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American Society of Clinical Oncology 2022 Annual Meeting

MELANOMA-SPECIFIC REPORT

Save Your Skin Foundation
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Table of Contents

INTRODUCTION **4**

GLOSSARY **4**

CARE DELIVERY AND REGULATORY POLICY **6**

Presentation: Expanding Clinical Trial Eligibility to Improve Their Generalizability and Advance Equity 6
Presentation: The Whole is Greater than the Sum of its Parts: Bringing the Patient into the P-Value 7
Poster: Can an artificial intelligence-based platform reduce physician burden and increase access to clinical trials? 8
Poster: Disparity in initiation of checkpoint inhibitors among metastatic melanoma and lung cancer 9
Poster: Impact of broadening trial eligibility criteria on the inclusion of patients with brain metastases in cancer clinical trials. 9
Poster: Circulating cytokines as predictors of response to immune checkpoint inhibitors (ICIs) in patients (pts) with melanoma (Mel) and non–small cell lung cancer (NSCLC) 10
Poster: A phase 1 first-in-human dose finding/randomized phase 2 study of IMM60 and pembrolizumab (PEM) in advanced melanoma and non–small cell lung cancer (NSCLC; IMP-MEL). Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma 11
Poster: Systematic assessment of tumor mutational burden calculation across different sequencing platforms and cancer types and its implication in clinical decision-making 11
Poster: Association between tumor mutational burden (TMB) and mutational profile and its effect on overall survival: A post hoc analysis of patients with TMB-high and TMB-low metastatic cancer treated with immune checkpoint inhibitors (ICI) 12
Poster: Safety, tolerability, and preliminary efficacy of nadunolimab, a first-in-class monoclonal antibody against IL1RAP, in combination with pembrolizumab in subjects with solid tumors 14

MELANOMA/SKIN CANCER **14**

Presentation: Vaccines in Melanoma: A Promising Road Ahead 14
Poster: Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study 17
Poster: Survival data of PRADO: A phase 2 study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma 18
Poster: Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512) 18
Poster: NeoTrio: Randomized trial of neoadjuvant (NAT) pembrolizumab (PEMBRO) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy 19
Poster: Nivolumab (NIVO) + relatlimab (RELA) versus NIVO in previously untreated metastatic or unresectable melanoma: OS and ORR by key subgroups from RELATIVITY-047 20
Poster: Atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with BRAFV600mutation–positive melanoma with central nervous system (CNS) metastases (mets): Primary results from phase 2 Tricotel study 22
Poster: Navtemadlin (KRT-232) activity after failure of anti-PD-1/L1 therapy in patients (pts) with TP53WT Merkel cell carcinoma (MCC) 23

Poster: A phase II clinical trial of camrelizumab (CAM, an IgG4 antibody against PD-1) combined with apatinib (APA, a VEGFR-2 tyrosine kinase inhibitor) and temozolomide (TMZ) as the first-line treatment for patients (pts) with advanced acral melanoma (AM) 23
Poster: A retrospective study of ipilimumab plus nivolumab in anti–PD-L1/PD-1-refractory Merkel cell carcinoma 24
Poster: Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067 24
Poster: Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy 26
Poster: Tumor mutational burden (TMB) in immune checkpoint inhibitor (ICI)-naïve and -experienced patients with metastatic melanoma treated with lifileucel, a tumor-infiltrating lymphocyte (TIL) cell therapy 26
Poster: Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: A multicenter, open-label, single-arm phase 2 study 27
Poster: Encorafenib plus binimetinib in patients with locally advanced, unresectable, or metastatic BRAFV600-mutant melanoma: Updated data from the multicenter, multinational, prospective, non-interventional longitudinal study BERINGMELANOMA 28
Poster: Dabrafenib (D) and trametinib (T) plus spartalizumab (S) in patients (pts) with previously untreated BRAF V600–mutant unresectable or metastatic melanoma: Three-year overall survival (OS) data from the randomized part 3 of the phase III COMBI-i trial 28
Poster: Efficacy and safety of nivolumab for locally advanced or metastatic cutaneous cell carcinoma (NIVOSQUACS trial) 29
Poster: Phase II study SECOMBIT (sequential combo immuno and target therapy study): A subgroup analysis with a longer follow-up 30
Poster: Efficacy and safety of cosibelimab, an anti–PD-L1 antibody, in patients with metastatic cutaneous squamous cell carcinoma 31
Poster: Anti-LAG-3 antibody LBL-007 in combination with toripalimab in patients with unresectable or metastatic melanoma: A phase Ⅰ, open-label, multicenter, dose escalation/expansion study 31
Poster: Overall survival (OS) with first-line atezolizumab (A) or placebo (P) in combination with vemurafenib (V) and cobimetinib (C) in BRAFV600 mutation-positive advanced melanoma: Second interim OS analysis of the phase 3 IMspire150 study 32
Poster: Efficacy and safety of sequencing with vemurafenib (V) plus cobimetinib (C) followed by atezolizumab (Atezo) in patients (pts) with advanced BRAFV600-positive melanoma: Interim analysis of the ImmunoCobiVem study 33
Poster: Merkel polyoma virus specific T-cell receptor transgenic T-cell therapy in PD-1 inhibitor refractory Merkel cell carcinoma 34
Poster: Camrelizumab plus apatinib for patients with advanced mucosal melanoma: A prospective single-arm study 34
Poster: Analysis of overall survival (OS) and relapse-free-survival (RFS) in the phase 1b clinical trial of anti–PD-1 ab (toripalimab) plus intralesional injection of OrienX010 in stage Ⅳ melanoma with liver metastases 35
Poster: IMPemBra, a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients with melanoma harboring the BRAFV600 mutation: Three-year survival data and translational analyses 36
Poster: Updated results from the skin cancer cohorts from an ongoing phase 1/2 multicohort study of RP1, an enhanced potency oncolytic HSV, combined with nivolumab (IGNYTE) 37
Poster: A phase II study to evaluate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors in patients with advanced melanoma: Final results of the IMM-101-015 trial 37
Poster: A phase 1b/2a study of safety and efficacy of NT-I7 in combination with anti-PD-L1 (atezolizumab) in patients with anti-PD-1/PD-L1 naïve or relapsed/refractory (R/R) high-risk skin cancers: The phase 1b report 38
Poster: Adjuvant dabrafenib plus trametinib (D + T) versus placebo in patients with resected stage III BRAFV600-mutant melanoma: Updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD 39
Poster: Survival update of neoadjuvant ipilimumab + nivolumab in macroscopic stage III melanoma: The OpACIN and OpACIN-neo trials 40

Poster: SALVO: Single-arm trial of ipilimumab and nivolumab as adjuvant therapy for resected mucosal melanoma 41
Poster: Efficacy and safety of "second adjuvant" therapy with BRAF/MEK inhibitors after resection of recurrent melanoma following adjuvant PD-1–based immunotherapy ... 41
Poster: Adjuvant temozolomide plus cisplatin versus high-dose interferon alpha-2b in resected mucosal melanoma: A randomized, multicenter, controlled, phase III trial ... 42
Poster: Neoadjuvant dabrafenib and trametinib (D+T) for stage III melanoma: Long-term results from the NeoCombi trial ... 42
Poster: [Ongoing] Randomized phase 3 trial of IO102-IO103 plus pembrolizumab versus pembrolizumab alone in patients with previously untreated, unresectable, or metastatic melanoma ... 43
Poster: [Ongoing] First-in-human clinical trial of an oncolytic adenovirus armed with TNFa and IL-2 in patients with advanced melanoma receiving adoptive cell transfer of tumor-infiltrating lymphocytes ... 44
Poster: [Ongoing] A randomized, controlled, open-label, phase 2 study of cemiplimab ± RP1 in patients with advanced cutaneous squamous cell carcinoma (CERPASS) ... 44
Poster: [Ongoing] DELTA-1: A global, multicenter, phase 2 study of ITIL-168, an unrestricted autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in adult patients with advanced cutaneous melanoma ... 45
Poster: [Ongoing] Optimization of Voyager V1 (VV1) oncolytic virus systemic delivery in combination with cemiplimab and ipilimumab in patients with melanoma and non–small cell lung cancer (NSCLC) ... 45
Poster: [Ongoing] Tocilizumab in combination with ipilimumab and nivolumab in solid tumors ... 47
Poster: [Ongoing] Design and rationale of a first-in-human (FIH) phase 1/1b study evaluating KIN-3248, a next-generation, irreversible (irrev), pan-FGFR inhibitor (FGFRi), in adult patients with solid tumors harboring FGFR2 and/or FGFR3 gene alterations ... 47
Poster: [Ongoing] DETECTION phase II/III trial: Circulating tumor DNA–guided therapy for stage IIB/C melanoma after surgical resection ... 48
Poster: Neo-adjuvant T-VEC plus nivolumab combination therapy for resectable early-stage or metastatic (IIIB-IVM1a) melanoma with injectable disease: The NIVEC trial ... 49

SYMPTOMS AND SURVIVORSHIP ... 51

Poster: Thromboembolism (TE) and association with survival in patients (pts) with melanoma receiving chemo– or immunotherapy ... 51
Poster: Association between unmet needs and utilization of emergency services among cancer survivors in Canada 52
Poster: [Ongoing] The RADIO trial: Randomized assessment of cisplatin dosing interval for ototoxicity with curative concurrent chemo-radiation for locally advanced head and neck squamous cell carcinoma ... 53
Poster: [Ongoing] Immune-related adverse events and symptom burden in patients with melanoma receiving adjuvant immune checkpoint inhibitor ... 53

OCULAR MELANOMA ... 54

Poster: Outcomes of combined ipilimumab/nivolumab in metastatic uveal melanoma: A prevalence meta-analysis ... 54
Poster: Safety and efficacy of combined melphalan percutaneous hepatic perfusion (M-PHP) and ipilimumab plus nivolumab (IPI+NIVO) in metastasized uveal melanoma (mUM): First results of the phase Ib part of the CHOPIN trial ... 54
Poster: Immune profiling of metastatic uveal melanoma and response to immune checkpoint inhibitors ... 55
Poster: Randomized phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma: The final analysis of cohort 1 ... 56

Introduction

From June 3-7th, the American Society of Clinical Oncology (ASCO) held its annual meeting in Chicago, Illinois. This conference brought together tens of thousands of oncologists, government representatives, and patient advocates to discuss advances in oncology and best practices developed over the year. This report outlines the extensive melanoma, non-melanoma skin cancer (NMSC), ocular melanoma, and survivorship-related material presented over the weekend, including talks, posters, and abstracts, with the exception of the ocular melanoma portion. These pieces are organized by content 'track' or category. Content from these presentations was sourced from the ASCO online meeting library after the conference. The report also includes a glossary of terms and acronyms frequently used throughout the report. If you have any questions, please contact taylorkathleen@saveyourskin.ca.

Glossary

Following are a list of oncology-related acronyms and terms that are frequently used in ASCO presentations, abstracts, and posters. Terms are also written in full during presentation, abstract, and poster summaries followed by bracketed acronyms for ease.

General terms:
DCR: disease control rate
ORR: objective response rate (complete response + partial response)
CP: complete response
PR: partial response
DOR: duration of response
DCR: duration of complete response
DOT: duration of treatment
tPFS: total progression-free survival
PFS: progression-free survival
RFS: relapse-free survival
DMFS: distant metastasis-free survival
OS: overall survival
TRAE: Treatment-related adverse events
CB: clinical benefit
QoL: quality of life
PD: progression of disease
TMB: Tumour mutational burden
ICI: immune checkpoint inhibitor(s)
BRAF: A human gene that encodes the BRAF protein, which impacts cell division. Mutations in these gene can impact the spread of cancer in the human body.

MCC: Merkel cell carcinoma
(C)SCC: (cutaneous) squamous cell carcinoma
BCC: basal cell carcinoma
DM: desmoplastic melanoma
AM: acral melanoma

Drug acronyms:
IPI: ipilimumab
NIVO: nivolumab
PEMBRO: pembrolizumab
RELA: relatlimab
D: dabrafenib
T: trametinib
A: atezolizumab
C: cobimetinib
V: vemurafenib
APA: apatinib
TMZ: temozolomide
E: encorafenib
B: binimetinib

Care-related (medical) terms:
Adjuvant: Treatment administered post-surgery with the intention of eliminating remaining cancer cells, reducing the chance of disease recurrence.
Neoadjuvant: Treatment administered before surgery in efforts to shrink the tumour and/or stop cancer spread.
Pharmacokinetic: Related to the process of drug absorption, distribution, metabolism, and excretion
Pharmacogenomic: Related to how a person's genes affect their response to certain medications.
RECIST v1.1: Version 1.1 of the RECIST guidelines. The RECIST standard is used to measure how well a cancer patient responds to treatment, primarily based on changes (or lack of) in tumours.
QW: Once weekly, as in treatment delivery. Numerical value is added with increased numbers of weeks (Q2W=two weeks, Q3W=three weeks, etc.)
ECOG: Eastern Cooperative Oncology Group. The ECOG Performance Status Scale refers to a measurement, formulated by ECOG, which describes a patient's ability to function independently in terms of caring for themselves, physical ability, and daily activity.
Kaplan-Meier Curve: Estimates the survival function of data in sets with missing values, suggesting the probability that a subject will survive until X time.

Organizations:
FDA: US Food and Drug Administration
FoCR: Friends of Cancer Research
NCI: National Cancer Institute
ASCO: American Society of Clinical Oncology

Care Delivery and Regulatory Policy

Presentation: Expanding Clinical Trial Eligibility to Improve Their Generalizability and Advance Equity

Presented by Dr Edward Kim, MD, MBA (City of Hope)

In this talk, Dr Edward Kim discussed possibilities for expanding clinical trial eligibility to make them more equitable. Kim argues that modernizing eligibility criteria looks like creating a new eligibility culture that only excludes when it is warranted by safety, creating and implementing new enrolment criteria, having to justify exclusions, and having more consistent and active discussions about these factors during trial design and FDA meetings. These issues need to move beyond the publishing stage to actually being implemented.

Kim began collecting this data in a co-authored 2015 paper titled "Modernizing Eligibility Criteria for Molecularly Driven Trials" in *Journal of Clinical Oncology* (33.25). This study raised questions about the actual impact of stripping away common trial exclusion criteria, such as including patients with brain metastases in trials. Kim et al. found that clinical trials have a median of 37 eligibility criteria each and that removing a portion of these would not have dramatic results. Further, they discerned that trials with fewer than 27 eligibility criteria would enrol more quickly. This publication was seen by the non-profit Friends of Cancer Research who decided to get involved, resulting in several follow-up articles which interrogated eligibility criteria-related questions such as minimum age and what makes someone qualify as an adult, whether eligibility can be determined by the number of Investigational New Drug (IND) applications received per year, and organ disfunction co-morbidities (especially for people in rural areas), and HIV exclusion (which is not usually verified). Recommendations based on these articles included assessment of specific eligibility criteria, such as brain metastases, minimum age, HIV/AIDS, organ dysfunction, prior and concurrent malignancies; and expanded recommendations for eligibility criteria, including washout periods and concomitant medications, prior therapies, lab reference ranges and test intervals, and performance status. Some of these recommendations were adopted by the National Cancer Institute's Cancer Therapy Evaluation Program's Generic Protocol Template and also FDA Guidance Documents.

Kim argues that the benefits of modernizing clinical trial eligibility would outweigh the consequences. The benefits would include fewer protocols, trial staff working more actively with

patients who are in-treatment, larger real-world population enrolled into trials, faster enrollment, quicker approvals of active drugs, and expanding trial opportunities for patients. The consequences include lower and slower enrolments, an increased burden on clinical trial staff, longer protocols, and a decreased rate of clinicians being able to get their patients into studies. Further, drugs that are marginally effective may not get approved in the current process, which is important because while 1/20 patients are currently eligible for clinical trials, 16/20 may be eligible for the approved drug, meaning that approving more marginally effective drugs offers more options to more patients. It is imperative that clinical trials treatments are considered in the context of "real world" populations.

Kim concludes by reiterating that there are many benefits to reassessing clinical trial enrolment criteria in terms of increasing trial and drug accessibility for cancer patients. In an ideal world, protocol design would begin with patients being eligible by default, with inclusion and exclusion being based on study objectives, scientific justification, should ensure a study population that is reflective of disease epidemiology, and address substantiated patient safety risks. Further, there should be open and ongoing monitoring and critical assessment of eligibility criteria going forward.

