A patient's journey through the immuno-oncology treatment landscape in melanoma

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Optimizing PD-1 blockade in melanoma: factors associated with patient selection

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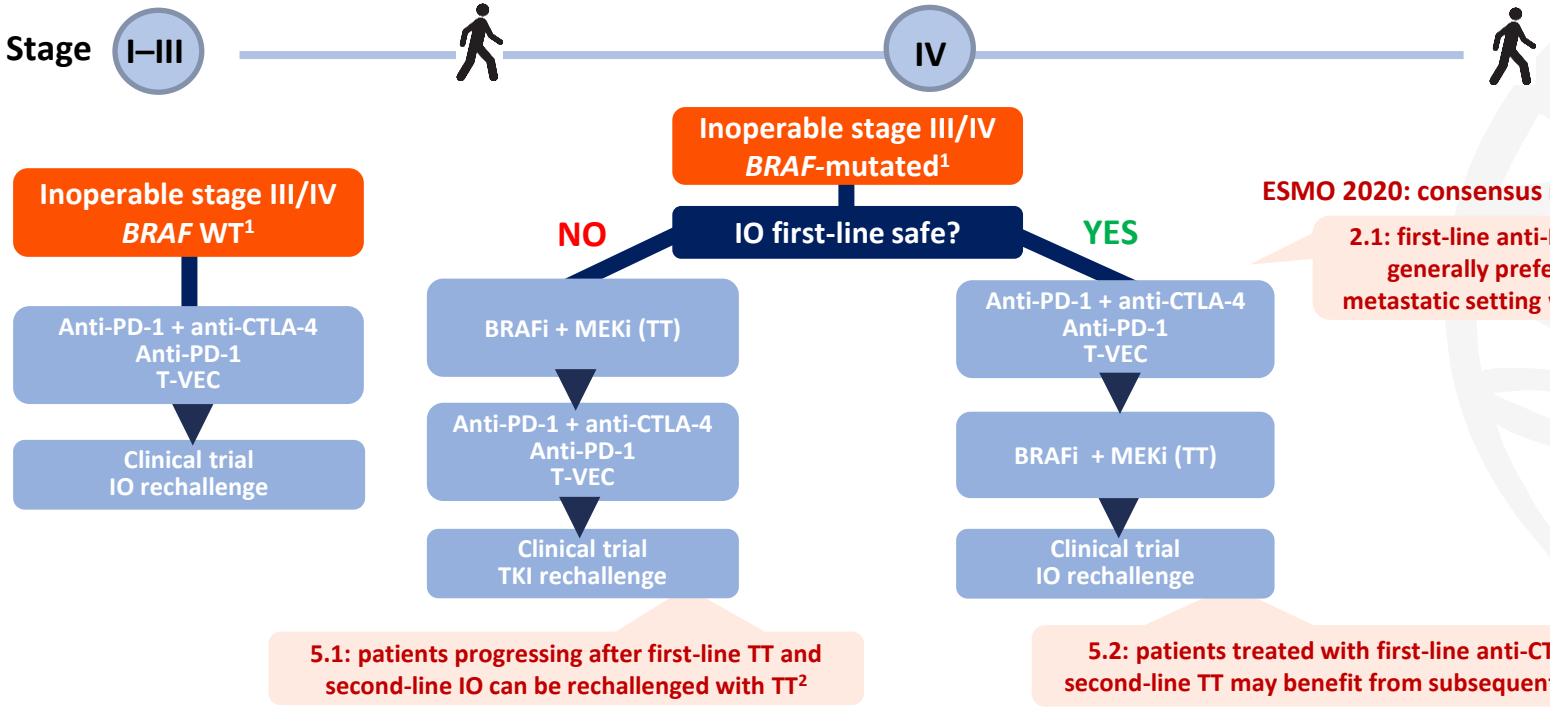
Tailored treatment decisions in melanoma: A definitive road map for patients?



BRAF, B-Raf proto-oncogene; BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; ESMO, European Society for MEdical Oncology; IO, immuno-oncology; LDH, lactate dehydrogenase; MEKi, mitogen-activated protein kinase kinase inhibitor; PD-1, programmed cell death protein-1; TKI, tyrosine kinase inhibitor; TT, targeted therapy; T-VEC, talimogene laherparepvec; WT, wild-type.

1. Michielin O, et al. *Ann Oncol.* 2019;30:1884–901; 2. Keilholz U, et al. *Ann Oncol.* 2020;S0923-7534-20-39939-7.

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PD-L1: An imperfect but relevant biomarker?

