LATEST DEVELOPMENTS

IN THE FIELD OF MELANOMA

Gil Awada, MD, PhD

Department of Medical Oncology

Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel - Jules Bordet Institute

Brussels, Belgium

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- Personal fees: Novartis, Biocartis
- Institutional research grants: Kom op tegen Kanker, Stichting tegen Kanker, Novartis

Outline

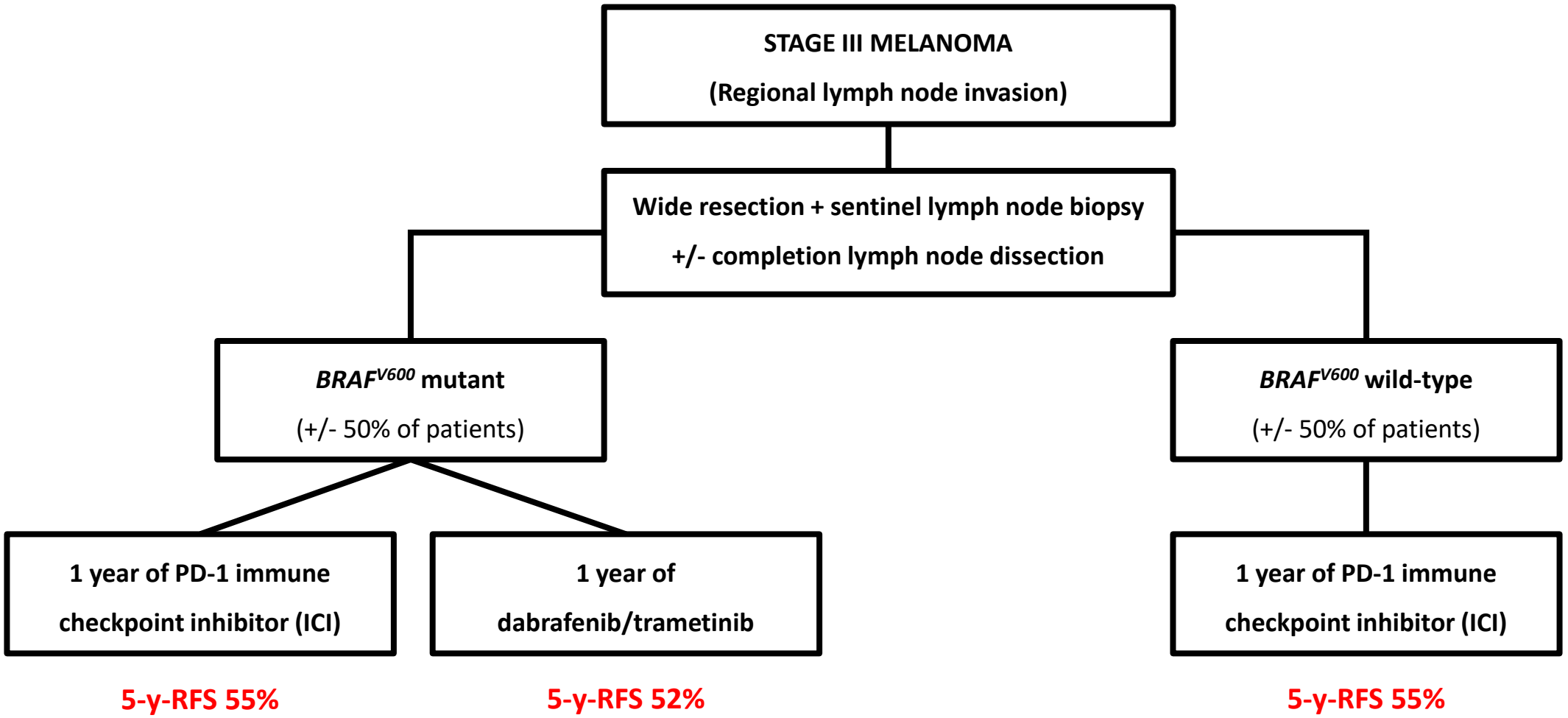
- **(Neo)adjuvant management of localized and locoregional melanoma**
  - **Neoadjuvant treatment of stage III melanoma: SWOG S1801, PRADO**
  - **Adjuvant treatment of stage II melanoma: KEYNOTE-716**

- **Managament of advanced melanoma**
  - **New data on therapeutic sequencing: DREAMseq, IMMUNED, SWOG S1616**
  - **Novel immunotherapeutic strategies: RELATIVITY-047, M14TIL, IMCgp100-202**
  - **Novel treatment combinations: LEAP-004**

- **Conclusion**

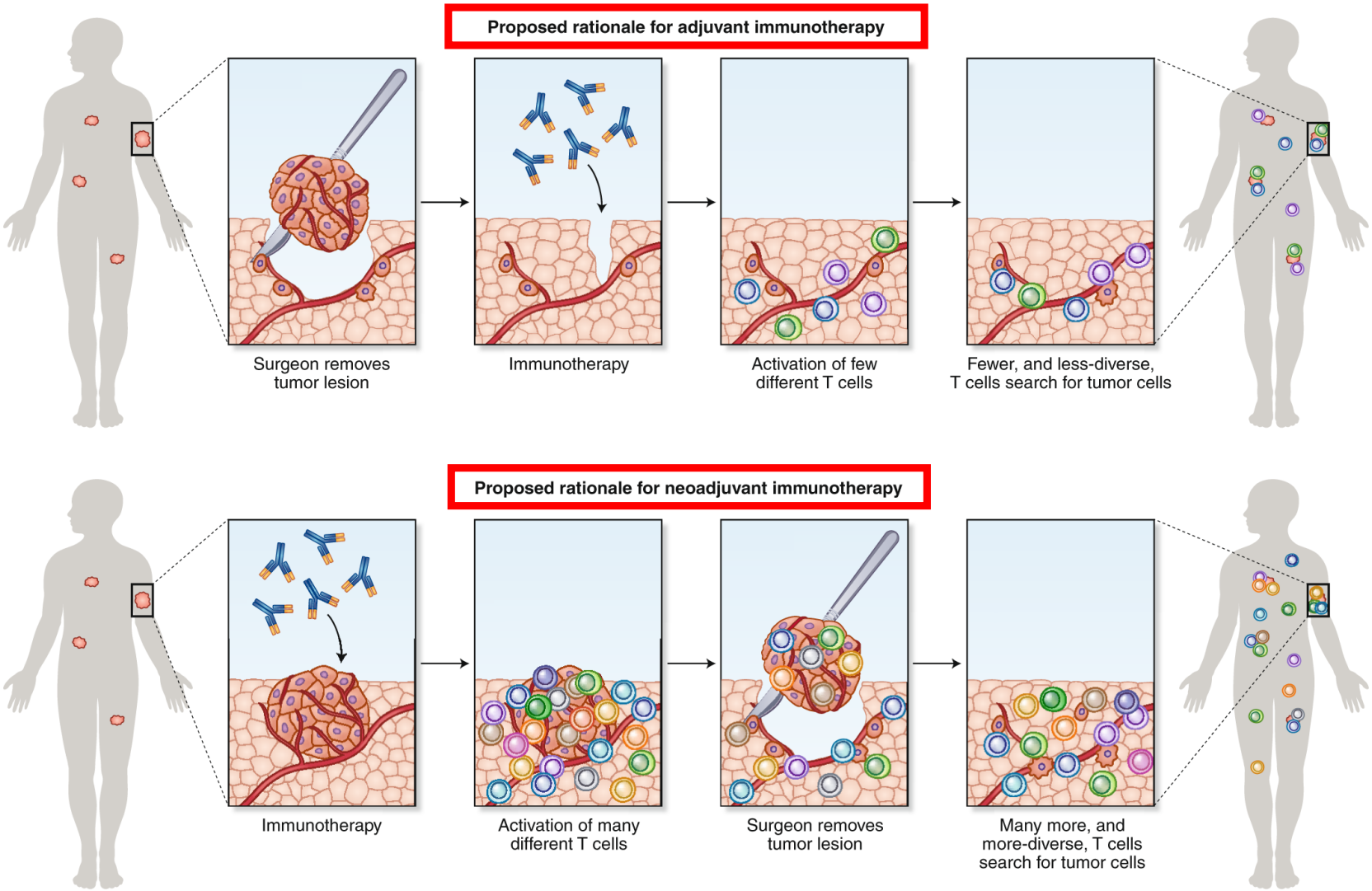
(Neo)adjuvant management of localized and locoregional melanoma

Adjuvant treatment of stage III melanoma



Based on data from CheckMate 238, COMBI-AD, KEYNOTE-05 and MSLT-II trials.

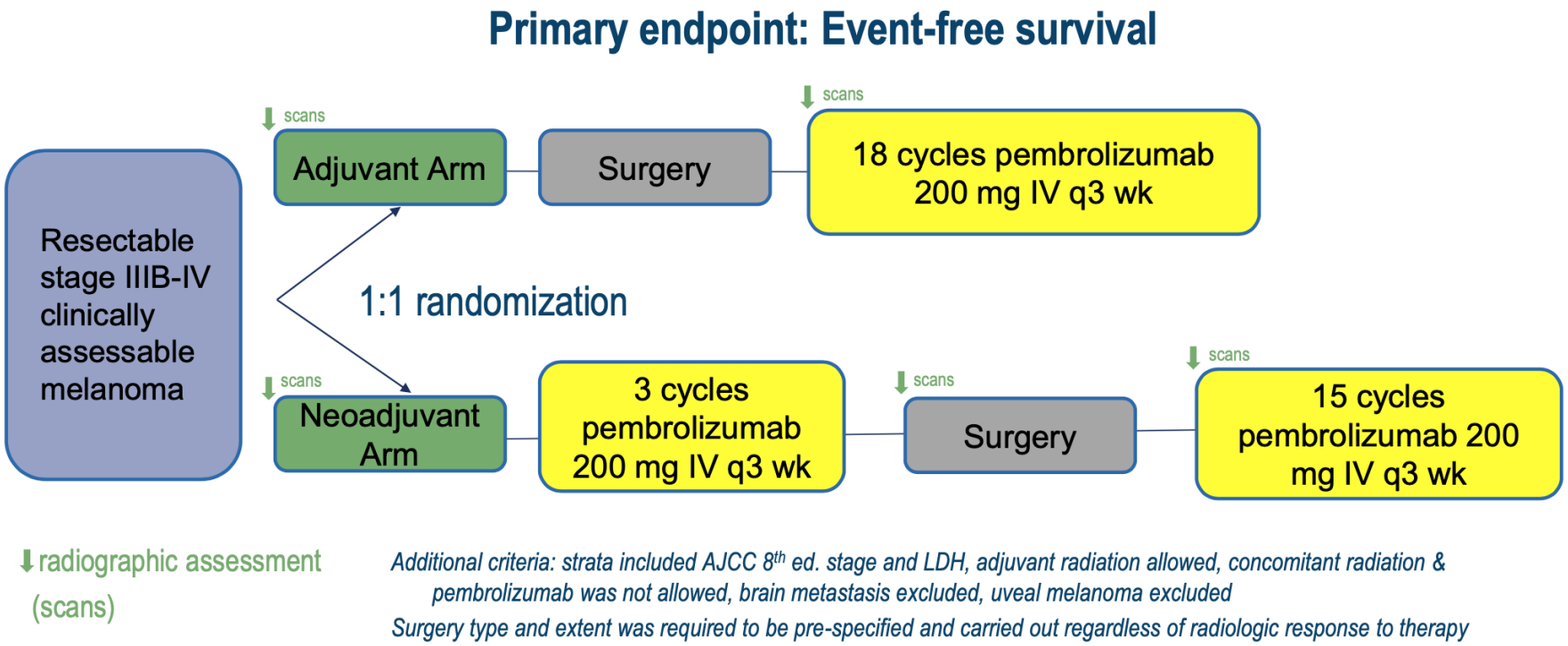
Neoadjuvant versus adjuvant treatment of melanoma



Versluis et al. Nature Medicine 2020.

