Improving Outcomes for PD-1 Resistant Melanoma: What's On the Horizon?

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Disclosures/ Potential Conflicts

Last 36 Mos

Consultant:

BMS, Merck, Novartis, Genentech/Roche, Pfizer, Exelixis, Aveo, Agenus, SeaGen, AstraZeneca, Calithera, Asher Bio, Neoleukin, Sanofi, COTA, Idera, Apexigen, Iovance

Advisory Boards:

Eisai, Novartis, Pfizer, Genentech/Roche, Merck, BMS, Pyxis Oncology, Werewolf, Fathom, Pneuma, Leads, X4 Pharma, ValoHealth, Surface, Simcha, Takeda, ScholarRock, Elpis, SAB Bio, OncoRena

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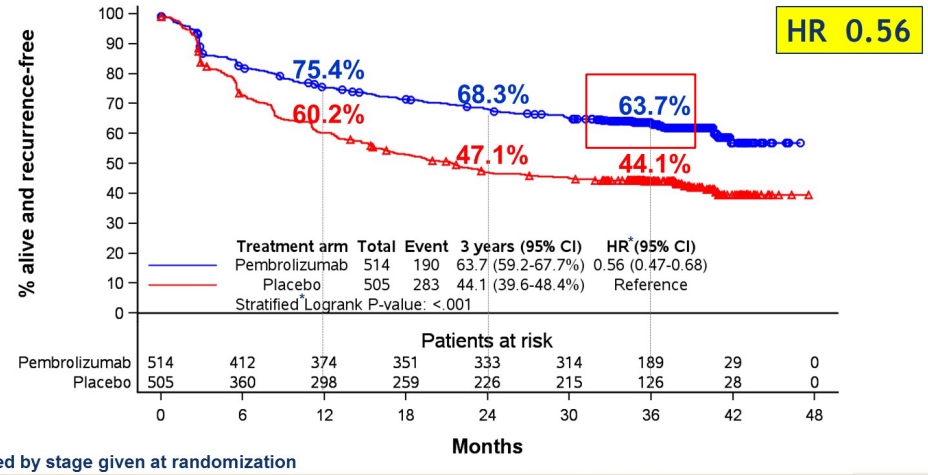
Stock Options: Werewolf, Pyxis Oncology

Other: UpToDate: Melanoma Section Editor

Why do we need additional strategies beyond anti-PD-1 therapy in melanoma?

EORTC 1325/KEYNOTE-54: New RFS analysis (ASCO 2020)

- ***Cut-off date*** (30-Sep-2019); duration of follow-up: median **3** years; **473** RFS events

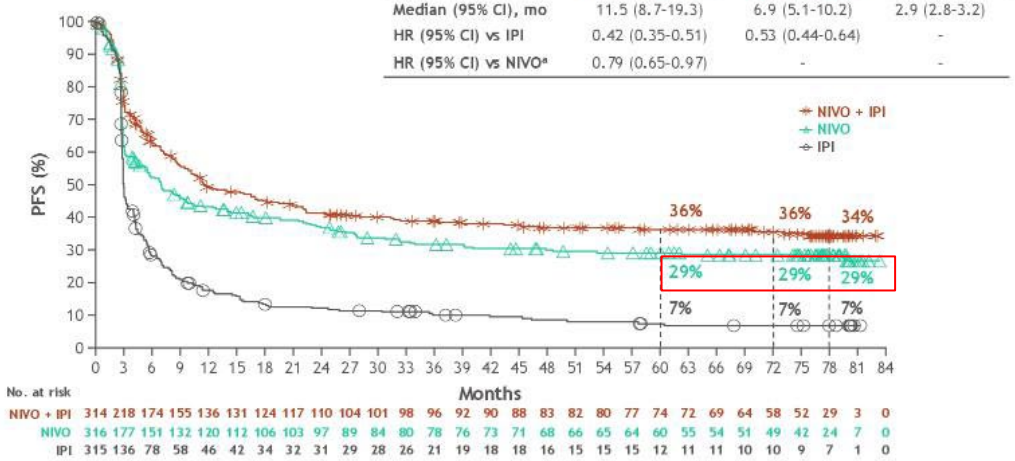


*Stratified by stage given at randomization

Checkmate 067

Progression-free survival

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	11.5 (8.7-19.3)	6.9 (5.1-10.2)	2.9 (2.8-3.2)
HR (95% CI) vs IPI	0.42 (0.35-0.51)	0.53 (0.44-0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65-0.97)	-	-



[a]Descriptive analysis.

Wolchok JD, et al, ASCO, 2021

Case: 50 yo woman with BRAF-mutant melanoma

- 50 yo woman with a h/o of Stage IIIB melanoma on R thigh presents with new inguinal adenopathy and multiple lung nodules 4 mos post adjuvant pembro x 1 yr.
- Biopsy reveals melanoma, BRAF V600E mutant. Brain MRI is without CNS mets.
- PS 0, LDH normal, no other significant medical conditions.
- How would you treat?

Case: 50 yr old with PD-1 resistant BRAF-m Melanoma Treatment Options

- Ipilimumab
- Nivo/ipi
- BRAF/MEK inhibitors
- Nivo/Rela
- Lenvatinib/pembro
- HD IL-2
- Experimental agents

Treatment options Post-PD-1 therapy

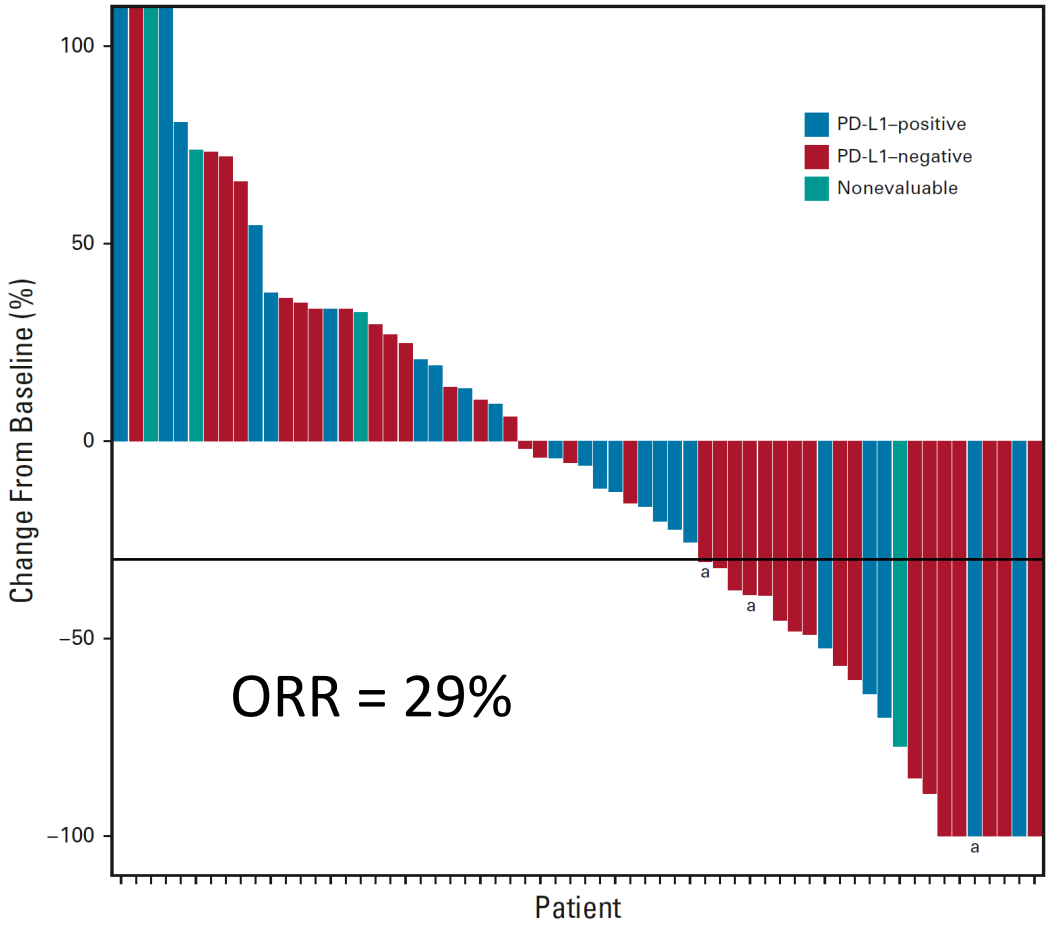
Standard:

