How to navigate current treatment for melanoma in a real world setting

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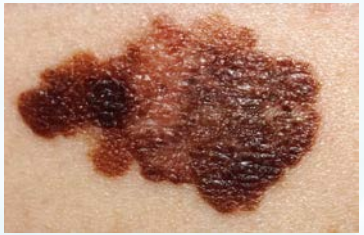
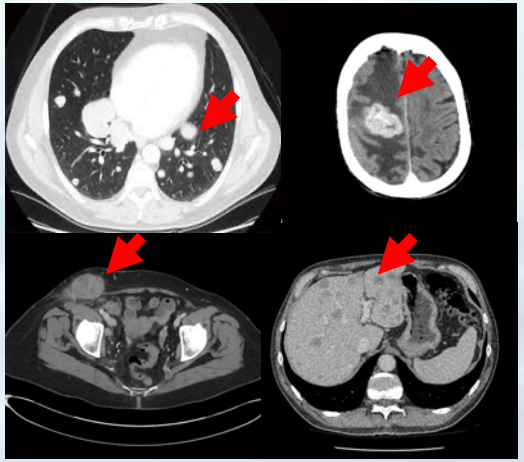
Melanoma – What's the problem?

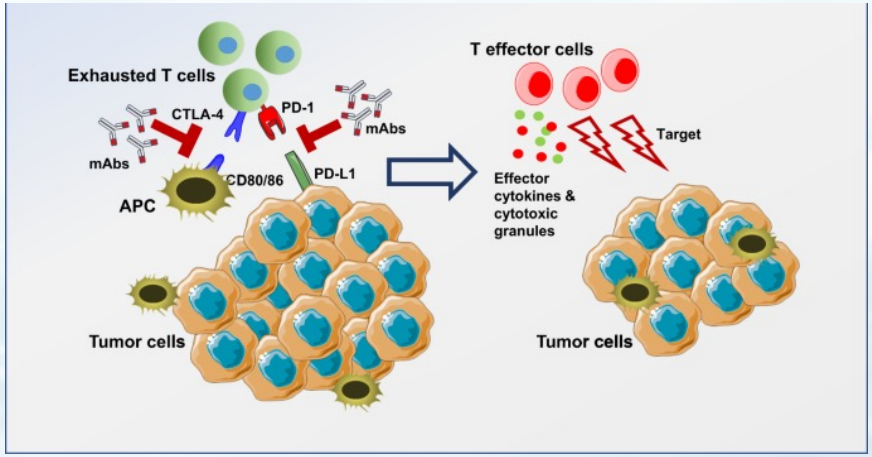


80% Cured

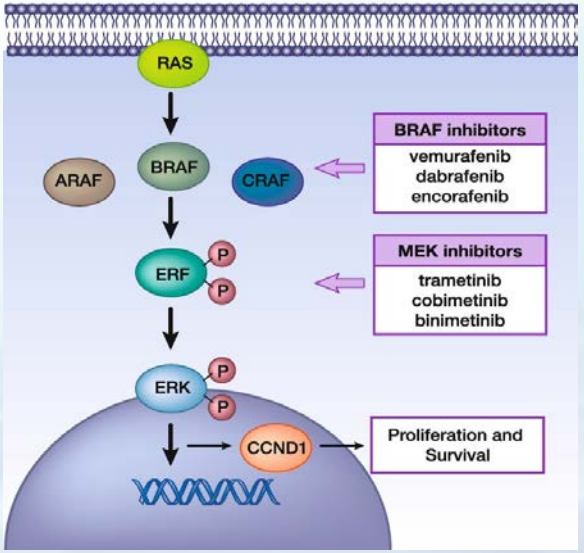
20% Recur



Two classes of drugs tested in clinical trials have revolutionized how we treat melanoma patients today



IMMUNE CHECKPOINT INHIBITORS



BRAF TARGETED THERAPY

Melanoma subtypes and molecular taxonomy

	BRAF	NRAS	KIT	GNAQ or GNA11
Cutaneous	45%*	20%	0-2%	-
Mucosal (1.5%)	5%	15%	10%	-
Acral (5%)	15%	15%	10%	-
Uveal (5%)	rare	rare	-	80%

**BRAF* and *NRAS* mutations are mutually exclusive*

Davies et al. Nature 2002;417:949-954; Curtin et al. NEJM 2005; Curtin et al. JCO 2006; Van Raamsdonk et al., NEJM 2010

Molecular taxonomy of cutaneous melanoma

Position 600 mutations	Frequency	Association
V600E	80%	Inverse relationship between prevalence and age
V600K	< 20%	Advancing age/ chronic sun damage
V600R	< 5%	Increased propensity to metastasise to lungs and brain?
Other	<1%	

Different genotypes exist within *BRAF*-mutant metastatic melanoma, representing biologically and clinically discrete subtypes, suggesting distinct etiology and behaviour

Menzies AM et al Clin Cancer Res 2012; 18: 3242-9

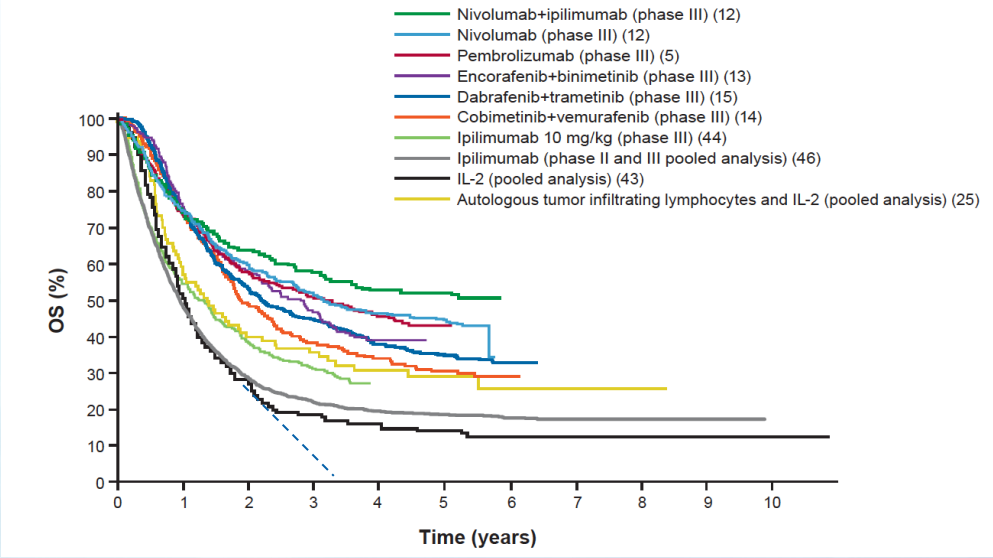
Molecular taxonomy of cutaneous melanoma

BRAF V600 mutation	Frequency	Response to BRAFi	Response to immunotherapy
V600E/K	40%/5%	++	++
Other	5%	-	++
BRAF WT	50%	-	++

BRAF mutation status does not influence response to immune checkpoint inhibitors

What has been achieved in the last 15 years?

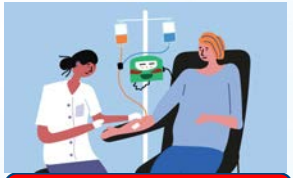
- Advanced melanoma:
  - survival gains from median <1 year to >3 years, with potential for cure in some patients
- Early melanoma:
  - 50% reduction in risk of recurrence



Michielin O, et al. *J ImmunoTher Cancer* 2020;8:e000948

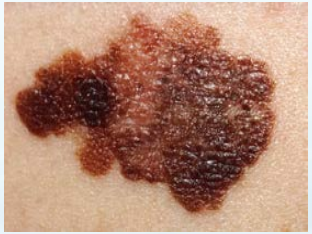
Melanoma clinical practice

Neoadjuvant

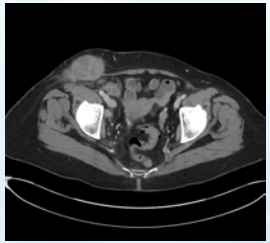


Adjuvant

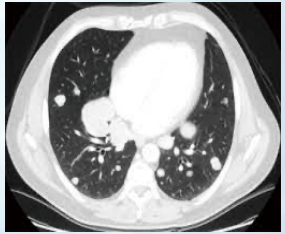
'Palliative'



Stages 1 - 2



Stage 3



Stage 4

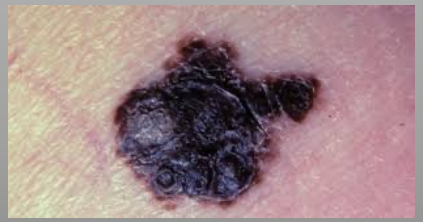
Primary prevention

Secondary Prevention

Cure?

The Real World: Case History

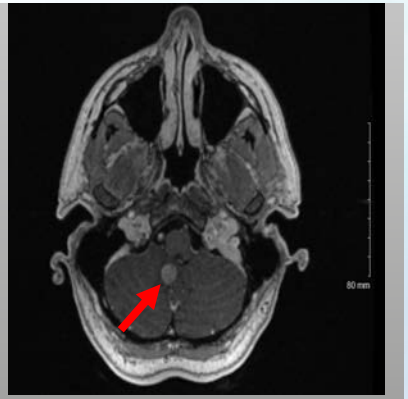
- 59 y Female
- PS 0
- No significant past medical history
- FH: Father died from lung cancer (heavy smoker)
- ***Oct 2019:***
  - Pigmented lesion on posterior chest wall
  - Enlarging and bleeding
  - pT4b, AJCC Stage IIC



- ***Sep 2020***:
  - Palpable node in right axilla – surgical axillary lymph node clearance
  - Resected AJCC Stage IIIC melanoma
- ***November 2020:***
  - Commenced adjuvant Pembrolizumab

Case History

- ***January 2021:***
  - Surveillance scan identified solitary cerebellar metastasis
  - Treated with stereotactic radiotherapy



Case History

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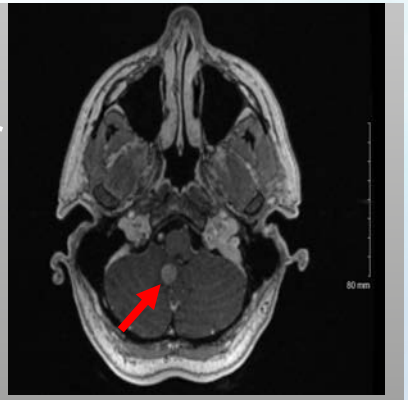
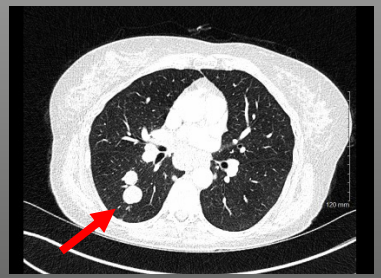
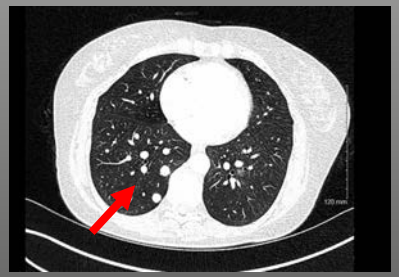
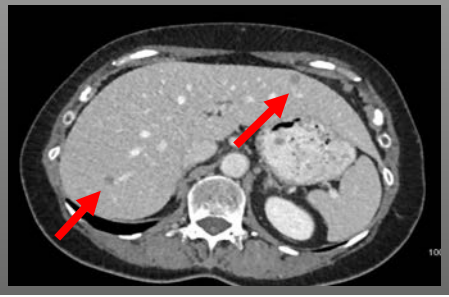


- ***July 2021***:
  - Surveillance imaging identified multiple lung and liver mets







Case History

- ***July 2021:***
  - Commenced ipilimumab + nivolumab

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- ***July 2021:***
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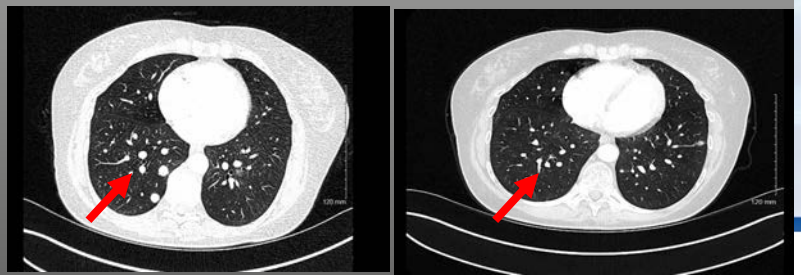
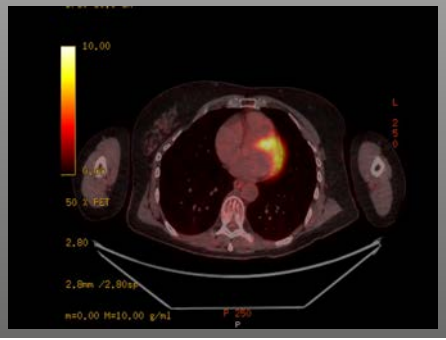
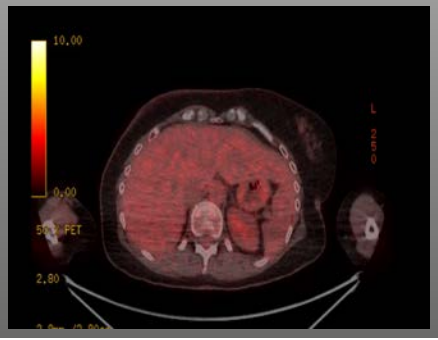
  - Adrenal insufficiency – treated with steroid replacement, long-term
- ***October 2021:***
  - Restaging scans confirmed early partial response



Case History

- ***June 2023:***
  - Complete radiological and metabolic response
  - Immunotherapy stopped after completing 2 years of treatment
- ***September 2024:***
  - Continues in complete remission, with good quality of life

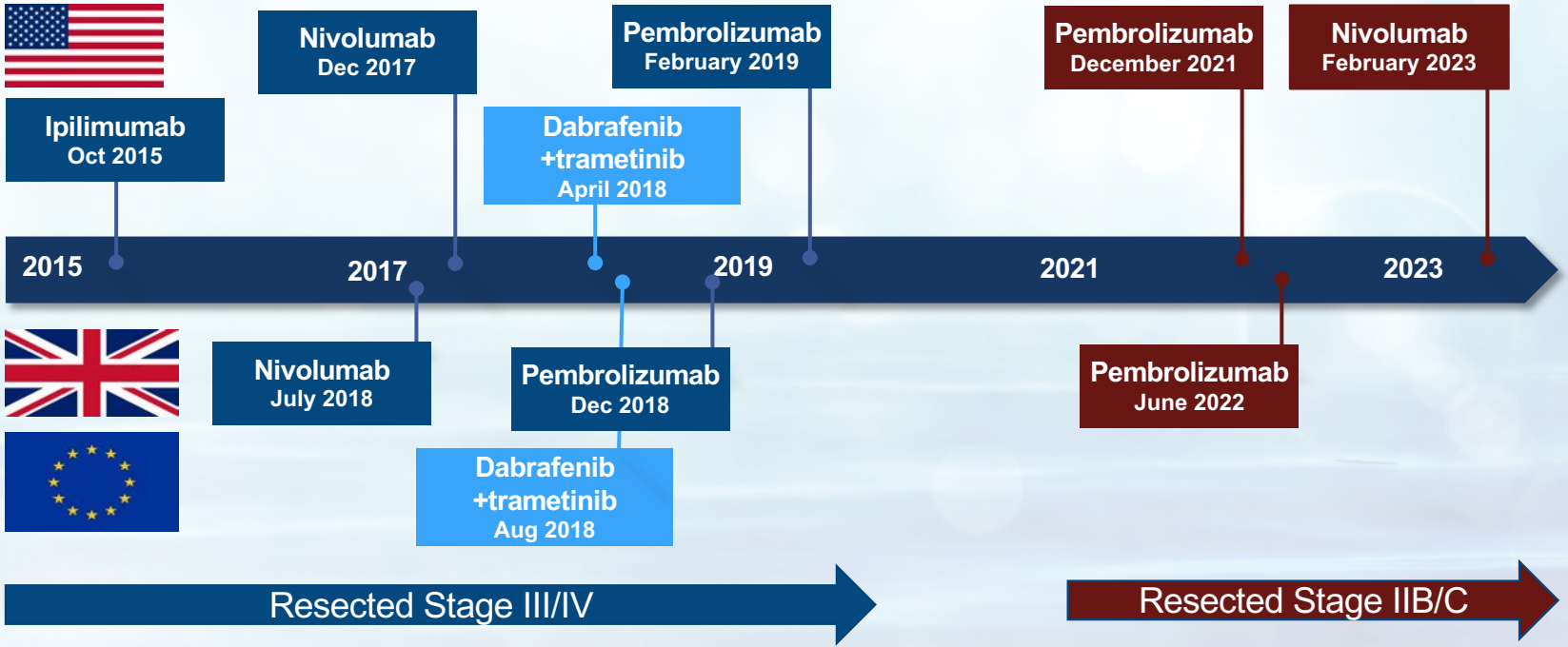




Let's Discuss..

- Management of early stage melanoma
  - Adjuvant therapy
  - Neoadjuvant therapy
- Management of advanced melanoma

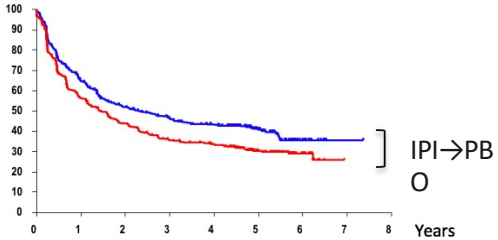
Approved treatments for melanoma in the adjuvant setting



Adjuvant therapy with checkpoint inhibitors and BRAF targeted therapy significantly improves relapse-free survival of resected stage III/IV melanoma

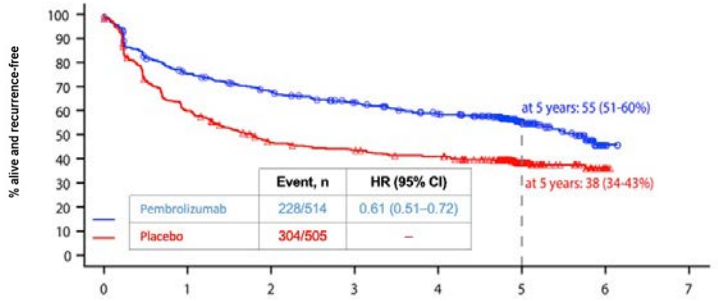
EORTC 18071[1]

- Ipilimumab 10 mg/kg vs placebo,
- Stage IIIA-C; RFS HR 0.76, OS HR 0.72



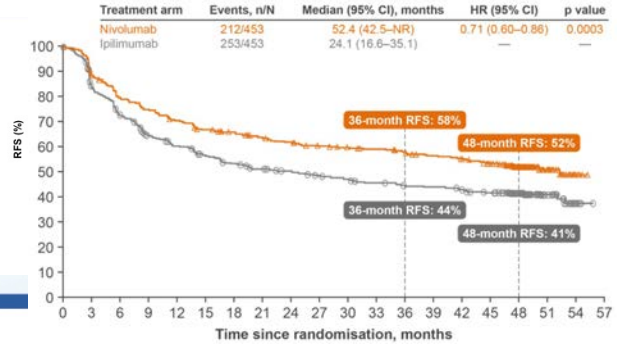
EORTC 1325[2]

- Pembrolizumab vs placebo,



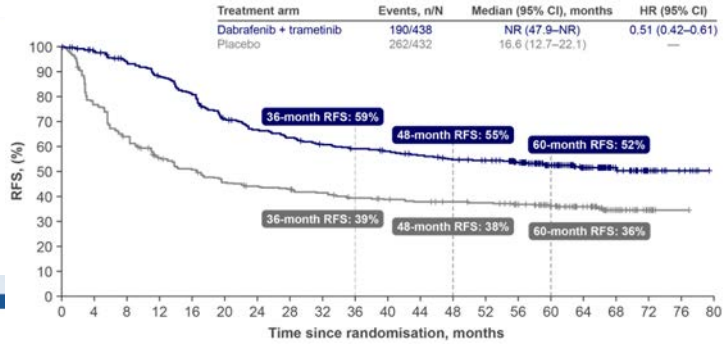
CheckMate 238[3]