Questions surrounding predictive value and clinical utility of PD-L1 in melanoma remain[1]

Limited predictive value?

IMspire-150[2]

Clinical benefit derived from first-line ATEZO+COB+VEM comparable between PD-L1-positive (≥1%) and PD-L1-negative (<1%) tumours

CheckMate-067[3]

Consistent with previous results, tumour PD-L1 expression alone (<5% vs. ≥5% thresholds) was not predictive of efficacy outcomes

Meta-analysis[4]

High PD-L1 expression did not correlate with OS (HR 0.93, 95% CI 0.57–1.52, p=0.781) or PFS (HR 0.82, 95% CI 0.43–1.54, p=0.535) benefit

Predicts response and outcomes?

CheckMate-238[5]

Higher PD-L1 status (≥1% vs. <1% and ≥5% vs. <5%) associated with higher 4-year RFS in patients receiving either adjuvant IPI or NIVO

Exploratory study[6]

Elevated PD-1 and PD-L1 serum concentrations at therapy baseline correlated with impaired BOR, PFS and OS in patients receiving PD-1 blockade, but not in patients treated with BRAFi

Meta-analysis[4]

PD-L1 overexpression correlated with absence of lymph node metastases (OR 0.46, 95% CI 0.22–0.95, p=0.036)

ATEZO, atezolizumab; BOR, best overall response; *BRAF*, B-Raf proto-oncogene; BRAFi, BRAF inhibitor; CI, confidence interval; COB, cobimetinib; IPI, ipilimumab; LDH, lactate dehydrogenase; NIVO, nivolumab; OR, odds ratio; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; RFS, recurrence-free survival; VEM, vemurafenib.

1. Michielin O, et al. *Ann Oncol.* 2019;30:1884–901; 2. Ascierto PA, et al. *Ann Oncol.* 2020;31:S672–S710; 3. Larkin J, et al. *N Engl J Med.* 2019;381:1535–46; 4. Yang J, et al. *Cancer Cell Int.* 2020;20:96; 5. Ascierto PA, et al. *Lancet Oncol.* 2020;20:1239–51; 6. Ugurel S, et al. *Ann Oncol.* 2020;31:144–53.

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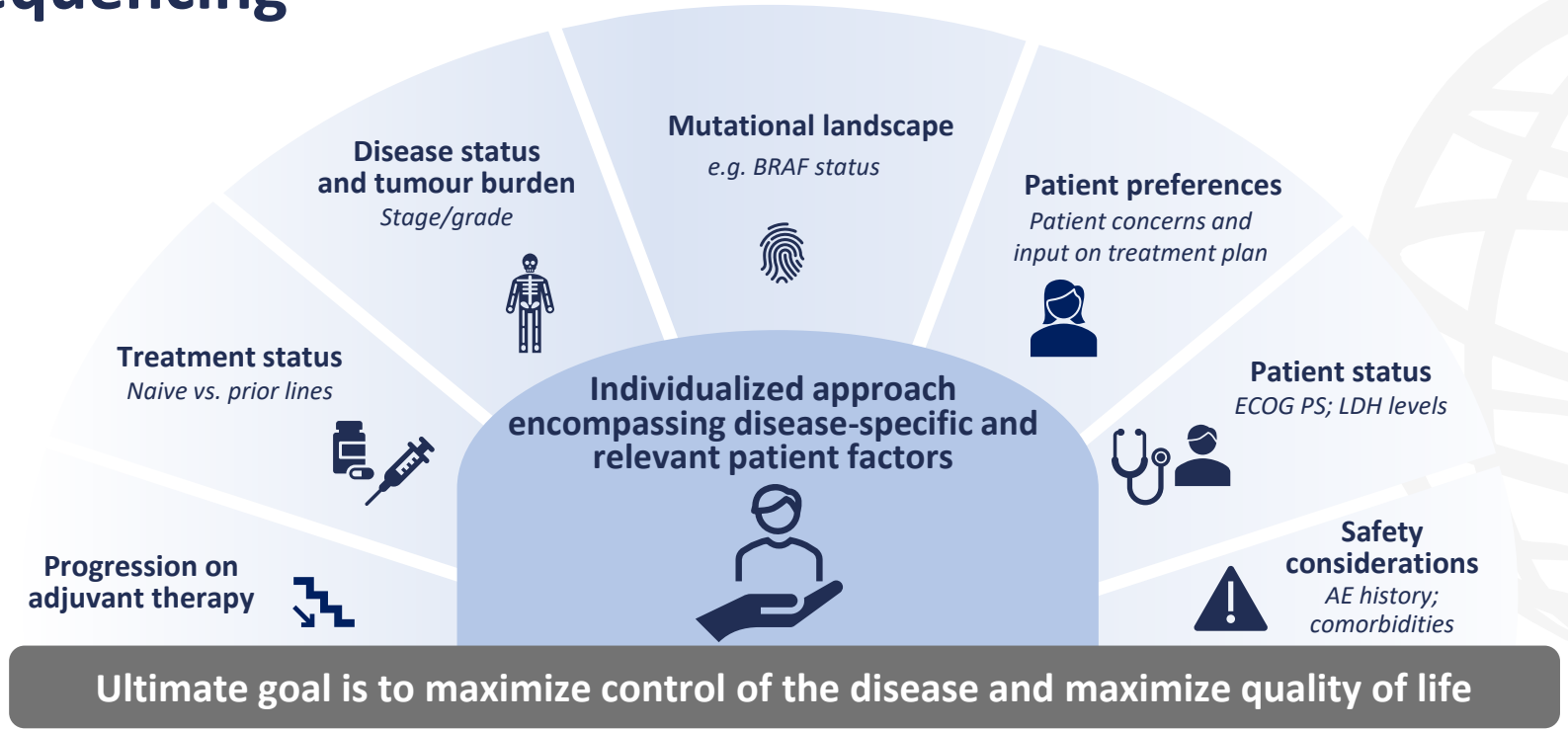
Multiple factors guide treatment selection and sequencing[1,2]



