Melanoma Research Review™

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In this issue:

Abbreviations used in this issue:

AM = acral melanoma; **CM** = cutaneous melanoma; **CPI**= checkpoint inhibitor; **CR** = complete response; **DC** = dendritic cell; **DCR** = disease control rate; **DFS** = disease-free survival; **DLT** = dose-limiting toxicity; **ICI** = immune checkpoint inhibition; **ITM** = in-transit metastases; **MTD** = maximum tolerated dose; **mUM** = metastatic uveal melanoma; **MUMPS** = Metastatic Uveal Melanoma Prognostic Score; **NGS** = next generation sequencing; **ORR** = overall response rate; **OS** = overall survival; **PR** = partial response; **PT** = per treatment; **SCFA** = short chain fatty acids; **TCGA** = The Cancer Genome Altas; **TCR** = T cell receptor; **TIL** = tumour-infiltrating lymphocyte; **TTSP** = time to subsequent progression after treatment of solitary progression; **TLPLDC** = tumour lysate, particle-loaded, dendritic cell; **TVEC** = talimogene laherparepvec; **UM** = uveal melanoma.

Welcome to the 44th issue of Melanoma Research Review.

The articles I have selected for commentary are those with some relevance to management of melanoma at present or in the future. Several of them require some background to understand their significance so bear with comments that include some introduction. One such Nature article utilises the latest immunological and analytical techniques to describe T cells in melanoma and another uses fairly detailed molecular biology techniques and jargon not in everyday use. Nevertheless, I think the articles have captured important trends in the ever-evolving treatment of melanoma.

Very best to all.

Kind Regards,

Professor Peter Hersey

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Multi-institutional, prospective, randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine to prevent recurrence in high-risk melanoma patients: A subgroup analysis

Authors: Chick RC, et al

Summary: The primary analysis of the trial in resected stage III/IV melanoma demonstrated TLPLDC is safe and improved 24-month disease-free survival (DFS) in the per treatment (PT) analysis. This subgroup analysis assessed the efficacy of TLPLDC within pre-specified and exploratory subgroups. There were no clinicopathologic differences between subgroups except stage IV patients were more likely to receive checkpoint inhibitors (CPIs). The authors reported in stage IV patients, 24-month DFS was 43% for vaccine versus 0% for placebo ($p = 0.098$) in the ITT analysis and 73% versus 0% ($p = 0.002$) in the PT analysis. They noted there was no significant difference in 24-month DFS when stratified by use of immunotherapy or CPI. For patients with resected recurrent disease, 24-month DFS was 88.9% versus 33.3% ($p = 0.013$) in the PT analysis. They also noted there was no benefit from vaccination in patients receiving up to three doses.

Comment: *In many respects this study is somewhat dated but an open mind to assess it is probably important.*

Cancer vaccines have been studied widely in melanoma, but with limited success. Cancer vaccines are less likely to achieve a meaningful effect in advanced, unresectable disease whereas activation of initial immune responses to tumours may be effective in patients with less advanced disease rendered disease-free by surgery. In this study the vaccine was produced from a sample (1 cm^3) of the patient's surgically resected tumour, which was lysed and loaded into yeast cell wall particles. Dendritic cells (DCs) from 50-60 ml of blood collected after G-CSF administration were from monocytes harvested from the blood and grown in GM-CSF and IL-4 for 2 days. The lysate was loaded on day 2 in the presence of cytokines and tetanus helper peptides. Vaccines were given IV monthly x 4 and at 6 and 12 months.

The results showed no differences in the 80 stage III resected patients compared to 32 controls. In the 23 resected stage IV patients versus 9 controls there were significant differences in DFS at 24 months (73.3% v 0%). These results were said not to be influenced by concomitant CPI treatments but the data on this is hard to dissect from the other variables. At least 4 vaccines were needed to see the benefits recorded.

