# Management of metastatic melanoma with new immunotherapy approaches beyond PD-1/CTLA-4 inhibitors

*Alix Devaux and Jean-Francois Baurain*

**Purpose of review**
If we may cure metastatic melanoma patients thanks *to* immune checkpoint inhibitors (ICI), it is fair to say that around 2/3 of the patients present primary or secondary resistance to ICI. Therefore, progresses are needed and numerous new treatments are tested either alone or in combination with cytolytic T-lymphocyte-associated protein 4 (CTLA-4) or (PD)-1 blockade to overcome this resistance. In this review, we focused on new immunotherapeutic approaches studied in advanced melanoma previously treated by anti-PD-1 (Programmed cell Death 1 receptor) or anti-CTLA-4 antibodies.

**Recent findings**
The different approaches have been classified based on 'the cancer immunity cycle'. These new strategies target either the T-cell priming and activation step, T-cell trafficking and tumor infiltration, or tumor antigen recognition by T-cell and tumor killing.

**Summary**
Most of these novel strategies are based on mAbs targeting T-cell inhibitory or stimulatory coreceptors. The second main focus is based on modifying the tumor micro-environment. Combination strategies seem promising in few patients and suggest that a deeper understanding of the resistance in individual patients is mandatory to go further.

**Keywords**
immune checkpoint inhibitors, immune resistance, immunotherapy, metastatic melanoma, tumor micro-environment

## INTRODUCTION

In the past decade, immunotherapy with immunostimulatory antibodies called immune checkpoint inhibitors (ICI) has drastically changed the prognosis of advanced melanoma, increasing median overall survival (OS) from 6 to 35 months [1]. Ipilimumab, an anti-cytolytic t-lymphocyte-associated protein 4 (CTLA-4) mAb, was the first ICI FDA approved, in 2011 [2]. Pembrolizumab, an anti-programmed cell death 1 receptor (PD-1) mAb was approved in 2014 with a greater benefit in OS and less toxicities than Ipilimumab [3]. In Checkmate-067, Ipilimumab was compared with Nivolumab or Nivolumab + Ipilimumab. At the 6.5 years median follow-up landmark analysis this trial confirms the superiority of anti-PD1 over anti-CTLA-4 in terms of response and OS [4▪]. The median OS of the combination reached an impressive 72 months. However, despite this evidence of long-lasting responses, around two third of the patients either do not respond (primary resistance, around 40%) or exhibit progression on or after ckeckpoint blockade discontinuation (acquired resistance, around 25%) [5].

The mechanisms of primary and acquired resistance are multiple and not yet fully understood, as reviewed in detail elsewhere [6]. Many other modalities of immunotherapy have been combined with CTLA-4 or PD-1 blockade to overcome resistance, we can classify them based on which step in the so-called cancer immunity cycle (Fig. 1). Briefly, we can divide this cycle in three steps: T-cell priming and activation, T-cell trafficking and tumor infiltration and tumor recognition and killing. For each step, we

Medical Oncology Department, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Bruxelles, Belgium

Correspondence to Jean-Francois Baurain, Medical Oncology Department, Cliniques universitaires Saint-Luc, 10 avenue Hippocrate, 1200 Bruxelles, Belgium. Tel: +32 2 764 5106/+32 2 764 5471; e-mail: jf.baurain@uclouvain.be

**Curr Opin Oncol** 2022, 34:123–130
DOI:10.1097/CCO.0000000000000821

1040-8746 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.



Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

## KEY POINTS

- Most of intratumoral injection strategies have shown responses in noninjected lesions, suggesting that there is an activation of new antitumor T cells.
- Further development of intratumoral injection strategies should be enriched with analysis of the function and the specificity of TILs extracted from injected and noninjected lesions.
- mAbs targeting other inhibitory or stimulatory coreceptors of T cells are the main current research axis to overcome primary and acquired resistance to PD-1/CTLA-4 blockade.
- A better understanding and characterization of the tumor microenvironment is needed to select the best immunotherapeutic approach for each patient.

describe some mechanisms of resistance and approaches to tackle them.

In this review, we focused on new immunotherapeutic approaches studied in advanced melanoma previously treated by anti-PD-1 or anti-CTLA-4 antibodies.

## T-CELL PRIMING AND ACTIVATION

Efficient antitumor T-cell immune response involves first an efficient antigen presentation and T-cell activation by dendritic cells. This step can fail if tumor cells express few antigens or dendritic cells maturation is impaired.