- Ipilimumab 10 mg/kg vs nivolumab,



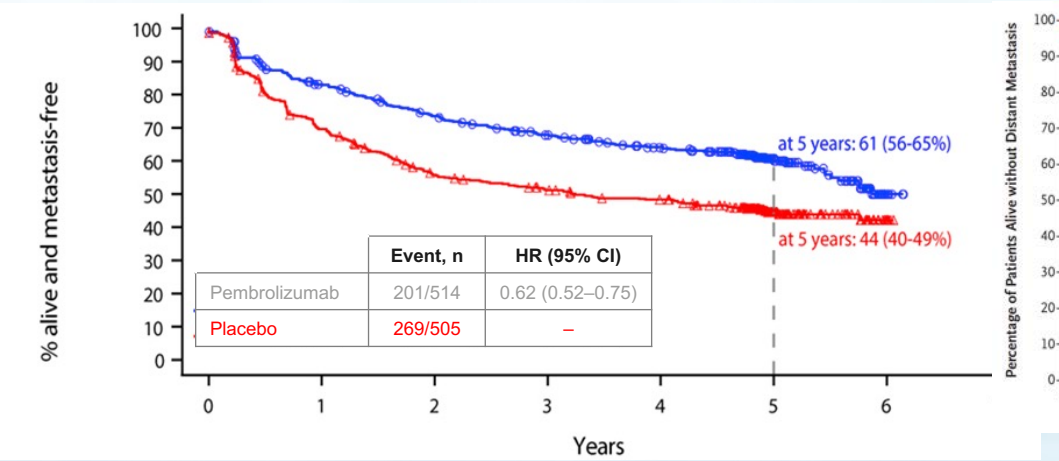
COMBI-AD[4]

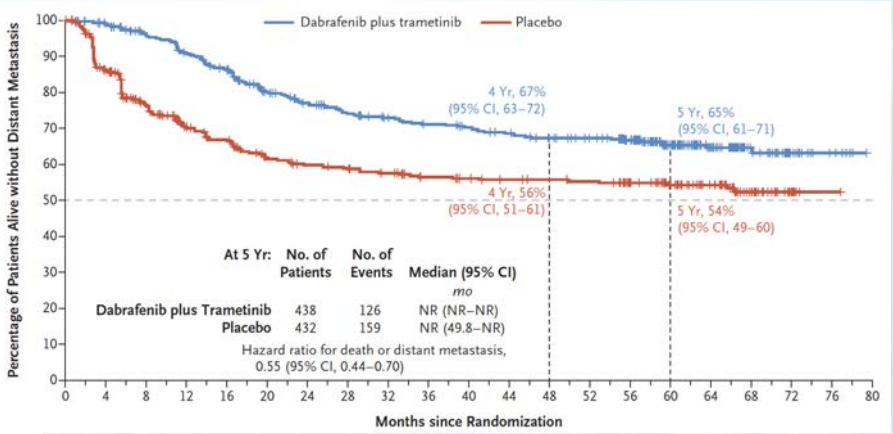
- Dabrafenib + trametinib vs placebo



1. Eggermont AMM et al, Lancet Oncol 2015; 2. Eggermont AMM et al, Lancet Oncol 2021; 3. Weber J et al NEJM 2017; 4. Dummer R et al, NEJM 2020

Adjuvant therapy with checkpoint inhibitors and BRAF targeted therapy significantly improves distant metastasis-free survival of resected stage III melanoma



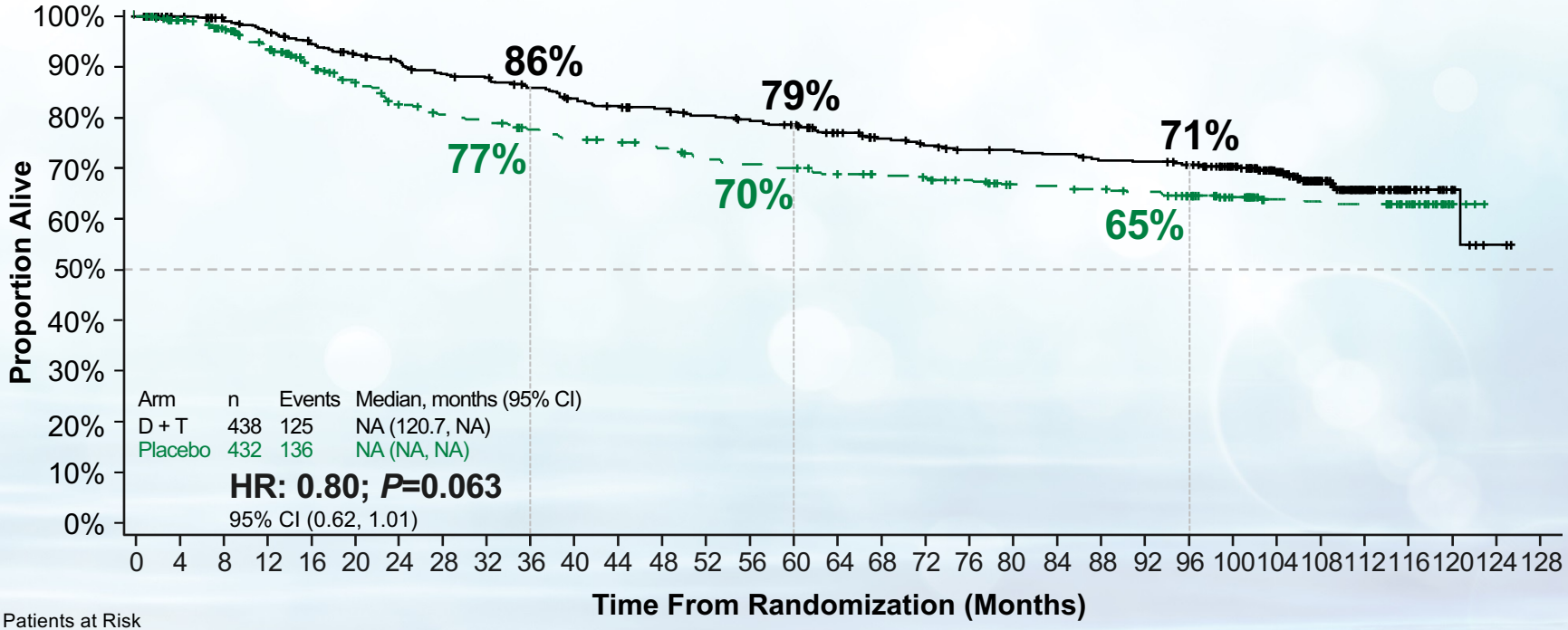


HR = 0.61: 39% relative risk reduction in distant disease recurrence with pembrolizumab vs placebo[1]

HR = 0.55: 45% relative risk reduction in distant disease recurrence with dabrafenib+ trametinib vs placebo[2]

1. Eggermont AMM et al. DOI:https://doi.org/10.1056/EVIDoa2200214; 2. Dummer R et al. NEJM 2020; 383: 1139-48

COMBI-AD final results: Overall survival (ITT)



Patients at Risk

D + T	438	416	407	395	381	370	362	351	347	336	325	318	312	305	299	294	279	268	261	255	254	251	246	245	240	222	173	124	75	27	8	2	0
Placebo	432	415	400	377	346	328	308	297	292	282	274	270	264	255	251	248	241	236	233	228	218	216	213	208	201	185	157	115	67	26	4	0	0

End of study 31 July 2023. Median follow-up: D+T 100.0 (0−125) months; Placebo 82.5 (1−122) months.

Long GV et al. NEJM 2024

Adjuvant systemic therapy is routinely available for resected stage III/IV melanoma patients

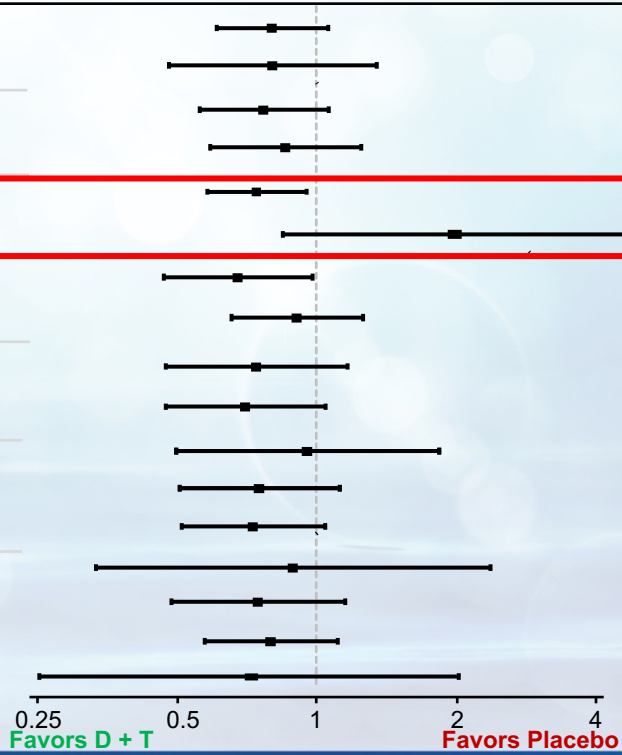
- **Dabrafenib with trametinib** is recommended, within its marketing authorisation, as an option for the adjuvant treatment of resected stage III BRAF V600 mutation-positive melanoma in adults
- **Pembrolizumab** is recommended, within its marketing authorisation, as an option for the adjuvant treatment of completely resected Stage III melanoma with lymph node involvement in adults
- **Nivolumab** is recommended, within its marketing authorisation, as an option for the adjuvant treatment of completely resected melanoma in adults with lymph node involvement or metastatic disease

Which adjuvant therapy to select?

- Consider
  - *BRAF* mutation status
    - Most mature data
    - Potential survival benefit?
    - Real world comparison favours targeted therapy
      - Lodde et al, EJC 2023: 2 year RFS 49% (PD-1) vs 67% (TT); Risk of recurrence HR 2.0
    - Less chance of cure in the advanced setting
    - Consider $BRAF^{V600}$ mutation variant

Combi-AD Subgroup Analysis: Effect of treatment on overall survival (ITT)

Subgroup	Category	Treatment (n/N)	HR (95% CI)
Age	<65 Years Old	D + T (95/353); Placebo (107/359)	**0.80 (0.61, 1.06)**
	≥65 Years Old	D + T (30/85); Placebo (29/73)	**0.80 (0.48, 1.34)**
Gender	Male	D + T (72/244); Placebo (79/239)	**0.77 (0.56, 1.06)**
	Female	D + T (53/194); Placebo (57/193)	**0.86 (0.59, 1.24)**
Mutation	*BRAF* V600E	D + T (110/397); Placebo (129/395)	**0.75 (0.58, 0.96)**
	BRAF V600K	D + T (15/41); Placebo (7/37)	**1.95 (0.84, 4.50)**
Ulceration	Ulceration	D + T (51/179); Placebo (63/177)	**0.68 (0.47, 0.98)**
	No Ulceration	D + T (72/253); Placebo (72/249)	**0.91 (0.65, 1.26)**
Nodal metastatic mass	Micrometastasis	D + T (34/152); Placebo (42/157)	**0.74 (0.47, 1.16)**
	Macrometastasis	D + T`(43/158); Placebo (55/161)	**0.70 (0.47, 1.04)**
Disease stage using AJCC7	Stage IIIA	D + T (21/83); Placebo (16/71)	**0.96 (0.50, 1.84)**
	Stage IIIB	D + T (40/169); Placebo (57/187)	**0.75 (0.51, 1.12)**
	Stage IIIC	D + T (62/181); Placebo (62/166)	**0.73 (0.51, 1.04)**
Disease stage using AJCC8	Stage IIIA	D + T (10/50); Placebo (7/39)	**0.89 (0.33, 2.36)**
	Stage IIIB	D + T (35/145); Placebo (48/154)	**0.75 (0.49, 1.15)**
	Stage IIIC	D + T (70/217); Placebo (73/214)	**0.80 (0.57, 1.11)**
	Stage IIID	D + T (8/22); Placebo (7/17)	**0.71 (0.25, 2.02)**

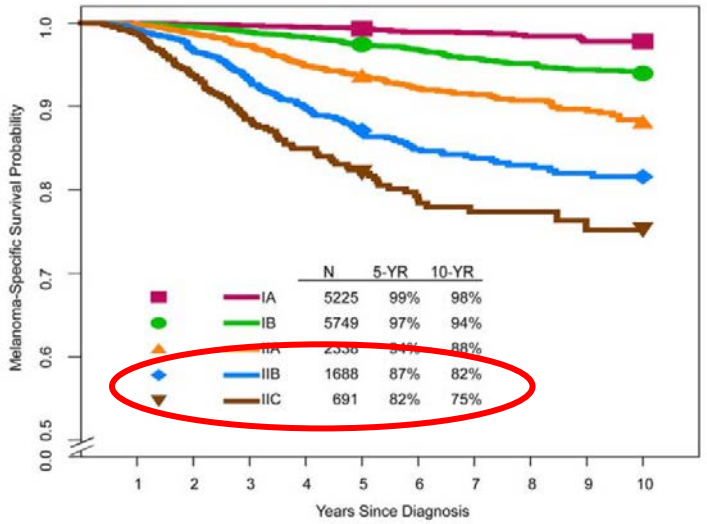


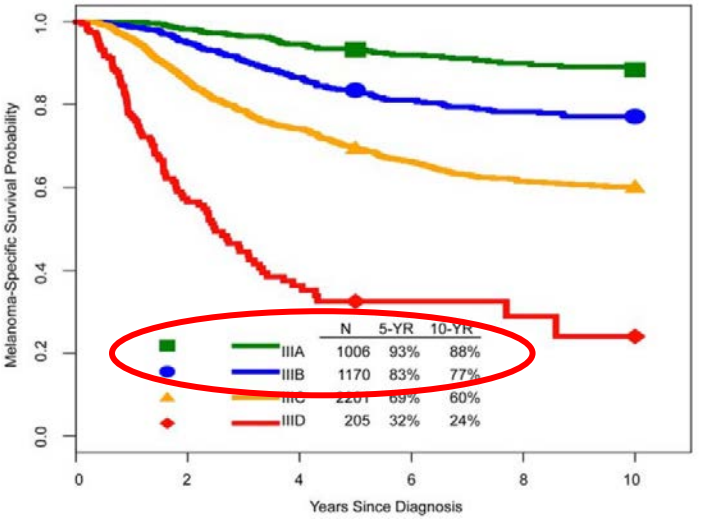
Long GV et al. NEJM 2024

Which adjuvant therapy to select?

- Consider
  - *BRAF* mutation status
  - Contra-indications to immunotherapy
  - Local resources
  - Patient preference

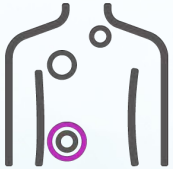
AJCC 8 Stage II and III

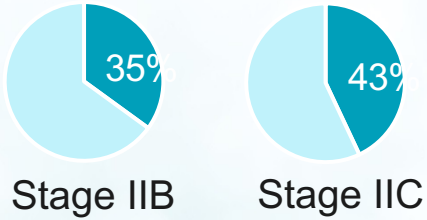




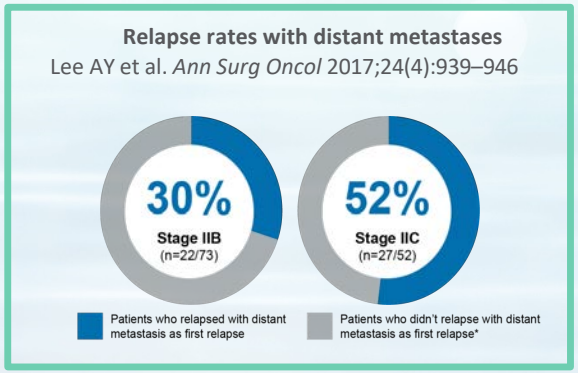
Gershenwald JE et al. *CA Cancer J Clin.* 2017; 67:472-492

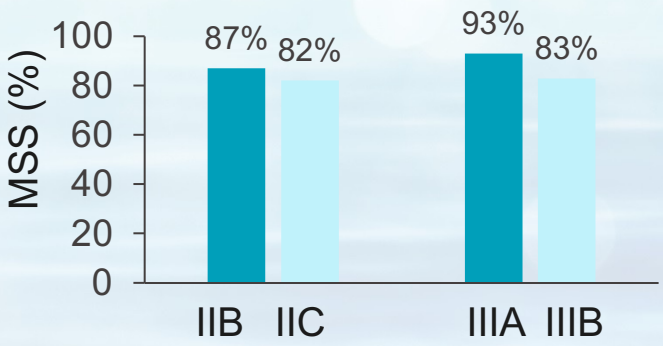
Outcomes after Resection of Stage II and III Melanoma



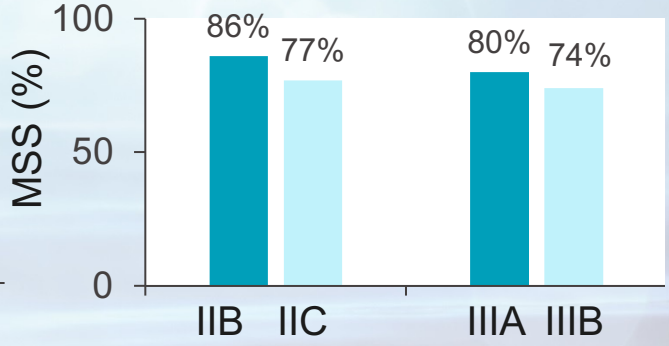


5-year risk of disease recurrence[a] (CMMR)[1]





5-year MSS rate (AJCCv8)[3]



5-year MSS rate[a] (CMMR)[1,2]

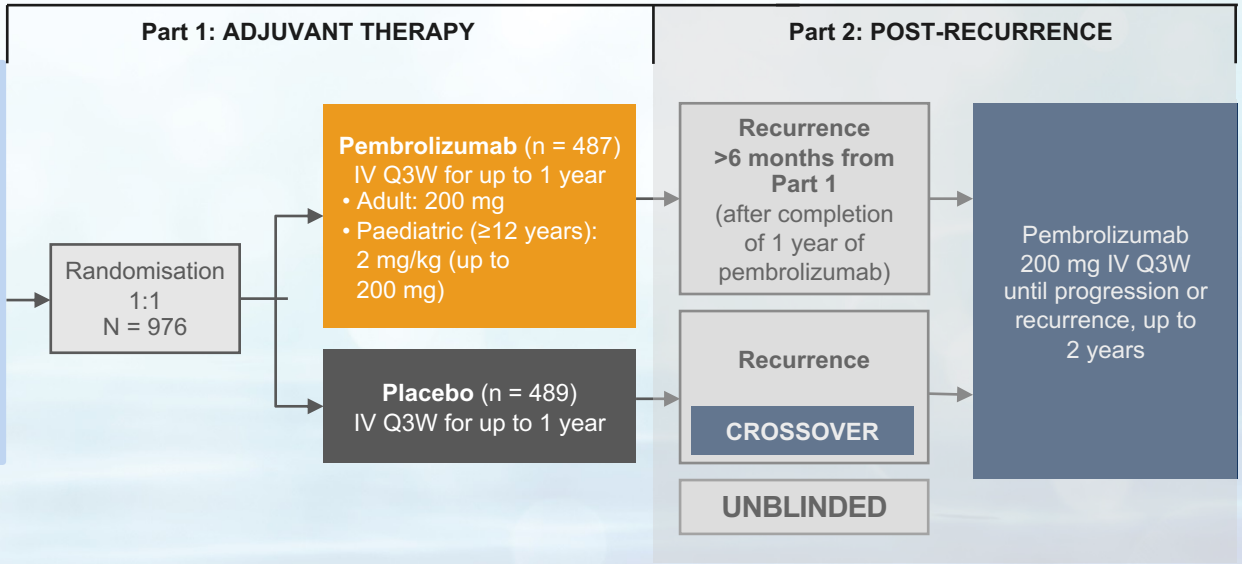
[a]Confirmatory cohort. AJCCv8, American Joint Committee on Cancer version 8; CMMR, Central Malignant Melanoma Registry; MSS, melanoma-specific survival.

1. Garbe C, et al. *J Clin Oncol* 2022. doi: 10.1200/JCO.22.00202. 2. Garbe C, et al. *J Clin Oncol* 2020;38:2543-2551. 3. Gershenwald JE, et al. *CA Cancer J Clin* 2017;67:472-92.

