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

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Maximizing therapeutic potential of PD-1 blockade in combination treatment regimens

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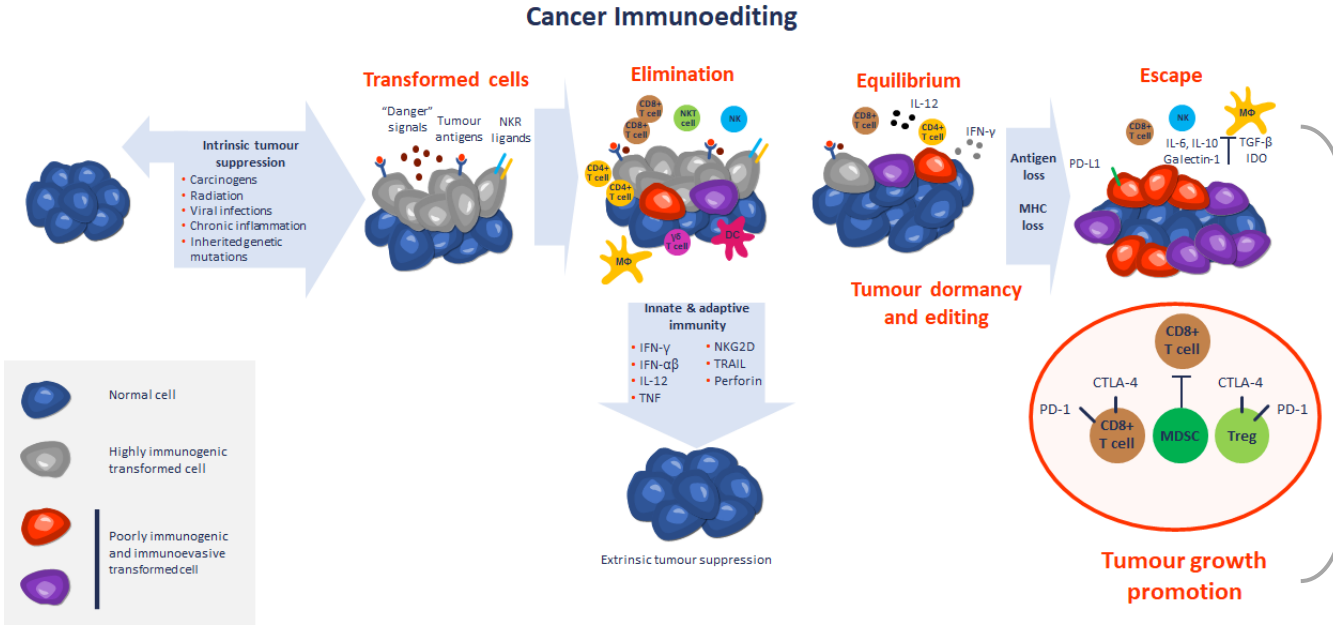
Targeting immunoediting: A basis for treatment

The ultimate goal is to restore T cell anti-tumour immunity in melanoma using ICI-based therapies



- **CTLA-4 blockade** restore T cell priming and activation
- **PD-1/PD-L1 blockade** abrogate PD-L1-mediated T cell inhibition

activating *vs.* **inhibitory**

CTLA-4, cytotoxic T lymphocyte-associated antigen-4; DC, dendritic cell; γδT, gammadelta T cell; ICI, immune checkpoint inhibitor; IDO, indoleamine-pyrrole 2,3-dioxygenase; IFN-, interferon-; IL-, interleukin-; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MΦ, macrophage; NK, natural killer cell; NKG2D, natural killer group 2, member D; NKR, NK receptor; NKT, natural killer T cell; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; TGF-β, transforming growth factor-beta; TNF, tumour necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand.

Image produced with permission from Schreiber RD, et al. *Science.* 2011;331:1565–70.

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KEYNOTE-006: Impact of first-line ICI on OS and PFS

Open-label, multicentre, RCT, phase III study in ipilimumab-naive patients with advanced melanoma

First-line ICI associated with improved OS and PFS in KEYNOTE-006 subgroup analysis

	Total study cohort		First-line ICI cohort	
	OS†, months	PFS†, months	OS†, months	PFS†, months
Combined PEMBRO Q2W or Q3W n=556	32.7	8.4	38.7	11.6
IPI Q3W n=278	15.9	3.4	17.1	3.7
	HR 0.73 95% CI 0.61–0.88 p=0.00049	HR 0.57 95% CI 0.48–0.67 p<0.0001	HR 0.73 95% CI 0.57–0.92 p=0.0036	HR 0.54 95% CI 0.44–0.67 p<0.0001

† OS and PFS median values shown. CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; IPI, ipilimumab; PFS, progression-free survival; OS, overall survival; PEMBRO, pembrolizumab; Q2/3W, every 2/3/ weeks; RCT, randomized controlled trial.

Robert C, et al. *Lancet Oncol.* 2019;20:1239–51.