Presentation: The Whole is Greater than the Sum of its Parts: Bringing the Patient into the P-Value

Jill Feldman, MA (EGFR Resisters Patient Group)

In this presentation, Jill Feldman offered the patient perspective on using real world data in clinical trials. As Feldman notes, while there have been great advances in cancer care, clinical trials still face the issue of excessive eligibility criteria, which homogenizes trial populations and data. As Feldman points out, "you can't quantify the context of a person's life," and patients with unique situations are often unable to meet the restrictions of trial eligibility restrictions. Making treatment decisions based on trial data alone also isn't realistic for most patients. This is especially true given the myriad of factors that patients must consider that treatment providers don't have to contend with in a meaningful way, such as balancing survival benefit with side effects, impact on family and caregivers, and on quality of life. Given the advances that have been made in the treatment space, patients no longer want to survive, but want to be able to live; and quality of life benefits are not ones that can be measured in a clinical trial. While clinical trial data is obviously essential for understanding the efficacy and safety of a product, it misses out on several nuances that patients consider when making treatment decisions.

Feldman then referenced Dr Edward Kim's previous discussion of modernizing clinical trial eligibility data (above), highlighting the incredible number of patients that could be included in trials if eligibility restrictions were more judicious and if exclusions required justification. However, Feldman believes that even these changes will not fully mediate all of the factors patients must contend with when making a decision. Real-world data can thus help move us in this direction, partly because it is as "messy" and "unpredictable" as the actual lives of patients.

Feldman then outlined her own experience Osimertinib (a targeted therapy) as adjuvant therapy, on which she experienced dramatic side effects despite positive data.

Feldman then discussed a project called Patient Priority, which was a collaboration between the EGFR [a lung cancer mutation] Resisters Patient Group, which Feldman founded, and Longevity Foundation. The project consisted of an institutional review board-approved survey which allowed comparison between the side effects experienced by EGFR Resisters Patient Group members on Osimertinib versus people in the FLAURA trial (osimertinib versus gefitinib or erlotinib). The members of the patient group, the real-world data set, reported more severe and widely experienced fatigue, which meaningfully affects patient quality of life, especially over the long term. Further, as Feldman points out, real world data demonstrated that the Medicaid expansion reduced time to treatment and disparities of patients with advanced cancer, indicating the continued need to advocate for the Affordable Care Act. Real world data, Feldman adds, can also be accrued faster than clinical trial data, which is an imperative consideration when time is such a limited quantity for cancer patients.

Feldman then shared that the Clinical Trial Transformation Initiative has developed recommendations for the use of real-world data to create actionable tools to assist in increasing trial eligibility criteria and enrolment, including patient reported outcome (PRO) data. This can help treatment providers look beyond trial data to answer questions other than whether a drug fits the purpose and is appropriate for patients.

Poster: Can an artificial intelligence-based platform reduce physician burden and increase access to clinical trials?

Limor Gortzak Uzan, MD (Trialjectory) et al.
Abstract #1552

This poster presented Trialjectory, a platform which uses artificial intelligence (AI) and a natural language process to monitor, analyze, and match patients to clinical trials. Currently the largest resource for clinical trial information is clinicaltrials.gov, which is directed at medical professionals and largely inaccessible for patients. Clinicaltrials.gov also does not have a trial matching service. As a trial-matching service that specifically targets patients, Trialjectory has the potential to reduce clinical trial access barriers.

To facilitate trial matching, patients are asked to fill out an extensive questionnaire of clinical data, including treatment history, disease characteristics, comorbidities, and general health. These questions are curated based on the eligibility criteria of available trials. The quiz allows patients to be matched to trials with a sensitivity rate of 90% and specificity of 95%. In addition to the matched results of the quiz, Trialjectory has a support team that is available via text, email, or phone.

Trialjectory was tested by 49,906 cancer patients between July 2019-December 2021. Of these patients, 49,199 (98.6%) were found to be eligible for clinical trials. This high figure demonstrates that Trialjectory is an excellent tool for democratizing access to clinical trials.

Poster: Disparity in initiation of checkpoint inhibitors among metastatic melanoma and lung cancer
Meng Li, PhD (University of Texas MD Anderson Cancer Center) et al.
Abstract #1583

This study aimed to elucidate disparities in patients initiating checkpoint inhibitor (ICI) therapy and assess area- and patient-related causes for delay in initiation. This retrospective study used Optum data regarding patients with newly diagnosed metastatic melanoma or lung cancer since the introduction of ICI therapies to these cancers. The melanoma cohort was diagnosed between January 2011-December 2020 and the lung cancer cohort between January 2015-December 2020. Independent variables included the country-level measures of population demographics, including race and class, number of oncologists per population, presence of a National Cancer Institute-affiliated (NCI) centre, and rurality. Patient-level characteristics include sex, age, dual eligibility, comorbidity, insurance, and year of diagnosis.

In these two cohorts collectively, the rates of patients receiving checkpoint inhibitors increased from 22% to 58% from 2011 to 2020, and 23% to 52% from 2015 to 2020. While areas with a higher percentage of Hispanic, black, and other minorities lived in high-density urban areas with NCI-designated centres and oncologists, areas with higher Hispanic populations were associated with lower rates of ICI initiation in both the melanoma and lung cancer cohorts. On a county basis, the percentage of minority populations was associated with slower initiation of ICIs in metastatic lung cancer patients. On the patient level, the melanoma cohort demonstrated significantly slower initiation of ICI therapy when associated with females, older age, dual eligibility, and commercial insurance enrolment. The data analyzed demonstrates that commercially insured metastatic melanoma and lung cancer patients in US counties with higher Hispanic populations initiated ICI therapy more slowly after cancer diagnosis, despite the higher rate of oncologists and NCI-centres. This demonstrates that there continue to be structural impediments to accessing treatments for non-white and minority populations.

Poster: Impact of broadening trial eligibility criteria on the inclusion of patients with brain metastases in cancer clinical trials
Joseph M. Unger, PhD, MS (Fred Hutchinson Cancer Research Center)
Abstract # 1505

This project examined responses to a 2017 call by ASCO, Friends of Cancer Research (FoCR), and the U.S. Food and Drug Administration (FDA) to amend eligibility criteria in clinical trials to make them more inclusive, including those related to brain metastases. This study analyzed whether the patterns of exclusions surrounding patients with brain metastases changed over time in response to the 2017 ASCO/FoCR/FDA call.

Data from clinicaltrials.gov was used to assess patterns of trial eligibility criteria in phase 1-3 interventional clinical trials in the US, for patients with advanced breast, colorectal, or lung

cancers (January 2013-October 2021).[1] Reviewers were blinded to the year of trial activation. The trials were categorized by whether patients with brain metastases were completely excluded, conditionally excluded, or included. In total, 1998 trials were evaluated.

Of these 1998 trials, patients with brain metastases were completely excluded from 196 trials (9.8%), conditionally excluded in 1459 trials (74.8%), and included in 307 trials (15.4%). In the period following the ASCO/FoCR/FDA recommendation (post-2017), there was a 92% increase in the odds of trials which included patients with brain metastases compared to conditional exclusion, with the estimated proportion of trials which included patients with brain metastases increasing from 9.2% pre-recommendation to 15.6% post-recommendation. The rate at which patients with brain metastases were conditionally excluded was also lower than estimated (76.9%, while the estimate was 85.3%). There was no meaningful difference in the number of trials in which patients with brain metastases were completely excluded (pre-recommendation: 7.5%, post-recommendation: 5.4%). Overall, the shift which took place after the ASCO/FoCR/FDA was largely between the categories of conditionally excluded to included, improving clinical trial access for patients with brain metastases.

Poster: Circulating cytokines as predictors of response to immune checkpoint inhibitors (ICIs) in patients (pts) with melanoma (Mel) and non–small cell lung cancer (NSCLC)

Guilia Pasello, MD (Medical Oncology 2, Istituto Oncologico Veneto IOV-IRCCS, Department of Surgery, Oncology and Gastroenterology, University of Padova) et al.
Abstract # 2549

The prospective real-world study presented in this poster enrolled melanoma and non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors. The endpoint was to verify an association between circulating cytokines and DCR, PFS, and OS. Blood was collected from patients at tumour assessment and before every treatment cycle for six cycles, until disease progression or after two years. The markets were categorized according to high or low levels and tested in univariate and multiple analyses.

The results from the T1-T2 blood samples of 78 enrolled patients demonstrated that high levels of IL-8 and IL-6 serums at the second cycle of immune checkpoint inhibitors, plus an increase of IL-8, can be strong predictors of OS and PFS for patients with advanced NSCLC and melanoma. Further data from the other cytokines tested in this study is upcoming.

[1] The poster in question was included in this report based on the frequency of brain metastases in melanoma patients.

Poster: A phase 1 first-in-human dose finding/randomized phase 2 study of IMM60 and pembrolizumab (PEM) in advanced melanoma and non–small cell lung cancer (NSCLC; IMP-MEL). Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma[2]
Lisa May Ling Tachiki, MD (University of Washington and Fred Hutchinson Cancer Research Center) et al.
Abstract # 2588

This study aimed to further knowledge about the optimal duration of treatment (DoT) using immune checkpoint inhibitors (ICI) in patients with Merkel cell carcinoma (MCC) and metastatic melanoma. ICI continuation in melanoma patients might be associated with higher rate of disease progression over time relative to ICI continuation, suggesting that a longer duration of treatment could improve outcomes. However, continuation at standard frequency doses is not viable either logistically or financially. This study tested maintenance dosing of anti-PD-1 antibodies at a reduced rate (2-3 months) to extend the duration of immune checkpoint inhibitor duration beyond two years.

Between 2014-2021, this study analyzed 23 patients with either MCC or melanoma who had previously experienced initial clinical benefit with anti-PD-1 at standard dose frequency, before being moved to the reduced dose frequency for the study. The efficacy and safety endpoints considered after the reduced frequency doses were the rates of immune-related adverse events and progression free survival. The costs between the initial two years of anti-PD-1 treatment at standard dose frequency was also compared to the costs of extended duration of treatment at a reduced frequency. The results suggested that reduced dosage frequency is an option for preserving positive patient outcomes in those treated with anti-PD-1 therapy without additional financial or logistical burden. The reduced frequency dose appears to sustain the safety and efficacy benefits of the standard dose.

Poster: Systematic assessment of tumor mutational burden calculation across different sequencing platforms and cancer types and its implication in clinical decision-making
Daqiang Sun (Tianjin Chest Hospital) et al.
Abstract # 2631

This study sought to fill in the knowledge gap about the effects of different cancer types, sequencing platforms, and calculation methods on the use of tumour mutation burdens (TMB) as a prediction biomarker for immune checkpoint inhibitor response, plus the cut-off value of TMBs as a method of predicting immunotherapy efficacy

[2] This poster also appeared in the "Developmental therapeutics—molecularly targeted agents and tumor biology" track with the title "Extended duration of anti-PD-1 therapy, using reduced frequency dosing, in patients with advanced melanoma and Merkel cell carcinoma."

Either whole exome sequencing (WES) or targeted panel sequencing was performed on 4,140 tumour samples using a variety of sequencing platforms and the public sequencing data from a further 3,680 samples were obtained, which contained WES and targeted panel sequencing.[3] These samples were used to assess the impact of various sequencing methods, sequencing platforms, and calculation methods on the calculation of TMB. The data from a further 71 lung cancer samples were used to predict the cut-off value for TMB for predicting immunotherapy response.

The results found that TMB values which were calculated by different sequencing methods or platforms showed no significant differences. Further, there was a 0.95 correlation of TMB calculated from a single-sample versus a paired-sample. Finally, the optimal cut-off value for TMB in lung cancer being treated with ICI was determined to be 8 through receiver-operating characteristic curve analysis, with patients having TMB of greater than 8 showing better outcomes with those of TMB less than 8.[4]

Poster: Association between tumor mutational burden (TMB) and mutational profile and its effect on overall survival: A post hoc analysis of patients with TMB-high and TMB-low metastatic cancer treated with immune checkpoint inhibitors (ICI)

Camila Bragança Xavier, MD (Hospital Sírio-Libanês) et al.
Abstract # 6232

This study analysed overall survival data from 1,661 post-treatment patients to assess the effects of tumour mutational burden (TMB), with and without the use of immune checkpoint inhibitors (ICI) on these survival rates. Overall survival was studied according to the patient's mutational status; when gene exhibited a correlation to overall survival, these were given a further Cox multivariate analysis by median TMB, median age, sex, histology, and microsatellite instability (MSI) status.[5] [6]

The results demonstrated that patients with a higher TMB saw increased overall survival when treated with ICI, with the median overall survival being 42 months for TMB-high patients and 15 months for TMB-low patients. In TMB-high patients, 22 genes were associated with higher overall survival on ICI (NTRK3, TERT, NOTCH3, RNF43, TET1, PTPRD, NCOA3, TENT5C, ZFHX3, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12) while five were associated with reduced overall survival on ICI (STK11, KEAP1, CIC, E2F3, TP53). For TMB-low tumours, eight genes were associated with

[3] Exome sequencing refers to the sequencing of the protein-coding regions of the genes in a genome.
[4] A receiver operating characteristic plot is a graphical plot which illustrates the diagnostic ability of the binary classifier system with a varied discrimination threshold.
[5] The Cox model is used to analyse survival time data in medical research by describing the relation between an event incidence and a set of covariates.
[6] Histology describes a tumour based on the abnormality of cancer cells and tissue when examined under a microscope, an indication of how quickly cancer cells are likely to spread.

higher overall survival (VHL, SETD2, PBRM1, BRAF, KDM5C, MAP2K1, CSF1R, RET) while 20 were related to reduced overall survival (TP53, H3C2, DAXX, SMARC4, STK11, SOX17, RB1, PIK3CA, CTNNB1, KMT2D, HLA-A, FBXW7, CDH1, RBM10, KEAP1, IGF1R, H3C11, EGFR, RUNX1, B2M). The Cox multivariate analysis confirmed 3 genes connected to superior overall survival (KDM5C, PBRM1, and VHL) and inferior overall survival (CTNNB1, DAXX, FBXW7, H3C2, H3C1, IGF1R, KMT2D, PIK3CA, RB1, SMARC4, SOX17, TP53). Histology and MSI only played a relevant role in patients with melanoma, TMB-low. This study demonstrated that genomic alterations in single cancer genes can be used to help define outcomes for TMB-high and TMB-low patients who are treated with ICI.

	BETTER OS	WORSE OS
TMB-H	*NTRK3*, TERT, NOTCH3, RNF43*, TET1*, PTPRD*, NCOA3, TENT5C*, ZFHX3*, RIT1, CCNE1, PPM1D, GATA2, ALK, DNMT1, PTPRT, MET, EPHA7, BCL6, SMO, CDK6, MED12*	*STK11*, KEAP1, CIC, E2F3*, TP53*
TMB-L	*VHL*, SETD2, PBRM1*, BRAF, KDM5C*, MAP2K1, CSF1R, RET*	*TP53*, H3C2*, DAXX*, SMARCA4*, STK11, SOX17*, RB1*, PIK3CA*, CTNNB1*, KMT2D*, HLA-A, FBXW7*, CDH1, RBM10, KEAP1, IGF1R*, H3C11*, EGFR, RUNX1, B2M*

*Genes that exhibited correlation with OS in both uni- and multivariate analysis.

Image taken from abstract (Bragança Xavier et al.)

Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology

Poster: Safety, tolerability, and preliminary efficacy of nadunolimab, a first-in-class monoclonal antibody against IL1RAP, in combination with pembrolizumab in subjects with solid tumors

Shekeab Jauhari, MD (Sarah Cannon Research Institute, Florida Cancer Specialists and Research Institute) et al.
Abstract #2527
Clinical trial number: NCT04452214

The CIRIFOUR study assessed the use of nadunolimab (CAN04) combined with pembrolizumab (PEMBRO) for patients with solid tumours who have experienced progression on prior anti-PD-(L)1 therapy. CAN04 is a fully humanized ADCC-enhanced IgG1 antibody which targets interleukin-1 receptor accessory protein (IL1RAP) and blocks 1α and IL-1β. IL-1 induces an immune suppressive microenvironment via recruitment of myeloid-derived suppressor cells. The primary endpoints of the study were tolerability and safety and secondary endpoints included responses and efficacy as per RECIST.