One therapeutic strategy is the intratumoral delivery of agents designed to promote antigen presentation in the tumor microenvironment (TME). Intralesional injection of talimogene laherparepvec (T-VEC), an oncolytic virus, was approved in 2015 to treat unresectable cutaneous or subcutaneous or nodal stage IIIB or IVA melanoma [7]. Oncoloytic viruses infect preferentially cancer cells leading to lysis of these cells and antigen release activating innate and adaptive antitumor immunity. Different phase II trials have evaluated the association of T-VEC and ICI (Ipilimumab or Pembrolizumab) for advanced melanoma. The association is reported to improve responses also in noninjected visceral lesions which is rarely if at all observed with ICI monotherapy [8]. However, the randomized phase III study Masterkey 265/Keynote 034 evaluating the benefit of adding TVEC to pembrolizumab failed to meet its primary endpoint, progression-free survival (PFS), with a median follow-up of 31 months [9]. The median PFS of the combination was 14.3 versus 8.5 months for pembrolizumab monotherapy [$P = 0.13$; hazard ratio 0.86 (0.71–1.04)]. Longer follow-up will tell whether OS benefit is observed.

PVSRIPO is an oncolytic poliovirus that infects $CD155^+$ (poliovirus receptor) cells which include tumor cells and antigen-presenting cells. Phase I trial in monotherapy in advanced melanoma with progressive disease (PD) after anti-PD-1 therapy had an overall response rate (ORR) of 33% with a good safety profile [10].

The oncolytic peptide LTX-315 is derived from the host defense peptide lactoferrin and perturbates both plasma and mitochondrial membrane integrity. This action releases danger-associated molecular pattern molecules and tumor antigens. A phase I study has been conducted with intratumoral administration of LTX-315 in patients with advanced cancer [11]. The safety profile was acceptable in the 39 injected patients and change in TME has been observed. Further evaluation is ongoing in clinical trials combining LTX-315 and anti-PD-1 antibodies.

Another approach is the activation of Toll-like receptors (TLR) on innate immune cells resulting in interferon production important for antigen presentation and T-cell priming. Rohatgi and Kirkwood [12] listed clinical trials using this strategy. Here, we highlight some results obtained in the anti-PD-1 refractory setting.

The ILLUMINATE-204 phase I/II trial evaluated intratumoral injection of Tilsotolimod, a synthetic TLR9 agonist oligonucleotide, in combination with ipilimumab for advanced melanoma refractory to anti-PD-1 antibody. The ORR was 22.4% with, in addition 49% of patients with a stable disease. Significantly, tumor reduction was also observed in noninjected lesions [13]. Here also, the preliminary results of the phase III (ILLUMINATE-301) are disappointing with an ORR of 8.8% for the combination versus 8.6% for ipilimumab alone. OS results are not yet available.

Vidutolimod (CMP-001) is a CpG-A virus-like particle that stimulates TLR9. A phase Ib trial studied intratumoral injection of CMP-001 in combination with pembrolizumab for patients with advanced melanoma after progression with anti-PD-1 therapy. Preliminary results showed an ORR of 24% for the combination and 22% for CMP-001 alone, with local and distant responses [14].

An emerging field of interest is STING agonists, activating the IFN-1 pathway to activate dendritic cells and improve antigen presentation. In the phase Ib, the cyclic dinucleotid ADU-S100 was injected in association with Spartalizumab (anti-PD-1 mAb) in advanced solid tumors and lymphomas. Partial responses (PRs) were observed in PD-1 refractory melanoma patients [15].

Therapeutic cancer vaccines with ex-vivo RNA-transfected dendritic cells were recently reviewed [16]. It was mainly studied in metastatic melanoma. Despite the fact that it is a personalized treatment



Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

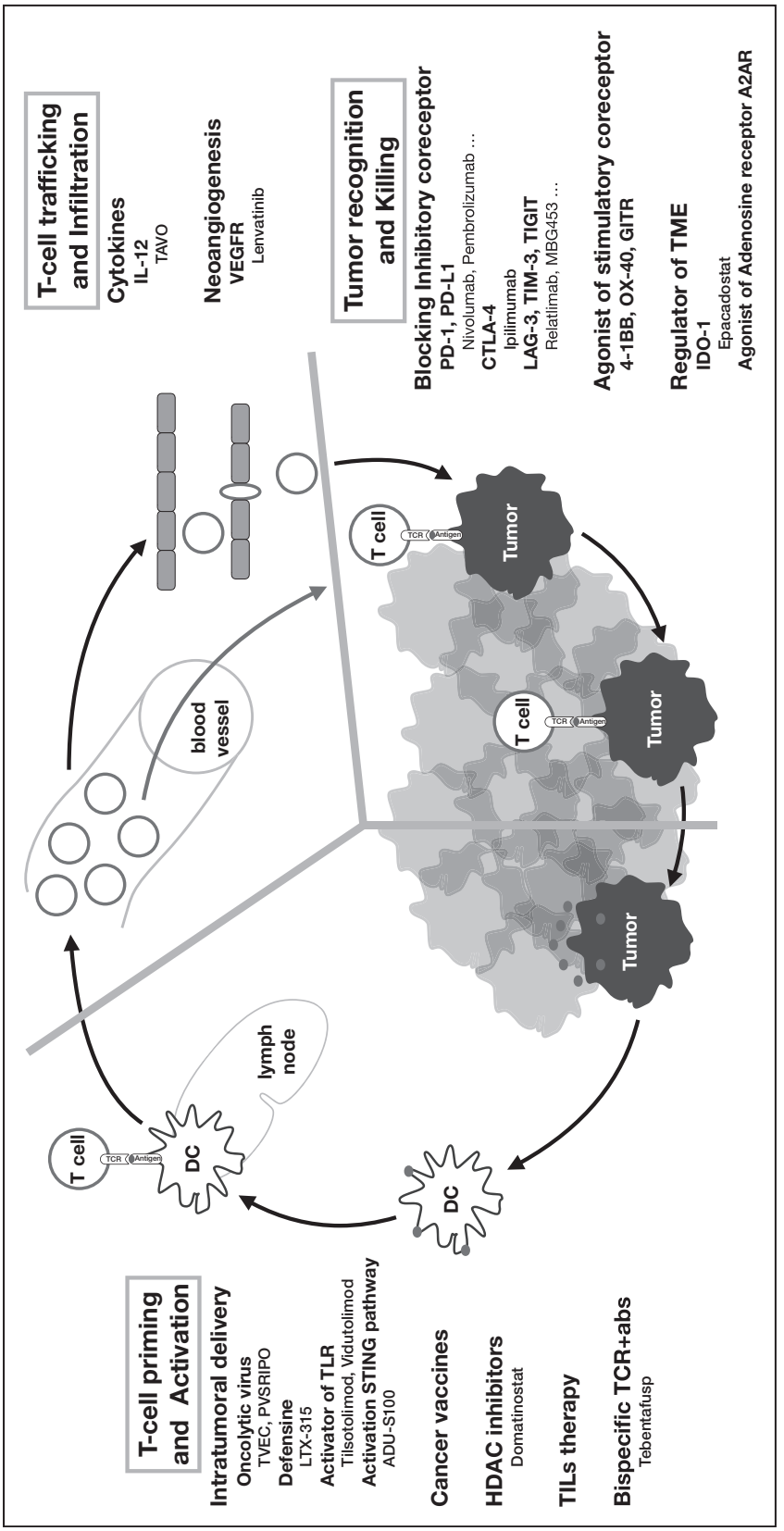


**FIGURE 1.** Three major sites of druggable immunoregulation in the 'Cancer Immunity Cycle' (Chen and Mellman, Immunity 2013). The Cancer Immunity Cycle proposed by Chen and Mellman has been divided in three major steps. For each step, we have listed the various drugs used in clinical trials in which metastatic melanoma patients have been included. Most of the new strategies are aimed to boost T-cell priming or to enhance tumor recognition and killing by T cells.

1040-8746 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

when dendritic cells are loaded with total tumor RNA, the results of clinical trials are disappointing with very few clinical responses [17▪▪]. One explanation could be an immunosuppressive TME in advanced stages altering the function of vaccine-induced T cells. Based on this rationale, several clinical trials are now exploring mRNA loaded dendritic cells vaccines in combination with CTLA-4 or PD-1 blockade.

Histone deacetylase (HDAC) inhibitors were reported to increase antigen expression by tumor cells and suppress Tregs and myeloid-derived suppressor cells (MDSCs). The phase Ib/II study ENCORE-601 associated Etinostat and Pembrolizumab in advanced melanoma patients previously treated by anti-PD-1 therapy. It showed an ORR of 19% [18]. The phase Ib SENSITIZE trial combined Domatinostat (another HDAC inhibitor) to Pembrolizumab for patients with advanced melanoma refractory to prior ICI therapy and showed preliminary results at the ASCO 2021 meeting. Out of 40 patients, they observed one complete response, two PRs and nine stable diseases [19].

Passive immunization modalities include T-cell adoptive transfer of tumor infiltrating lymphocytes (TILs), TCR-engineered T cells or CAR-T cells. TILs therapy consists in reinfusing in-vitro stimulated autologous TILs after lymphodepletion treatment followed by IL-2. A phase II evaluated the safety and efficacy of Lifileucel in patients with metastatic melanoma pretreated with anti-PD-1 or anti-BRAF therapy. The ORR was 36.4% and the median duration of response (mDOR) was not reached at 17 months of median study of follow-up [20].

Several TCR-engineered T cells recognize the melanocyte-specific antigens gp100 and MART-1. Tebentafusp is a soluble fusion protein containing an antigp100.A2 high-affinity TCR and an anti-CD3 single chain fragment that redirects T cells against melanoma cells and melanocytes. The phase I/II included metastatic cutaneous and uveal melanoma either pretreated or naive of standard therapy. The 1 year OS rate was 65% for both cutaneous and uveal melanoma with an ORR of 8.6% [21]. Recently, the phase III trial comparing Tebentafusp versus standard of care (DTIC, pembrolizumab or ipilimumab) in metastatic uveal melanoma showed the superiority of this new approach. The median OS was 21.7 months for patients treated with Tebentafusp versus 16 months for patients randomized in the control arm with a hazard ratio of 0.51 (95%, 0.37–0.71) [22▪▪].