Their summary is: "Given the promising findings of our trial thus far, further study of TLPLDC in a well-selected patient population is warranted. As previously discussed, CPI are currently a standard option for systemic adjuvant treatment in stage III and stage IV melanoma. Therefore, the phase III trial of TLPLDC will compare TLPLDC + PD-1 inhibitor versus placebo + PD-1 inhibitor alone in patients with resected stage IV melanoma. The aim of the study will be to determine whether the addition of TLPLDC, a personalised vaccine, increases the efficacy of the PD-1 inhibitor in preventing melanoma recurrence."

Reference: Cancer Med 2021 Jul;10(13):4302-4311
Abstract

Phase I-II open-label multicenter study of palbociclib + vemurafenib in BRAF^{V600MUT} metastatic melanoma patients: Uncovering CHEK2 as a major response mechanism

Authors: Louveau B, et al

Summary: The objective of this study was to determine the maximum tolerated dose (MTD) of palbociclib when added to vemurafenib. Patients with BRAF$^{V600E/KMUT}$ metastatic melanoma harbouring CDKN2A loss and RB1 expression were included and stratified according to previous BRAF inhibitor treatment (no pre-treatment: n = 3; pre-treatment: n= 15). Treatment comprised palbociclib once daily for 14 days followed by a 7-day break + continuous dosing of vemurafenib. One patient experienced dose-limiting toxicity (DLT) in the no previous BRAF inhibitor treatment cohort and 5 experienced DLT in the BRAF inhibitor pre-treated cohort; with the MTD defined as palbociclib 25 mg and vemurafenib 960 mg. The researchers highlighted there was no significant evidence for drug-drug interactions. The median progression-free survival was 2.8 months, and 5 (27.8%) patients showed a clinical response. They also reported the baseline differential mRNA expression analysis and in vitro data revealed the role of CHEK2 in the response to palbociclib.

Comment: The introduction revises why this study is important. The MAPK pathway in melanoma controls the transcription of cell-cycle proteins such as cyclin Ds and cyclin-dependent kinases and promotes the activity of cyclin D–CDK4/6, a key regulator of the G1–S transition. After activation, cyclin D associates with CDK4/6, forming a complex that phosphorylates Rb and dissociates the transcriptionally repressive Rb–E2F complex. The E2F transcription factor promotes cell-cycle entry, leading to proliferation and survival.

To date, the cyclin D–CDK4/6–INK4–Rb pathway is dysregulated in up to 90% of melanomas, with the loss of CDKN2A-p16INK4A expression as well as CCND1 or CDK4 amplification. Inhibitors of CDK4/6 such as palbociclib, abemaciclib, and ribociclib are already available in clinical practice and have been shown to significantly improve survival in HR+/HER2– advanced metastatic breast cancer. The 3 inhibitors have similar as well as different toxicities, so it was considered important to establish a safe dose in the patient population likely to be treated by CDK4/6 inhibitors. Palbociclib may have more specific to CDK4. The studies included concomitant treatment with vemurafenib. Baseline levels of the DNA repair associated CHEK2 proteins were considered possible predictors of response and will be investigated in future studies.

One of the surprising effects of CDK4/6 inhibitors were their effects on the immune system such as increased IFN production, suppression of Treg cells and increased T cell activity. They were able to reverse a resistance profile in melanoma treated by anti-PD1 associated with TEx (Jerby-Arnon). Many trials with other targeted agents are in progress in melanoma so watch this space.

Reference: Clin Cancer Res 2021 Jul 15;27(14):3876-3883
Abstract

Clinical characteristics and therapy response in unresectable melanoma patients stage IIIB-IIID with in-transit and satellite metastases