Neoadjuvant treatment of stage III melanoma

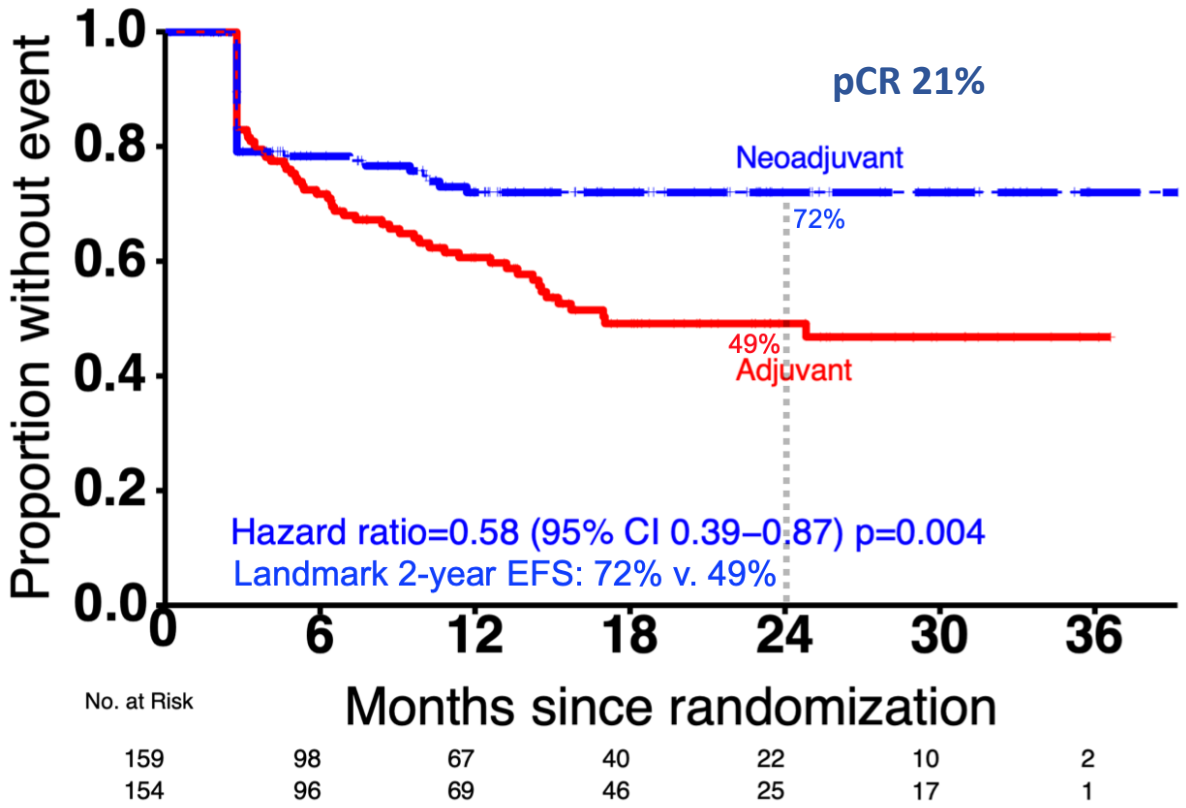
- **SWOG S1801: phase 2 trial of neoadjuvant versus adjuvant pembrolizumab (PEMBRO) for resectable stage III-IV melanoma**



Patel et al. ESMO 2022.

Neoadjuvant therapy of stage III melanoma

- **SWOG S1801: phase 2 trial of neoadjuvant versus adjuvant PEMBRO for resectable stage III-IV melanoma**



Event-Free Survival (EFS) – primary endpoint

Measured from the date of randomization to the first of the following events:

- Progression or toxicity that rendered a study participant unable to receive surgery
- Failure to begin adjuvant therapy within 84 days of surgery
- Melanoma recurrence after surgery (local, regional, or distant)
- Death from any cause

Study participants who did not register to adjuvant therapy were assigned an EFS of 84 days*

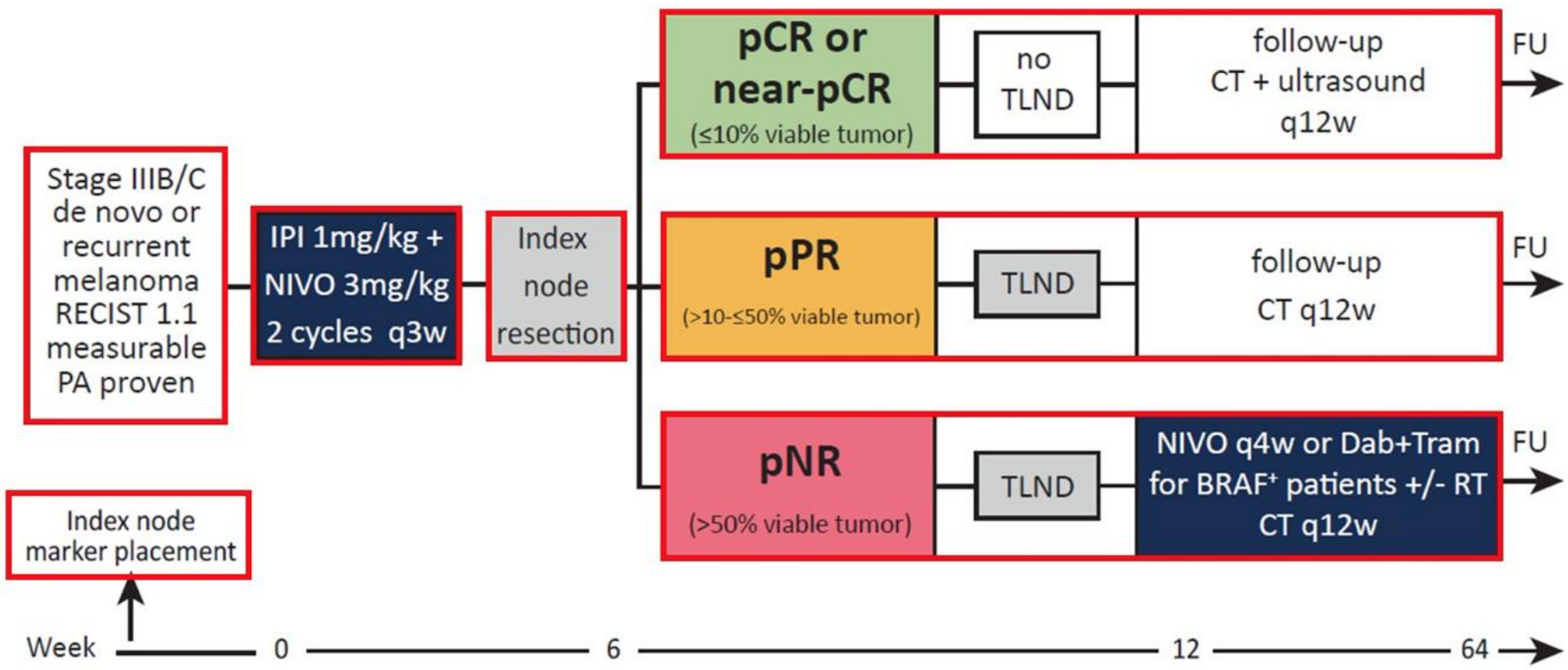
Event	Adjuvant (n=67)	Neoadjuvant (n=38)
Unable to receive surgery		
Toxicity	0	1
➡ Disease progression	0	12
Other (co-morbidities, scheduling issue)	1	1
Unable to start adjuvant therapy		
Toxicity	0	3
➡ Unable to resect all disease	1	1
➡ Disease recurrence (local, regional, distant)	16	9
Refusal by study participant	2	1
Adjuvant radiation extended past 84-day window	1	0
➡ Melanoma recurrence after starting adjuvant therapy	44	9
Death as first event	2	1

➡ *Denotes protocol-defined tumor related events*

Patel et al. ESMO 2022.

Neoadjuvant therapy of stage III melanoma

- **PRADO: phase 2 trial of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma**



pCR + near-pCR = major pathologic response (MPR)

Primary endpoints:

- **Confirmation of pathologic response rate of IPI1 + NIVO3**
- **Show that patients with MPR in index lymph node can be spared TLND without impact on RFS**
- **Prolong RFS in patients with pNR by adding adjuvant systemic therapy**

Blank et al. ASCO 2022.

Neoadjuvant therapy of stage III melanoma

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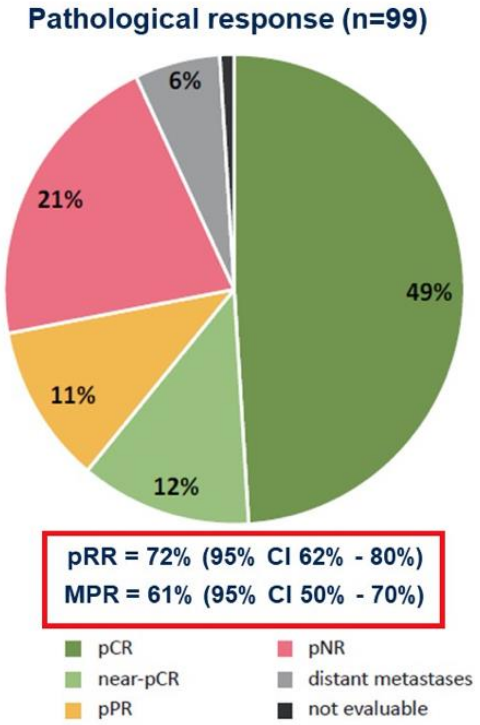
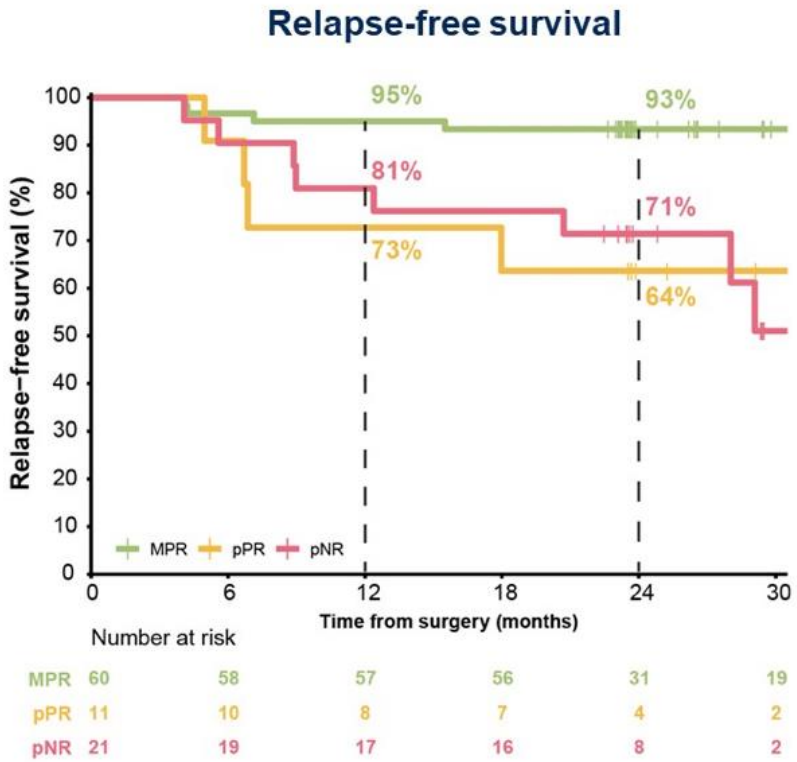
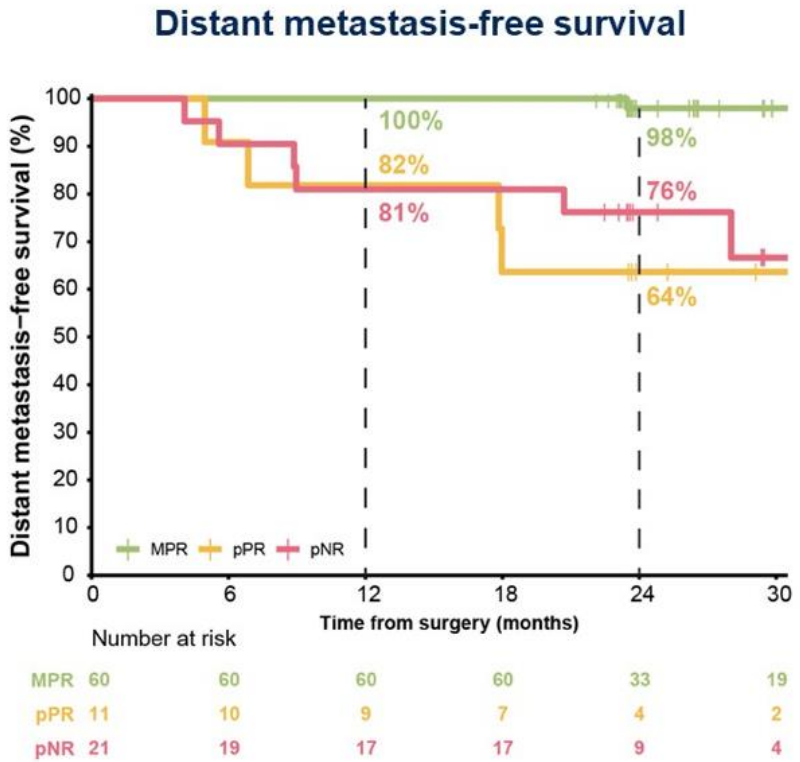






Blank et al. ASCO 2022.