Participants included patients with malignant melanoma, metastatic non-small cell lung cancer, and head and neck squamous cancer who had progressed after receiving anti-PD-(L)1 therapy for more than 12 weeks. These patients received standard PEMBRO dosing accompanied by 5mg/kg of CAN04 weekly. Serious adverse events occurred in 47% of participants, though only two of these were considered to be treatment-related. Decreased IL-6 was observed during treatment after the four-week mark; reduced neutrophil-lymphocyte ratio (NLR) also appeared after the first treatment and persisted throughout the study. Decreased IL-6 and NLR were most significant in the patients who saw the longest duration of disease control. This combination was considered tolerable and safe, while demonstrating evidence of prolonged disease control.

Melanoma/Skin Cancer

Presentation: Vaccines in Melanoma: A Promising Road Ahead

Ryan J. Sullivan, MD (Massachusetts General Hospital)

In this session, Dr. Ryan J. Sullivan spoke about the history and current landscape of melanoma vaccines. Sullivan begins by noting that successful vaccines, including those for cancer, must either induce antigen-specific T-cell activation and/or boost antibody formation against the target. If you can use vaccines to prevent cancer development, such Gardasil or other HPV vaccines, cancer outcomes improve. Vaccines can also act as an adjuvant therapy after surgery or potentially treat metastatic tumour(s). Antigens that can be utilized for cancer

treatment include those that are overexpressed in cancer relative to other tissues, cancer testes antigens, tumor-specific antigens, neoantigens (Hollingsworth and Jansen, *NPJ Vaccines* 2019 quoted in Sullivan).

Alongside antigen selection, adjuvant selection in the vaccine is also imperative. In vaccines, the adjuvant refers to the component that stimulates the innate immune response to the antigen. These rely on pattern recognition receptors and are often derived from innate immune activators for microbial detection. For vaccines that are designed to generate cell mediated immunity, RIG-I-like receptor agonists and toll-like receptor are used often as well. Different adjuvants can be used based on what antibodies you are trying to stimulate, so you can create a customized antigen.

While vaccines have not always yielded efficacy, Sullivan has consistently seen the ability in his patients to develop antitumor immunization. Efficacy would be increased by integrating T-cells, which would ideally kill existing tumours. Thinking around vaccines has shifted to consider combining tumor vaccines with immune checkpoint antagonists and immune checkpoint agonists.

Sullivan notes that there has been an increasing uptick of medical studies in cancer vaccines, including for melanoma. However, many of these report either negatively or non-efficacious vaccines. Sullivan cites a 2004 National Cancer Institute (NCI) report that summarized patients treated across dozens of trials both within and outside of the NCI, which showed a response rate of just over 3% (Rosenberg et al. *Nat Med* 2004).

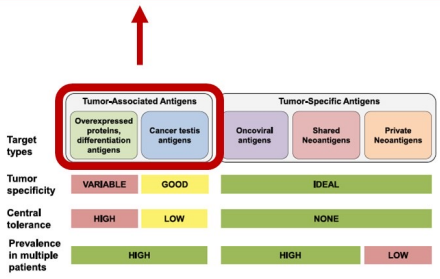
9

Vaccines in Melanoma: Decades of failure

- 2004 Report:
  - 1306 patients across 74 trials, 43 responders (3.3%)
  - 30 peptide vaccine trials (11 responses in 381 pts; 2.9%)
  - 9 trials of viral vaccine trials (3 of 160; 1.9%)
  - 35 trials of various approaches including peptides, viral, tumor cell, DC, HSP (29 of 765; 3.8%)

Rosenberg, Yang, Restifo. *Nat Med* 2004

MART-1, gp100, ES, g209-2M, MART-27L, TRP-2, tyr3D, Tyrosinase, MAGE-12, NY-ESO-1, Her2/neu, Telomerase, PSA, CEA, MAGE-3A1



Hollingsworth and Jansen. *NPJ Vaccines* 2019

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: Ryan J. Sullivan

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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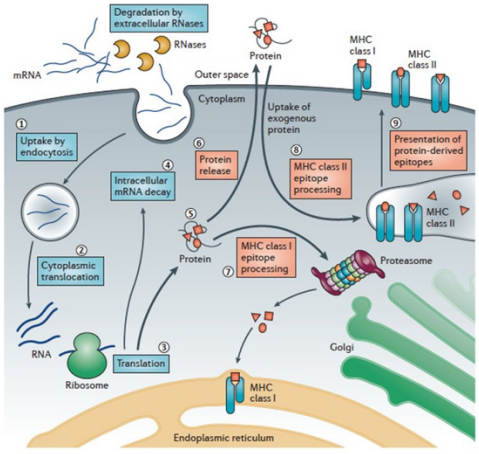
Slide taken from presentation (Sullivan)

However, despite all this, Sullivan suggests that there are some things to be hopeful about. One of these is advances in T-cell receptor signaling, T-cell antigen binding prediction, and sequencing technology, which offer the potential to develop better vaccines. There has also been the advent of neoantigen vaccinations. The latter requires tumor excision, which means that DNA and RNA sequencing can be performed on targeted tumors to identify HLA typing, neoepitopes, and mutations, which can inform custom vaccines. Sullivan cites a study in which two participants had recurrent stage 4 m1b resected melanoma; they both received PD-1 therapy with their vaccines, which led to an increase in neoepitope T-cell clones, and they had a complete response to therapy. Based on these results, the same researchers began another PD-1 inhibitor trial with nivolumab (NIVO). Patients received three months of NIVO while their vaccines were created, then given the vaccine. The results were encouraging, with a strong generation of neoantigen-specific reactions in CD4 and CD8 cells. Sullivan also mentioned an upcoming trial by Roche Genentech that will compare pembrolizumab (PEMBRO) versus PEMBRO plus the vaccine, and another study of adjuvant PEMBRO +/- neoepitope vaccine for resected high-risk stage III melanoma. These studies (IMCODE-011/GO40559 and Keynote-942) have completed accrual and there should be data in the next six to 12 months. These are only two of several studies Sullivan highlights which will be testing the combination of PEMBRO and vaccines in the coming year, including testing both peptide and mRNA vaccines.

15

Vaccines in Melanoma: The Road Ahead

- Advances in sequencing technology, T cell receptor sequencing, and T cell/antigen binding prediction create feasibility to develop better vaccines[1]
- Moving beyond peptides
  - mRNA has many qualities that make it an ideal deliver of antigenic stimulus for vaccines[2]
  - Altering the packaging of mRNA can enhance stability and translatability[3,4]



[1]Fritsch et al. *Cancer Immunol Res* 2014
[2]Sahin et al. *Nat Rev Drug Discov* 2014
[3]Grudzien-Nogalska et al. *RNA* 2007
[4]Kuhn et al. *Gene Ther* 2010

2022 ASCO ANNUAL MEETING #ASCO22 PRESENTED BY: Ryan J. Sullivan

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Slide taken from presentation (Sullivan)

Sullivan closed by highlighting alternative vaccination strategies, such as vaccinating what is expressed in the tumor microenvironment, such as anti-IDO and anti-PD-L1 cells, which can destroy expressing T-cells. These vaccines can also be given in combination with checkpoint inhibitors.

Poster: Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: The phase 3 KEYNOTE-716 study
Georgina V. Long, MD, PhD, FRACP (Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals) et al.
Abstract # LBA9500
Clinical trial number: NCT03553836.

Previous studies of the phase III double-blind KEYNOTE-716 have seen that pembrolizumab (PEMBRO) significantly improved recurrence-free survival relative to placebo for patients with resected AJCC-8 stage IIB or IIC melanoma. This abstract presents more recent data from analysis of recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) with a longer follow-up period.

This study included 976 patients who have undergone complete resection of cutaneous stage IIB or IIC melanoma with negative sentinel lymph node biopsy. In part one of the study, patients were randomized 1:1 between PEMBRO (200 mg) and placebo Q3W for 17 cycles. This treatment continued until unacceptable toxicity or disease recurrence. Patients were eligible for additional cycles of PEMBRO Q3W in the second part of the trial if they received the placebo in part one or did not see disease progression within six months of completing part one. The study endpoint was RFS, with DMFS being a secondary endpoint.

The resulting data demonstrated that, at the median follow-up of 26.9 months, the adjuvant PEMBRO significantly improved DMFS (88.1%) relative to the placebo (82.2%). Further, the data showed a consistent reduction in recurrence risk with the PEMBRO (81.2%) relative to the placebo (72.8%). However, there were more treatment-related adverse effects grade three or higher for patients treated with PEMBRO (137 patients, 28.4%) than the patients treated with placebo (97 patients, 20%). While six deaths occurred during the trial, none of these were treatment related. Overall, the data suggests that in patients with resected stage IIB and IIC melanoma, adjuvant PEMBRO significantly reduced risk of recurrent and improved DMFS relative to placebo.

Poster: Survival data of PRADO: A phase 2 study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma

Christian U. Blank, MD, PhD (Netherlands Cancer Institute) et al.
Abstract #9501
Clinical trial number: NCT02977052.

This abstract presented updated data from the OpACIN-neo study, in which patients with resectable stage III melanoma were treated with neoadjuvant ipilimumab (IPI) 1mg/kg + nivolumab (NIVO, l1N3) 3mg/kg over two cycles. This regimen showed a 96.9% rate of relapse-free survival in patients with pathologic response versus 35.5% for non-responders. This data raises questions as to whether therapeutic lymph node dissection (TLND) could be omitted for patients who achieve a significant pathologic response and also whether patients who did not respond could benefit from additional adjuvant therapy. This study (PRADO) used an extension cohort from the phase II OpACIN-neo study and aimed to confirm the safety and pathologic response rate of neoadjuvant l1N3 and to assess response-driven subsequent therapy.

99 patients were enrolled; those with stage III melanoma received with at least cycle of neoadjuvant l1N3. Patients with stage III melanoma received two cycles of neoadjuvant l1N3 after marked placement in the lymph node index. At week six, patients with a partial response and patients with no response underwent TLND, the latter group also receiving adjuvant NIVO or dabrafenib + trametinib for 52 weeks with the possibility of radiotherapy. The primary endpoints were recurrence-free survival at two years and pattern recognition receptors in the indexed lymph nodes.

The results demonstrate that TLND omission in patients with major pathological responses resulted in improved quality of life and decreased surgical morbidity. The estimated two-year recurrence-free survival rate for patients with major pathologic response was 93.3% and estimated DMFS was 100%. The result indicated that the elimination of adjuvant therapy based on lymph node index could be a safe approach, while patients with no response benefitted from adjuvant therapy (63.6% DMFS rate). The final data cut-off was February 2022, so more results from this study may be upcoming.

Poster: Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512)

Kari Lynn Kendra, MD, PhD (The Ohio State University Comprehensive Cancer Center, Department of Internal Medicine) et al.
Abstract # 9502
Clinical trial number: NCT02775851.

This trial included patients with desmoplastic melanoma (DM), a rare type of melanoma defined by a “dense fibrous collagen matrix.” This melanoma, like others, is associated with high UV exposure and a high mutational load. Due to the frequency of local relapses, the standard of

care for DM is radiation therapy or wide excision surgery. Historically, metastatic DM has a high response rate to PD-1 blockade therapy (Eroglu et al. 2018), so this study tested whether neoadjuvant treatment with ani-PD-1 monotherapy would induce pathologically confirmed regressions, allowing for less extensive local treatments. The primary endpoint was a pathological complete response, with 25% seen as a threshold of promise for future study. The secondary endpoints were median overall survival, clinical response rate, and safety/tolerability of neoadjuvant pembrolizumab.

In this study, 29 patients with histologically confirmed resectable DM who also had clinical evidence of residual disease received pembrolizumab (PEMBRO) 200mg for three weeks followed by excision. Pathological complete response was noted in 15/27 (56%) of patients and the clinical response rate was 52%. While median overall survival was not reached, the data shows that neoadjuvant pembrolizumab in patients with resectable DM can result in a high rate of pathological complete responses with high tolerance, supporting the possibility of PD-1 blockade therapy pre-surgery.

Poster: NeoTrio: Randomized trial of neoadjuvant (NAT) pembrolizumab (PEMBRO) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy

Georgina V. Long, MD, PhD, FRACP (Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals) et al.
Abstract # 9503
Clinical trial number: NCT02858921.

This study (NeoTrio) set out to determine the ideal combination of anti-PD-1 and BRAF-TT for patients with stage III melanoma using neoadjuvant pembrolizumab (PEMBRO) and dabrafenib + trametinib. In this trial, 60 patients with resectable and RECIST stage III, BRAF V6000-mutant melanoma were randomized 1:1:1 between three arms, all of which involved six weeks of neoadjuvant PEMBRO. The first arm was PEMBRO by itself, the second was D+T followed by PEMBRO, and the third was concurrent D + T + PEMBRO. The primary endpoint was pathological response rate and pathological complete response at six weeks. The secondary endpoints were event-free survival, RECIST response, overall survival, recurrence-free survival, and adverse events.

The pathological complete response and pathological response rate were the highest in the concurrent D + T + PEMBRO, but the arms with PEMBRO alone and in sequence with D + T had similar responses. Events occurred the most frequently in the solo PEMBRO arm. The arm with concurrent D + T + PEMBRO had the highest toxicity rate. Recurrences were not seen in the PEMBRO solo arm but were in the other arms. Follow-up is ongoing.

	ALONE (n=20)	SEQ (n=20)	CON (n=20)
pRR	11 (55%)	10 (50%)	16 (80%)
pCR	6	4	10
Near-pCR	2	2	1
pPR	3	4	5
pNR	7	10	3
RECIST ORR/CR	60% / 10%	45% / 0%	70% / 30%
No. Events	7*	6	4^
No. Recurred by pCR/near-pCR/pPR/pNR	0/0/2/3	0/1/0/5	1/0/2/0
No. Death	3	1	2
1-yr EFS (95% CI)	80% (64-100)	80% (64-100)	79% (62-100)

*2 pts and^1 pt progressed prior to surgery; no CLND was performed.

Image taken from abstract (Long et al.)

Poster: Nivolumab (NIVO) + relatlimab (RELA) versus NIVO in previously untreated metastatic or unresectable melanoma: OS and ORR by key subgroups from RELATIVITY-047

Hussein A. Tawbi, MD, PhD (The University of Texas MD Anderson Cancer Center) et al.
Abstract # 9505
Clinical trial number: NCT03470922.

This study reports overall response rate data from the phase II/III RELATIVITY-047 trial of nivolumab (NIVO) + relatlimab (RELA) as a fixed-dose combination, which was demonstrated to improve progression-free survival for patients with untreated unresectable or metastatic melanoma. Relative to solo NIVO, NIVO + RELA showed a better overall survival and progression-free survival.

At the later follow-up date, progression-free survival continued to be better with the combination treatment, and overall response rate and survival were also improved with the combination. Overall response rate was notably significant for patients with LAG-3 expression,

PD-L1 expression, and BRAF wild-type. In all of the patients treated, the NIVO + RELA combination maintained a manageable safety profile.

	Patients, n		mOS, months (95% CI)			ORR, % (95% exact CI)	
Subgroup	N+R	N	N+R	N	Unstratified HR (95% CI)	N+R	N
Overall	355	359	NR	34 (25.2–NR)	0.81 (0.64–1.01)	43 (37.9–48.4)	33 (27.8–37.7)
Metastasis stage M1c*	151	127	34 (17.9–NR)	22 (13.8–33.2)	0.78 (0.56–1.08)	37 (29.4–45.3)	29 (21.4–37.9)
High tumor burden (≥ Q3)†	84	75	17 (10.8–34.0)	9 (6.2–19.1)	0.75 (0.51–1.11)	32 (22.4–43.2)	23 (13.8–33.8)
LDH ≤ ULN	225	231	NR	NR	0.76 (0.55–1.06)	50 (43.1–56.5)	35 (28.5–41.2)
LDH > ULN	129	128	17 (10.8–31.5)	14 (9.7–21.0)	0.81 (0.59–1.11)	32 (23.9–40.6)	29 (21.2–37.6)

CI, confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; mOS, median overall survival; NR, not reached; N, nivolumab; N+R, nivolumab plus relatlimab; n, number of patients; Q3, quartile 3; R, relatlimab; ULN, upper limit of normal. *AJCC v8; †Tumor burden quartile as determined by BICR at baseline;ˆUnstratified HR was 0.81 and stratified HR was 0.80.

Image taken from abstract (Tawbi et al.)