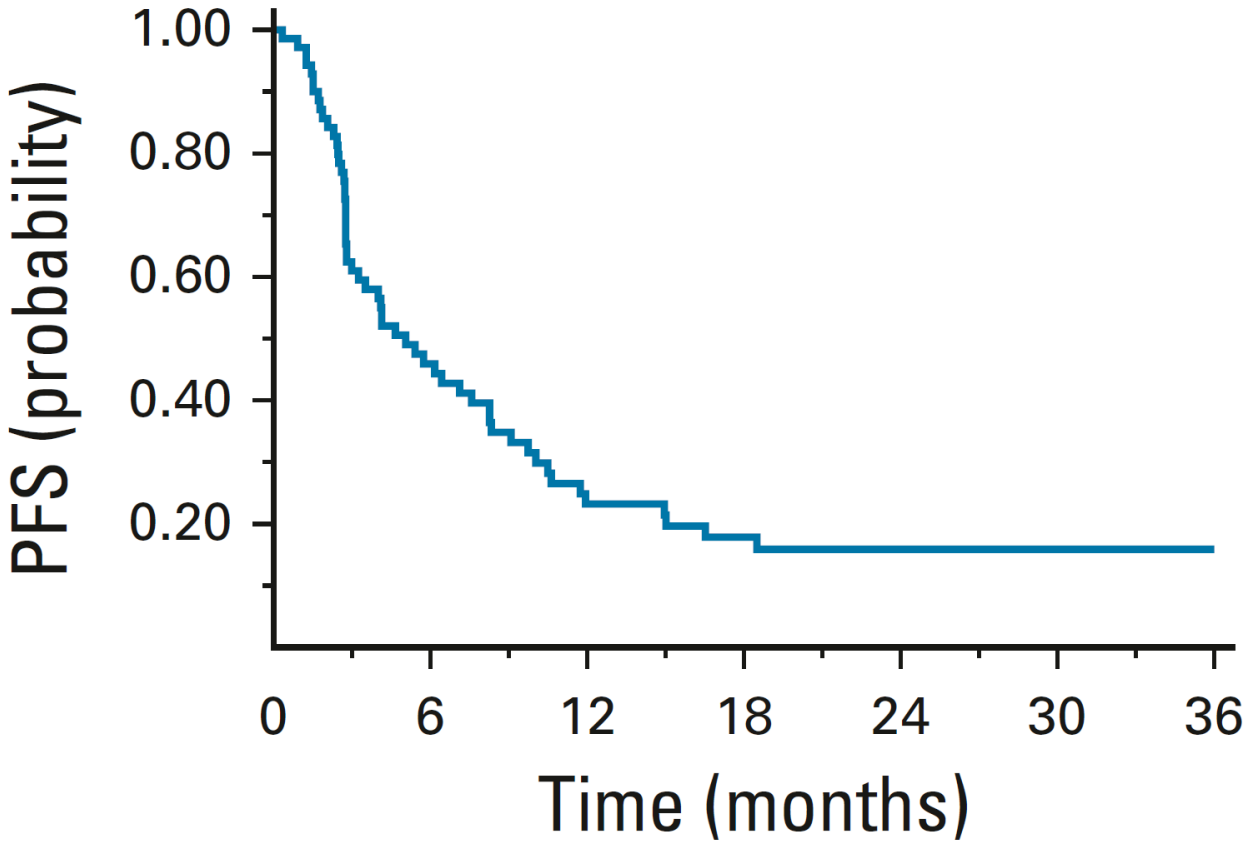
- Salvage ipilimumab
- Salvage anti-PD-1/ipilimumab
- BRAF/MEK inhibitor therapy (if BRAF mut disease)
- HD IL-2

Other options:

- TIL Therapy (currently investigational)
- Anti-PD-1 plus anti-LAG-3
- Lenvatinib/pembro
- Clinical trials

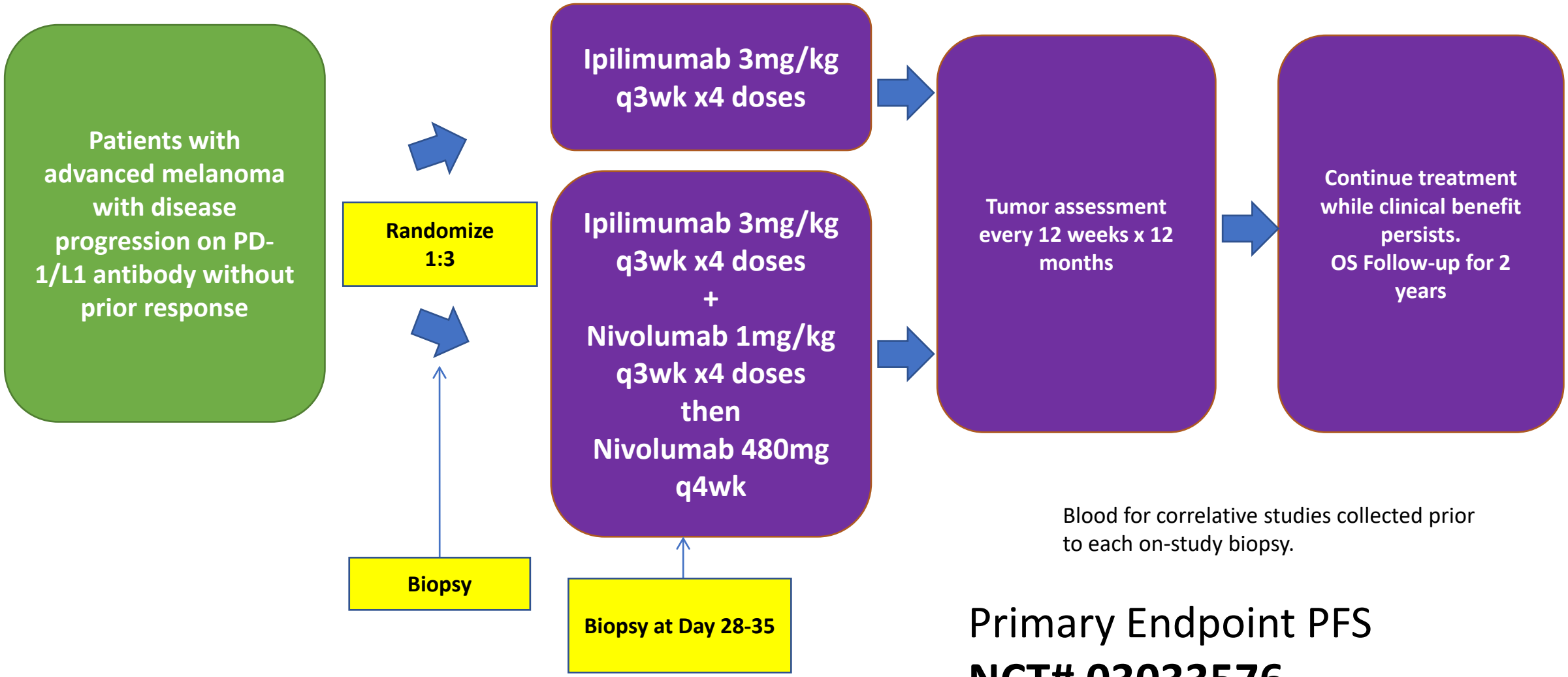
Salvage Pembrolizumab/Ipilimumab





Olson DJ, et al, J Clin Oncol, 2021

SWOG 1616: Study Schema



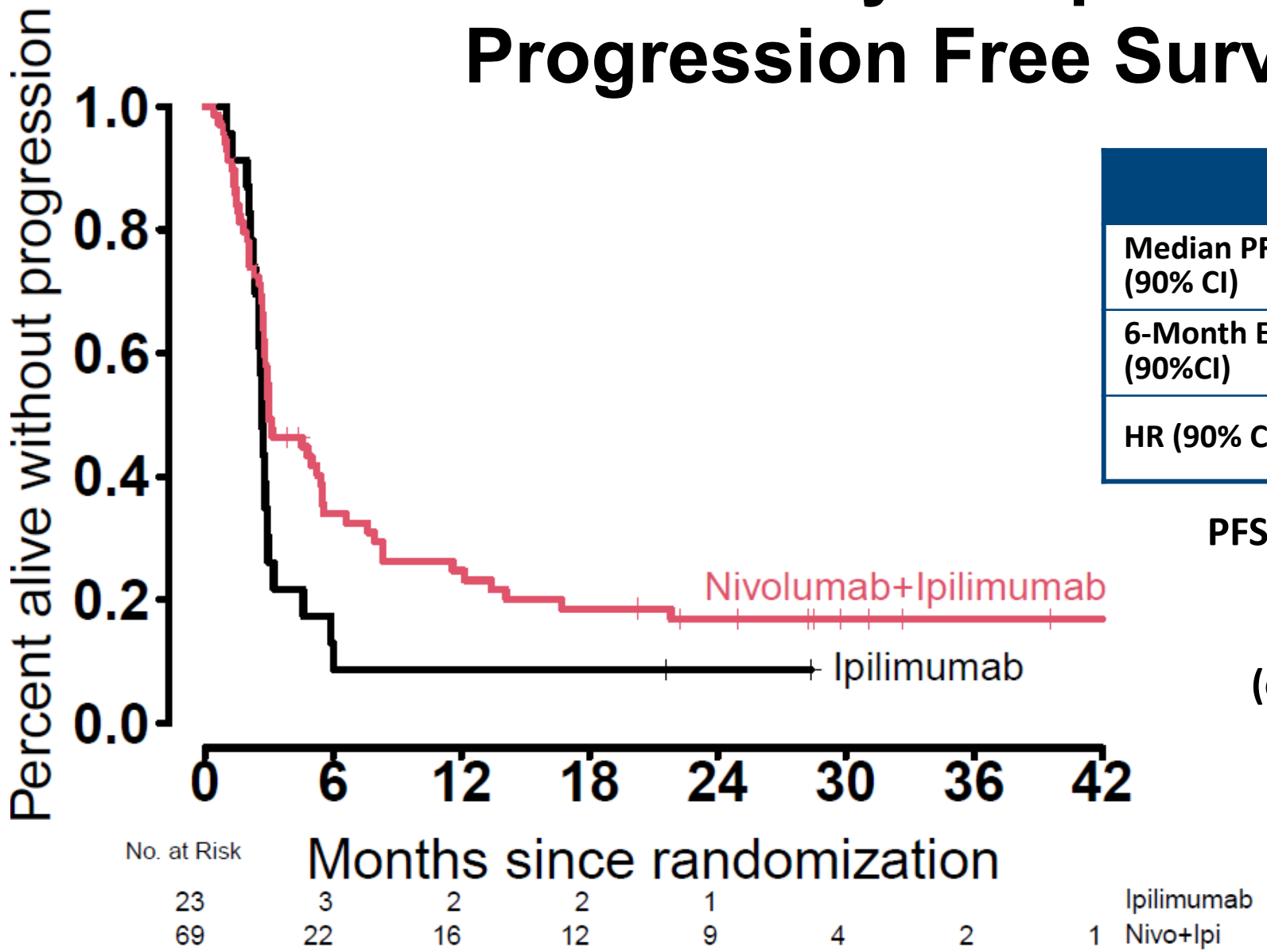
Blood for correlative studies collected prior to each on-study biopsy.

