Navigating the emerging complexities of melanoma treatment: New insights for clinical practice

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Translating the long-term survival results in melanoma to the clinic

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What are the 5-year survival rates for agents targeting the MAPK pathway in patients with metastatic melanoma?

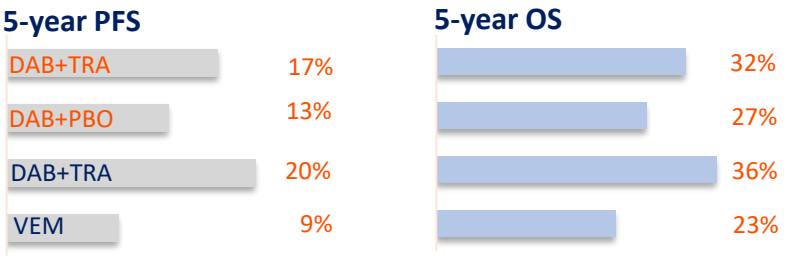
5-year survival rates for targeted therapies in metastatic melanoma

Evidence for use of BRAF + MEK inhibition vs single-agent BRAF inhibitor

COMBI-d & COMBI-v

COMBI-d: Dabrafenib + trametinib vs PBO
COMBI-v: Dabrafenib + trametinib vs vemurafenib
In untreated *BRAF*-mutant melanoma

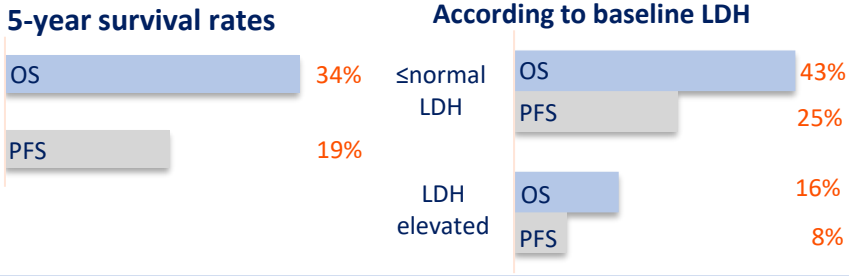
COMBI-d N=423
COMBI-v N=704



COMBI-d & COMBI-v

Dabrafenib + trametinib
Pooled analysis in untreated *BRAF*-mutant melanoma

N=563



BRAF, v-raf murine sarcoma viral oncogene homolog B1; DAB, dabrafenib; LDH, lactate dehydrogenase; PBO, placebo; PFS, progression-free survival; OS, overall survival; TRA, trametinib; VEM, vemurafenib.

Robert C, et al. *N Engl J Med.* 2019;381:626–36.

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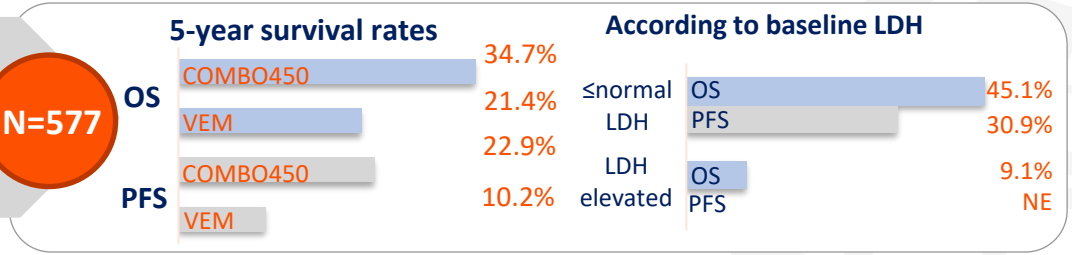
5-year survival rates for targeted therapies in metastatic melanoma

COLUMBUS phase III trial (part 1)[1,2]

Encorafenib + binimetinib (COMBO450) vs encorafenib or vemurafenib in untreated or progressed *BRAF*-mutant melanoma after first-line immunotherapy

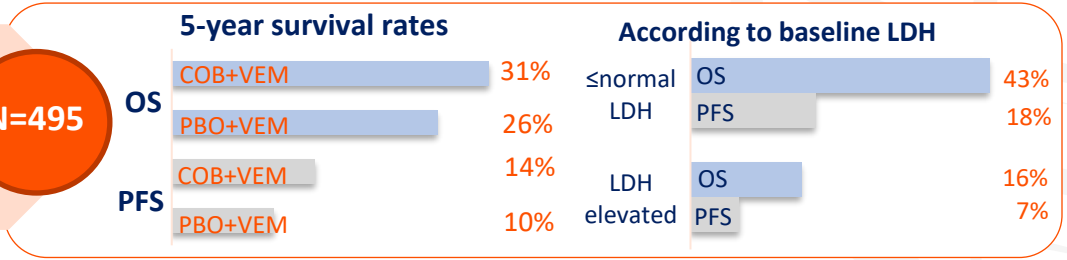
N=577



coBRIM study[3]

Cobimetinib + vemurafenib vs vemurafenib in untreated *BRAF*-mutant melanoma

N=495



BRAF, v-raf murine sarcoma viral oncogene homolog B1; COM, cobmietinib; LDH, lactate dehydrogenase; NE, non-evaluable; OS, overall survival; PBO, placebo; PFS, progression-free survival; VEM, vemurafenib.

1. Dummer R, et al. *J Clin Oncol.* 2021;39(Suppl. 15);9507; 2. Dummer R, et al. Oral presentation. ASCO 2021. Abstr 9506; 3. Ascierto P, et al. *Clin Cancer Res*. 2021. doi: 10.1158/1078-0432.CCR-21-0809.