Poster: Atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with BRAFV600mutation–positive melanoma with central nervous system (CNS) metastases (mets): Primary results from phase 2 Tricotel study

Reinhard Dummer, MD (Skin Cancer Center, University Hospital of Zurich) et al.
Abstract #9515
Clinical trial number: NCT03625141

This study hopes to fill a gap in melanoma research, which is the lack of treatment options for melanoma patients with central nervous system metastases. These patients have also been only minimally included in studies evaluating intracranial activity of targeted therapies and immunotherapies. The second cohort of this study (Tricotel, phase II) evaluated the efficacy and safety of atezolizumab (A) + cobimetinib (C) + vemurafenib (V) in patients with BRAF V600 mutated melanoma who also have central nervous system metastases (including patients receiving corticosteroids).

The study enrolled 65 patients who had melanoma with central nervous system metastases. At baseline, 49% of these patients had elevated lactate dehydrogenase and 37% were on corticosteroids. The intracranial overall response rate was 58% in patients on corticosteroids, who saw a progression-free survival of 7.2 months and duration of response of 10.2 months. For asymptomatic patients, the overall response rate was 46%, progression-free survival was 5.5 months and duration of response was 5.7 months. In 60 patients who received the A + C + V combination, 70% saw grade 3-4 adverse events. The data suggests that adding A to the combination of C + V can provide significant intracranial activity for patients with central nervous system metastases in BRAF V600-mutated melanoma, particularly those receiving corticosteroids.

Intracranial outcomes (N = 65).

	IRC	Investigator
ORR, % (95% CI)	42 (29–54)	51 (38–63)
Median DOR, mo (95% CI)	7.4 (5.7–11.0)	7.4 (5.6–10.2)
Median PFS, mo (95% CI)	5.3 (3.8–7.2)	5.8 (5.4–7.4)
6-mo PFS rate, % (95% CI)	41 (28–53)	48 (36–61)

Image taken from abstract (Summer et al.).

Poster: Navtemadlin (KRT-232) activity after failure of anti-PD-1/L1 therapy in patients (pts) with TP53WT Merkel cell carcinoma (MCC)
Michael K.K. Wong, MD, PhD (The University of Texas MD Anderson Cancer Center) et al.
Abstract #9506
Clinical trial number: NCT03787602

This study (KRT-232-103) tested the use of Navtemadlin (KRT-232) for $TP53^{WT}$ Merkel cell carcinoma. Navtemadlin is an orally available murine double minute 2 regulator that restores p53 activity, inducing apoptosis of $TP53^{WT}$ tumours. In an effort to confirm appropriate dosage, the study randomly assigned 31 patients various dosages of oral Navtemadlin in either 21- or 28-day cycles until they reached either unacceptable levels of toxicity or disease progression. The dosage options were: 240 mg 7 days (D) on/14D off or 5D on/23D off, 180 mg 5D on/23 D off or 7D on/21D off, or 120 mg 7D on/14D off. The primary endpoint was discovery of the recommended phase II dose, determined by objective response rate.

While treatment-emergent adverse events were seen in 100% of patients (with 68% being grade 3-4), these effects were more well tolerated in Navtemadlin doses of less than 180mg. This dosage level also saw longer treatment durations and fewer dose reductions. Based on these results, the 240mg dosage arms were closed to further enrolment, as were the 120mg arms due to a low response rate. The 180mg dosage has been selected for further evaluation based on a 25% confirmed overall response rate accompanied by a 38% unconfirmed response rate, and a 63% disease control rate. This data suggests that Navetemadlin could be a promising targeted agent for Merkel cell carcinoma patients who have failed anti-PD-1/L1 therapy and that regulating the p53 pathway is a possible therapeutic strategy for Merkel cell carcinoma.

Poster: A phase II clinical trial of camrelizumab (CAM, an IgG4 antibody against PD-1) combined with apatinib (APA, a VEGFR-2 tyrosine kinase inhibitor) and temozolomide (TMZ) as the first-line treatment for patients (pts) with advanced acral melanoma (AM)
Lu Si, MD (Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital and Institute) et al.
Abstract #9508
Clinical trial number: NCT04397770

This study was a phase II study of camrelizumab (CAM) + apatinib (APA) + temozolomide (TMZ) for improved efficiency and objective response rate (ORR), as PD-1 monotherapy when used as a first line treatment for advanced melanoma has offered an ORR of less than 20%. The primary endpoint was ORR (per RECIST 1.1), with secondary endpoints of disease control rate (DCR), progression-free survival (PFS), safety, and overall survival. Until intolerable toxicity or disease progression, patients received iv CAM (200mg q2w), iv TMZ

(200mg/m2 d1-5, q4w) and po APA (250mg qd). Fifty patients were enrolled and the median follow-up was 12.1 months.

At the time of follow-up, the ORR was 64.6% and DCR was 95.8%. The median PFS was not reached, with 12-month PFS being 62.9%. Median overall survival was also not reached, with a 12-month rate of 82.3%. 94% of participants experienced treatment-related adverse events, though no treatment-related deaths occurred. This combination of CAM + APA + TMZ has continued to demonstrate promise as a first-line treatment for patients with advanced melanoma, though a phase III randomized trial would be a good option for continued efficiency.

Poster: A retrospective study of ipilimumab plus nivolumab in anti–PD-L1/PD-1-refractory merkel cell carcinoma

Sophia Shalhout, PhD (Division of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School) et al.
Abstract #9521

This poster outlined a retrospective study that evaluated objective clinical response to ipilimumab (IPI) + nivolumab (NIVO) in advanced Merkel cell carcinoma that is refractory to anti-PD-L1/PD-1 treatment. Medical records of 13 patients with advanced Merkel cell carcinoma from Massachusetts General Brigham Hospital and affiliates were investigated (2016-2021); these patients had all seen disease progression on immunotherapy (either pembrolizumab, avelumab, or NIVO) and were then re-challenged with the combination of IPI + NIVO. Patients were included even if they had been treated with cytotoxic chemotherapy, surgery, or radiation after the immunotherapy treatment were included.

Of the 13 patients assessed in the study, four (31%) experienced grade III/IV immune-related adverse events. Further, none of the patients assessed achieved an objective RECISTv1.1/irRECIST response to the IPI + NIVO combination. Disease stabilized in three patients (23%); median overall survival was 4.7 months and the median progression-free survival was 1.3 months.

Poster: Long-term survival in advanced melanoma for patients treated with nivolumab plus ipilimumab in CheckMate 067

F. Stephen Hodi, MD (Dana-Farber Cancer Institute) et al.
Abstract #9522
Clinical trial number: NCT04540705

This study reported sustained efficacy outcomes at 7.5 years for the combination of nivolumab (NIVO) + ipilimumab (IPI), which has achieved a melanoma-specific survival rate of 56%. This study used follow-up data from the 945 patients in the original CheckMate 067 study. In the original study, patients with untreated, unresectable stage III/IV melanoma received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W, followed by NIVO 3 mg/kg Q2W (n = 314), NIVO 3

mg/kg Q2W + placebo (n = 316), or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) based on metastasis stage, BRAF mutation status, and PD-L1 status. Primary endpoints were overall survival and progression-free survival in NIVO + IPI, NIVO, and IPI.

At the 7.5-year point, median overall survival was 72.1 months at 58% (NIVO + IPI), 36.9 months at 45% (NIVO), and 19.9 months at 19% (IPI). 36% of the NIVO + IPI, 49% of NIVO, and 66% of IPI-treated patients received subsequent therapy. Of patients alive at 7.5 years, 106/138 (77%, NIVO + IPI), 80/115 (70%, NIVO), and 27/60 (45%, IPI) were off treatment and had never received subsequent systemic therapy. None of the 10 deaths since the 6.5-year follow-up were treatment-related. Overall, the extended follow-up period continues to demonstrate the efficacy of the NIVO + IPI combination.

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS: all pts, mo (95% CI)	72.1 (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
7.5-y OS rate: all pts, % (95% CI)	48 (42–53)	42 (36–47)	22 (18–27)
***BRAF* mutant subgroup**	57 (47–66)	42 (32–52)	25 (17–34)
Median MSS: all pts, mo (95% CI)	NR (71.9–NR)	49.4 (35.1–NR)	21.9 (18.1–27.4)
7.5-y MSS rate: all pts, % (95% CI)	55 (50–61)	47 (41–52)	26 (21–32)
Median PFS: all pts, mo (95% CI)	11.5 (8.9–20.0)	6.9 (5.1–10.2)	2.9 (2.8–3.1)
7.5-y PFS rate: all pts, % (95% CI)	33 (27–39)	27 (22–33)	7 (4–11)

Image taken from abstract (Hodi et al.)

Poster: Androgen receptor blockade promotes response to BRAF/MEK-targeted therapy
Michael White, MD, MSc (The University of Texas MD Anderson Cancer Center) et al.
Abstract #9523

This poster addresses the high resistance rates to BRAF +/- MEK inhibition as a treatment for melanoma, along with the sexual dimorphism that has occurred with BRAF +/- MEK inhibitor treatment, a phenomenon which is poorly understood. The data came from clinical cohorts of BRAF-mutated melanoma patients (792 total; 430 male, 362 female) who were treated with BRAF/MEKi in either the metastatic or neoadjuvant setting. Of special interest were rates of progression-free survival (PFS), major pathologic response (MPR), clinical benefit (CB), overall survival (OS), and relapse-free survival (RFS).

The study determined that female patients saw improved rates of CB, OS, MPR, and PFS relative to men. MPR was higher for women (66% in women vs 14% in men), as was RFS (64% in women vs 32% in women). Additionally, data from the COMBI-D and METRIC trials was analysed and demonstrated improved OS and PFS at the two-year mark in female patients versus male patients. In male patients, however, androgen receptor (AR) expression increased during treatment, suggesting that BRAF/MEKi may induce AR expression in tumours.[7] These results suggest that AR blockade could promote BRAF/MEKi response in melanoma patients, and should continue to be studied in clinical trials involving melanoma and other cancer types.

Poster: Tumor mutational burden (TMB) in immune checkpoint inhibitor (ICI)-naïve and -experienced patients with metastatic melanoma treated with lifileucel, a tumor-infiltrating lymphocyte (TIL) cell therapy
Harriet M. Kluger, MD (Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital) et al.
Abstract #9542
Clinical trial numbers: NCT03645928; NCT02360579

This study was conducted in response to data from *Schumacher Science* (2015) which suggests that cutaneous melanoma is characterized by high tumour mutational burden (TMB), which in turn is associated with increased tumour-specific neoantigen expression and increased responses to immune checkpoint inhibitors (ICI). As the TMB for tumours that recur after ICI is not currently well-defined, this study sought to investigate potential associations between TMB, ICI therapy, and lifileucel, which is a one-time, autologous TIL cell therapy currently being in investigated for use in patients with advanced melanoma. All 28 patients across both cohorts had metastatic or unresectable melanoma. In cohort 1A, a single dose of pembrolizumab was given after tumour harvest and before nonmyeloablative lymphodepleton, resuming after lifileucel, for up to two years.

[7] The androgen receptor regulates the development and growth of the prostate.

Cohort 1A had seven patients while cohort 2 had 21; the overall response rates to this treatment regimen were 71.4% in cohort 1A and 38.1% in cohort 2. In 1A, 57.1% of patients had high TMB (greater than 10 mut/MB) and 19% had high TMB in cohort 2. In cohort 1A, the overall response rate for those with low TMB 66.7% and was 75% for those with high TMB; in cohort 2, the response rate for those with low TMB was 41.1% and 25% in those with high TMB. TMB was ultimately not associated with response to lifileucel. Another important note is that patients with high TMB was often lower in tumour which had been previously exposed to ICI than those which were ICI-naïve.

Poster: Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: A multicenter, open-label, single-arm phase 2 study
Lili Mao (Key laboratory of Carcinogenesis and Translational Research) et al.
Abstract #9525
Clinical trial number: NCT04091217

This study assessed the safety and efficacy of atezolizumab + bevacizumab as a first-line theory for patients with advanced mucosal melanoma, as anti-PD-1 monotherapy is currently a standard therapy for patients with cutaneous melanoma. This was an open-label, multicenter, single-arm, phase II study which administered atezolizumab (A) (12000mg) + bevacizumab (7.5mg/kg) every three weeks by intravenous infusion. The primary endpoint was objective response rate, and secondary endpoints included overall survival, progression-free survival, disease control rate, safety, and duration of response.

43 patients were enrolled in this study, 23 (53.5%) with metastatic mucosal melanoma and 20 (46.5%) had unresectable melanoma. Data cut-off was 13.4 months and which time 40 patients were evaluable for response. In the stage I analysis set, the best confirmed objective response rate was 40.9%, which included eight partial responses and one complete response. The median progression-free survival was 8.2 months. While the median overall survival was not reached, 12-month overall survival was 76%. The median duration of response was 12.5 months. 90.7% of patients experienced treatment-related adverse events, with 25.6% of these being greater than grade 3. Overall, A + bevacizumab showed manageable safety and promising efficiency in patients with advanced mucosal melanoma.

Poster: Encorafenib plus binimetinib in patients with locally advanced, unresectable, or metastatic BRAFV600-mutant melanoma: Updated data from the multicenter, multinational, prospective, non-interventional longitudinal study BERINGMELANOMA

Erika Richtig (Department of Dermatology, Medical University of Graz) et al.
Abstract #9526
Clinical trial number: NCT04045691

BERING^{MELANOMA} tested the use of the encorafenib + binimetinib (E + B) with a broader population and under real-world conditions, relative to the selected populations that participated in the COLUMBUS trial (clinical trial number: NCT01909453) which showed a five-year overall survival of 35% and five-year progression-free survival of 23%. The BERING^{MELANOMA} trial is an ongoing, prospective, longitudinal, multi-national, non-interventional study that assesses quality of life, safety, and effectiveness of E + B therapy for patients metastatic or advanced melanoma. The study aims to include up to 750 patients, which 280 being included to date. Patients who had undergone more than one year of prior therapy with an immune checkpoint inhibitor in the palliative setting and those with prior BRAF/MEK inhibition were excluded.

The data presented at ASCO is the second interim snapshot based on 200 patients. The median estimated E + B treatment duration was 11.6 months, largely in the 1L-setting (60%). Treatment adaptations were required for 40% of patients with toxicity being the main reason; adverse events were reported in 86% of patients, with 34% of these being grade 3-4. This sample of the use of E + B in a real-world setting suggests a poorer prognosis relative to the COLUMBUS study, the tolerability profile is consistent between COLUMBUS and BERING^{MELANOMA}. The next data snapshot will be prepared after enrolment of 300 patients.

Poster: Dabrafenib (D) and trametinib (T) plus spartalizumab (S) in patients (pts) with previously untreated BRAF V600–mutant unresectable or metastatic melanoma: Three-year overall survival (OS) data from the randomized part 3 of the phase III COMBI-i trial

Reinhard Dummer (University Hospital Zürich Skin Cancer Center) et al.
Abstract #9527
Clinical trial number: NCT02967692

This poster offered three-year overall survival data from the COMBI-i part 3 trial (NCT02967692), which failed to shoe progression-free survival benefit. COMBI-i was a placebo-controlled, double-blind study, in which patients were randomized 1:1 to receive either spartalizumab (S) + dabrafenib (D) + trametinib (T) or placebo + D + T until either unacceptable toxicity or progression. Aside from the primary endpoint of progression-free survival, which was not met, safety and exploratory overall survival analyses were performed.

At the data cut-off (October 2021; median follow-up of 42.8 months), the median overall survival was not reached in the S + D + T arm and was 40.4 months in the placebo + D + T arm. There were 113 deaths in the former arm and 126 in the latter. The estimated three-year overall survival rates were 60.1% in the first arm and 52.9% in the placebo arm. An overall survival benefit was observed in the S + D + T arm in three subgroups: patients older than 65, PD-L1 negative, lesion diameters that were greater than 66mm at baseline, and patients with more than three metastatic sites. Adverse events occurred in 99.3% of patients in the first arm and 97.3% percent in the placebo arm. The data from this three-year cut-off point was consistent with the primary analysis of the COMBI-i trial, with the placebo + D + T arm showing a higher overall survival rate than that previously observed for D+T alone.