Primary Endpoint PFS

NCT# 03033576

Vanderwalde et al AACR 2022

Primary Endpoint
Progression Free Survival



	NIVO+IPI (N=69)	IPI (N=23)
Median PFS, mo (90% CI)	3.0 (2.8, 5.3)	2.7 (2.5, 2.9)
6-Month Estimate (90%CI)	34% (25%, 44%)	13% (4%,27 %)
HR (90% CI) vs. IPI	0.63 (0.41, 0.97)	--

PFS was statistically significantly improved with nivo+ipi compared to ipi (one-sided p-value = 0.037)

Median Duration of Follow-Up: 28.3 months

VanderWalde et al AACR 2022

Objective Response

Response	Ipilimumab (n=23)		Nivolumab + Ipilimumab (n=69)		P-value
	N	%	N	%	
Complete Response	0	0	6	9%	
Partial Response	2	9%	13	18%	
Stable Disease	3	13%	14	20%	
Progressive Disease	18	78%	35	51%	
Not Evaluable	0	0%	1	1%	
Objective Response (90% CI)	2	**9% (2%-25%)**	19	**28% (19%-38%)**	**0.05**

Objective Response Rate was higher for combination therapy than ipi alone

Is survival better with salvage Nivo/Ipi or BRAFi/MEKi in anti-PD-1 refractory BRAF mut melanoma?

- ORR for BRAFi/MEKi similar as first or second line tx from EA6134 DREAMSeq *Atkins MB, et al, ASCO Plenary Session, 2021*

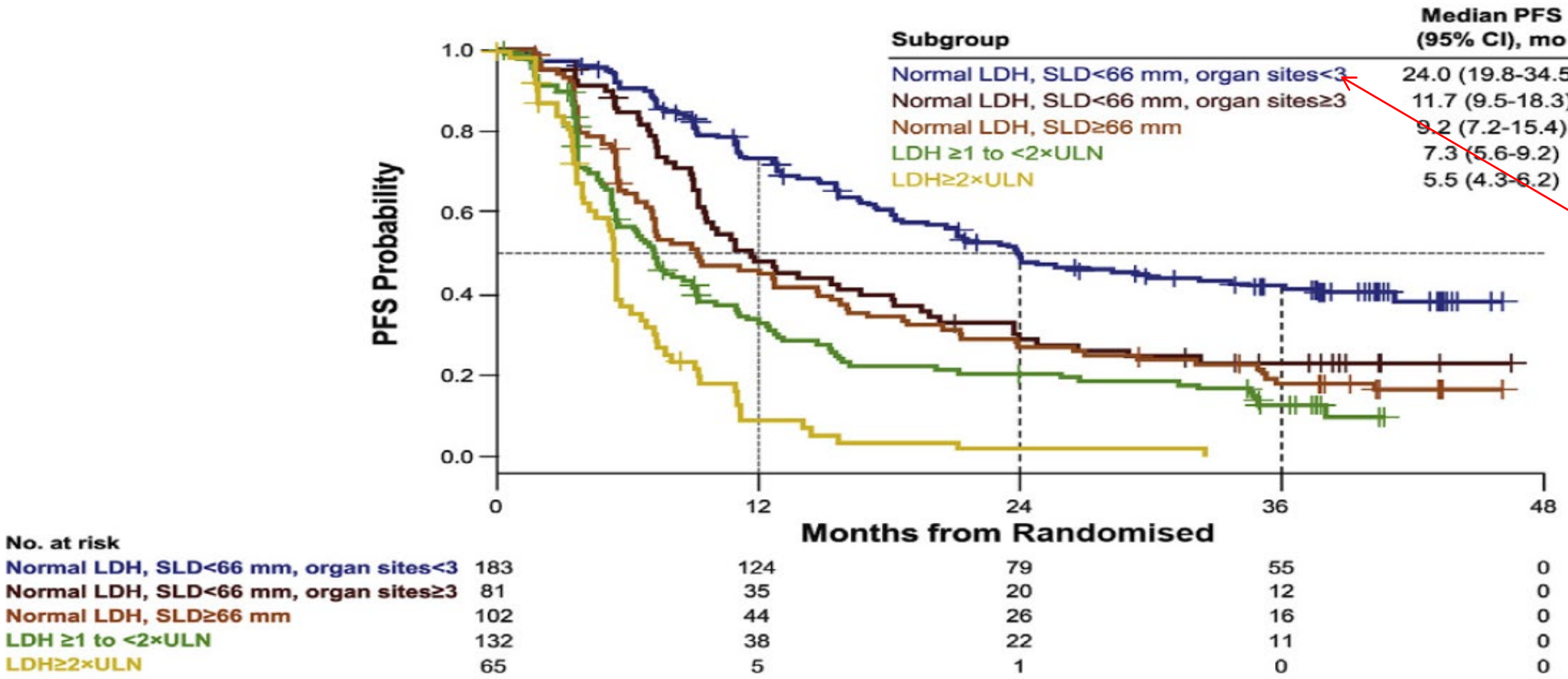
	Pembro/Ipi[2]	Nivo/ipi[1]	Enco/Bini[3]
ORR BRAF mut	29% 25%	28% NR	64%
mPFS	3.0mos	5mos	14.9mos
12month PFS	~25%	~25%	56%
24month PFS	<20%	<20%	37%

Do we need a DREAMSeq2 for the anti-PD-1 failure population?

1. Vanderwalde A, et al, AACR, 2022.
2. Olson D, et al, J Clin Oncol, 2021.
3. Ascierto PA, et al, Eur J Cancer, 2020.

Where Do We See the Most Benefit With BRAFi/MEKi?

Pooled data for dabrafenib/trametinib from COMBI-d and COMBI-v



ORR 83%
CR 42%

CR indicates complete response; LDH, lactate dehydrogenase; SLD, baseline sum of lesion diameters; ULN, upper limit of normal.

Schadendorf D, et al. *Eur J Cancer.* 2017;82:45-55.

What about salvage nivolumab/relatlimab?

- **FDA approved based on frontline data (Relativity 047)**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma

Hussein A. Tawbi, M.D., Ph.D., Dirk Schadendorf, M.D., Evan J. Lipson, M.D., Paolo A. Ascierto, M.D., Luis Matamala, M.D., Erika Castillo Gutiérrez, M.D., Piotr Rutkowski, M.D., Ph.D., Helen J. Gogas, M.D., Christopher D. Lao, M.D., M.P.H., Juliana Janoski De Menezes, M.D., Stéphane Dalle, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean-Jacques Grob, M.D., Shivani Srivastava, M.D., Mena Abaskharoun, Pharm.D., Melissa Hamilton, M.P.H., Sarah Keidel, M.B., Ch.B., Katy L. Simonsen, Ph.D., Anne Marie Sobiesk, Ph.D., Bin Li, Ph.D., F. Stephen Hodi, M.D., and Georgina V. Long, M.D., Ph.D., for the RELATIVITY-047 Investigators*

Tawbi H, et al, N Engl J Med 2022

Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti–LAG-3; BMS-986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated With Anti–PD-1/PD-L1 Therapy

Dose Escalation N = 8 (advanced solid tumors)

→ **Relatlimab (80 mg) + Nivolumab (240 mg) IV Q2W**

→ **Dose Expansion N = 262**

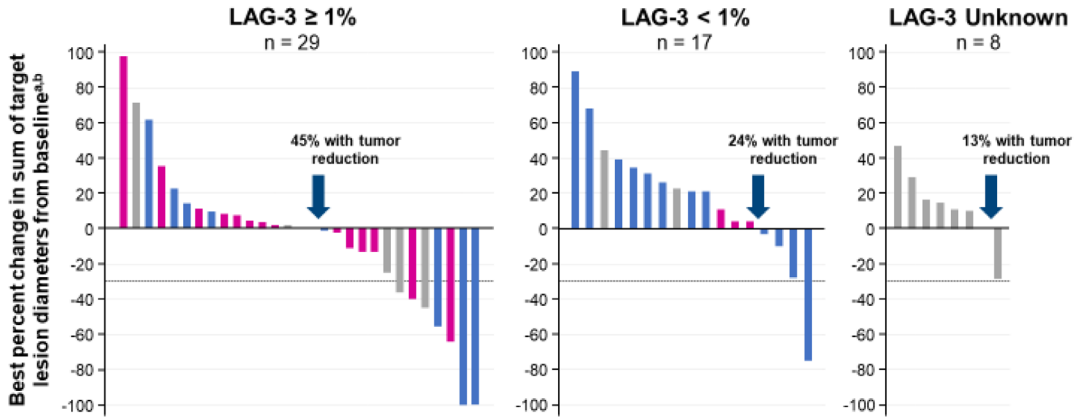
Efficacy: Melanoma (progressed during prior I-O) n = **68**[b]

Safety: All patients

Study Endpoints (dose expansion)

- **Co-Primary:** Preliminary efficacy and safety/tolerability
- **Other:** Immunogenicity, QTc, PK, PD, biomarkers

Best Change in Target Lesion Size by LAG-3 and PD-L1 Expression



Pink: PD-L1 ≥ 1% **Blue**: PD-L1 < 1% **Gray**: PD-L1 unknown

[a]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic
[b]One patient with best change from baseline > 30% had a best response of SD.