Authors: Zaremba A, et al

Summary: This retrospective study evaluated tumour characteristics of 191 patients with initially unresectable stage III in-transit metastases (ITM) and satellite metastases and analysed disease kinetics. Median follow-up time was 30.5 months from unresectable ITM. Progression to stage IV was observed in 56.5% of cases. The authors reported patients without distant metastasis were more often female, older (>70 years) and presented as stage III with lymph node or ITM at initial diagnosis in 45.7% of cases. They also found melanoma located on the leg had a significantly better overall survival (OS) from time of initial diagnosis compared to non-leg localised primaries (HR = 0.61; p = 0.017), but not from diagnosis of unresectable stage III (HR = 0.67; p = 0.06). Forty percent of patients received local therapy for satellite and ITM. Overall response rate (ORR) to all local first-line treatments was 38%; disease control rate (DCR) was 49%. In total, 72.3% of patients received systemic therapy for unresectable stage IIIB-D. ORR for targeted therapy (n = 19) was highest with 63.2% and DCR was 84.2% compared to an ORR of 31.4% and a DCR of 54.3% in PD-1 treated patients (n = 70). Patients receiving PD-1 and intralesional talimogene laherparepvec (TVEC; n = 12) had an ORR of 41.7% and a DCR of 75%.

Comment: Most clinicians treating melanoma would have patients with ITM and satellite metastases that may recur locally but do not progress systemically. This well-run study is a welcome addition to the literature on these patients. It reviews the clinical characteristics and their response to treatment. Their review of ICI shows a wide variation in responses from 58%-31%. There was also a wide range of responses to local treatments which have varied widely. These included intralesional IL-2, TVEC and many others as well as isolated limb perfusion or infusion. Relevant histopathology findings comparing leg primaries and those at other sites were the higher incidence of NMM in legs (42.7% cf 25.7%). Ulceration, BRAF mutation status, histological subtype and primary tumour stage did not show an association with survival in univariate analysis. What is missing from the article are molecular biology studies that might provide insights into the clinical characteristics of these forms of melanoma.

Reference: Eur J Cancer 2021 Jul;152:139-154
Abstract

Intratumour microbiome associated with the infiltration of cytotoxic CD8+ T cells and patient survival in cutaneous melanoma

Authors: Zhu G, et al

Summary: The investigators used cutaneous melanoma (CM) RNA sequencing data from The Cancer Genome Altas (TCGA) study to investigate the association between intratumour-residing gut microbiota, infiltrating CD8+ T cells and patient survival outcomes. They found patients with low levels of CD8+ T cells have significantly shorter survival than those with high levels; low vs high adjusted HR 1.57 (p = 0.002). Intratumour bacteria of the *Lachnoclostridium* genus ranked top in a positive association with infiltrating CD8+ T cells (correlation coefficient = 0.38, $p = 9.4 \times 10^{-14}$), followed by *Gelidibacter* (0.31, $p = 1.13 \times 10^{-9}$), *Flammeovirga* (0.29, $p = 1.96 \times 10^{-8}$) and *Acinetobacter* (0.28, $p = 8.94 \times 10^{-8}$). They also found these intratumour genera positively correlated with chemokine CXCL9, CXCL10 and CCL5 expression. The high *Lachnoclostridium* load significantly reduced the mortality risk (p = 0.0003). However, no statistically significant correlation was observed between intratumour *Lachnoclostridium* abundance and the levels of either NK, B or CD4+ T cells.

Comment: There are now many studies showing that microbiome in the gut influence survival outcomes in melanoma. In general, the explanations for this include production of short chain fatty acids (SCFA) like butyrate that inhibit or increase immune responses or increase innate immunity by interaction with Toll like receptors on lymphocytes. Another is that bacteria can engage in antigenic mimicry of melanoma antigens and increase or decrease immune responses against the melanoma. Previous studies showed that responders to immune checkpoint blockade with long-term remission had a higher abundance of *Lachnospiraceae* than non-responders in melanoma renal clear cell carcinoma and non–small cell lung cancer. The present study has used RNAseq data from 447 patients in TCGA to examine the relationship between the presence of *Lachnospiraceae* (a high SCFA producer) and several other bacteria genus in the tumour and immune infiltration into the tumour. 369 of the patients had information about tumour-infiltrating lymphocytes (TILs). Positive results were restricted to increases in CD8+ T cells in the TILS. They also make an association with production of chemokines that attract T cells so that antigenic mimicry is not necessarily involved. They conclude: "These findings suggest that modulating gut microbiomes may be a novel approach in treating CM. In particular, it is warranted to explore whether or not and how *Lachnoclostridium* can enhance CD8+ T cell infiltration and improve immunotherapy"