Poster: Efficacy and safety of nivolumab for locally advanced or metastatic cutaneous cell carcinoma (NIVOSQUACS trial)

Roland Lang (Department of Dermatology and Allergology, Paracelsus Medical University Salzburg) et al.
Abstract #9528
Clinical trial number: NCT04204837

Immune checkpoint inhibition with PD-1 antibodies has become the standard of treatment for advanced cutaneous squamous cell carcinoma (cSCC). This study (NIVOSQUACS) evaluated safety and efficiency of nivolumab (NIVO), a PD-1 antibody, in patients with locally advanced or metastatic cSCC, including patients with concomitant hematological malignancies, who are often excluded from clinical trials (CHM).[8] The trial included 31 patients with metastatic and/or histologically confirmed locally advanced cSCC and at least one measurable lesion as per RECIST v1.1. Between July 2017 and October 2020, patients received NIVO intravenously (240mg) every two weeks for up to two years; all participants received at least one dose of NIVO. The primary endpoint was investigator assessed overall response rate (ORR; as per RECIST v1.1). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), and overall survival (OS).

At the time of enrolment, 51.6% percent of participants had loco-regional metastatic cSCC, 25.8% had distant metastatic disease, and 19.4% had locally advanced cSCC. At the time of data cut-off (March 2021), five patients (16.1%) were continuing treatment, one patient had completed the treatment protocol, and 25 (80.5%) patients had discontinued therapy. Of the 29 evaluable patients, 12 achieved a partial response and seven a complete response, indicating a DCR of 68.9%, ORR of 65.2%, and median PFS of 11.1 months. Treatment-related adverse events occurred in 18 patients (58.1%). Like other anti-PD-1 agents in advanced cSCC, NIVO demonstrated robust anti-tumour activity. While patients with CHM saw a slightly reduced OS and ORR, NIVO proved to be effective for this group with no change in safety signals.

[8] Hematological malignancies are cancers that begin in blood-forming tissue (immune system, bone marrow).

Poster: Phase II study SECOMBIT (sequential combo immuno and target therapy study): A subgroup analysis with a longer follow-up
Paolo Antonio Ascierto, MD, BC (Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale") et al.
Abstract #9535
Clinical trial number: NCT02631447

The SECOMBIT study was a randomized three arm phase II study which used the targeted therapy combination encorafenib + binimetinib (E + B) and the immunotherapy combination ipilimumab + nivolumab (IPI + NIVO). The study explored these combinations in both sequences and also the "sandwich" strategy, which consists of a short course of targeted therapy followed by combination immunotherapy. This poster presented updated data with subgroup analysis. From Nov 2016-May 2019, this study enrolled 251 patients with metastatic, untreated BRAFV600 melanoma. Patients were randomized between Arm A (E + B until progression of disease (PD), followed by I + N), or Arm B (I + N until PD, followed by E + B) or Arm C (E + B for 8 weeks, followed by I + N until PD, followed by E + B). The primary endpoint of the study was overall survival, with secondary endpoints of two- and three-year survival rate, total progression-free survival (tPFS), duration of response, best overall response rate, and biomarker evaluation.

The data from this study demonstrates that the primary endpoint of overall survival was met in each arm; the three-year overall survival was 53% in arm A, 63% in arm B, and 60% in arm C. Three-year tPFS was 34% in arm A, 56% in arm B, and 54% in arm C. As per the table below, these figures fluctuated depending on whether participants had greater or fewer than three metastatic sites and lactate dehydrogenase level.[9] At the time of data cut-off for this poster (37.1-month median follow-up), tPFS and overall survival rates are higher in arms B and C. Analysis of secondary endpoints is ongoing.

					2-year OS	3-year OS	2-year OS	3-year OS	2-year OS	3-year OS	2-year OS	3-year OS
	2-year tPFS	3-year tPFS	2-year OS	3-year OS	< 3ms	< 3ms	≥ 3ms	≥ 3ms	nLDH	nLDH	eLDH	eLDH
Arm A	44%	34%	62%	53%	70%	62%	50%	36%	73%	67%	50%	42%
Arm B	65%	56%	73%	63%	74%	63%	72%	61%	76%	69%	67%	50%
Arm C	57%	54%	69%	60%	79%	64%	54%	54%	70%	56%	65%	65%

tPFS = time from randomization to second progression; OS = overall survival; ms = no. of metastatic sites; nLDH = normal LDH levels; eLDH = elevated LDH levels.

Inage taken from poster abstract (Ascierto et al.)

[9] Lactate dehydrogenase tests assess tissue damage levels.

Poster: Efficacy and safety of cosibelimab, an anti–PD-L1 antibody, in patients with metastatic cutaneous squamous cell carcinoma
Philip Clingan, MD (Southern Medical Day Care Centre, Wollingong, Australia) et al.
Abstract #9537
Clinical trial number: NCT03212404

This poster outlined the results of study CK-301-101, which enrolled patients with a variety of advanced cancers, including cutaneous squamous cell carcinoma (CSCC), for treatment with cosibelimab. Cosibelimab is an anti-PD-L1 antibody capable of inducing complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) against tumour cells. This poster presented a primary analysis of the registration-enabling expansion cohort in patients with metastatic advanced (CSCC). Patients with ECOG performance status of zero or one with metastatic CSCC that was not amenable to local therapy were eligible for this trial. Cosibelimab was given intravenously to 78 participants at a fixed dose of 800mg every two weeks. The primary endpoint was confirmed objective response rate (as per RECIST v1.1) and the key secondary endpoint was duration of response.

All 78 participants in the study were eligible for safety and efficacy evaluation. The confirmed objective response rate was 47.4%; 76% of responses were ongoing at the time of data cut-off. The Kaplan–Meier estimation of maintained response at 6 and 24 months was respectively 88.1% and 72.5%. Treatment-related adverse events were reported in 54 patients (69.2%). The data demonstrates that treatment with cosibelmimab monotherapy resulted in a solid overall response rate and offered a manageable and predictable safety profile in patients with metastatic CSCC.

Poster: Anti-LAG-3 antibody LBL-007 in combination with toripalimab in patients with unresectable or metastatic melanoma: A phase Ⅰ, open-label, multicenter, dose escalation/expansion study
Xue Bai (Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education Beijing) et al.
Abstract #9538
Clinical trial number: NCT04640545

This trial tested the efficacy and safety of LBL007 with Toripalimab for patients with metastatic or unresectable melanoma. LBL007 is a fully human lg64 monoclonal antibody which targets human Lymphocyte-activation gene3 (LAG-3) and toripalimab is an anti-PD-1 antibody which has been approved for melanoma treatment in China. 37 patients were enrolled with or without prior anti-PD-(L)1 treatment. In the dose escalation phase, patients were given LBL-007 (0.25/1/3/6 mg/kg) /Toripalimab (3 mg/kg) intravenously and in the expansion phase patients received LBL-007 (3/6 mg/kg)/Toripalimab (3 mg/kg), also intravenously. The primary endpoint was safety, with secondary endpoints of efficiency, pharmacodynamics, and pharmacokinetics.

In the dose escalation phase, no dose-limiting toxicity was observed and the maximum tolerated dose was not reached. For the 32 radiologically evaluable patients, the objective response rate was 12.5%, while the disease control rate 53.1%. In a subtype analysis of patients who were anti-PD-(L)1 treatment-naïve patients, separated by acral and mucosal melanoma patients, the objective response rate was 27.3% versus 0% respectively, and the disease control rate was respectively 81.8% and 50%. For patients resistant to anti-PD-(L)1 treatments, the disease control rate was 18.2%. Overall, the combination of LBL007+toripalimab proved to be well tolerated and displayed promising efficiency as a treatment for metastatic and unresectable melanoma, particularly in patients with anti-PD-(L)1 naïve acral melanoma.

Poster: Overall survival (OS) with first-line atezolizumab (A) or placebo (P) in combination with vemurafenib (V) and cobimetinib (C) in BRAFV600 mutation-positive advanced melanoma: Second interim OS analysis of the phase 3 IMspire150 study

Grant A. McArthur, PhD, FRACP, MBBS (Melanoma and Skin Service and Cancer Biology and Therapeutics Program, Peter MacCallum Cancer Centre) et al.
Abstract #9547
Clinical trial information: NCT02908672

This poster presented data from the second overall survival analysis of the IMspire150 (NCT02908672), which in primary analysis demonstrated improved progression-free survival using first-line atezolizumab (A) + vemurafenib (V) + cobimetinib (C) versus placebo + V+ C for patients with $BRAF^{V600}$ mutated advanced melanoma. At the initial primary reporting cutoff of 18.9 months, data was immature but suggested that the combination of A+V+C would have a greater overall survival rate than placebo + V + C. The trial enrolled 514 patients with stage IV or unresectable stage IIIc $BRAF^{V600}$ mutated melanoma who were treatment naïve. Participants were 1:1 randomized to receive 28-day cycles of either A + V + C or P + V + C. All patients received V + C in the first cycle, with either A or placebo being added from cycle two onwards.

At the time of data cut-off (September 8, 2021), 273 overall survival events had occurred. For the A+V+C arm, median follow-up was 29.1 months, and the follow-up was 22.8 months for the placebo arm. At the 12-month mark, the A + V + C arm saw overall survival rates of 76.1%, with the overall survival in the placebo arm being 76.5% at 12 months. Median duration of response (21 months with A, 12.6 months with placebo) and overall response rates (66.7% with A, 65% at placebo) remained consisted with the results reported at primary analysis. A + V + C continues to demonstrate a consistent, if not statically significant, improvement in overall survival, alongside a continued duration of response for previously untreated patients with $BRAF^{V600}$-postive advanced melanoma.

Poster: Efficacy and safety of sequencing with vemurafenib (V) plus cobimetinib (C) followed by atezolizumab (Atezo) in patients (pts) with advanced BRAFV600-positive melanoma: Interim analysis of the ImmunoCobiVem study
Dirk Schadendorf, MD (Department of Dermatology, University Hospital Essen) et al.
Abstract #9548
Clinical trial number: NCT02902029

The ImmunoCobiVem (randomized, phase II) study evaluated safety and efficacy of using atezolizumab (ATEZO) after treatment with vemurafenib (V) + cobimetinib (C) for patients with BRAFV600 mutated advanced melanoma. Patients who have not previously been treated for melanoma received three months of V (960mg, twice per day) alongside 60mg of C daily for 21-28 days. Patients who did not experience treatment interruption due to adverse events were then randomized 1:1 to continue V + C (arm A) or switching to receiving 1200mg of ATEZO every three weeks (arm B). In the case of treatment-related adverse events, patients crossed over to the other arm. The endpoints were multiple points of progression-free survival, duration of complete response, overall survival, overall response rate, and safety.

Between November 2016-December 2019, 185 patients were enrolled and randomized between arm A (69 patients) or arm B (66 patients). In the randomized phase, duration of complete response and overall response rate was higher in arm A before crossover and in arm B after crossover (table below). The median treatment duration across treatment phases was 11.2 months for arm A and 10.7 months for arm B. Grade 3-4 adverse events occurred in 55% of patients in arm A and 64% in arm B; these events led to discontinuation in 10% pf patients in arm A and 12% in arm B. This data demonstrates that an early switch from the combination of V + C to ATEZO is safe and feasible, but tumour control is only maintained in a subset of patients on subsequent immune checkpoint inhibitor monotherapy. Crossover to targeted therapy yields greater responses than to immune checkpoint inhibitor.

	Arm A		Arm B	
PFS	Events/pts	Median, mo (95% CI)	Events/pts	Median, mo (95% CI)
PFS1	42/67	13.9 (9.9–16.6)	51/65	5.9 (5.4–8.3)
PFS2	18/21	12.6 (8.3–17.0)	21/35	14.9 (8.6–25.6)
PFS3	18/21	2.8 (2.0–3.1)	21/35	6.0 (2.4–12.6)
Response, % (95% CI)	ORR	DCR	ORR	DCR
Run-in phase	74 (62–83)	99 (92–100)	74 (63–83)	98 (92–100)
Randomized phase				
Before crossover	67 (55–77)	72 (61–82)	36 (26–48)	42 (31–54)
After crossover	5 (1–23)	10 (3–29)	40 (26–56)	54 (38–70)

Image taken from abstract (Schadendorf et al.)

Poster: Merkel polyoma virus specific T-cell receptor transgenic T-cell therapy in PD-1 inhibitor refractory Merkel cell carcinoma
Joshua Veatch, MD, PhD (Hutchinson Cancer Research Center) et al.
Abstract #9549
Clinical trial information: NCT03747484

This trial tested whether adoptive transfer of autologous T-cells that are transduced with the Merkel polyoma virus (MCPyV)-specific T-cells could increase clinical responses in PD-1 inhibitor refractory patients. The study saw five patients who have MCPyV positive and HLA-A02 PD-1 inhibitor refractory metastatic Merkel cell carcinoma be treated with T-cells which have been transduced with a T-cell receptor targeting an HLA-A02 restricted MCPyV epitope. In order to facilitate T-cell expansion, single fraction radiation was administered to lesions on three patients prior to their T-cell transfer; a further two patients received lymphodepleting chemotherapy plus cyclophosphamide and fludarabine before T-cell transfer. 14 days after T-cell infusion, patients received anti-PD-1/PD-L1 therapy.

No dose limiting toxicities or cytokine release syndrome was observed after T-cell infusion. The two patients treated with lymphodepleting chemotherapy saw greater T-cell persistence relative to the three patients who were treated with single fraction radiation. The transgenic T-cells frequently persisted at tumour sites for greater than one month after cell transfer. Four of the trial patients experienced progressive disease. The trial demonstrated that while MCPyV specific transgenic T-cells are safe and can result in a clinical response, this clinical activity is limited by downregulation of class I major histocompatibility complex (MHC) expression in tumours.[10] A future trial is needed to create strategies to increase class I MHC expression in Merkel tumours.

Poster: Camrelizumab plus apatinib for patients with advanced mucosal melanoma: A prospective single-arm study
Zhengyun Zou (Nanjing Drum Tower Hospital) et al.
Abstract #9550
Clinical trial number: ChiCTR1900023277)

This study, which was aimed at Chinese patients due to mucosal melanoma being the second most frequent subtype in Asian populations, investigated the safety and efficacy of camrelizumab and apatinib for patients with advanced mucosal melanoma. 30 patients were enrolled in this single-arm study between April 2019-January 2022 and received 200mg of

[10] The major histocompatibility complex is a locus on vertebrate DNA that contains polymorphic genes that code the cell surface proteins in the adaptive immune system.

camrelizumab every two weeks and 500mg of apatinib every day until either intolerable toxicity or disease progression. The primary endpoint was objective response rate as per RECIST v1.1.

At the median follow-up point of 8.1 months, the overall response rate was 42.9% and the disease control rate was 81%. The median progression-free survival was 7.7 months in patients with first-line camrelizumab + apatinib. Exploratory analysis of the data found that patients with high T-cell receptor diversity had an overall better prognosis. Overall, the combination of camrelizumab + apatinib showed favourable overall response and disease control rates, alongside tolerable safety, in patients with advanced mucosal melanoma.

Characteristics	Patients (n = 30)
Age (years), median (range)	62 (35-77)
Sex (male/female)	13/17
Current therapy line (1/≥2)	27/3
Prior chemotherapy (perioperative therapy/for advanced disease/no)	12/3/15
Primary site (head and neck/esophagus/vagina and cervix/rectum)	16/2/7/5
Metastatic site (liver/lung/lymph node)	7/11/12
Lactate dehydrogenase level (≤upper limit of normal/ > upper limit of normal)	20/10
Gene mutation (BRAF/C-KIT/NRAS/unknown)	3/3/8/2

Image taken from abstract (Zou et al.)

Poster: Analysis of overall survival (OS) and relapse-free-survival (RFS) in the phase 1b clinical trial of anti–PD-1 ab (toripalimab) plus intralesional injection of OrienX010 in stage Ⅳ melanoma with liver metastases

Chuanliang Cui, MD (Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute) et al.
Abstract #9551
Clinical trial number: NCT04206358

This poster reported the regression-free survival and overall survival rates of toripalimab (anti-PD-1 ab) in combination with intrahepatic OrienX010 injections, which are a HSV-1-derived oncolytic virotherapy. This trial was directed to patients with advanced melanoma that had metastasized to the liver. Participants received intravenous toripalimab every two weeks combined with intratumoral injections of OrienX010, also every two weeks until either disease

progression or intolerance. Liver biopsies were performed at baseline and at first tumour evaluation (8-12 weeks). The primary endpoint of the study was safety, with secondary endpoints including disease control rate (DCR), progression-free survival (PFS), and overall response rate (ORR).