ORR = 15% (9/61)

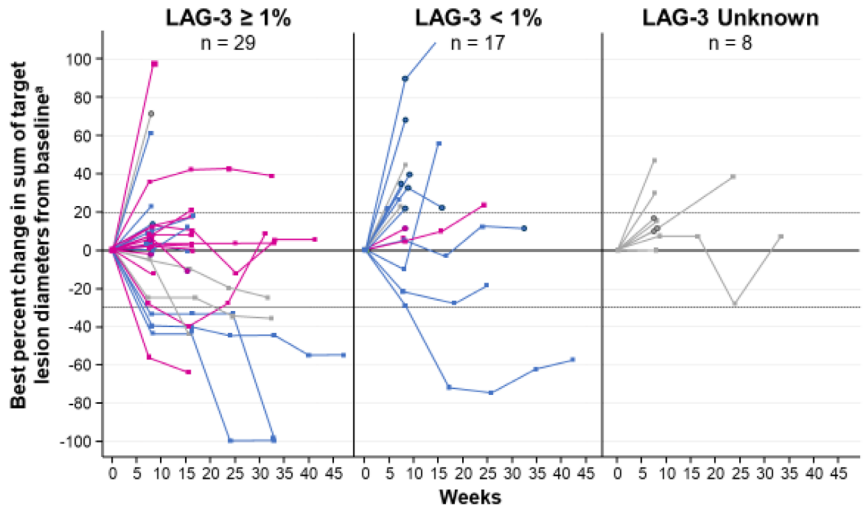
Safety of Relatlimab 80 mg + Nivolumab 240 mg Q2W

	All Patients[a] N = 270	
	Any Grade n (%)	Grade 3–4 n (%)
Any TRAE[b]	137 (51)	27 (10)
TRAEs in ≥ 5% of patients		
Fatigue	30 (11)	0
Pruritus	19 (7.0)	0
Diarrhea	18 (6.7)	3 (1.1)
Arthralgia	17 (6.3)	0
Infusion-related reaction	15 (5.6)	0
Any serious TRAE[b]	18 (6.7)	12 (4.4)
Serious TRAEs in > 1 patient		
Colitis	4 (1.5)	3 (1.1)
Pneumonitis	2 (0.7)	2 (0.7)
Myocarditis[c]	2 (0.7)	0
Pyrexia	2 (0.7)	0
Any TRAE leading to discontinuation[b]	11 (4.1)	8 (3.0)

- The safety profile of the melanoma prior PD-(L)1 cohort was similar to that of the overall population
- No treatment-related deaths were reported[d]

TRAE, treatment-related adverse event.
[a]Patients treated with relatlimab 80 mg + nivolumab 240 mg in the dose-escalation and -expansion phases as of the June 15, 2017, data cutoff.
[b]Safety evaluated per CTCAE v4.0 during treatment and up to 135 days after discontinuation. [c]There were a total of 4 myocarditis events (1.5%), all of which were grade 1, and 2 of which were serious AEs. [d]One TRAE of grade 5 myocarditis was observed with relatlimab 240 mg + nivolumab 240 mg Q2W.

Depth and Duration of Response by LAG-3 and PD-L1 Expression



- Responses were more likely in patients with LAG-3 expression ≥ 1%
- PD-L1 expression did not appear to enrich for response

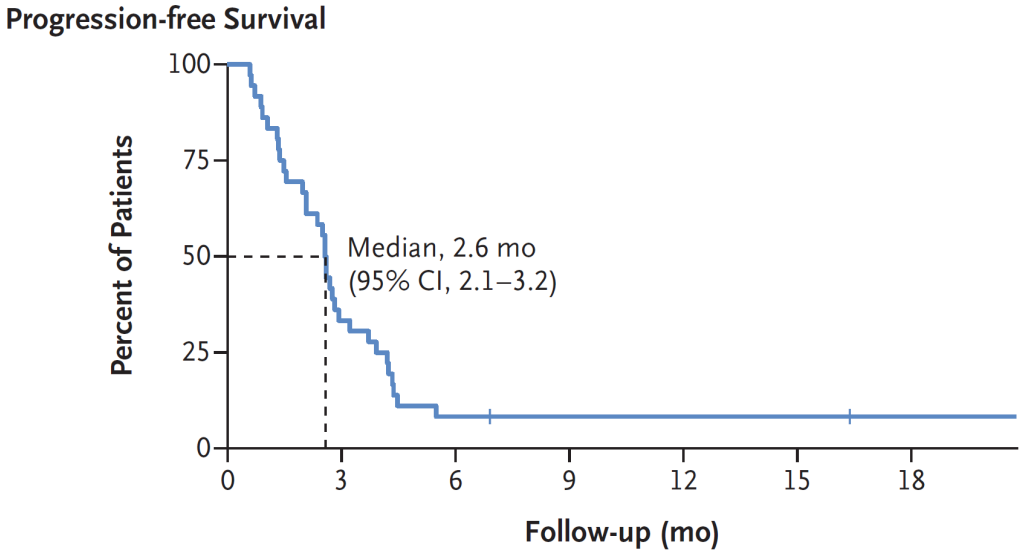
Pink: PD-L1 ≥ 1%
Blue: PD-L1 < 1%
Gray: PD-L1 unknown
o: Appearance of new lesions

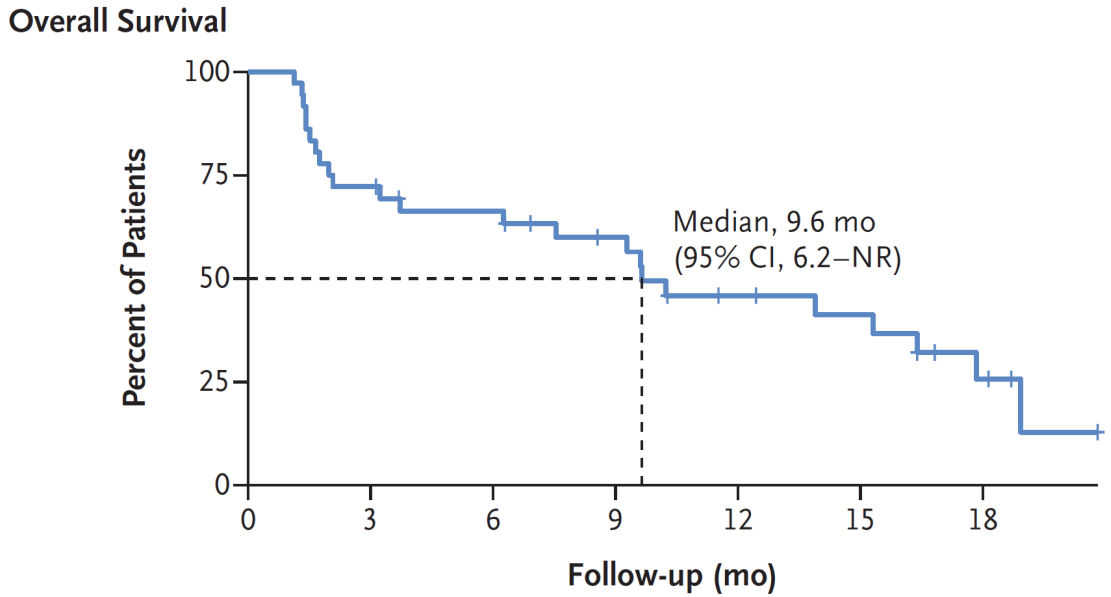
[a]Six patients with clinical progression prior to their first scan and 1 patient with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.

Ascierto PA, et al. *ESMO* 2017

CTLA-4 Blockade after Relatlimab and Nivolumab

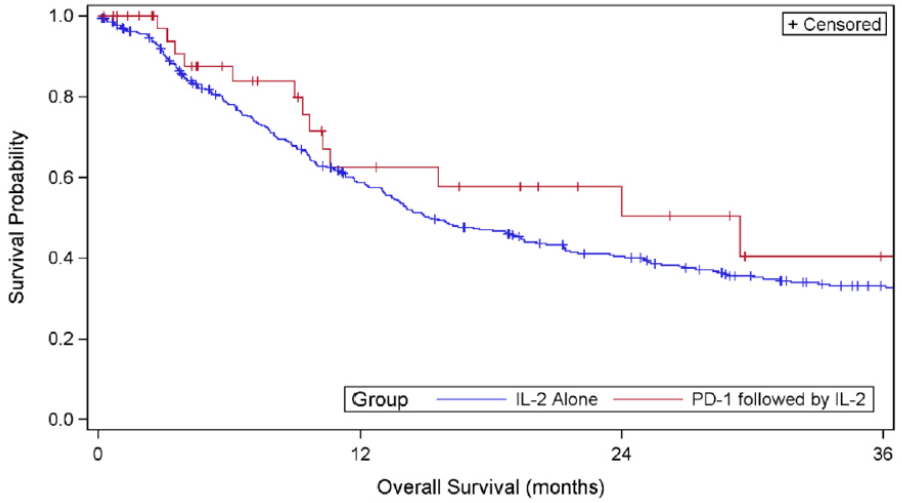
- Correspondence, *Menzies AM et al, N Eng J Med, 2022*
- 36 patients treated with ipilimumab (+/- nivolumab) after Nivo/Rela
- ORR = 11%