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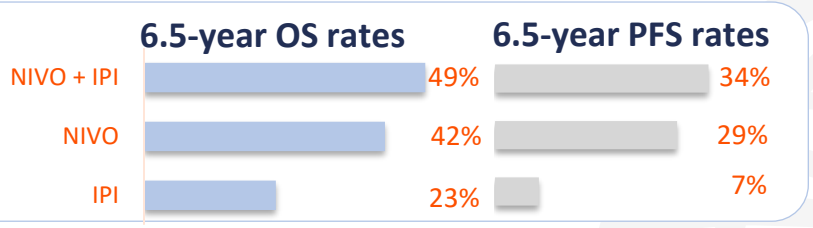
What are the long-term survival rates for immunotherapy in the treatment of metastatic melanoma?

Long-term survival rates for immunotherapy in metastatic melanoma

CheckMate 067 phase III trial[1]

Nivolumab +/- ipilimumab vs ipilimumab in untreated metastatic melanoma

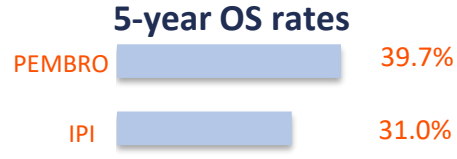
NIVO+IPI: N=314
NIVO: N=316
IPI: N=315



KEYNOTE-006 phase III trial[2]

Pembrolizumab vs ipilimumab
Ipilimumab-naïve and ≤1 prior Tx for *BRAF*-mutant metastatic melanoma

PEMBRO: N=556
IPI: N=278



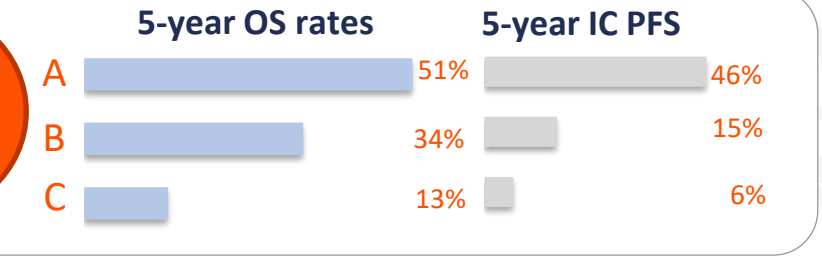
Median DOR: NR
All pts who completed therapy in CR still alive at 5 years

ABC phase II study[3]

Nivolumab +/- ipilimumab
in patients with melanoma BM
naïve to anti-PD-1/PD-L1/PD-L2/CTLA-4

- Asymptomatic BM, naïve for local brain therapy
  - Cohort A: NIVO+IPI
  - Cohort B: NIVO
- Symptomatic BM, prior Tx*
  - Cohort C: NIVO

Cohort
A: N=35
B: N=25
C: N=16



*failed local brain therapy/neuro-symptoms/leptomeningeal disease
BM, brain metastases; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DOR, duration of response; IC, intracranial; IPI, ipilimumab; NIVO, nivolumab; NR, not reached; PD-1 programmed cell death protein-1; PD-L1, programmed death-ligand 1; PEMBRO, pembrolizumab; PFS, progression-free survival; pts, patients; OS, overall survival; Tx, treatment.

1. Wolchok JD, et al. *J Clin Oncol.* 2021;39(suppl 15):Abst 9506; 2. Long GV, et al. *J Clin Oncol.* 2020;38(suppl 15):Abst 10013; 3. Long G, et al. *J Clin Oncol.* 2021;39(suppl 15):Abstr 9508.

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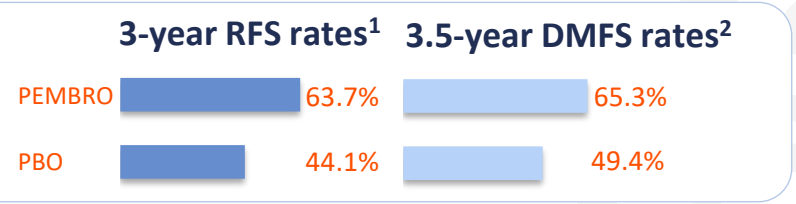
What is the role of adjuvant targeted therapies and immune checkpoint inhibitors in high-risk melanoma?

Key data for adjuvant targeted therapies and anti-PD-1 agents in high-risk melanoma

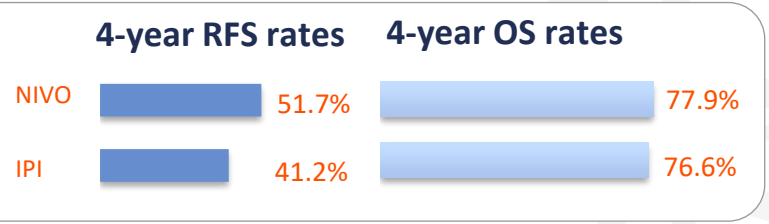
EORTC 1325-MG/KEYNOTE-054 trial[1,2]
Adjuvant pembrolizumab vs placebo
in resected high-risk stage III melanoma

N=1,019



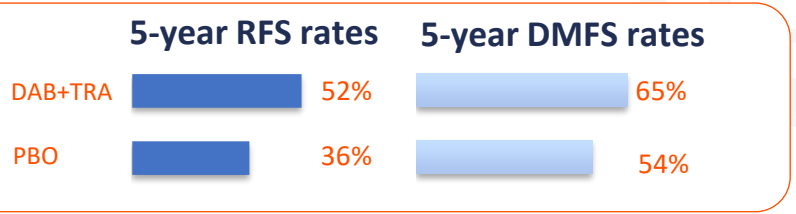
CheckMate 238 phase III trial[3]
Adjuvant nivolumab vs ipilimumab
in resected stage IIIB, IIIC and IV melanoma

N=906



COMBI-AD phase III trial[4]
Dabrafenib + trametinib vs two
matched placebos in resected stage III
BRAF-mutant melanoma

N=870



BRAF, v-raf murine sarcoma viral oncogene homolog B1; DAB, dabrafenib; DMFS, distant metastasis-free survival; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PBO, placebo; PEMBRO, pembrolizumab; PD-1, programmed cell death protein 1; RFS, recurrence-free survival; TRA, trametinib.

