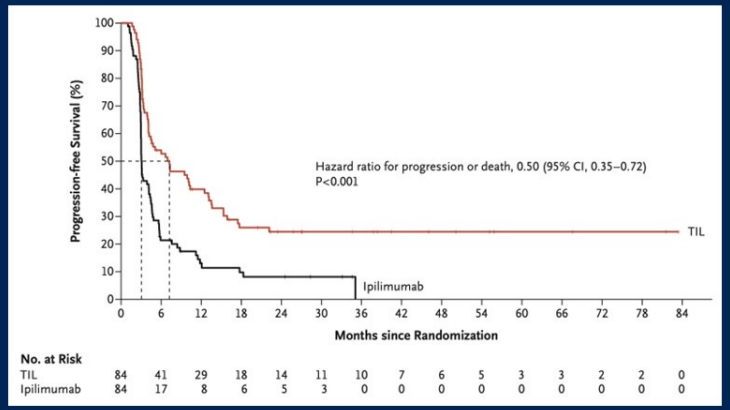






Phase III Trial of Tumour Infiltrating Lymphocytes (TILs) Demonstrated Benefit Compared with Ipilimumab





Rohaan MW, et al. NEJM 2022; 387: 2113-25

FDA grants accelerated approval to lifileucel for unresectable or metastatic melanoma

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On February 16, 2024, ...accelerated approval

Overview

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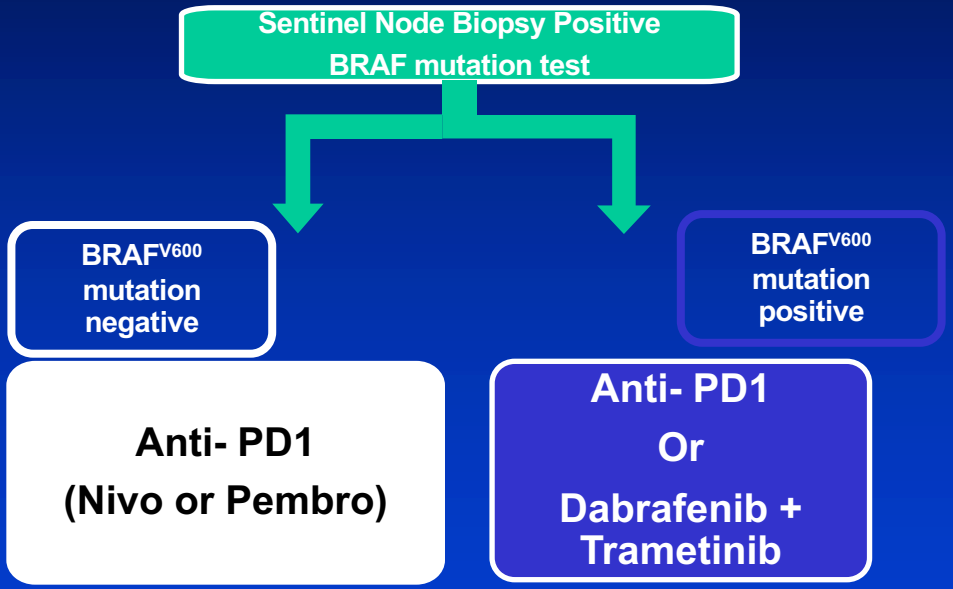
Adjuvant Therapy Approach (Stage III)