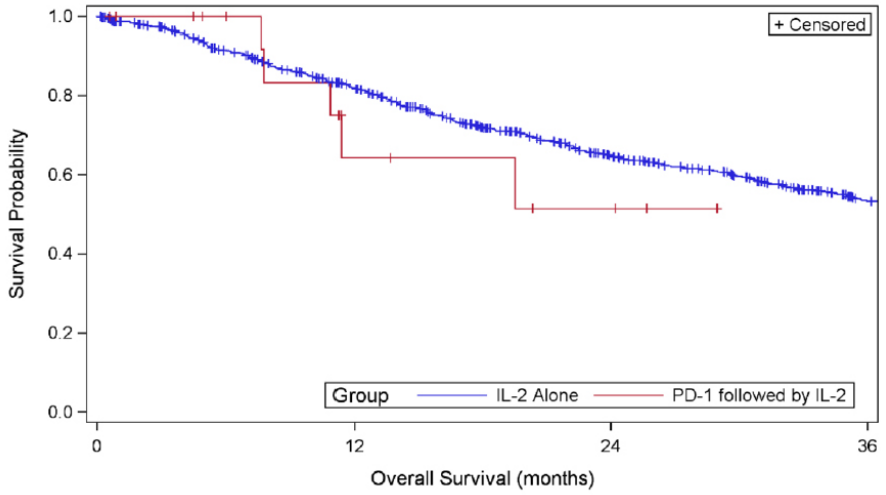




High Dose IL-2 in PD-1 refractory tumors

- 57 patients (40 mMel, 17 mRCC) who received IL-2 following anti-PD-1/PD-L1 therapy
- ORR: 9/40 (23%) mMel and 4/17 (24%) RCC
- Majority of responses were durable





*Compared to large mMel and mRCC IL-2 registry

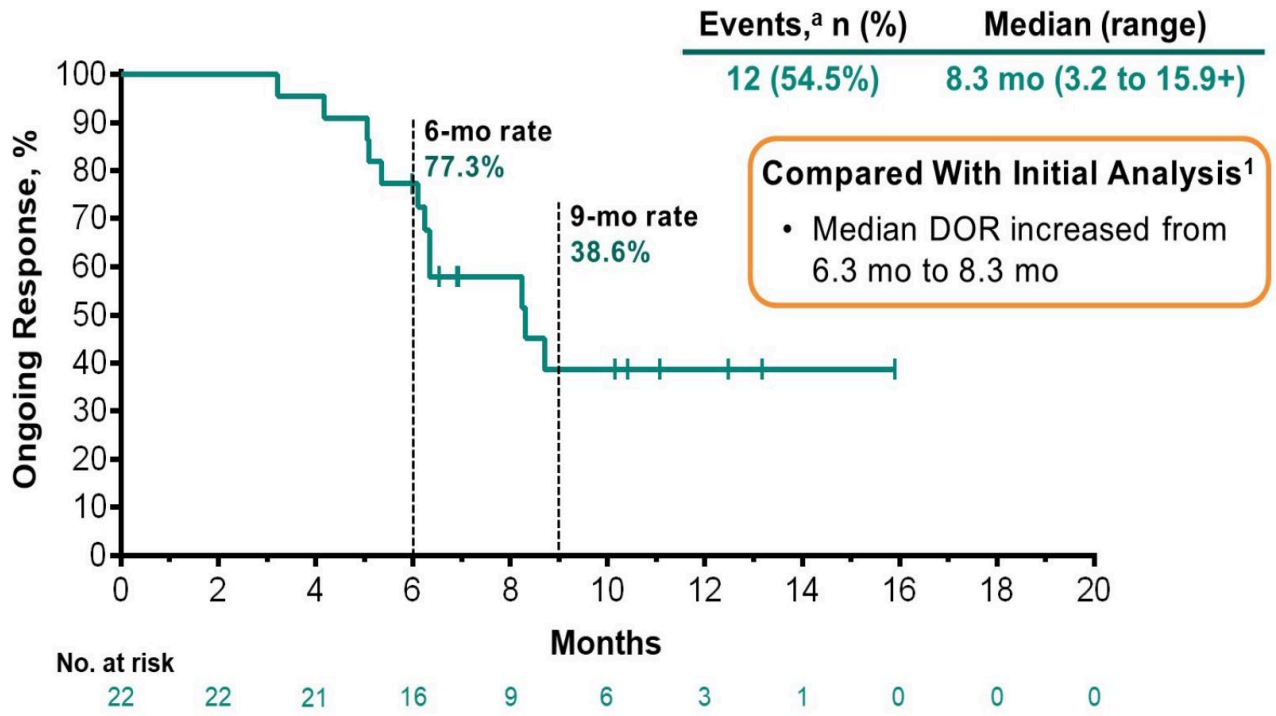
Buchbinder E, et al, JITC, 2019

LEAP-004 Study (Lenvatinib + Pembrolizumab in PD-1 Refractory Met Melanoma

Objective Response

	Total Population N = 103
ORR, % (95% CI)	**21.4% (13.9-30.5)**
DCR, % (95% CI)	66.0% (56.0-75.1)
Best overall response, n (%)	
CR	3 (2.9%)
PR	19 (18.4%)
SD	46 (44.7%)
PD	30 (29.1%)
Not assessed[a]	5 (4.9%)