KEYNOTE-716: The efficacy and safety of pembrolizumab in patients with completely resected Stage IIB or IIC melanoma were studied in a multicentre, randomised, double-blind, placebo-controlled Phase 3 trial[1]

Select Eligibility Criteria:

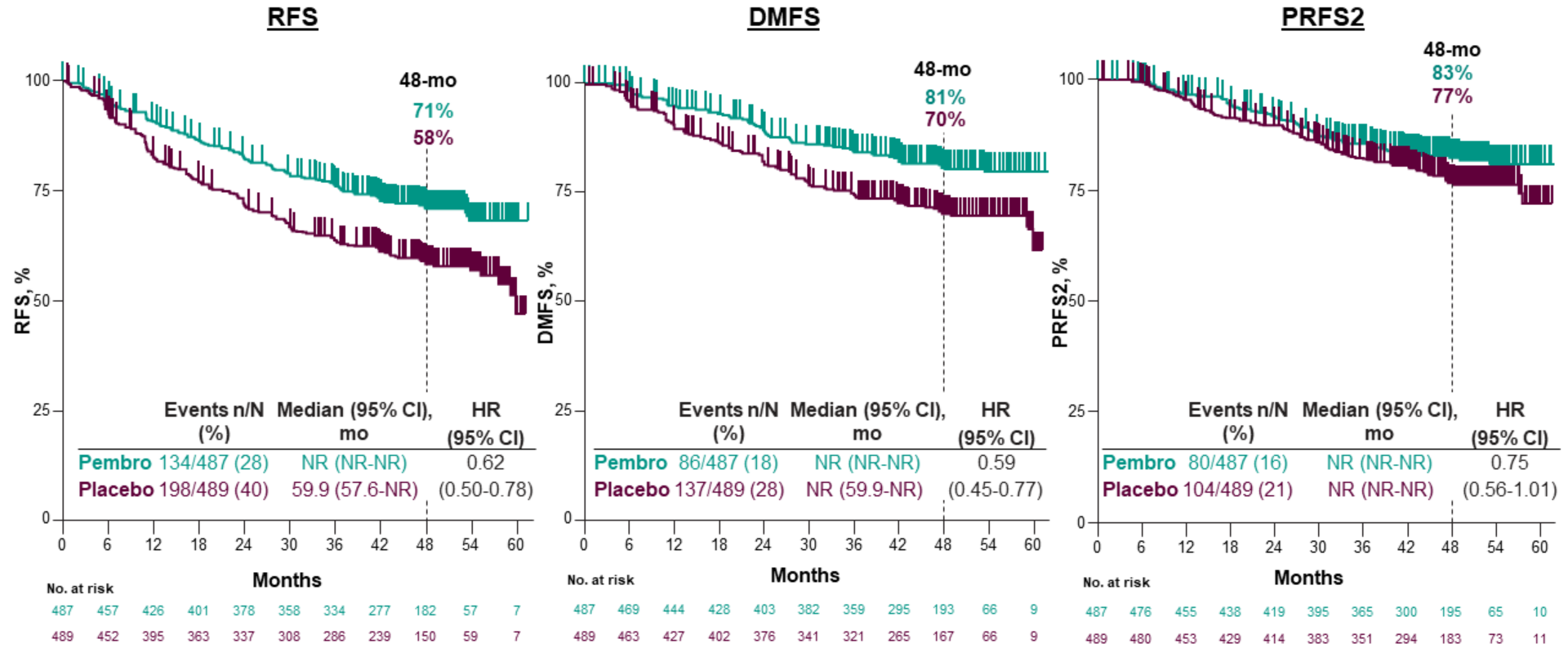
- Age ≥12 years
- With completely resected Stage IIB or IIC melanoma
- No previous treatment for melanoma beyond complete surgical resection
- ECOG PS 0 or 1



Patients underwent imaging at 6 months from the date of randomisation, then every 6 months from years 2 to 4 after randomisation, and then once in year 5 from or until recurrence, whichever came first, or as clinically indicated.

1. Luke JJ et al. *Lancet* 2022;399:1718–1729

RFS, DMFS, and PRFS2 in Part 1



PRFS2 was defined as time from randomization to first disease progression beyond the initial unresectable disease recurrence, second recurrence, or death.
Data cutoff date: Feb 16, 2024.

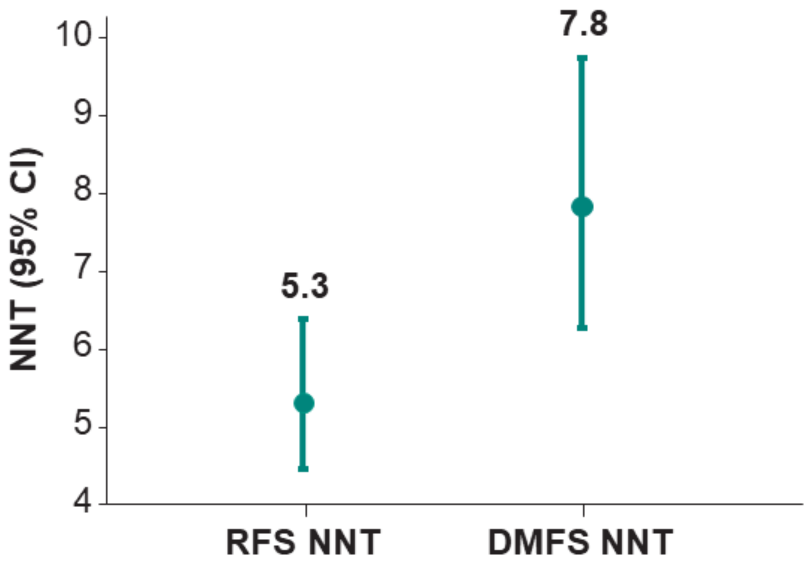
KEYNOTE-716: The safety profile of pembrolizumab was as previously seen in stage III [1]

	Pembrolizumab		Placebo	
Events, n (%)[a]	**N = 483**		**N = 486**	
All	462 (96)		445 (92)	
Treatment-related	400 (83)		309 (64)	
Grade ≥3	83 (17)		24 (5)	
Discontinued	77 (16)		12 (2)	
Died	0		0	
Immune-mediated events and infusion reactions	182 (38)		45 (9)	
Treatment-related events ≥15%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Fatigue	103 (21)	1 (<1)	92 (19)	1 (<1)
Hypothyroidism	77 (16)	0	13 (3)	0
Arthralgia	81 (17)	2 (<1)	39 (8)	0
Pruritus	119 (25)	3 (1)	52 (11)	0
Rash	78 (16)	7 (1)	34 (7)	1 (<1)
Diarrhea	90 (19)	5 (1)	56 (12)	1 (<1)

IA1 Data Cutoff: December 04, 2020.

1. Long GV et al. Presented At American Society Of Oncology Meeting June 3 -7, 2022

Number Needed to Treat by RMST for RFS and DMFS



Calculation of NNT based on RMST

$$\mathrm{NNT}_{\mathrm{RMST}}(t) = \frac{1}{(\mathrm{RMST}_{\mathrm{P}}(t)/\mathrm{RMST}_{\mathrm{C}}(t)) - 1}$$

For this analysis:

$\mathrm{RMST}_{\mathrm{p}}(t)$ = Total area under the Kaplan-Meier curve to 60 months in the pembrolizumab arm

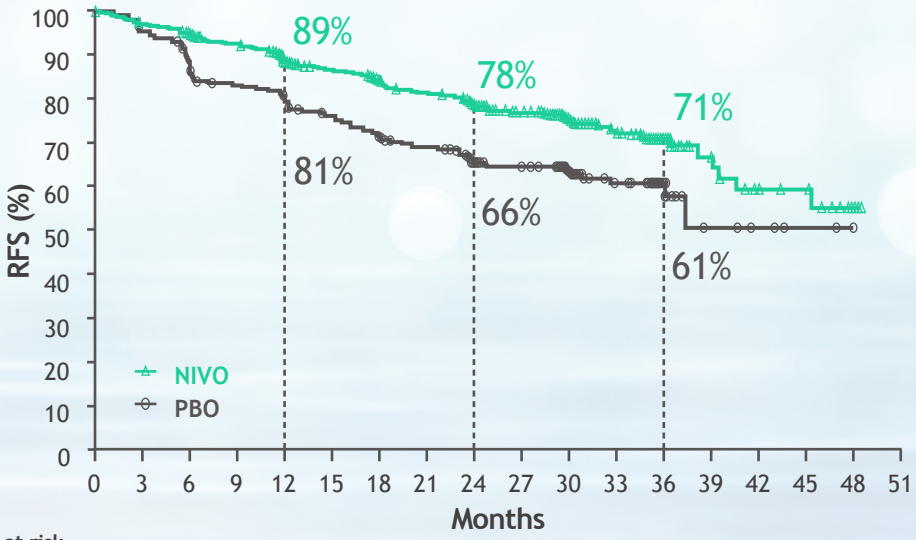
$\mathrm{RMST}_{\mathrm{c}}(t)$ = Total area under the Kaplan-Meier curve to 60 months in the placebo arm

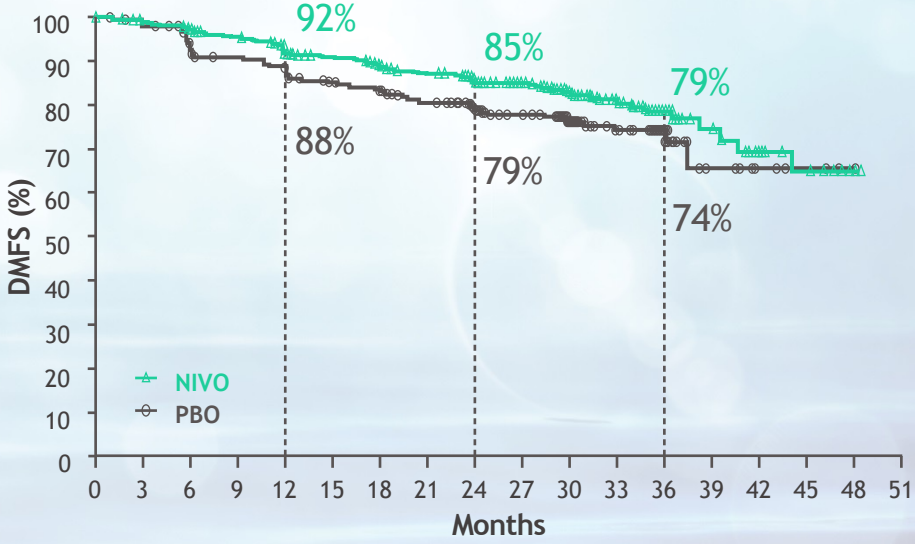
RMST, restricted mean survival time. NNT calculated the number of additional patients that need to be treated to produce a beneficial result or prevent a harmful event in 1 additional patient.
NNT was analyzed by Victoria Wurcel of MSD Argentina, Mónica María Rojas Rojas of MSD Colombia, and Adelphi Values PROVE, Bollington, UK.

CheckMate 76K: RFS and DMFS (27mo min f/up)

RFS[a]	NIVO	PBO
Events, n/N	133/526	95/264
Median, months (95% CI)	NR (40.7–NR)	NR (36.1–NR)
Stratified HR (95% CI)	0.62 (0.47–0.80)	

DMFS[b]	NIVO	PBO
Events, n/N	96/526	61/264
Median, months (95% CI)	NR	NR
Stratified HR (95% CI)	0.72 (0.52–1.00)	





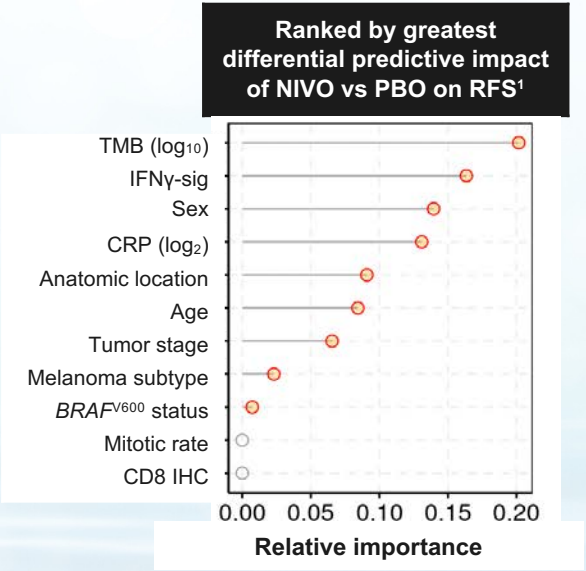
No. at risk

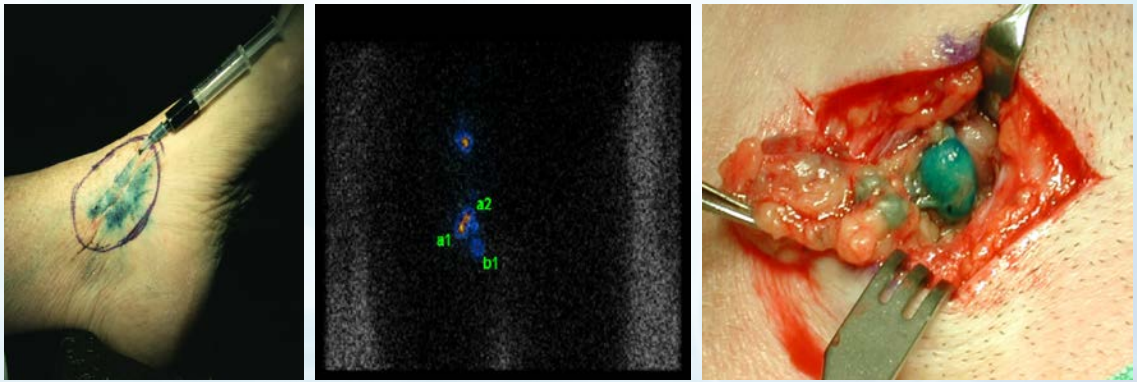
NIVO	526	492	474	456	430	413	396	380	342	310	217	171	82	28	19	15	4	0
PBO	264	244	224	208	201	186	176	165	145	136	94	62	24	6	4	2	1	0

NIVO	526	505	493	478	452	442	428	413	375	345	242	190	91	31	21	15	4	0
PBO	264	253	236	226	219	207	202	190	170	156	112	79	33	9	5	3	1	0

[a]RFS was defined as the time between randomization and first recurrence (recurrence events included local, regional, or distant recurrence, new primary melanomas [including *in situ*], and death [due to any cause]). [b]DMFS was defined as time between randomization and first distant recurrence or death (due to any cause).

Other Considerations..





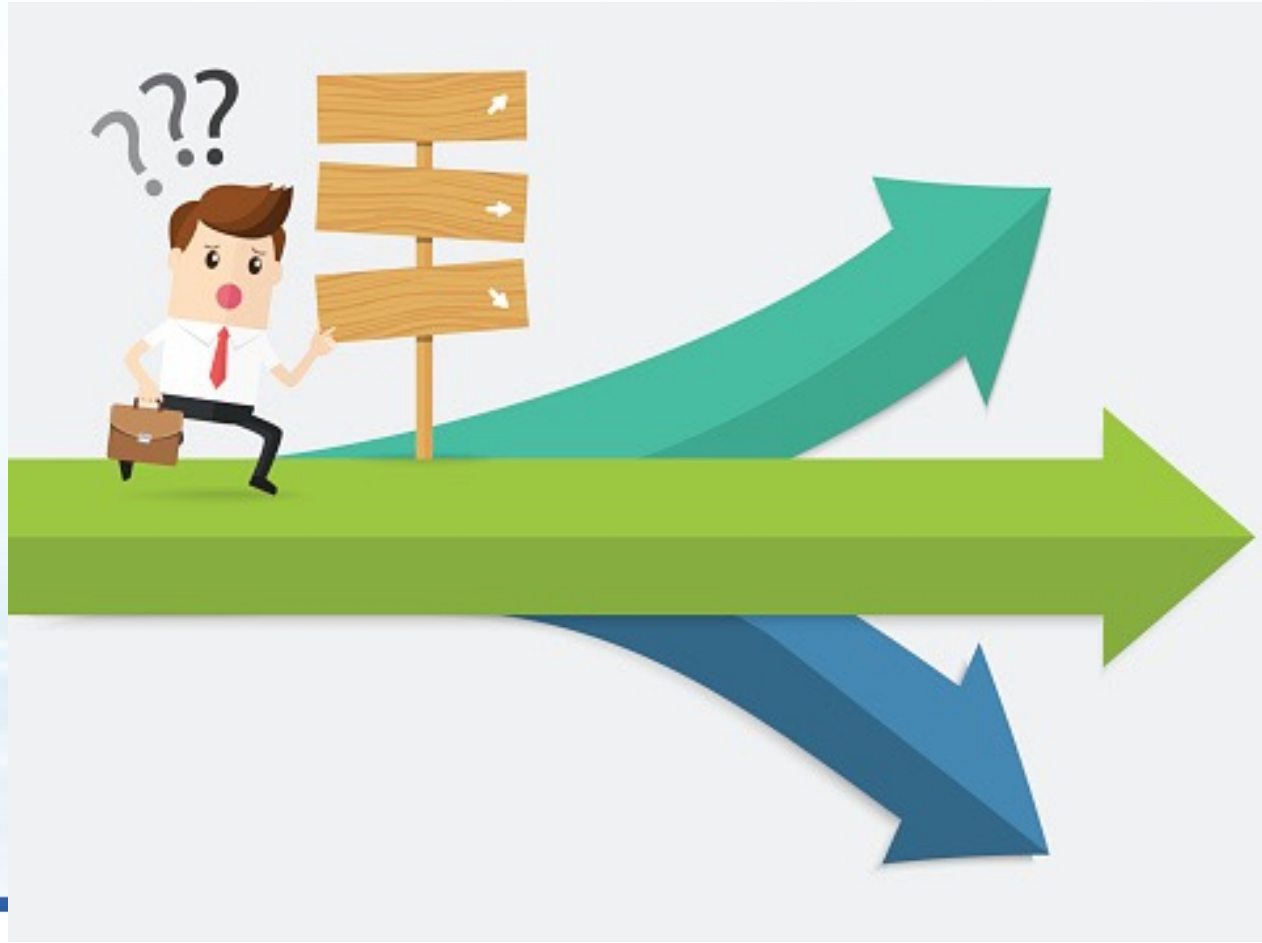
Morton & Cochran, 1990

Predictive Factors?

Role of SLNB?