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Combination ICI + TT: Learnings from COMBI-i

Combined PD-1, BRAF and MEK inhibition in advanced *BRAF*-mutant melanoma

Phase I outcomes[1]

Safety run-in cohort: SPART+DAB+TRA

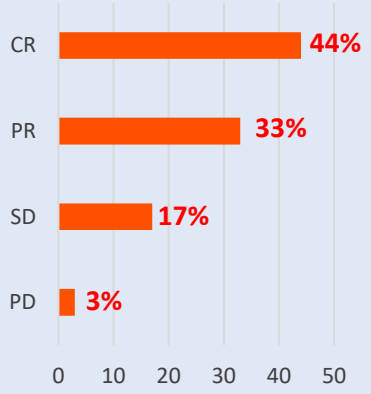
OS†, months	PFS†, months
NE	23
95% CI NE–NE	95% CI 12–NE

Survival rates	at 1 year	at 2 years
PFS, %	67	41
OS, %	86	74

Best overall response

N=36

Confirmed ORR (CR+PR) 78%; 95% CI 61–90



Phase III study did not meet primary endpoint (PFS)[2]

	OS†, months	PFS†, months
SPART + DAB+TRA	NR	16.2
Placebo+ DAB+TRA	NR	12.0
	HR 0.79 (95% CI 0.59–1.05)	HR 0.82 (95% CI 0.65–0.03, p=0.42)

Further OS follow-up may provide additional insights

† OS and PFS median values shown. *BRAF*, B-Raf proto-oncogene; CI, confidence interval; CR, complete response; DAB, dabrafenib; HR, hazard ratio; ICI, immune checkpoint inhibitor; MEK, mitogen-activated Protein kinase kinase; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q4W, every 4 weeks; SD, stable disease; SPART, spartalizumab; TRA, trametinib; TT, targeted therapy.

1. Dummer R, et al. *Nat Med.* 2020;26:1557–63; 2. Nathan P, et al. *Ann Oncol.* 2020;31:S1172.

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Combination ICI + TT: Learnings from KEYNOTE-022

Randomized phase II trial in patients with treatment-naive *BRAF*-mutant, advanced melanoma

Combination TT/ICI therapy conferred numerically longer PFS and DoR than TT alone

Patients achieving objective response

	Objective response	Median DoR
PEMBRO+DAB+TRA N=60	63.3%	18.7 months (95% CI 10.1–22.1)
DAB+TRA+PLACEBO N=60	71.7%	12.5 months (95% CI 6.0–14.1)

Survival data

	OS†	PFS†
PEMBRO+DAB+TRA N=60	NR	16.0
DAB+TRA+PLACEBO N=60	23.4	10.3
	HR 0.76 (95% CI 0.41–1.39 p=0.185)	HR 0.66 (95% CI 0.40–1.07 p=0.043)

† OS and PFS median values shown; CI, confidence interval; DAB, dabrafenib; DoR, duration of response; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; TRA, trametinib; TT, targeted therapy.

Ascierto PA, et al. *Nat Med.* 2019;25:941–6.

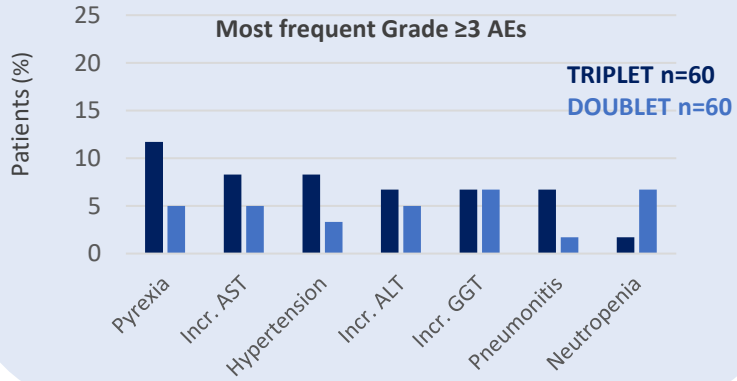
Combination ICI + TT: Emerging safety profiles

KEYNOTE-022[1]

TRIPLET: PEMBRO Q3W + DAB+TRA
DOUBLET: PLACEBO Q3W + DAB+TRA

Median treatment exposure:
9.6 months

TRAEs leading to treatment discontinuation:
TRIPLET – 41.7%
DOUBLET – 21.7%

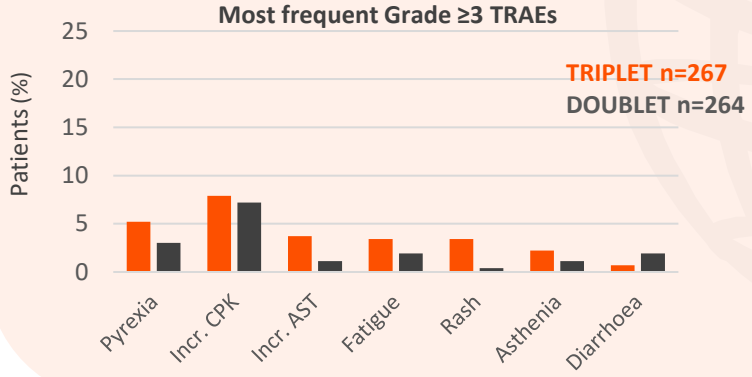


COMBI-i (phase III)[2]

