Neoadjuvante Therapie des malignen Melanoms

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Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition: keine

2. Beratungs- bzw. Gutachtertätigkeit: keine

3. Besitz von Geschäftsanteilen, Aktien oder Fonds: keine

4. Patent, Urheberrecht, Verkaufslizenz: keine

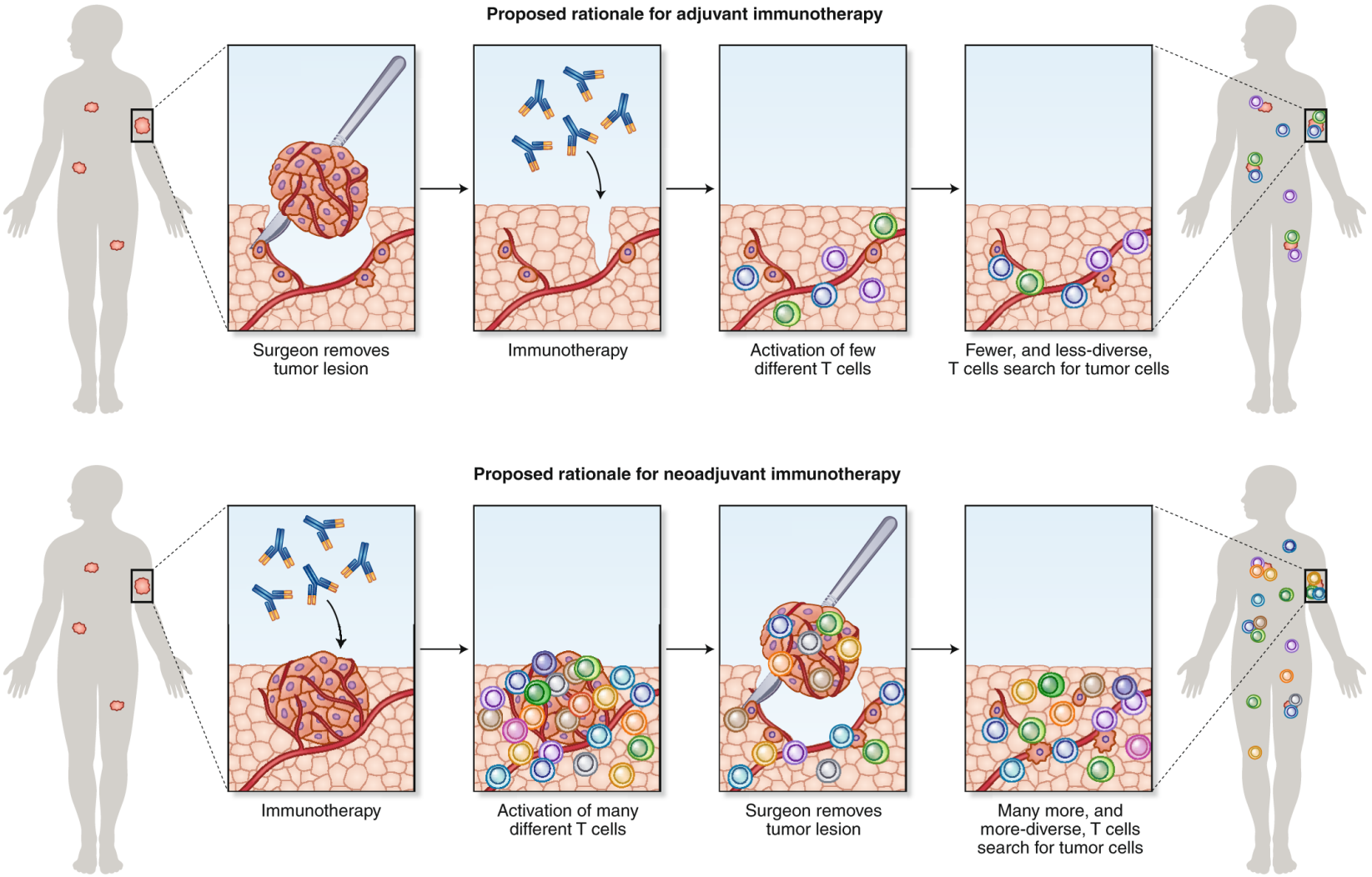
5. Honorare: BMS, Astra Zeneca, MSD, Kyte und Gilead

6. Finanzierung wissenschaftlicher Untersuchungen: BMS

7. Andere finanzielle Beziehungen: keine

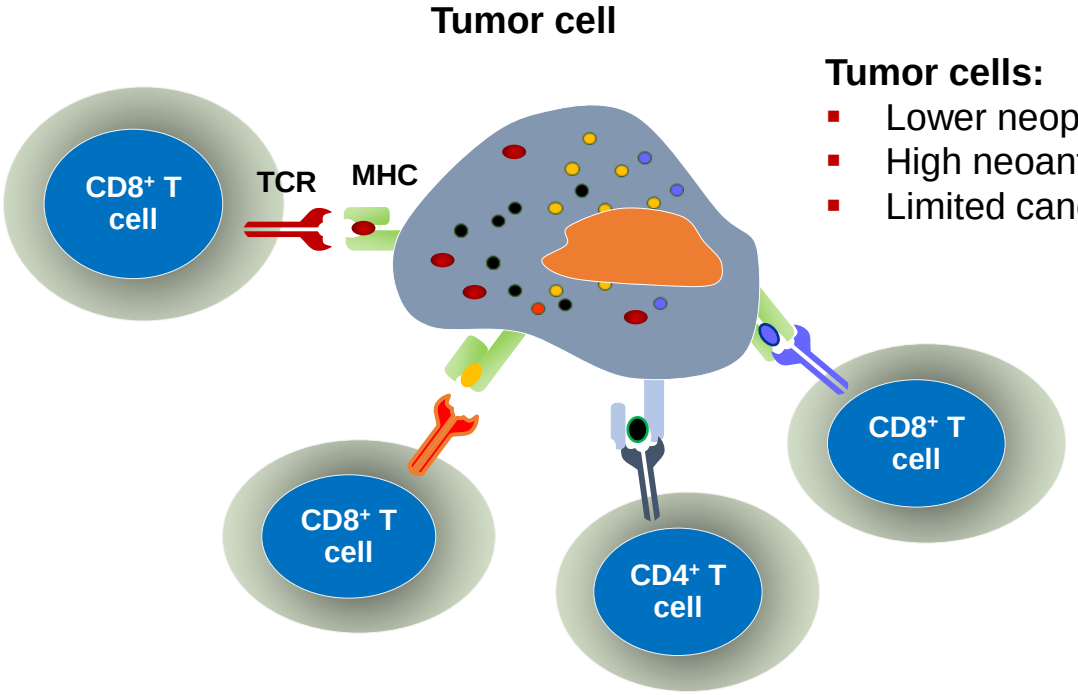
8. Immaterielle Interessenkonflikte: keine

Neoadjuvant and adjuvant approaches to immunotherapy



Nature Medicine volume 26, pages475–484 (2020)

Rationale for neoadjuvant therapies



Tumor cells:

- Lower neoplastic burden
- High neoantigen burden
- Limited cancer cell clonal divergency

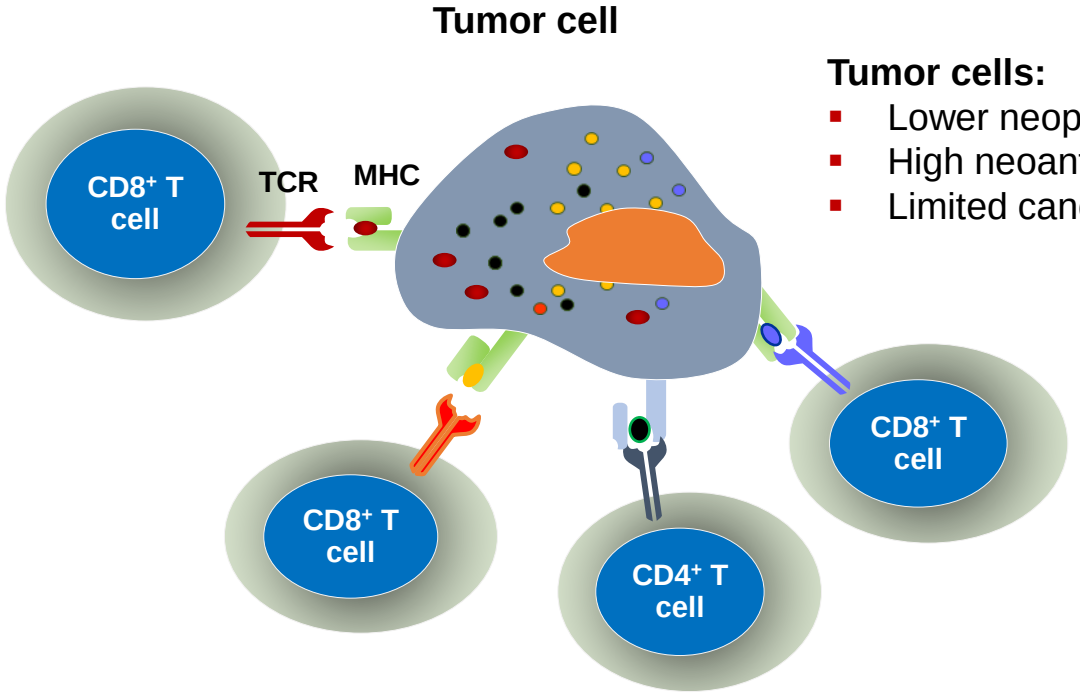
Broad immune activation:

- many different T cell clones
- broad repetoire of TCR
- exposure to a broad range of antigens
- Immunologic tumor conditioning
- Early expansion of memory T cells

Impaiment of T cell function:

- T cell function is less impaired in early stage
- less immunosuppression by tumor cells
- PD-L1 positive exosomes,
- cancer associated inflammation
- Cancer cell intrinsic metabolic changes

Rationale for neoadjuvant therapies



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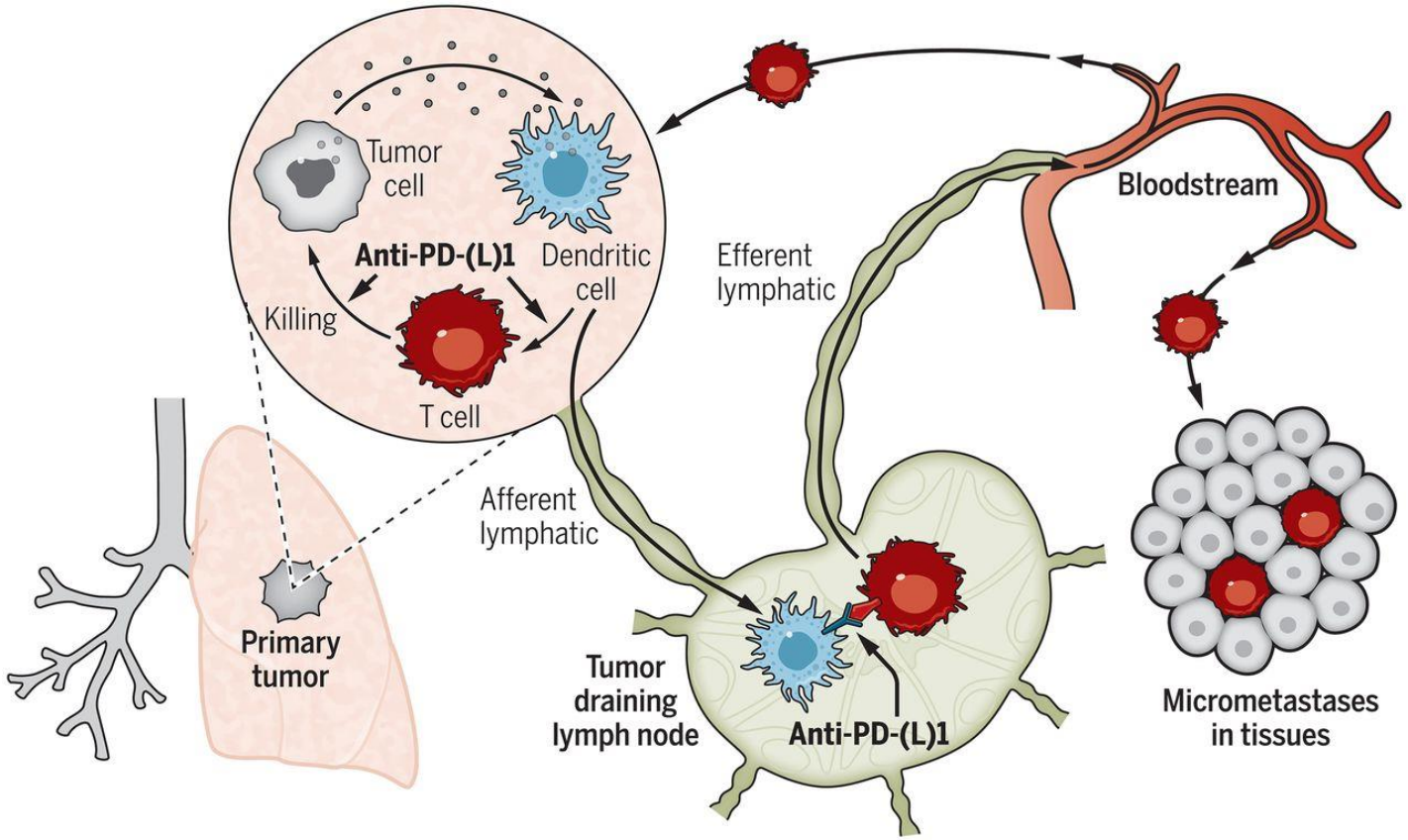
- cancer associated inflammation
- Cancer cell intrinsic metabolic changes

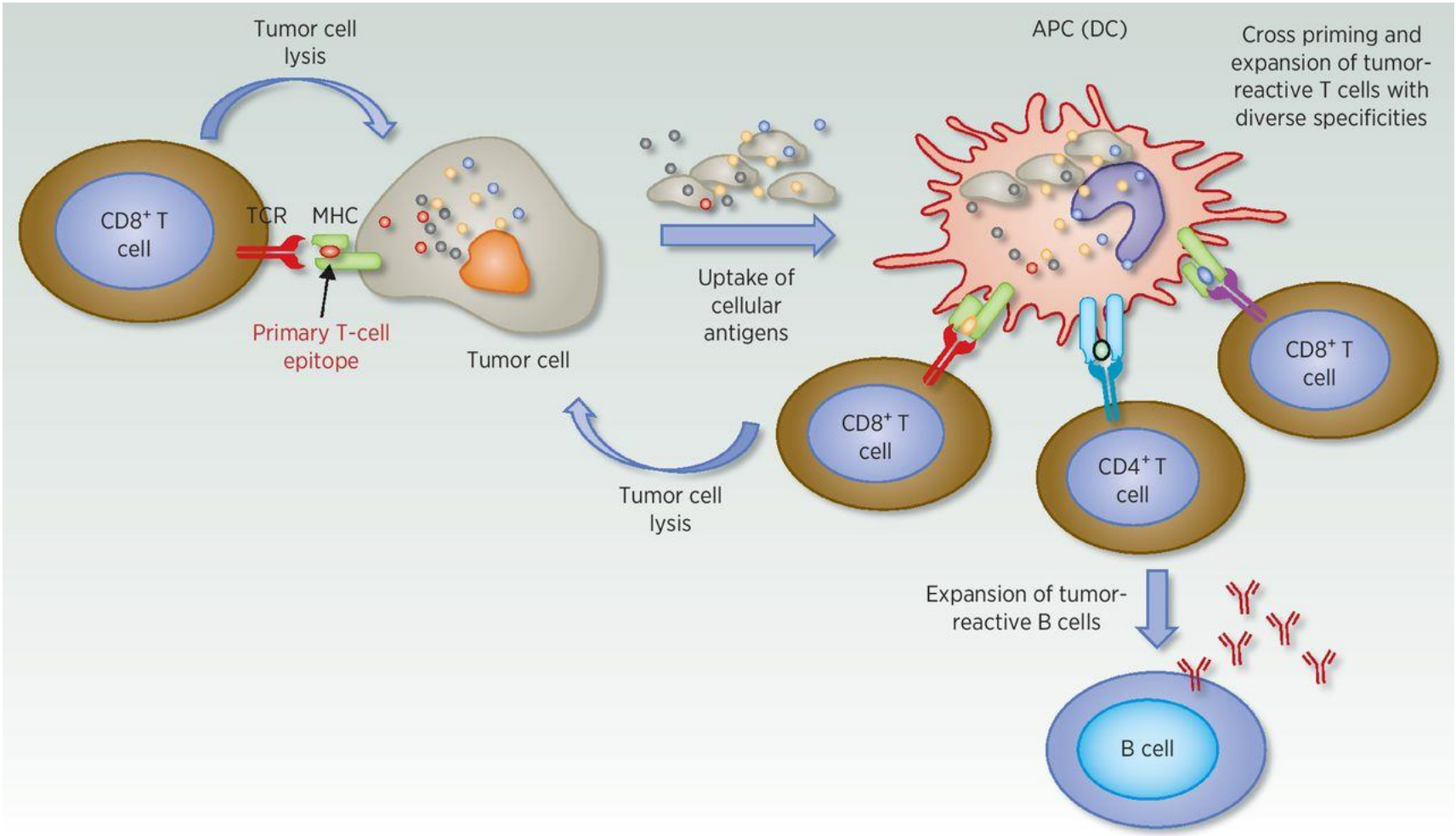
- **Early window of opportunity to identify potential biomarkers of ICI efficacy**
- **Development of predictive models**
- **Testing of novel compounds and combinations**