Accessing patients earlier in the pathway

- Raise awareness wrt recurrence risks in stage II melanoma
  - Stage IIC = Stage IIIB in terms of survival outcomes
  - 5 year melanoma specific survival: IIC = 77-82%, IIIB = 74-83%
- Discuss opportunities for treating, in particular, stage IIC patients
  - Number needed to treat to benefit 1 patient likely <8[1]
- The fine balance between benefits and risks for individual patients requires careful consideration
- Consider biological biomarkers of response
  - TMB, IFNγ signature

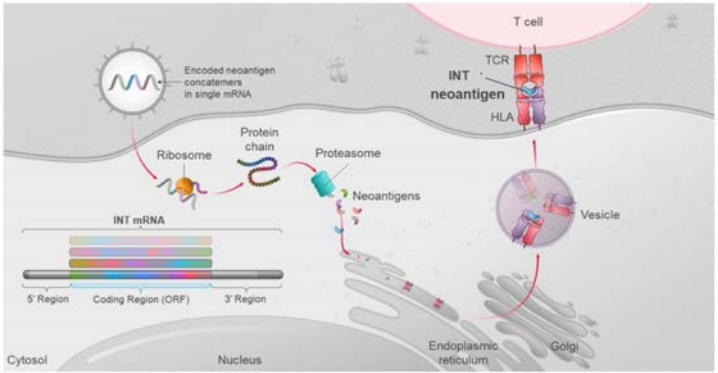



The More
The Better

Individualised Neoantigen Therapy

A Khattak V940 AACR 2023

mRNA-4157 (V940) Mechanism of Action

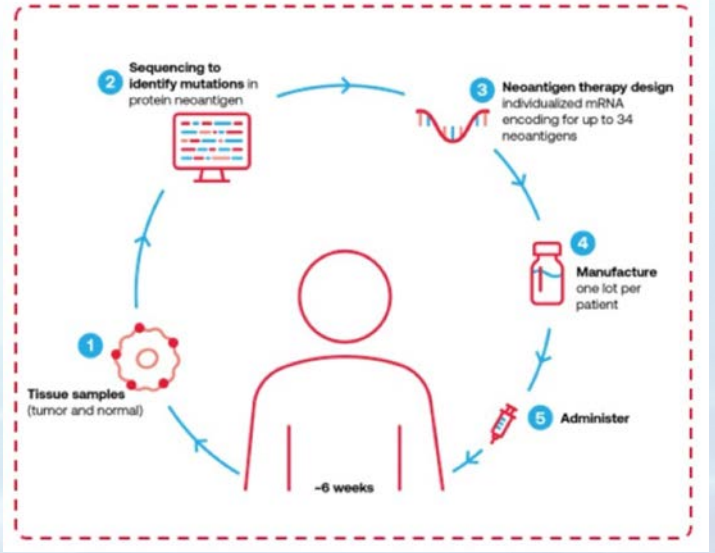


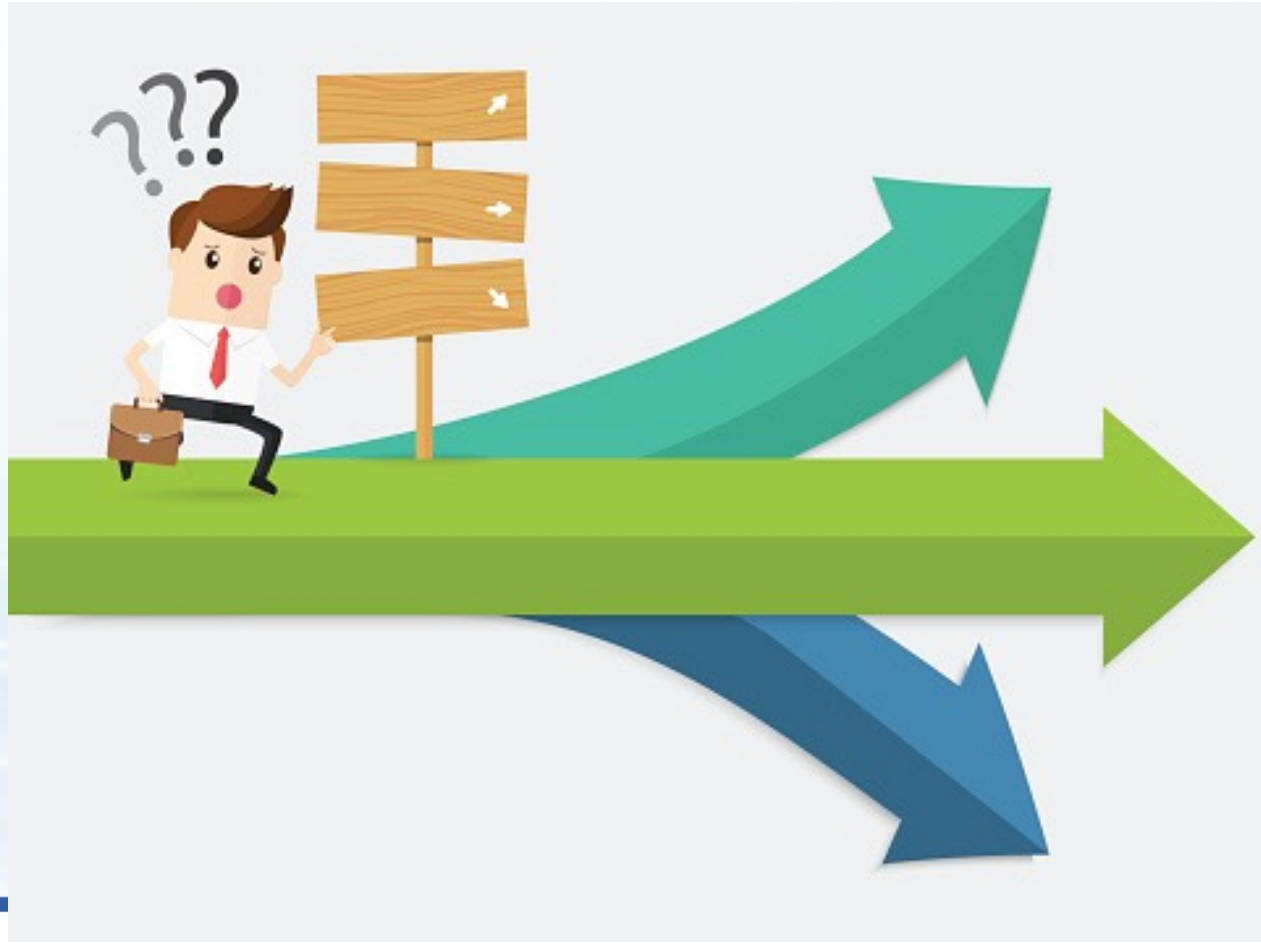
mRNA-4157 (V940) is a **customizable** individualized neoantigen therapy encoding up to 34 neoantigens

Targeting of neoantigens by T-cells has been demonstrated to **drive antitumor responses**[1]

The modified mRNA **platform** was implemented for the COVID-19 vaccine (mRNA-1273), demonstrating its **utility and adaptability**[2]

HLA, human leukocyte antigen; mRNA, messenger RNA; ORF, open reading frame; PCV, personalized cancer vaccine; RFS, recurrence-free survival; TCR, T-cell receptor.
1. Wirth TC, Kühnel F. *Front Immunol*. 2017;8:1848. 2. Baden LR, et al. *N Engl J Med*. 2021;384(5):403-416.



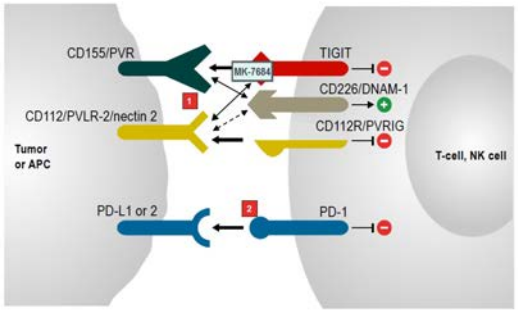


More isn't always better, sometimes more is just more.

KEYVIBE 010: Interim and only analysis

Mechanism of Action: Anti-TIGIT mAb (MK-7684, Vibostolimab)

- Pre-clinical models using anti-TIGIT monoclonal antibodies indicate that FcγR engagement is required for maximal anti-tumor response by TIGIT blockade[1]
- The presence of FcγR engagement is associated with enhanced myeloid cell activation[1]
- **MK-7684** (vibostolimab) is a humanized, IgG1 monoclonal antibody that binds TIGIT and blocks its interaction with its ligands, CD112/nectin 2 and CD155/PVR[2]
- **MK-7684A** is a coformulation of vibostolimab with pembrolizumab
- Blocking additional ligand-receptor interactions, such as PD-L1/PD-1, may enhance the antitumor response[3]

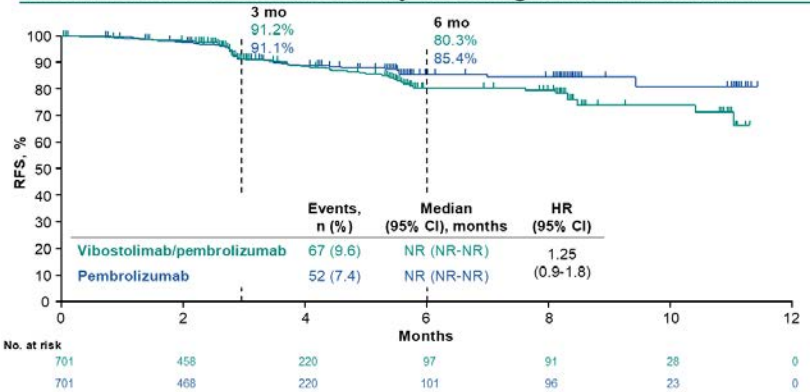


1. Han J et al. Front Immunol. 2020; 11: 573405. 2. Golan T et al. Presented at SITC 2018. 3. Hung AL et al. Oncoimmunology. 2018;7(8):e1466769.
Image adapted from Anderson AC et al. Immunity. 2016;44(5):989-1004 and Harjunpaa H and Guillerey C. Clinical and Experimental Immunology. 2016;200:108-119.

MSD

G Long KEYVIBE-010 SMR 2024

Recurrence-Free Survival by Investigator Assessment



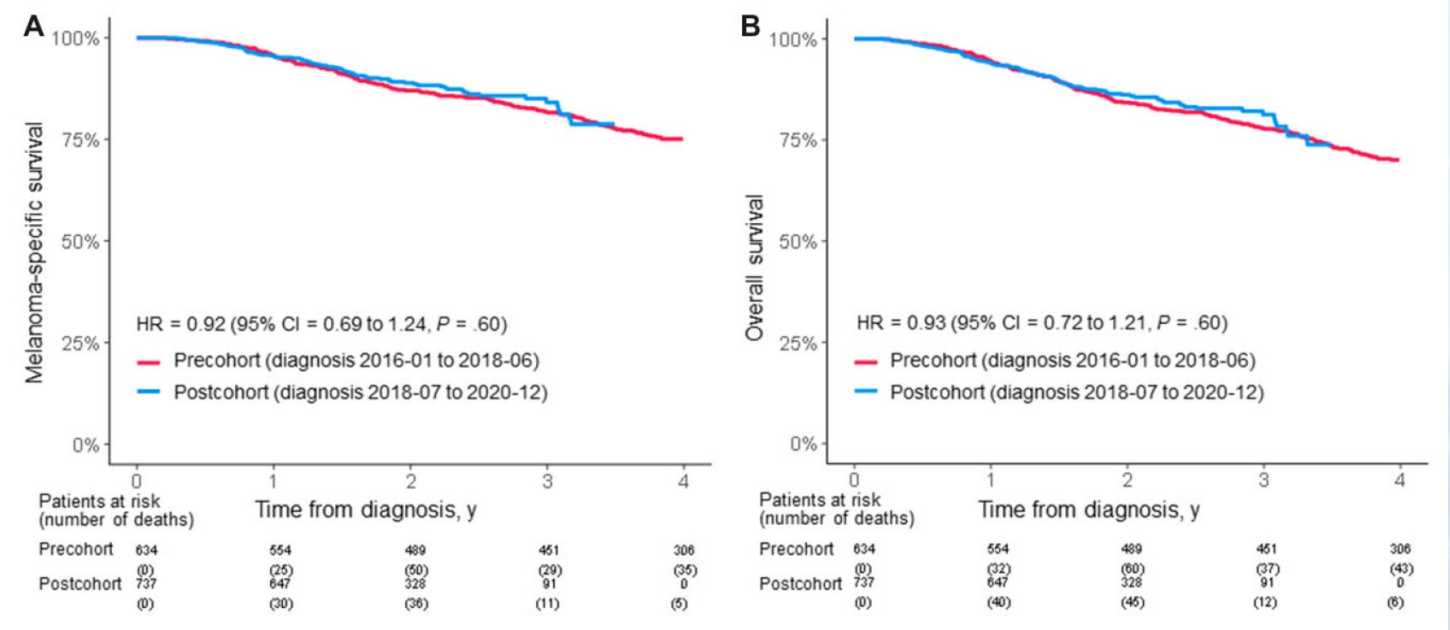
Data cutoff date: March 6, 2024.

Presented by Georgina V. Long

Grade 3-5 TRAEs:

- 16% vibostolimab/pembrolizumab
- 7% pembrolizumab

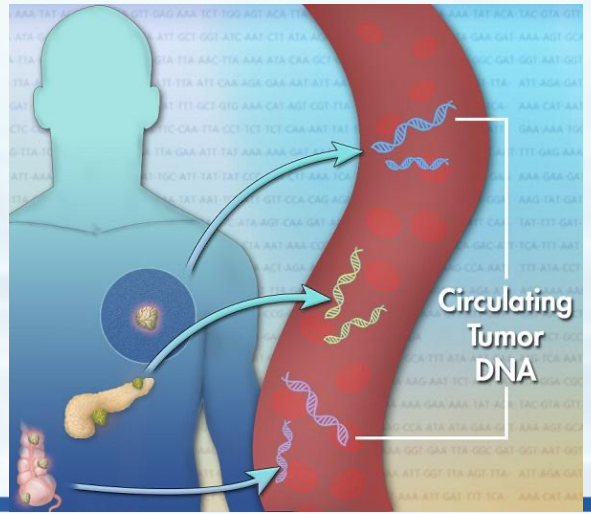
A Word of Caution…
Results of the Swedish Nationwide Registry-based Study



1371 patients with stage III melanoma in Sweden, 2016-2020; 2 cohorts defined by introduction of adjuvant therapy. F/up until end 2021

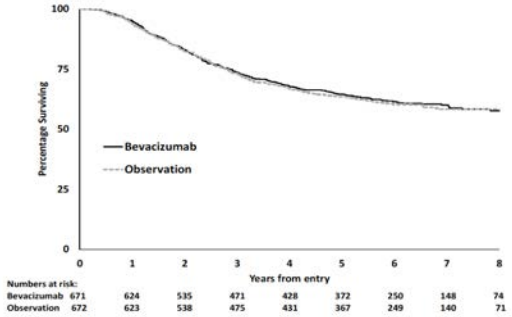
Helgadottir H, et al. JNCI 2023

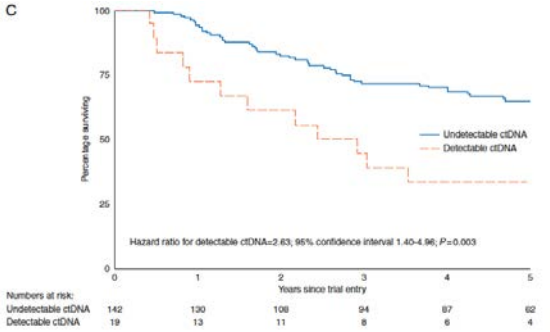
DETECTION



Lee R et al, Annals Oncol 2018;29: 490-6

AVAST-M
Adjuvant aVAStin Trial in high risk Melanoma





DETECTION-2 Feasibility

5 year follow up

50 patients
From 8 sites

Key inclusion
- Stage IIB/IIC/IIIA melanoma
- BRAF/NRAS/TERT promoter mutated
- ECOG PS 0/1

Randomise 1:1

Arm A
Approved physicians choice adjuvant anti -PD-1 or targeted therapy (depending on disease stage/BRAF mutation status) for 1 year

Arm B
ctDNA monitoring every 3 months for years 1 -3, then 6 monthly for years 4 & 5

- ctDNA negative — Continue monitoring
- ctDNA negative — Local relapse → Surgery +/- adjuvant therapy if approved indication
- ctDNA detected at any timepoint (including post local relapse) → Treatment with physicians choice approved therapy

ctDNA storage

Store ctDNA samples for retrospective analysis in the main trial

Chief Investigator: Prof Paul Lorigan
Coordinating centre: Southampton CTU
Recruitment period: 12 months
No. of sites: 8 (open 1 per month)

Co-Primary Endpoints:

Recruitment rate

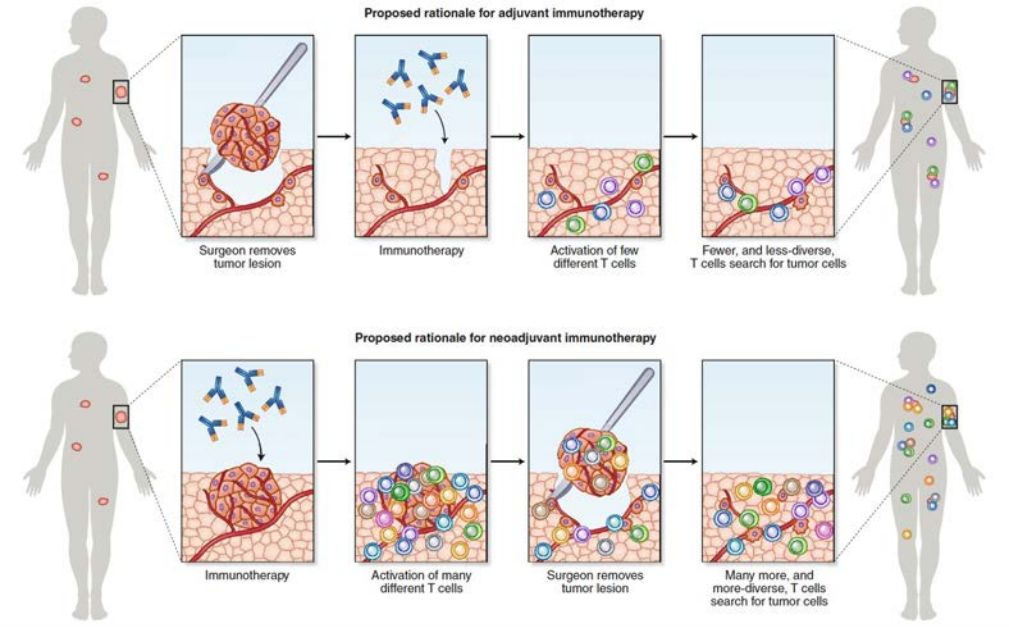
Proportion of ctDNA sample results returned <=10 working days from sample being taken

Feasibility Criteria:

Randomised >= 50 patients within a 12 month period
Review recruitment limitations & review Phase III criteria

95% of samples returned within 10 working days

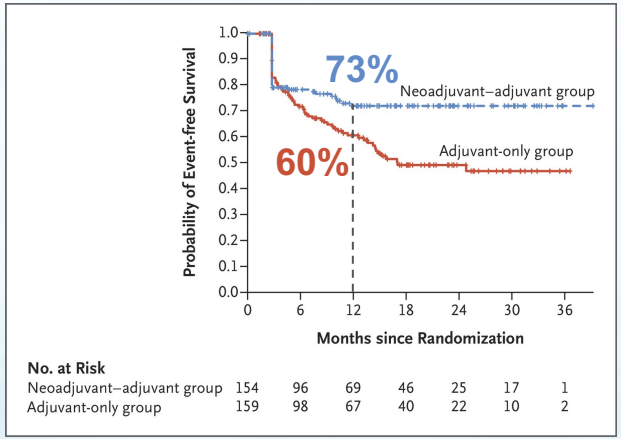
Neoadjuvant therapy – Strong biological rationale



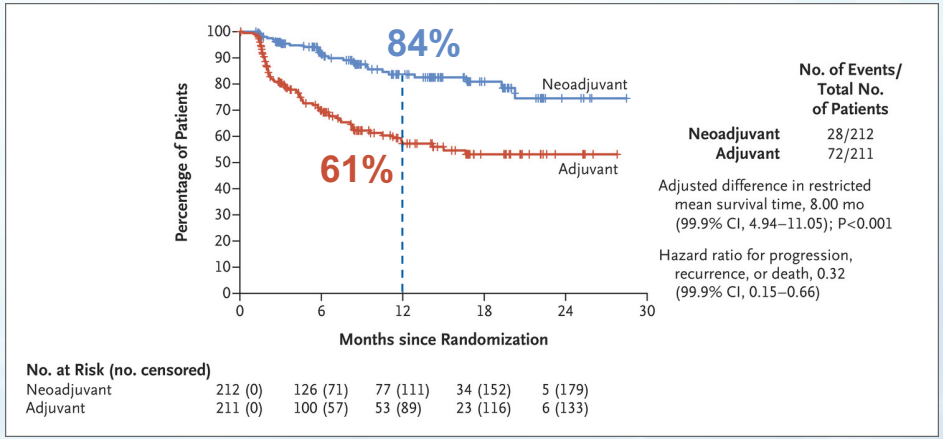
Versluis JM et al, Nature Medicine 2023

Checkpoint inhibitors in high-risk stage III resectable melanoma

SWOG S1801[1]



NADINA[2]



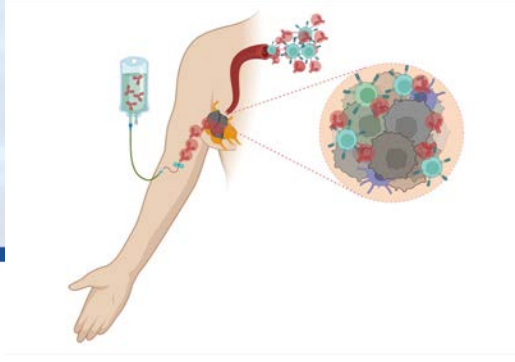
2022 SWOG S1801	Neoadjuvant PD-1	Surgery	Adjuvant PD-1	**HR 0.58** vs adjuvant PD-1 (EFS)[6]
2024 NADINA	Neoadjuvant PD-1 plus CTLA-4	Surgery	Response-directed adjuvant PD-1 or BRAF/MEK	**HR 0.32** vs adjuvant PD-1 (EFS)[7]

1. Patel SA, et al. N Engl J Med. 2023;388:813–823; 2. Blank CU, et al. N Engl J Med. 2024;00:00–00. *1-yr EFS rates estimated from KM curve.