Neoadjuvant therapy in cutaneous squamous-cell carcinoma

- **Phase 2 trial of neoadjuvant cemiplimab for stage II-IV cutaneous squamous-cell carcinoma**

Pts with resectable stage II-IV (M0) cuSCC

↓

Cemiplimab 350 mg Q3Wx4

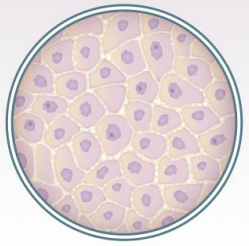
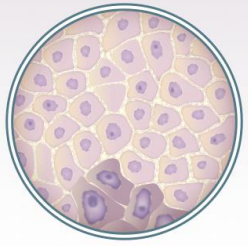
↓

Surgery with curative intent

Primary endpoint: pCR

Tumor Response to Neoadjuvant Cemiplimab

Resectable stage II, III, or IV (M0) cutaneous squamous-cell carcinoma

Pathological Complete Response	Pathological Major Response
	
Absence of viable tumor cells in surgical specimen	Presence of viable tumor cells that constitute ≤10% of surgical specimen
Independent Review 40 patients (51%; 95% CI, 39 to 62)	**Independent Review** 10 patients (13%; 95% CI, 6 to 22)
Investigator Assessment 42 patients (53%; 95% CI, 42 to 65)	**Investigator Assessment** 10 patients (13%; 95% CI, 6 to 22)

Adverse Events during Study Period

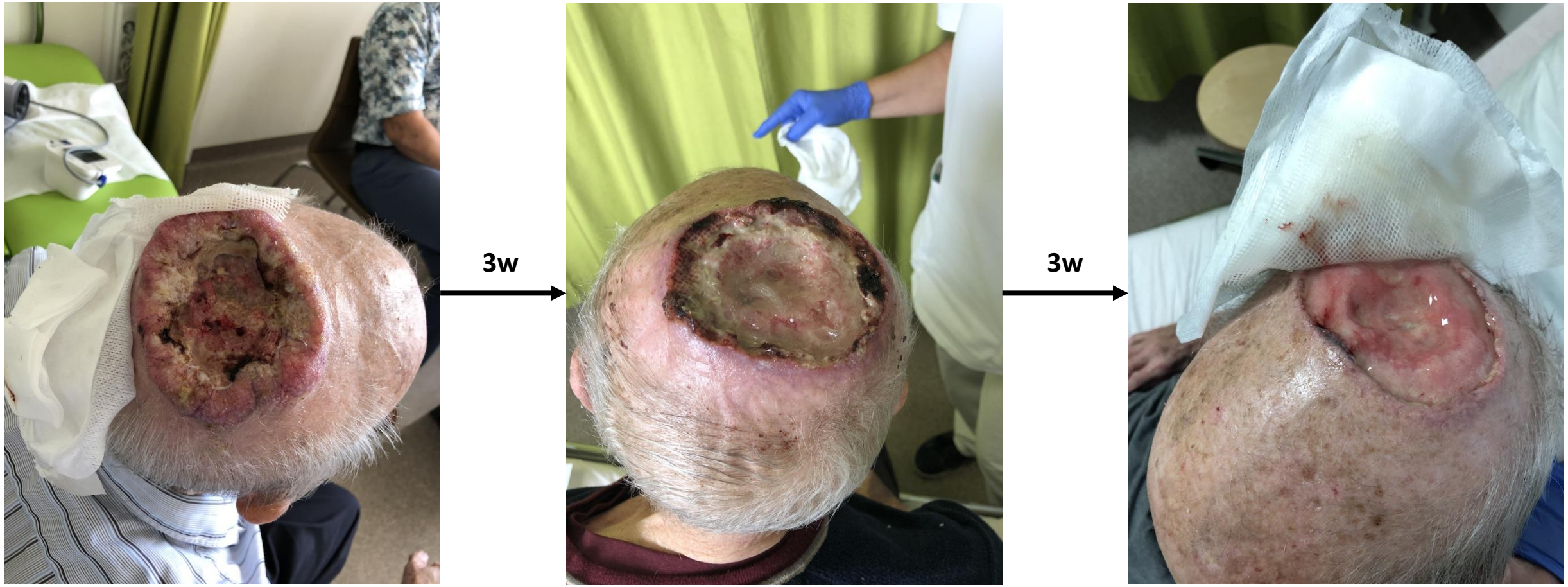
Adverse Event	Any Grade	Grade ≥3
	no. of patients (%)	
Any event	69 (87)	14 (18)
Serious event	13 (16)	10 (13)
Event that led to discontinuation of treatment	1 (1)	1 (1)
Event that led to death	4 (5)	4 (5)
Event of any grade that occurred in ≥1 patient or grade ≥3 event		
Fatigue	24 (30)	1 (1)*
Diarrhea	11 (14)	1 (1)*
Nausea	11 (14)	0
Maculopapular rash	11 (14)	0

* Grade 3 adverse events that occurred during the study period were observed in 8 patients (10%) who received neoadjuvant cemiplimab. A patient may have had more than one grade 3 adverse event.

Gross et al. N Engl J Med 2022.

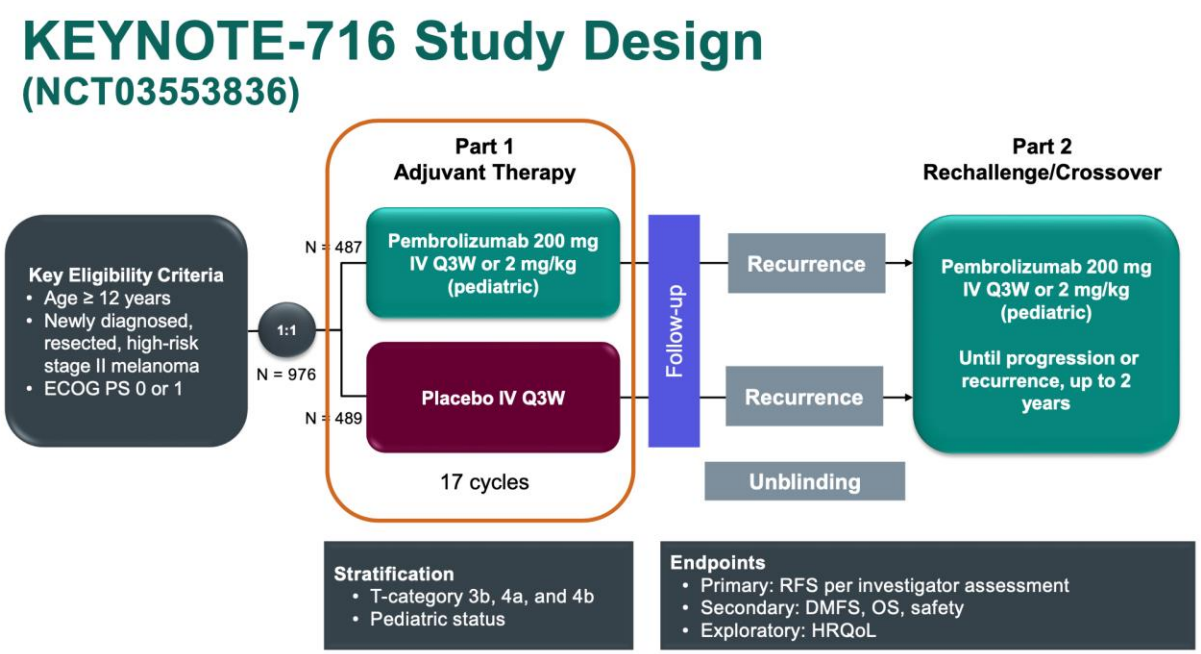
Neoadjuvant therapy in cutaneous squamous cell carcinoma

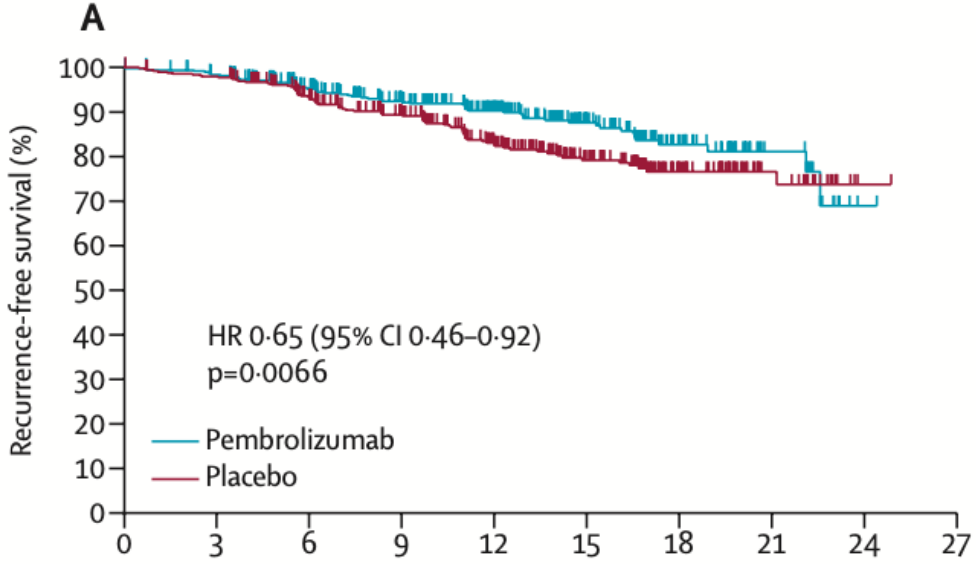
- **Case: 90-year-old male with locally advanced inoperable cuSCC of the scalp treated with cemiplimab**



Adjuvant treatment of stage II melanoma

- **KEYNOTE-716: adjuvant pembrolizumab in stage IIB/IIC melanoma**





Number at risk (number censored)

Pembrolizumab	487 (0)	465 (14)	401 (65)	340 (115)	249 (199)	149 (294)	71 (365)	21 (414)	1 (432)	0 (433)
Placebo	489 (0)	475 (4)	400 (59)	336 (106)	229 (192)	149 (263)	77 (331)	27 (381)	1 (406)	0 (407)

	Pembrolizumab group (n=487)	Placebo group (n=489)
Patients with an event	72 (15%)	115 (24%)
Local, regional, or locoregional*	38 (8%)	50 (10%)
Distant recurrence	31 (6%)	60 (12%)
Death	3 (1%)	5 (1%)

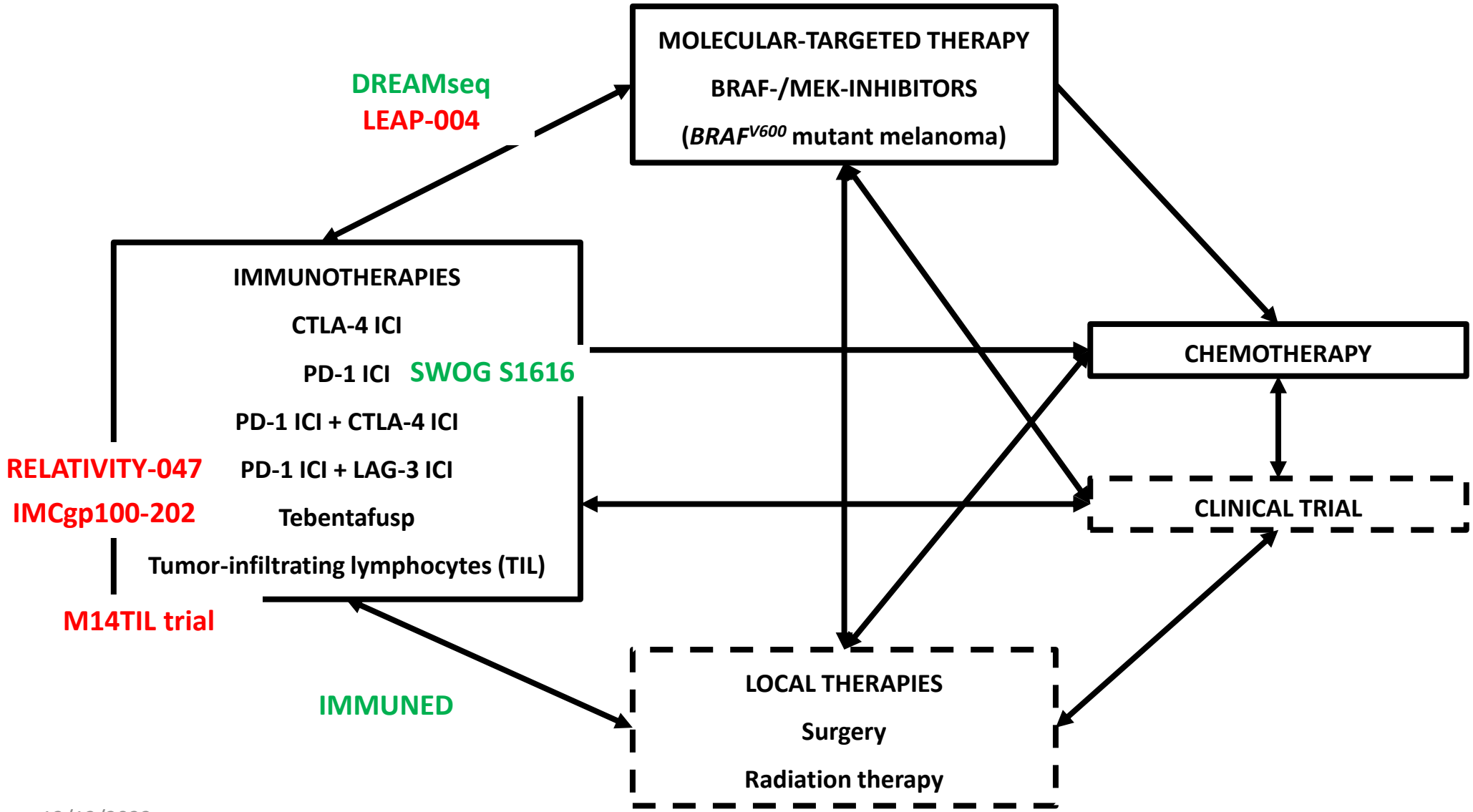
Luke et al. ESMO 2021; Luke et al. Lancet Oncol 2022.