AE, adverse event; *BRAF*, B-Raf proto-oncogene; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

1. Michielin O, et al. *Ann Oncol.* 2019;30:1884–901; 2. Keilholz U, et al. *Ann Oncol.* 2020;S0923-7534-20-39939-7.

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PD-1 blockade: Safety considerations

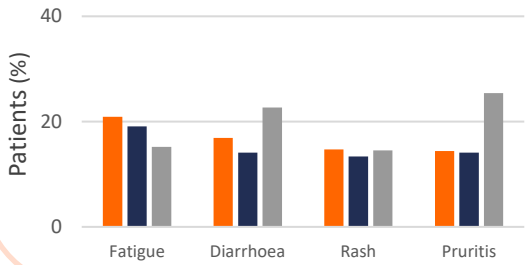
KEYNOTE-006[1]

Advanced melanoma
(incl. *BRAF*-mutant melanoma)

PEMBRO 10 mg/kg **Q2W** *or* **Q3W**
IPI 3 mg/kg Q3W

TRAEs (≥ Grade 3) :
PEMBRO Q2W: 13.3
PEMBRO Q3W: 10.1%
IPI: 19.9%

Most frequent TRAEs (any grade)



CheckMate-067[2]

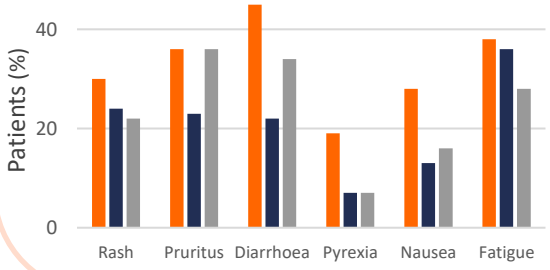
Treatment-naive *BRAF*-WT melanoma

NIVO 1mg/kg + **IPI** 3mg/kg Q3W x 4 doses followed by
NIVO 3mg/kg Q2W + **IPI-matched placebo** OR
IPI 3mg/kg Q3W x 4 doses + **NIVO-matched placebo**

TRAEs (any grade) leading to discontinuation:
NIVO + IPI: 42%
NIVO: 13%
IPI: 15%

Most frequent TRAEs (any grade)

NIVO + IPI, N=313 NIVO, N=313 IPI, N=311



COMBI-i[3]

Advanced *BRAF*-mutant melanoma

Triplet arm: SPART + DAB + TRA
Doublet arm: DAB + TRA + PLACEBO

Any TRAE	Grade ≥3 TRAEs	Discontinuation*
98.5%	54.7%	31.8%
87.5%	33.3%	14.4%

IMspire-150[4]

Advanced or metastatic *BRAF*-mutant melanoma

Triplet arm: ATEZO + VEM + COB
Doublet arm: VEM + COB + PLACEBO

Any TRAE	Grade ≥3 TRAEs	Discontinuation*
99%	79%	13%
99%	73%	16%

*Any grade TRAE leading to discontinuation ≥1 study drug. AE, adverse event; ATEZO, atezolizumab; *BRAF*, B-Raf proto-oncogene; COB, cobimetinib; DAB, dabrafenib; IPI, ipilimumab; NIVO, nivolumab; PEMBRO, pembrolizumab; Q2/3/4W, every 2/3/4 weeks; SPART, spartalizumab; TRA, trametinib; TRAE, treatment-related AE; VEM, vemurafenib.