Two potential mechanisms for the enhancement of systemic antitumor T cell immunity after neoadjuvant PD-1 blockade



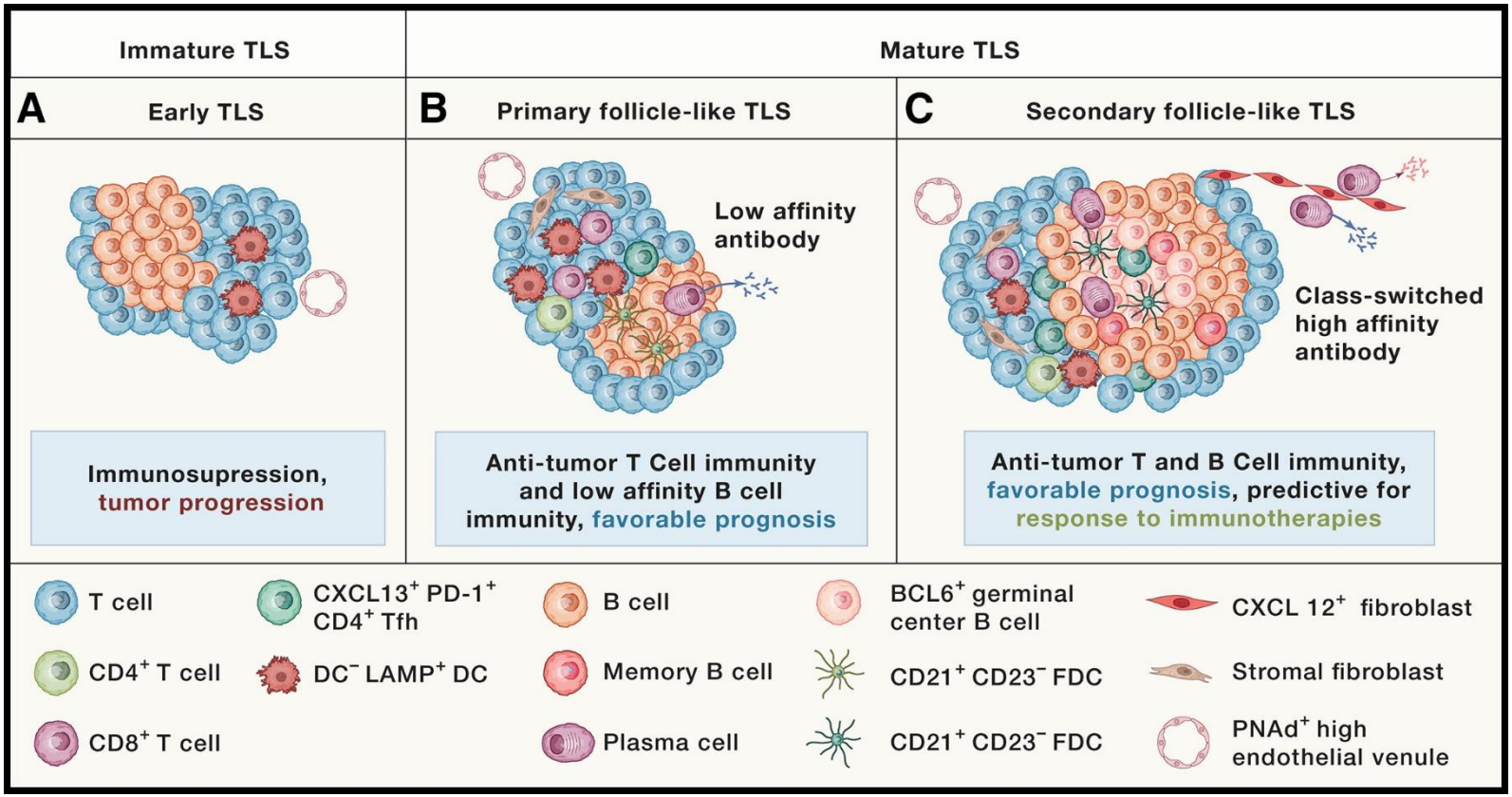
SCIENCE 31 Jan 2020, Vol 367, Issue 6477

The Role of Antigen Spreading in the Efficacy of Immunotherapies



Brossart P. Clin Cancer Res. 2020 Sep 1;26(17):4442-4447

Tertiary lymphoid structures and B cells



(A) Immature or early TLS contain mature dendritic cell lysosomal associated membrane glycoprotein (DC-LAMP)+ dendritic cells (DCs) in the T cell zone.
(B) Within mature TLS, primary follicle-like TLS have in addition T follicular helper (Tfh) cells and CD21+ follicular dendritic cells (FDCs) network allowing T cell immunity activation and low-affinity antibody production.
(C) Secondary follicle-like TLS are characterized by the presence of a germinal center (GC) with B cell lymphoma 6 (BCL6) positive GC B cells, CD21+CD23+ FDC allowing the production of memory B cells and high-affinity antibody secreting plasma cells.

Immunity Volume 56, Issue 10, 10 October 2023, Pages 2254-2269

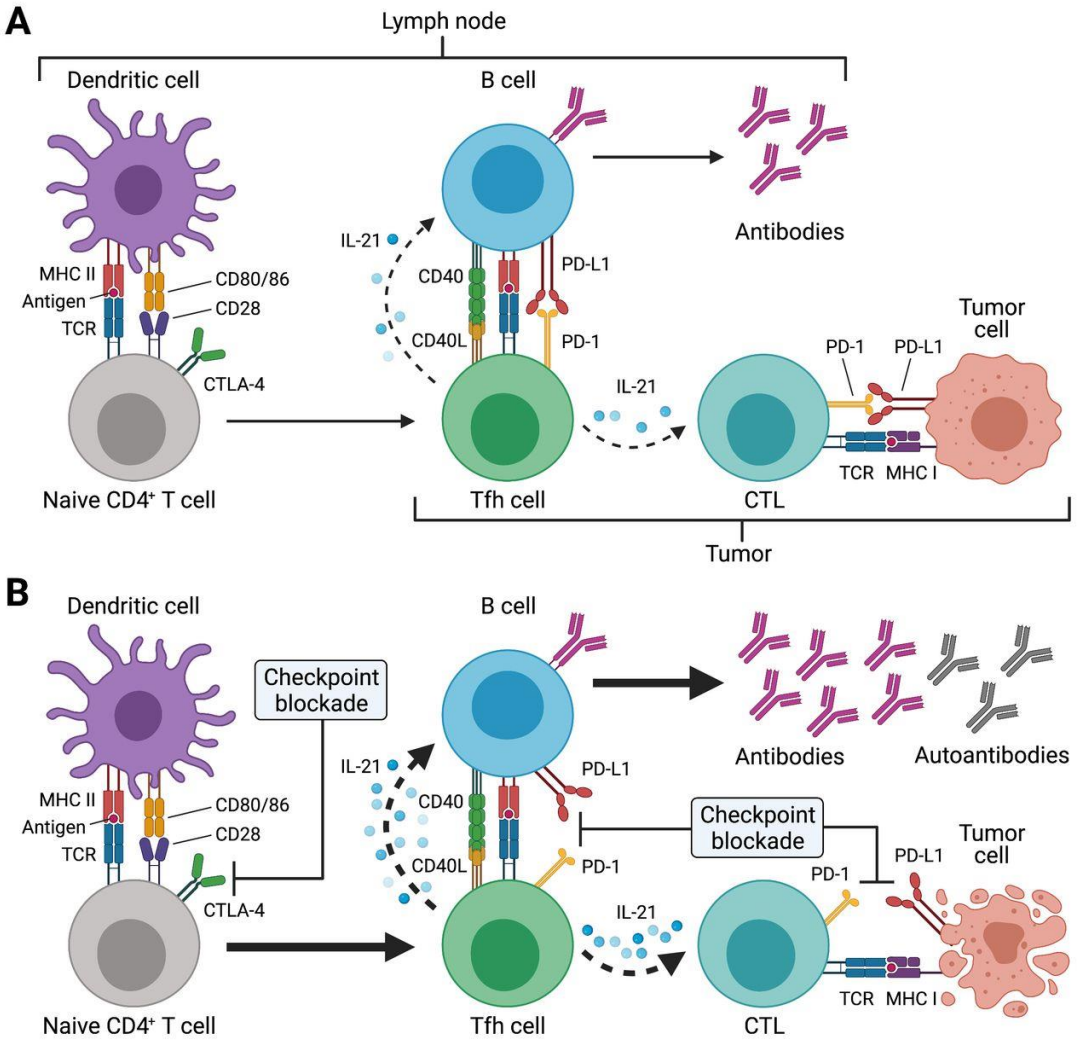
Tertiary lymphoid structures

- Tertiary lymphoid structures (TLS) are lymphoid organs that develop in non-lymphoid tissues in response to antigen persistence in an inflamed microenvironment.
- TLS can be sites of induction or reactivation of anti-tumor immunity.
- TLSs have an essential role in supporting local and systemic T and B cell antitumor responses.
- Presence of TLSs in TME is associated with better outcome.
- Gene signature associated with tertiary lymphoid structures predicted clinical outcomes in cohorts of patients treated with immune checkpoint blockade.
- T cells in tumours without tertiary lymphoid structures had a dysfunctional molecular phenotype.
- **Neoadjuvant immunotherapy induces the formation and maturation of TLS, which were associated with superior pathologic response, improved relapse free survival, and expansion of the intratumoral T and B cell repertoire.**
- In areas of tumor regression and TLS: increased expression of T cell memory markers and expansion of $CD8^+$ cytotoxic and tissue resident memory clonotypes.

Immunity Volume 56, Issue 10, 10 October 2023, Pages 2254-2269

Nat Rev Cancer. 2023 Sep 27.; bioRxiv. 2023 Oct 26:2023.10.16.562104.

Potential effects of immune checkpoint inhibitor (ICI) treatment on T follicular helper (Tfh) cell responses

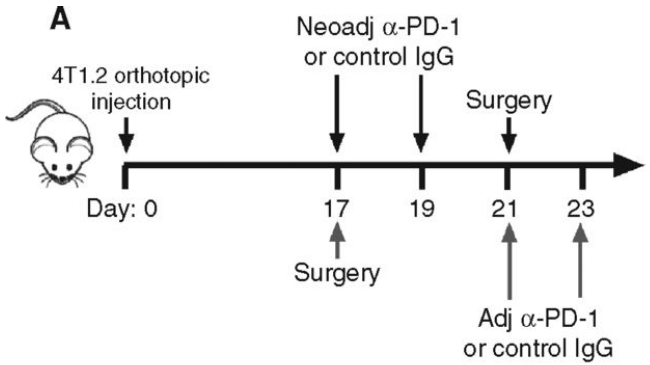


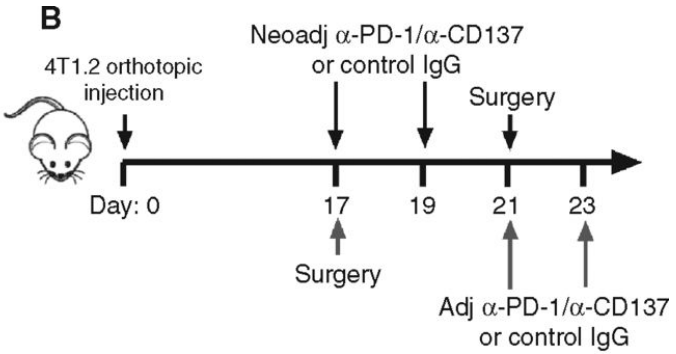
Baumjohann D, Brossart P. J Immunother Cancer. 2021 Jun;9(6):e002588

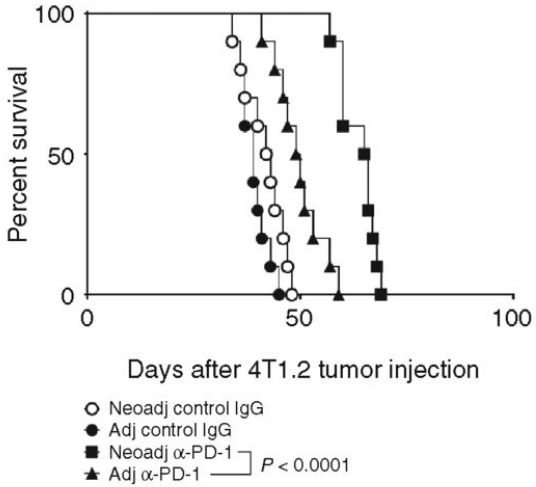
Gutiérrez-Melo N, Baumjohann D.Trends Cancer. 2023 Apr;9(4):309-325

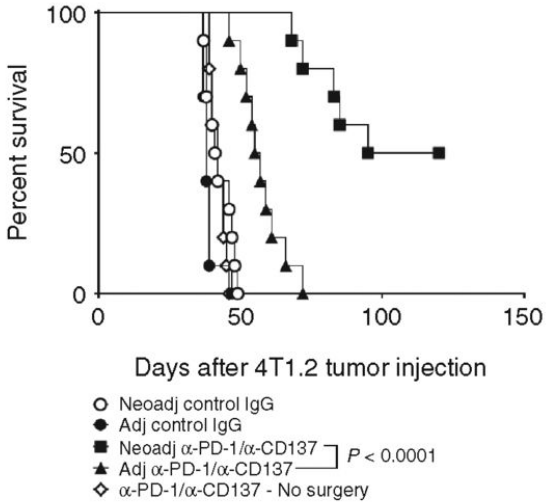
Evidence from preclinical studies

Improved Efficacy of Neoadjuvant Compared to Adjuvant Immunotherapy to Eradicate Metastatic Disease