1. Eggermont A, et al. *J Clin Oncol.* 2020;38:3925–36; 2. Eggermont A, et al. *Lancet Oncol.* 2021;22:643–54; 3. Ascierto P, et al. *Lancet Oncol.* 2020;21:1465–77; 4. Dummer R, et al. *N Engl J Med*. 2020;383:1139–48.

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KEYNOTE–716: Adjuvant pembrolizumab in patients with completely resected high-risk stage II melanoma

ESMO 2021: Adjuvant pembrolizumab in stage IIB or IIC melanoma[1,2]

Treatment		**Adjuvant pembrolizumab** every 3 weeks or PBO
Patient population		**N=976** Aged ≥12 years with completely resected high-risk stage IIB or IIC melanoma
Primary outcome	**RFS**	At median follow-up 14.4 months Significantly prolonged RFS vs PBO: HR **0.65**, p=0.007 Recurrence rates for **pembrolizumab** vs PBO: **11.1%** vs 16.8%
Secondary outcomes	DMFS, OS, **safety**	For **pembrolizumab** vs PBO Grade ≥3 any cause AEs: **25.9%** vs 17.1% Grade ≥3 TRAEs: **16.1%** vs 4.3% Discontinuations due to TRAEs**:** **15.3%** vs 2.5% Deaths: **0** vs 4 (any-cause) irAEs: **Mostly grade 1 or 2**

- Based on these data, the FDA has accepted a new sBLA for pembrolizumab for the adjuvant treatment of adult and pediatric (≥12 years) patients with stage IIB or IIC melanoma following complete resection
- The FDA granted the application Priority Review and assigned a PDUFA, or target action, date of 4 December 2021

AE, adverse event; DMFS, distant metastasis-free survival; FDA, US Food and Drug Administration; HR, hazard ratio; irAE, immune-related AE; OS, overall survival; PBO, placebo; PDUFA, Prescription Drug User Fee Act; RFS, recurrence-free survival; sBLA, supplemental Biologics License Application; TRAE, treatment-related adverse event.

1. ClinicalTrials.gov. Available at : www.clinicaltrials.gov/ct2/show/NCT03553836 (accessed Sept 2021); 2. Luke J, et al. *Ann Oncol.* 2021:32(suppl. 5):S1283–346.

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What is the potential role of neoadjuvant targeted therapies and immune checkpoint inhibitors in high-risk melanoma?

Neoadjuvant therapy in high-risk melanoma

Pooled analysis from six clinical trials of anti-PD-1-based **immunotherapy or BRAF/MEK targeted therapy** from the INMC[1]

N=192
pCR occurred in 40% of all pts

- Targeted therapy (n=51) pCR: 47%
- Immunotherapy (n=141) pCR: 33%
  - Anti-PD-1 monotherapy (n=37) pCR: 20%
  - IPI + NIVO (n=104) pCR: 43%

Very few relapses with pCR, near pCR or pPR
2-year RFS: 96%

pCR correlated with improved RFS and OS
RFS: pCR 2-year **89%** vs no pCR 50%, p<0.001
OS: pCR 2-year **95%** vs no pCR 83%, p=0.027

Neoadjuvant and adjuvant **nivolumab with anti-LAG-3 (relatlimab)** for pts with resectable stage III melanoma[2]

29 pts underwent Tx followed by surgical assessment of pathological response

Primary objective: pCR rate

Neoadjuvant nivolumab and relatlimab achieved high rates of pCR: 59% and MPR: 66%
At a median follow-up of 16.2 months, pts with MPR had improved RFS vs those without MPR, with no relapse observed to date

BRAF, v-raf murine sarcoma viral oncogene homolog B1; INMC, International Neoadjuvant Melanoma Consortium; IPI, ipilimumab; LAG-3, lymphocyte activation gene-3; MPR, major pathologic response; NIVO, nivolumab; OS, overall survival; pCR, pathological complete response; PD-1, programmed cell death protein 1; pPR, partial pathological response; pts, patients; RFS, recurrence-free survival; Tx, treatment.

1. Menzies AM, et al. *Nat Med*. 2021;27:301–9; 2. Amaria R, et al. *J Clin Oncol*. 2021;39(suppl 15):Abstr 9502.

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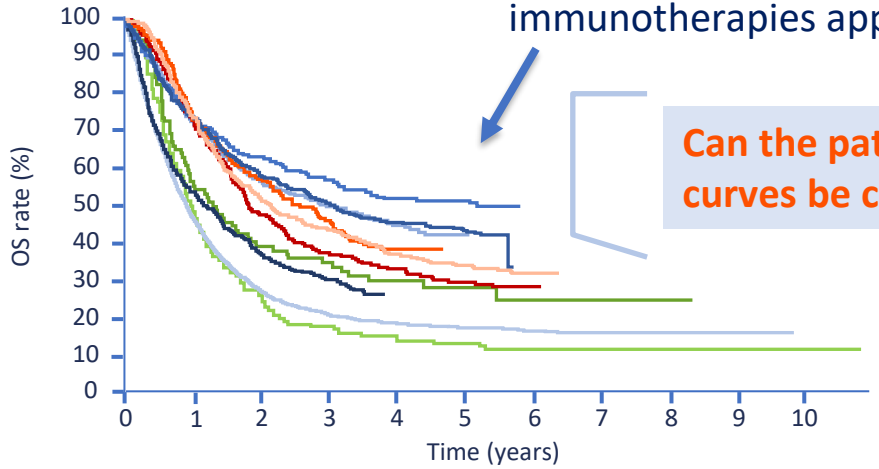
Can long-term control be defined in advanced melanoma?