## T-CELL TRAFFICKING AND TUMOR INFILTRATION

Another research axis is to turn noninflammed or so-called cold tumors, that is with low amounts of TILs, into 'hot' tumors to improve responsiveness to PD-1 blockade.

Downregulation of chemokines might explain poor tumor infiltration by T cells. Algazi *et al.* [23] forced intratumoral expression of the pro-inflammatory cytokine IL-12 in metastatic or unresectable melanomas with low-TIL contents. The interim results of the phase II trial KEYNOTE 695 combining intratumoral electroporation of IL-12 plasmid (TAVO) and pembrolizumab in PD-1-refractory advanced melanoma showed an ORR of 30% with 6% of CR. Responses were observed in electroporated as well as nonelectroporated lesions (distant or visceral) [24]. Significantly, translational work on tumors showed enhanced immune responses even in nonelectroporated lesions (increasing of TILs, new T-cell clonotypes and cellular immune response transcriptional signatures) [23].

T-cell trafficking and infiltration might be increased by acting on neoangiogenesis with tyrosine kinase inhibitors. The update findings of the LEAP-004 phase II study evaluating the combination of Lenvatinib and Pembrolizumab in advanced melanoma previously treated with anti-PD-1 were presented at ASCO 2021 with an ORR of 21.4% [25]. There were 46% of grade at least 3 adverse events and 60% of interruption or doses reduction but only 8% of patients discontinued the treatment.

## TUMOR RECOGNITION AND KILLING

TILs may be dysfunctional because of an immunosuppressive TME with either molecules produced by the tumor cells or immunosuppressive cells such as regulatory T cells (Tregs) or MDSCs. Moreover, T cells may express other inhibitory coreceptors than PD-1 and CTLA-4, or carry stimulatory coreceptors. Targeting these alternative checkpoints could reverse T-cell exhaustion (Fig. 2).

LAG-3, lymphocyte activation gene 3, is an inhibitory coreceptor present on activated T cells, activated B cells, and natural killer (NK) cells. It is closely related to CD4 and binds also to MHC class II molecules [26,27]. It is upregulated after persistent antigenic stimulation and often coexpressed with PD-1 and TIGIT [12]. Recently, Shen *et al.* [28] observed that melanoma patients with blood LAG-$3^+$ $CD8^+$ T cells had poor outcomes after ICI treatment, suggesting that targeting LAG-3 could provide a clinical benefit. The phase I/IIa studying the safety and preliminary clinical activity of the association of anti-LAG-3 antibody Relatlimab and Nivolumab after prior immunotherapy in advanced melanoma patients reported an ORR of 16% [29]. RELATIVITY-047 phase II/III study compared Nivolumab with or without Relatlimab in first line



Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

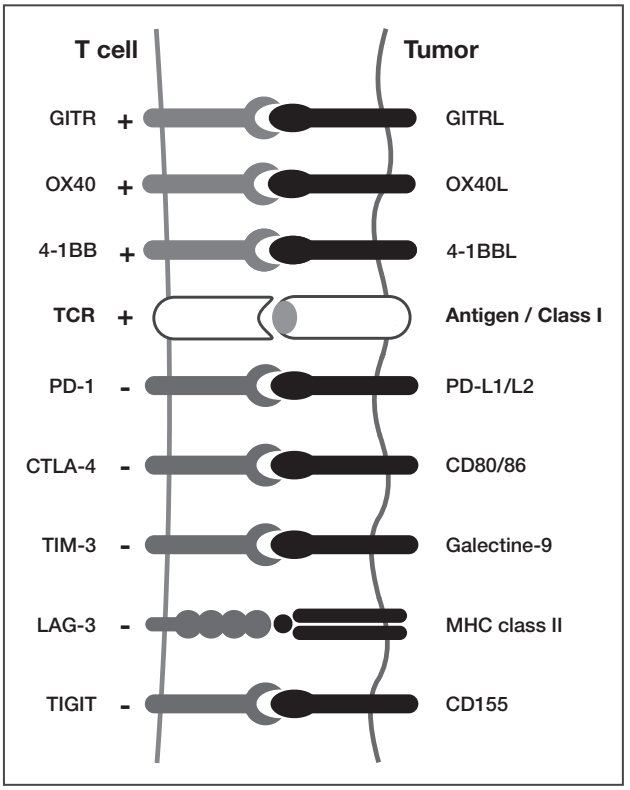


**FIGURE 2.** T-cell inhibitory and stimulatory coreceptors that can be targeted by blocking mAbs in clinical trials. T cells recognize specifically tumor through the binding of their tumor cell receptor to a given antigen presented by HLA class I molecules. The fine tuning of this activation is made by the interaction of several stimulatory or inhibitory coreceptors. Seven of them are represented here and are targeted in various clinical trials for advanced melanoma patients. HLA, human leukocyte antigen.

advanced melanoma. Primary results were presented at ASCO 2021 and showed a significant benefit in PFS: 10.1 versus 4.6 months with a hazard ratio of 0.75 (0.62–0.92). This benefit was observed in all subgroups, with a manageable safety profile [30].