Duration of Response

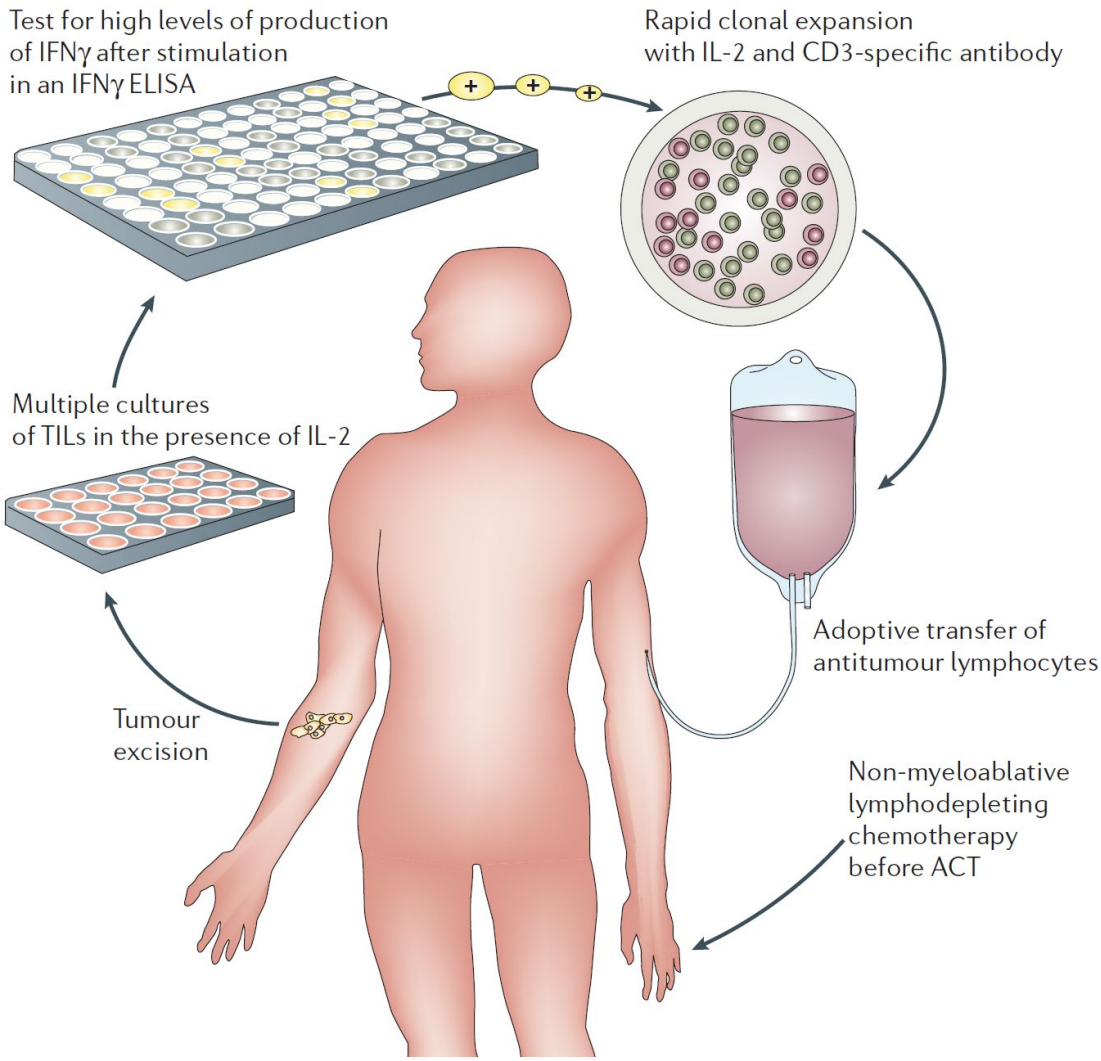


Arance et al ASCO 2021

Listed as an option in NCCN Guidelines

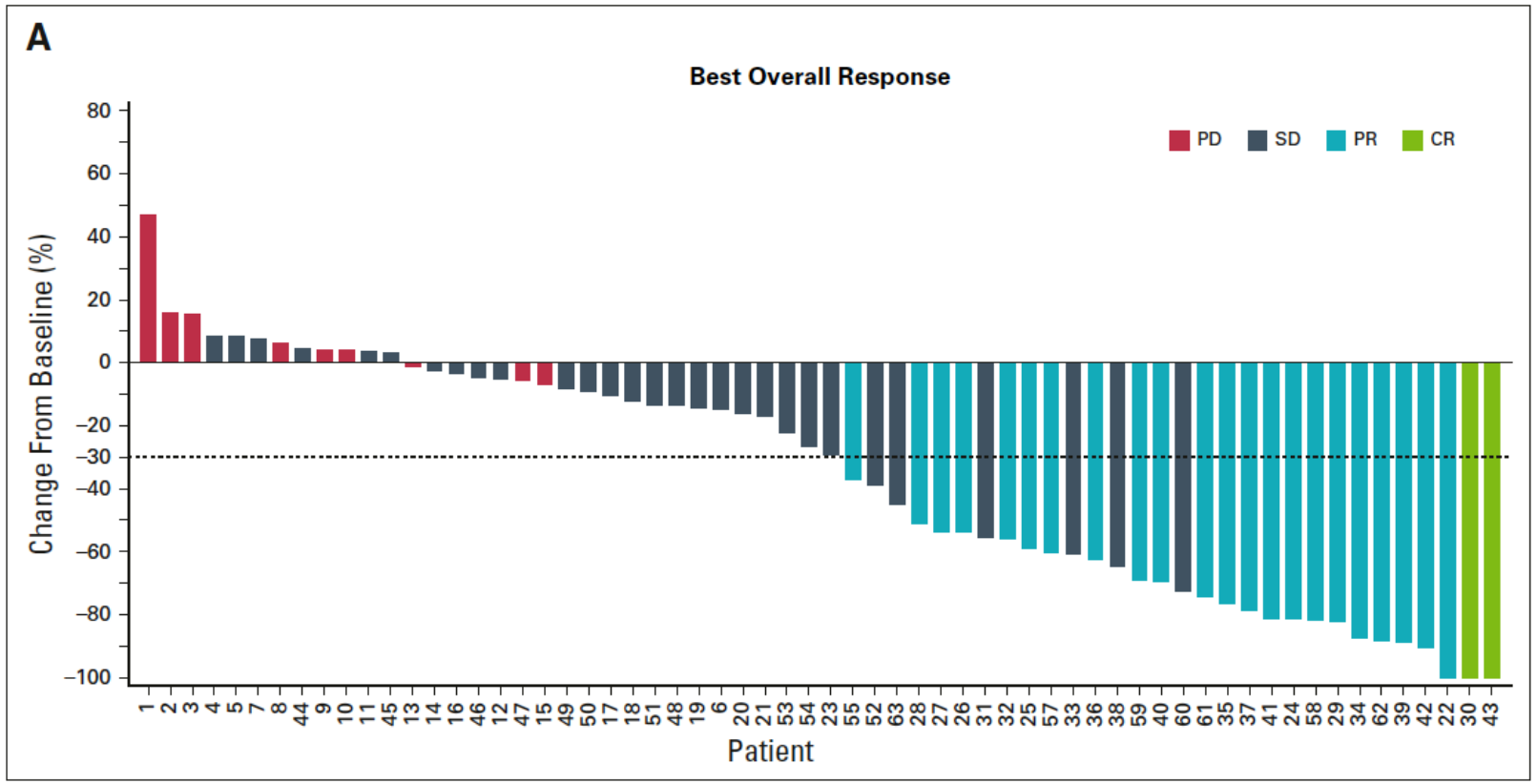
Adoptive Cell Therapy with Tumor Infiltrating Lymphocyte (TIL) therapy

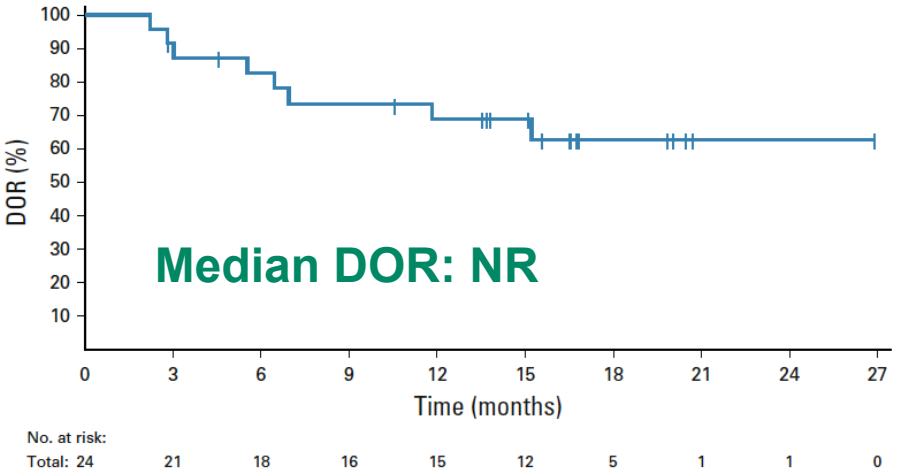
- TIL are expanded ex-vivo
- TIL selected for melanoma recognition
- Lymphodepletion reduces suppressive immune cell population
- After TIL infusion, IL-2 is administered.

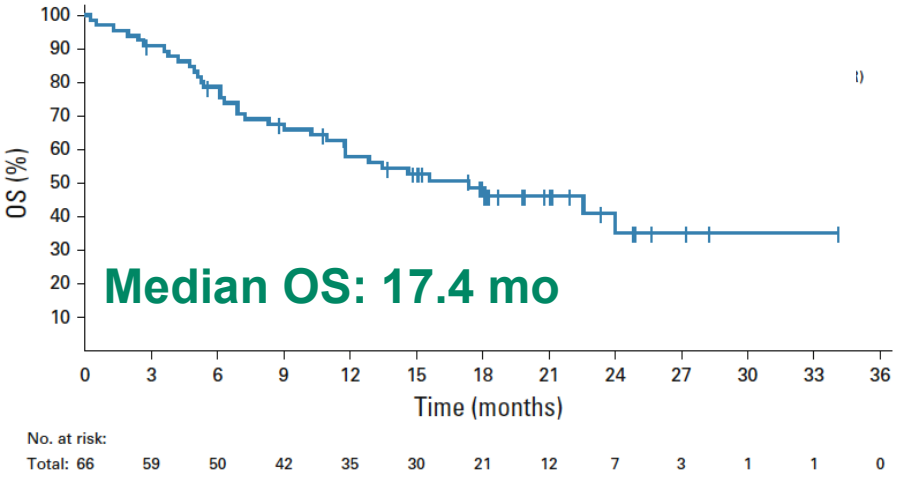


Gattinoni L, *et al.*, Nat Rev, 2006

Lifileucel for PD-1 Refractory Melanoma







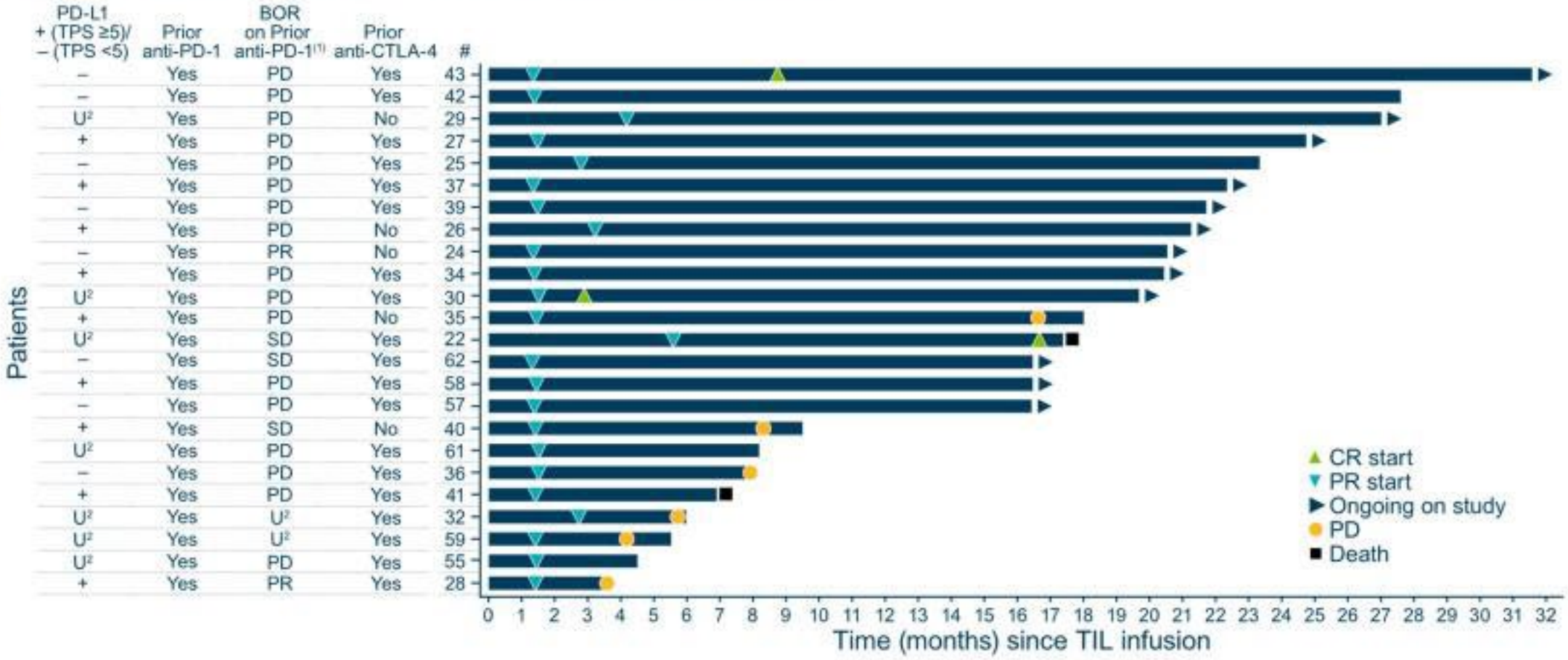
ORR: 36%
(95% CI, 25 to 49)