Reference: Eur J Cancer 2021 Jul;151:25-34
Abstract

Independent commentary by Peter Hersey, FRACP, D Phil

Peter Hersey is an honorary Professor of Immuno Oncology in the University of Sydney and a faculty member of the Melanoma Institute Australia. He has conducted a number of phase I to III trials of immunotherapy in melanoma, including use of modified peptide antigens and dendritic cell vaccines. He has taken a leading role in studies investigating properties of melanoma cells that make them resistant to treatment and new treatment approaches to overcome these properties. He is generally recognized as a pioneer of immunotherapy for melanoma in Australia, and has participated in most of the key clinical trials on immunotherapy with immune checkpoint inhibitors. He continues translational research on melanoma in the Centenary Institute as joint holder of a NHMRC program grant on melanoma.

Identification of genetic mutations related to invasion and metastasis of acral melanoma via whole-exome sequencing

Authors: Lim Y, et al

Summary: The investigators applied multi-region whole-exome sequencing to investigate possible pathogenic mutations related to invasion and metastasis in acral melanoma (AM). They analysed five multi-regional samples of primary and metastatic AM and histologically normal tissue adjacent to the tumour in two AM patients. The sequencing results of superficial and deep lesions and primary and metastatic lesions of AM were compared. The investigators identified significantly deleterious mutations that are likely to be related to invasion and metastasis of AM. Significantly deleterious mutations such as SKA3, MAST4, CNNM1, KIAA1549L, and SLC26A10 were found only in the deep lesion, but not in the superficial lesion. Significantly deleterious mutations present only in the metastatic lesion were ANO1, CPEB1, EP300, INADL, MAP1B, MAP7D1, MARCH6, NETO1, PRKCE, SBK1, TNRC6A, USP13, WDR74, and ZNF827.

Comment: Acral melanoma is a subtype of CM occurring in acral areas such as the sole, palm, and nail apparatus. AM is a subtype constituting a major proportion of all CM in darker-skinned races and is known to have a worse prognosis than CM overall. The authors recognise their study was limited by the small number of samples but point to it being meaningful because the study compared deep and superficial lesions in an AM patient, and primary AM with skin metastatic lesions. Pioneer studies on AM by Bastian et al reported that the most frequently amplified regions in AM were 11q13, 22q11-13, and 5p15. The most frequently amplified region, 11q13, contained known oncogenes FGF3, FGF4, and CCND1 (CyclinD1). Subsequent studies from Melanoma Institute Australia researchers (*Newell F et al, Nat Commun. 2020 Oct 16;11(1):5259*) on 63 AM melanoma confirmed amplifications and mutations of cKIT as well as complex rearrangements and amplifications of TERT, CDK4, MDM2, CCND1, PAK1 and GAB2.

The focus of the present paper was on genes involved in metastasis. They reviewed previous studies and conclude that several genes including CNNM1, USP13, ZNF827, WDR74, CPEB1 and EP300 might be related to invasion and metastasis of AM. Further studies with a larger number of samples were considered necessary to validate their results. In addition, because the study only used whole genome sequencing it was difficult to elucidate the potential role of these genes. This paper is definitely for molecular biologists but adds information about potential targeted treatments of value that are discussed more extensively in Newell et al. Perhaps the main targeted treatments are the CDK4/6 inhibitors referred to in another commentary

Reference: J Dermatol 2021 Jul;48(7):999-1006
Abstract

The use of noninvasive imaging techniques in the diagnosis of melanoma: A prospective diagnostic accuracy study

Authors: MacLellan AN, et al

Summary: The researchers compared dermatologist's clinical examination at the bedside, teledermatology, and noninvasive imaging techniques (FotoFinder, MelaFind, and Verisante Aura). Lesions from 184 patients were imaged, assessed, and excised. Skin specimens were assessed by 2 blinded pathologists. Fifty-nine lesions from 56 patients had a histopathologic diagnosis of melanoma, whereas 150 lesions from 128 patients were diagnosed as benign. The researchers reported sensitivities and specificities were, respectively, MelaFind (82.5%, 52.4%), Verisante Aura (21.4%, 86.2%), and FotoFinder Moleanalyzer Pro (88.1%, 78.8%). The sensitivity and specificity of the teledermoscopist (84.5% and 82.6%) and local dermatologist (96.6% and 32.2%) were also compared.