Long-term control of advanced melanoma

Long-term OS curves for targeted therapies and immunotherapies appear to plateau at 3–4 years



Can the patients represented in the tails of these curves be considered as functionally cured?

Patients diagnosed with advanced melanoma can be considered in long-term remission if they have responded to treatment and have been off treatment for at least 2 years without disease progression

IL2, interleukin-2; OS, overall survival; TIL, tumour infiltrating lymphocyte.

Michielin O, et al. *J Immunother Cancer.* 2020;8:e000948. Figure reproduced with permission.

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Maximizing survival outcomes in melanoma and poor prognosis

Prof. Paolo A Ascierto

National Tumour Institute
"Fondazione G. Pascale" Unit of
Melanoma, Cancer Immunotherapy
and Innovative Therapy, Naples, Italy

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Which patients with metastatic melanoma have the best survival outcomes?

Baseline characteristics of patients with metastatic melanoma may influence response to treatment

Baseline factors associated with longer OS[1,2]

- **No/minimal brain metastasis** (≤3 [size <2 cm])
- **Low tumour burden** (<3 organs involved?)
- **Normal LDH**

Patients present characteristics resulting in **active immune surveillance** against cancer cells

Baseline factors associated with more rapid disease progression[1,2]

- **Multiple brain metastases** (>3)
- **High tumour burden** (>3 organs involved?)
- **High LDH**

Patients present characteristics resulting in **inactive or impaired immune surveillance** against cancer cells

LDH, lactate dehydrogenase, OS, overall survival.

1. Ascierto P and Dummer R. *Oncoimmunology*. 2018;7:e1468955; 2. Michielin O, et al. *J Immunother Cancer*. 2020;8:e000948.

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How important are first-line treatment choices in optimizing survival in patients with melanoma?

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First-line immunotherapy vs targeted therapy in *BRAF*-mutated patients

Should all patients with *BRAF* mutation be treated with first-line targeted therapy or immunotherapy?

Are patients who do not respond to first-line therapy harder to manage?

Real-world study of first-line immunotherapy vs targeted therapy

Nivolumab + ipilimumab vs BRAF + MEK inhibitor

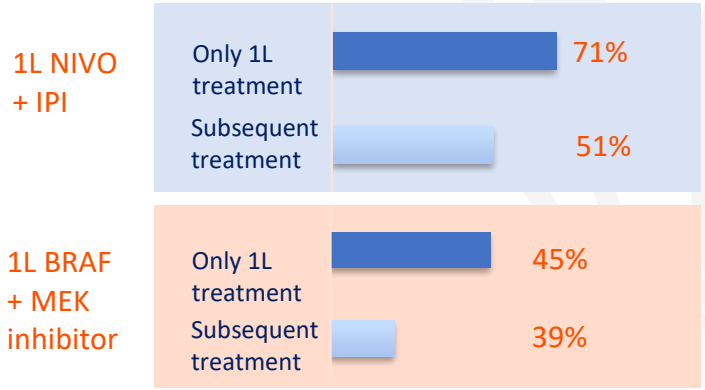
Flatiron Health electronic medical record database

32% lower risk of death with nivolumab + ipilimumab vs BRAF + MEK inhibitor*

At follow-up of 15–16 months:

64% of nivolumab + ipilimumab treated patients were alive vs 43% in BRAF + MEK inhibitor group

Survival rates



*After adjusting for baseline characteristics. 1L, firstline; *BRAF*, B-Raf murine sarcoma viral oncogene homolog B; IPI, ipilumumab; NIVO, nivolumab.

Pavlick A, et al. *Future Oncol.* 2021;17:689–99.

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How do data from clinical trials impact treatment sequencing options for patients with advanced melanoma?

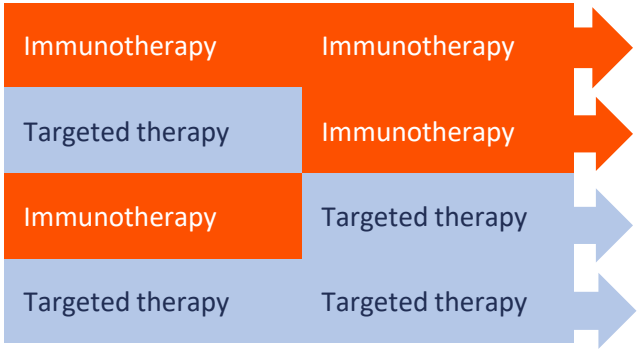
Insights for optimal sequencing of immunotherapy and targeted therapy

ESMO 2021: Retrospective study of sequential immunotherapy and targeted therapy in stage IV melanoma

Stage IV melanoma pts (N=1,046)

396 patients of the entire cohort received at least two lines of systemic therapy

- n=248 pts received treatment in the following sequences:



- n=148 received other combinations of 1L and 2L treatment approaches

Patient group	Median OS (months)	5-year OS (%)
All pts	19	29
Pts receiving ≥2 systemic therapies (n=396)	21	25
IT-IT (n=91)	36	34
TT-IT (n=83)	18	16
IT-TT (n=41)	17	32
TT-TT (n=33)	32	31

p=0.677

p=0.084

No statistically significant difference in OS between the four sequences or the IT-TT and TT-IT sequences

1L, first line; 2L, second line; IT, immunotherapy; OS, overall survival; pts, patients; TT, targeted therapy.