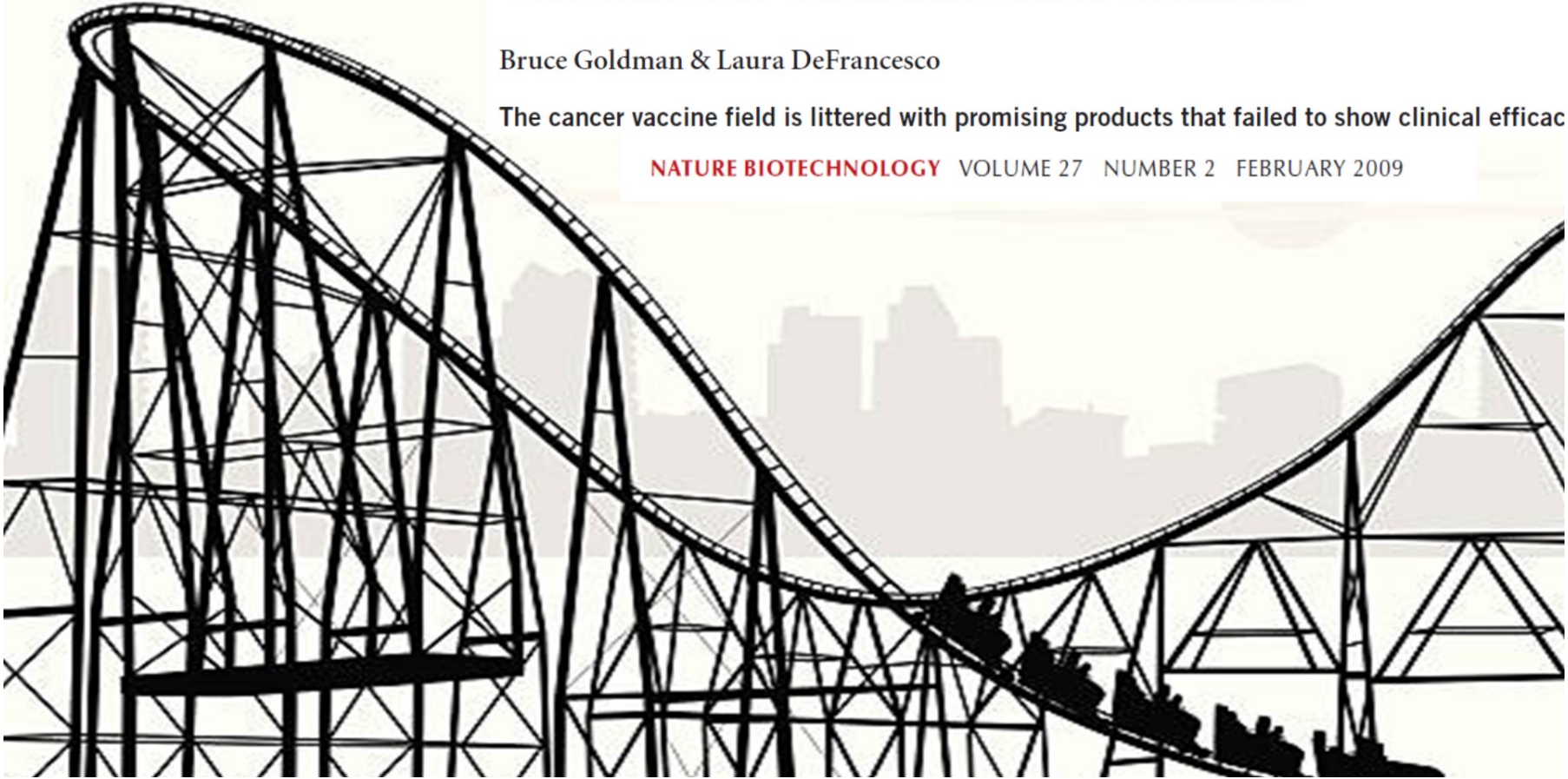


The cancer vaccine roller coaster

Bruce Goldman & Laura DeFrancesco

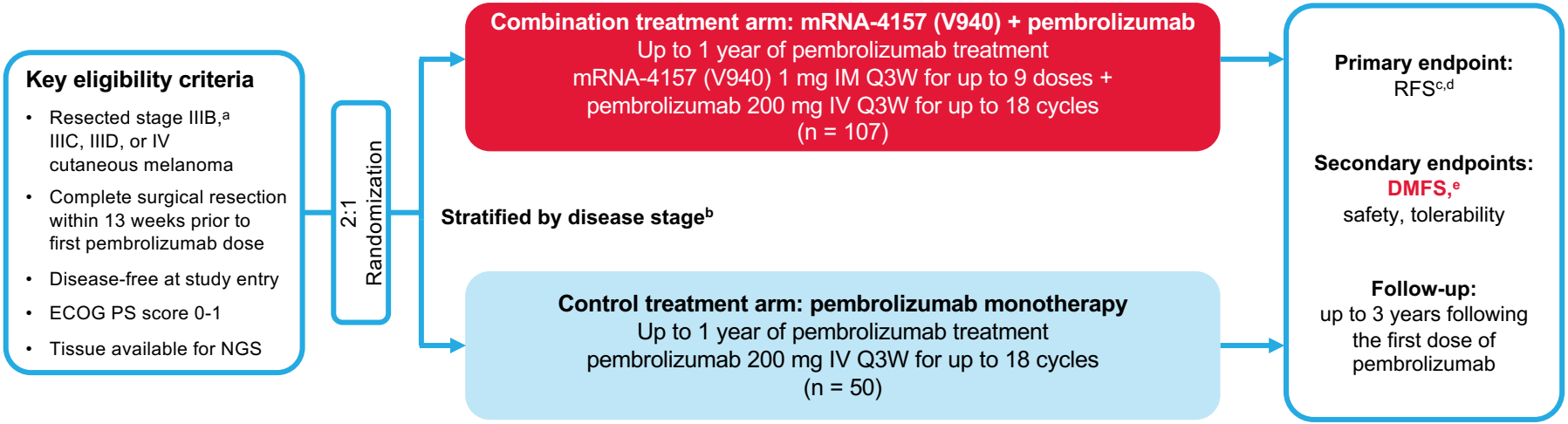
The cancer vaccine field is littered with promising products that failed to show clinical efficac

NATURE BIOTECHNOLOGY VOLUME 27 NUMBER 2 FEBRUARY 2009



mRNA-4157-P201/KEYNOTE-942 (NCT03897881) Study Design

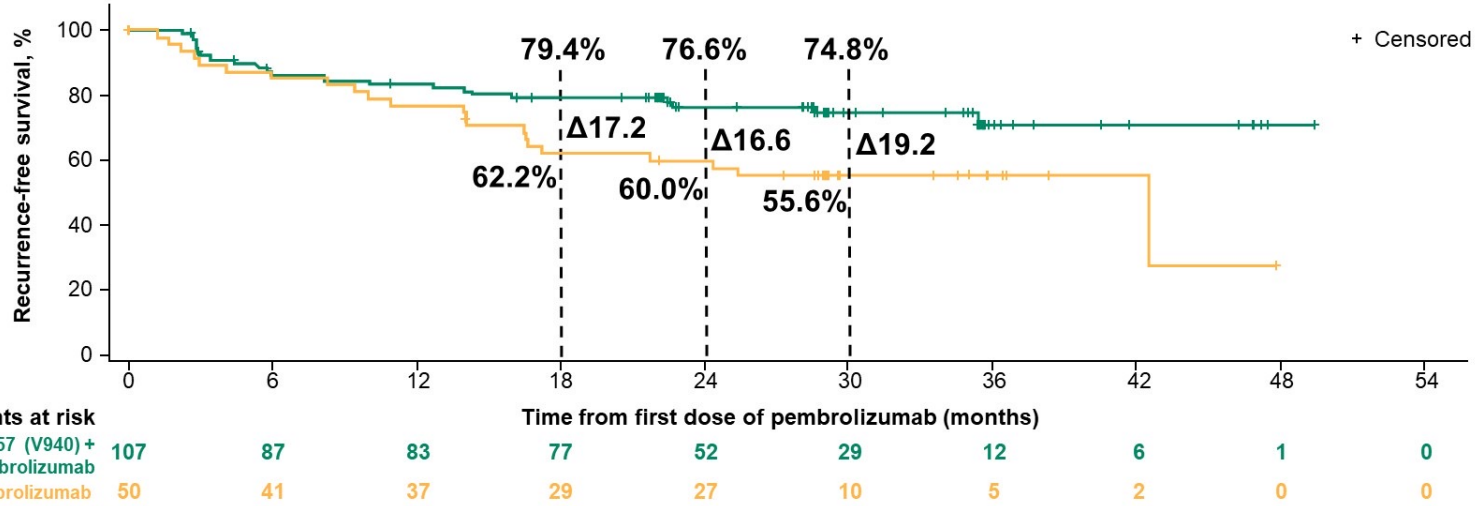
Randomized, phase 2, open-label study in adjuvant resected melanoma patients at high risk of recurrence



Designed with 80% power to detect an HR of 0.5 with ≥40 RFS events (with a 1-sided alpha of 0.1)
DMFS analysis was prespecified for testing following positive RFS in the ITT population[f]
Median follow-up[g]: 23 months for mRNA-4157 (V940) + pembrolizumab
24 months for pembrolizumab monotherapy

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual. [c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. [d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed. [e]Investigator-assessed DMFS was defined as the time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause. [f]The stratified log-rank test was used for comparison. [g]Time of database cutoff was November 14, 2022.