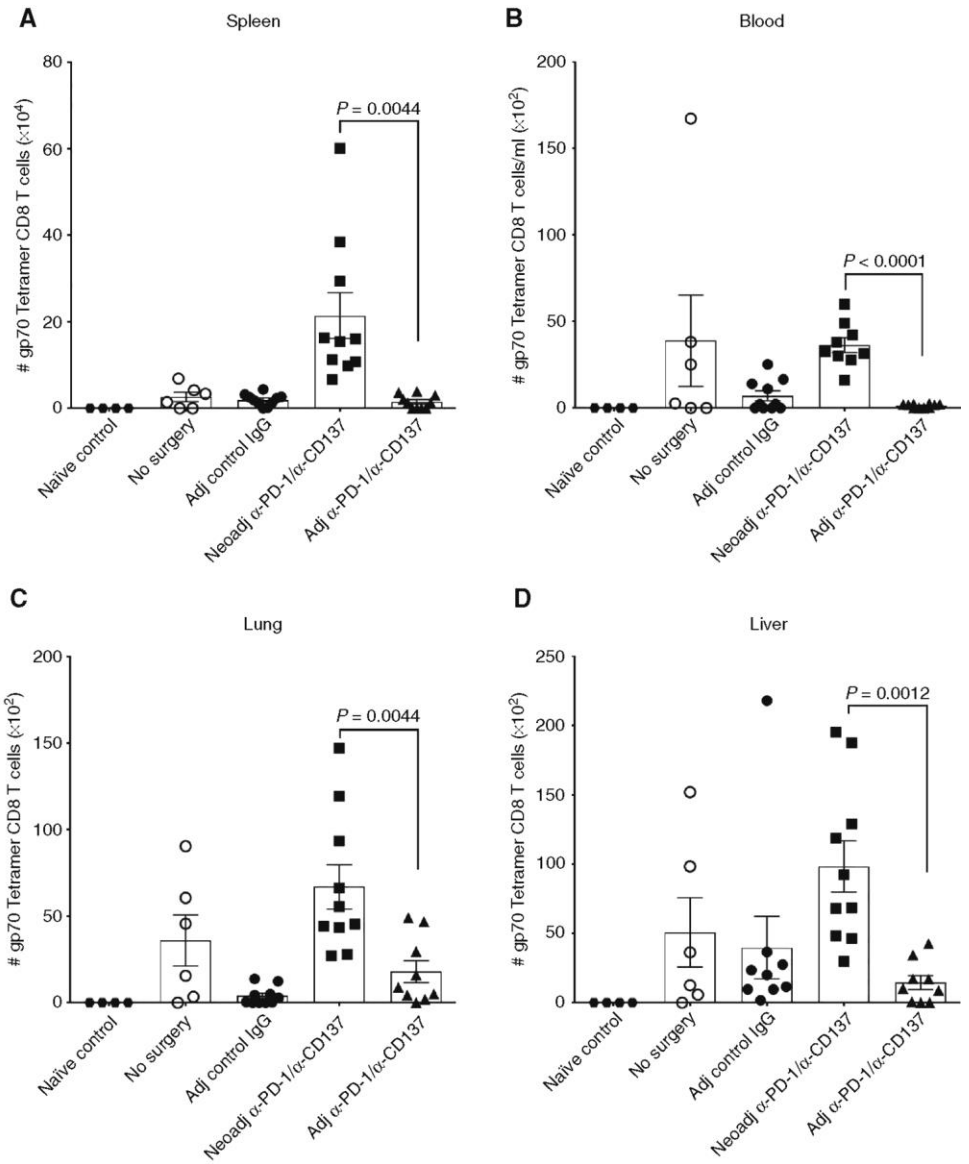






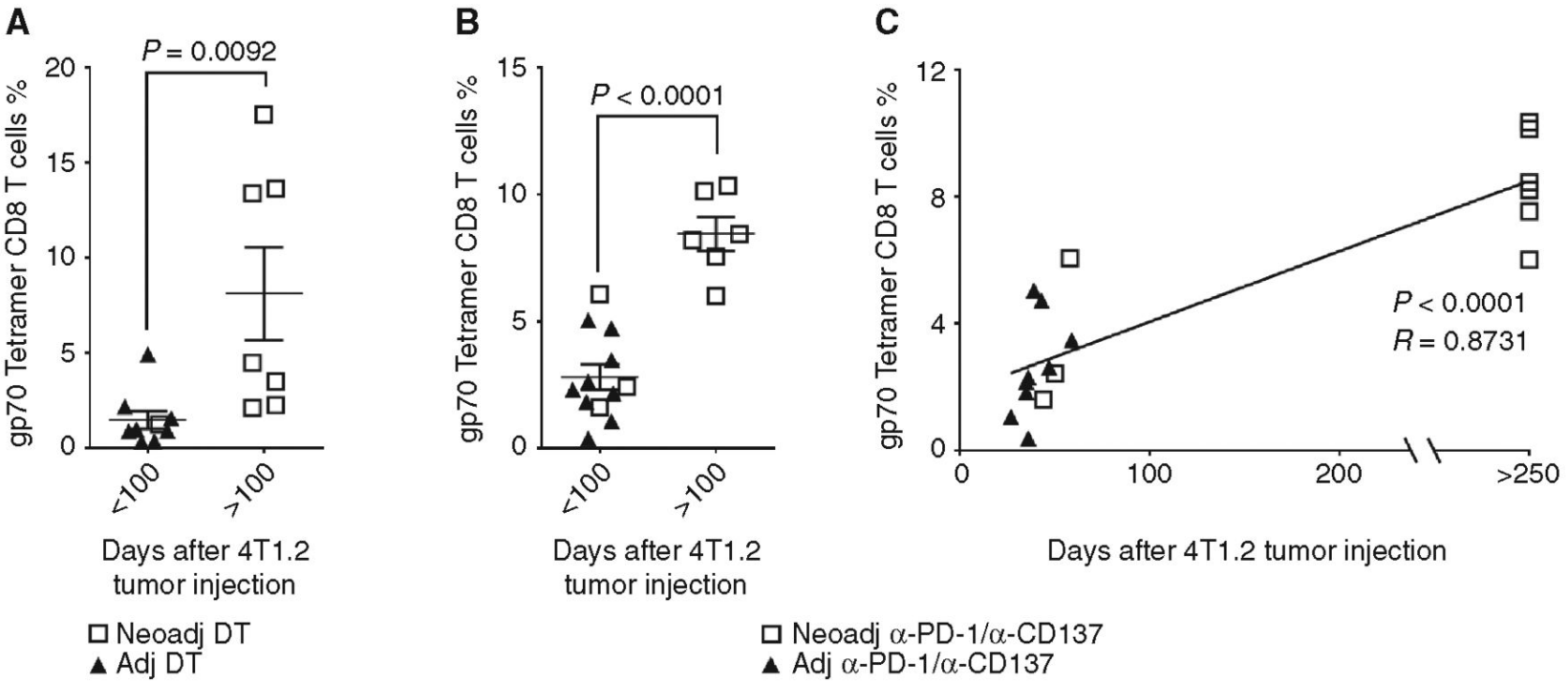
Cancer Discov. 2016;6(12):1382-1399. doi:10.1158/2159-8290.CD-16-0577

Neoadjuvant therapy leads to systemic expansion of gp70 tumor–specific CD8$^+$ T cells



Cancer Discov. 2016;6(12):1382-1399. doi:10.1158/2159-8290.CD-16-0577

Tumor-specific CD8$^+$ T cells are a biomarker of outcome



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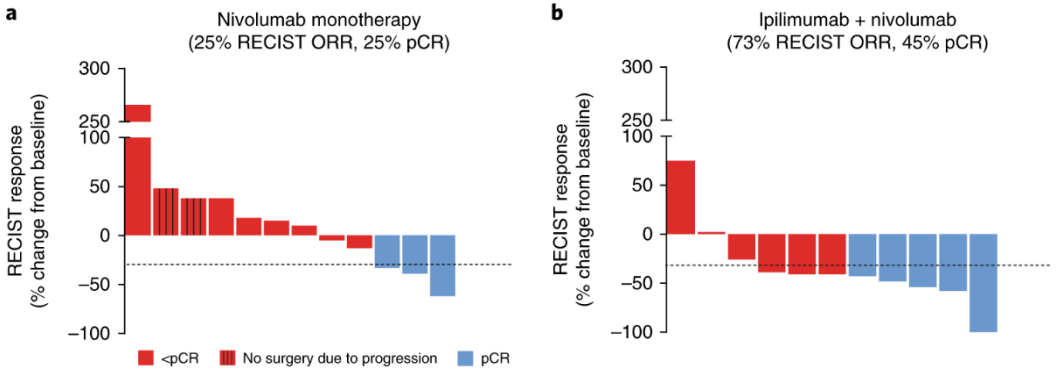
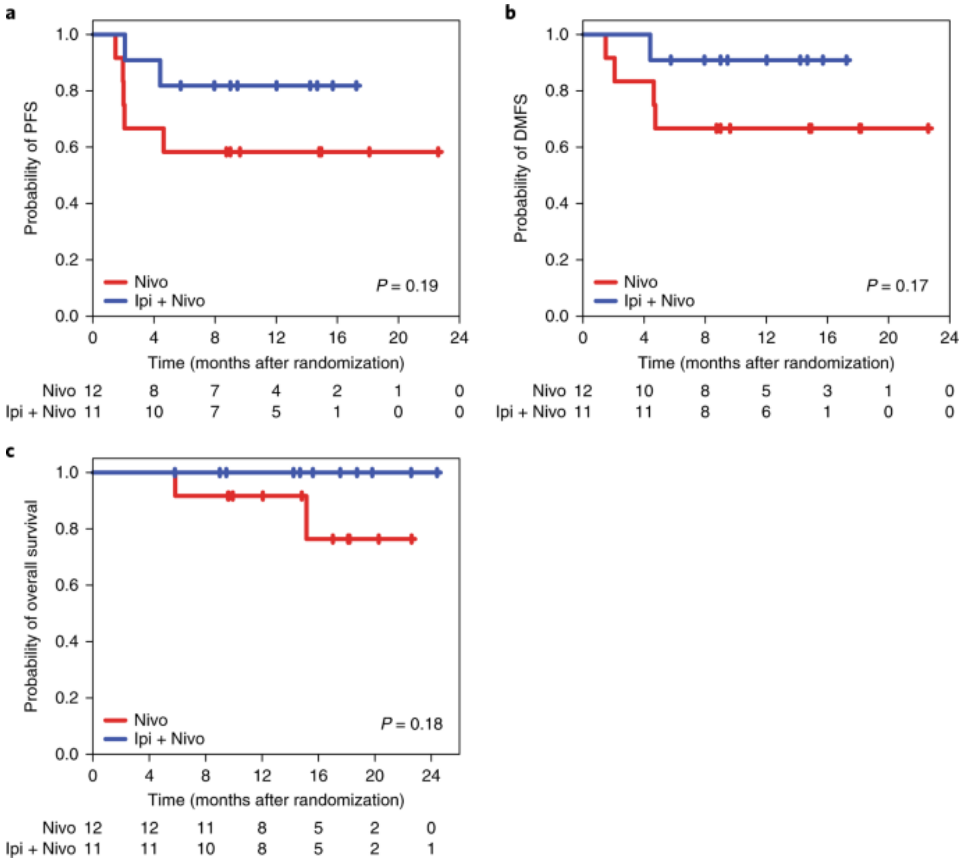
Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

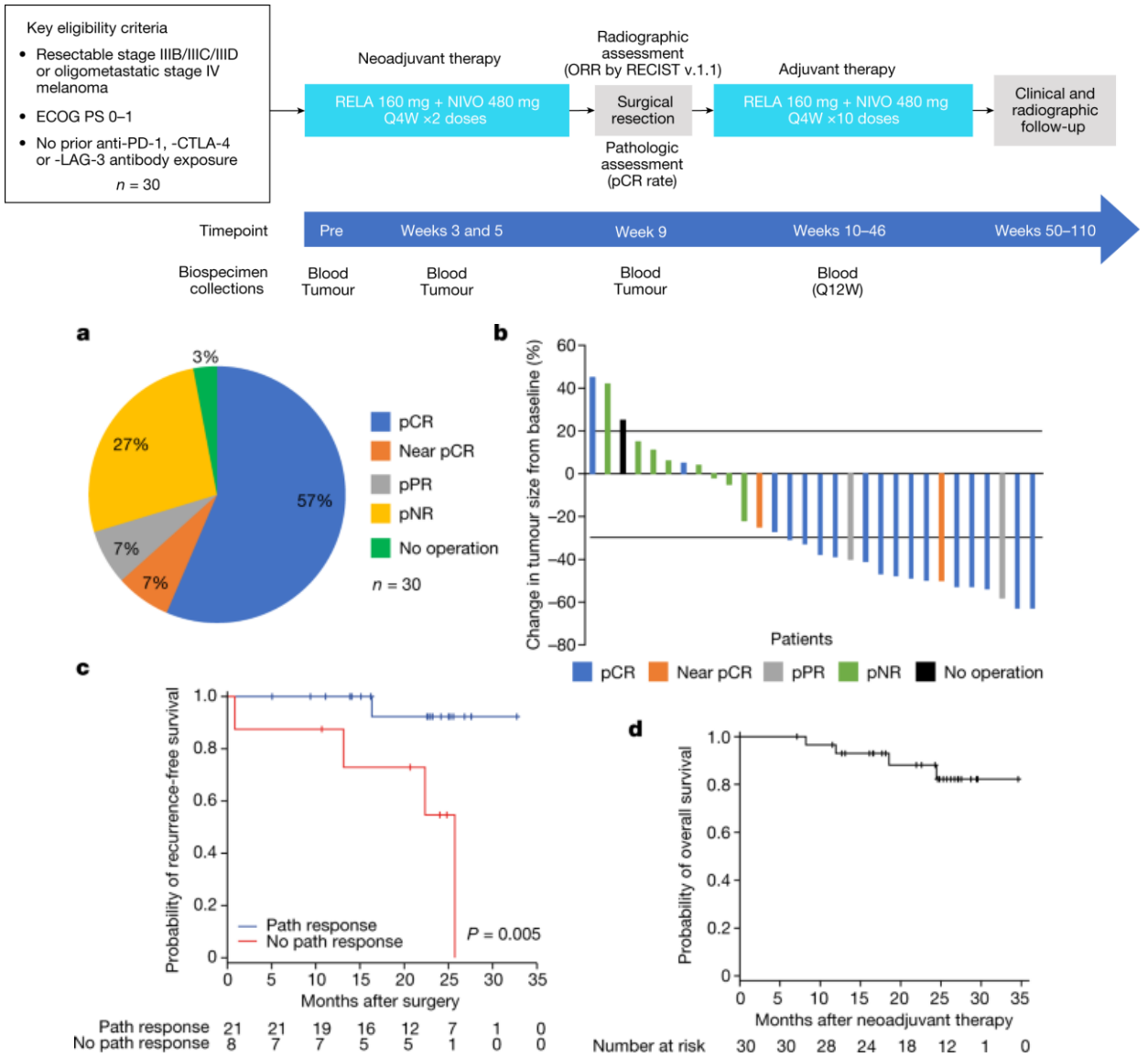




- Higher lymphoid infiltrates and a more clonal and diverse T cell infiltrate in responders
- Neoadjuvant ipilimumab + nivolumab expand more tumor-resident T cell clones in the peripheral blood compared to adjuvant ipilimumab + nivolumab
- Higher relapse rate in patients without expansion of resident T cell clones
- Batf3+ Clec9+ DC and IFNg signature are associated with improved ORR and survival
- TMB is associated with higher rate of pathological responses