Amaral T, et al. *Ann Oncol.* 2021;32(suppl. 5):S867–905.

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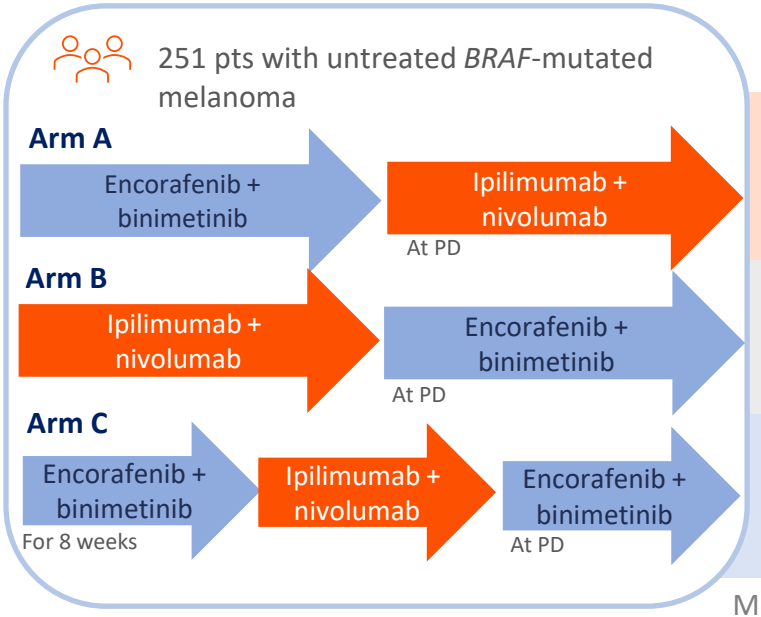
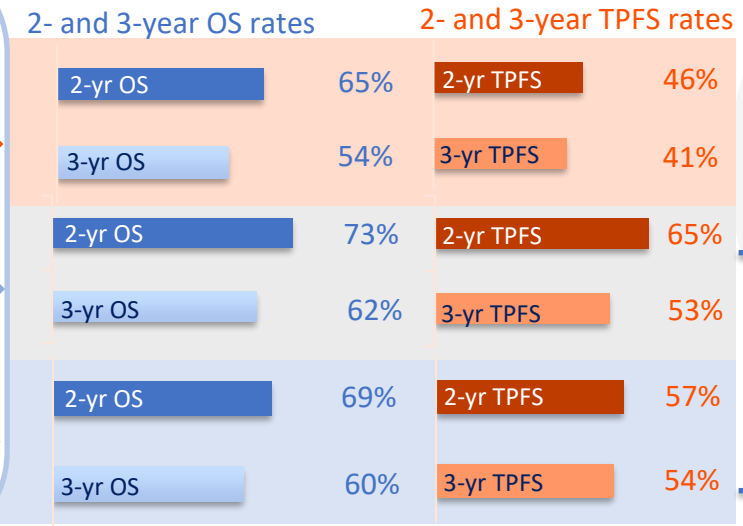
Insights for optimal sequencing of immunotherapy and targeted therapy

ESMO 2021 – SECOMBIT: Sequential Combo Immuno and Target Therapy





Median follow-up: 32.2 months

The primary endpoint was met in each arm: **≥30** pts alive at 2 years

Trend for more **favourable survival rates in arms B and C** vs arm A

BRAF, v-raf murine sarcoma viral oncogene homolog B1; OS, overall survival; pts, patients; PD, progressive disease; TPFS, total progression-free survival; yr, year.

Ascierto P, et al. *Ann Oncol.* 2021;32(suppl. 5):S1283–346.

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Can the use of biomarkers help to predict which patients may benefit from first-line targeted therapy or immunotherapy?

Predictive biomarkers for clinical decision-making

Predictive biomarkers in melanoma[1,2]

Validated

BRAF^{V600} mutation

Emerging

- TMB and neoantigen expression
- Concomitant molecular alterations
- Checkpoint expression: PD-L1, LAG-3
- CD8$^+$ T cells at tumour invasive margin
- IL-6, IL-8 and IL-17 expression
- Immune-related gene expression profile
- TCR profiling

Is PD-L1 a reliable biomarker for targeting PD-1/PD-L1 in melanoma?[3]

Theoretically, high PD-L1 should predict response to anti-PD-1 immunotherapy

However, PD-L1 expression is dynamic and transient with intra-patient and intratumour heterogeneity

PD-L1 status should be combined with other criteria, such as TMB, CD8$^+$, and PD-1 in T cells

Can we stratify according to the IFN-γ signature?[4]

- DOMINI trial stratified pts with stage IIIB–D melanoma according to IFN-γ signature from tumour biopsies (N=40)
- Identify IFN-γ high pts who can benefit from NIVO ± DOM alone vs IFN-γ low pts who might need an alternative Tx

BRAF, B-Raf murine sarcoma viral oncogene homolog B1; CD8, cluster of differentiation 8; DOM, domatinostat; IFN-γ sign, interferon-gamma signature; IL, interleukin; LAG-3, lymphocyte activation gene-3; NIVO, nivolumab; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; TCR, T-cell receptor; TMB, tumour mutational burden; Tx, treatment.