Sustained improvement of RFS primary efficacy endpoint

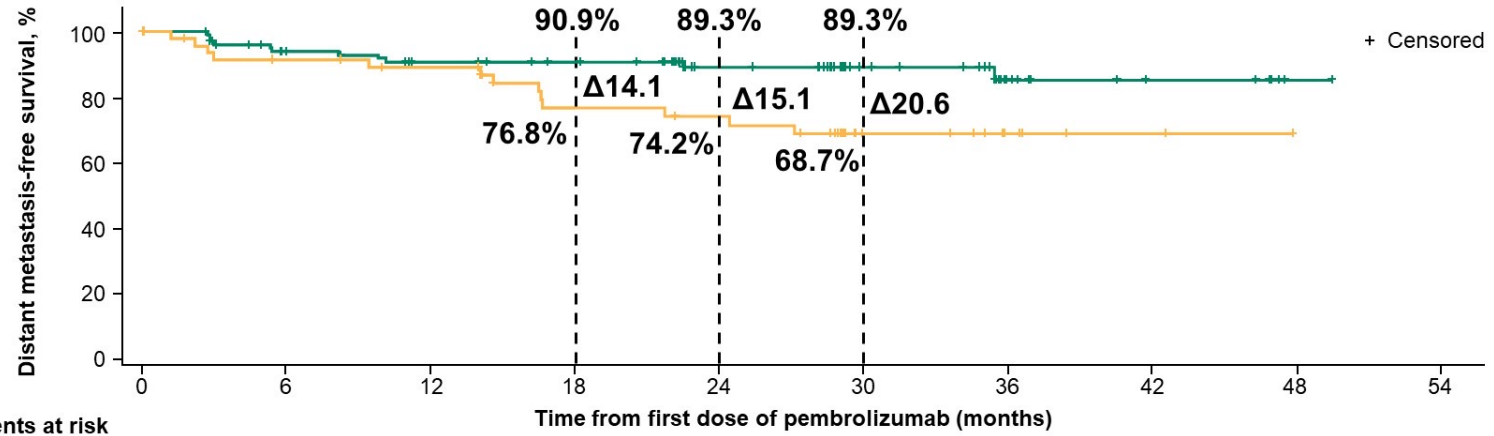


Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	87	83	77	52	29	12	6	1	0
Pembrolizumab	50	41	37	29	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288–0.906) *P* = 0.019[b]
pembrolizumab	42.51 (16.59–NE)	44.0 (22/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were 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 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing. NE, not estimable.

Sustained improvement of DMFS secondary endpoint



Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	89	82	78	52	30	12	6	1	0
Pembrolizumab	50	42	39	30	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	10.3 (11/107)	0.384 (0.172–0.858) *P* = 0.015[b]
Pembrolizumab	NE	26.0 (13/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were 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 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of DMFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing.

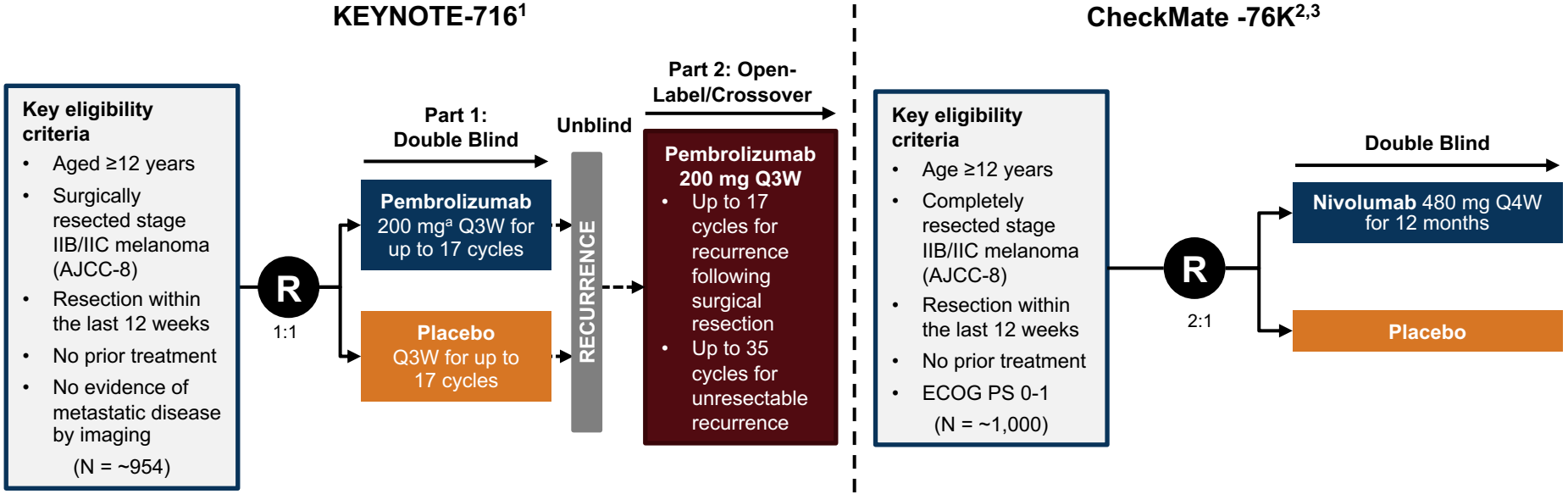
3-year safety follow-up on safety demonstrates a manageable profile consistent with the primary analysis

	mRNA-4157 (V940) + pembrolizumab (n = 104)		Pembrolizumab (n = 50)	
Event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any AE	104 (**100%**)	36 (**34.6%**)	46 (**92.0%**)	18 (**36.0%**)
Any treatment-related AE	104 (**100%**)	26 (**25.0%**)	41 (**82.0%**)	10 (**20.0%**)
Serious AE[a]	15 (**14.4%**)		5 (**10.0%**)	
Immune-related AE[b]	39 (**37.5%**)	11 (**10.6%**)	18 (**36%**)	7 (**14.0%**)