TRIPLET: SPART Q4W + DAB+TRA
DOUBLET: Placebo Q4W + DAB+TRA

Median follow-up:
27.2 months

TRAEs (any grade) leading to discontinuation of ≥1 study drug:
TRIPLET – 31.8%
DOUBLET – 14.4%



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CPK, creatine phosphokinase; DAB, dabrafenib; HR, hazard ratio; ICI, immune checkpoint inhibitor; Incr., increased; Q3/4W, every 3/4 weeks; SPART, spartalizumab; TRA, trametinib; TRAE, treatment-related AE.

1. Ascierto PA, et al. *Nat Med.* 2019;25:941–6; 2. Nathan P, et al. *Ann Oncol.* 2020;31:S1172.

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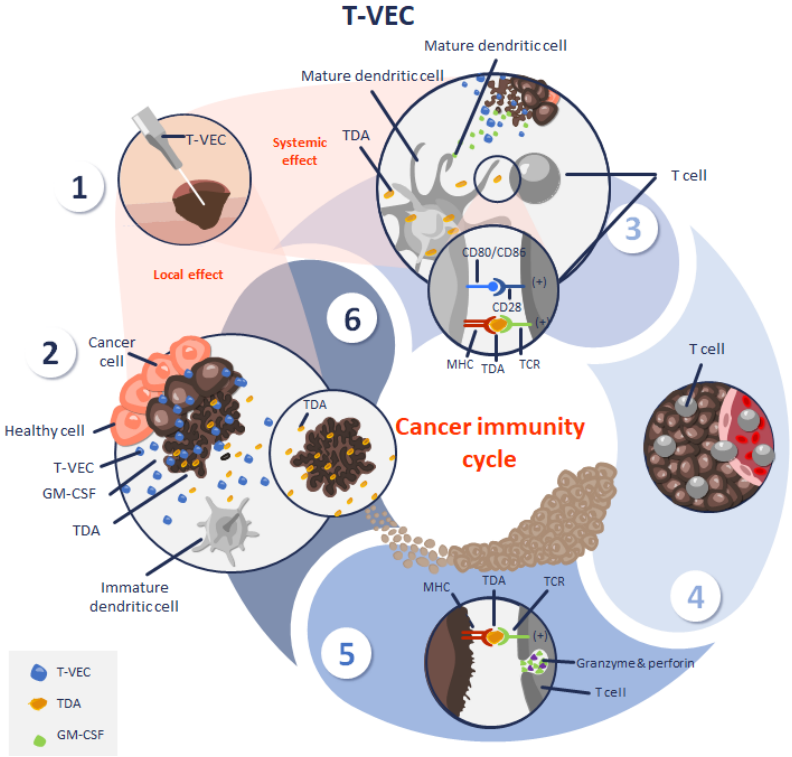
Emerging strategies in melanoma: ICI + oncolytic viruses



T-VEC

KEYNOTE-034[1]

Phase III trial in unresected melanoma
T-VEC in combination with PEMBRO

MASTERKEY-115[2]

Phase II trial in unresected melanoma
T-VEC + PEMBRO following progression on prior PD-1 blockade

NCT01740297[3,4]

Phase II trial in unresectable stage IIIB–IV melanoma
T-VEC in combination with IPI

Image produced with permission from: Harrington KJ, et al. *Expert Rev Anticancer Ther.* 2015;5:1389–403.
GM-CSF, granulocyte macrophage colony stimulationg factor; ICI, immune checkpoint inhibitor; IPI, ipilimumab; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PEMBRO, pembrolizumab; T cell receptor; TDA, tumour-derived antigens; T-VEC, talimogene laherparepvec. 1. NCT02263508; 2. NCT04068181; 3. NCT01740297 (Clinical Trials available at https://clinicaltrials.gov/ Accessed October 2020); 4. Chesney J, et al. *J Clin Oncol.* 2018;36:1658–67.

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Finding a path to optimized treatment in melanoma

Impact of anti-PD-1 therapy on treatment journey by stage

Neoadjuvant approaches incorporating PD-1 blockade prior to resection are anticipated to play a major role in the future management of early-stage disease

PD-1 blockade now well-established in treatment of stage III–IV melanoma

Good tolerability of PD-1 blockade in stage IV melanoma has led to the development of combination treatment strategies for use in subsequent lines of therapy

ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein-1; TT, targeted therapy.
Dummer R. Personal communication, Nov 2020.

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