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ASCO 2023 Annual Meeting

SKIN CANCERS AND OCULAR MELANOMA DATA UPDATES

Save Your Skin Foundation
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Introduction

Every year, the American Society of Clinical Oncology Annual Meeting is held at the beginning of June in Chicago, Illinois, and is followed by post-ASCO recap events globally. After attending the ASCO Annual Meeting and follow-up events, Save Your Skin Foundation is pleased to highlight a selection of the exciting data from the past year. This shortlist includes data highlights from trials relating to melanoma and non-melanoma skin cancers (NMSC), and uveal (ocular) melanoma. Please keep in mind that ASCO is an international association, and therefore studies outlined in this report are not exclusive to Canada. At the end, you will also find a glossary of commonly used abbreviations and a collection of news articles relating to these trials for further reading. Thank you for your time and support of Save Your Skin Foundation.

Melanoma/Skin Cancer Trial Data

Abstract #9501: **Significant durable response with fianlimab (anti-LAG-3) and cemiplimab (anti-PD-1) in advanced melanoma: Post adjuvant PD-1 analysis.**
Clinical trial #: NCT03005782
Omid Hamid, MD (The Angeles Clinic & Research Institute, A Cedars-Sinai Affiliate)

- Treatment with anti-LAG-3 Ab fianlimab + anti-PD-1 Ab cemiplimab has demonstrated an ORR of 63.8% across two cohorts of advanced PD-(L)1 naïve metastatic melanoma patients
- This study investigates the effect of fianlimab + cemiplimab in combination on patients who have previously received anti-PD-1 therapy
- The study enrolled three cohorts of adult patients with metastatic or unresectable melanoma (excluding uveal melanoma). Participants received fianlimab 1600 mg +

cemiplimab 350 mg IV Q3W for 12 months, with tumour measurements being performed every 6-9 weeks
    - 23.5% of participants had received prior treatment for melanoma in the neoadjuvant or adjuvant setting, including 13.3% being treated with anti-PD-1 therapy
- Overall investigator-assessed ORR was 61.2% (12 complete responses, 48 partial responses)
    - ORR was 60.9% in participants who had received prior adjuvant therapy for melanoma and 61.5% in participants who have previously received anti-PD-1 treatment
- Grade 3 or higher TRAE occurred in 43.9% of participants
- The combination of fianlimab + cemiplimab showed high clinical activity in advanced melanoma, suggesting that dual LAG-3 blockade can produce activity with significant ORR in patients who have already received anti-PD-1 therapy with a safety profile similar to anti-PD-1 monotherapy

Abstract #9502: **Nivolumab (NIVO) plus relatlimab (RELA) vs NIVO in previously untreated metastatic or unresectable melanoma: 2-year results from RELATIVITY-047.**
Clinical trial #: NCT03470922
Hussein A. Tawbi, MD, PhD (University of Texas MD Anderson Cancer Center)

- This abstract reported two-year follow-up data from RELATIVITY-047, which assessed the combination of nivo + rela versus nivo as a monotherapy
    - The study randomised patients 1:1 to receive the combination of NIVO 480 mg + RELA 160 mg or solo NIVO 480 mg every four weeks
    - The combination saw a slight improvement in overall survival and a more significant ORR
- At the two-year follow-up point, the combination showed median 10.2 month PFS, OS of 51.5% at 48 months, and ORR of 43.7%
- TRAEs leading to the discontinuation of treatment occurred in 17.2% of participants receiving the combination therapy and 8.6% receiving the monotherapy, and grade 3-4 TRAES in 22% of patients on the combination and 12% on the monotherapy
- Overall, NIVO + RELA presents a consistent benefit in PFS, OS, and ORR with a predictable safety profile

	NIVO + RELA (n = 355)	NIVO (n = 359)
Median PFS, months (95% CI)	10.2 (6.5–14.8)	4.6 (3.5–6.5)
HR (95% CI)	0.81 (0.67–0.97)	
Median OS, months (95% CI)	NR (31.5–NR)	33.2 (25.2–45.8)
HR (95% CI)	0.82 (0.67–1.02)	
OS rate, % (95% CI)		
24 months	61.8 (56.5–66.6)	58.3 (52.9–63.2)
36 months	54.1 (48.6–59.3)	48.4 (42.9–53.8)
48 months	51.5 (45.9–56.9)	42.5 (36.4–48.5)
ORR, % (95% CI)	43.7 (38.4–49.0)	33.7 (28.8–38.9)
Median MSS, months (95% CI)	NR (NR–NR)	46.6 (33.2–NR)
HR (95% CI)	0.77 (0.61–0.97)	