mRNA-4157 (V940) + pembrolizumab (n = 104), n (%)	Grade 1	Grade 2	Grade 3	Grade 4/5	Total (n = 104)
Patients with mRNA-4157 (V940)–related AE[c]	**35 (33.7%)**	**51 (49.0%)**	**12 (11.5%)**	**0**	**98 (94.2%)**
Fatigue	40 (38.5%)	18 (17.3%)	5 (4.8%)	0	63 (60.6%)
Injection site pain	37 (35.6%)	22 (21.2%)	0	0	59 (56.7%)
Chills	48 (46.2%)	3 (2.9%)	0	0	51 (49.0%)
Pyrexia	34 (32.7%)	15 (14.4%)	1 (1.0%)	0	50 (48.1%)
Headache	20 (19.2%)	13 (12.5%)	0	0	33 (31.7%)
Injection site erythema	29 (27.9%)	4 (3.8%)	0	0	33 (31.7%)
Influenza-like illness	21 (20.2%)	10 (9.6%)	0	0	31 (29.8%)
Nausea	23 (22.1%)	3 (2.9%)	0	0	26 (25.0%)
Myalgia	16 (15.4%)	5 (4.8%)	1 (1.0%)	0	22 (21.2%)

Safety analyses were conducted in the safety population, which was defined as all randomly assigned patients who received ≥ 1 dose of treatment. Grading per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. [a]Serious AEs were not evaluated by toxicity grade; [b]Based on established list of pembrolizumab immune-related AEs (CMQ Pembrolizumab AEOSI); [c]mRNA-4157 (V940)–related AEs included events attributed by the investigator to mRNA-4157 (V940) alone as well as events attributed to both mRNA-4157 (V940) and pembrolizumab. AE, adverse event; AEOSI, adverse event of special interest; CMQ, customized MedDRA queries.

Ongoing Trials of Adjuvant Anti–PD-1 Antibodies for Stage IIB/C Melanoma

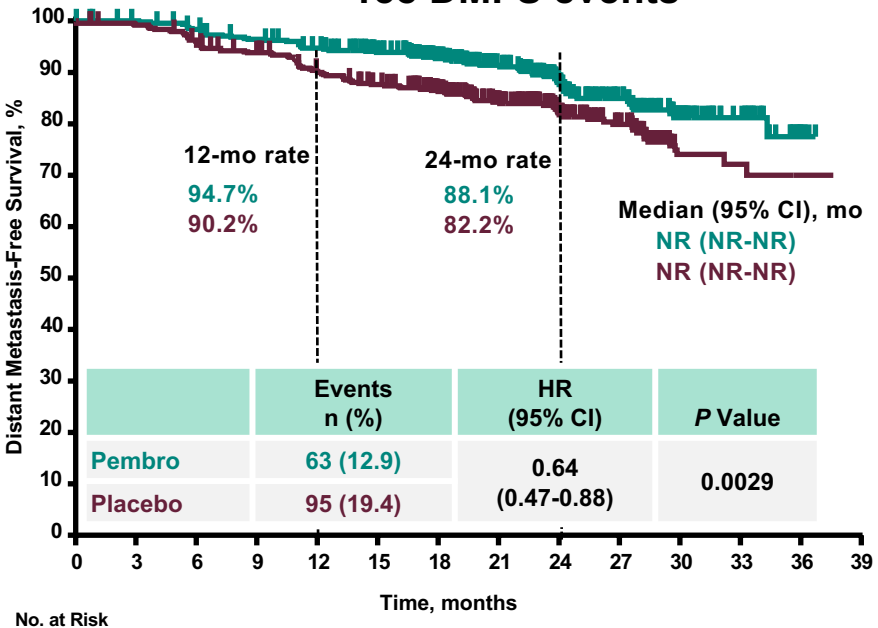


[a] Adult dosage; eligible patients aged 12 to <18 years receive 2 mg/kg Q3W.

1. Carlino MS et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract TPS9596. 2. https://clinicaltrials.gov/ct2/show/NCT04099
3. https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001230-34/AT.

DMFS: ITT Population

Median follow-up: 27.4 months[1]
158 DMFS events

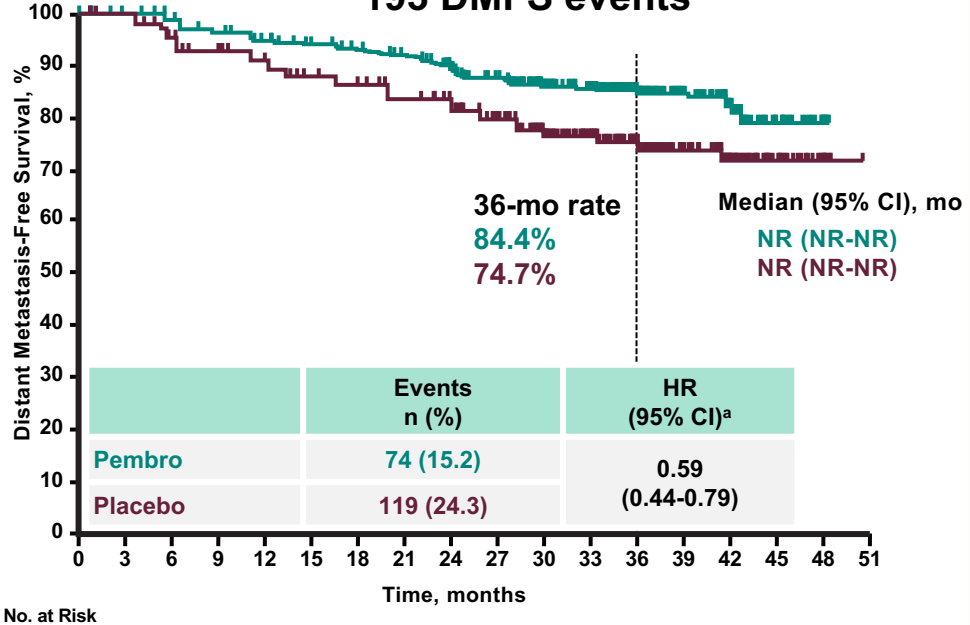


	Events n (%)	HR (95% CI)	*P* Value
Pembro	63 (12.9)	0.64 (0.47-0.88)	0.0029
Placebo	95 (19.4)		

No. at Risk

487	480	469	456	443	421	375	318	217	157	79	35	5	0
489	482	465	448	424	406	363	303	204	156	65	37	5	0