1. Robert C, et al. *N Engl J Med.* 2015;372:2521–32; 2. Larkin J, et al. *New Engl J Med.* 2019;381:1535–46 (and Supplementary Appendix); 3. Nathan P, et al. *Ann Oncol.* 2020;31:S1172; 4. Gutzmer R, et al. *Lancet.* 2020;395:1835–44.

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Emerging biomarkers show promise but need validation

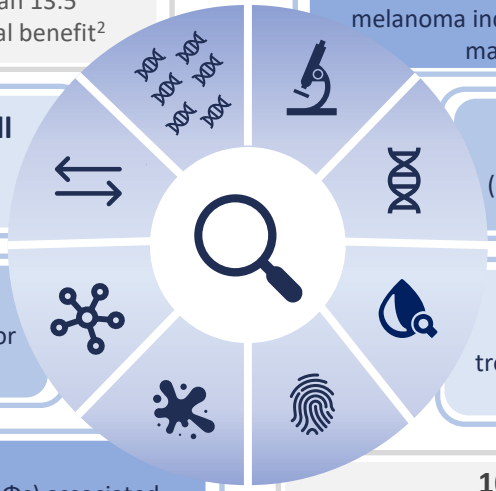
Will a composite biomarker 'fingerprint' fulfil the requirements of a clinical grade test in future?

TMB
Melanoma associated with high TMB (median 13.5 mut/Mb)[1] shown to correlate with ICI clinical benefit[2]

Spatial co-proximity: CD8+T/tumour cell
Independent biomarker of response to PD-1 blockade but requires further validation[3]

Collagen type III
High formation and cross-linking associated with poor OS and PFS in patients with metastatic melanoma[4]

VICM
Elevated VICM (secreted by activated M1 MΦs) associated with improved TTP and OS in patients with melanoma receiving therapeutic PD-1 blockade[5]



PR
OpACIN 4-year survival data in patients with stage IIIB–C melanoma indicate PR following neoadjuvant IPI+NIVO may predict long-term outcomes[6]

POLE mutations
POLE and concomitant oncogenic co-mutations (including *BRAF* and *CDKN2A*) potential predictive marker associated with ICI clinical benefit[7]

LDH
Elevated baseline LDH associated with greater treatment benefit with ATEZO+VEM+COB in PD-L1-negative *BRAF*-mutant melanoma[8]

10-protein biomarker signature
Undergoing validation in a large prospective cohort study PROPHETIC study (NCT04056247)[9]

ATEZO, atezolizumab; *BRAF*, B-Raf proto-oncogene; *CDKN2A*, cyclin-dependent kinase inhibitor-2A; COB, cobimetinib; ICI, immune checkpoint inhibitor; IPI, ipilumab; LDH, lactate dehydrogenase; MΦs, macrophages; mut/Mb, mutations per megabase; NIVO, nivolumab; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; *POLE*, DNA polymerase-ε; PR, pathologic response; TMB, tumour mutational burden; TTP, time-to-progression; VEM, vemurafenib; VICM, citrullinated and matrix metalloproteinase-degraded vimentin.

1. Chalmers ZR, et al. *Genome Med.* 2017;9:34; 2. Krieger T, et al. *Diagn Pathol.* 2020;15:6–16; 3. Slagter M, et al. *J Clin Oncol.* 2020;38:10038; 4. Jensen C, et al. *J Clin Oncol.* 2020;38:S3049; 5. Jensen C, et al. *Ann Oncol.* 2020;31:S281; 6. Versluis JM, et al. *Ann Oncol.* 2020;31:S672–S710; 7. Garmezy B, et al. *J Clin Oncol.* 2020;38:3008; 8. Ascierto PA, et al. *Ann Oncol.* 2020;31:S672–S710 Abstract 1102P; 9. Shaked Y, et al. *J Clin Oncol.* 2020;38:10037.

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