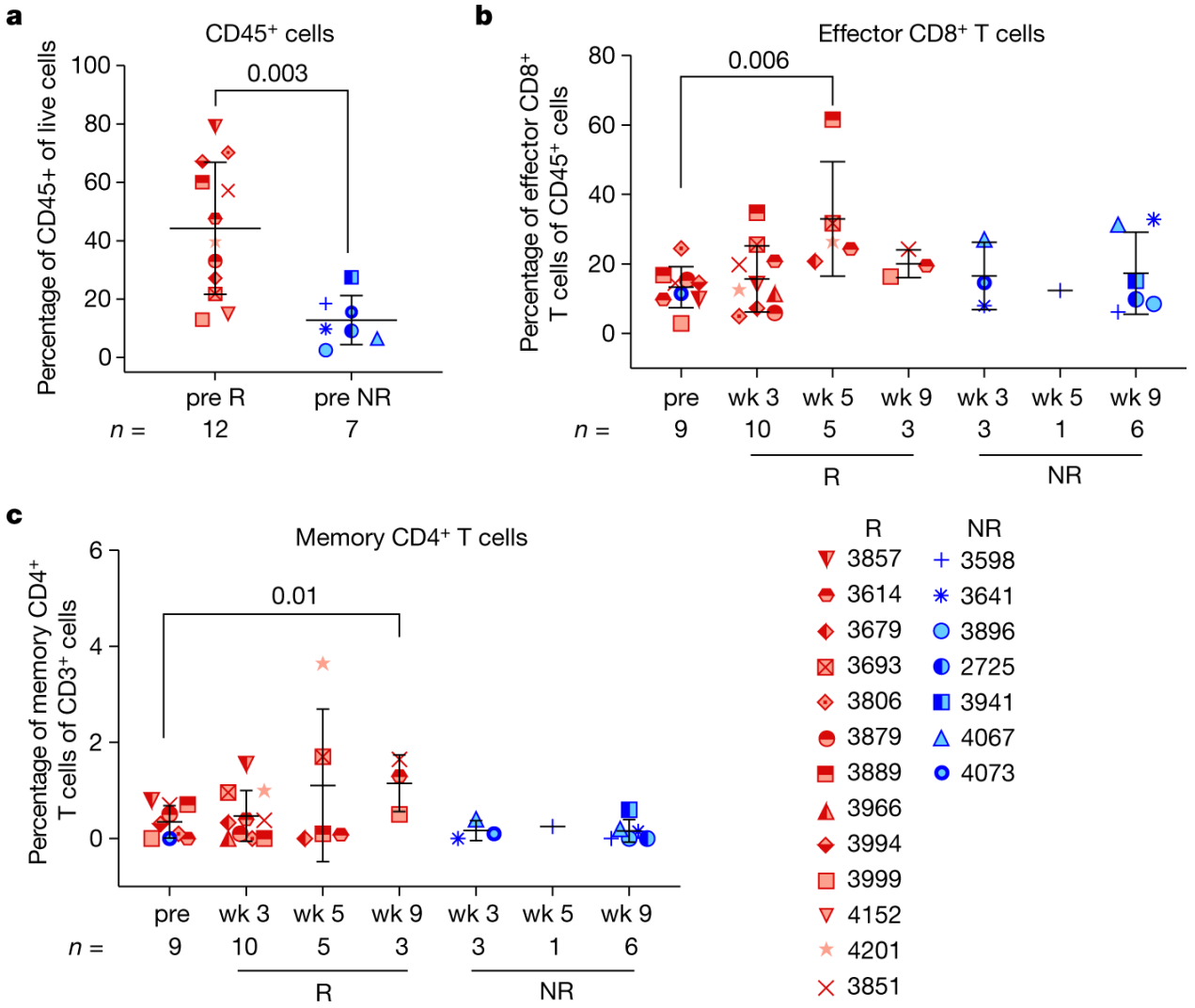
Nature Medicine 26, pages475–484 (2020) Nature Medicine 24, pages1649–1654 (2018); Nature Medicine 24, pages1655–1661 (2018)

Neoadjuvant relatlimab and nivolumab in resectable melanoma



Nature. 2022 Nov;611(7934):155-160.

Neoadjuvant relatlimab and nivolumab in resectable melanoma



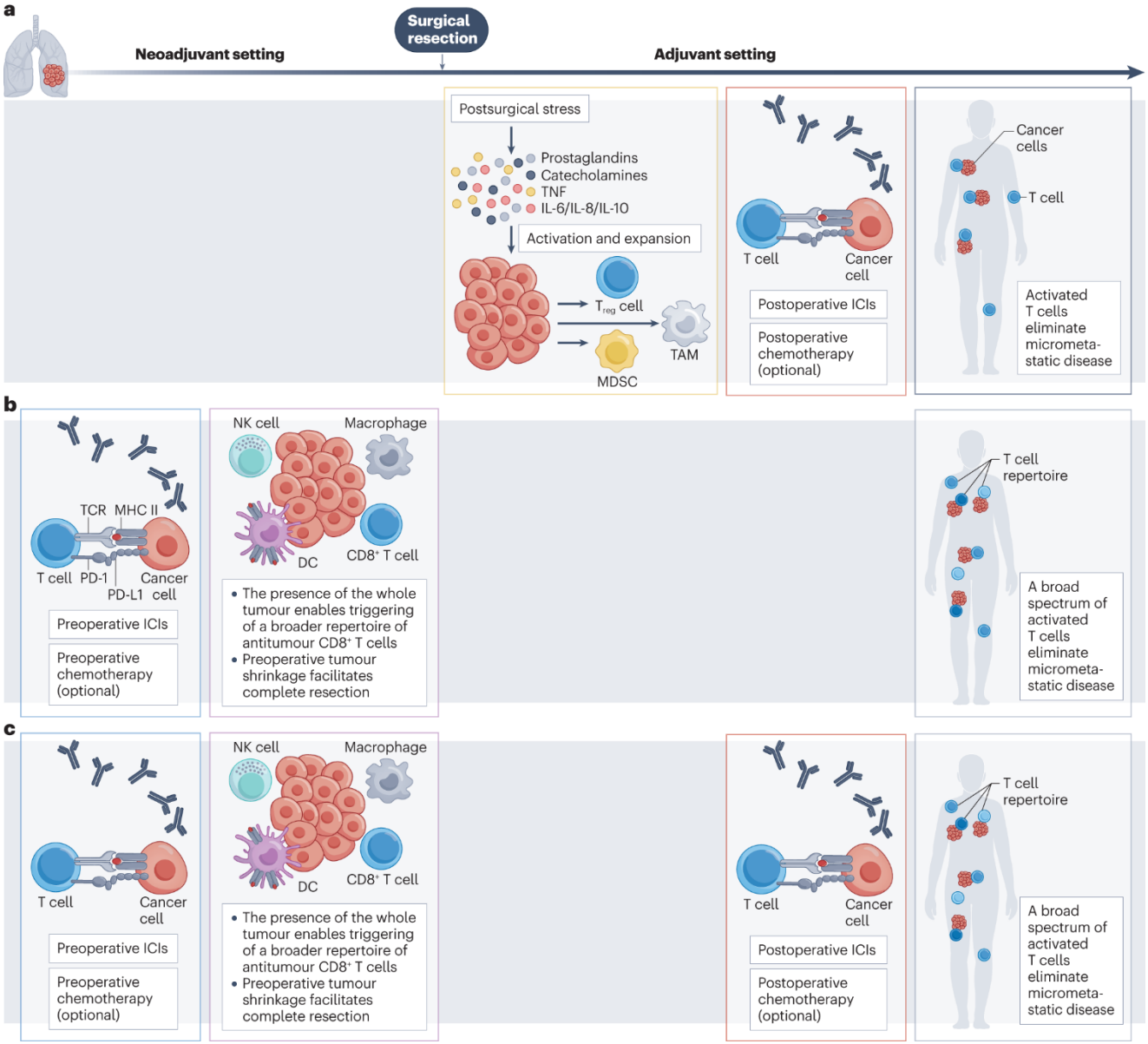
Nature. 2022 Nov;611(7934):155-160.

Neoadjuvant relatlimab and nivolumab in resectable melanoma

- LAG-3 and PD-1 levels in baseline tumour samples did not correlate with pathologic response.
- In tumours, the frequency of $CD45^+$ cells was higher in pretreatment samples of responders, defined as patients with less than 50% tumour viability at surgery, compared to pretreatment samples of non-responders (NRs; greater than or equal to 50% tumour viability)
- Unsupervised clustering identified an effector $CD8^+$ T cell subset ($CD8^+CD45RO^{low}$) and a memory $CD4^+$ T cell subset ($CD4^+CD45RO^+TCF7^+CD28^+BTLA^+TIGIT^+$) that were increased in posttreatment tumour specimens versus pretreatment in patients with favourable response.
- The increases in these cell populations were not appreciated in the NR patient group.
- The frequency of an M2-like macrophage subset decreased in tumours after treatment in patients with favourable response.
- In blood, there was a trend for increased $EOMES^+CD8^+$ T cells in patients with favourable versus non-favourable response after treatment.

Nature. 2022 Nov;611(7934):155-160.

Strategies for implementation of immunotherapy in the postoperative setting (part a), the preoperative setting (part b) and the perioperative setting (part c).



Nature Reviews Clinical Oncology volume 20, pages664–677 (2023)

Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma

Phase 2 trial

Patients with clinically detectable, measurable stage IIIB to IVC melanoma that was amenable to surgical resection

Randomization: three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group).

The primary end point was event-free survival in the intention-to-treat population.

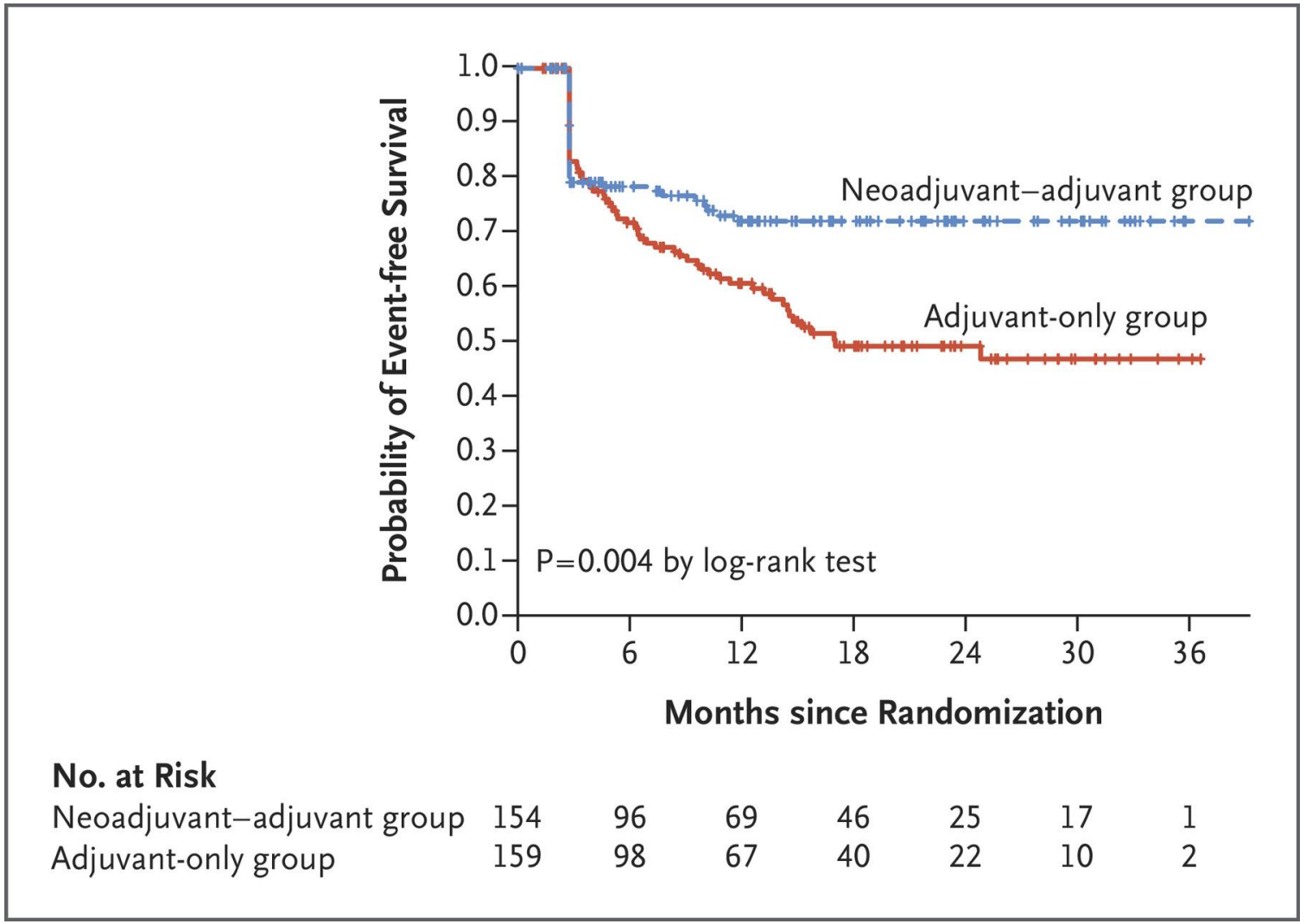
N. Engl. J. Med. 388, 813–823 (2023

Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Neoadjuvant–Adjuvant Group (N=154)	Adjuvant-Only Group (N=159)
Median age (range) — yr	64 (19–90)	62 (22–88)
Sex — no. (%)		
Female	62 (40)	48 (30)
Male	92 (60)	111 (70)
Zubrod's performance-status score — no. (%)†‡		
0	113 (73)	125 (79)
1	39 (25)	33 (21)
2	1 (<1)	0
LDH level — no. (%)		
Low or normal	132 (86)	138 (87)
High	22 (14)	21 (13)
Disease stage — no. (%)§		
IIIB	62 (40)	64 (40)
IIIC	69 (45)	74 (47)
IIID	9 (6)	10 (6)
IV	14 (9)	11 (7)
Primary melanoma subtype — no. (%)†		
Cutaneous or unknown	143 (93)	153 (96)
Acral	4 (3)	5 (3)
Mucosal	4 (3)	0
Ulceration — no. (%)†		
Yes	56 (36)	46 (29)
No	50 (32)	58 (36)
Unknown	46 (30)	55 (35)
BRAF mutation status — no. (%)		
Mutated	41 (27)	38 (24)
Wild-type	62 (40)	64 (40)
Unknown	51 (33)	57 (36)
Previous BRAF and MEK adjuvant therapy — no. (%)		
Yes	3 (2)	1 (1)
No	151 (98)	158 (99)
Previous radiotherapy — no. (%)		
Yes	2 (1)	1 (1)
No	152 (99)	158 (99)

Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma

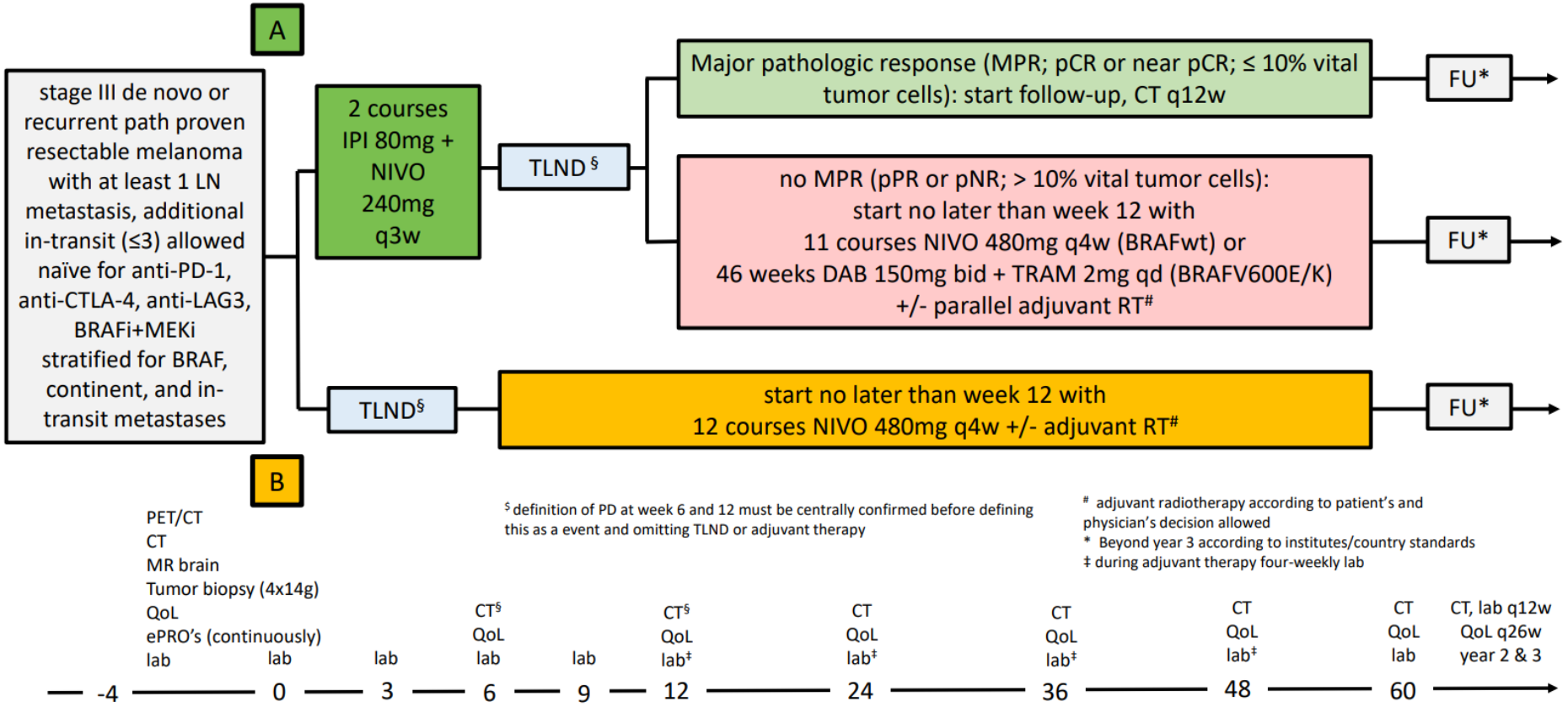


No. at Risk

Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

N. Engl. J. Med. 388, 813–823 (2023

NADINA - study design



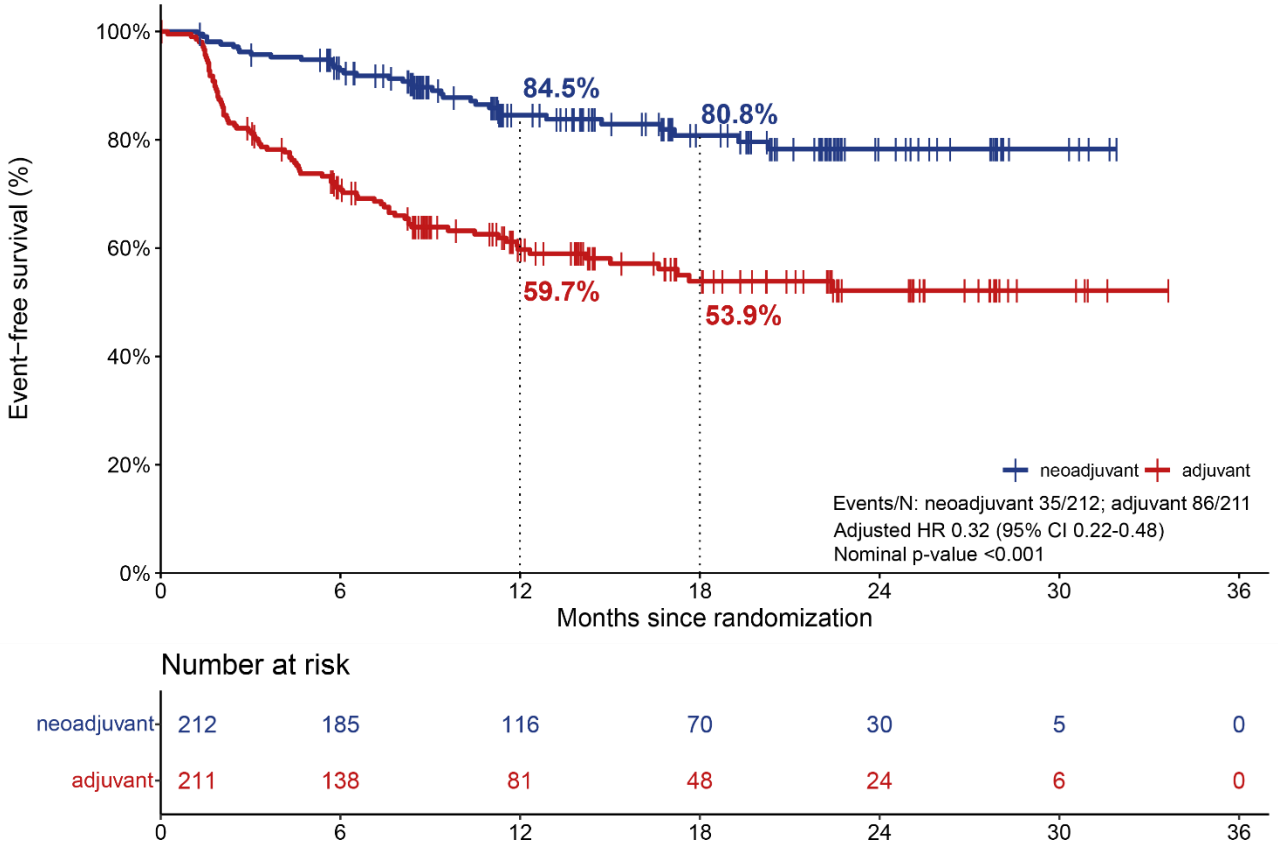
N Engl J Med. 2024 Jun 2. doi: 10.1056/NEJMoa2402604.

NADINA – Objectives and Endpoints

- **Primary endpoint**
  - Event-free survival: randomization to progression, recurrence, or death due to melanoma/treatment
- **Key secondary endpoint**
  - Overall survival
- **Secondary endpoints**
  - Pathological response rate
  - Recurrence-free survival
  - **Distant metastasis-free survival:** randomization to first distant metastasis, death due to melanoma/treatment
  - Adverse events
  - Surgical complications
  - Health-related quality of life

N Engl J Med. 2024 Jun 2. doi: 10.1056/NEJMoa2402604.

Updated event-free survival

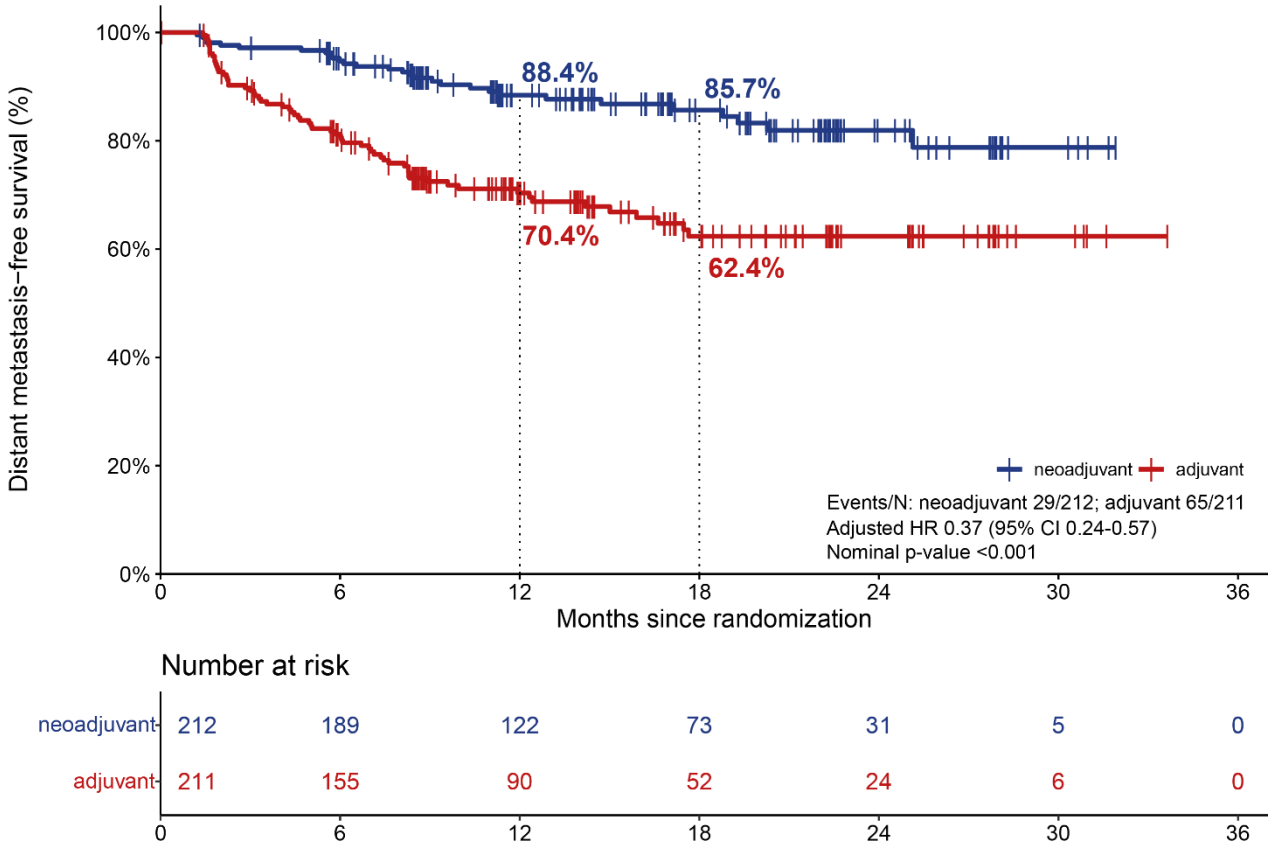


Median follow-up of 15.4 months (95% CI 9.0-22.4).

Censoring at last CT scan or death

N Engl J Med. 2024 Jun 2. doi: 10.1056/NEJMoa2402604.

Distant metastasis-free survival



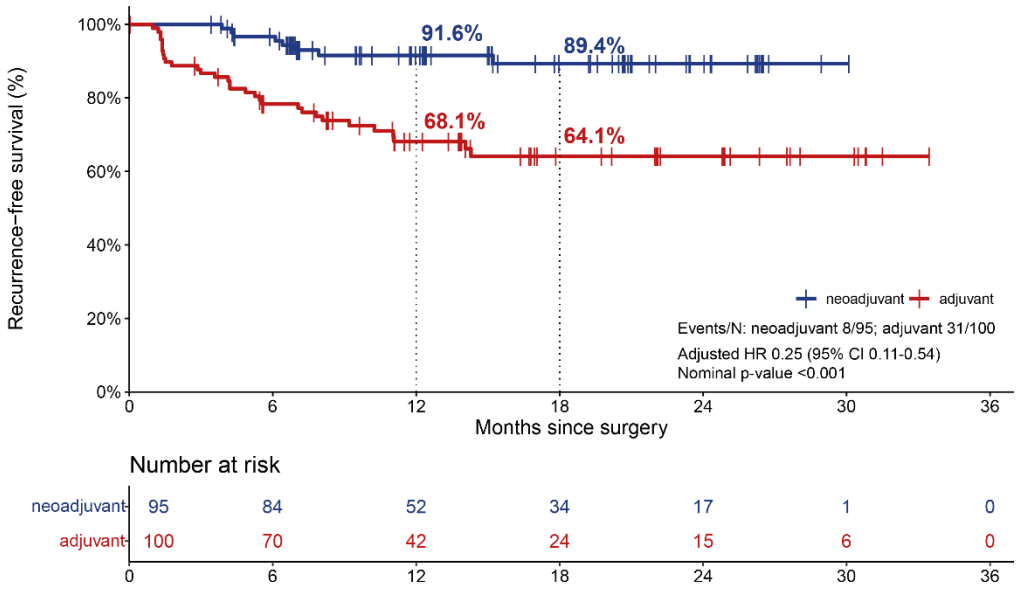
Location of first distant metastasis

	Neoadjuvant (29 patients)	Adjuvant (65 patients)
Lung	9	19
Brain	8	6
Liver	8	17
Distant lymph node	5	13
Spleen	5	2
Bone	4	14
Abdominal [2]	4	3
(Sub)cutaneous	4	12
Abdominal-/chest wall	1	4
Peritoneum	1	2
Adrenal gland	1	1
Breast	0	2
Muscle	0	2
Mediastinum	0	1

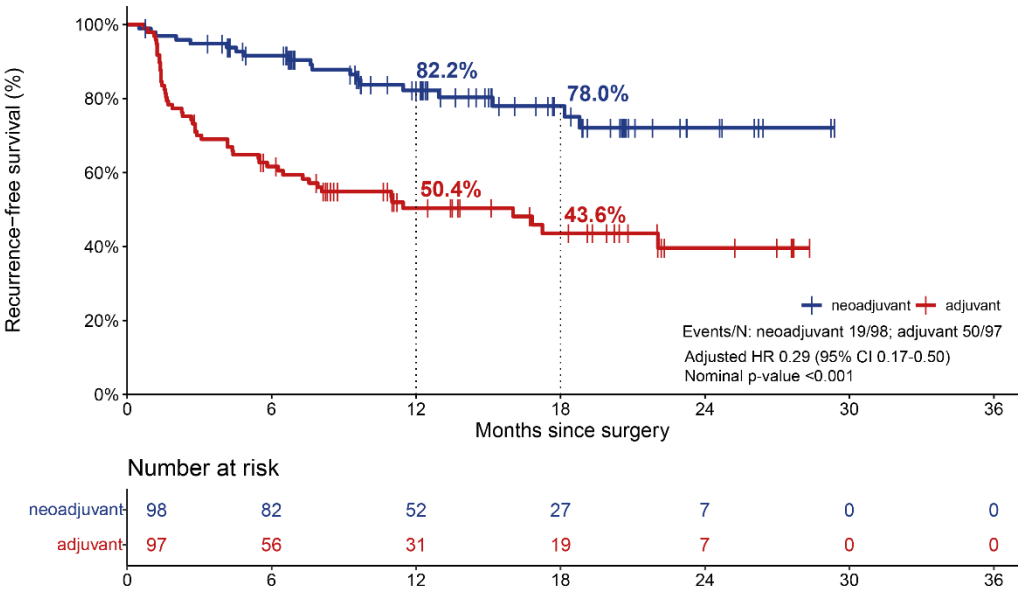
[1] Multiple locations could be involved at the time of first distant metastasis.
[2] Abdominal metastases include metastases in pelvis and intestines, but do not include liver or adrenal glands.