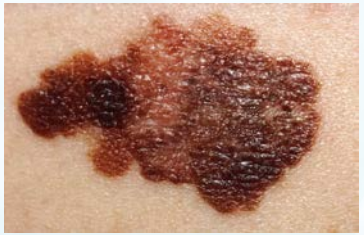
Not regulatory approved in Norway

Neoadjuvant Therapy – The Future?

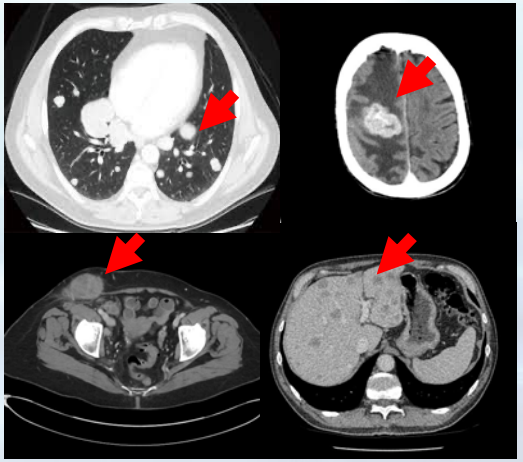
- Strong biological rationale
- Model for drug development & biomarker testing
- Personalisation of treatment
  - Early identification of patients with responsive or resistant disease
- De-escalation of subsequent interventions
  - Omission of unnecessary surgery
  - Reduced need for adjuvant radiotherapy
  - Avoidance of protracted adjuvant systemic therapy
- Gains in patient QOL
- Intelligent use of finite resources



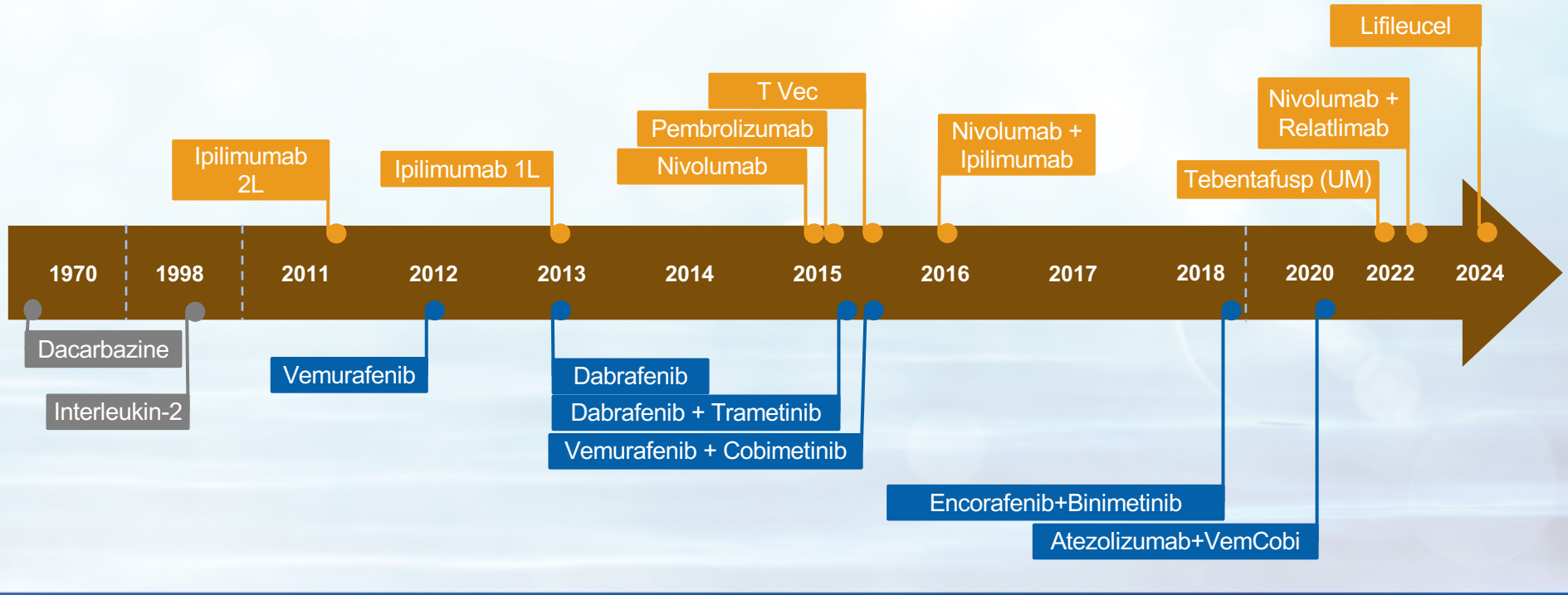
Melanoma – What's the Problem?



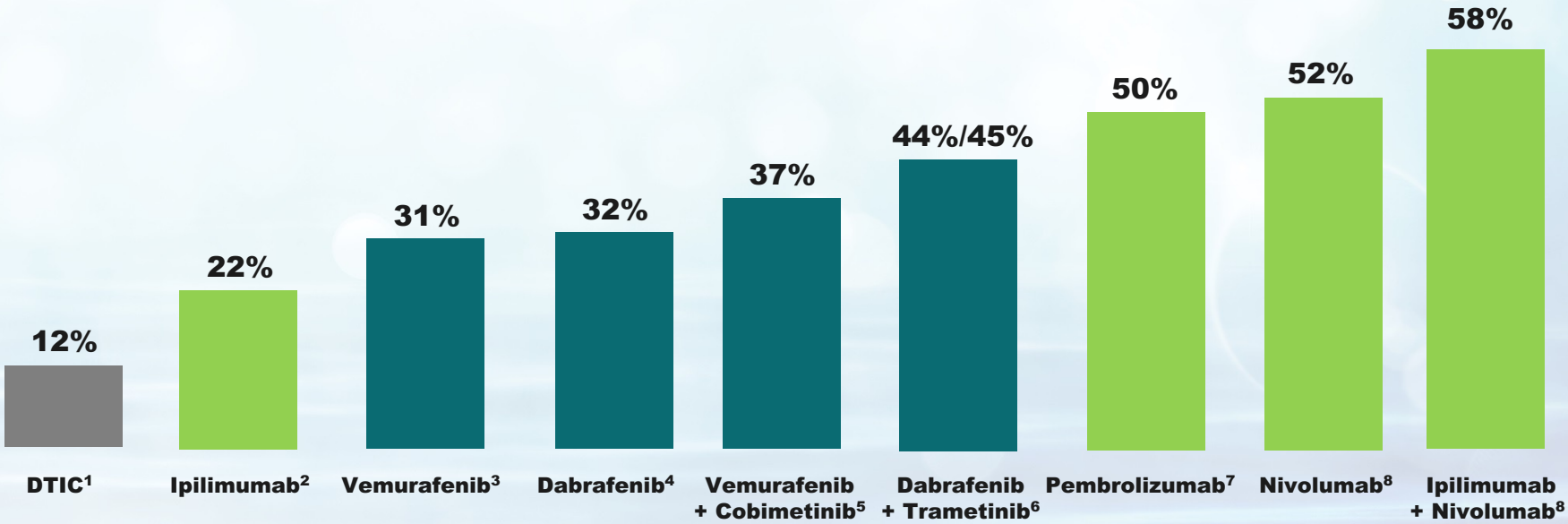
20% Recur



The advanced melanoma treatment revolution

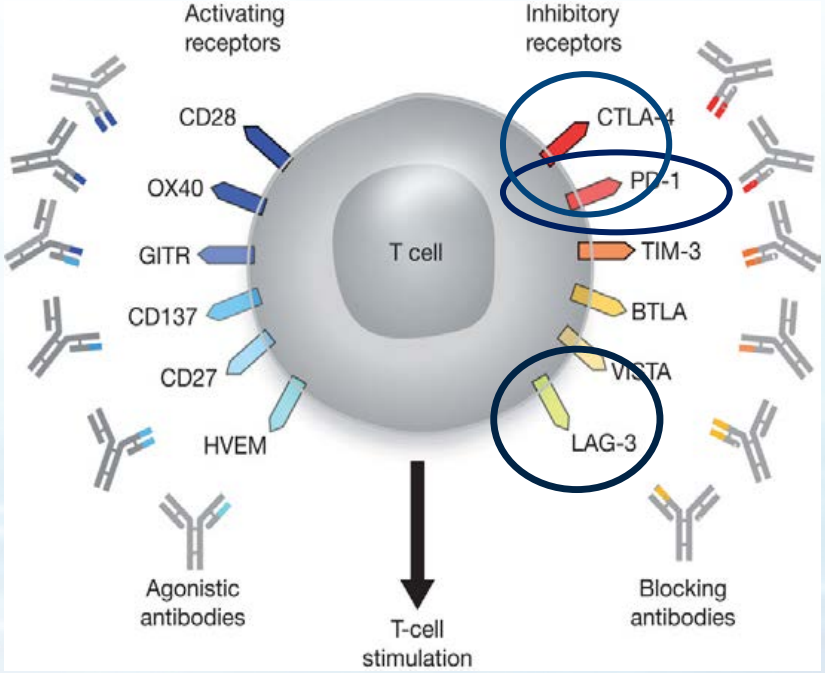


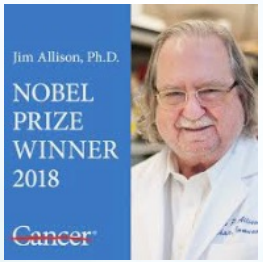
Immune checkpoint inhibitors and BRAF targeted therapy have significantly improved 3-year overall survival for patients with stage IV melanoma

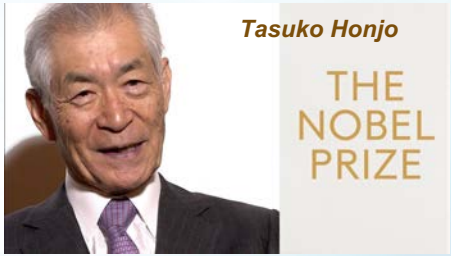


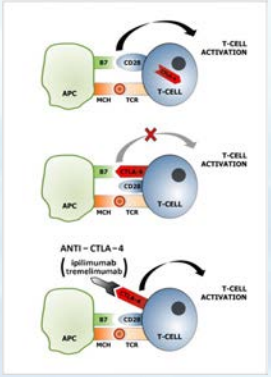
1. Middleton et al, 2000; 2. Hodi et al, 2010; 3. Chapman et al, 2011; 4. Hauschild et al, 2013; 5. Larkin et al, 2014; 6. Robert et al, 2019a; Robert et al, 2019b; Wolchock et al, 2022

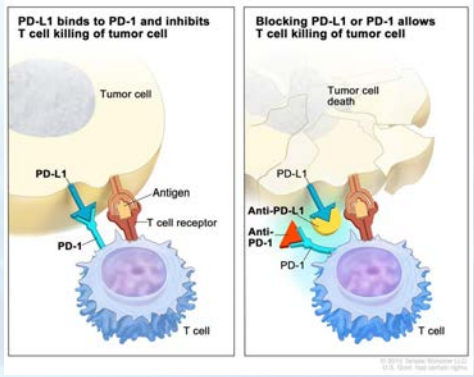
First line therapy for patients with metastatic melanoma: how do we choose?





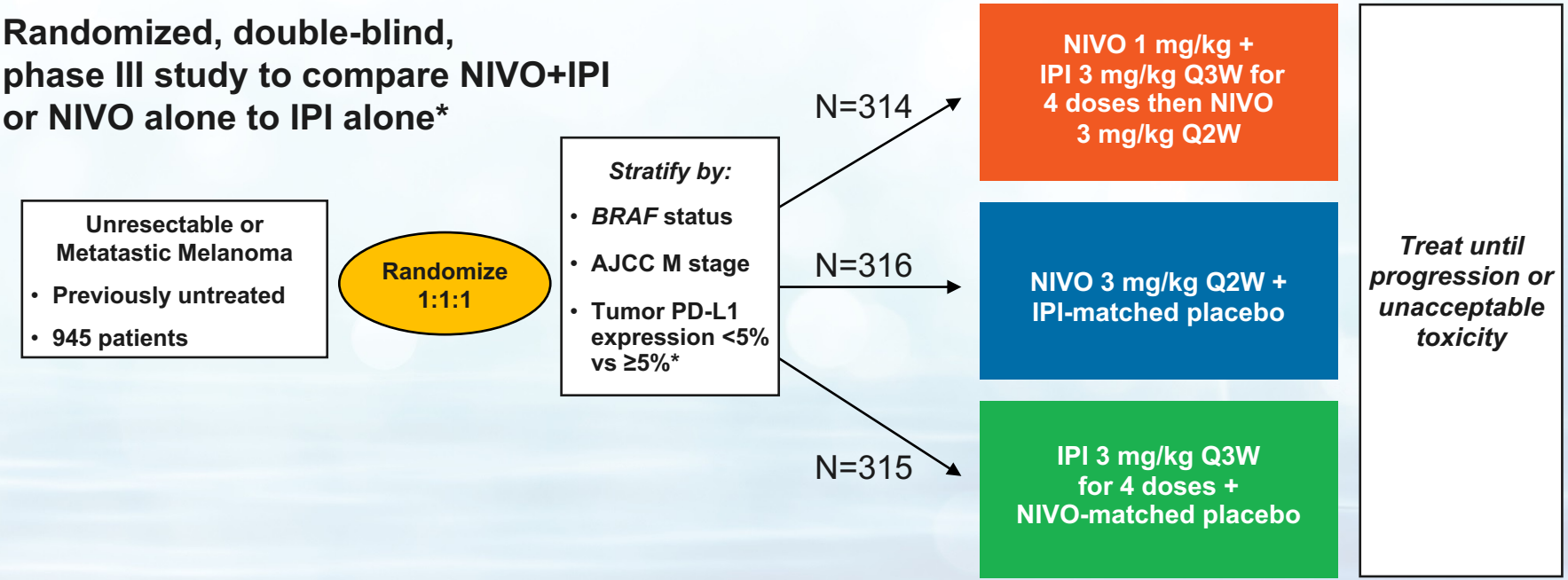






CheckMate 067: Established ipilimumab+nivolumab as the gold standard of care

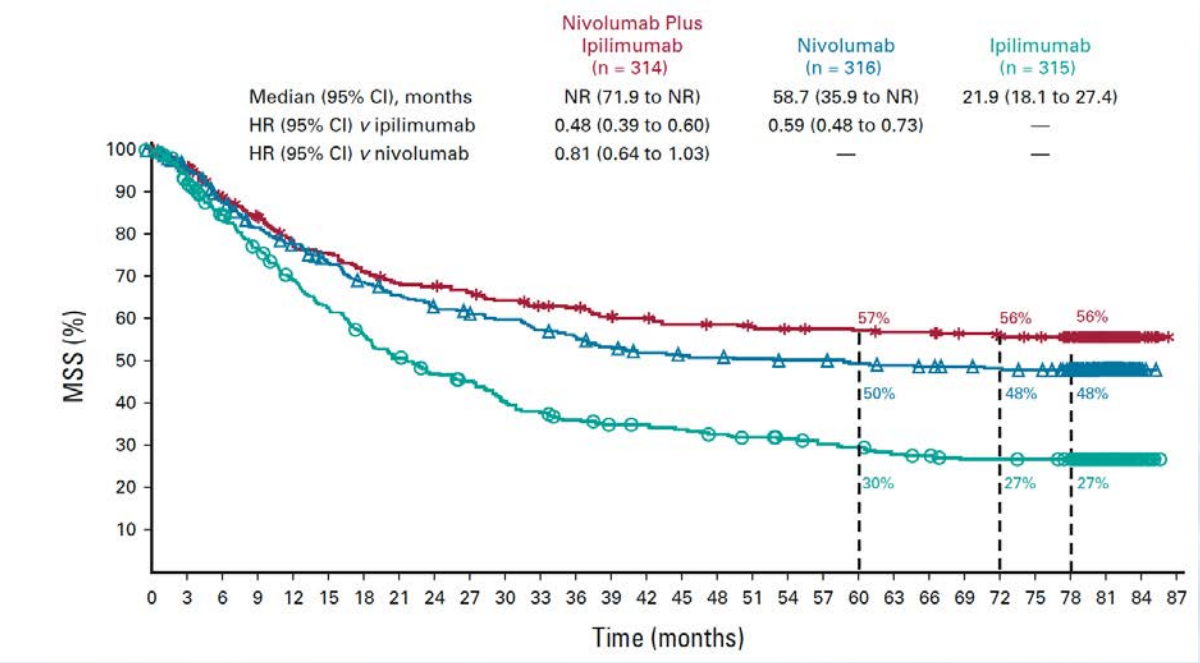
Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



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*

CHECKMATE 067 trial long term outcomes: Some patients may be cured



Nivo+ipi

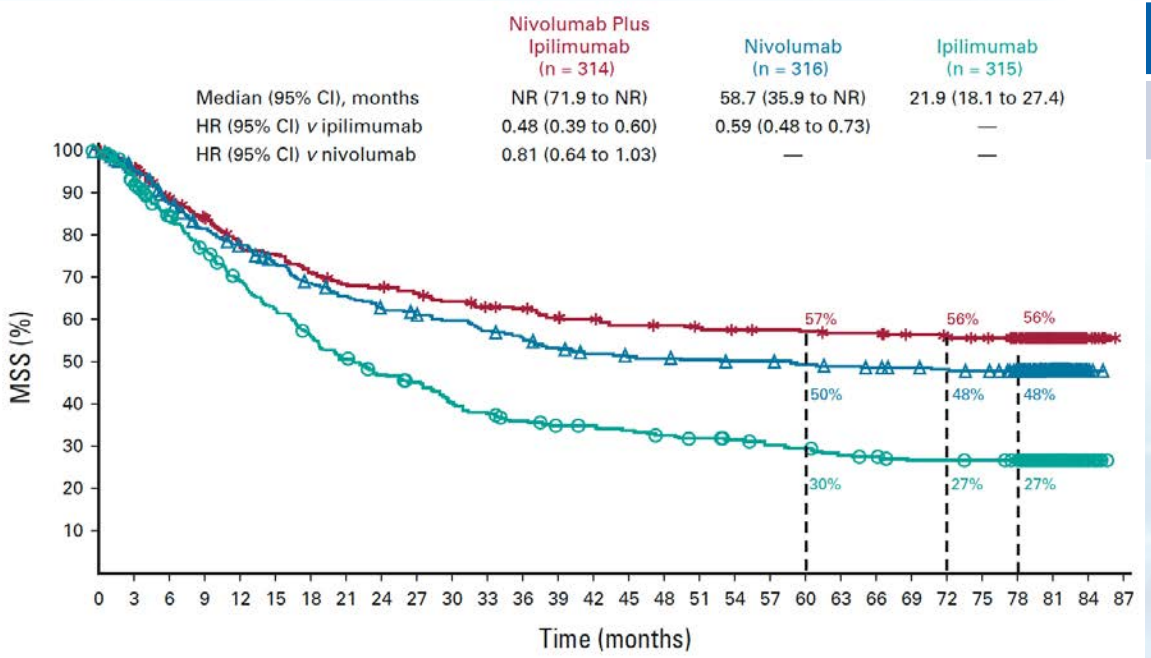
Nivolumab

Ipilimumab

10 year f/up = cure?