Adjuvant treatment of stage II melanoma

- **COLUMBUS-AD**

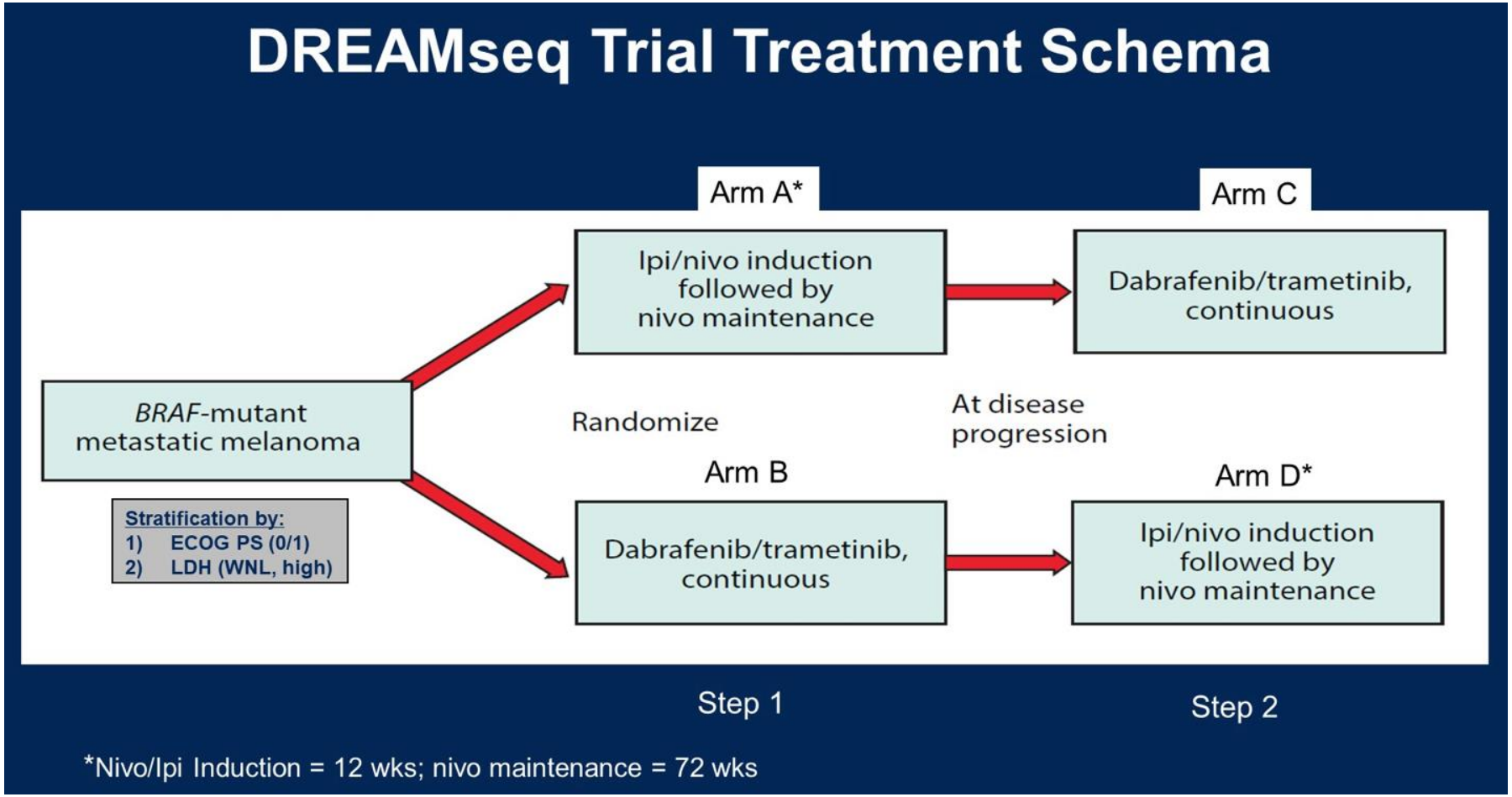
Management of advanced melanoma

Management of advanced melanoma



Therapeutic sequencing in advanced *BRAF*^{V600} mutant melanoma

- **DREAMseq**



Primary endpoint:

2-y-OS of

A → C

versus

B → D

Atkins et al. ASCO Plenary Series 2021.

Therapeutic sequencing in advanced *BRAF*^{V600} mutant melanoma

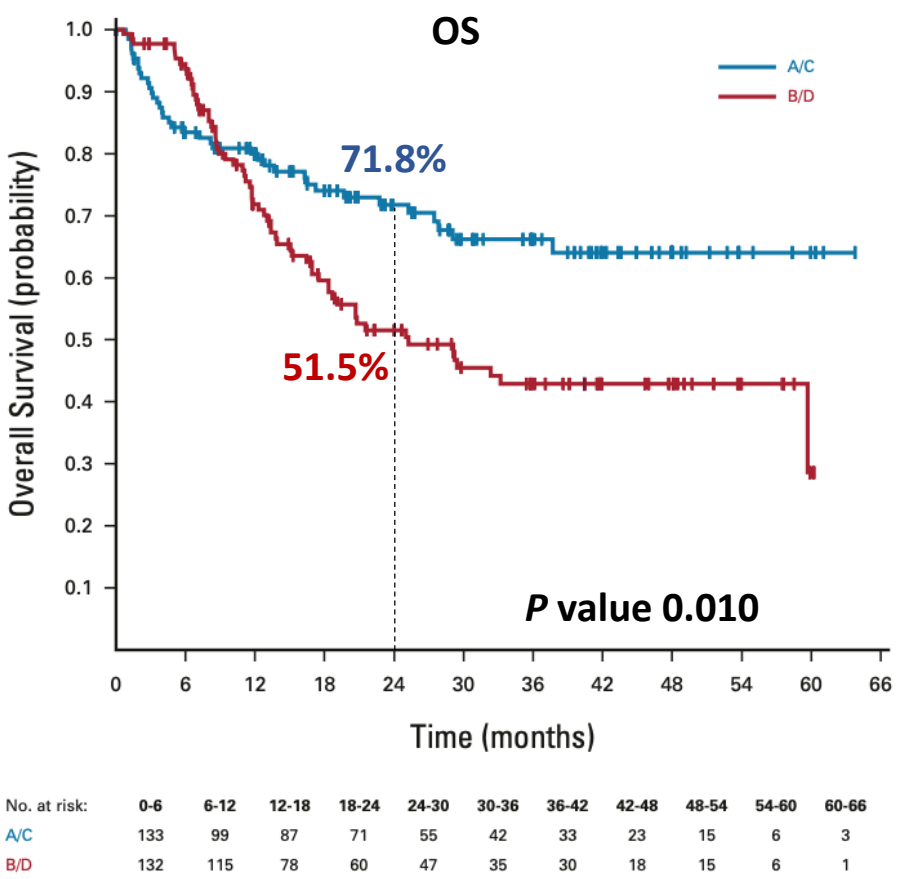
- **DREAMseq**

A/C :

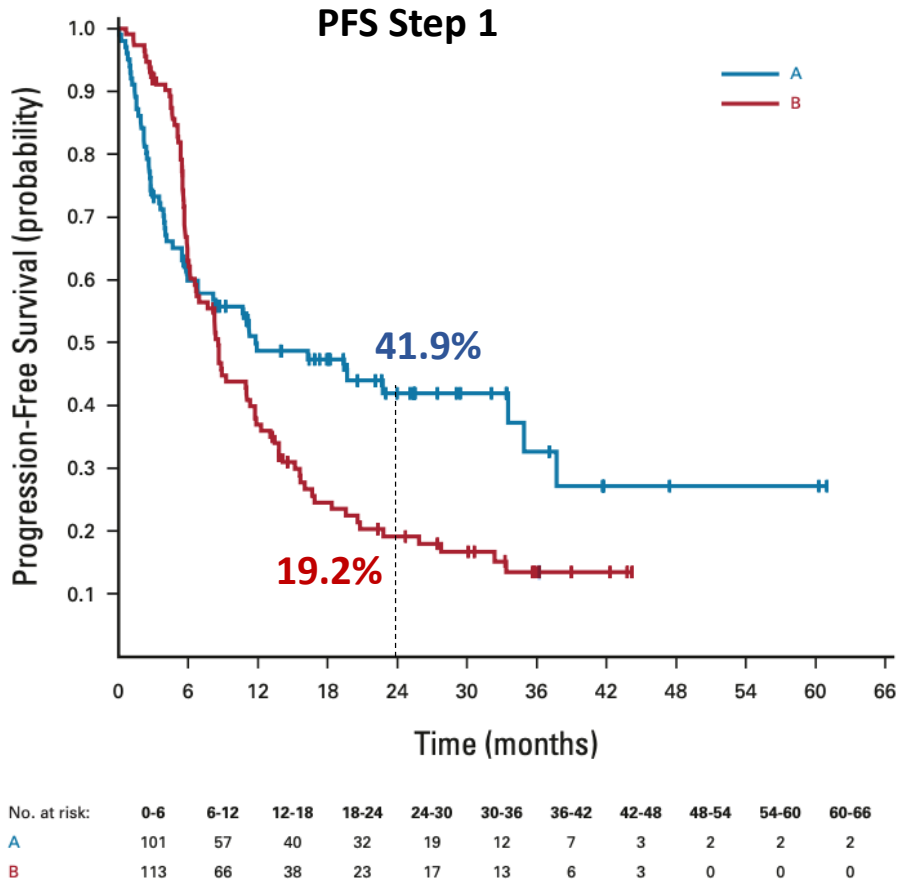
NIVO/IPI → DAB/TRA

B/D :

DAB/TRA → NIVO/IPI



No. at risk:	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
A/C	133	99	87	71	55	42	33	23	15	6	3
B/D	132	115	78	60	47	35	30	18	15	6	1



No. at risk:	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-66
A	101	57	40	32	19	12	7	3	2	2	2
B	113	66	38	23	17	13	6	3	0	0	0

Atkins et al. ASCO Plenary Series 2021; Atkins et al. J Clin Oncol 2022.

Treatment escalation after progressive disease on PD-1 ICI

- <u>SWOG S1616</u>: NIVO/IPI versus IPI in patients with melanoma that did not respond to PD-1 ICI

Stage IV melanoma with PD after 1L PD-1/PD-L1 immune checkpoint inhibitors

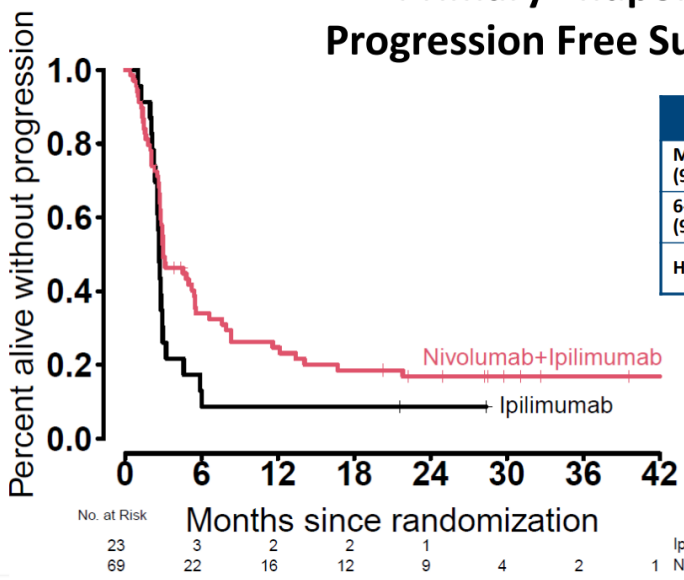
R 1:3

IPI3 x 4

(IPI3 + NIVO1) x 4 → NIVO3 for 1 y

Primary endpoint
PFS

Primary Endpoint
Progression Free Survival

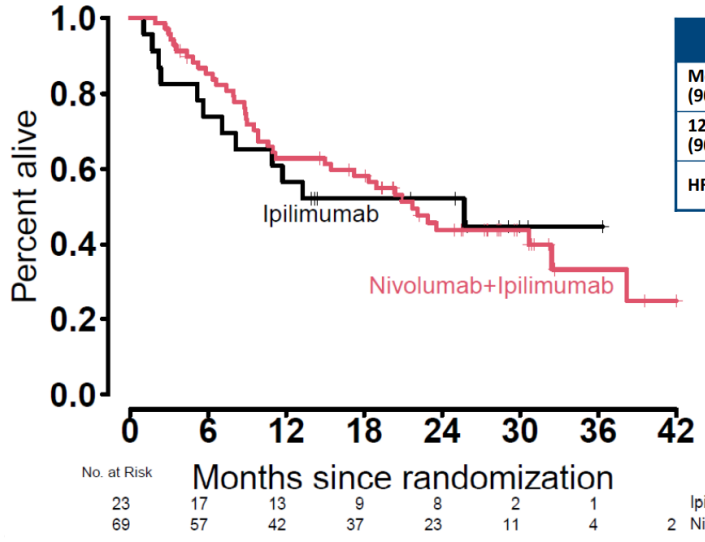


	NIVO+IPI (N=69)	IPI (N=23)
Median PFS, mo (90% CI)	3.0 (2.8, 5.3)	2.7 (2.5, 2.9)
6-Month Estimate (90%CI)	34% (25%, 44%)	13% (4%,27 %)
HR (90% CI) vs. IPI	0.63 (0.41, 0.97)	--

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

ORR
28% vs 9% (*P* 0.05)

Overall Survival



	NIVO+IPI (N=69)	IPI (N=23)
Median OS, mo (90% CI)	21.7 (15.4, 32.4)	25.7 (8.1, NR)
12-Month OS (90%CI)	63% (52%, 72%)	57% (38%, 71%)
HR (90% CI) vs. IPI	0.93 (0.54, 1.60)	--

OS was not statistically different with nivo+ipi compared to ipi (one-sided p-value = 0.408)

VanderWalde et al. AACR 2022.