Recurrence-free survival according to stage (AJCC 8th edition)

Stage IIIB

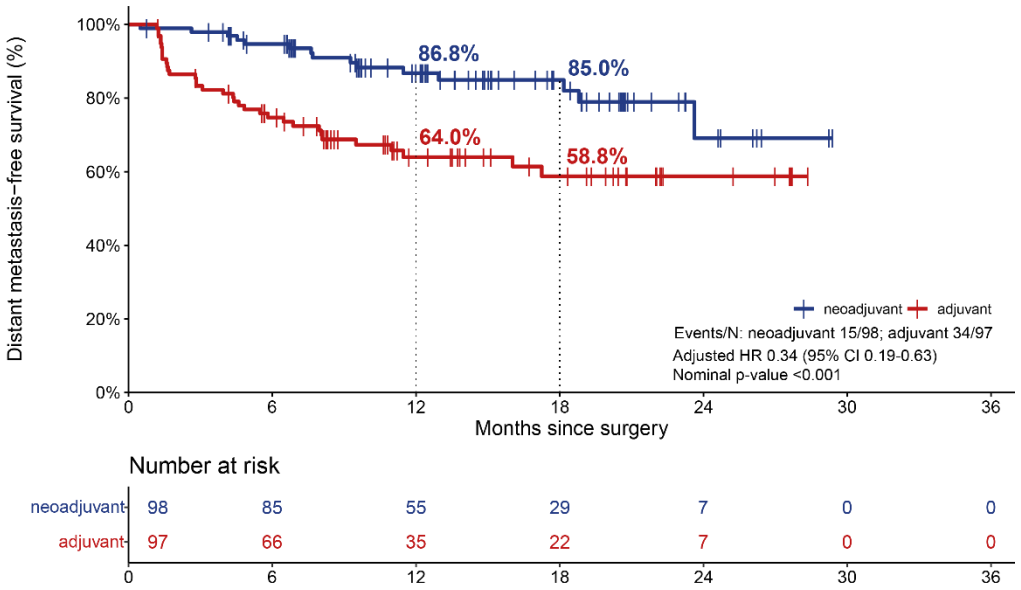


Stage IIIC

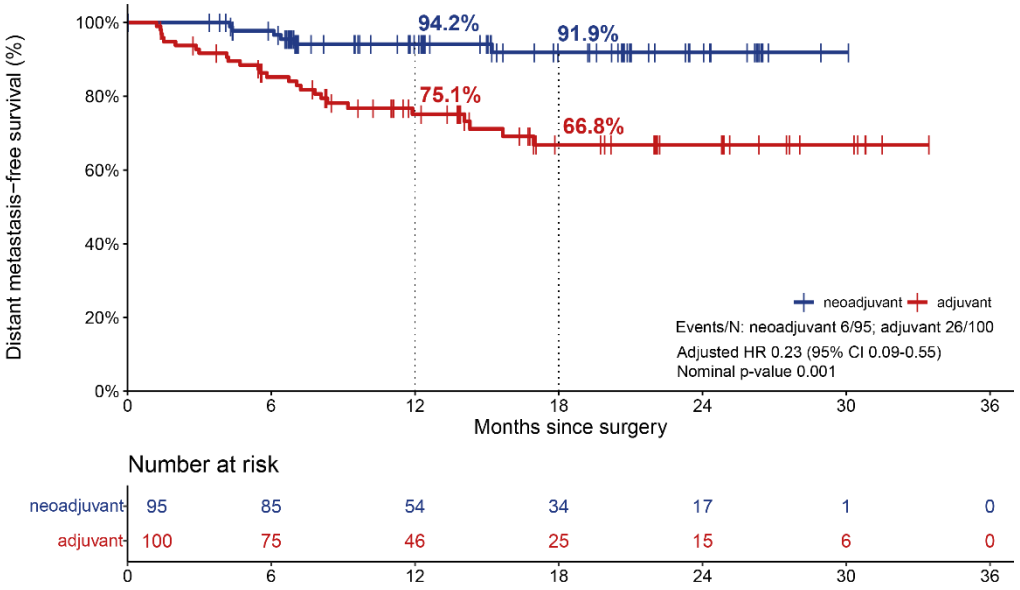


Distant metastasis-free survival according to stage (AJCC 8th edition)

Stage IIIB



Stage IIIC



Distant metastasis-free survival is defined in this subgroup-analysis as time from surgery (instead of randomization), because the subgroups were based on pathological staging which was not known before surgery.

Final pathological- and radiological responses in the neoadjuvant arm

Radiological response category	No. of patients (%)
Complete response	27 (12.7%)
Partial response	52 (24.5%)
Stable disease	91 (42.9%)
Progressive disease	34 (16.0%)
Non-evaluable/ not done	8 (3.7%)

R 37.2

ORR, objective response rate (radiological).

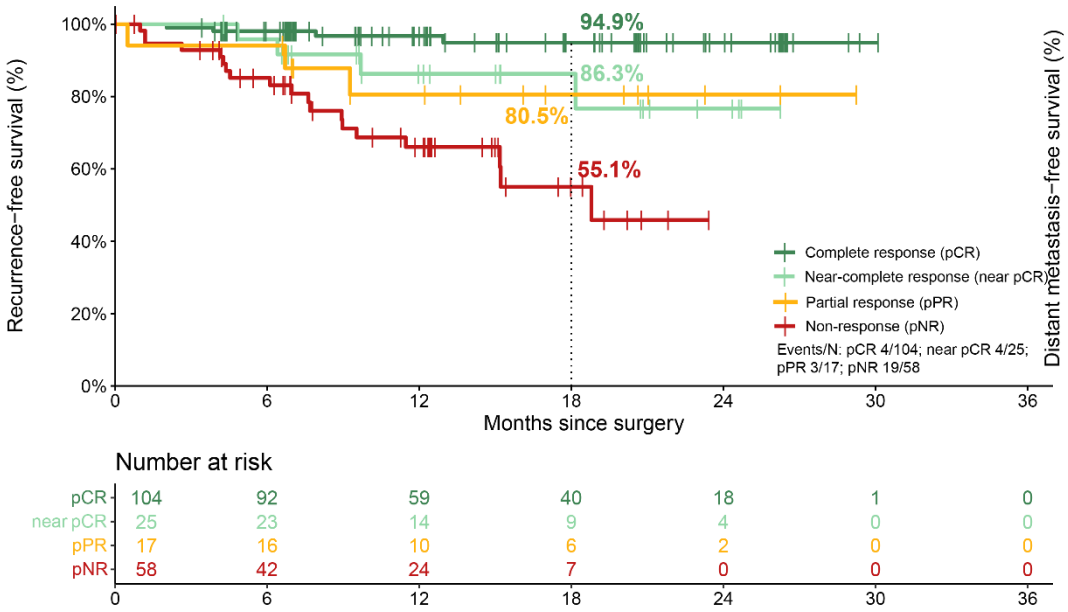
Pathological response category	No. of patients (%)
pCR	95 (44.8%)
near pCR	25 (11.8%)
pPR	17 (8.0%)
pNR	58 (27.4%)
Progression	5 (2.4%)
No surgery	3 (1.4%)

R 60.8

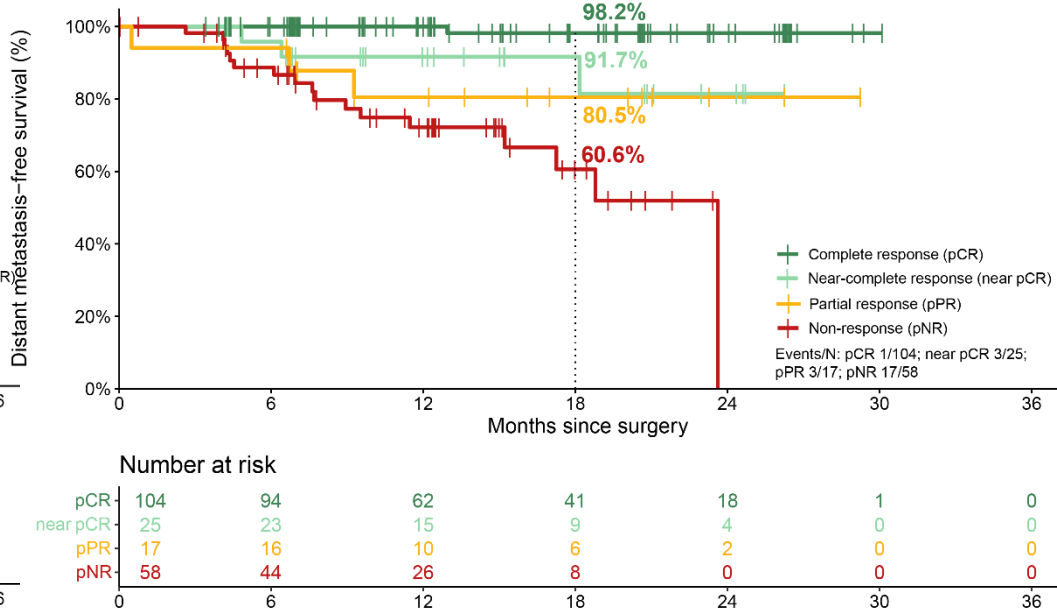
MPR, major pathologic response (≤10% residual viable tumor); pCR, pathologic complete response (0% residual viable tumor), near pCR, pathologic near complete response (1-10% residual viable tumor); pPR, pathologic partial response (11-50% residual viable tumor); pNR, pathologic non-response (>50% residual viable tumor).

RFS & DMFS based on pathological response in the neoadjuvant arm

Recurrence-free survival



Distant metastasis-free survival



At 18 months for MPR subgroup: RFS 93.1%; DMFS 96.0%.

RFS at 12 months for pCR 96.7%; near pCR 86.3%; pPR 80.5%; pNR 66.1%. DMFS at 12 months for pCR 100% ; near pCR 91.7%; pPR 80.5%; pNR 72.2%.

Distant metastasis-free survival is defined in this subgroup analysis as time from surgery (instead of randomization), because the subgroups were based on pathological response which was not known before surgery.

Summary

- The event-free survival benefit for neoadjuvant ipilimumab + nivolumab remains consistent with 6 months longer follow-up (HR=0.32, nominal p<0.001);
- Neoadjuvant ipilimumab + nivolumab results in an improved DMFS as compared to standard of care adjuvant PD-1 blockade (HR=0.37, nominal p<0.001);
- The RFS & DMFS benefit for neoadjuvant ipilimumab + nivolumab is observed in both stage IIIB and stage IIIC melanoma;
- The final MPR rate in NADINA is 60.8%, the final radiological objective response rate (ORR) rate is 37.2%;
- Patients in the neoadjuvant arm with a MPR or ORR have favorable EFS and DMFS at 18 months;
- Neoadjuvant ipilimumab plus nivolumab is superior to adjuvant nivolumab and should be considered as a new standard of care treatment.

KEYMAKER-U02 Substudy 02C: Neoadjuvant Pembrolizumab and Investigational Agents Followed by Adjuvant Pembrolizumab for Stage IIIB-D Melanoma

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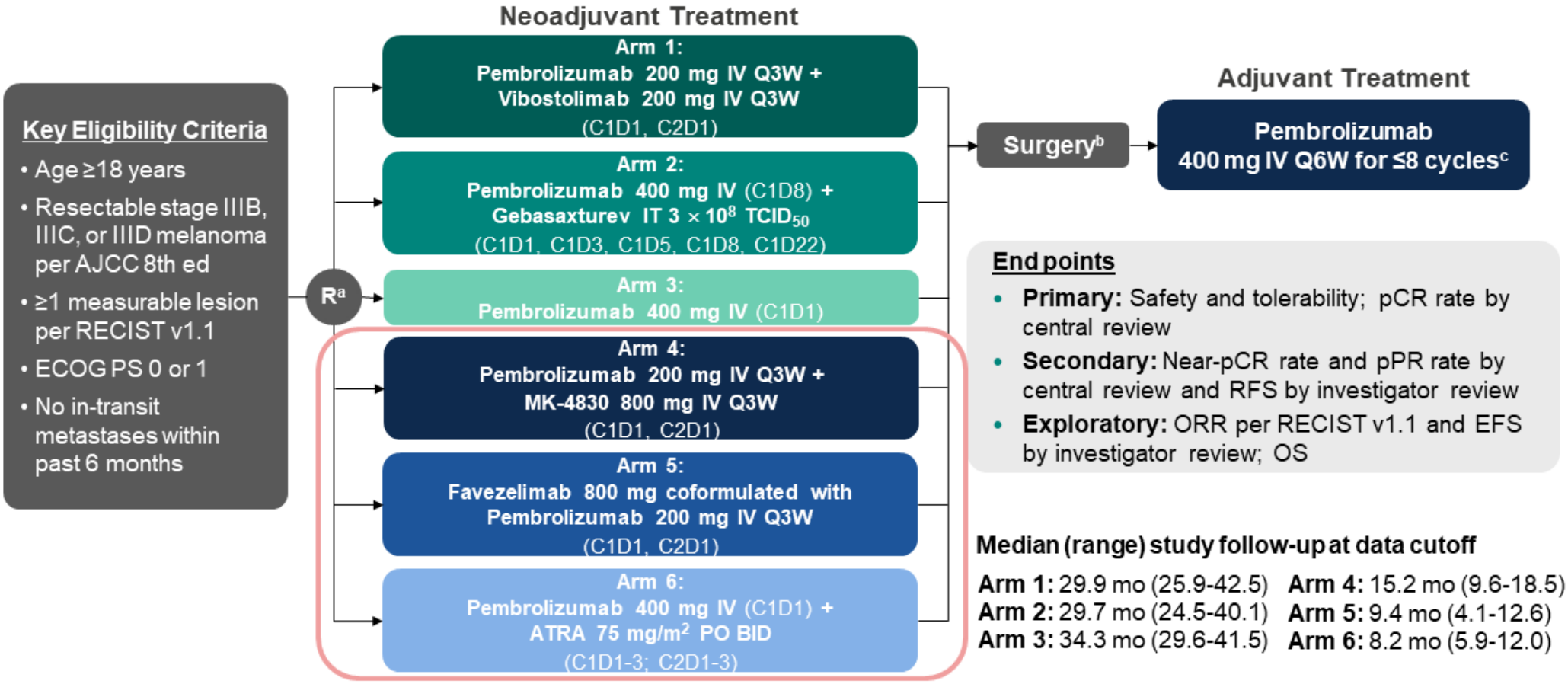
Background

- Substudy 02C of the phase 1/2 KEYMAKER-U02 trial is evaluating neoadjuvant pembrolizumab + investigational agents or pembrolizumab alone followed by adjuvant pembrolizumab in patients with stage IIIB-D melanoma
- Treatment arms initiated include:
  - **Arm 1:** pembrolizumab (anti–PD-1) + vibostolimab (anti-TIGIT)
  - **Arm 2:** pembrolizumab + gebasaxturev (V937, coxsackievirus A21)
  - **Arm 3:** pembrolizumab alone
  - **Arm 4:** pembrolizumab + MK-4830 (anti-ILT4)
  - **Arm 5:** favezelimab (anti–LAG-3) coformulated with pembrolizumab (favezelimab/pembrolizumab)
  - **Arm 6:** pembrolizumab + all-trans retinoic acid (ATRA)

KEYMAKER-U02 Substudy 02C Study Design (NCT04303169)



End points

- **Primary:** Safety and tolerability; pCR rate by central review
- **Secondary:** Near-pCR rate and pPR rate by central review and RFS by investigator review
- **Exploratory:** ORR per RECIST v1.1 and EFS by investigator review; OS

Median (range) study follow-up at data cutoff

Arm 1: 29.9 mo (25.9-42.5)
Arm 2: 29.7 mo (24.5-40.1)
Arm 3: 34.3 mo (29.6-41.5)
Arm 4: 15.2 mo (9.6-18.5)
Arm 5: 9.4 mo (4.1-12.6)
Arm 6: 8.2 mo (5.9-12.0)