Median follow-up: 39.4 months
193 DMFS events



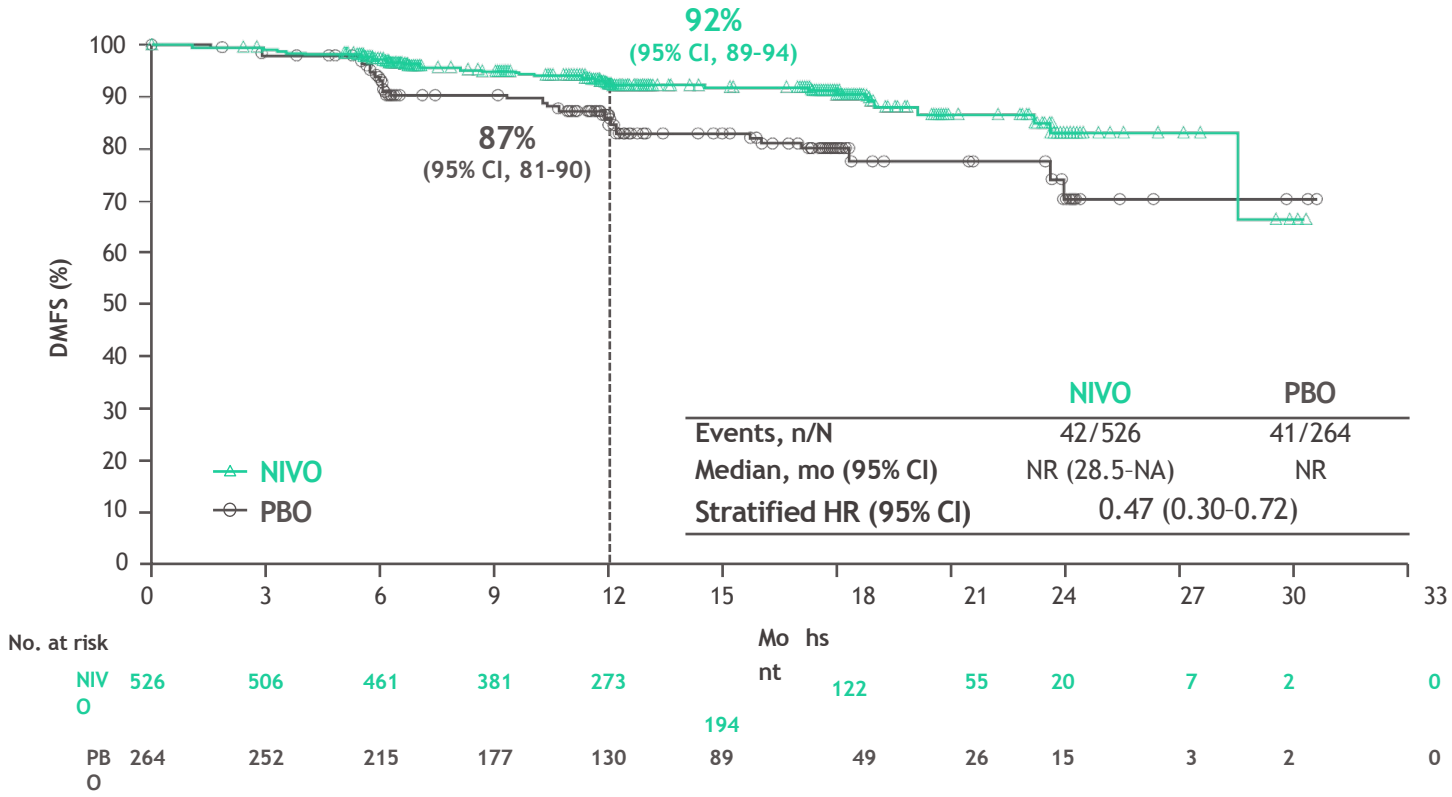
	Events n (%)	HR (95% CI)[a]
Pembro	74 (15.2)	0.59 (0.44-0.79)
Placebo	119 (24.3)	

No. at Risk

487	480	469	456	444	434	427	417	396	376	322	276	185	130	71	22	5	0
489	482	463	449	427	412	402	389	372	350	287	243	176	131	62	32	7	0

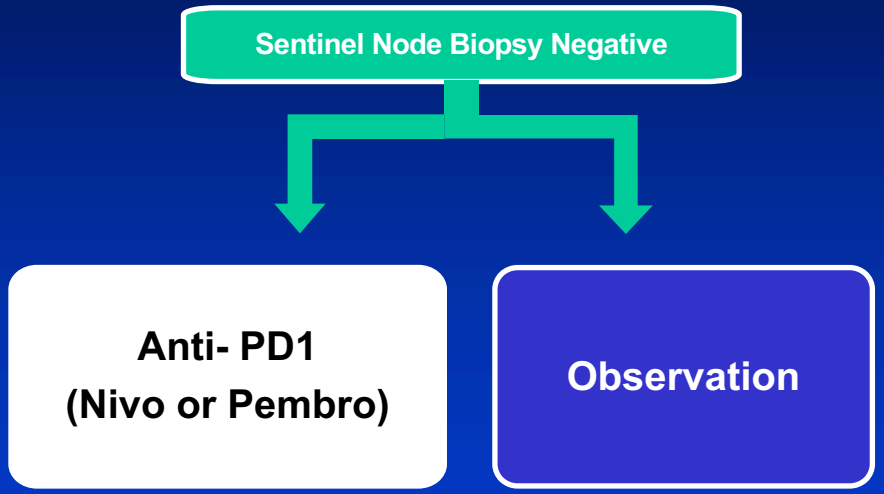
Long GV et al. *Lancet Oncol*. 2022;23(11):1378-1388.