ICI as adjuvant therapy for advanced melanoma

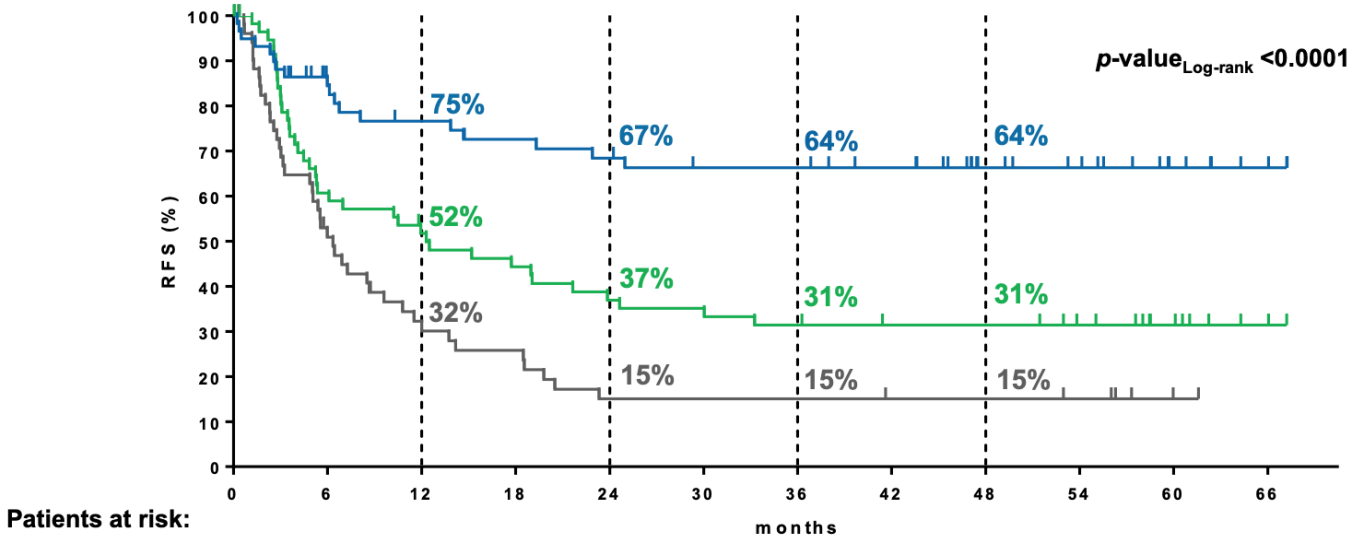
- IMMUNED: adjuvant NIVO or NIVO/IPI versus placebo in stage IV melanoma with NED

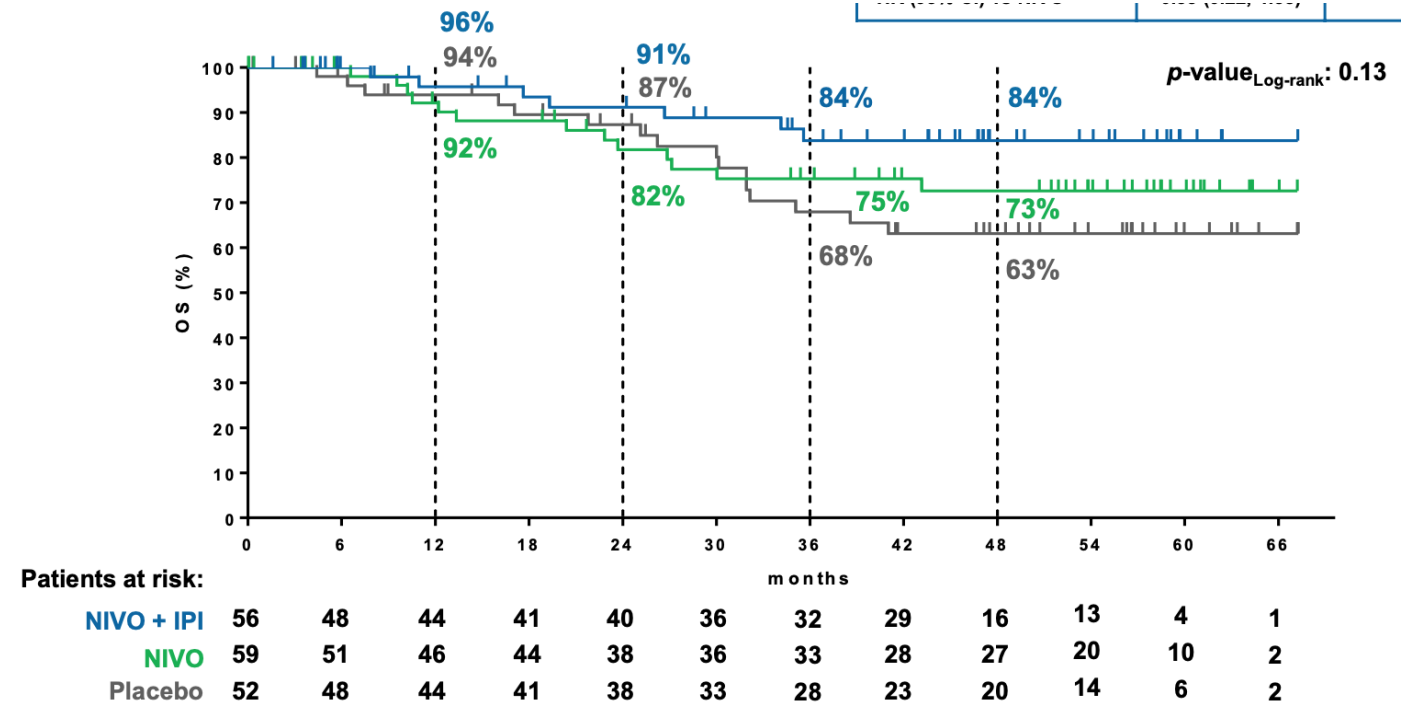
Stage IV melanoma with NED after surgery or radiotherapy

- (IPI3 + NIVO1) x 4 → NIVO3 for 1 y
- NIVO3 for 1 y
- Placebo for 1 y

Primary endpoint: RFS

M1a 40% / M1b 29% / M1c 31%
98% <3 metastatic sites

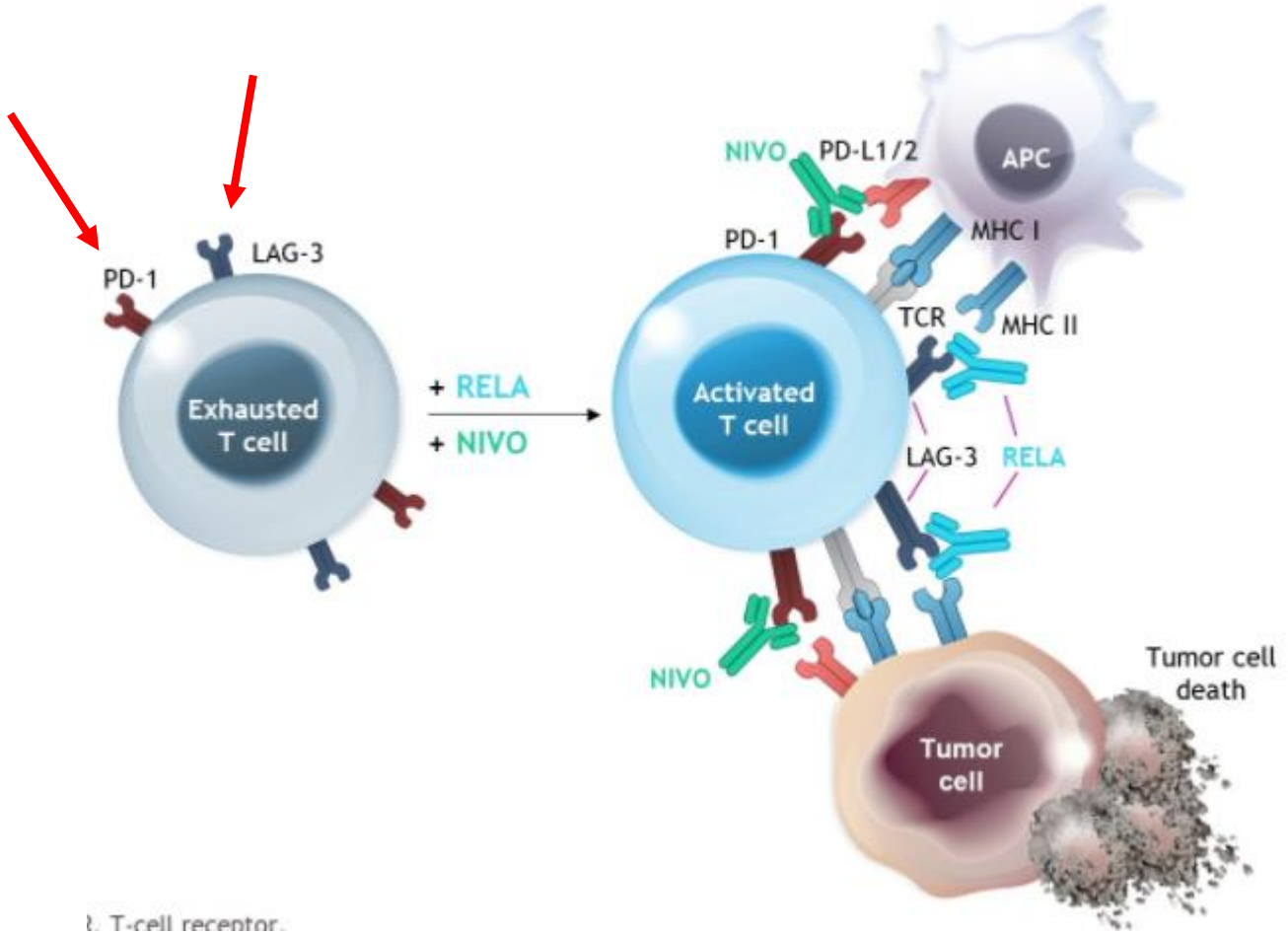




Schadendorf et al. ESMO 2022.

New kid on the block: LAG-3 ICI relatlimab (RELA)

- **RELATIVITY-047: phase 3 trial of RELA+NIVO versus NIVO in previously untreated advanced melanoma**



Blockade of LAG-3 (lymphocyte-associated antigen 3) by RELA leads to increased T-cell activation

RELA is investigated in combination with nivolumab (NIVO)

Lipson et al. ASCO Annual Meeting 2021.

New kid on the block: LAG-3 ICI relatlimab (RELA)

- **RELATIVITY-047: phase 3 trial of RELA+NIVO versus NIVO in previously untreated advanced melanoma**

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

Stratification factors
- LAG-3[a]
- PD-L1[b]
- *BRAF*
- AJCC v8 M stage

N = 714

R 1:1

- NIVO 480 mg + RELA 160 mg FDC IV Q4W
- NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[c]

Secondary endpoints
- OS
- ORR by BICR[c]

Endpoints were tested in hierarchy
- PFS → OS → ORR

	Primary disclosure	Updated disclosure
Database lock date Median follow-up, mo Minimum follow-up, mo[d]	March 9, 2021 13.2 1.3	October 28, 2021 19.3 8.7
Data disclosed	Primary endpoint • PFS	Primary endpoint • Updated PFS Secondary endpoints • OS[e] • ORR

Tawbi et al. ASCO Annual Meeting 2022.

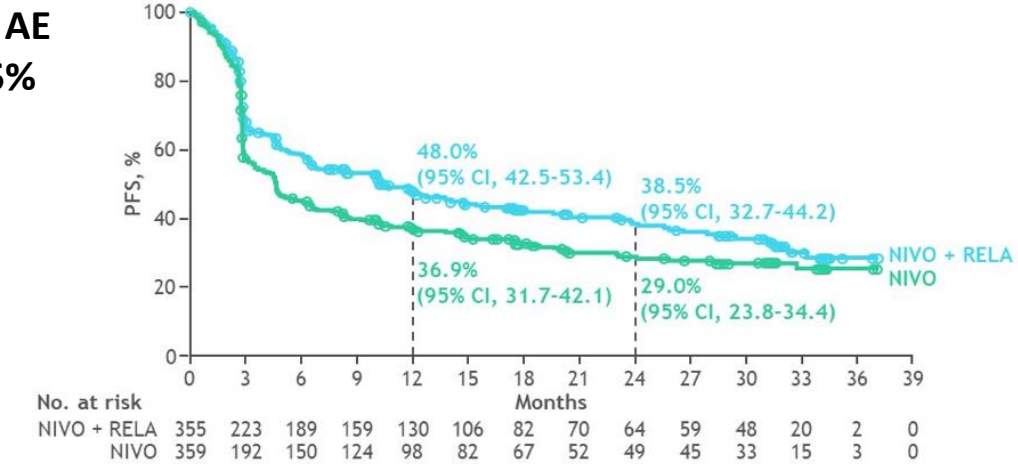
New kid on the block: LAG-3 ICI relatlimab (RELA)

- **RELATIVITY-047: phase 3 trial of RELA+NIVO versus NIVO in previously untreated advanced melanoma**

Grade 3/4 AE
43% vs 35%

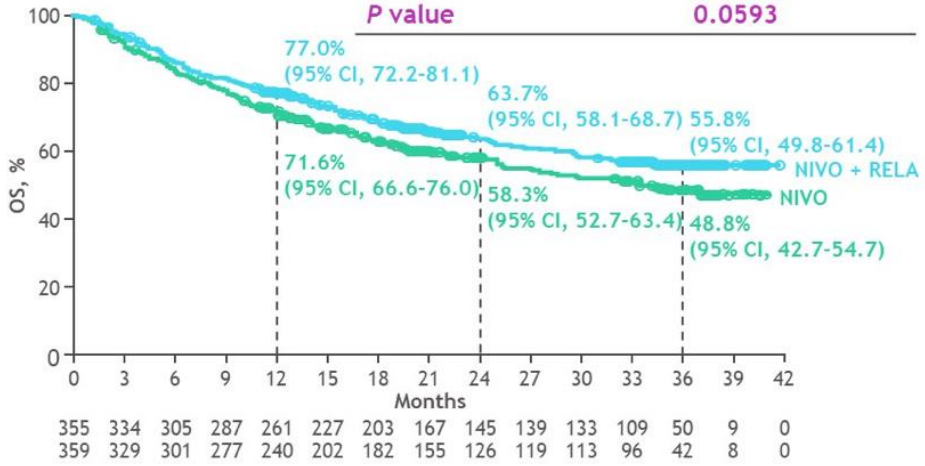
Updated PFS by BICR

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	



OS

	NIVO + RELA (n = 355)	NIVO (n = 359)
mOS, mo (95% CI)	NR (34.20-NR)	34.10 (25.23-NR)
HR (95% CI)	0.80 (0.64-1.01)	
P value	0.0593	



Confirmed ORR by BICR	NIVO + RELA (n = 355)	NIVO (n = 359)
ORR % (95% CI)	**43.1** (37.9-48.4)	**32.6** (27.8-37.7)

Tawbi et al. ASCO Annual Meeting 2022.