1. Tarhini A, Kudchadkar R. *Cancer Treat Rev.* 2018;71:8–18; 2. Tobin R, et al. *Front Oncol*. 2019;9:1223; 3. Garutti M, et al. *Cancers (Basel).* 2021;13:1819; 4. Blank C, et al. *Ann Oncol.* 2021;32(suppl. 5):S1283–346.

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What is the future of new and emerging combination therapies for improving outcomes in patients with melanoma?

Integrating novel combination therapies into practice

Expanded treatment options in patients with advanced melanoma may have potential for improved OS and durable responses[1,2]

IMspire150: First-line BRAF + MEK + immunotherapy combination[3]

- Randomized, double-blind, phase III study in unresectable stage IIIC–IV, *BRAF*^{V600} mutant melanoma
- Atezolizumab + vemurafenib + cobimetinib (n=255) vs placebo + vemurafenib + cobimetinib (n=258)

At follow-up of 18.9 months:
PFS: 15.1 months vs 10.6 months (HR 0.78; 95% CI 0.63-0.97; p=0.025)

Should novel triple combinations be used in the first-line setting for patients who have a poor prognosis?

RELATIVITY-047 trial: Dual inhibition of the **LAG-3** and **PD-1** pathways with the combination of nivolumab + relatlimab demonstrated a statistically significant PFS benefit vs nivolumab monotherapy[4]

BRAF, v-raf murine sarcoma viral oncogene homolog B1; CI, confidence interval; HR, hazard ratio; LAG-3, lymphocyte activation gene-3; PD-1, programmed cell death protein-1; PFS, progression-free survival.

1. Michielin O, et al. *J Immunother Cancer.* 2020;8:e000948. doi:10.1136/ jitc-2020-000948; 2. FDA approvals. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-braf-v600-unresectable-or-metastatic-melanoma (accessed July 2021); 3. Gutzmer R, et al. *Lancet*. 2020;395:1835–44;
4. Lipson EJ, et al. *J Clin Oncol.* 2021;(Suppl. 15):9503.

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Evolving treatment options and future directions for melanoma

Dr Allison Betof Warner

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New York, USA

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How is the treatment landscape evolving in melanoma?

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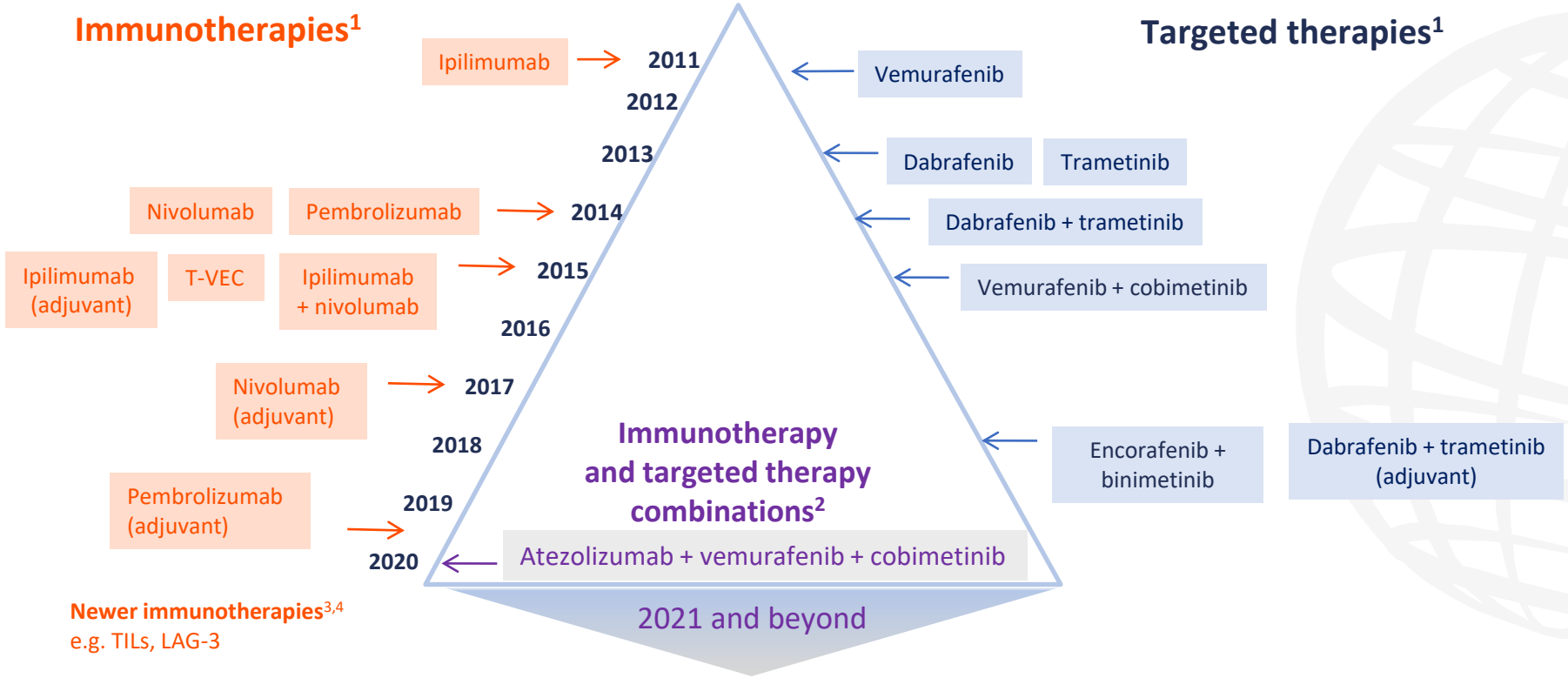
The treatment landscape in melanoma



LAG-3, lymphocyte activation gene 3; T-VEC, talimogene laherparepvec; TIL; tumour-infiltrating lymphocyte.