23 patients were enrolled in this trial from July 2019-January 2022, with 20 of these patients being evaluable for efficiency. The median rate of overall survival was 18.6 months and PFS was 7 months; the ORR was 15% and DCR was 50%. The response rate for injected lesions was 35%, 27.8% for non-injected liver lesions, and 26.7% for extra-hepatic metastases. Biopsies were performed on 15 patients at the time of first tumour evaluation to assess TIL infiltration. At this time, the median PFS for patients with impressive TIL infiltration was 7.8 months, while patients with less TIL infiltration saw a median PFS of 4.1 months. The median overall survival of patients with no residual melanoma cells was 19.7 months. Overall, the combination of toripalimab + intrahepatic OrienX010 injection has demonstrated excellent overall survival and long PFS for melanoma patients with liver metastases.

Poster: IMPemBra, a phase 2 study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in patients with melanoma harboring the BRAFV600 mutation: Three-year survival data and translational analyses

Elisa A. Rozeman, MD (Netherlands Cancer Institute) et al.
Abstract #9552
Clinical trial number: NCT02625337

This poster presented three-year data from a phase IIB trial which tested the optimal duration of MAPKi (MAPK pathway inhibition) alongside combined dabrafenib (D) + trametinib (T) + pembrolizumab (PEMBRO). For BRAFV600-mutated melanoma patients, the combination of MAPKi and anti-PD-(L)1 have historically offered high response rates but also high rates of treatment-related adverse events. Previous data from this same study has shown that toxicity was related to duration of D + T, response rates increased after addition of D + T, and no suspected unexpected serious adverse reactions. The primary endpoints were treatment adherence, safety, and determining the immune-activating capacity of the regimes. Secondary endpoints were progression-free survival (PFS), objective response rate (ORR), and overall survival.

In this trial, patients started with 200mg of PEMBRO every three weeks; after the first two cycles, patients were randomized to continue solo PEMBRO (cohort one), to receive intermittent D + T weekly for two weeks (cohort two), or twice for two weeks (cohort three), or continuously for six weeks (cohort four). The overall response rate was 75% in cohorts one and two and 88% in cohorts three and four. CD8+ T cell infiltration and PD-L1 expression was observed after six weeks of PEMBRO. After a median follow-up of 43.5 months, the median PFS treated with solo PEMBRO was 10.6 month versus 32.3 months for those treated with PEMBRO D+T. Three-year overall survival rates for those who received PEMBRO was 25%,

and 50% for those treated with the combination. Relative to solo PEMBRO, the combination of PEMBRO + D+ T is a tolerable and effective regimen that should be considered for further investigation.

Poster: Updated results from the skin cancer cohorts from an ongoing phase 1/2 multicohort study of RP1, an enhanced potency oncolytic HSV, combined with nivolumab (IGNYTE)

Mohammed M. Milhem, MD (University of Iowa) et al.
Abstract #9553
Clinical trial number: NCT03767348

The IGNYTE study is a multicohort phase I-II study which evaluates the efficacy and safety of the enhanced potency oncolytic HSV RPI when used in combination with nivolumab (NIVO) in a range of tumour type. This combination has previously demonstrated good tolerability and anti-tumour activity. Participants received RP1 via intertumoural injections every two weeks for four months, the first dose by itself and the second dose onwards with the addition of the addition of NIVO. This poster presented updated results from the initial melanoma and anti-PD1 naïve non-melanoma skin cancer (NMSC) cohorts.

The current median duration of response 13.27 months for the melanoma cohort and 7.32 months for NMSC. The biomarker data taken from biopsies indicated a robust T-cell infiltration, plus an increase in post-treatment tumour inflammation gene signature. This data demonstrates that RP1+NIVO can provide durable anti-tumour activity for skin cancer patients, including melanoma patients with anti-PD1/anti-CTLA-4 failed melanoma, and is well tolerated.

Poster: A phase II study to evaluate the safety and efficacy of IMM-101 in combination with checkpoint inhibitors in patients with advanced melanoma: Final results of the IMM-101-015 trial

Alberto Fusi (St. George's University Hospitals NHS Foundation Trust, St. George's University of London) et al.
Abstract #9554
Clinical trial number: NCT03711188

IMM-101, a suspension of heat-killed whole cell mycobacterium obuense, enhances dendritic cell maturation and immune response. Clinical trials including IMM-101 have shown promising efficiency for melanoma as adjunctive and single agent therapy. IMM-101-015 is an open-label phase IIA study investigating the efficacy and safety of IMM-101 in combination with the checkpoint inhibitors for patients with advanced melanoma who were either treatment-naïve or experienced disease progression during PD-1 blockade. IMM-101 was alternated with nivolumab (NIVO), though patients in cohort B also had the option to switch from NIVO to ipilimumab (IPI) if their disease continued to progress. Samples were obtained to assess tumour

biomarkers and immune correlatives throughout the trial. The trial's primary endpoint was safety, tolerability, and overall response rate as per RECIST v1.1.

This trial treated 16 patients between October 2018-May 2021; all patients were evaluated for response. Cohort A saw an overall response rate of 73%, while all participants in cohort B experienced progressive disease. The median progression-free survival of cohort A was 10.2 months and 41% of patients were progression-free at 18 months. Grade 3 treatment-related adverse events occurred in 63% of patients and no grade 4 events occurred. The combination of IMM-101 with NIVO was therefore safe while demonstrating antitumour activity in treatment-naïve patients with advanced melanoma.

Poster: A phase 1b/2a study of safety and efficacy of NT-I7 in combination with anti-PD-L1 (atezolizumab) in patients with anti-PD-1/PD-L1 naïve or relapsed/refractory (R/R) high-risk skin cancers: The phase 1b report

Brian Gastman, MD (Cleveland Clinic Lerner College of Medicine) et al.
Abstract #9561
Clinical trial number: NCT03901573

This poster presented the findings of a phase Ib/IIa study which tested the efficacy and safety of NT-I7 in combination with atezolizumab (A) for patients with checkpoint inhibitor naïve or refractory/relapsed high-skin skin cancers (Merkel cell carcinoma, cutaneous squamous cell carcinoma). NT-I7, or efineptakin alfa, is a long-acting human IL-7 which can increase the functionality and number of T-cells in peripheral blood and within the tumours. The endpoints of phase Ib were to evaluate preliminary antitumour activity, pharmacokinetics, maximum tolerated dose and recommended phase II dose, and dose-limiting toxicity.

The 16 enrolled patients (as of January 14, 2022) received NT-I7 IM every 3 weeks (Q3W) at 3 dose levels (DL1-3): 120, 360, and 840 µg/kg or Q6W at DL4 1200 µg/kg, and A intravenously (1200 mg Q3W). Maximum tolerable dosage was not reached, though all patients experienced treatment-related adverse events <grade 4. 11 participants saw stable disease, meaning the disease control rate was 69%. Data further shows that the immunophenotyping of memory T-cell subsets demonstrates a 30-fold expansion of the stem cell memory CD8+ T-cell subset at dosage level 4, alongside a five-fold expansion in most T-cell subsets. The combination of NT-I7 and A showed promising anticancer and safety activity, while increasing total lymphocyte, the T-cell compartment, and the CD8+ T-cell subset. Ongoing efficacy and safety updates will be reported from the phase IIa trial.

Poster: Adjuvant dabrafenib plus trametinib (D + T) versus placebo in patients with resected stage III BRAFV600-mutant melanoma: Updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD

Dirk Schadendorf, MD (University Hospital Essen, Essen and German Cancer Consortium) et al.
Abstract #9563
Clinical trial number: NCT01682083

This poster reported five-year distant metastases-free survival (DMFS) data from the phase III COMBI-AD trial for patients with stage III cutaneous melanoma, including data from specific prognostic subgroups. COMBI-AD tested the combination of adjuvant dabrafenib (D) + trametinib (T) versus placebo for patients with resected stage III $BRAF^{V600}$ mutated melanoma. DMFS was a secondary endpoint for the initial study, with the primary endpoint being relapse-free survival. Data analysis for DMFS was performed according to the Kaplan-Meier structure.

At the five-year data cut-off, DMFS rates were higher for patients with stages IIIB-D melanoma who were receiving the adjuvant D + T relative to placebo (see table below), alongside patients with macroscopic (D + T: 63.3%; placebo 47.1%) or microscopic (D + T: 75.3%; placebo 62.5%) lymph node involvement. Patients with stage IIIA disease saw better DMFS on the placebo arm (84.%) than the D + T (73.5%). This data demonstrates the importance of staging, treatment type, and interferon-gamma gene expression signature as important variables in determining five-year DMFS subgroups. This retrospective analysis demonstrated that D + T can provide long-term DMFS benefit relative to placebo for $BRAF^{V600}$ mutated melanoma patients, stage IIIB-D.

	Stage								Lymph node involvement			
	IIIA		IIIB		IIIC		IIID		Macroscopic		Microscopic	
	D + T	PBO	D + T	PBO	D + T	PBO	D + T	PBO	D + T	PBO	D + T	PBO
Statistic	n = 50	n = 39	n = 145	n = 154	n = 217	n = 214	n = 22	n = 17	n = 158	n = 161	n = 152	n = 157
5-year DMFS rate, %	75.3	84.5	66.5	52.8	63.0	50.8	64.6	25.6	63.3	47.1	75.3	62.5
HR (95% CI)	1.24 (0.42-3.63)		0.56 (0.38-0.83)		0.54 (0.39-0.75)		0.20 (0.07-0.55)		0.52 (0.37-0.75)		0.49 (0.31-0.79)	
Log-rank *P*	0.695		0.004		< 0.001		0.001		< 0.001		0.002	

Image taken from abstract (Schadendorf et al.)

Poster: Survival update of neoadjuvant ipilimumab + nivolumab in macroscopic stage III melanoma: The OpACIN and OpACIN-neo trials
Judith M. Versluis, MD (Netherlands Cancer Institute) et al.
Abstract #9572
Clinical trial numbers: NCT02437279, NCT02977052

This poster presented updated overall survival and relapse-free survival from the OpACIN and OpACIN-neo trials. OpACIN was the first trial which tested neoadjuvant ipilimumab (IPI + nivolumab (NIVO) versus the adjuvant version of the same combination. In OpACIN, which included 20 macroscopic stage III melanoma patients, the neoadjuvant arm saw a two-year relapse-free survival rate of 80% and an 78% pathological response rate. The following OpACIN-neo trial tested three different dosing schedules of neoadjuvant IPI+NIVO on 86 macroscopic stage III melanoma patients, ultimately identifying 2 cycles IPI 1 mg/kg + NIVO 3 mg/kg q3w as the most favorable dosing schedule (pathologic response rate: 77%, 20% grade 3-4 immune-related adverse events).

At a median follow-up of 68.6 months for OpACIN, estimated five-year relapse-free survival and overall survival rates for the neoadjuvant arm were 70% and 90% respectively, with the adjuvant arm seeing 60% relapse-free survival and 70% overall survival. At median follow-up of 46.8 months for OpACIN-neo, median relapse-free survival and overall survival was not reached. Patients who responded had a three-year relapse-free survival rate of 95.3% versus 36.8% of non-responding patients. The updated data from these trials confirms the durability of responses of neoadjuvant combination checkpoint inhibition for high-risk stage III melanoma.

	3-year RFS (95%CI)	3-year OS (95%CI)
OpACIN	80.0% (58.7-100.0)	90.0% (73.2-100.0)
OpACIN-neo	81.9% (74.1-90.6)	91.9% (86.3-97.8)
Arm A	86.7% (75.3-99.7)	90.0% (79.9-100.0)
Arm B	79.3% (65.9-95.5)	93.3% (84.8-100.0)
Arm C	79.2% (64.5-97.2)	92.3% (82.6-100.0)

Image taken from abstract (Versluis et al.)

Poster: SALVO: Single-arm trial of ipilimumab and nivolumab as adjuvant therapy for resected mucosal melanoma
Lisa A. Kottschade, APRN, CNP, MSN (Mayo Clinic) et al.
Abstract #9573
Clinical trial number: NCT03241186

SALVO was a single-arm, multicenter clinical trial which tested “flip dose” ipilimumab (IPI, 1mg/kg q3w x4 cycles) + nivolumab (NIVO, 3 mg.kg q3w x4 cycles), followed by NIVO (480 mg q4w x 11 cycles) in patients with mucosal melanoma. The 35 participants were required to have had R0/R1 resection less than 90 days prior to trial registration, no prior systemic therapy other than adjuvant radiation, ECOG 0/1, and no uncontrolled autoimmune disease or other invasive cancer. The primary endpoint was recurrence-free survival.

Of the 35 patients on the study as of December 2021, 31 have completed the treatment phase; 20 of these have recurred, 6 ended therapy due to adverse effects, and 8 died. Recurrence-free survival rates and one- and two-years were 50% and 37% respectively, and overall survival rates were respectively 87% and 68%. The median recurrence-free survival was 10.3 months. Relative to no therapy, flip dose IPI + NIVO after resection is associated with improved outcomes. Long-term follow-up is ongoing.

Poster: Efficacy and safety of "second adjuvant" therapy with BRAF/MEK inhibitors after resection of recurrent melanoma following adjuvant PD-1–based immunotherapy
Amelia M. Taylor, FRACP, MBBS (Melanoma Institute Australia)
Abstract #9575

This poster outlined results from the first study to examine patient outcomes after receiving second adjuvant targeted therapy for melanoma after having failed adjuvant PD-1 based immunotherapy, particularly in $BRAF^{V600}$ mutated melanoma. 55 patients were included in the trial, with 91% of these having $BRAF^{V600E}$ mutations; 42% of these patients had stage IIIB melanoma and 44% had stage IIIC melanoma. Previously undergone adjuvant PD-1 therapy included nivolumab (NIVO) (71%), NIVO + ipilimumab (IPI) (14%), pembrolizumab (PEMBRO) (13%) and PEMBRO + mRNA-4157 vaccine (2%), with initial recurrence after mean 8.4 months.

The second targeted therapy patients underwent for this trial was primarily the combination of dabrafenib (D) + trametinib (T) (95%), while a small portion of patients received encorafenib (E) + binimetinib (B) (5%). After a median follow-up period of 21.4 months, 31% of patients have recurred. The mean duration of treatment was 9 months, with 20% stopping for toxicity-related reasons. At 12 months, 90% of patients were free of distant recurrence and 72% were recurrence-free. Most recurrences occurred after stopping their second targeted therapy. While recurrence-free survival in second-line targeted therapy appears to be shorter relative to

first-line trials, second-line targeted therapy appears to be effective and safe for preventing further recurrence.

Poster: Adjuvant temozolomide plus cisplatin versus high-dose interferon alpha-2b in resected mucosal melanoma: A randomized, multicenter, controlled, phase III trial

Bin Lian, MD, BS (Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute) et al.
Abstract #9578
Clinical trial number: NCT03435302

This phase III trial followed up a phase II study which demonstrated promising outcomes using adjuvant temozolomide (TMZ) + cisplatin (CHEMO) versus high-dose interferon alpha-2B (HDI) for patients with resected mucosal melanoma. The primary endpoint was relapse-free survival, with secondary endpoints of overall survival, safety, and distant metastasis-free survival.

204 patients with completely resected stage I-III mucosal melanoma were randomized 1:1 to receive either TMZ + CHEMO (temozolomide 200 mg/m2/day orally on days 1-5 + cisplatin 75 mg/m2 intravenously on days 1-3, repeated every 3 weeks for six cycles) or HDI (15×106 U/m2/day on days 1-5 each week for 4 weeks followed by 9×106 U three times per week for 48 weeks). Consistent improvements in distant metastasis-free survival, overall survival, and relapse-free survival in the CHEMO arm in several subgroups relative to the HDI arm. 22.3% of patients in the CHEMO arm and 57% in the HDI arm experienced grade 3 or 4 treatment-related adverse events. This data suggests that the use of adjuvant TMZ + CHEMO led to lower risk of relapse and distant metastasis for patients with resected mucosal melanoma.

Poster: Neoadjuvant dabrafenib and trametinib (D+T) for stage III melanoma: Long-term results from the NeoCombi trial

Alexander M. Menzies, PhD, FRACP, MBBS (Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals) et al.
Abstract #9580
Clinical trial number: NCT01972347

This poster reports the five-year outcomes of the NeoCombi trial, which tested the neoadjuvant combination of dabrafenib (D) + trametinib (T) for patients with resectable stage III melanoma. The 35 enrolled patients received the standard dose of neoadjuvant D + T for 12 weeks, followed by 40 more weeks of adjuvant D + T. The primary endpoints of this study were RECIST response rate and complete pathological response at week 12 and secondary endpoints were overall survival, relapse-free survival, and toxicity.