Comment: The following are key segments from the paper.

A number of noninvasive, computer-assisted methods have been developed for use at the bedside to facilitate a timely diagnosis of melanoma without the need for an expert dermatologist, including multispectral instrumentation, Raman spectroscopy, reflectance confocal microscopy, and artificial intelligence with dermatoscopic algorithms.

This study was a prospective analysis of patients from Atlantic Canada who were treated in the Pigmented Lesion Clinic in the Division of Clinical Dermatology and Cutaneous Science, Dalhousie University, Halifax, Nova Scotia. Patients were recruited from general dermatology clinics at the QEII Health Sciences Centre, from private community clinics, and on referral from family practices.

Two hundred nine lesions were analysed from 184 patients. Fifty-nine lesions from 56 patients had a histopathologic diagnosis of melanoma or melanoma in situ, whereas 150 lesions from 128 patients were diagnosed as benign.

The study found that adding computer analysis of dermoscopic images (FotoFinder) complemented clinical diagnostic accuracy by reducing the number of missed melanomas. When the FotoFinder Tuebinger was used as an aid to the clinical diagnosis, both the melanomas that were missed by the local dermatologists were captured. When it was used to complement the remote dermatologist, the number of missed melanomas was reduced from 4 to 3. Of the 4 cases, 3 were listed as histopathologically challenging, with a diagnosis of melanoma favoured, but not definitive. Seventeen cases initially diagnosed histopathologically as equivocal and suspicious for melanoma were also considered atypical on clinical examination, as well as on teledermoscopy, illustrating that the challenges faced by examining dermatologists may be shared by pathologists.

They conclude: "The study demonstrates that the highest sensitivity and specificity of the instruments were established with the FotoFinder Moleanalyzer Pro, which could be a valuable tool to assist with, but not replace, clinical decision making."

Reference: J Am Acad Dermatol 2021 Aug;85(2):353-359
Abstract

Development of a Metastatic Uveal Melanoma Prognostic Score (MUMPS) for use in patients receiving immune checkpoint inhibitors

Authors: Kelly D, et al

Summary: This single-centre retrospective cohort study evaluated the characteristics associated with ICI benefit in patients with metastatic uveal melanoma (mUM). The study cohort comprised of 71 patients with mUM who received anti-PD1/L1 ± anti-CTLA4 ICI. Of these, 54 received anti-PD1/L1 alone, and 21 received anti-PD1/L1 + anti-CTLA4. The median clinical progression-free survival (cPFS) was 2.7 months, and the median OS was 10.0 months. The authors reported the variables associated with a good prognosis for both cPFS and OS were: ≥2 years from the initial diagnosis to metastatic disease (n = 25), LDH < 1.5 × ULN (n = 45), and absence of bone metastases (n = 66). They developed a Metastatic Uveal Melanoma Prognostic Score (MUMPS). Patients were divided into 3 MUMPS groups based on the above prognostic variables: Poor prognosis, Intermediate prognosis and Good prognosis. Good prognosis patients experienced longer cPFS (6.0 months) and OS (34.5 months) than patients with intermediate (2.3 months cPFS, 9.4 months OS) and poor prognosis disease (1.8 months cPFS, 3.9 months OS); p < 0.0001. The authors noted MUMPS has potential prognostic value, however, further validation is warranted to determine its role in selecting ICI treatment management for mUM.

Comment: This is a retrospective cohort study of mUM patients. The study aimed to identify clinical characteristics that were predictive of benefit from treatment with ICIs in patients with mUM. The essential results are described in the abstract but in this era of selective patient treatments little discussion was given to the molecular testing results. Impact Genetics comprises probes against chromosome 3 loss, chromosome 8q gain and chromosome 6p gain (25% patients). NGS (next generation sequencing) was on BAP1, BRAF, CDK4, CDK6, CDKN2A, GNA11, GNAQ, KIT, NRAS and SF3B1 (70% patients). No single gene was associated with response to ICI or the 3 clinical groups.