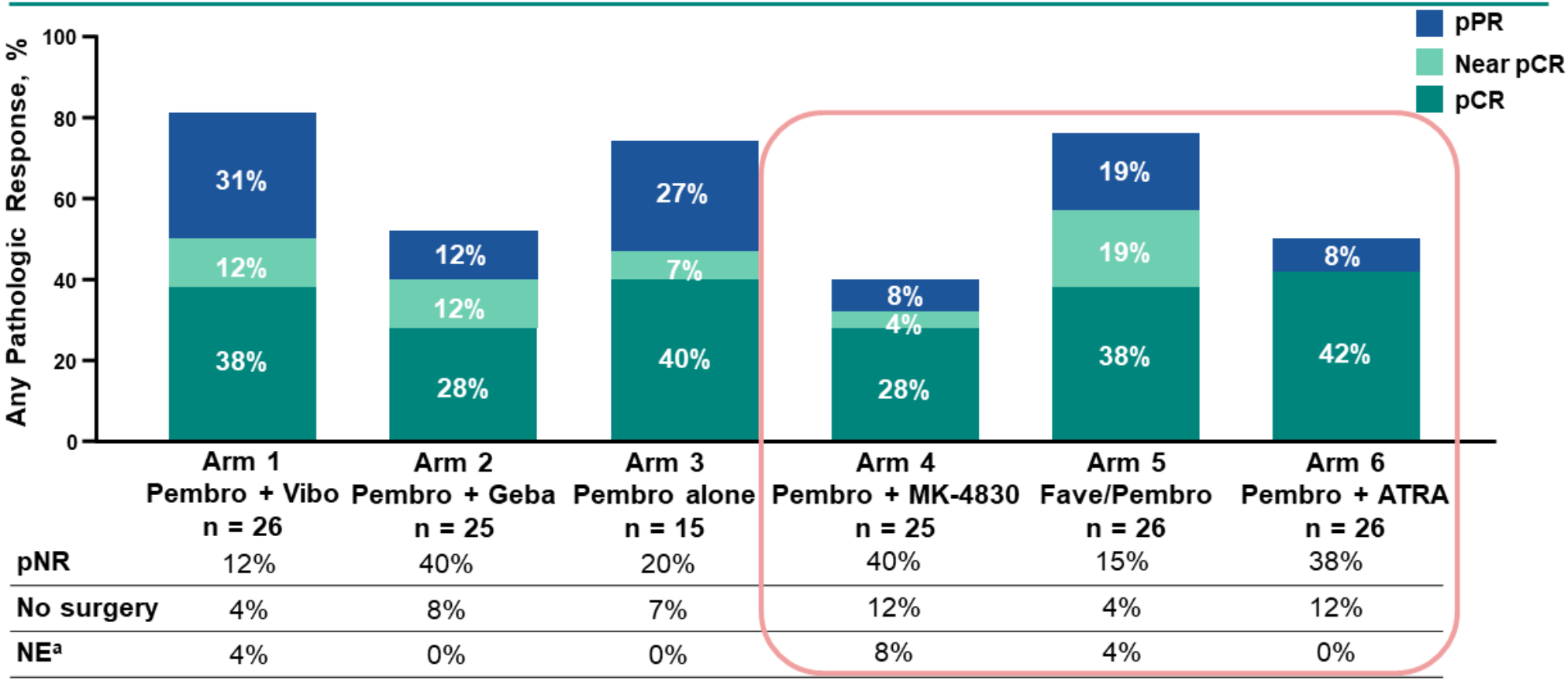
[a]Patients were randomly allocated across all open treatment arms. [b]Surgical resection was performed 6 weeks after the first dose of neoadjuvant study intervention. [c]Total treatment duration of approximately 1 year, including neoadjuvant and adjuvant therapy. Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Baseline Characteristics

	Arm 1 Pembro + Vibo n = 26	Arm 2 Pembro + Geba n = 25	Arm 3 Pembro alone n = 15	Arm 4 Pembro + MK-4830 n = 25	Arm 5 Fave/Pembro n = 26	Arm 6 Pembro + ATRA n = 26
Age, median (range), years	60 (18-78)	60 (32-82)	66 (40-79)	63 (21-83)	61 (36-82)	65 (30-85)
Sex, male, n (%)	17 (65)	13 (52)	8 (53)	15 (60)	18 (69)	14 (54)
ECOG PS 0, n (%)	24 (92)	22 (88)	15 (100)	24 (96)	23 (88)	23 (88)
Tumor stage, n (%)[a]						
IIIB	15 (58)	12 (48)	6 (40)	12 (48)	14 (54)	14 (54)
IIIC	10 (38)	13 (52)	9 (60)	13 (52)	12 (46)	12 (46)
***BRAF* mutation status, n (%)[b]**						
Mutant	12 (46)	19 (76)	3 (20)	13 (52)	11 (42)	14 (54)
Wild type	14 (54)	6 (24)	12 (80)	11 (44)	15 (58)	12 (46)
Lymph-node involvement, n (%)						
1	14 (54)	17 (68)	6 (40)	19 (76)	12 (46)	15 (58)
>1	12 (46)	8 (32)	9 (60)	6 (24)	14 (54)	11 (42)

[a]Stage IV disease at baseline for 1 patient in arm 1, which was identified after the patient was randomly assigned and treated (protocol deviation). [b]*BRAF* mutation status was missing for 1 patient in arm 4.
Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Pathological Response Summary



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pNR	12%	40%	20%	40%	15%	38%
No surgery	4%	8%	7%	12%	4%	12%
NE[a]	4%	0%	0%	8%	4%	0%

Pathologic response was assessed by central review. pCR = complete absence of viable tumor in the treated tumor bed. Near pCR >0% but ≤10% of viable tumor cells in the treated tumor bed. pPR >10% but ≤50% of viable tumor cells in the treated tumor bed. pNR >50% of viable tumor cells in the treated tumor bed. NE = surgery completed but tissue not evaluable by central review. [a]Arm 1: no residual disease or recurrence (n = 1); arm 4: no tumor bed identified and no recurrence reported (n = 1, each); and arm 5: patient consent withdrawal (n = 1). Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

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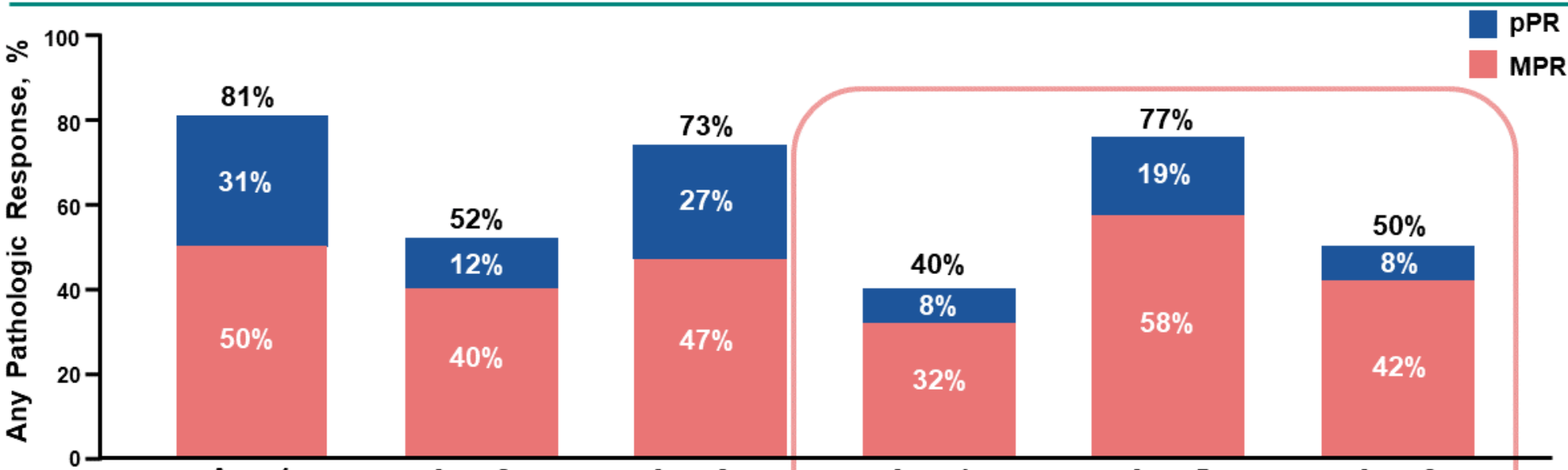

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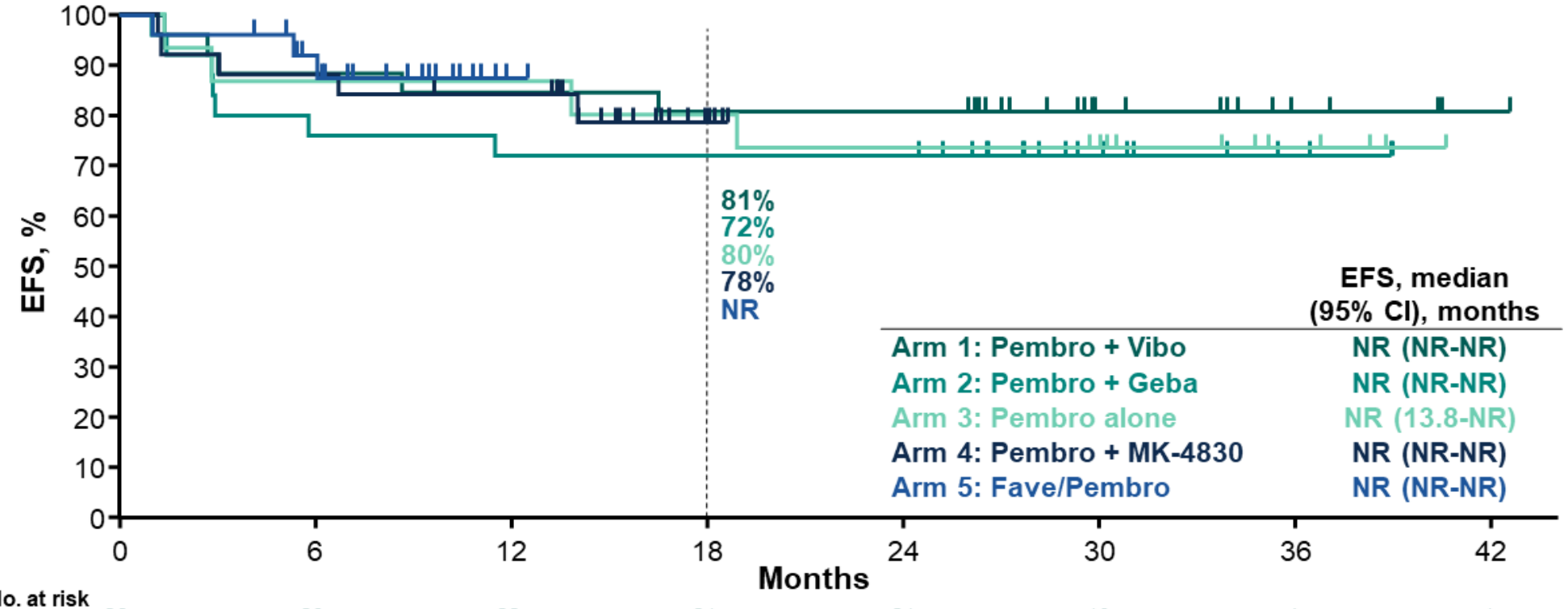
Objective Response Rate per RECIST v1.1

	Arm 1 Pembro + Vibo n = 26	Arm 2 Pembro + Geba n = 25	Arm 3 Pembro alone n = 15	Arm 4 Pembro + MK-4830 n = 25	Arm 5 Fave/Pembro n = 26	Arm 6 Pembro + ATRA n = 26
ORR, % (95% CI)	50 (30-70)	32 (15-54)	27 (8-55)	44 (24-65)	35 (17-56)	35 (17-56)
Best overall response, n (%)						
CR	2 (8)	0	1 (7)	3 (12)	1 (4)	2 (8)
PR	11 (42)	8 (32)	3 (20)	8 (32)	8 (31)	7 (27)
SD	9 (35)	10 (40)	9 (60)	10 (40)	13 (50)	10 (38)
PD	4 (15)	7 (28)	2 (13)	3 (12)	3 (12)	7 (27)
PD resulting in unresectable tumor	1 (4)	2 (8)	1 (7)	2 (8)	1 (4)	3 (12)
NE or no assessment	0	0	0	1 (4)	1 (4)	0

Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Event-Free Survival by Investigator Review

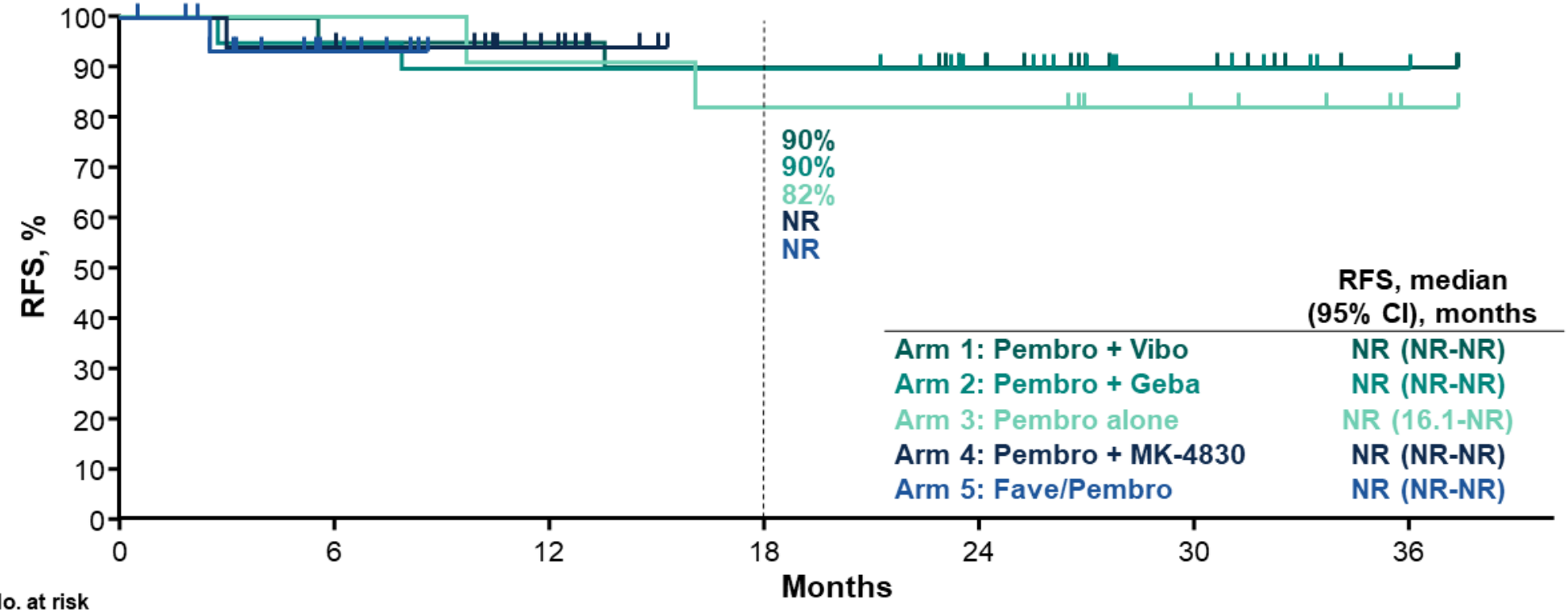


No. at risk

26	23	22	21	21	10	4	1
25	19	18	18	18	8	3	0
15	13	13	12	11	9	4	0
25	22	20	4	0			
26	20	1	0				

Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Recurrence-Free Survival by Investigator Review



No. at risk						
20	19	19	18	15	8	2
19	18	17	17	11	5	1
11	11	10	9	9	5	1
17	16	8	0			
18	7	0				