At the data cut-off of August 17th, 2021, median follow-up was 60 months with 95% of participants. In the neoadjuvant phase, no patients progressed, and 49% had a complete response. At the five-year mark, overall survival was 80%, distant metastasis-free survival was 57%, and relapse-free survival was 40%. Most recurrences occurred within the first two years, with 21 patients in total seeing recurrence. This data suggests that while neoadjuvant D + T in stage III melanoma demonstrates impressive early disease-fighting activity, patients are at a high risk of recurrence. However, pathologic response to this treatment offers an indicator of recurrence potential, leaving the opportunity to switch treatments for these patients.

	5y RFS	5y DMFS	5y OS
All (N=35)	40%	57%	80%
pCR (N=17)	53%	59%	88%
Non-pCR (N=18)	28%	55%	71%

Image taken from abstract (Menzies et al.)

Poster: [Ongoing] Randomized phase 3 trial of IO102-IO103 plus pembrolizumab versus pembrolizumab alone in patients with previously untreated, unresectable, or metastatic melanoma

Inge Marie Svane, MD, PhD (National Center for Cancer Immune Therapy, CCIT-DK, Copenhagen University Hospital) et al.
Abstract #TPS9589
Clinical trials number: NCT05155254

This project aimed to continue creating innovative approaches to treating metastatic or unresectable melanoma, as patients are increasingly becoming resistant to nivolumab and ipilimumab, which are currently the standard first-line therapies for these diseases. IO102-IO103 is an immune-modulatory therapy which targets cancer immune resistance pathways that are mediated by IDO and PD-L1, This trial is a randomized, multicenter two-arm trial which investigated IO102-IO103 + pembrolizumab (PEMBRO) for safety and efficacy versus solo PEMBRO. The primary endpoint is progression-free survival and secondary endpoints include durable response rate, overall response rate, duration of response, complete response rate, disease control rate, time to response, safety, and overall survival.

At the time of ASCO 2022, enrolment for this study was ongoing, with a target of 300 patients at 100 sites across 20 countries. Patients are going to be randomized 1:1 to receive either 200mg of PEMBRO intravenously (IV) every three weeks for up to two years, or 200mg of PEMBRO IV on the same schedule with the addition of IO103-IO102 85-85 µg and Montanide

adjuvant subcutaneously on days one and eight of the first and second cycles, and the first day of every cycle following.

Poster: [Ongoing] First-in-human clinical trial of an oncolytic adenovirus armed with TNFa and IL-2 in patients with advanced melanoma receiving adoptive cell transfer of tumor-infiltrating lymphocytes

Inge Marie Svane, MD, PhD (National Center for Cancer Immune Therapy, CCIT-DK, Copenhagen University Hospital) et al.
Abstract #TPS9590
Clinical trial number: NCT04217473

This trial aimed to increase access to patients who can benefit from immunotherapies by using TILT-123, an ocolytic adenovirus which is designed to enable checkpoint inhibition and T-cell therapies. This route targets recurrent or refractory stage III/IV patients, who are ineligible for many available therapies but can receive adoptively transferred tumour-infiltrating lymphocytes (ACT-TIL) treatments. This trial aims to evaluate the addition of TILT-123 together with ACT-TILs in human subjects with advanced melanoma

At the time of ASCO 2022, recruitment for this study was active. To be eligible, patients must present at least one operable/biopsiable tumour for the production of tumour-infiltrating lymphocytes and a second injectable lesion for administration of the ILT-123. The primary endpoint of this study is safety (by day 36) and secondary endpoints of tolerability, safety, antitumour responses, and tumour immune repolarization. By June 2022, cohorts 1-3 had been completed without dose limiting.

Poster: [Ongoing] A randomized, controlled, open-label, phase 2 study of cemiplimab ± RP1 in patients with advanced cutaneous squamous cell carcinoma (CERPASS)

Andrew Mark Haydon, MD (The Alfred Hospital) et al.
Abstract #TPS9593
Clinical trial number: NCT04050436

This phase II study is currently evaluating the safety and efficacy of cemiplimab ± RP1 versus cemiplimab alone for patients with advanced cutaneous squamous cell carcinoma (CSCC). Cemiplimab is a PD-1/PD-L1 inhibitor, while RP1 is an oncolytic virus (HSV-1) which expresses a fusogenic glycoprotein and granulocyte macrophage colony stimulating factor. Past studies have demonstrated that RP1 is capable of inducing immogenic tumour cell death and providing systemic anti-tumour activity that is further improved by anti-PD-1 therapy. This global and multicentre trial is enrolling with unresectable or metastatic locally advanced CSCC who are not candidates for either radiation therapy or surgery. Patients are only eligible if they have not received prior anti-PD-1/PD-L1 antibodies or oncolytic viruses. Primary endpoints for

this trial are complete response rate and overall response rate and secondary endpoints include progression-free survival, safety, overall survival, and duration of response.

Trial participants will be randomized in a 2:1 ratio between combination therapy or monotherapy, respectively. In the combination arm, patients will receive intertumoral injections of solo RP1 at a starting dose of 1 × 106 plaque-forming units (PFU)/mL, followed by up to seven doses of RP1 at 1 × 107 PFU/mL Q3W alongside the same dose of cemiplimab. Patients in the monotherapy arm receive intravenous cemiplimab (350mg) Q3W for up to 108 weeks. Tumour assessments are performed every nine weeks. At the time of ASCO 2022, this trial was seeking to enroll 180 patients from centres in Europe, Canada, Australia, and the USA.

Poster: [Ongoing] DELTA-1: A global, multicenter, phase 2 study of ITIL-168, an unrestricted autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in adult patients with advanced cutaneous melanoma

Brian Gastman, MD (Cleveland Clinic Lerner College of Medicine) et al.
Abstract #TPS9594
Clinical trial number: NCT05050006

This poster outlined the progress of DELTA-1, which is a global, multicentre, phase II study of the use of ITIL-168 for patients with cutaneous melanoma which has relapsed or is refractory to a PD-1 inhibitor, patients intolerant to anti-PD-1 treatment, or patients who do not respond optimally to anti-PD-1 treatment. Patients in the first category will be enrolled in cohort one and cohorts two and three will respectively enroll patients in the latter circumstances. The primary endpoint of the study is objective response rate, with secondary endpoints of progression-free survival, duration of response, disease control rate, and overall survival.

Patients in this trial will receive five days of lymphodepleting chemotherapy followed by a single ITIL-168 infusion and supportive IL-2. Primary analysis will be performed when patients from cohort one have been followed for at least six months after the first post-treatment disease assessment. At the time of ASCO 2022, Recruitment for this study was ongoing.

Poster: [Ongoing] Optimization of Voyager V1 (VV1) oncolytic virus systemic delivery in combination with cemiplimab and ipilimumab in patients with melanoma and non–small cell lung cancer (NSCLC)

Jose Lutzky, MD (University of Miami Sylvester Comprehensive Cancer Center) et al.
Abstract #TPS9595
Clinical trial number: NCT0491105

This trial is aimed at patients who are intolerant or do not respond to immune checkpoint inhibitor therapy. Voyager V1 (VV1) is an oncolytic vesicular stomatitis virus that is engineered to express human interferon beta (IFNβ) to enhance cellular anti-tumour immune responses and tumour selectivity. Phase I of this study tested the use of VV1 alongside Cemiplimab (an anti-

PD-1 antibody), leading to study amendments shifting focus to optimizing efficiency, including use of higher VV1 doses or triplet combinations.

Patients with advanced melanoma who have seen disease progression on anti-PD1 are currently being enrolled to analyse the safety, immunogenic activity, and anti-tumour activity of the combination of VV1 + cemiplimab., potentially with an additional injection of VV1 on patients with accessible lesions. Patients will continue to receive cemiplimab intravenously Q3W until intolerable toxicity or disease progression. Once at least six patients in the melanoma cohort have received this higher dosage of VV1, a third melanoma cohort will open to experiment with a triplet combination which includes ipilimumab. Each melanoma cohort will require a response in at least two patients in the first stage to add more in the second stage. The study also includes biopsies in increasingly high numbers of melanoma patients at each stage. At the time of ASCO 2022, this study was ongoing in the United States.

Poster: [Ongoing] ATTAC-MCC: Phase I/II study of autologous CD8+ and CD4+ transgenic T cells expressing a high affinity MCPyV-specific TCR combined with checkpoint inhibitors and class I MHC-upregulation in patients with metastatic MCC refractory to PD-1 axis blockade
Joshua Veatch, MD, PhD (Hutchinson Cancer Research Center) et al.
Abstract #TPS9596
Clinical trial information: NCT03747484

This study puts forward the hypothesis that cellular immune therapies that target the Merkel cell polyomavirus (MCPyV) could provide clinical benefit to patients who become refractory to immune checkpoint inhibitor treatments. This ongoing phase I/II open-label trial is testing FH-MCVA2TCR in combination with anti-PD-L1 checkpoint inhibitor treatment to upregulate MHC-I expression in tumour cells. In this process, TCR T products are manufactured from patients' own white blood cells, with this cell product being administered on day 0. Afterwards, patients receive an agent to upregulate MHC-1 on tumour cells and an anti-PD-l1 checkpoint inhibitor for up to a year.

The primary endpoint of stage I was to determine tolerability and safety based on dose-limiting toxicity after the first infusion. The main objective of phase II was safety based on adverse events and preliminary efficacy based on tumour response (as per RECIST 1.1). Secondary endpoints include T cell phenotype, cellular kinetics of TCR T cells, tumour infiltration kinetics, and MHC-I expression dynamics. At the time of ASCO 2022, this trial was recruiting.

Poster: [Ongoing] Tocilizumab in combination with ipilimumab and nivolumab in solid tumors

Noha Abdel-Wahab, MD, PhD (Assiut University Hospital, Faculty of Medicine) et al.
Abstract #TPS9600
Clinical trial number: NCT04940299

While combination treatment using anti-CTLA-4 and anti-PD-1 has shown good response rates for several cancers, it is also associated with up to 60% grade 3/4 immune-related adverse events that lead to treatment discontinuation. This trial was a phase II, open-label, single centre study that evaluated the use of combined tocilizumab (TOCI), an anti-IL6; ipilimumab (IPI), an anti-CTLA4; and nivolumab (NIVO), an anti-PD1. Primary endpoints are safety and tolerability, with secondary endpoints of overall survival and antitumour activity.

35 treatment-naïve advanced cutaneous melanoma patients are being recruited, 10 in the initial cohort and 25 in an expansion cohort. Patients with brain metastases, a population often excluded from clinical studies, are eligible for this trial. In all three cohorts, subcutaneous (SQ) TOCI (162 mg/2 weeks) is administered up to 12 weeks, and those in the melanoma-specific cohort also receive IPI (3 mg/kg) + NIVO (1 mg/kg) is administered intravenously every 3 weeks for 4 doses, then NIVO (480 mg/4 weeks) up to 2 years. Imaging takes place every twelve weeks for two years or until progression or dose-limiting toxicities. At the time of ASCO 2022, this trial was recruiting at M.D. Anderson Cancer Center.

Poster: [Ongoing] Design and rationale of a first-in-human (FIH) phase 1/1b study evaluating KIN-3248, a next-generation, irreversible (irrev), pan-FGFR inhibitor (FGFRi), in adult patients with solid tumors harboring FGFR2 and/or FGFR3 gene alterations

Lipika Goyal, MD (Mass General Cancer Center, Harvard Medical School) et al.
Abstract #TPS9601
Clinical trial number: NCT05242822

FGFR1-4 gene alterations are observed in ~7% of human cancers, with 3 FDA-approved FGFR inhibitor treatments for patients with an FGFR mutation and solid tumours. However, FGFR inhibitors often sees resistance mutations that reduce duration of response, with up to 67% of patients treated with an FGFR inhibitor demonstrating resistance at the time of relapse. This study is testing KIN-3248, a small molecule pan-FGFR inhibitor that is structurally designed to inhibit the secondary kinase domain mutation association with disease progression, for patients with advanced and metastatic solid tumours. Primary endpoints are tolerability/safety (in part A), objective response rate, preliminary antitumour activity, disease control rate, duration of stable disease, and duration of response (in part B); secondary endpoints include pharmacokinetic and pharmacodynamic assessments, including measures of FGFR pathway modulation.

This is a first-in-human, multicentre, non-randomized, phase I in which patients receive KIN-3248 continuously in 28-day cycles until disease progression or drug intolerance. Part A of

the study will observe dose-escalation of single-agent KIN-3248, while part B will evaluate a selected dose of KIN-3248 in three cohorts of patients based on FGFR mutations. At the time of ASCO 2022, this trial was recruiting.

Poster: [Ongoing] DETECTION phase II/III trial: Circulating tumor DNA–guided therapy for stage IIB/C melanoma after surgical resection
Rebecca Lee, MRCP, BSc, MBChB (The Christie NHS Foundation Trust) et al.
Abstract #TPS9603
Clinical trial number: NCT04901988

It has been clinically established that circulating tumour DNA (ctDNA) is a biomarker of progression or tumour burden in many cancers, which can identify molecular relapse or minimal residual disease. This study aimed to test whether the likelihood of relapse can be identified by ctDNA analysis, and therefore acted upon in a clinically relevant timeframe; further, the study seeks to determine whether early treatment of molecular recurrence with immune therapy can improve outcomes for patients with resected stage IIB/C melanoma. Primary endpoints include determining whether early treatment of molecular recurrence with nivolumab (NIVO) can improve overall survival and if molecular relapse following curative intent surgery can be identified before clinical relapse.

This is a phase II/III study across four Australian and 21 United Kingdom centres. Patients with stage IIB/C melanoma were included, as are patients with BRAF/NRAS/TERT mutant cutaneous melanoma. Patients with ctDNA will be randomized 1:1 in a double-blind method to either continue follow-up with investigators if they develop disease recurrence or treated with NIVO (480mg) intravenously every four weeks. At the time of ASCO 2022, enrollment was ongoing in Australia and the United Kingdom.

Poster: [Ongoing] The NADINA trial: A multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma
Minke W. Lucas, MSc (Netherlands Cancer Institute) et al.
Abstract #TPS9605
Clinical trial number: NCT04949113

This international, randomized, phase III trial seeks to compare the efficacy of neoadjuvant ipilimumab (IPI) + nivolumab (NIVO) with solo adjuvant NIVO for patients with macroscopic stage III melanoma. 240 patients with de novo or recurrent melanoma with at least one clinical detectable lymph node will be randomized to adjuvant or neoadjuvant treatment.[11] The primary endpoint is event-free survival.

[11] De novo variants refer to mutations that appear for the first time in one family member.

Patients in arm A receive 2 cycles of IPI (80mg) + NIVO (240mg) and will undergo therapeutic lymph node dissection at week six. Arm B will undergo upfront therapeutic lymph node dissection, followed by 12 cycles of NIVO (480mg). In the case of non-response or partial response, surgery is followed by 11 cycles of adjuvant NIVO or 46 weeks of adjuvant dabrafenib + trametinib (in the case of BRAF mutation). This trial is currently recruiting in the Netherlands.

Poster: Neo-adjuvant T-VEC plus nivolumab combination therapy for resectable early-stage or metastatic (IIIB-IVM1a) melanoma with injectable disease: The NIVEC trial

Maartje W. Rohaan, MD (Division of Medical Oncology, Netherlands Cancer Institute) et al.
Abstract #TPS9607
Clinical trial number: NCT04330430

Studies have demonstrated that talimogene laherparepvec (T-VEC), which is a modified herpes simplex type-1 virus, can offer a durable and high response rate and a mild toxicity profile for patients with unresectable stage IIIB-IVm1a melanoma. T-VEC has also been shown to heighten immune response and elicit an abscopal effect in melanoma when it is given in combination with immune checkpoint inhibitors (ICI). This study fills in a knowledge gap by testing the potential benefit of T-VEC+ICI in the neo-adjuvant setting, analysing the safety and efficacy of T-VEC + nivolumab (NIVO), followed by surgical resection, in patients with resectable stage IIIB-IVM1a melanoma. The primary endpoint is pathologic response rate, with secondary endpoints of safety, event-free survival, and rate at which the treatment is able to delay surgery.