Their final paragraph poses a challenge for future studies in uveal melanoma. "However, due to the smaller sample size and missing genomic data—we could not assess the relationship between genomic driver mutations and ICI response in this cohort of mUM patients. Indeed, the difference in the incidence of BAP1 mutations between the anti-PD1/L1 and the anti-PD1 + anti-CTLA4 group may be particularly relevant. BAP1 is a multifunctional tumour suppressor, and BAP1 mutations in UM are associated with activation of regulatory immune cells and an immunosuppressive tumour microenvironment. This could contribute to resistance to ICI and differences in clinical outcomes; however, this is not well understood and is still being elucidated."

Reference: Cancers (Basel) 2021 Jul 20;13(14):3640
Abstract

The role of local therapy in the treatment of solitary melanoma progression on immune checkpoint inhibition: A multicentre retrospective analysis

Authors: Versluis JM, et al

Summary: The study cohort included patients with metastatic melanoma treated with ICI with solitary progression as first progressive event from 17 centres in 9 countries. The authors identified 294 patients with solitary progression after stable disease in 15%, partial response in 55% and complete response in 30%. The median follow-up was 43 months; the median time to solitary progression was 13 months, and the median time to subsequent progression after treatment of solitary progression (TTSP) was 33 months. The estimated 3-year OS was 79%; median OS was not reached. The authors reported treatment consisted of systemic therapy (18%), local therapy (36%), both combined (42%) or active surveillance (4%). In 44% of patients treated for solitary progression, no subsequent progression occurred. For solitary progression during ICI (n = 143), the median TTSP was 29 months. Both TTSP and OS were similar for local therapy, ICI continuation and both combined. For solitary progression post ICI (n = 151), the median TTSP was 35 months. TTSP was higher for ICI recommencement plus local therapy than local therapy or ICI recommencement alone (p = 0.006), without OS differences.

Comment: This is a well conducted study that examines the benefit of local treatment of solitary recurrences during or following ICI immunotherapy in a large cohort of 294 patients. The results dispel the notion that all is lost for such patients in that overall median survival was not reached and estimated 3-year OS was 79%. Highest estimated TTSP was in bone (69%) and lymph node (61%) sites and lowest in liver (29%) and adrenal gland. They caution as follows: "inherent to our retrospective study design, selection bias cannot be excluded, comprehensive data on reasons for treatment choices were not available and some subgroups were small. However, a prospective randomised controlled trial, is unlikely to be performed because of the rapidly changing treatment landscape and the number of patients needed."

They also question whether more intensive treatment is needed for treatment of recurrences after cessation of ICI. Conclusion: "This study demonstrates that in almost half of patients treated for solitary melanoma progression, no subsequent progression occurred. In patients with solitary progression post ICI, combining local therapy and ICI recommencement was associated with later onset of subsequent progression, but not with improved OS compared with single-modality treatment. This indicates that local therapy only is a reasonable option. There is less evidence supporting local therapy for solitary progression during ICI. In general, this study suggests that local therapy can benefit patients and may be associated with favourable long-term outcomes."

Reference: Eur J Cancer 2021 Jul;151:72-83
Abstract

Phenotype, specificity and avidity of antitumour CD8⁺ T cells in melanoma

Authors: Oliveira G, et al

Summary: The authors showed tumour specificity shapes the expression state of intratumoural CD8⁺ T cells by linking the antigenic specificity of T cell receptors (TCRs) and the cellular phenotype of melanoma-infiltrating lymphocytes at single-cell resolution. They found non-tumour-reactive T cells were enriched for viral specificities and exhibited a non-exhausted memory phenotype, whereas melanoma-reactive lymphocytes predominantly displayed an exhausted state that encompassed diverse levels of differentiation but rarely acquired memory properties. These exhausted phenotypes were observed both among clonotypes specific for public overexpressed melanoma antigens (shared across different tumours) or personal neoantigens (specific for each tumour). The recognition of such tumour antigens was provided by TCRs with avidities inversely related to the abundance of cognate targets in melanoma cells and proportional to the binding affinity of peptide-human leukocyte antigen (HLA) complexes. They also reported persistence of TCR clonotypes in peripheral blood was negatively affected by the level of intratumoural exhaustion and increased in patients with a poor response to immune checkpoint blockade, consistent with chronic stimulation mediated by residual tumour antigens.