Table 1: Data table accompanying #9502

Abstract #9511: **Randomized phase II trial of dabrafenib and trametinib with or without navitoclax in patients (pts) with BRAF-mutant (MT) metastatic melanoma (MM) (CTEP P9466).**
Clinical trial # NCT01989585
Zeynep Eroglu, MD (H. Lee Moffitt Cancer Center and Research Institute)

- This randomised phase II study compared the combination of Dabrafenib + Trametinib (DT) along with Navitoclax (N) against DT by itself
    - N is a BH3-mimetic which inhibits BCL-xL, BCL-2, and BCL-W
    - DT has shown a 48% ORR after treatment with immune checkpoint inhibition (Atkins et al., JCO 2022)
- In this trial, patients with BRAF mutated melanoma were randomised 1:1 to either DT (150 mg of D, 2 mg T) or DT + N (DT + 225 mg of N)
    - 68% of participants had previously received immune checkpoint inhibition, but those who had received prior BRAF therapy were ineligible
- Treatment-related toxicities were mild and were consistent across both groups
- The observed ORR was 84% for DTN and 80% for DT
- At the medium follow-up of 25.9 months, there was a slightly higher OS with DTN (36 months) versus DT (25 months)
- PFS was the same across both groups

Abstract #LBA9503: **Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial.**
Clinical trial #: NCT03897881
Adnan Khattak (One Clinical Research and Edith Cowan University, Perth, Western Australia, Australia)

- mRNA-4157 is a novel mRNA-based personalised cancer vaccine which is capable of encoding up to 34 patient-specific tumour neoantigens
- This randomised phase II trial has previously met the primary RFS endpoint in patients with resected stage IIIB/C/D and IV melanoma
- mRNA-4157 (1mg) was administered intramuscularly every 3 weeks for a total of 9 doses and pembrolizumab (PEMBRO) (200mg) intravenously was given every 3 weeks or solo
- This study has demonstrated a clinically meaningful and statistically significant improvement in RFS when the mRNA vaccine is used in combination with PEMBRO, relative to PEMBRO alone
    - The combination of mRNA vaccine + PEMBRO has also demonstrated a reduction in the risk of death or recurrence by 44%
- At the median follow up of 23/24 months (combination/solo PEMBRO), RFS was reported in 22.4% on the combination ar3m and 40% of patients on the monotherapy arm
    - 18-month RFS rates were 78.6% and 62.2% in the combination and monotherapy arms, respectively and there was also an improvement in DMFS in the combination versus the monotherapy (18-month DMFS rates of 91.8% 76.8%)
- This study demonstrated that mRNA-4157 in combination with PEMBRO can offer statistically significant DMFS compared to PEMBRO, suggesting that a personalised neoantigen approach has potential benefit for cancer patients

Abstract #9504: **Association of biomarkers (BMs) with efficacy of adjuvant nivolumab (NIVO) vs placebo (PBO) in patients with resected stage IIB/C melanoma (CA209-76K).**
Clinical trial #: NCT04099251
Georgina V. Long, MD, PhD, FRACP **(**Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals)

- The phase III Checkmate-76K trial (CA209-76K) demonstrated that adjuvant NIVO has the potential to significantly prolong RFS for stage IIB/C melanoma patients
- In this segment of the trial, select biomarkers were analysed for their association with RFS in early-stage melanoma that has been treated with an anti-PD-1 agent

- In this study, primary tumour and serum biomarkers were tested, including BRAF, TMB, and tumour cell PD-L1 expression as continuous variables (high versus low levels)
- The results demonstrated that lower CRP, along with higher IFNγ-sig, TMB, and % CD8+ T cells, are associated with prolonged RFS with NIVO but not the placebo; there was a greater benefit from NIVO than placebo across all biomarkers, including BRAF-V600 mutations
- Composite analysis of biomarkers will continue to be evaluated for their potential to optimise risk/benefit stratification for NIVO