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

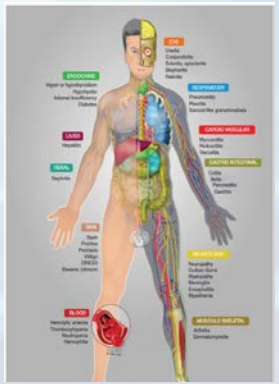
G3= severe

G4= life threatening

Nivo+ipi

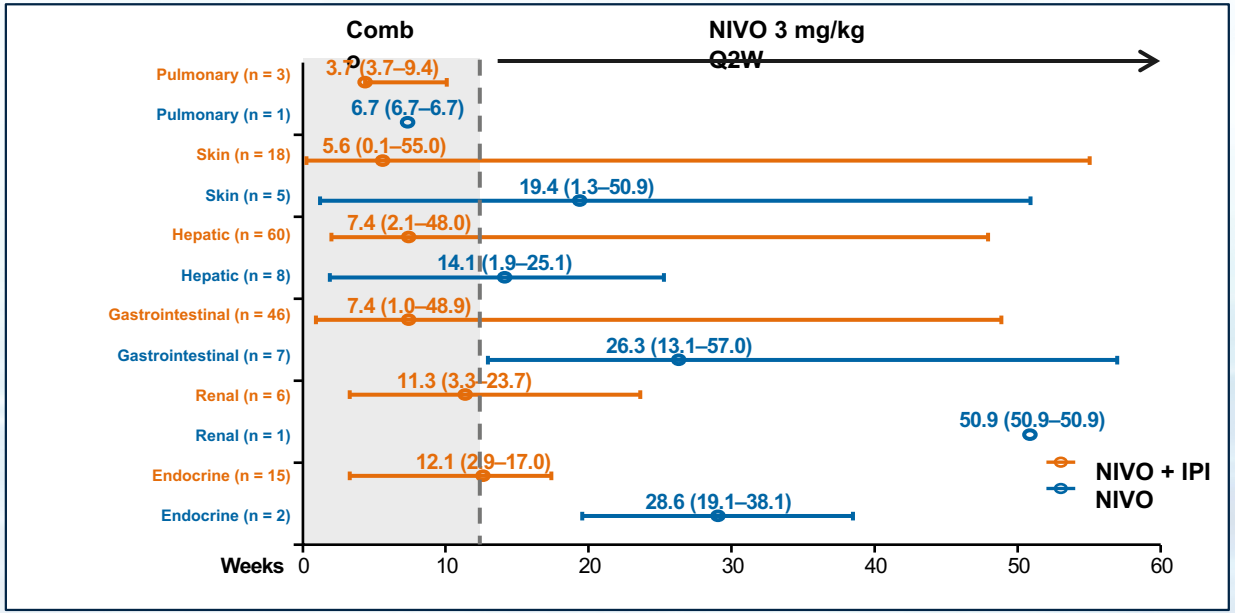
Nivolumab

Ipilimumab

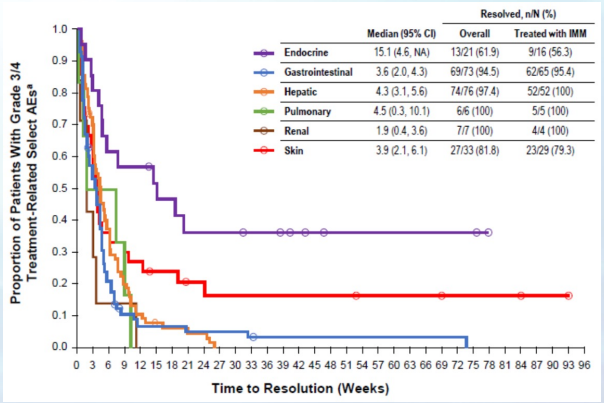


Wolchock JD, et al. NEJM 2017; 377: 1345-56; J Clin Oncol 2022; 40: 127-37

CHECKMATE 067 trial has taught us to recognize and manage complex immune-related adverse events

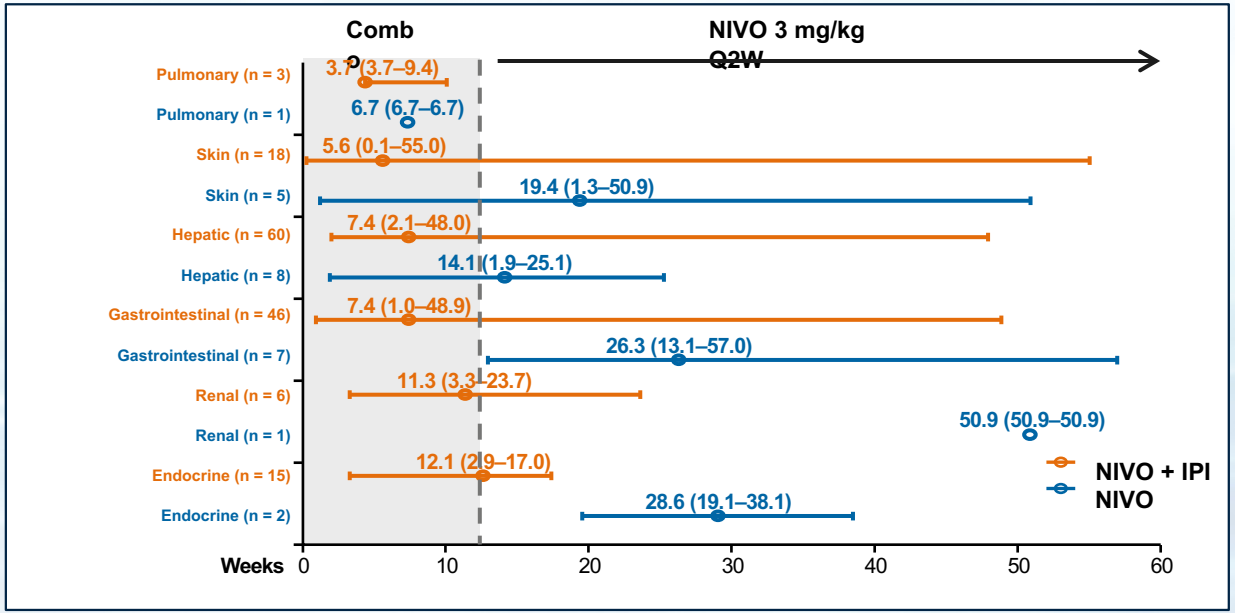


Time to onset of grade ≥3 irAEs. Larkin J, et al. ECC 2015; abstract 3303.

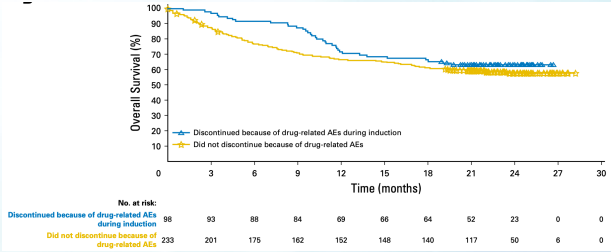


Time to resolution of grade ≥3 irAEs for pts receiving nivo+ipi. Sznol M, et al. ESMO 2016; abstract 1123P.

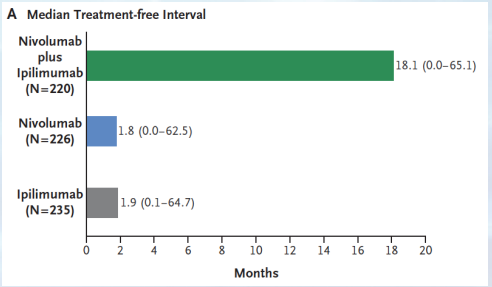
CHECKMATE 067 trial has taught us to recognize and manage complex immune-related adverse rvents



Time to onset of grade ≥3 irAEs. Larkin J, et al. ECC 2015; abstract 3303

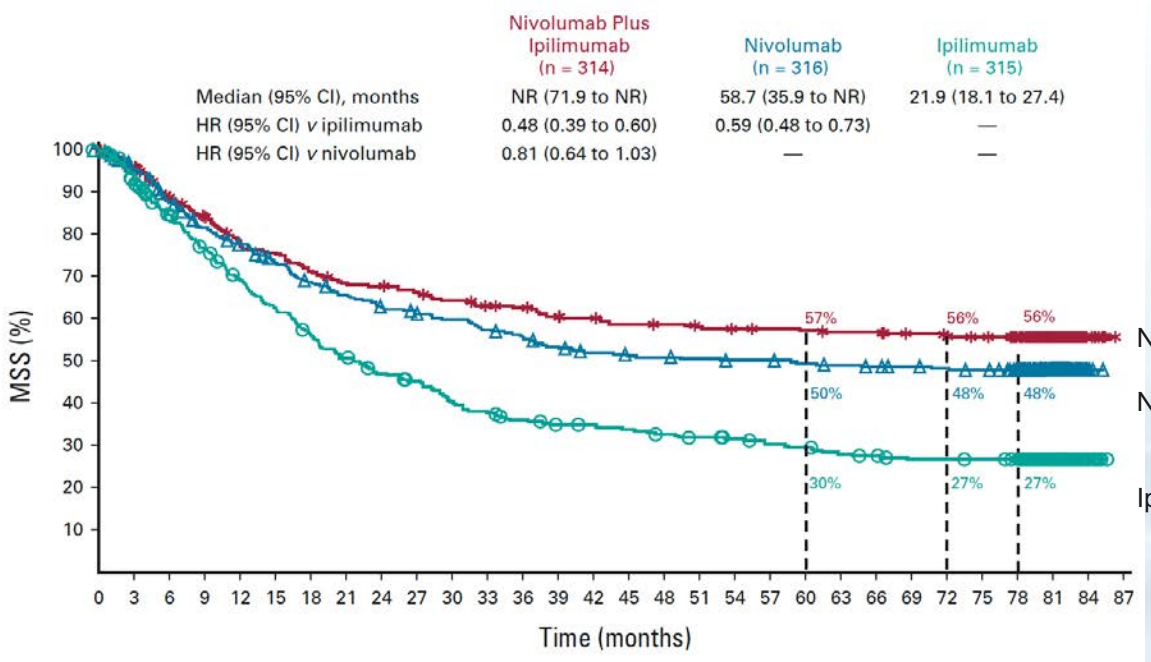


Schadendorf D, et al. J Clin Oncol 2017; 35: 3807-14t

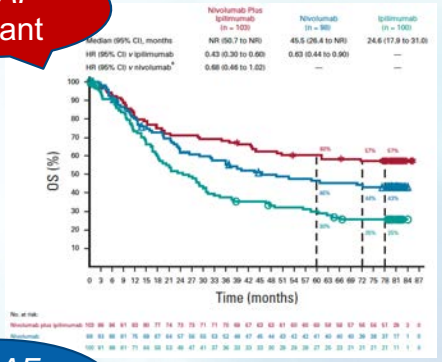


Larkin J, et al. 2019; 381: 1535-46

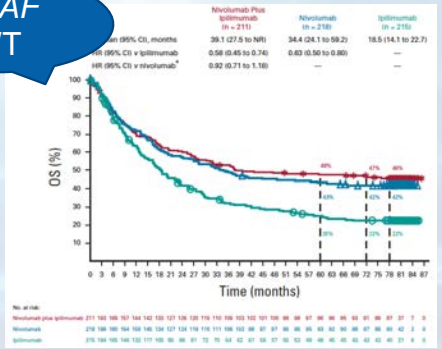
CHECKMATE 067 trial long term outcomes: Does *BRAF* status matter?



BRAF mutant

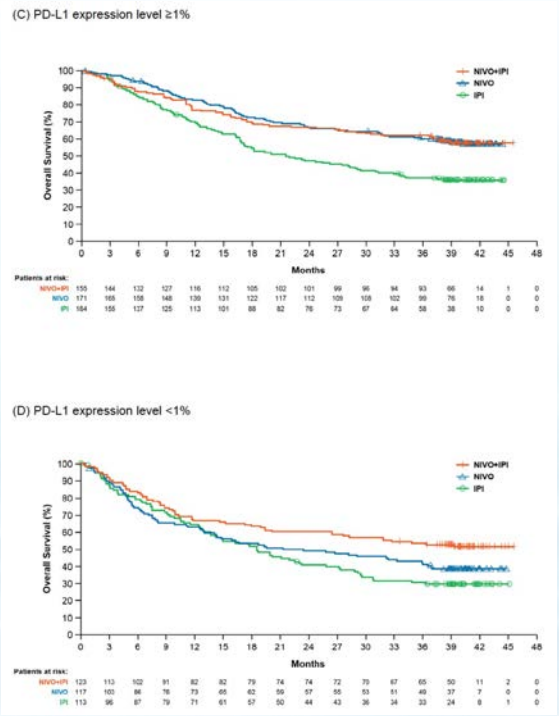


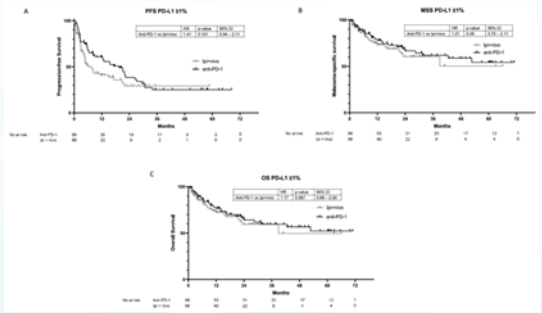
BRAF WT

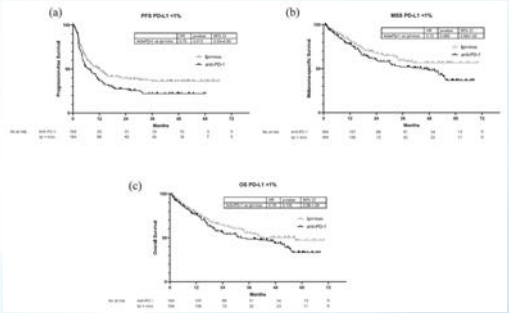


Wolchock JD, et al. J Clin Oncol 2022; 40: 127-37

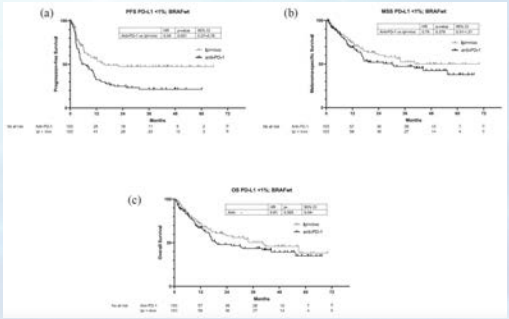
CHECKMATE 067 trial: What about PD-L1 expression?







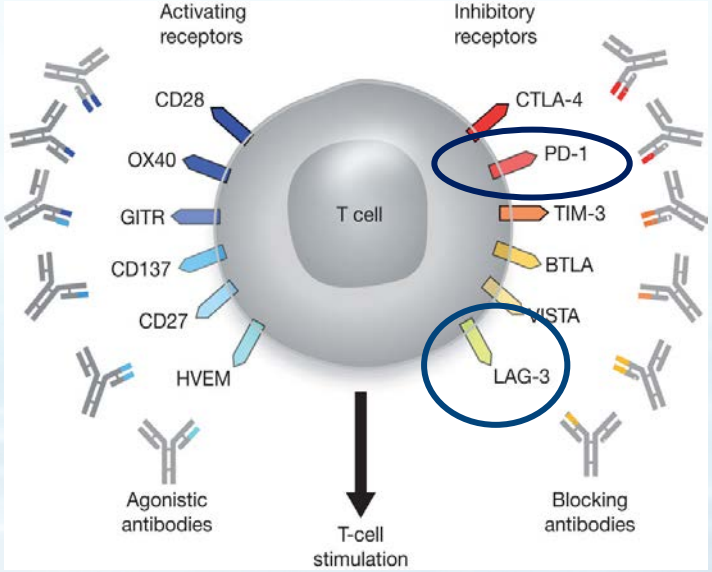
In a large-scale, Danish population-based study, improved clinical outcomes with nivo+ipi was not evident in patients with ≥1% tumor PD-L1 expression

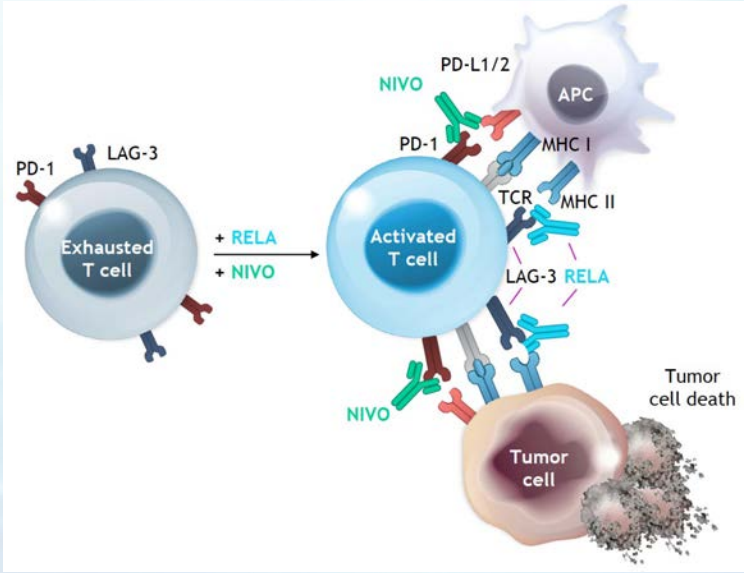


Wolchock JD, et al. N Engl J Med 2017; 37: 1345-56

Ellerbaek E, et al. E J Cancer 2024; 198: 113476

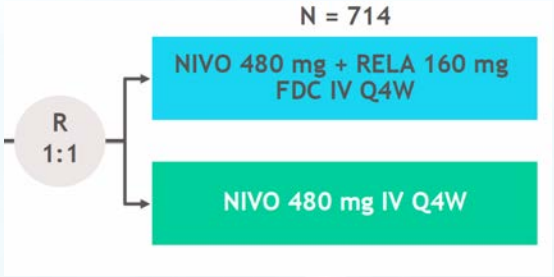
Can we improve outcomes by targeting other immune checkpoints?