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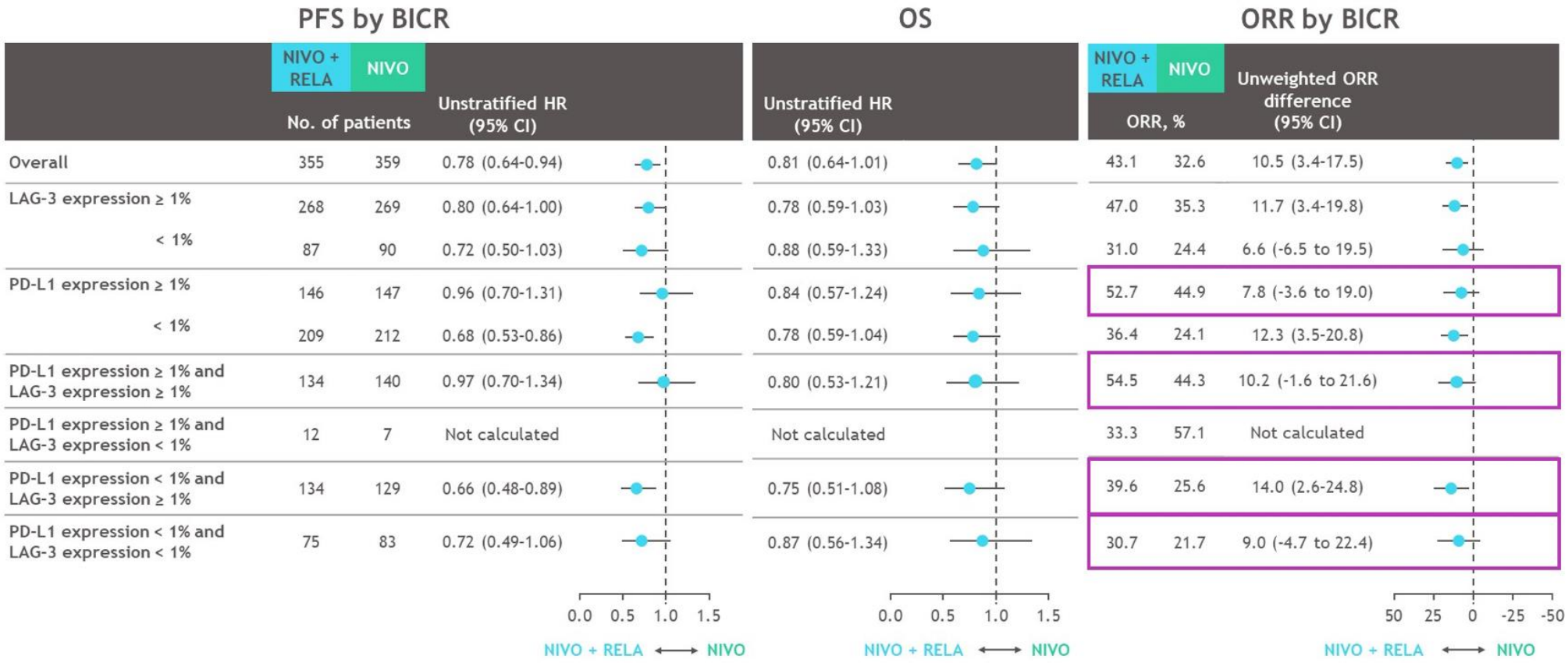


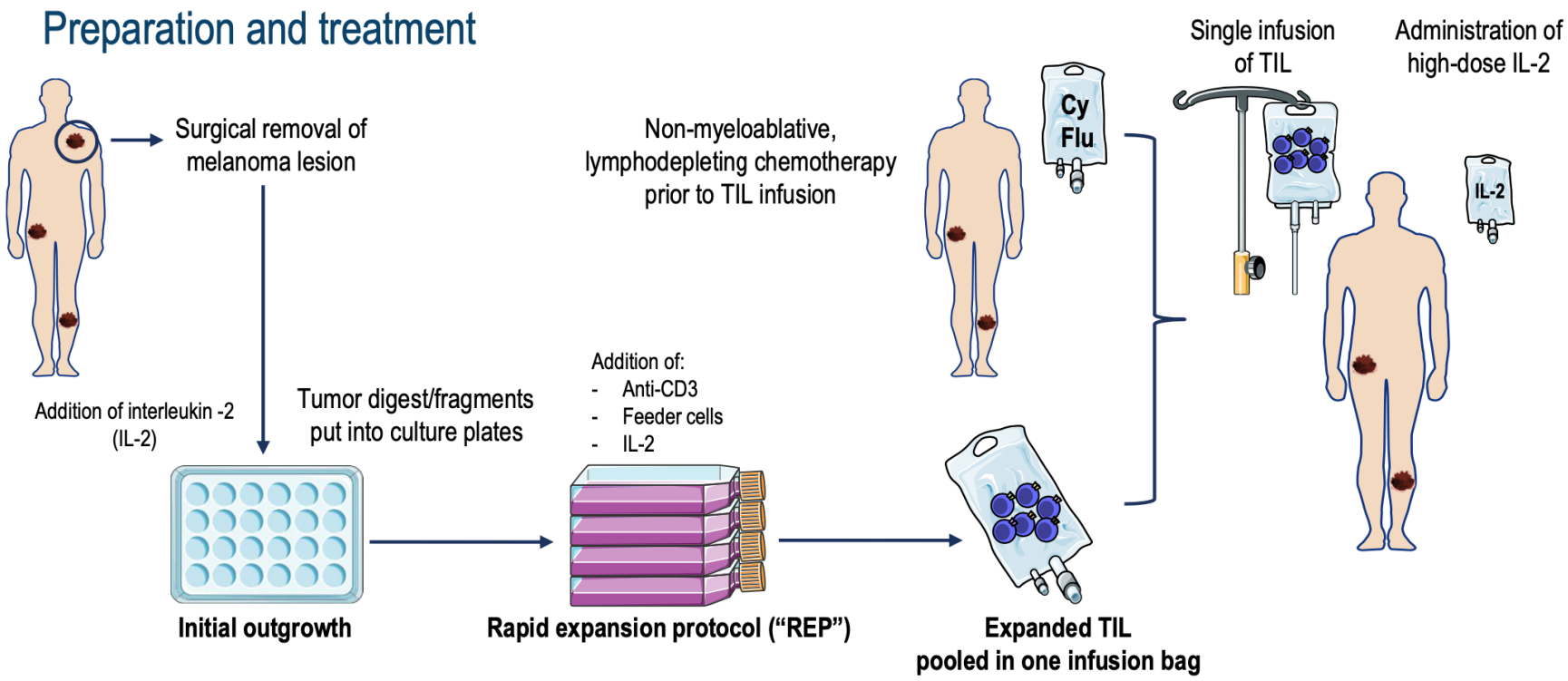
Positive recommendation of EMA for the first-line treatment of advanced melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%

- PFS, OS, and ORR favored NIVO + RELA over NIVO regardless of LAG-3 and PD-L1 expression (stratification factors)

Tawbi et al. ASCO Annual Meeting 2022.

New kid on the block: TIL therapy

- **M14TIL: phase 3 trial of tumor-infiltrating lymphocytes (TIL) versus IPI in advanced melanoma**



Haanen et al. ESMO Congress 2022.

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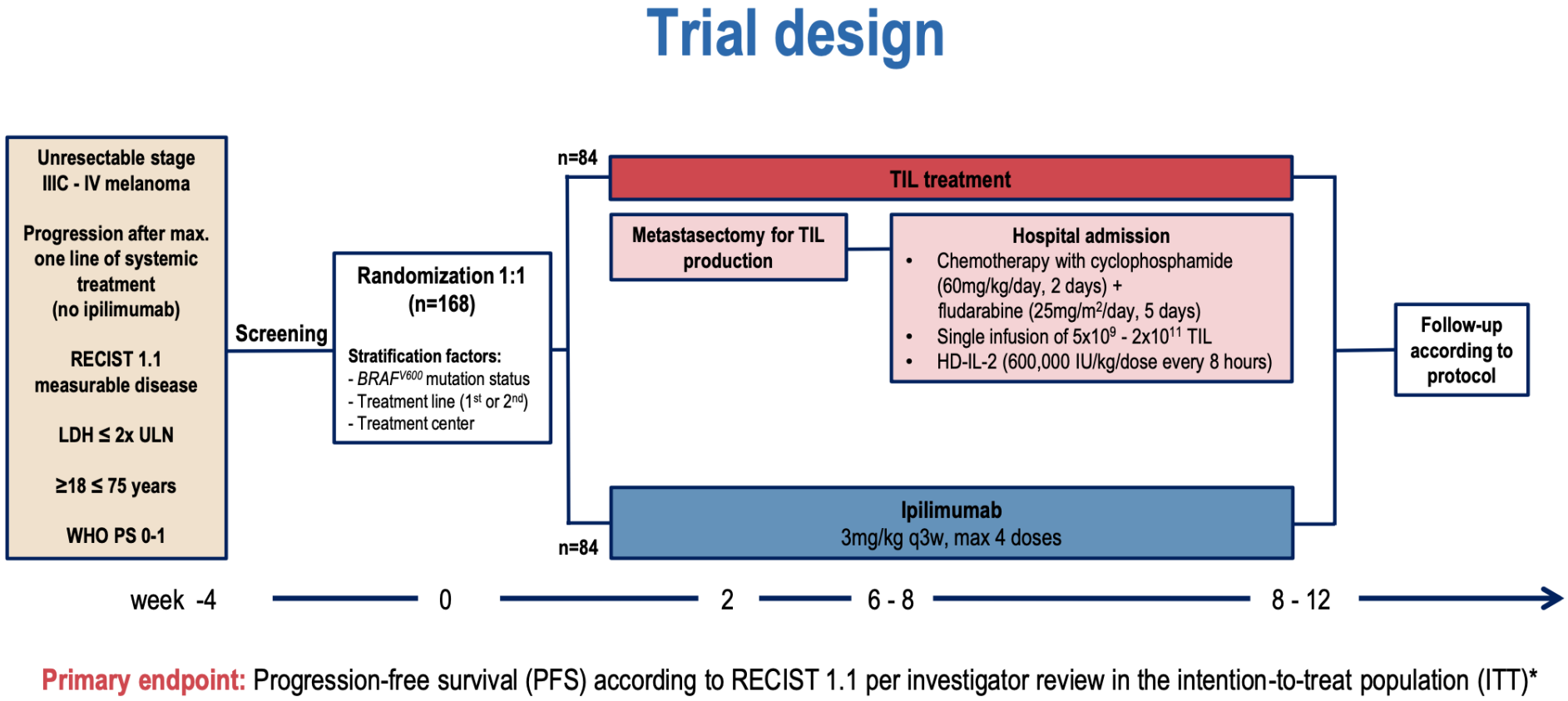

Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

Haanen et al. ESMO Congress 2022.