Secondary endpoint: DMFS



Presented by Georgina V Long

Adjuvant Therapy Approach (Stage IIB and IIC)



Overview

- Background and current options
- Advances in PD-1 refractory melanoma
- Advances in adjuvant therapy
- Neoadjuvant immunotherapy (ASCO plenary)

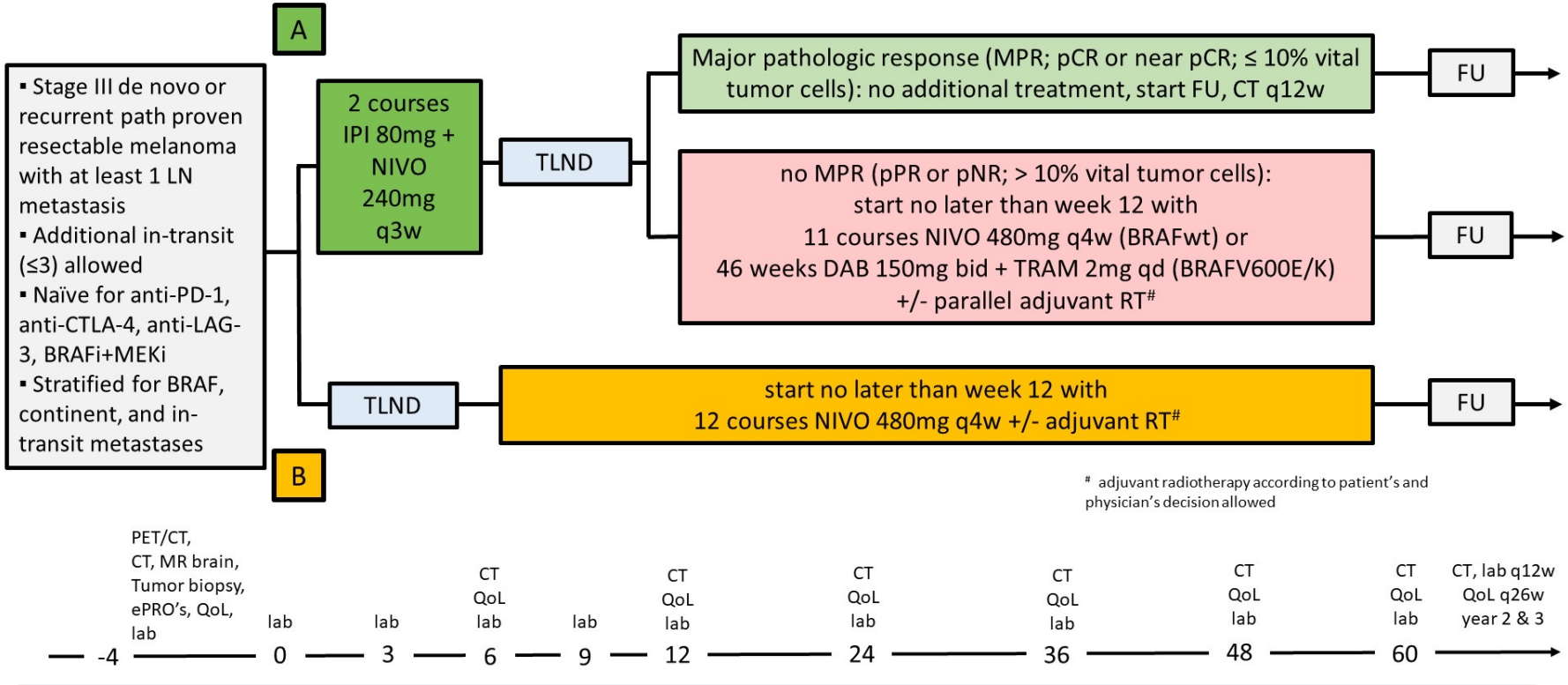
2024 ASCO ANNUAL MEETING

Neoadjuvant Nivolumab Plus Ipilimumab Versus Adjuvant Nivolumab in Macroscopic, Resectable Stage III Melanoma: The Phase 3 NADINA Trial

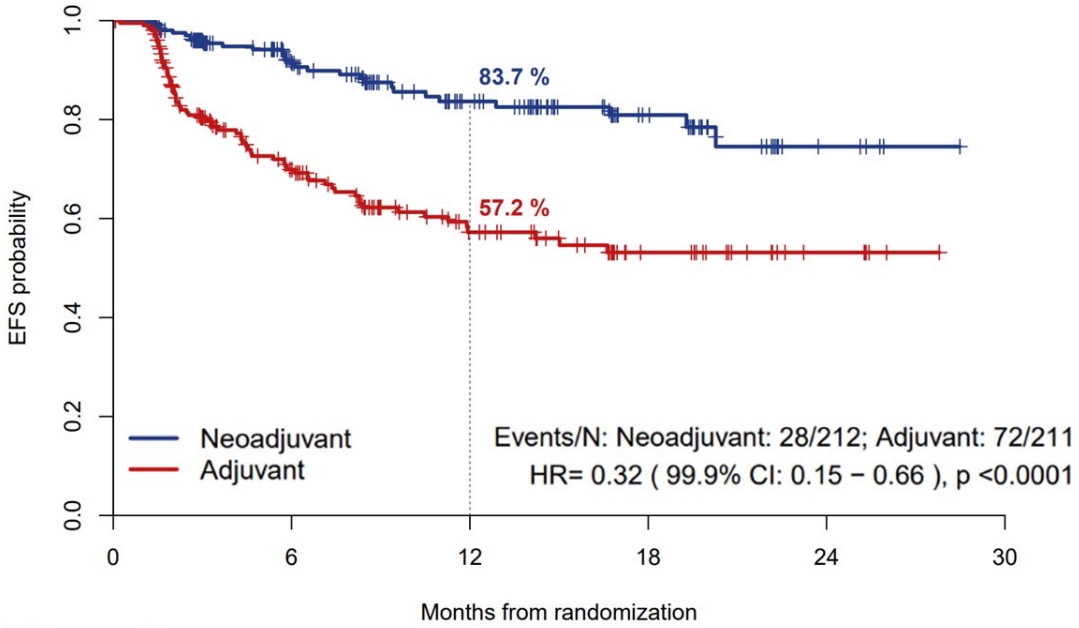
Christian U. Blank, M.W. Lucas, R.A. Scolyer, B.A. van de Wiel, A.M. Menzies, M. Lopez-Yurda, A.C.J. van Akkooi, W.J. van Houdt, R.P.M. Saw, A. Torres-Acosta, S.N. Lo, G.A.P. Hospers, M.S. Carlino, J.W.B. de Groot, E. Kapiteijn, K.P.M. Suijkerbuijk, P. Rutkowski, S. Sandhu, A.A.M. van der Veldt, G.V. Long