TIM-3, T-cell immunoglobulin mucin receptor 3, is another inhibitory coreceptor expressed on a variety of immune cells, including melanoma TILs [31]. It is considered to be a marker of exhausted T cells and is coexpressed with PD-1, LAG-3 and TIGIT on $CD8^+$ T cells [31]. Ongoing trials with antibodies targeting TIM-3 in combination with anti-PD-1 therapy in advanced solid tumors were recently reviewed by Acharya *et al.* [32]. Based on these preliminary data, the efficacy of this combination in melanoma patients after anti-PD-1 treatment appears limited [33,34].

TIGIT, T-cell immunoreceptor with Ig and ITIM domains, is another inhibitory coreceptor expressed on immune cells including activated T cells, NK cells and Tregs [35] but also highly on melanoma cells [36]. A recent review listed ongoing phase I/II trials with anti-TIGIT antibodies [35]. All studies are recruiting for the moment.

Another strategy is to activate T-cell stimulatory coreceptors with agonist antibodies. These new targets include OX-40, GITR and 4-1BB, alone or in combination with ICI. These receptors are upregulated on T cells after TCR activation. Significantly, depending on the TME, targeting OX-40 and GITR could also have an effect on Tregs, impairing their suppressive activity because they are also highly expressed on activated Tregs and thus could be eliminate by ADCC [37–39]. Concerning the stimulation of OX-40, promising preclinical data could not be translated into early phase clinical trials [37]. Table 1 summarizes ongoing phase I/II targeting stimulatory coreceptors. Currently, there are 6 ongoing studies in monotherapy or in combination with anti-PD-1/PD-L1 or 4-1BB agonist antibodies for advanced solid tumors including melanoma. There are also six ongoing phase 1 trials with anti-GITR agonist antibodies. No clinical response was observed with monotherapy in previously treated advanced solid tumors but preliminary data in combination with PD-1 blockade seems encouraging [40]. Two early clinical trials are currently testing an anti4-1BB antibody in combination with anti-PD-1 in metastatic melanoma progressing after ICI treatment. There is also a phase I ongoing with a bispecific antibody targeting both PD-1 and 4-1BB (NCT03809624).

IDO1, indoleamine 2,3-dioxygenase 1, is an IFN-inducible enzyme that catabolizes tryptophan to kynurenine, depleting the microenvironment in tryptophan which is important for T lymphocyte function. IDO1 is expressed, sometimes constitutively, in several tumors including melanoma. In most reports, its expression was associated with worse prognosis [41]. Several phase II trials showed promising antitumor activity of the combination Epacadostat and anti-PD-1 antibody [8]. However, the ECHO-301 phase III study in previously untreated advanced melanoma failed to demonstrate a survival benefit for combining Epacadostat and Pembrolizumab versus Pembrolizumab alone [42]. The results were reviewed with possible explanations for failure [43▪▪]. Since then, many ongoing trials with IDO1 inhibitors have been terminated. Nevertheless, an interesting phase II evaluates the association of Epacadostat with peptide vaccines (containing 12 class I MHC-restricted melanoma peptides) in stage III/IV melanoma including PD on anti-PD-1 treatment (NCT01961115).

Extracellular adenosine (eADO) is considered as a major immunosuppressive factor in the TME.