(Sarnaik et al. *J Clin Oncol* 2021)

C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

- 79% of responders had received prior ipilimumab
- Responses deepen over time



[1] BOR is best overall response on prior anti-PD-1 immunotherapy
[2] U: unknown
[3] Patient 22 BOR is PR

Other Active TIL therapy studies in Melanoma (US only)

Sponsor	Title	ClinicalTrials.gov Identifier
Iovance	Study of Autologous Tumor Infiltrating Lymphocytes in Patients With Solid Tumors	NCT03645928
Instil Bio	ITIL-168 in Advanced Melanoma (DELTA-1)	NCT05050006
University of Pittsburgh	Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma	NCT03467516
NIH	A Prospective Randomized and Phase 2 Trial for Metastatic Melanoma Using Adoptive Cell Therapy With Tumor Infiltrating Lymphocytes Plus IL-2 Either Alone or Following the Administration of Pembrolizumab	NCT02621021
MD Anderson	Genetically Modified T-Cells Followed by Aldesleukin in Treating Patients With Stage III-IV Melanoma	NCT01955460

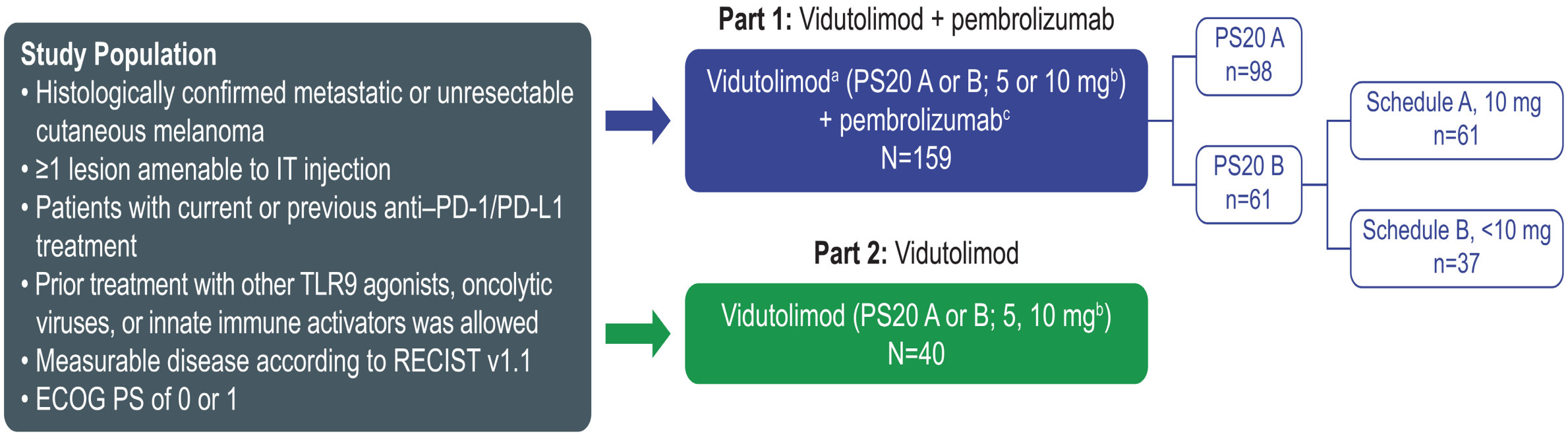
Other emerging IO strategies in patients with PD-1 refractory melanoma

- TLR 9 agonist (CMP-001) + anti-PD-1 therapy
- Tavokinogene telseplasmid (tavo; pIL-12) Electroporation (EP) + Pembrolizumab.

- *IL-2 agonists + anti-PD-1 (beyond BemPEG)*
- *Novel CTLA4 Abs (eg. botensilimab)*
- *Many others in early development*

vidutolimod + pembrolizumab

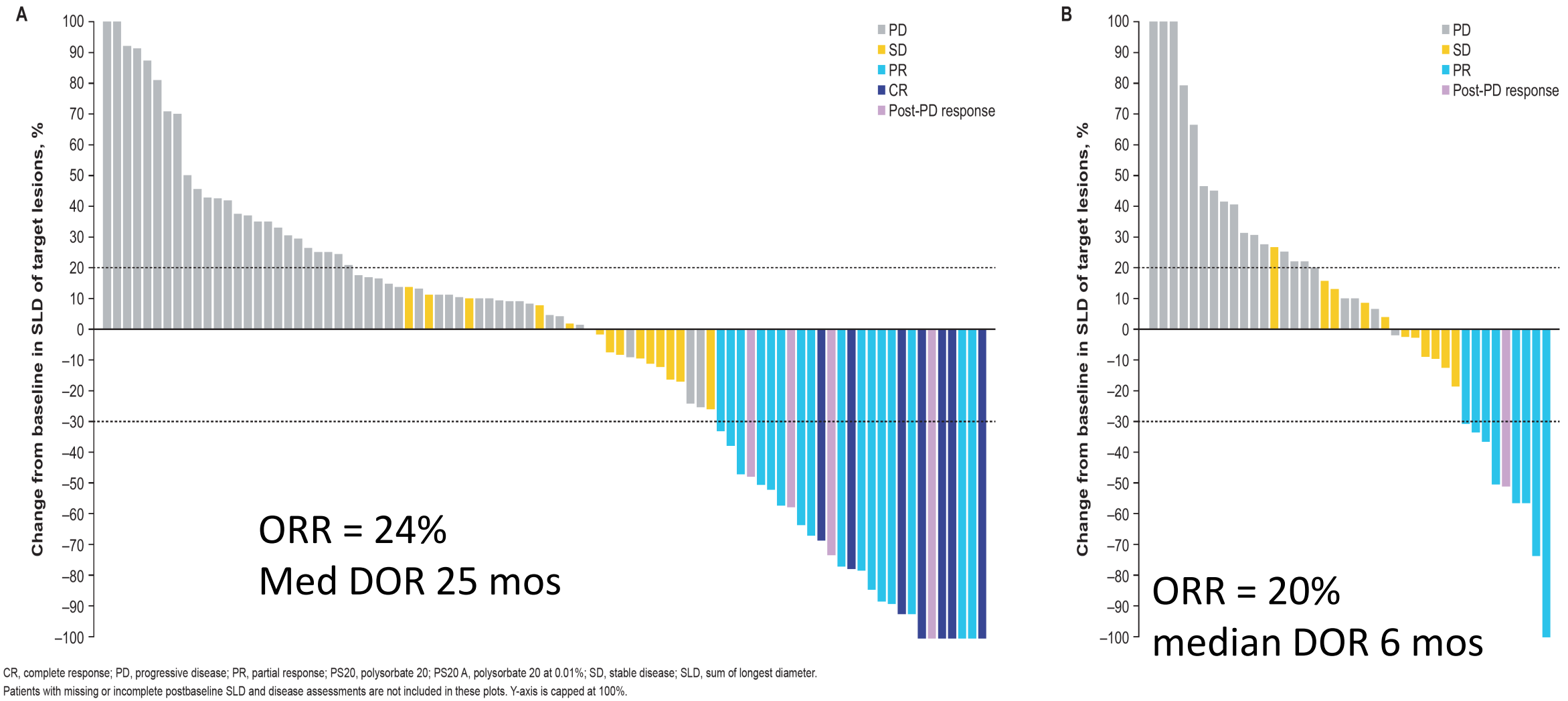
Figure 1. CMP-001-001 Study Design



Two schedules of vidutolimod administration were evaluated:
Schedule A: weekly for 7 weeks, then Q3W until discontinuation
Schedule B: weekly for 2 weeks, then Q3W until discontinuation (schedule B will be evaluated in the part 1 dose-escalation phase only)

Kirkwood J, et al, SITC, 2021

Figure 3. Best Change in Tumor Size Patients Receiving (A) Vidutolimod PS20 A + Pembrolizumab (n=98) and (B) Vidutolimod Monotherapy (N=40)