lay abstract

NADINA - Trial Design

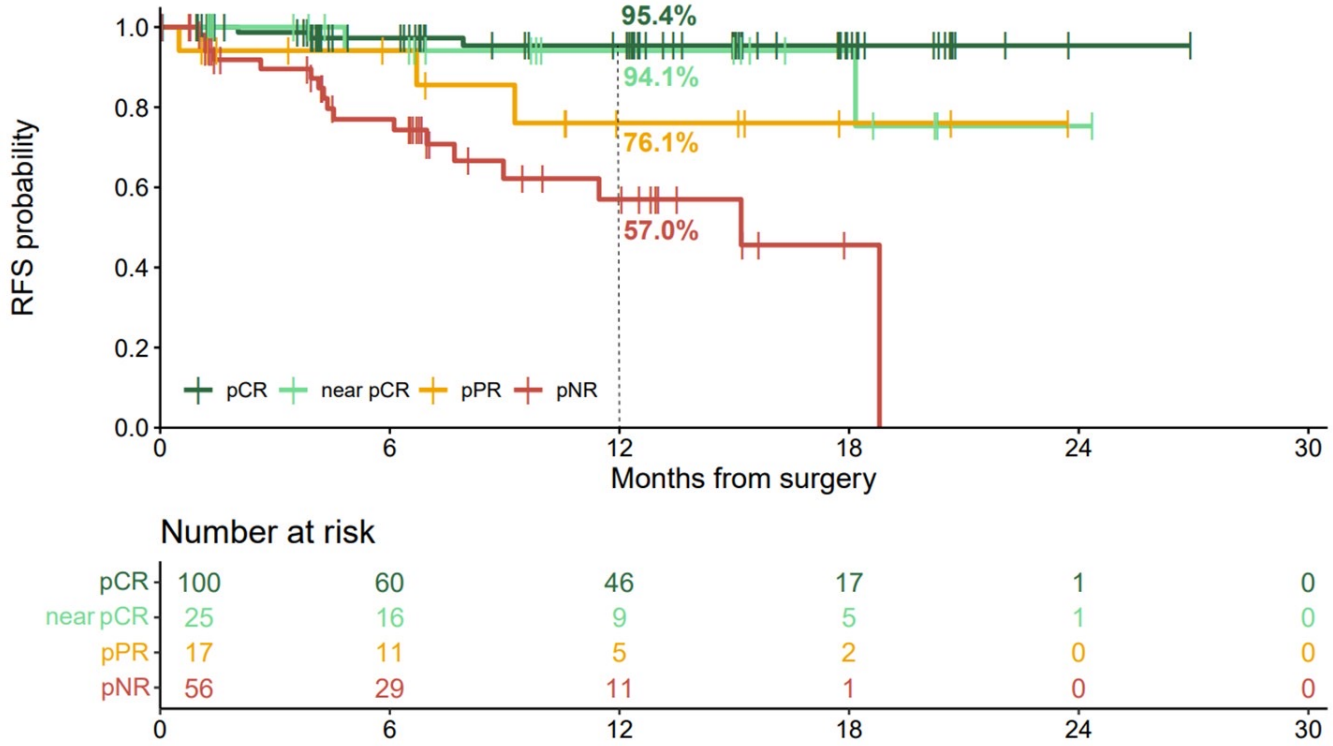


NADINA – Primary Endpoint: Event-Free Survival (EFS)



# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

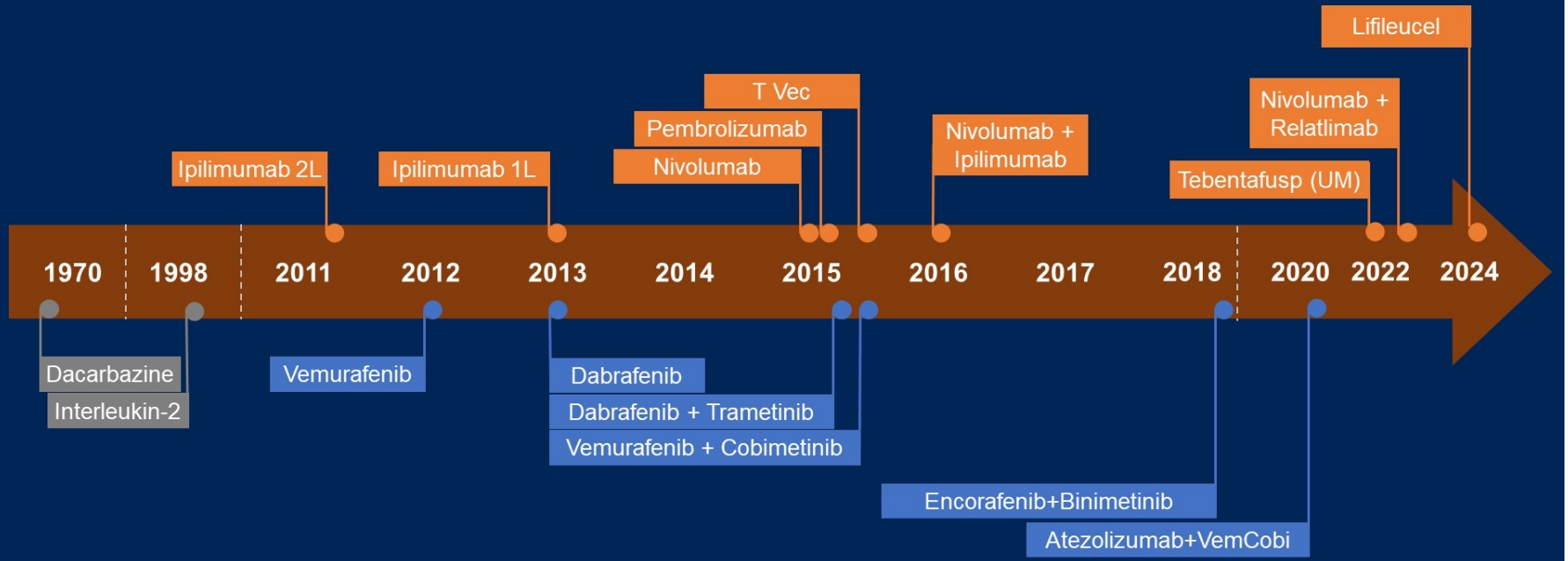
NADINA – RFS According to Pathologic Response