1. Michielin O, et al. *J Immunother Cancer.* 2020;8:e000948; 2. FDA approvals. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-braf-v600-unresectable-or-metastatic-melanoma (accessed July 2021); 3. Nuyen K, et al. *Dermatol Online J.* 2020;26:13030/qt24g3k7z5; 4. Lipson EJ, et al. *J Clin Oncol.* 2021;39(Suppl.15):Abstr 9503.

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What other triplet combination therapies are being evaluated in unresectable or metastatic melanoma?

Investigational triplet combination therapies for unresectable or metastatic melanoma

KEYNOTE-022 phase II trial[1]
Post-hoc analysis at 36.6 mos of follow-up
Pembrolizumab + dabrafenib + trametinib
in *BRAF*-mutant melanoma

N=120

- Median PFS: **16.9** mos vs doublet* (10.7 mos)
- Median OS: NR vs doublet (26.3 mos)
- Grade 3–5 TRAEs: **58%** vs doublet (25%)

TRIDeNT phase II single centre trial[2]
Nivolumab + dabrafenib + trametinib
in *BRAF*-mutant melanoma +/- BM

N=24

- ORR: **89%** in 19 evaluable patients
- 15 PR and 2 CR
- 6/24 patients discontinued due to toxicities

COMBI-I trial, phase III trial (part 3)[3]
Median follow-up 27.2 mos
Spartalizumab + dabrafenib + trametinib
in *BRAF*-mutant melanoma

N=532

- Primary endpoint (PFS vs doublet) not met
- Analyses of OS benefit ongoing
- Median PFS: **16.2** mos vs doublet* (12.0 mos)
- TRAEs grade ≥3: **55%** vs placebo (33%)

*Doublet therapy=placebo, dabrafenib + trametinib.
BM, brain metastases; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CR, complete response; mos, months; NR, not reached; OS, overall survival; PFS, progression-free survival; PR, partial response; ORR, overall response rate; TRAE, treatment-related adverse event.
1. Ferucci P, et al. *J Immunother Cancer.* 2020;8:e001806; 2. Burton E, at al. *Ann Oncol.* 2019;30(Suppl. 5):v533–63; 3. Nathan P, et al. *Ann Oncol.* 2020;31(Suppl. 4):S1172.

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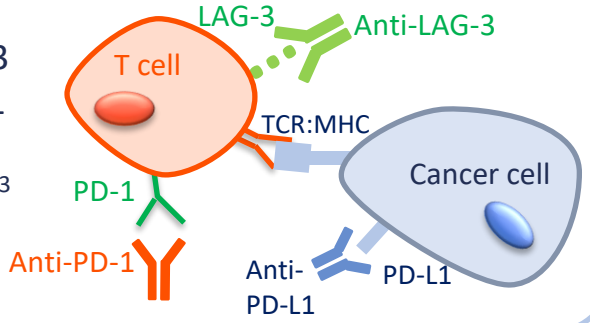
What is the most promising immune checkpoint inhibitor other than CTLA-4 and PD-1 in metastatic melanoma?

Targeting the LAG-3 immune checkpoint

Rationale

- LAG-3 inhibits T-cell activity, and is upregulated in melanoma[1]
- Relatlimab is a human IgG4 antibody that blocks LAG-3 and restores effector function of exhausted T cells[1]

Targeting LAG-3 along with PD-1 facilitates T-cell reinvigoration[2,3]



Evidence: Dual inhibition of LAG-3 + PD-1

RELATIVITY-047 phase II/III trial[1]

Relatlimab + nivolumab FDC (n=355) vs nivolumab (n=359) in first-line advanced melanoma

- Median **PFS: 10.1** mos vs nivolumab (4.6 months, HR 0.75; p=0.0055)
- PFS2*: Not reached vs nivolumab (20 months, HR 0.77)[4]
- TRAEs grade 3/4: **18.9%** vs nivolumab (9.7%)
- Treatment discontinuation: 14.6% vs 6.7%

Neoadjuvant and adjuvant nivolumab + relatlimab in pts with resectable clinical stage III melanoma[5]

- 29 pts underwent treatment followed by surgical assessment of pathologic response
- **pCR: 59% and MPR: 66%**

*PFS2 defined as the time from randomization to progression on subsequent therapy or death per investigator assessment.

FDC, fixed-dose combination; HR, hazard ratio; IgG4, immunoglobulin G4; LAG- 3, lymphocyte activation gene-3; MHC, major histocompatibility complex; MPR, major pathologic response; pts, patients; pCR, pathological complete response; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; TCR, T-cell receptor; TRAE, treatment-related adverse event.

1. Lipson E, et al. Presented at: 2021 ASCO Annual Meeting. June 6, 2021. Abstr 9503; 2. Ruffo E, et al. *Semin Immunol.* 2019;42:101305; 3. Long L, et al. *Genes Cancer.* 2018;9:176–89; 4. Hodi, F et al. *Ann Oncol.* 2021;32(Suppl. 5):S867–905; 5. Amaria R, et al. *J Clin Oncol.* 2021;39(Suppl. 15);Abstr 9502. Figure adapted from: Long L, et al. *Genes Cancer.* 2018;9:176–89.