1040-8746 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

**Table 1.** Ongoing clinical trials with agonist antibodies to stimulatory coreceptors for advanced melanoma patients

| Target | Study title | Phase | CT Identifier |
|---|---|---|---|
| OX-40 | Study of INBRX-106 and INBRX-106 in combination with Pembrolizumab in patients with locally advanced or metastatic solid tumors | I | NCT04198766 |
| | Study of OX40 agonist PF-04518600 alone and in combination with 4-1BB agonist PF-05082566 (∗) | I | NCT02315066 |
| | SL-279252 (PD1-Fc-OX40L) in subjects with advanced solid tumors or lymphomas | I | NCT03894618 |
| | A study of Avelumab in combination with other cancer immunotherapies in advanced malignancies (JAVELIN Medley) (#) | Ib/II | NCT02554812 |
| | A phase 1/2, open-label, dose-escalation, safety study of INCAGN01949 in subjects with advanced or metastatic solid tumors | I/II | NCT02923349 |
| | A phase 1/2 study exploring the safety, tolerability, and efficacy of INCAGN01949 in combination with immune therapies in subjects with advanced or metastatic malignancies | I/II | NCT03241173 |
| GITR | Trial of TRX518 (Anti-GITR mAb) in stage III or IV malignant melanoma or other solid tumors | I | NCT01239134 |
| | Phase 1 open-label study of TRX518 monotherapy and TRX518 in combination with gemcitabine, Pembrolizumab, or Nivolumab | I | NCT02628574 |
| | A study of ASP1951 in subjects with advanced solid tumors | Ib | NCT03799003 |
| | Phase 1 study of local modulation of immune receptor function to enhance immune responses to dendritic cell vaccination in subjects with metastatic melanoma | I | NCT01216436 |
| | A study of INCAGN01876 in participants with advanced or metastatic solid tumors | I/II | NCT02697591 |
| | Phase 1/2 study exploring the safety, tolerability, and efficacy of INCAGN01876 combined with immune therapies in metastatic malignancies | I/II | NCT03126110 |
| 4-1BB | Study of OX40 agonist PF-04518600 alone and in combination with 4-1BB agonist PF-05082566 (∗) | I | NCT02315066 |
| | A study of Avelumab in combination with other cancer immunotherapies in advanced malignancies (JAVELIN Medley) (#) | Ib/II | NCT02554812 |
| | Study of INBRX-105 in patients with solid tumors | I | NCT03809624 |

Three stimulatory receptors expressed on T-cells are targeted by agonist antibodies. For each of these receptors, we have listed the ongoing clinical trials in which advanced melanoma patients could be included. For each trial, the type of study and the clinical trial.gov (CT) identifier has been indicated.
Symbols ∗ and # are used to highlight that it is the same study.

The canonical pathway is mediated by two enzymes: first, CD39 catabolizing ATP in ADP and then ADP in AMP, second, CD73 that converts AMP to eADO. CD73 is also implicated in the noncanonical adenosine pathway. Activated T cells upregulate the expression of high-affinity adenosine receptor A2AR. A2AR activation on T cells downregulates TCR signaling and stimulates expression of inhibitory coreceptors (PD-1, LAG-3, TIM-3, TIGIT), thus impairing T-cell activation, proliferation, survival and cytokines production. This pathway could also promote the differentiation of $CD4^+$ T cells into Tregs. Moreover, hypoxia and chronic inflammation induce high-tumor expression of CD39, CD73 and increase A2AR expression by T cells [44▪▪]. In some tumors including melanoma, CD73 is upregulated as compared with normal tissues and it is correlated with more aggressive tumors displaying an invasive phenotype and poor prognosis [44▪▪,45]. Of note, for metastatic melanoma patients, high levels of blood CD73 is a biomarker of poor responses to Nivolumab [46]. A phase I study with a small molecule inhibitor of CD73, alone or in combination with pembrolizumab, is ongoing in advanced solid tumors including melanoma (NCT04148937).

## CONCLUDING REMARKS

At this point in time, there is not yet sufficient evidence indicating superiority of one of these combinations over the others or over the dual blockade of PD-1 and CTLA-4.



Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

More fundamental, translational and clinical work is warranted to successfully overcome primary and acquired resistance to current immunostimulatory antibodies administered to patients with cancer. Moreover, we need more work around predictive biomarkers as well as a better understanding of how the TME is modified during and after treatment in the patients that display clinical responses to these treatments.

## Acknowledgements

*We would like to thank Prof Coulie from de Duve Institute for his advices and comments on the topic discussed in this review.*

## Financial support and sponsorship

*None.*

## Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Diamantopoulos P, Gogas HJ. Melanoma immunotherapy dominates the field. Ann Transl Med 2016; 4:269.
2. Hodi FS, O'Day SJ, McDermott DF, *et al.* Improved survival with Ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363:711–723.
3. Robert C, Schachter J, Long GV, *et al.* Pembrolizumab versus Ipilimumab in advanced melanoma. N Engl J Med 2015; 372:2531–2532.
4. ■ Wolchok JD, Chiarion-Sileni V, Grob J-J, *et al.* Checkmate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. J Clin Oncol 2021; 39(15_Suppl):9506.

The article illustrates the long-term benefit of anti-progressive disease (PD)-1 antibodies and suggest that a third of the metastatic melanoma patients could be cured.