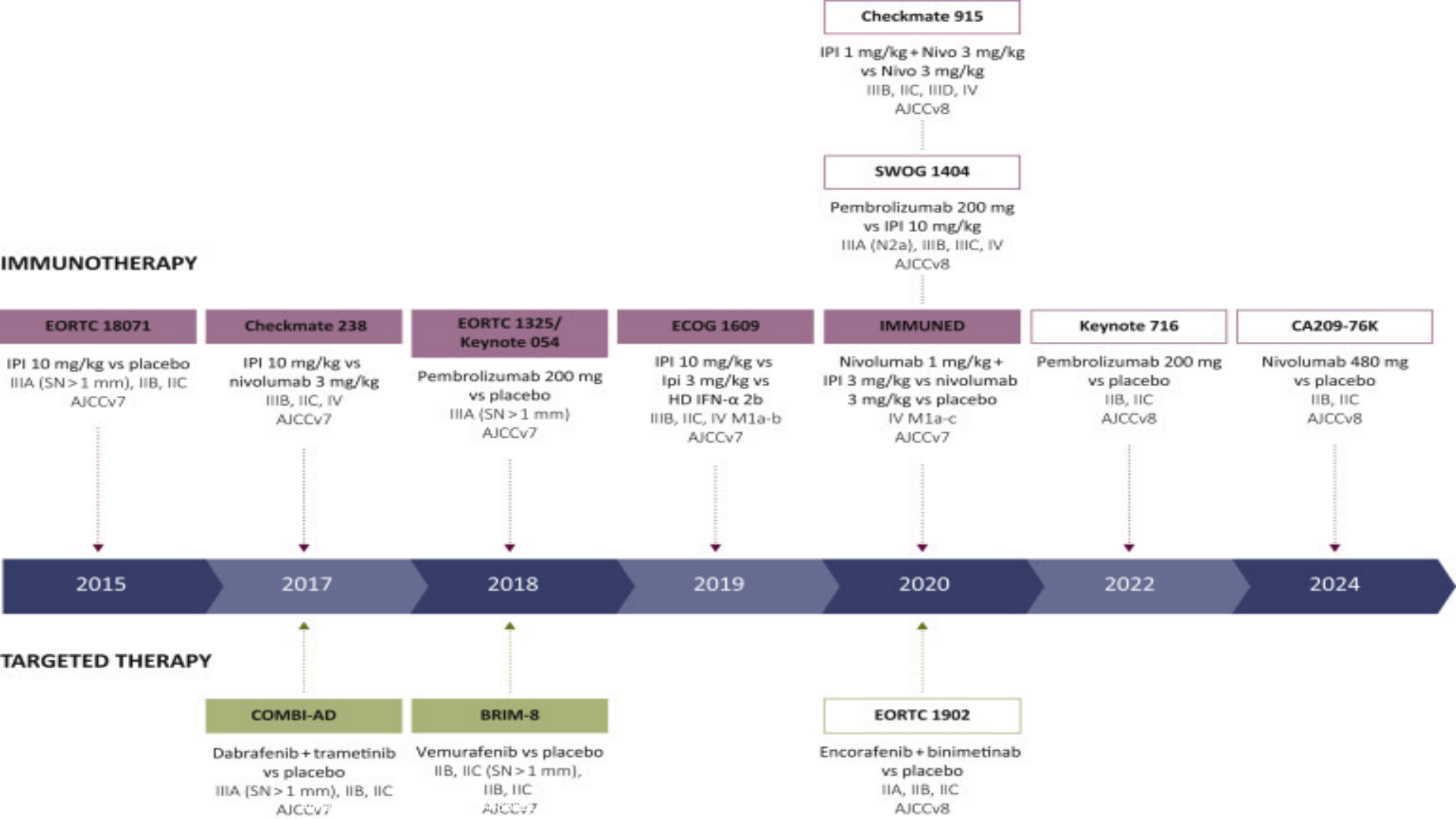


Conclusions

- NADINA is the first neoadjuvant checkpoint inhibitor phase 3 trial in melanoma
- It is also the first phase 3 trial for any solid tumor testing a neoadjuvant checkpoint inhibitor combination without chemotherapy
- Neoadjuvant combination of ipilimumab + nivolumab results in a highly statistically signifcant EFS benefit as compared to standard of care adjuvant PD-1 blockade (HR=0.32, $p<0.0001$)
- Nearly 60% of patients in neoadjuvant arm needed only 6 weeks of treatment
- All subgroups benefit from neoadjuvant ipilimumab + nivolumab

The Stage IV Melanoma Treatment Revolution




Checkmate 915
IPI 1 mg/kg + Nivo 3 mg/kg vs Nivo 3 mg/kg
IIIB, IIC, IIID, IV
AJCCv8
SWOG 1404
Pembrolizumab 200 mg vs IPI 10 mg/kg
IIIA (N2a), IIIB, IIIC, IV
AJCCv8
IMMUNOTHERAPY
EORTC 18071
IPI 10 mg/kg vs placebo
IIIA (SN > 1 mm), IIB, IIC
AJCCv7
Checkmate 238
IPI 10 mg/kg vs nivolumab 3 mg/kg
IIIB, IIC, IV
AJCCv7
EORTC 1325/ Keynote 054
Pembrolizumab 200 mg vs placebo
IIIA (SN > 1 mm)
AJCCv7
ECOG 1609
IPI 10 mg/kg vs Ipi 3 mg/kg vs HD IFN-α 2b
IIIB, IIC, IV M1a-b
AJCCv7
IMMUNED
Nivolumab 1 mg/kg + IPI 3 mg/kg vs nivolumab 3 mg/kg vs placebo
IV M1a-c
AJCCv7
Keynote 716
Pembrolizumab 200 mg vs placebo
IIB, IIC
AJCCv8
CA209-76K
Nivolumab 480 mg vs placebo
IIB, IIC
AJCCv8
2015
2017
2018
2019
2020
2022
2024
TARGETED THERAPY
COMBI-AD
Dabrafenib + trametinib vs placebo
IIIA (SN > 1 mm), IIB, IIC
AJCCv7
BRIM-8
Vemurafenib vs placebo
IIB, IIC (SN > 1 mm), IIB, IIC
AJCCv7
EORTC 1902
Encorafenib + binimetinab vs placebo
IIA, IIB, IIC
AJCCv8

Summary & Conclusions

- Immunotherapy is a mainstay for therapy of melanoma stages II-IV
- Patients refractory to PD-1 therapy represent an area of unmet need.
  - T-cell therapy recently approved
- RNA vaccine looks promising in adjuvant therapy
- Neoadjuvant therapy is a new standard of care for macroscopic stage III melanoma