This single arm, single centre, phase II study includes 24 patients with treatment-naïve stage IIIB-IVM1a melanoma with injectable disease, resectable satellite or in-transit metastases, and/or tumour positive lymph nodes will be included. Participants will receive three doses of nivolumab (240mg flatdose) and four courses of T-VEC (up to 4mL, first dose as seroconversion dose) every two weeks, followed by surgical resection in week nine. Enrollment for this trial started in June 2020 and at the time of ASCO 2022, approximately half of the 24 planned patients had received treatment.

Poster: [Ongoing] A first-in-human, phase 1b study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of neoadjuvant use of ph-762 administered intratumorally in subjects with advanced melanoma

Caroline Robert, MD, PhD (Gustave Roussy and Paris-Saclay University) et al.
Abstract #TPS9608
Clinical trial number: 2021-002859-10

This study set out to evaluate the safety profile of neoadjuvant PH-762 administered via IT injection in subjects with resectable stage IIIB/IIIC/IIID or IV melanoma in order to

determine potential immunologic and pathologic tumour responses, the recommended phase II dose, and pharmacokinetics after IT injection. PH-762 is a potent RNAi molecule which targets PD-1 with chemical and structural modifications that can improve cell and tissue uptake. The primary endpoint of this study is to determine a safe dose of PH-762 prior to tumour resection based on dose-limiting toxicity. Secondary endpoints are immunological response in tumour tissue and blood samples.

Participants received injections of PH-762 weekly into a designated tumour lesion for four weeks prior to surgical excision. The dosage of PH-762 will be adjusted to tumour volume to ensure equivalent dosage among patients. The follow-up period for data will be six weeks. At the time of ASCO 2022, this trial was ongoing in France.

Poster: [Ongoing] ARTISTRY-6: Nemvaleukin alfa monotherapy in patients with advanced mucosal and cutaneous melanoma

Jeffrey S. Weber, MD, PhD (Laura and Isaac Perlmutter Cancer Center, NYU Langone Health)n et al.

Abstract #TPS9609

Clinical trial number: NCT04830124

Despite the overall success of checkpoint inhibitor therapy for melanoma, approximately 50% of patients do not initially respond to this form of treatment. Thus, more novel approaches are needed for melanoma that provide more durable clinical benefit. This trial (ARTISTRY-6) is testing the use of nemvaleukin alfa (nemvaleukin, ALKS 4230), an engineered cytokine which selectively binds the intermediate-affinity interleukin-2 receptor complex to activate $CD8^{+}$T and natural killer (NK) cells, for patients with advanced melanoma. It is a phase II, global, multicentre, open-label study which is currently recruiting. The primary endpoint is evaluation of overall response rate based on antitumour activity. Secondary endpoints include quality of life, safety, predictive biomarkers, immunogenicity, pharmacokinetics, and pharmacodynamic effects.

Nemvaleukin will be administered to participants who have who have previously received treatment with an anti-PD-(L)1 therapy (with or without anti-CTLA-4 therapy) and maintain adequate hematologic reserve, and hepatic and renal function. Patients will be given nemvaleukin until intolerable toxicity or progression. At the time of ASCO 2022, recruitment for this trial was ongoing.

Symptoms and survivorship

Poster: Thromboembolism (TE) and association with survival in patients (pts) with melanoma receiving chemo– or immunotherapy

Tamara A. Sussman, MD (Dana-Farber Cancer Institute) et al.
Abstract #12082

Emerging data suggests that there is a correlation between arterial thromboembolism (ATE) and venous thromboembolism (VTE) and immune checkpoint inhibitors in patients with melanoma. This study further analysed the incidence of thromboembolism in melanoma patients treated with cytokine therapy (CY), immune checkpoint inhibitor therapy, and chemotherapy, alone or in combination. The team used the SEER-Medicare database to evaluate rates of TE in melanoma patients treated between 2008-2019 with either cytokine therapy (IL2, IFN), immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab), or chemotherapy (BRAF/MEK inhibitors, antineoplastic agents), with evaluation taking place within two years of treatment initiation.

The analysis included 13,124 patients, 48.9% of whom had received solo chemotherapy; 31.8% chemotherapy + immune checkpoint inhibitor therapy; 14.8% solo immune checkpoint inhibitor therapy; 2.8% chemotherapy + cytokine therapy; and 1.7% solo cytokine therapy. Incidence of CTE was highest at three months after starting therapy, with the most frequent events occurring in those who received chemotherapy + immune checkpoint inhibitor (19.6 events/100 people), those who received solo chemo (17.1 events/100 people), and solo immune checkpoint inhibitor (15.4 events/100 people). More details about these statistics can be found in the table below. Incidences of ATE and VTE were correlated with worse overall survival than in patients who did not have either. The data demonstrates that melanoma patients treated with immune checkpoint inhibitors and chemotherapy demonstrate a high incidence of TE, which is associated with worse odds of survival.

	ICI		Chemo		CY		Chemo+ICI		Chemo+CY	
	VTE	ATE	VTE	ATE	VTE	ATE	VTE	ATE	VTE	ATE
3 months	15.4	7.7	17.1	9.7	7.7	7.7	19.6	10.1	10.1	10.0
6	13.8	7.0	14.5	8.8	7.4	9.0	16.0	9.1	7.0	8.4
9	12.4	6.9	12.6	8.0	5.8	6.9	14.4	8.7	6.4	7.3
12	11.1	6.4	11.1	7.4	6.2	6.7	12.8	8.4	5.0	5.7
24	8.9	5.7	8.9	6.4	3.8	5.1	9.6	6.7	4.0	4.3

Image taken from abstract (Sussman et al.)

Poster: Association between unmet needs and utilization of emergency services among cancer survivors in Canada
Megan E Delisle, MD, MSc, MPH (University of Ottawa) et al.
Abstract #12131

This study takes data from a 2016 survey authored by the Canadian Partnership Against Cancer (CPAC) and proposes an association between data from said survey and emergency services utilization within the first three years after treatment completion. The CPAC survey sought to understand patient experiences in the transition from primary care to follow-up, and patient responses indicated high rates of unmet emotional, practical, and physical needs. Patients who initially responded to the CPAC survey had non-metastatic colorectal, hematologic, breast, prostate, or melanoma cancers. "High" emergency services utilization was categorized as accessing these services three or more times per year.

This study included 8,911 participants, 80.5% of whom reported at least one unmet emotional, practical, or physical care need. The relationship between reported unmet needs and emergency services use was assessed using multivariable logistic regression.[12] 3.9% of participants reported high emergency service utilization, which the study authors believe is related to the unmet need expressed in the survey. Other causes for emergency service use identified by the study authors include high oncologist utilization, being unable to find a healthcare provider for follow-up care, high primary care provider utilization, bring enrolled in clinical trials, having a chronic condition, and citing their experience with follow-up cancer care as "fair" or "poor." Overall, there appears to be a correlation between high unmet needs and use of emergency services in the first three years after completion of cancer treatment. Continued efforts to improve the post-treatment experience of melanoma patients and survivors are required to lessen the burden on healthcare systems.

	High ES Utilizers	Low ES Utilizers	
	% (n)	% (n)	P-value
Unmet Practical Needs	53.2% (183)	31.8% (2723)	<0.01
Unmet Emotional Needs	78.5% (270)	63.8% (5465)	<0.01
Unmet Physical Needs	71.5% (246)	60.5% (5180)	<0.01

Image taken from abstract (Delisle et al.)

[12] Multivariate logic regression is a formula that is used to predict the relationship(s) between independent and dependent variables.

Poster: [Ongoing] The RADIO trial: Randomized assessment of cisplatin dosing interval for ototoxicity with curative concurrent chemo-radiation for locally advanced head and neck squamous cell carcinoma
Sara Kuruvilla, FRCPC (London Health Sciences Centre) et al.
Abstract #TPS12144
Clinical trial number: NCT03649048

The current standard of care for patients with locally advanced squamous cell carcinoma in the head and neck (LASCCHN) is curative chemoradiation (CRT) with cisplatin. While the toxicity of this combination has been studied, there is a knowledge gap regarding hearing loss associated with this regimen. This study tested whether low dose cisplatin is associated with a reduced frequency of hearing loss relative to the standard high dose cisplatin given to LASCCHN patients on CRT. The authors hypothesized that differences in the pharmacogenomic markers MATE1 and COMT affect risk for ototoxicity.[13] The authors hope that this prospective study will assist in their larger goal to develop a personalized treatment pathway that incorporates predictive pharmacogenomic markers to improve survivorship outcomes and tolerability of curative CRT in patients with LASCCHN. The primary endpoint would be to measure the change in incidence rate of hearing loss higher than grade 2 and hearing-related quality of life at one year after treatment. Secondary endpoints would be to assess differences between the two doses in affects such as loco-regional control, global quality of life, and survival.

This will be an open label, randomized clinical trial in which eligible LASCCHN patients slated to receive primary CRT will be stratified by tumour p16 status before being randomized 1:1 to either high dose (100mg/m2 Q3W) or low dose cisplatin (40mg/m2 Q1W). At the time of ASCO 2022, this trial was recruiting in Ontario.

Poster: [Ongoing] Immune-related adverse events and symptom burden in patients with melanoma receiving adjuvant immune checkpoint inhibitor
Noha Abdel-Wahab, MD, PhD (Assiut University Hospital, Faculty of Medicine) et al.
Abstract #TPS12147
Clinical trial number: NCT04990726

This prospective study puts forward two hypotheses: that elevated expression of pro-inflammatory cytokines and T-cell signatures during treatment can correlate to symptom burden and toxicity, and adverse events and long-term inflammation that are induced by adjuvant immune checkpoint inhibitors can increase symptom burden and negative impact quality of life. The preliminary data from this study identified that the interleukin-6/Th-17 pathway could be a possible mediator of immune-related adverse events and that immune reactivity and increases in inflammatory cytokines might be associated with symptom burden in survivors of cancer. They

[13] Ototoxicity refers to balance or hearing problems developed due to medication use.

were also able to prioritize 30 genetic markers that confer risk for immune-related adverse events for melanoma patients treated with immune checkpoint inhibitors.

This prospective study will enlist a longitudinal cohort to assess potential symptom burden/toxicity and immune correlates in melanoma patients being treated with adjuvant immune checkpoint inhibitors. At the time of ASCO 2022, recruitment was ongoing, with a plan to enrol 240 participants.

Ocular Melanoma

Poster: Outcomes of combined ipilimumab/nivolumab in metastatic uveal melanoma: A prevalence meta-analysis

Ceren Durer (SUNY Upstate Medical University) et al.
Abstract #9534

This study aimed to assess efficacy and safety of the combination treatment of the immunotherapy ipilimumab (IPI) + nivolumab (NIVO) for metastatic uveal melanoma, a cancer which currently has a prognosis of less than 50% at one year. Therefore, novel approaches are needed to improve the outcomes for ocular melanoma patients. For this meta-analysis, a literature review was conducted and eight studies (five in phase II, three retrospective) were selected for investigation. The endpoints considered included complete response (CR), overall response rate (ORR), and grade three or higher hepatic toxicity and diarrhea/colitis. The pooled prevalence of CR was 2.1%, with ORR at 13.7%. The median OS ranged from 12.7 to 19.1 months. More than 50% of patients experienced treatment-related adverse events, with 26.2% experiencing hepatic toxicity at grade three or higher. The collected results suggest that the combined checkpoint blockade IPI + NIVO showed an ORR of 13.7%, improved clinical activity relative to a single-agent checkpoint inhibitor.

Poster: Safety and efficacy of combined melphalan percutaneous hepatic perfusion (M-PHP) and ipilimumab plus nivolumab (IPI+NIVO) in metastasized uveal melanoma (mUM): First results of the phase Ib part of the CHOPIN trial

Thaïs M.L. Tong, MD, MSc (Leiden University Medical Center, Department of Medical Oncology/Radiology) et al.
Abstract #9560
Clinical trial number: NCT04283890

This poster outlined some results of the CHOPIN trial, which tested the combo of ipilimumab (IPI) + nivolumab (NIVO) plus melphalan percutaneous hepatic perfusion (M-PHP), which has been used to treat liver-only uveal melanoma. However, patients frequently develop

extrahepatic disease after treatment with M-PHP.[14] Here, efficacy and safety results of phase IB of CHOPIN are reported.

This trial included seven patients with measurable hepatic mUM and WHO PS 0-1.[15] Patients received six weekly doses of M-PHPs (melphalan 3mg/kg, max 220mg) combined with four courses of IPI + NIVO with escalating dosage that varied between the cohorts (cohort 1: 1mg/kg each IPI + NIVO; cohort 2: IPI 1mg/kg + NIVO 3mg/kg). The primary endpoint was safety, with secondary endpoints of overall survival, best overall response (as per RECIST v1.1), and progression-free survival. Grade 3-4 treatment-related adverse events were experienced by 66% of participants in cohort 1 and 75% in cohort 2. The best overall response was one complete response, five partial responses, and one stable disease; the according overall response rate was 85.7%. All patients are currently alive, and the median progression-free survival is currently 22.4 months. Therefore, promising overall response rates, overall survival, and progression-free survival have been demonstrated in the combination of M-PHP+IPI+NIVO. The randomized phase II trial that will compare M-PHP versus M-PHP + IPI + NIVO is currently recruiting.

Poster: Immune profiling of metastatic uveal melanoma and response to immune checkpoint inhibitors

Yusra F. Shao, MD (Barbara Ann Karmanos Cancer Institute, Wayne State University) et al.
Abstract #9565

This study aimed to determine which tumour markers are correlated with improved survival in uveal melanoma patients who have been treated with immune checkpoint inhibitor therapy. Tumour samples of 450 uveal melanoma patients had both DNA and RNA sequencing performed at Caris Life Sciences in Phoenix, Arizona. Other factors analysed include tumour mutational burden, PDL1, *NCOA2* gene amplification, and median RNA expression. Other factors such as real-world overall survival (obtained from insurance claims), time on treatment, and progression-free survival (as per Kaplan-Meier analysis) were also considered.

Several correlations were found between tumour type and treatment experience/survival. For example, data demonstrated that immune checkpoint inhibitor patients did not see a difference in time on treatment based on their PDL1 levels being high versus low, and a similar lack of difference was seen in time on treatment for patients with high versus low LAG3 expression. Shao et al. also found that patients with *NCOA2* amplification saw a worse real-world overall survival than those without *NCOA2* amplification. Further, 98% of the uveal melanoma tumour samples expressed low tumour mutational burden and 95% were *NF1*-wildtype; the latter was further associated with a higher real-world overall survival. Finally, there was no time on treatment in immune checkpoint inhibitor treated patients by *SF3B1* or *BAP1* mutational status.

Overall, these assessments suggest that uveal melanoma lacks the normal markers of response to immune checkpoint inhibitor therapy. Patients who had been treated with immune

[14] Extrahepatic refers to disease occurring outside the liver.
[15] Hepatic disease occurs within the liver.

checkpoint inhibitors did not see standard markers of poor prognosis impact their survival rates, suggesting that there is a poor prognosis for uveal melanoma regardless of traditional prognostic markers.

Poster: Randomized phase II study of adjuvant sunitinib or valproic acid in high-risk patients with uveal melanoma: The final analysis of cohort 1
Rino S. Seedor, MD (Sidney Kimmel Medical College of Thomas Jefferson University) et al.
Abstract #9586
Clinical trial number: NCT02068586

This poster outlined the final analysis of the first cohort of a phase II randomized trial where high-risk uveal melanoma patients were given six months of adjuvant sunitinib or valproic acid (VPA). Within six months of treatment for primary uveal melanoma, patients were randomized 1:1 for either sunitinib (25mg/day) or VPA (750mg/day) for six months. The primary endpoint of this study was two-year overall survival, aiming for 85%. The secondary endpoints include ability to complete adjuvant treatment, toxicity assessment, and systemic relapse-free survival.

88 patients (45 sunitinib, 43 VPA) were enrolled in the study. At the median follow-up of 52.6 months, both treatment arms met the primary end point of 95.6% two-year survival of sunitinib, 90.7% VPA. For sunitinib, the 18-month relapse-free survival rate was 75.6% and 62.8% for VPA. While there was a marginal trend of superior relapse-free survival in sunitinib over VPA, the survival benefit of sunitinib relative to VPA diminished over three years. Cohort two (data forthcoming) has been assembled to investigate the prolonged improvement of relapse-free survival and overall survival and safety with 12 months of sunitinib, and cohort three with adjuvant sunitinib + VPA is currently ongoing.