New kid on the block: TIL therapy

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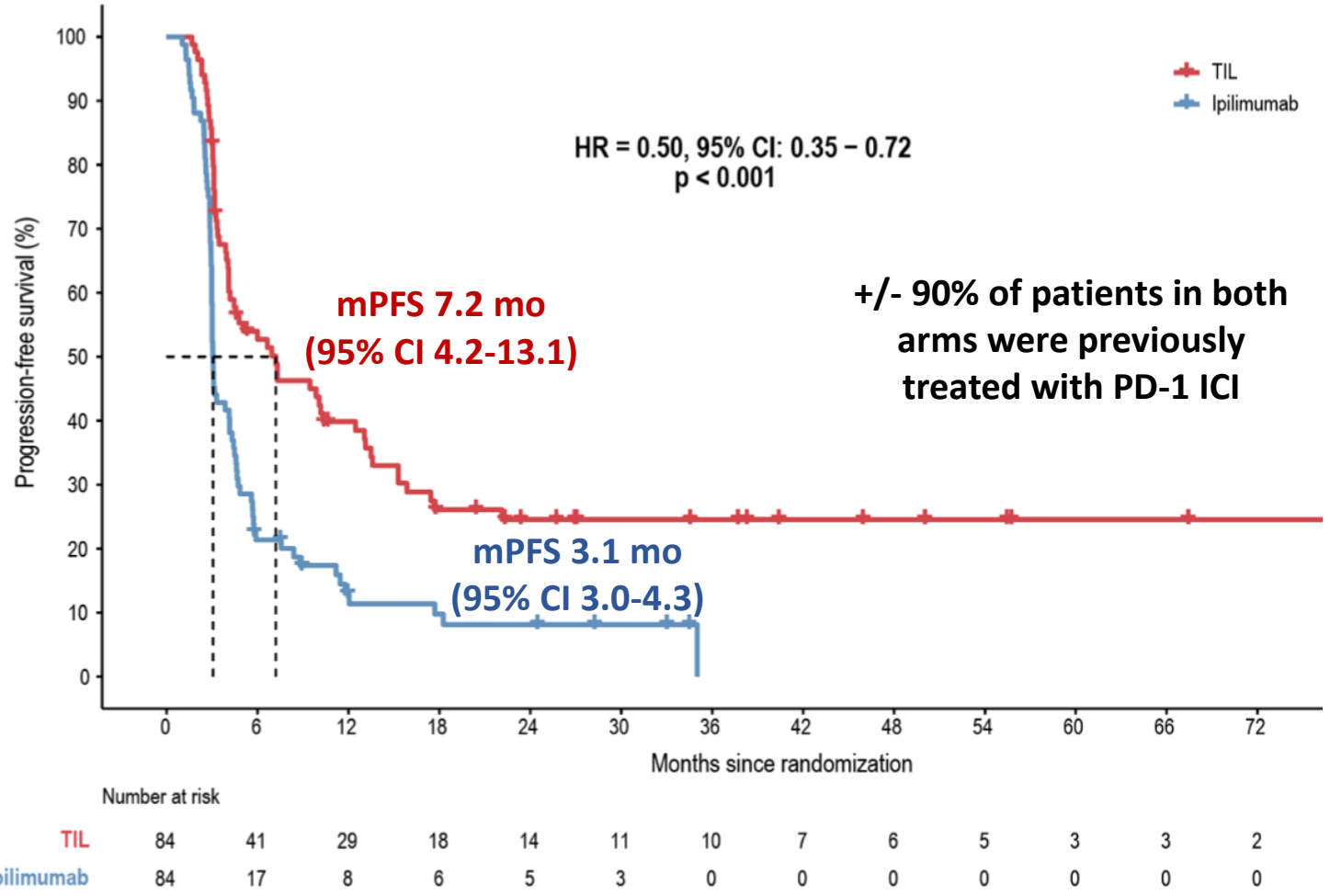
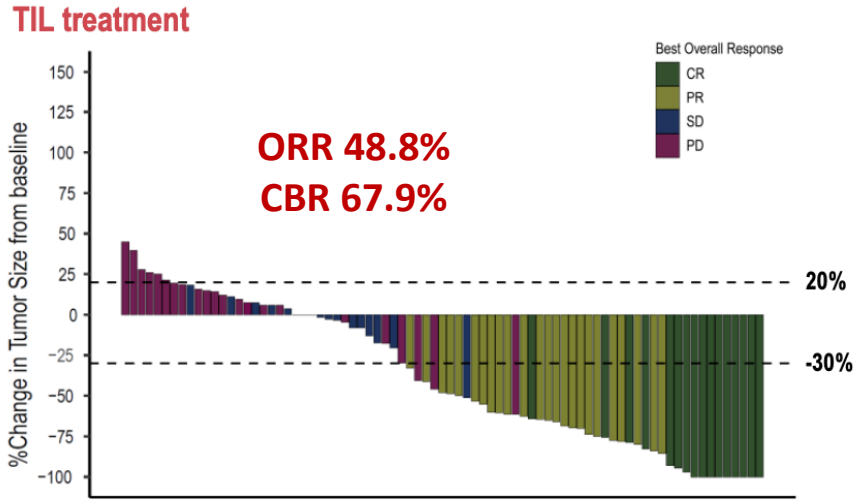
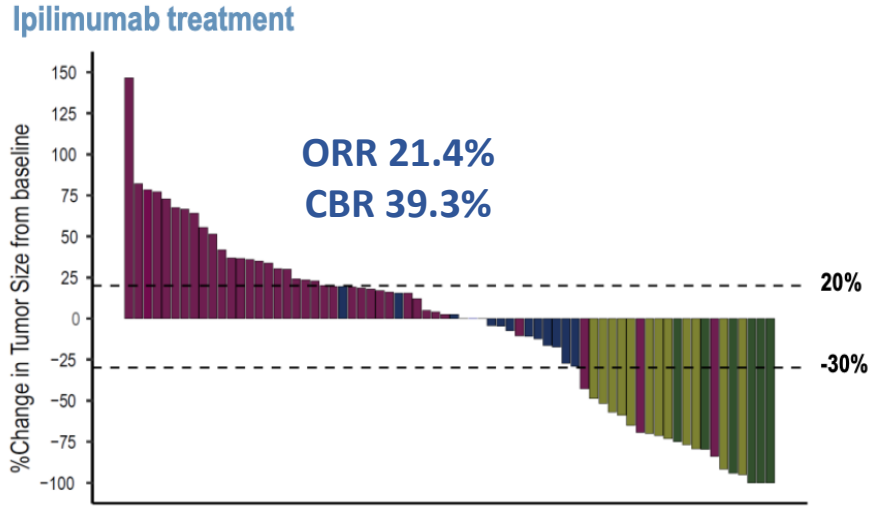


+/- 90% of patients in both arms were previously treated with PD-1 ICI

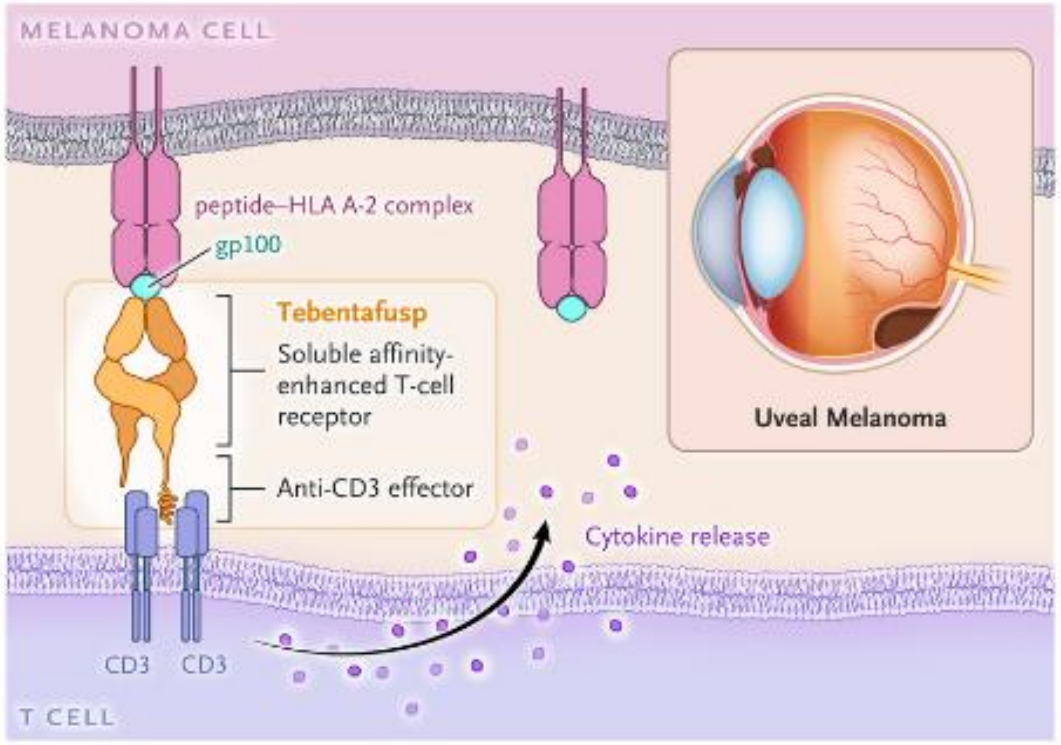


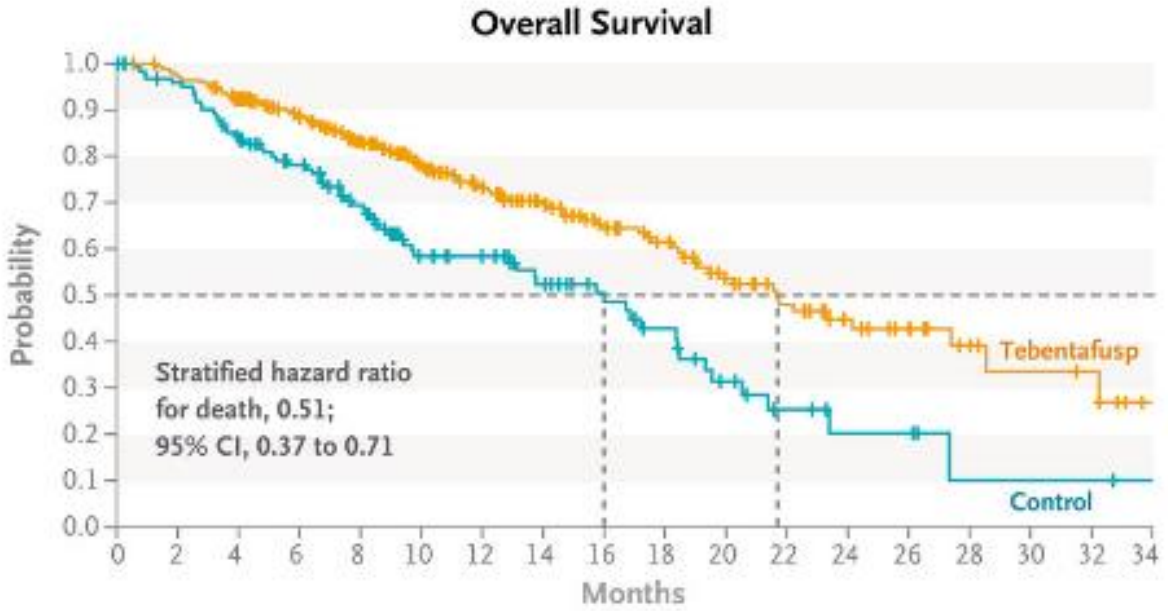


Haanen et al. ESMO Congress 2022.

New kid on the block: tebentafusp

- **<u>IMCgp100-202</u>: tebentafusp versus IC (PEMBRO, IPI or DTIC) in HLA-A*02-01 positive uveal melanoma**



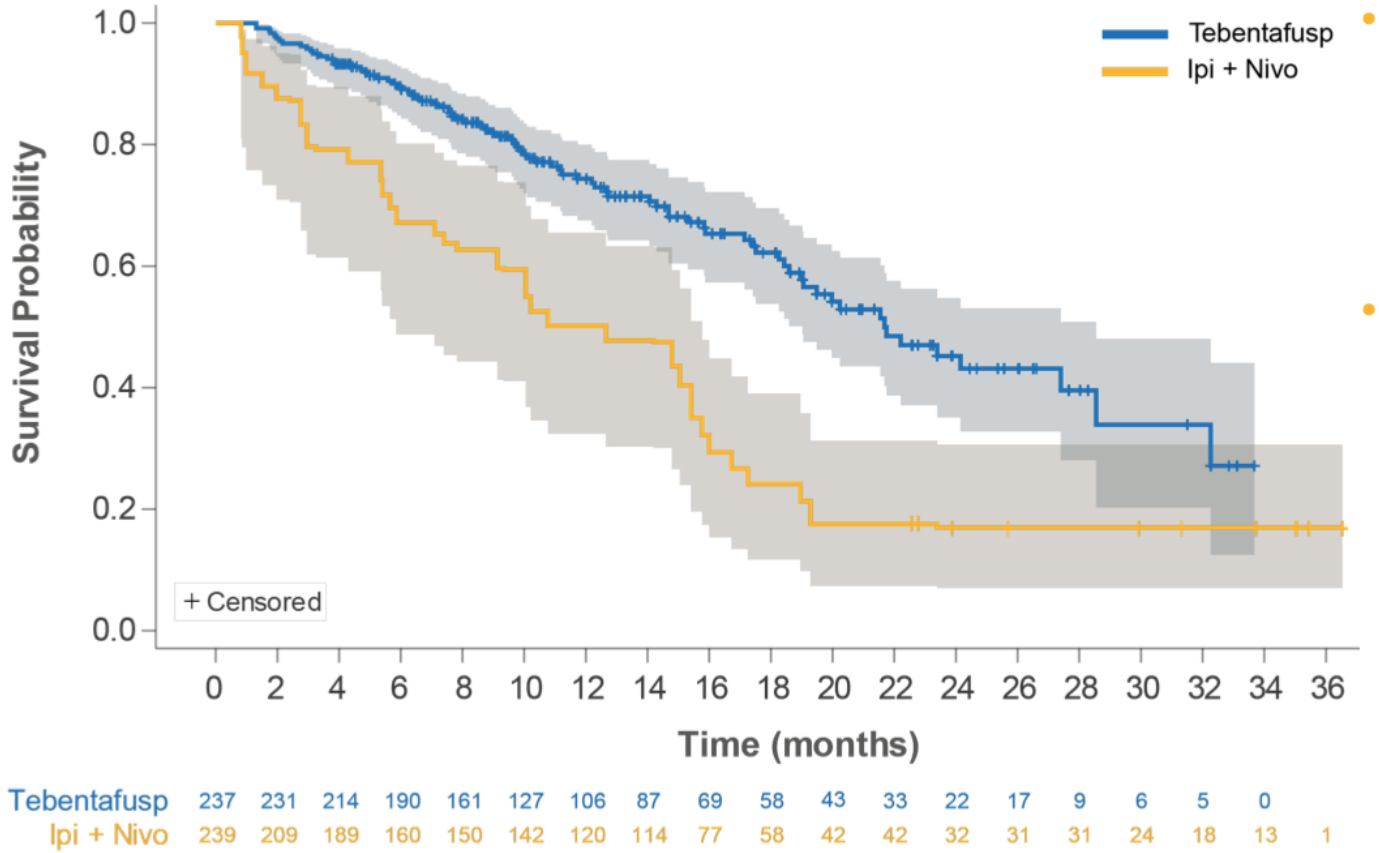


1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

Nathan et al. N Engl J Med 2021.