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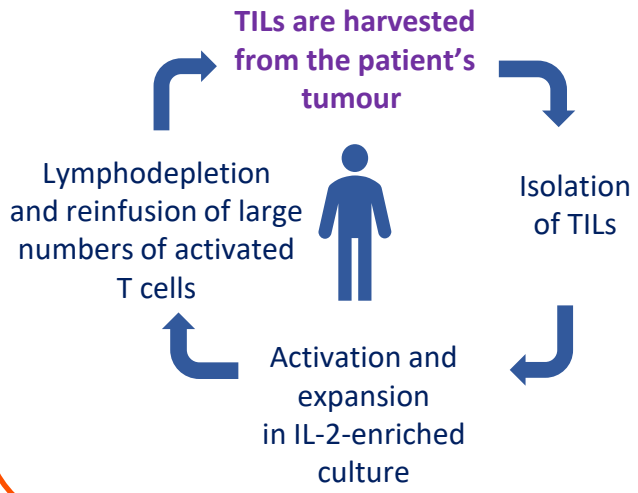
What is the rationale and evidence for TIL therapy in metastatic melanoma?

Advancing TIL therapy in metastatic melanoma

- TILs recognize antigens specific to the individual patient's tumour[1]
- TILs produce durable responses in pre-treated metastatic melanoma[2]

Production of TIL therapy[1]



Challenges of TIL treatment[1]

- Requires dedicated laboratory facilities to expand T cells
- Long production time (patients may progress and became ineligible for treatment)
- IL-2-associated toxicity

IL-2, interleukin-2; TIL, tumour-infiltrating lymphocyte.

1. Rohaan M, et al. *J Immunother Cancer*. 2018;6:102; 2. van den Berg J, et al. *J. Immunother Cancer.* 2020;8:e000848.

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Evidence for TIL therapy in metastatic melanoma

In a 2019 systematic review and meta-analysis for TILs in pre-treated metastatic melanoma, the estimated ORR was **41%** and CRR was **12%**[1]

Phase II trial of lifileucel (LN-144) in pre-treated metastatic melanoma (cohort 2)[2]

- **66 pts** received TIL infusion
- TIL production time: **22 days**
- Mean prior therapies: **3.3**
- Median follow-up: **18.7 months**

- ORR: **36%**
- DCR: **80%**
- DOR: **NR**
- mOS: **17.4 months**

In subgroup of pts refractory to anti-PD-1/PD-L1 therapy (n=42)
ORR: **41%**
DCR: **81%**

Retrospective analysis of TILs for compassionate use treatment of metastatic melanoma[3]

21 pts received TIL infusion and IL-2

- Mean prior therapies: **3**
- Median follow-up: **52.2 months**
- Imaging-evaluable patients: n=15

- ORR: **53%**
- CRR: **13%**
- DCR: **73%**
- mOS: **21.3 months**

In subgroup of pts refractory to anti-PD-1 therapy (n=12)[4]
ORR: **58%**, CRR: **8%**
mOS: **21.3 months**

Study to determine cut-off for %TILs as a prognostic factor in early-stage melanoma (N=361):

- Pts with stage I/II melanoma with high %TILs had significantly improved RFS compared to pts with low %TILs[5]

%TILS, percentage of TILs; CRR, complete response rate; DCR, disease control rate; DOR, duration of response; IL-2, interleukin-2; NR, not reached; ORR, overall response rate; mOS, median overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; pts, patients; RFS, relapse-free survival; TIL, tumour-infiltrating lymphocyte.

1. Dafni U, et al. *Ann Oncol.* 2019;30:1902–13; 2. Sarnaik A, et al. *J Clin Oncol.* 2021;39:2656–66; 3. Hawkins R, et al. Presented at: AACR 2021. April 10, 2021. Abstr LB150; 4. Pillai M, et al. *Ann Oncol.* 2021;32(Suppl. 5):S867–905 Abstr 1058P; 5. Chatziioannou E, at al. *Ann Oncol.* 2021;32(Suppl. 5):S867–905 Abstr 1055P.

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What data from ESMO 2021 on predictive/prognostic biomarkers is of interest for melanoma?

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TMB as a biomarker for response to immunotherapy in patients with melanoma

- TMB represents the number of mutations per megabase (mut/Mb) of DNA present in a tumour specimen[1]
- Melanoma is associated with a high TMB (median 13.5 mut/Mb)[2]
- TMB is shown to correlate with ICI clinical benefit[3]
- TMB can be measured using comprehensive genomic profiling[2]

ESMO 2021: TMB assessment using NGS for prediction of response to immunotherapy in metastatic melanoma[4]

Pts with cutaneous melanoma treated with immunotherapy with radiographic or metabolic **CR** ≥6 months **AND** pts with **EP*** had immunotherapy-naïve tissue sequenced with the TSO 500

- 18 EP samples and 34 CR tumours sequenced
- 31/34 CRs ongoing
- **50%** of EP and **56%** of pts with CR had anti-PD-1 monotherapy (remainder had combination therapy)

TMB correlated strongly with CR ($p<0.001$) with a median TMB of 13.3 (EP) vs 53.2 (CR)

TMB as a continuous variable correlated strongly with CR (OR of 1.03 for every 1 mut/Mb TMB increase) ($p=0.014$)

*confirmed disease progression within 6 months, including stage III patients on adjuvant immunotherapy.

CR, complete response; DNA, deoxyribonucleic acid; EP, early progression; ICI immune checkpoint inhibitor; NGS, next generation sequencing; OR, odds ratio; PD-1, programmed cell death protein 1; pts, patients; TMB, tumour mutational burden; TSO, TrueSight Oncology.

1. Addeo A, et al. *Crit Rev Oncol Hematol.* 2021;163:103374; 2. Chalmers Z, et al. *Genome Med.* 2017;9:34; 3. Krieger T, et al. *Diagn Pathol.* 2020;15:6–16; 4. Humphries T, et al. *Ann Oncol.* 2021;32(Suppl. 5):S867–905.Abstr 1053P.

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