5. Kluger HM, Tawbi HA, Ascierto ML, *et al.* Defining tumor resistance to PD-1 pathway blockade: recommandations from the first meeting of the SITC immunotherapy resistance taskforce. J Immunother Cancer 2020; 8:e000398.
6. Gide TN, Wilmott JS, Scolyer RA, *et al.* Primary and acquired resistance to immune checkpoint inhibitors in metastatic melanoma. Clin Cancer Res 2018; 24:1260–1270.
7. Bommareddy PK, Patel A, Hossain S, *et al.* Talimogene Laherparepvec (T-VEC) and other oncolytic viruses for treatment of melanoma. Am J Clin Dermatol 2017; 18:1–15.
8. Trojaniello C, Luke JJ, Ascierto PA, *et al.* Therapeutic advancements across clinical stages in melanoma with a focus on targeted immunotherapy. Front Oncol 2021; 11:670726.
9. Gogas HJ, Ribas A, Chesney J, *et al.* MASTERKEY-265: a phase III, randomized, placebo(Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB-IVM1c melanoma (MEL). Ann Oncol 2021; 32(Suppl_5):S867–S905.
10. Beasley GM, Nair SK, Farrow NE, *et al.* Phase I trial of intratumoral PVSRIPO in patients with unresctable, treatment-refractory melanoma. J Immunother 2021; 9:e002203.
11. Spicer J, Marabelle A, Baurain JF, *et al.* Safety, antitumor activity, and T-cell responses in a dose-ranging Phase I trial of the oncolytic peptide LTX-315 in patients with solid tumors. Clin Cancer Res 2021; 27:2755–2763.
12. Rohatgi A, Kirkwood JM. Beyond PD-1: the next frontier for immunotherapy in melanoma. Front Oncol 2021; 11:640314.
13. Haymaker C, Andtbacka RHI, Johnson DB, *et al.* Final results from ILLUMINATE-204, a phase I/II trial of intratumoral tilsotolimod in combination with ipilimumab in PD-1 inhibitor refractory advanced melanoma. Ann Oncol 2020; 31(Suppl_4):S736.
14. Milhem M, Zakharia Y, Davar D, *et al.* Intratumoral injection of CMP-001, a Toll-like receptor 9 (TLR9) agonist, in combination with pembrolizumab reversed programmed death receptor (PD-1) blockade resistance in advanced melanoma. J Immunother Cancer 2020; 8(Suppl_3):A186–A187.
15. Meric-Bernstam F, Sandhu SK, Hamid O, *et al.* Phase Ib study of MIW815 (ADU-S100) in combination with spartalizumab (PDR001) in patients (pst) with advanced/metastatic solid tumors or lymphomas. J Clin Oncol 2019; 37(15_Suppl):2507–12507.
16. Dörrie J, Schaft N, Schuler G, *et al.* Therapeutic cancer vaccination with ex vivo RNA-transfected dendritic cells – an update. Pharmaceutics 2020; 12:92.
17. ■■ Chakraborty C, Sharma AR, Bhattacharya M, *et al.* From COVID-19 to cancer mRNA vaccines: moving from bench to clinic in the vaccine landscape. Front Immunol 2021; 12:679344.

The article is an interesting review of the state of the art in term of mRNA vaccine.

18. Sullivan RJ, Moschos SJ, Johnson ML, et al. Efficacy and safety of Entinostat (ENT) and Pembrolizumab (PEMBRO) in patients with melanoma previously treated with anti-PD-1 therapy. *Abstract Presented at AACR Annual Meeting 2019.*
19. Hassel JC, Berking C, Schlaak M, *et al.* Results from the phase Ib of the SENSITIZE trial combining domatinostat with pembrolizumab in advanced melanoma patients refractory to prior checkpoint inhibitor therapy. J Clin Oncol 2021; 39(15_Suppl):9545–19545.
20. Sarnaik A, Khushalani NI, Chesney JA, *et al.* Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies. J Clin Oncol 2020; 38(15_Suppl):10006–110006.
21. Middleton MR, McAlpine C, Woodcock VK, *et al.* Tebentafusp, a TCR/anti-CD3 bispecific fusion protein targeting gp100, potently activated antitumor immune responses in patients with metastatic melanoma. Clin Cancer Res 2020; 26:5869–5878.
22. ■■ Nathan P, Hassel JC, Rutkowski P, *et al.* Overall survival benefit with tebentafusp in metastatic uveal melanoma. N Engl J Med 2021; 385:1196–1206.

The article shows the result of a randomized phase III trial with a new bispecific technology (TCR+antibody). Tebentafusp is able to increase overall survival in uveal melanoma, a disease knows to be resistant to anti-PD1.