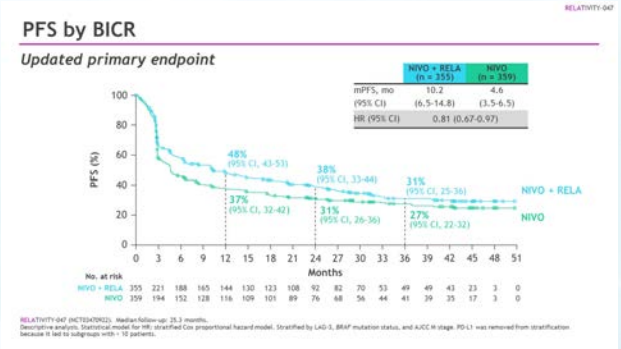


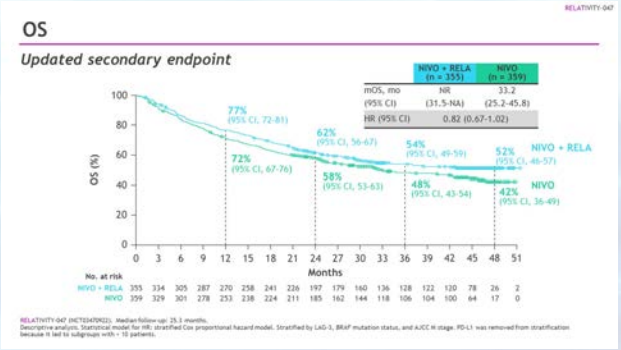
Relatlimab blocks LAG-3 and restores T cell function

RELATIVITY 047: Nivolumab + Relatlimab (Opdualag) improves relapse-free survival and maintains quality of life compared with nivolumab alone



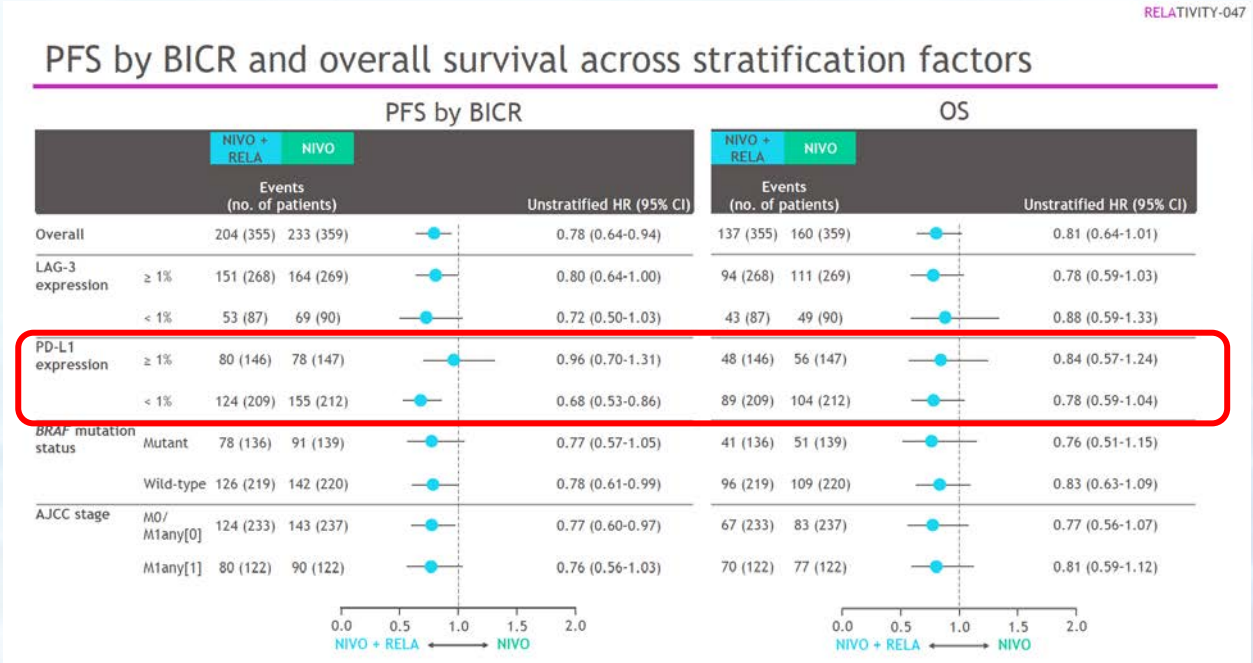
	Nivo+Rela	Nivo
Treatment-related AEs	84% Any 21% G3-4	72% Any 11% G3-4



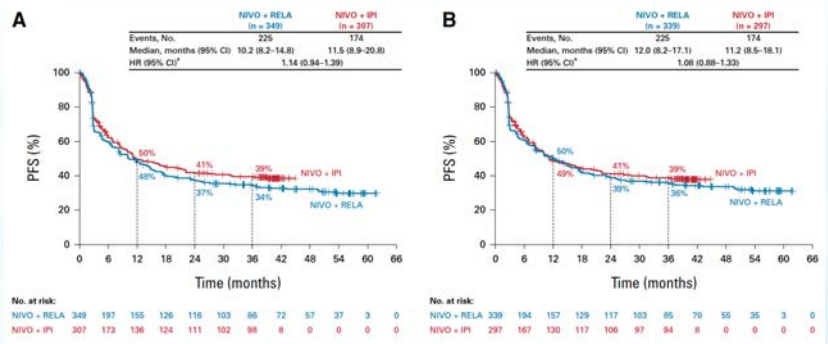


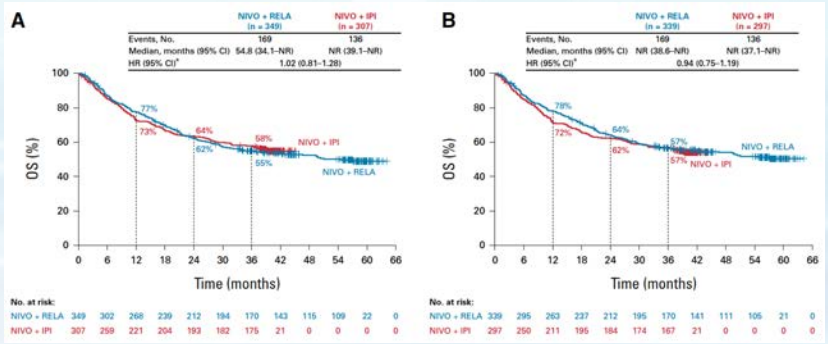
Tawbi H, et al. NEJM 2022; 386: 24-34; Schadendorf D, et al. EJC 2023; 187: 164-173

EMA: Opdualag is indicated for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD L1 expression < 1%



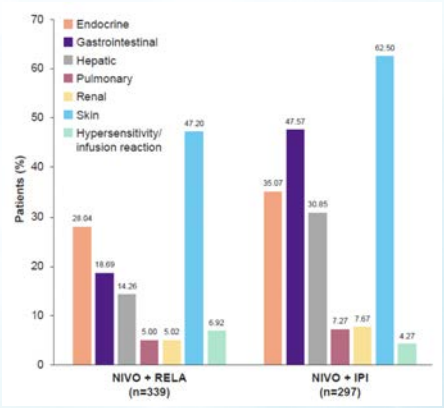
Indirect comparison of Nivolumab + Relatlimab versus Nivolumab + Ipilimumab – *interpret with caution!*



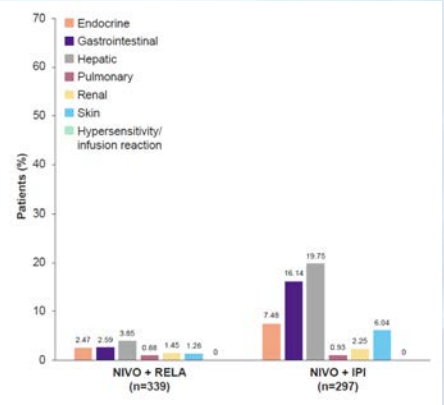


Long G et al, J Clin Oncol Aug 2024

Any grade Select TRAEs



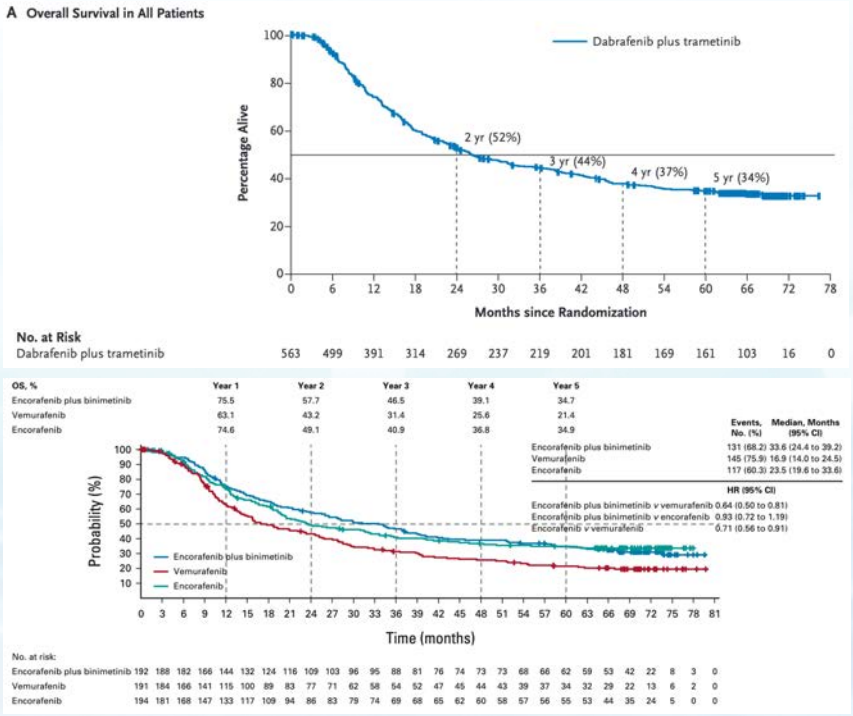
Grade 3&4 Select TRAEs



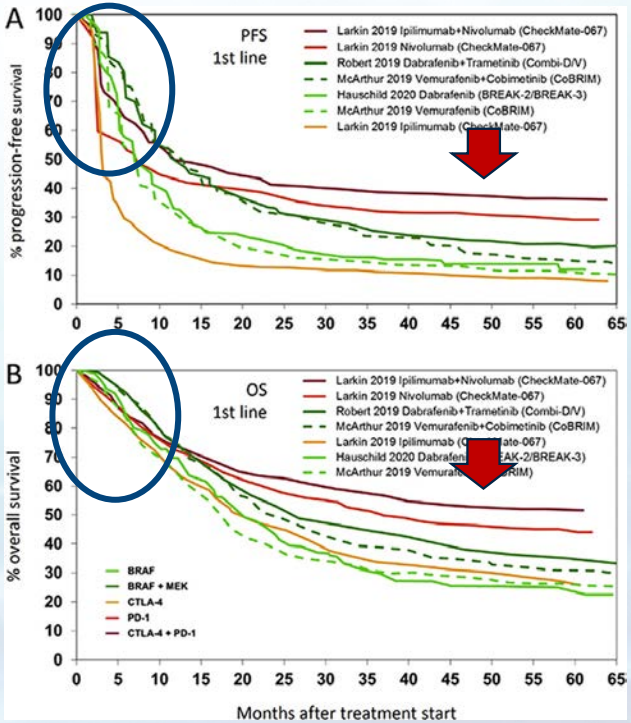
Factors determining choice of first line treatment for metastatic melanoma

- Patient factors
  - Age
  - Performance status
  - Co-morbidities
  - History of autoimmune disease
- Tumour characteristics
  - PD-L1 status
  - BRAF status
- Prior therapy
  - Adjuvant
  - Neoadjuvant

Optimal treatment for *BRAF* mutant stage IV melanoma



Robert C, et al. NEJM 2019; 381: 626-36; Dummer R, et al. 2022: 40: 4178-88

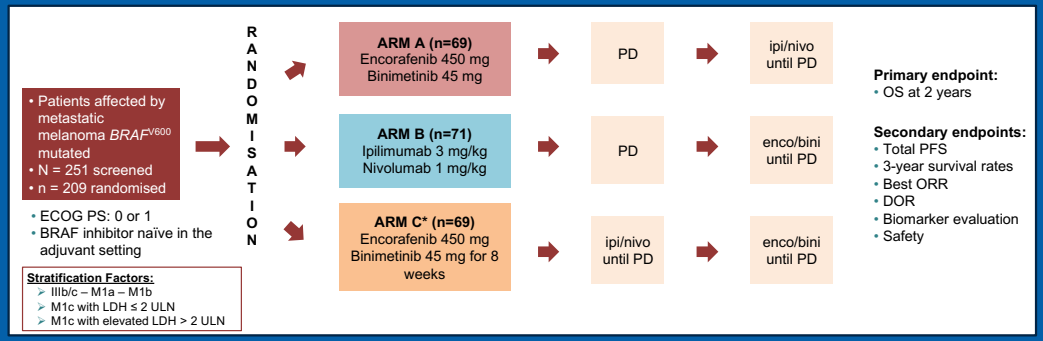


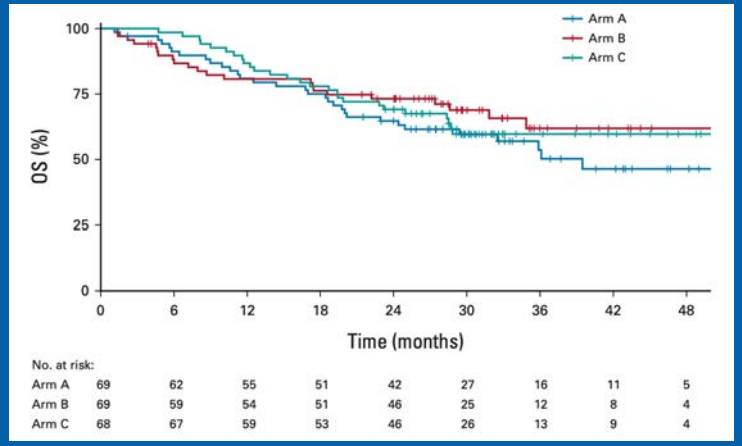
Ugurel S, et al. E J Cancer 2020; 130: 126-38

BRAF mutant metastatic melanoma

- What is optimal first line therapy?

SEquential COMBo Immuno and Target therapy (SECOMBIT) Study (NCT02631447)



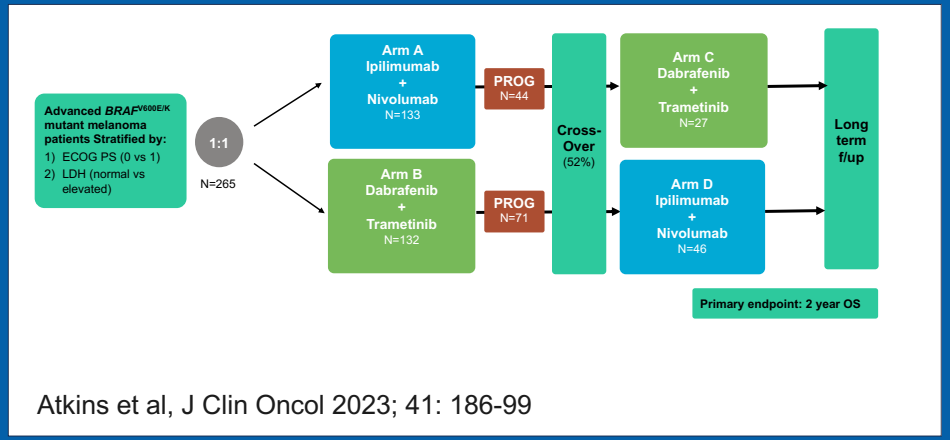


Ascierto PA, et al. J Clin Oncol 2022; 41: 212-21

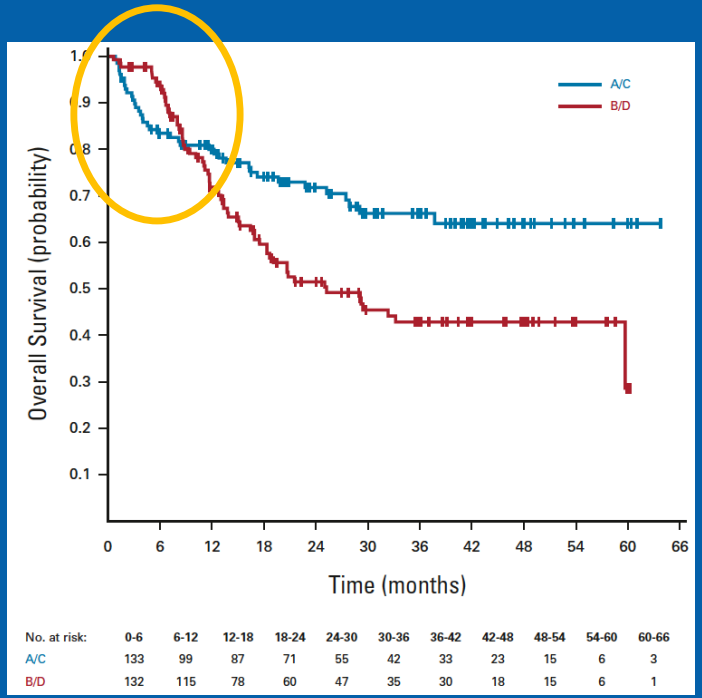
BRAF mutant metastatic melanoma

- What is optimal first line therapy?

DREAMSEQ: Study design
Open-label, randomised phase 3 trial



Atkins et al, J Clin Oncol 2023; 41: 186-99



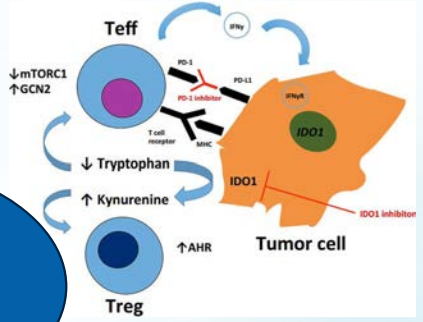
Which patients are best treated with BRAF-targeted agents today?

- 1st Line Metastatic
  - rapidly progressing metastatic disease, high disease burden (including multiple brain metastases) and/or poor performance status
  - Elderly/frail patients
  - contra-indications to immunotherapy

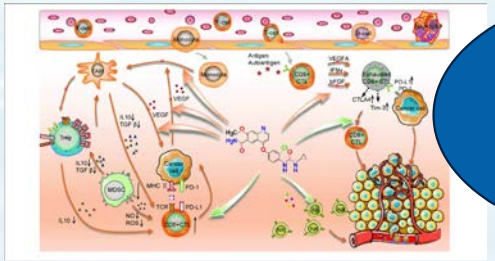
- 2nd Line Metastatic
  - On progression after 1st line immunotherapy

What Strategies Haven't Worked?

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

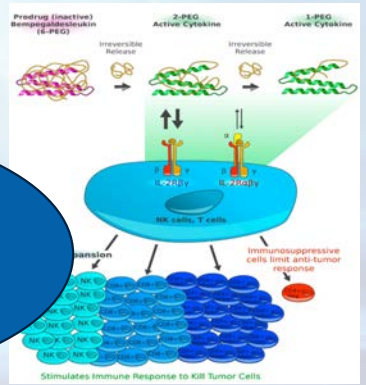


KEYNOTE-252[4]
Epacadostat+
pembrolizumab



LEAP-004[6]
Lenvatinib+
pembrolizumab

PIVOT IO 001[5]
Bempegaldesleuki
n+nivolumab



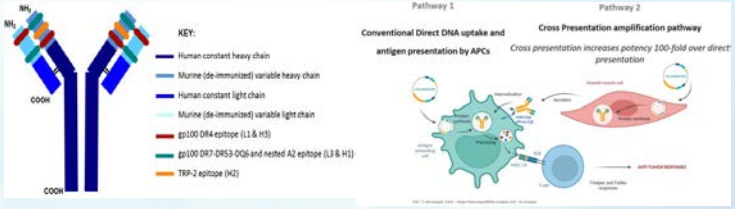
1. Ascierto PA et al, 2019; 2. Gutzmet R et al, 2020; 3. Dummer R et al, 2022; 4. Long GV et al, 2019; 5. Diab A et al, 2023; 6. Arance A et al, 2023

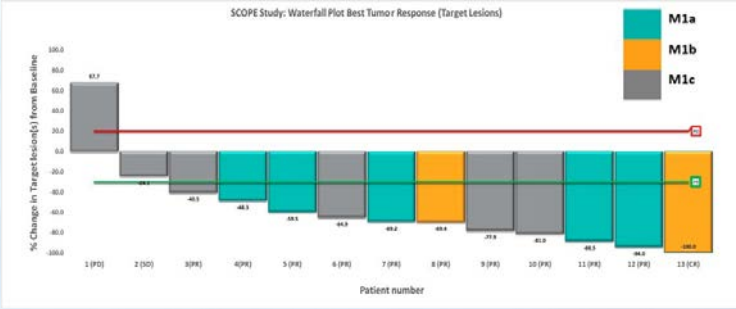
Where Next?

REGENERON®

IMMUNOCORE

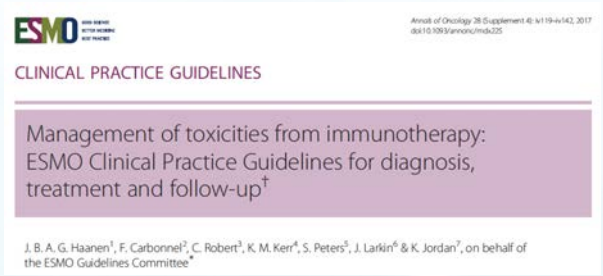
SCANCELL





Shaw, H et al, ASCO 2024 Abstract 9535

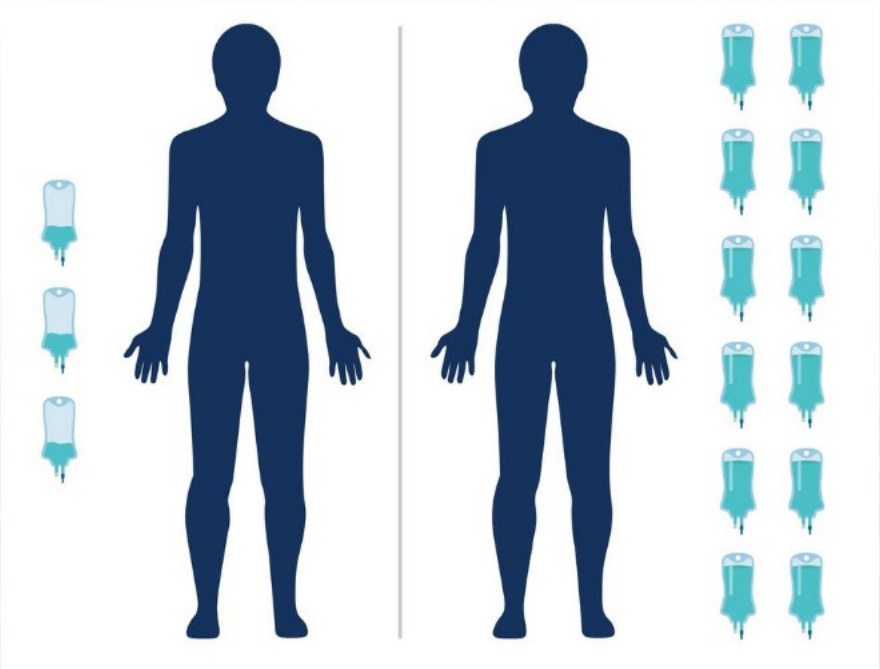
Survivorship on and after immunotherapy: A growing area of importance



Pinato DJ, et al. JAMA Oncol 2019; 5: 1774-8

Bjork JR, et al. Nat Med 2024; 30: 785-96

How much treatment is needed?



OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

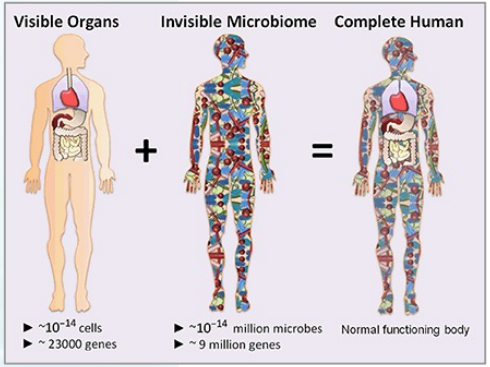
Optimal drug dose?
Treatment duration?

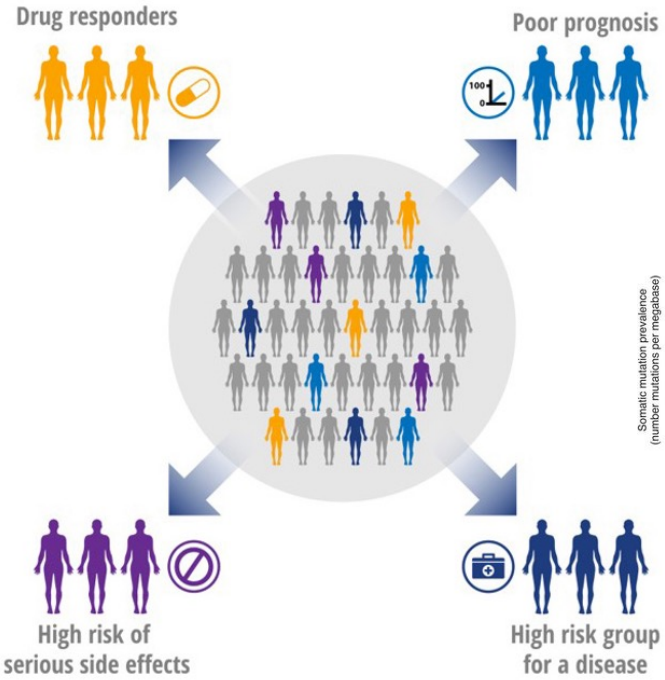
REFINE

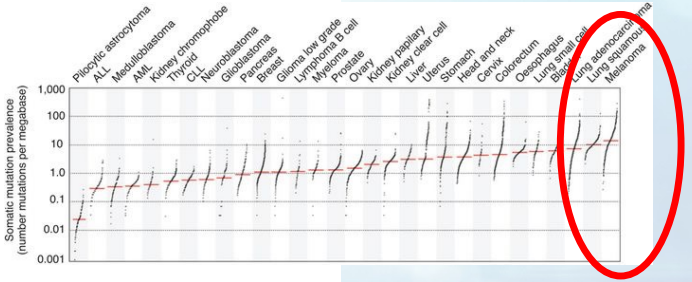
THE JON MOULTON CHARITY TRUST

DANTE
Investigating the duration of anti-PD1 monoclonal antibody treatment for metastatic melanoma

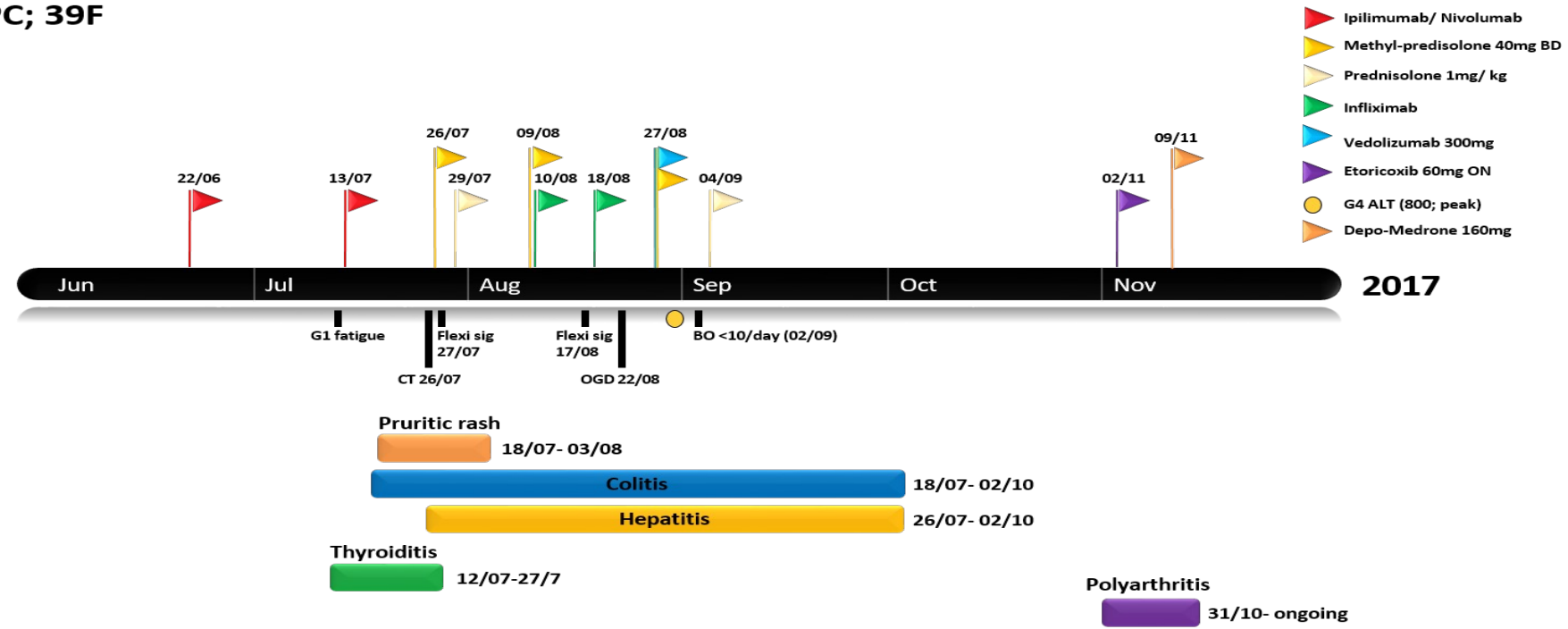
Can we predict response or toxicity?





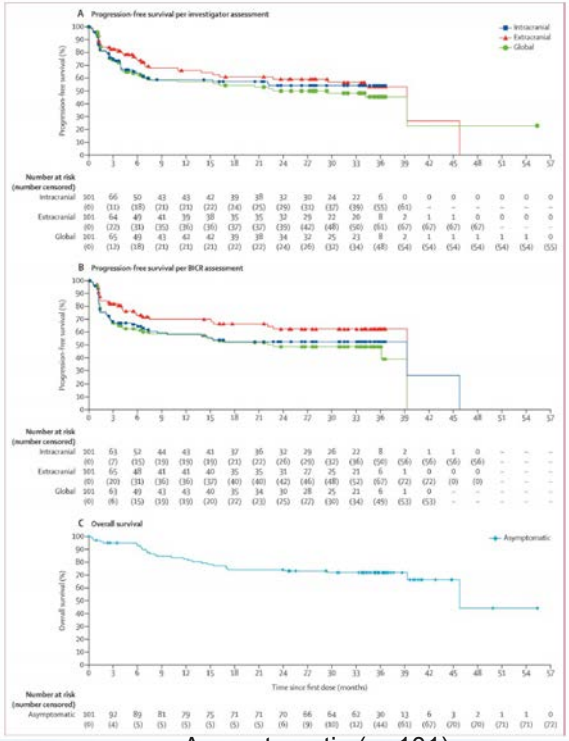


PC; 39F

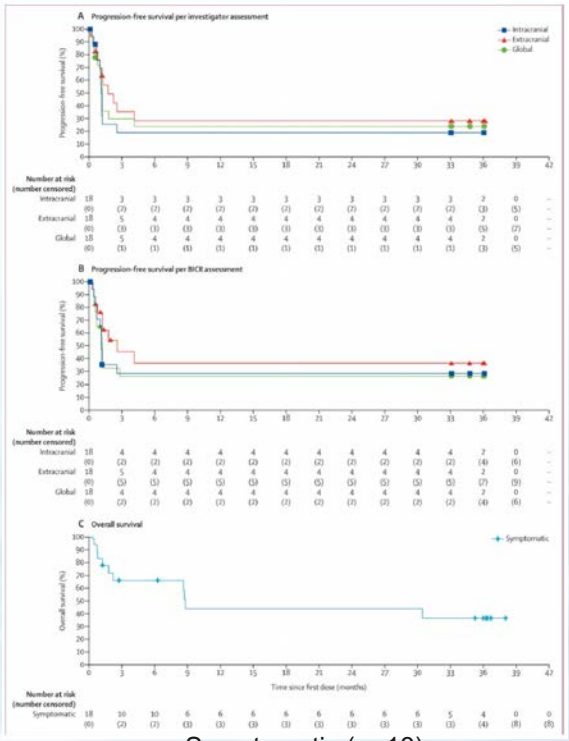


CTAP (26/07): no features of colitis; small bowel thickening
Flexi sig (27/07): mild non-specific chronic inflammation
Flexi sig (17/08): patchy mild to moderate active inflammation with increased crypt apoptosis; CMV IHC negative
OGD (22/08): moderate to severe active chronic inflammation with mucosal erosions and increased crypt apoptosis in duodenum; minor reactive changes in stomach; CMV IHC negative
Adeno/ EBV/ CMV PCR (23/08): negative
Stool sample (27/07; 10/08; 15/08): negative for Salmonella, Shigella, Campylobacter & Escherichia coli O157, Cryptosporidium, C.difficile

Brain Metastases: Optimal management is informed by Checkmate204 and ABC phase II trials



Asymptomatic (n=101)



Symptomatic (n=18)

	A (ipi+nivo)	B (nivo)	C (nivo)
All patients	n=35	n=25	n=16
ICR	51%	20%	6%
5-yr IC PFS	46%	15%	6%
5-yr OS	51%	34%	13%
Rx naïve	n=27	n=19	n=4
ICR (Rx naïve)	59%	21%	25%
5-yr IC PFS (Rx naïve)	52%	14%	.
5-yr OS (Rx naïve)	55%	40%	25%
TRAE G3/4	63%	20%	13%

Asymptomatic pts were randomized to cohorts A or B
Pts who were symptomatic, failed local therapy or had leptomeningeal disease were allocated to cohort C

Long GV et al, ASCO 2021 abstract 9508

Tawbi HA et al, Lancet Oncol 2021;22: 1692-1704

When first line anti-PD1 based therapy fails..

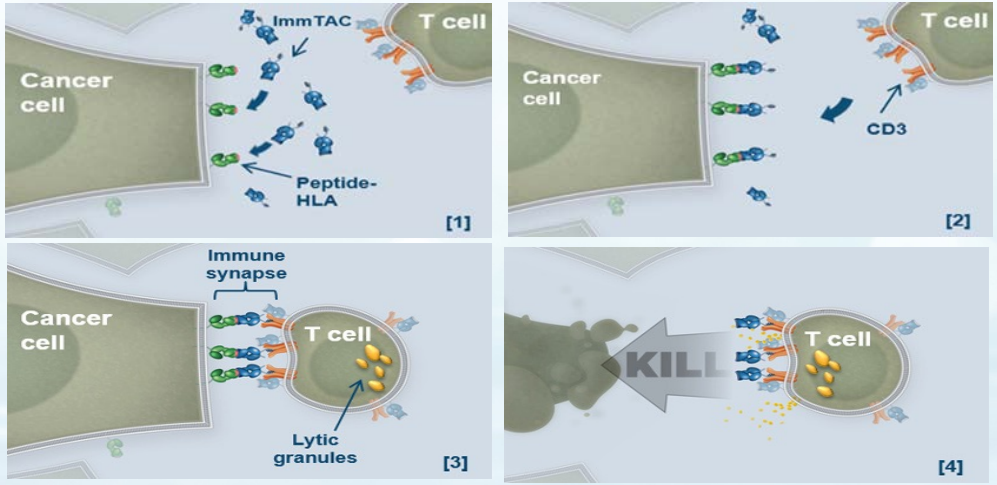
When first line anti-PD1 based therapy fails..SWOG1616 sets a bar

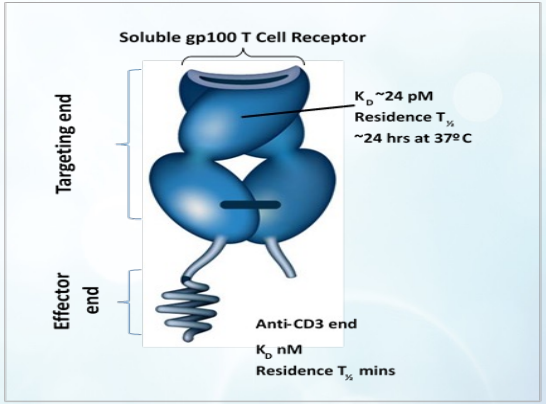
	Ipi+Nivo (N=70)	Ipilimumab (N=24)	
6 mo PFS	34%	13%	HR 0.63 (90% CI 0.41-0.97) p=0.04
ORR	28%	9%	p=0.05
OS			HR 0.83 (90% CI 0.50-1.39) p=0.28
≥ Grade 3 AEs	57%	35%	
CD8 T cell infiltrate			No difference in baseline or changes with treatment between responding and non-responding patients

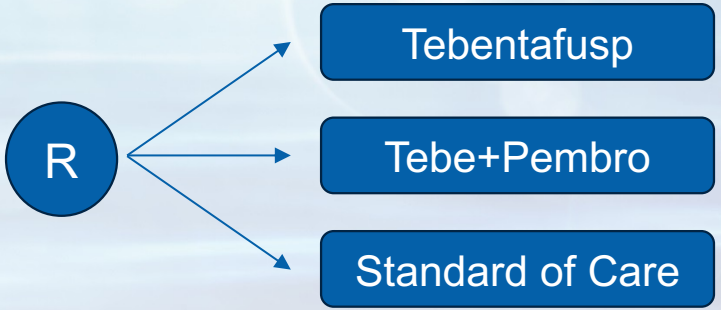
VanderWalde A, et al. Nature Medicine 2023;29:2278-85

Not regulatory approved in Norway

Tebentafusp – TebeAM trial is currently recruiting

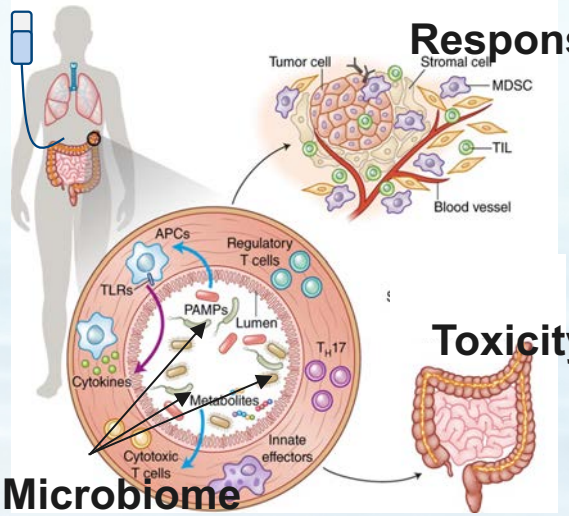


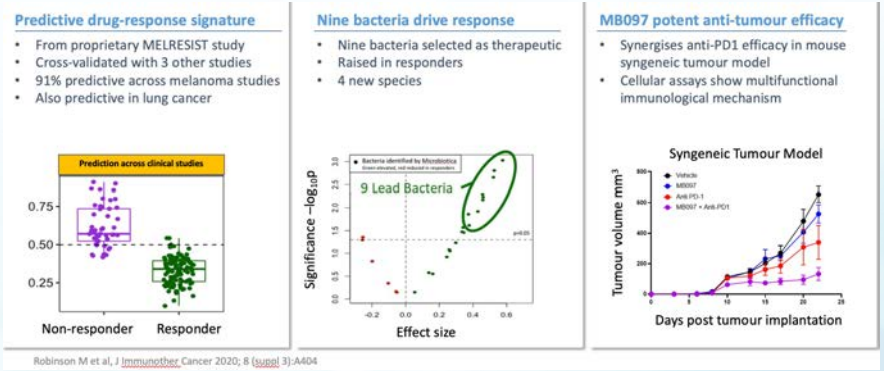




Melody-1

microbiotica





Study Design

The "no preconditioning" cohort: Goes straight to treatment

Same treatment: For both cohorts - up to 24 weeks, MB097 (2 oral caps/d) + pembrolizumab i.v. q3w

For Responders: Extended Treatment Period Up to 81 additional weeks on pembrolizumab only, no MB097

S | R

n=20 → MB097 + pembrolizumab

n=20 → vanco + w/o → MB097 + pembrolizumab

EOT → pembrolizumab only / Safety FU (SOC)

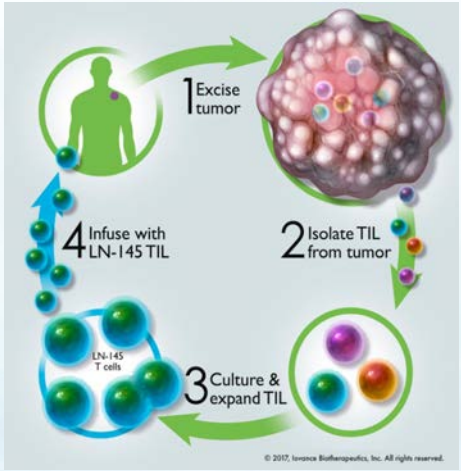
The preconditioning cohort: Gets 5d oral vancomycin 125mg qid followed by 2 days washout (w/o)

S: Screening
R: Randomization
EOT: End Of Treatment

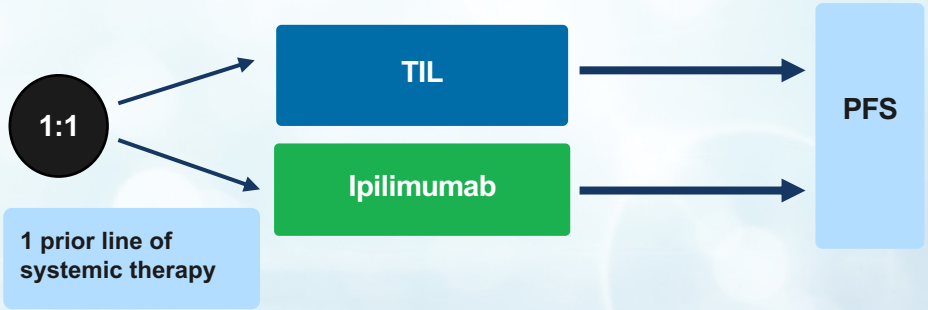
For Non- Responders: Up to 12 weeks in the safety follow-up period receiving Standard of Care (SOC)

Primary end point: Safety
Secondary endpoints: Efficacy; engraftment

Tumour Infiltrating Lymphocytes (TILs) generate durable responses in pretreated melanoma patients



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



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

SUMMARY

- With so many new approvals for both early and advanced melanoma, navigating the treatment landscape is increasingly challenging
- One size does not fit all: the goal is to personalise therapy, taking into account individual host and tumour characteristics, as well as patient preference
- This requires a multidisciplinary approach, involving medics, surgeons, pathologists, scientists, radiologists and specialist nurses, as well as public health physicians
- Despite considerable advances, many patients continue to die from this disease, so clinical trials remain a priority treatment option