New kid on the block: tebentafusp

- **Tebentafusp versus NIVO/IPI in a propensity score analysis**

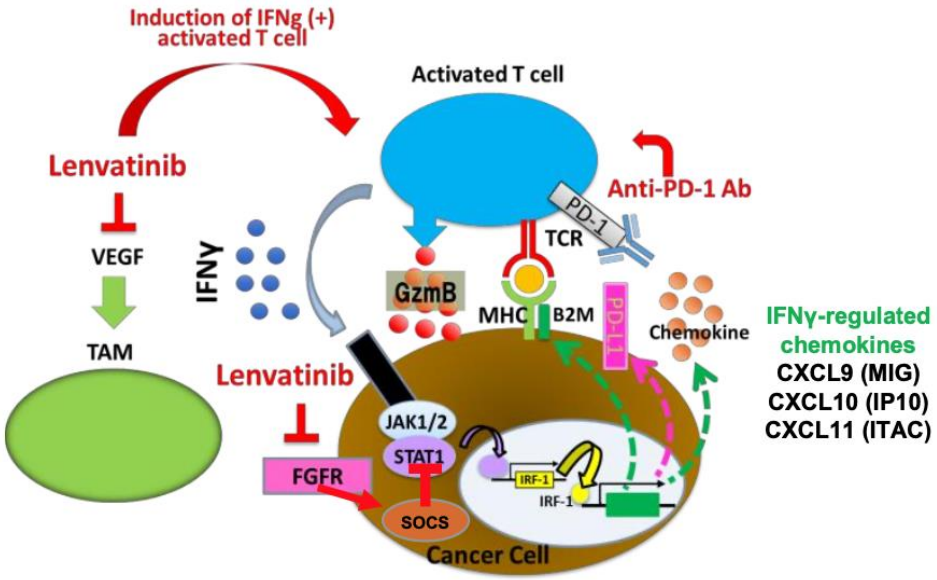


- The IPTW adjusted OS favored tebe, HR 0.43 (95% CI 0.29-0.64); 1-yr OS 74% vs 50%, respectively
- Sensitivity analyses showed consistent superior OS for tebe with all IPTW HRs <0.48

Piulatset al. ESMO 2022.

Novel combinations

- **LEAP-004: phase 2 trial of PEMBRO + lenvatinib in patients previously treated with PD-(L)1 ICI**



Participants

- Unresectable stage III or IV melanoma[a]
- Confirmed PD per iRECIST[1b] on or within 12 wk of last dose of anti–PD-(L)1 given alone or in combination (including with anti–CTLA-4) for ≥2 doses
  - ≤25% with PD on anti–CTLA-4 + anti–PD-(L)1
- No limit to number of previous therapies
- Measurable disease confirmed by blinded, independent central review (BICR)

N ≈ 100

Pembrolizumab
200 mg IV Q3W
for up to 35 cycles

+

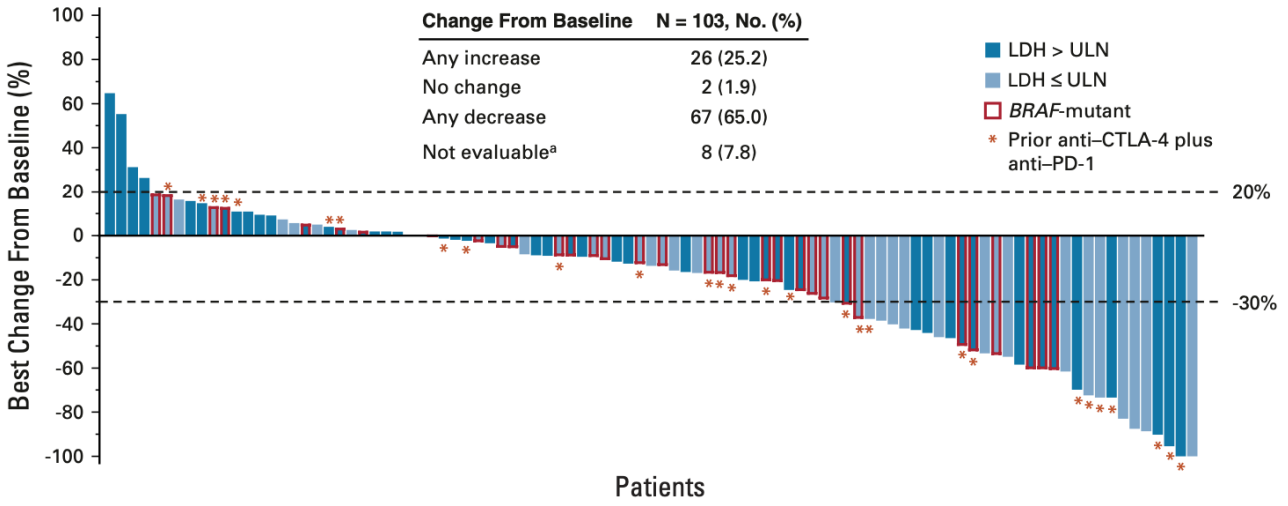
Lenvatinib
20 mg PO QD

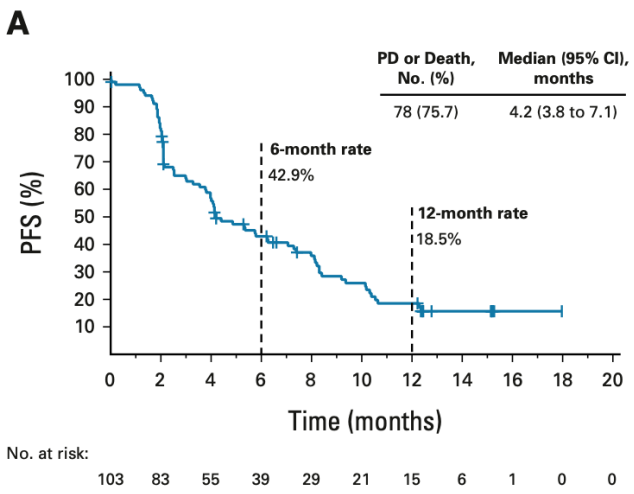
Continued until PD, unacceptable toxicity, or patient or physician decision[c]

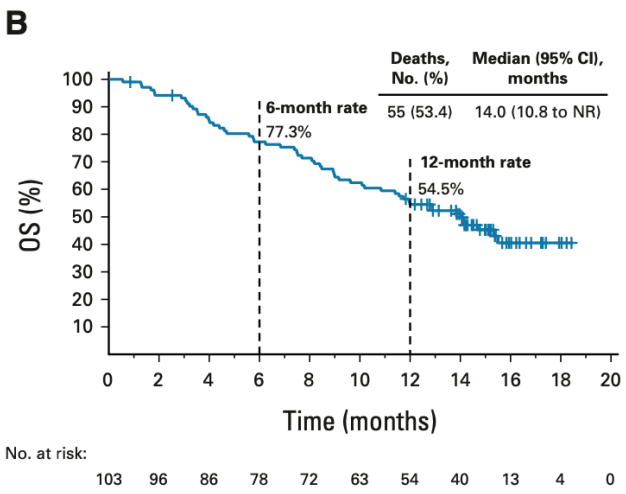
Arance et al. ESMO 2020; Arance et al. J Clin Oncol 2022.

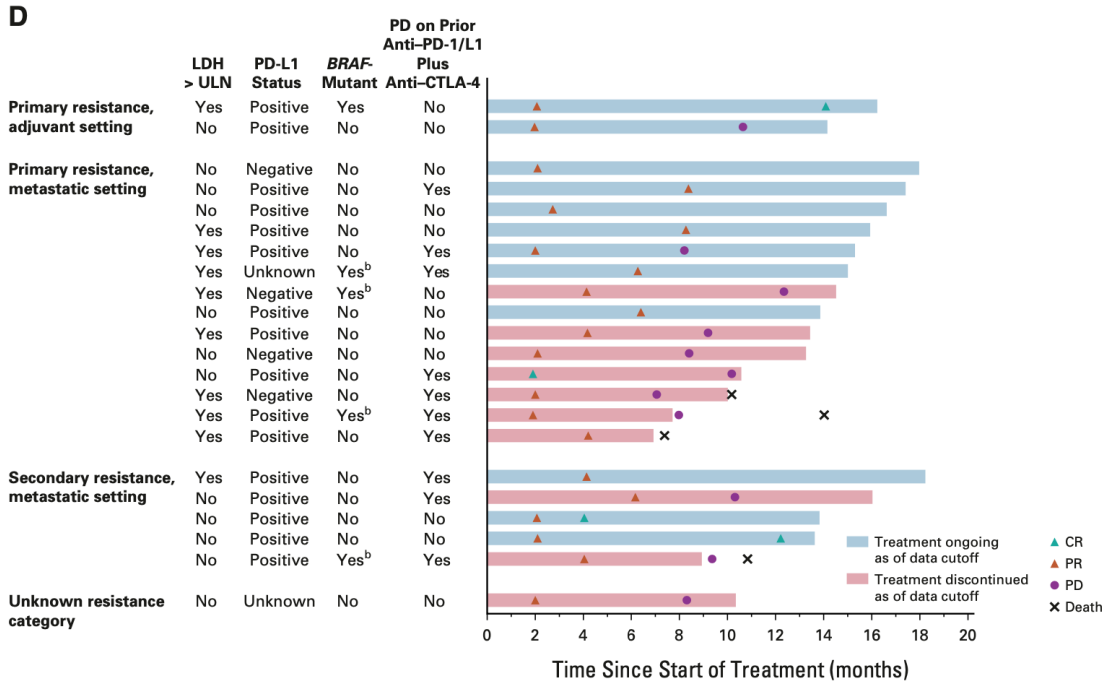
Novel combinations

- **LEAP-004: phase 2 trial of PEMBRO + lenvatinib in patients previously treated with PD-(L)1 ICI**









ORR 22/103 (21.4%), mDOR 8.3 mo

AE in 96.1% of patients, including 45.6% G3-5

LEAP-003 (phase 3): PEMBRO/LENVA vs PEMBRO/PLB

Arance et al. ESMO 2020; Arance et al. J Clin Oncol 2022.

Conclusions and perspectives

- **(Neo)adjuvant management of localized and locoregional melanoma:**
  - **Neoadjuvant therapy of locoregional melanoma and (in)operable cuSCC with ICI shows interesting results, but needs confirmation in phase 3 trials (PRADO; SWOG S1801)**
  - **Adjuvant PEMBRO is indicated after resection of stage IIB/C melanoma, but the NNT to prevent 1 recurrence is 14 (KEYNOTE-716)**
- **Treatment sequencing in advanced melanoma:**
  - **NIVO/IPI followed by dabrafenib/trametinib appears to be the optimal treatment sequence in advanced *BRAF*^{V600} mutant melanoma (DREAMseq)**
  - **NIVO/IPI is superior to IPI monotherapy after prior failure of PD-1 ICI in terms of ORR and PFS, but not OS, in a phase 2 trial (SWOG S1616)**
  - **Adjuvant therapy of stage IV melanoma with NED after radiotherapy/surgery with NIVO/IPI or NIVO is superior to follow-up in terms of RFS (IMMUNED)**

Conclusions and perspectives

- **Novel immunotherapeutic strategies:**
  - **Combined blockade of LAG-3 (with RELA) and PD-1 (with NIVO) is superior to NIVO monotherapy in terms of PFS, but not in terms of OS, and is approved by EMA for advanced PD-L1 <1% melanoma (RELATIVITY-047)**
  - **TIL therapy is superior to IPI in PD-1 ICI refractory melanoma (M14TIL), but requires a production process which can only be applied in specialized centers (patient selection)**
  - **Tebentafusp is a new standard-of-care in advanced HLA-A*02-01 positive uveal melanoma (IMCgp100-202)**
- **Novel treatment combinations :**
  - **The combination of lenvatinib plus PEMBRO shows promising results in advanced PD-1 ICI refractory melanoma (LEAP-004). A phase 3 trial in the first-line setting is underway.**

Thank you for your attention!

Questions?

Gil Awada, MD, PhD

Gil.Awada@uzbrussel.be

Gil.Awada@bordet.be