23. Algazi AP, Twitty CG, Tsai KK, *et al.* Phase II trial of IL-12 plasmid transfection and PD-1 blockade in immunologically quiescent melanoma. Clin Cancer Res 2020; 26:2827–2837.
24. Fernandez-Penas P, Carlino MS, Tsai KK, *et al.* Durable responses and immune activation with intratumoral electroporation of pIL-12 plus pembrolizumab in actively progressing anti-PD-1 refractory advanced melanoma: KEYNOTE 695 interim data. Presented at the *2020 SITC Virtual Annual Meeting*; November 9-14, 2020, abstract 799.
25. Arance AM, de la Cruz-Merino L, Petrella TM, *et al.* Lenvatinib plus pembrolizumab for patients with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: update findings of LEAP-004. *Presented at the 2021 ASCO Annual Meeting*; June 6, 2021, abstract 9504.
26. He Y, Rivard CJ, Rozeboom L, *et al.* Lymphocyte-activation gene-3, an important immune checkpoint in cancer. Cancer Sci 2016; 107:1193–1197.
27. Lythgoe MP, Liu DSK, Annels NE, *et al.* Gene of the mont: lymphocyte-activation gene 3 (LAG-3). J Clin Pathol 2021; 74:543–547.
28. Shen R, Postow MA, Adamow M, *et al.* LAG-3 expression on peripheral blood cells identifies patients with poorer outcomes after immune checkpoint blockade. Sci Transl Med 2021; 13:eabf5107.
29. Ascierto PA, Bono P, Bhatia S, *et al.* Efficacy of BMS-986016, a monoclonal antibody that targets lymphocyte activation gene-3 (LAG-3), in combination with nivolumab in pts with melanoma who progressed during prior anti-PD-1/PD-L1 therapy (mel prior IO) in all-comer and biomarker-enriched populations. Ann Oncol 2017; 28(Suppl_5):611–612.
30. Lipson EJ, Tawbi HAH, Schadendorf D, *et al.* Telatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase III results from RELATIVITY-047 (CA224-047). J Clin Oncol 2021; 39(15_Suppl):9503–19503.
31. Fourcade J, Sun Z, Benallaoua M, *et al.* Upregulation of TIM-3 and PD-1 expression is associated with tumor antigen-specific $CD8^+$ T cell dysfunction in melanoma patients. J Exp Med 2010; 207:2175–2186.
32. Acharya N, Sabatos-Peyton C, Carrizosa Anderson A. TIM-3 finds its place in the cancer immunotherapy landscape. J Immunother Cancer 2020; 8:e000911.
33. Mach N, Curigliano G, Santoro A, *et al.* 1202P: Phase (Ph) II study of MBG453 + spartalizumab in patients (pts) with nonsmall cell lung cancer (NSCLC) and melanoma pretreated with anti-PD-1/L1 therapy. Ann Oncol 2019; 30(Suppl_5):491–492.
34. Curigliano G, Gelderblom H, Mach N, *et al.* Phase I/Ib clinical trial of sabatolimab, an anti-TIM-3 antibody, alone and in combination with spartalizumab, an anti-PD-1 antibody, in advanced solid tumors. Clin Cancer Res 2021; 27:3620–3629.
35. Chauvin J-M, Zarour HM. TIGIT in cancer immunotherapy. J Immunother Cancer 2020; 8:e000957.
36. Chauvin J-M, Pagliano O, Fourcade J, *et al.* TIGIT and PD-1 impair tumor antigen-specific $CD8^+$ T cells in melanoma patients. J Clin Invest 2015; 125:2046–2058.

1040-8746 Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved. 

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

**37.** Aspeslagh S, Postel-Vinay S, Rusakiewicz S, *et al.* Rationale for anti-OX40 cancer immunotherapy. Eur J Cancer 2016; 52:50–66.

**38.** Willoughby J, Griffiths J, Texs I, *et al.* OX40: structure and function – what questions remain? Mol Immunol 2017; 83:13–22.

**39.** Zhu MMT, Burugu S, Gao D, *et al.* Evaluation of glucocorticoid-induced TNF receptor (GITR) expression in breast cancer and across multiple tumor types. Mod Pathol 2020; 33:1753–1763.

**40.** Zappasodi R, Sirard C, Li Y, *et al.* Rational design of anti-GITR-based combination immunotherapy. Nat Med 2019; 25:759–766.

**41.** van Baren N, Van den Eynde B. Tumoral immune resistance mediated by enzymes that degrade tryptophan. Cancer Immunol Res 2015; 3:978–985.

**42.** Long GV, Dummer R, Hamid O, *et al.* Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomized, double-blind study. Lancet Oncol 2019; 20:1083–1097.

**43.** Van den Eynde BJ, van Baren N, Baurain J-F. Is there a clinical future for IDO1 ■■ inhibitors after the failure of Epacadostat in melanoma. Annu Rev Cancer Biol 2020; 4:241–256.

The review analyses in detail the reason of the failure of a randomized phase III trial and the basis of jumping directly from phase I data to unselected phase III. It gives some rationale to further development of drugs targeting tumor microenvironment.

**44.** Allard B, Allard D, Buisseret L, *et al.* The adenosine pathway in immune- ■■ oncology. Nat Rev Clin Oncol 2020; 17:611–629.

The review is showing the importance of the adenosine pathway and the rationale of targeting it in melanoma.

**45.** Monteiro I, Vigano S, Faouzi M, *et al.* CD73 expression and clinical significance in human metastatic melanoma. Oncotarget 2018; 9:26659–26669.

**46.** Morello S, Capone M, Sorrentino C, *et al.* Soluble CD73 as biomarker in patients with metastatic melanoma patients treated with nivolumab. J Transl Med 2017; 15:244.




Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.