Comment: This Nature paper is definitely for immunologists and conducted by one of the leading groups in tumour immunology related to melanoma. It is a single cell study on TILs from melanoma. They show that TILs include non-tumour as well as tumour reactive T cells which is not new. Tumour reactive TILs were recognised by their expression of exhausted phenotypes by which they mean expression of inhibitory receptors such as PD1, LAG3, TIM3 and CD39 as well as other criteria. The tumour reactive T cells recognised so called public specificities such as MART1 or neoantigens that had higher TCR affinities. The high affinity exhausted neoantigen T cells were relatively low in the circulation compared to T cells recognising the public melanoma antigens.

These findings are analogous to those of Harbst et al, from the Denmark group referred to in these selections. That study found that many TCR specificities in the tumour did not grow out for inclusion in the TILs used in treatment which may have been because the effective T cells had an exhausted phenotype as described by Oliveira et al. The authors conclude: "Our data therefore underscore the importance of generating new non-exhausted T cells to achieve a productive antitumour response and this might derive from ex-vivo revived intratumoural tumour-specific TPE precursors or TEM cells endowed with regenerative potential." CD39 positive T cells in particular were shown by this group in other studies to be associated with poor responses. All in all, the studies highlight the need for treating T cell exhaustion to improve treatment by immunotherapy with ICI or adoptive immunotherapy.

Reference: Nature 2021 Aug;596(7870):119-125
Abstract

Clinical efficacy of T-cell therapy after short-term BRAF-inhibitor priming in patients with checkpoint inhibitor-resistant metastatic melanoma

Authors: Borch TH, et al

Summary: This phase I/II clinical trial evaluated the use of vemurafenib priming before TIL harvest and adoptive T cell therapy. Patients (n =12) with checkpoint inhibitor-resistant metastatic melanoma were treated with vemurafenib for 7 days before tumour excision and during the following weeks until TIL infusion. TILs were grown from tumour fragments, expanded in vitro and reinfused to the patient preceded by a lymphodepleting chemotherapy regimen and followed by interleukin-2 infusion. The researchers observed no unexpected toxicity and treatment was well tolerated. Of 12 patients, 1 achieved a complete response (CR), 8 achieved partial response (PR) and 3 achieved stable disease. A PR and the CR are ongoing for 23 and 43 months, respectively. In vitro anti-tumour reactivity was found in TILs from 10 patients, including all patients achieving objective response. Serum and tumour biomarker analyses indicate that baseline cytokine levels and the number of T cell clones may predict response to TIL therapy. In addition, TCR sequencing suggested skewing of TCR repertoire during in vitro expansion, promoting certain low frequency clonotypes.

Comment: It is accepted that BRAFV600 targeted treatments also induce an immune response against melanoma. This study has attempted to exploit this by treating patients who were to be treated by adoptive immunotherapy with a short 7-day course of vemurafenib prior to resection of the melanoma metastasis. The idea being that TILs from the tumour would be further primed by exposure to antigen released by vemurafenib treatment. The patients had failed treatment with ICI. The patient numbers were small so not much can be concluded about efficacy even though there was 1 CR and 8 PRs in 12 patients. A very extensive analysis of TILs was conducted including RNA Seq analysis. This data allowed them to conclude that many of the TCR specificities in the tumour were not detected in TILs possibly because the important TILs could not be expanded. There was no difference between responders and non-responders to vemurafenib and they were unable to conclude that vemurafenib increased the TIL response or the clinical response. The paper contains a wealth of immunological findings and it is reassuring that the investigators reported results without undue bias.

Reference: J Immunother Cancer 2021 Jul;9(7):e002703
Abstract