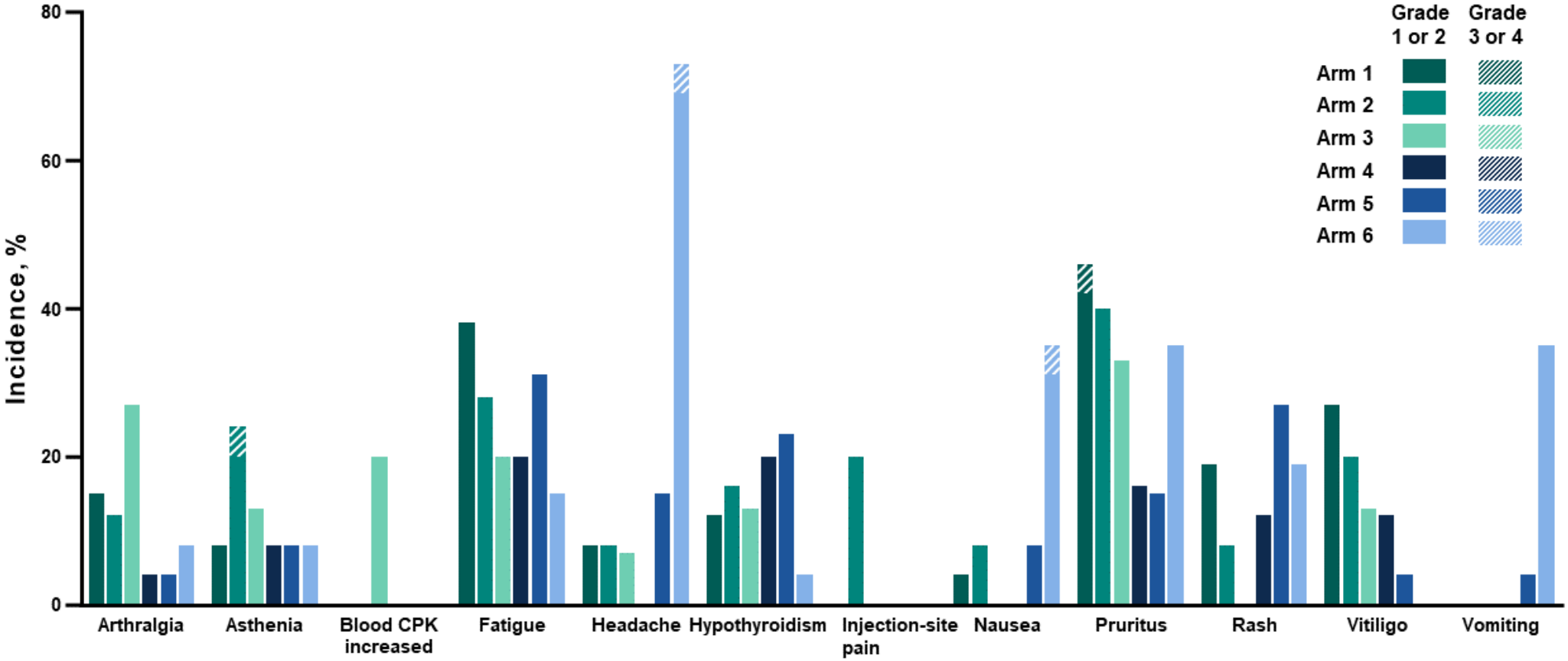
Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Adverse Event Summary

	Arm 1 Pembro + Vibo n = 26	Arm 2 Pembro + Geba n = 25	Arm 3 Pembro alone n = 15	Arm 4 Pembro + MK-4830 n = 25	Arm 5 Fave/Pembro n = 26	Arm 6 Pembro + ATRA n = 26
Treatment-related AEs						
Any grade	24 (92)	21 (84)	12 (80)	19 (76)	23 (88)	25 (96)
Grade 3 or 4[a]	2 (8)	7 (28)	1 (7)	4 (16)	4 (15)	2 (8)
Led to discontinuation[b]	3 (12)	6 (24)	0	2 (8)	2 (8)	3 (12)
Immune-mediated AEs and infusion reactions						
Any grade	8 (31)	10 (40)	4 (27)	11 (44)	10 (38)	6 (23)
Grade 3 or 4[a]	2 (8)	4 (16)	0	2 (8)	5 (19)	0
Led to discontinuation[b]	1 (4)	3 (12)	0	1 (4)	2 (8)	2 (8)

All values are n (%). [a]No grade 5 AEs occurred. [b]Discontinuation of any drug. Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Treatment-Related AEs With Incidence ≥20%



Database cutoff: Jan 24, 2024 (arms 1-5); May 14, 2024 (arm 6).

Conclusions

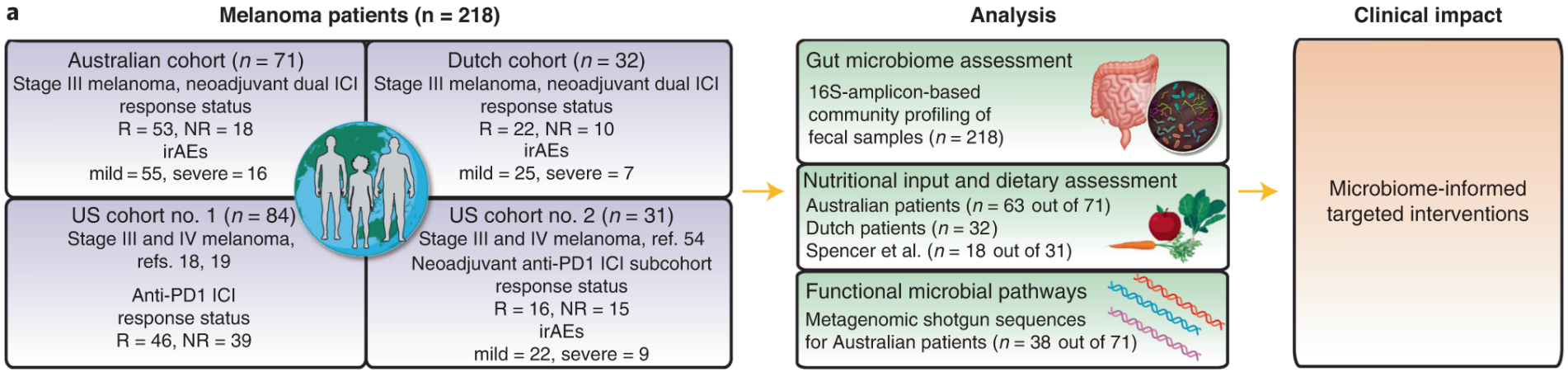
- Promising antitumor activity was observed with pembrolizumab in patients with stage IIIB-D melanoma
  - pCR rate was 40% with pembrolizumab alone and 28-42% with pembrolizumab-based combination therapies
- Numerically higher rates of major pathologic response were observed with favezelimab coformulated with pembrolizumab; direct comparisons to other arms are restricted because of limited data
  - Known status of baseline biomarkers may enable better comparisons
- AE profiles were manageable in all treatment arms
  - Few patients discontinued any drug due to treatment-related AEs
  - No deaths occurred due to treatment-related AEs

Medizinische Klinik und Poliklinik III
für Onkologie, Hämatologie, Immun- und Zelltherapien,
Rheumatologie und Klinische Immunologie
Universität Bonn

Vielen Dank für Ihre Aufmerksamkeit!

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

Gut (fecal) microbiota signatures and dietary patterns of 103 trial patients from Australia and the Netherlands treated with neoadjuvant ICIs for high risk resectable metastatic melanoma were prospectively profiled baseline and performed an integrated analysis with data from 115 patients with melanoma treated with ICIs in the United States.



Nature Medicine volume 28, pages2344–2352 (2022

Diet-driven microbial ecology underpins associations between cancer immunotherapy outcomes and the gut microbiome

- We observed geographically distinct microbial signatures of response and immune-related adverse events (irAEs). Response rates were higher in *Ruminococcaceae*-dominated microbiomes than in *Bacteroidaceae*-dominated microbiomes.
- Poor response was associated with lower fiber and omega 3 fatty acid consumption and elevated levels of C-reactive protein in the peripheral circulation at baseline.
- Together, these data provide insight into the relevance of native gut microbiota signatures, dietary intake and systemic inflammation in shaping the response to and toxicity from ICIs

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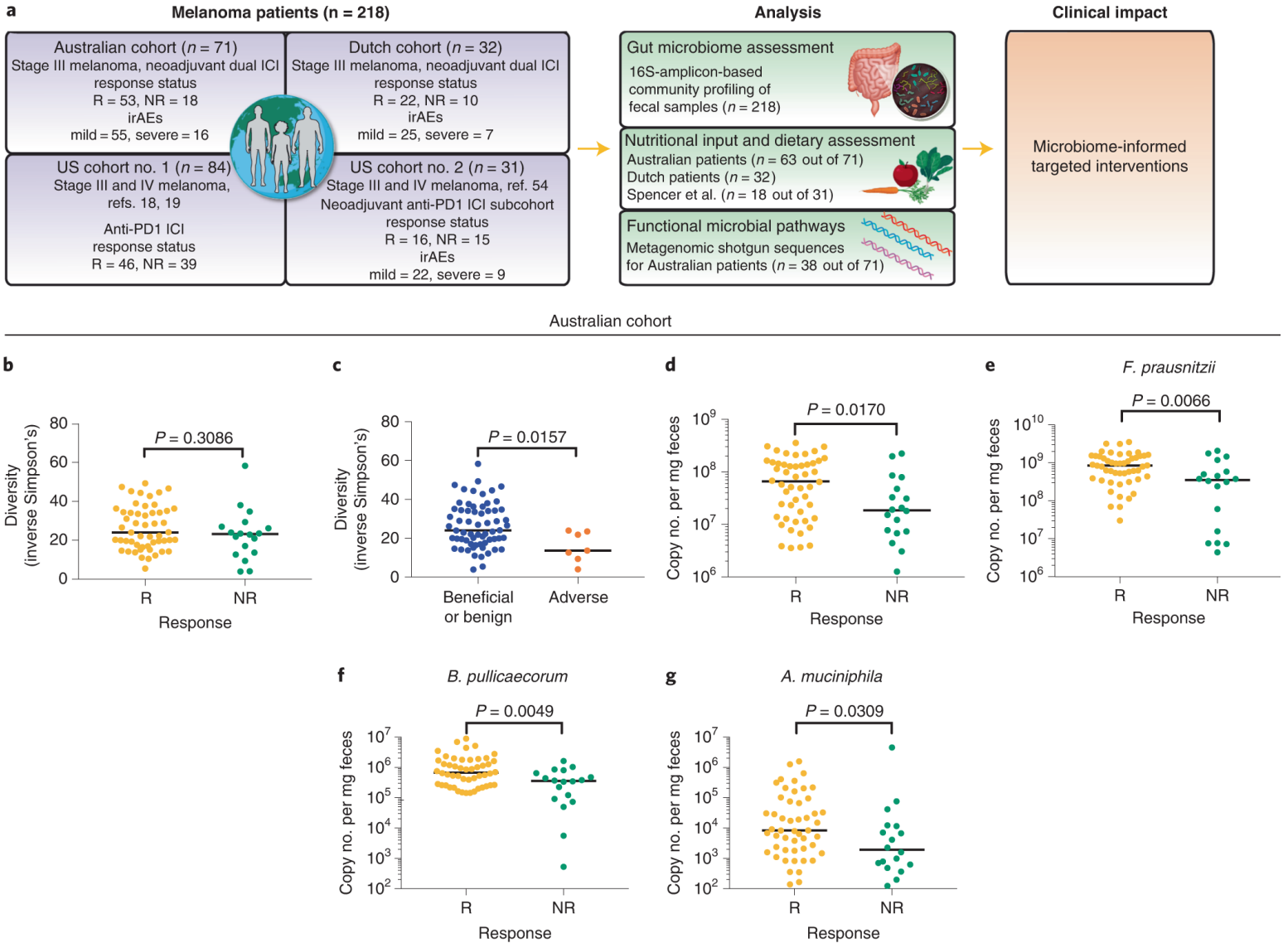
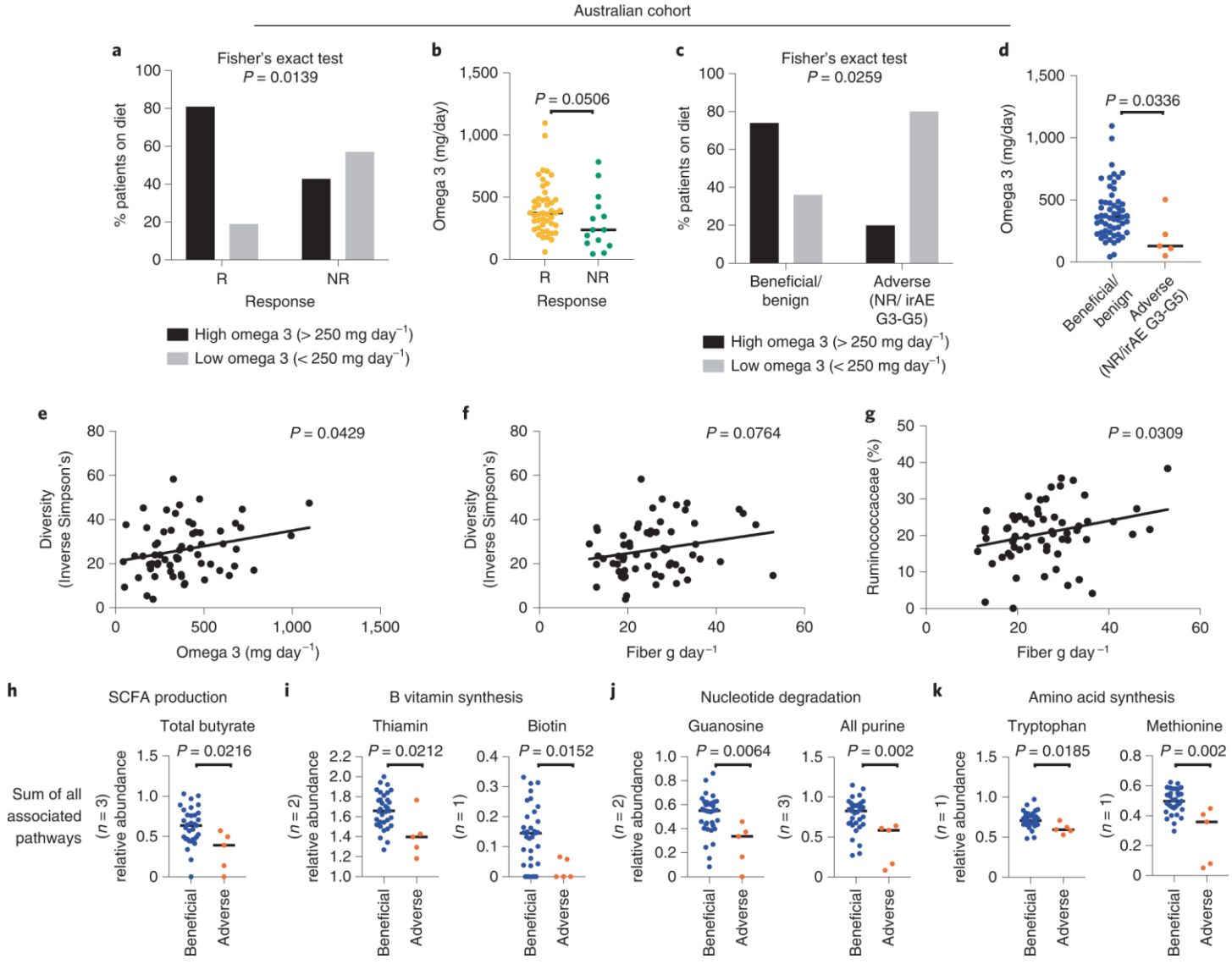


Nature Medicine volume 28, pages2344–2352 (2022)

Microbial functions and dietary nutrient intake that promote gut integrity are associated with protection from irAEs and lack of response



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