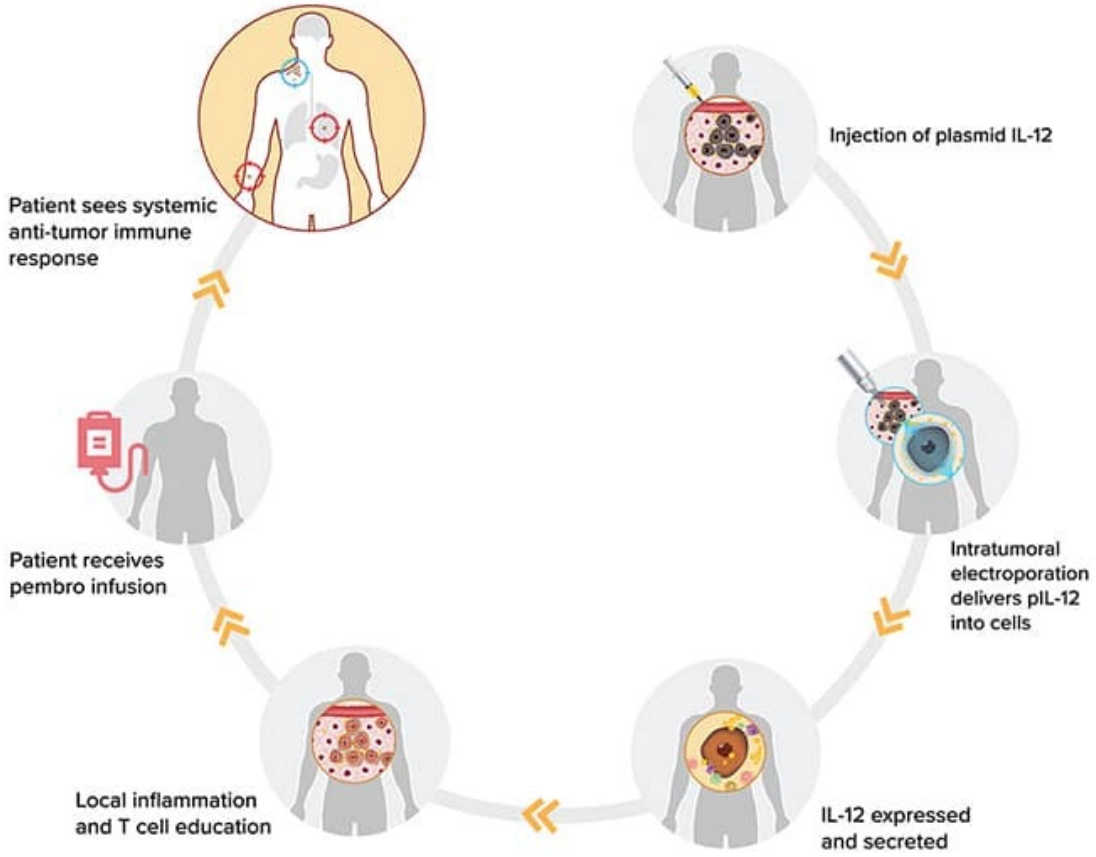


CR, complete response; PD, progressive disease; PR, partial response; PS20, polysorbate 20; PS20 A, polysorbate 20 at 0.01%; SD, stable disease; SLD, sum of longest diameter.
Patients with missing or incomplete postbaseline SLD and disease assessments are not included in these plots. Y-axis is capped at 100%.

Kirkwood J, et al, SITC, 2021

Tavokinogene telseplasmid (TAVO)

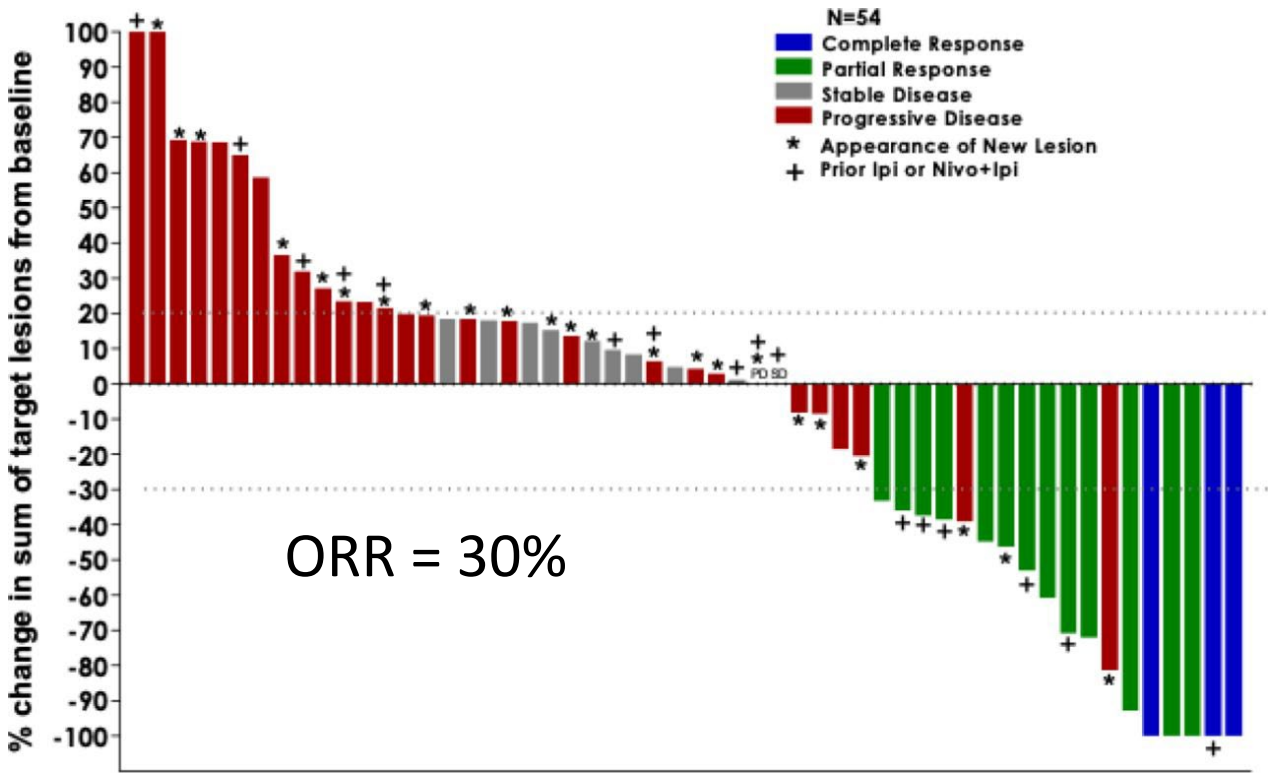
- IL12 triggers T cell and NK cell activation, Th1 polarization of CD4þ cells, reduces Treg activity
- TAVO = electroporated plasmid IL-12 administered intratumorally
- Administered days 1, 5, 8 every 6 weeks.
- Activity as a single agent and in comb with pembrolizumab in “cold” tumors.

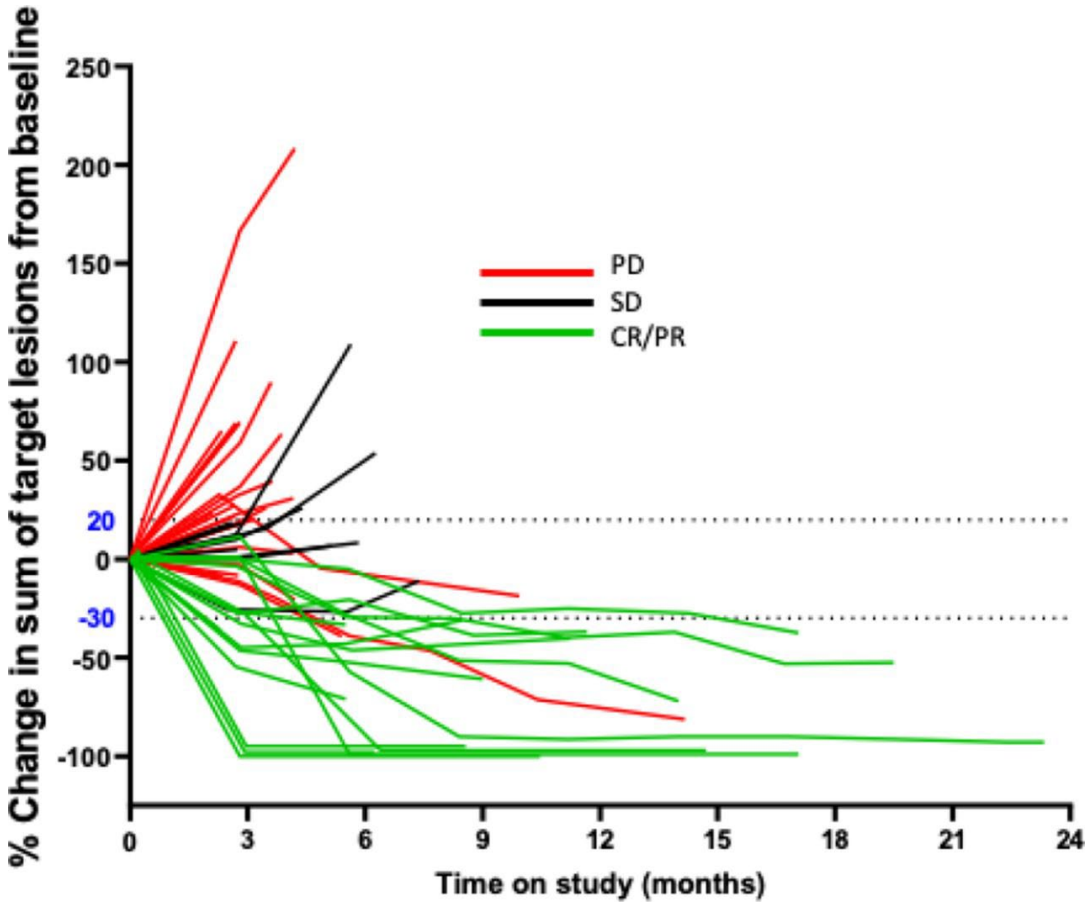


www.keynote695.com

Algazi AP, et al, Clin Cancer Res, 2020

Best confirmed overall response by RECIST v1.1 after confirmed progression on anti PD-1.





Pablo Fernandez-Penas et al. J Immunother Cancer 2020;8:A477-A478

Case: Treatment options

- Ipilimumab
- Nivo/ipi
- BRAF/MEK inhibitors
- Nivo/Rela
- Lenvatinib/pembro
- HD IL-2
- Experimental agents

Summary/Conclusions

- Salvage nivo/ipi is more active than ipi alone in PD-1 refractory melanoma.
- Salvage BRAFi/MEKi is active in BRAF V600 mutant melanoma and can be curative in patients with low volume disease.
- Potential concerns of salvage nivo/ipi efficacy after nivo/rela
- TIL therapy is an effective therapy post-PD-1.

- Many other options being explored with no definitive answers and still an unmet need.