Abstract # LBA9505: **Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study.**
Clinical trial #: NCT03553836
Jason J. Luke, MD, FACP (UPMC Hillman Cancer Center)

- This abstract presented the final DMFS analysis from KEYNOTE-716
- Eligible patients had resectable stage IIB or IIC cutaneous melanoma with a negative sentinel lymph node biopsy
    - Patients were randomly assigned to either 200 mg of PEMBRO or placebo every three weeks
- At the median follow-up time of 39.4 months, PEMBRO had improved DMFS (84.4% versus 74.7%) and RFS (76.2% versus 63.4%) relative to placebo, in both cases regardless of cancer stage
- No new safety signals were observed during this time

Abstract #9506: **Non-comparative, open-label, international, multicenter phase I/II study of nivolumab (NIVO) ± ipilimumab (IPI) in patients (pts) with recurrent/metastatic Merkel cell carcinoma (MCC) (CheckMate 358).**
Clinical trial #NCT02488759
Shailender Bhatia, MD (Division of Medical Oncology, University of Washington and Fred Hutchinson Cancer Center)

- PD-(L)1 blockades (such as NIVO) have demonstrated improved survival outcomes for patents with metastatic MCC, especially when in combination with anti-CTLA-4 (IPI)
- CheckMate 358 assessed the NIVO + IPI combination in two non-randomized cohorts of MCC patients

- All eligible patients in this study had received at least two prior therapies but no prior immune checkpoint inhibitor therapy
    - Patients were eligible regardless of PD-(L)1 status
- For 24 months (bar consent withdrawal, unacceptable toxicity, or disease progression), patients received either NIVO (3 mg/kg) + IPI (1 mg/kg) or solo NIVO (240mg)
- After a 24.4 month median follow up, the combination of NIVO + IPI demonstrated a 58.1% ORR
    - 32.6% of participants who discontinued treatment from the combination arm did so due to disease progression, and 25.6% for reasons related to treatment toxicity
- The solo NIVO arm had a 62.5 month median follow-up and saw a 60% ORR
    - 28% of treatment discontinuation from this arm was related to disease progression and 25.6% to drug-related toxicity
- This data shows that both the combination of NIVO + IPI and solo NIVO show clinical benefit in patients with advanced MCC, and therefore there is no suggestion of additional efficacy when IPI is added to NIVO, especially as there is a higher incidence of TRAEs

	NIVO (n = 25)	NIVO + IPI (n = 43)
ORR, n (% [95% CI])	15 (60.0 [38.7–78.9])	25 (58.1 [42.1–73.0])
Complete response, n (%)	8 (32.0)	8 (18.6)
Partial response, n (%)	7 (28.0)	17 (39.5)
Median DOR, m (95% CI)	60.6 (16.7–NA)	25.9 (10.4–NA)
Median PFS, m (95% CI)	21.3 (9.2–62.5)	8.4 (3.7–24.3)
Median OS, m (95% CI)	80.7 (23.3–NA)	29.8 (8.5–48.3)
Any-grade/grade 3/4 TRAE, %	84.0/28.0	83.7/46.5

Table 2: Data table accompanying abstract #9506

Abstract #9507: **Towards organ preservation and cure via 2 infusions of immunotherapy only, in patients normally undergoing extensive and mutilating curative surgery for cutaneous squamous cell carcinoma: An investigator-initiated randomized phase II trial—The MATISSE trial.**
Clinical trial number #NCT04620200
Charlotte L. Zuur, M.D., PhD. (Department of Head and Neck Surgical Oncology, Netherlands Cancer Institute)

- The MATISSE trial comparatively tested neoadjuvant NIVO + IPI and solo NIVO in patients with locally advanced cutaneous Squamous Cell Carcinoma (CSCC), a population for whom the current standard of care is (often invasive) surgery with adjuvant radiotherapy
- Patients were randomised between the solo NIVO (3mg/kg) arm and the combination arm (3mg/kg NIVO + 1mg/kg IPI)
- Grade 3-4 immune-related adverse events occurred in 12% of patients
- 53% of patients receiving the combination treatment achieved a major pathologic response, which was achieved in 40% of the solo NIVO arm
    - A major pathological response is defined as <10% residual viable cancer cells in the surgical resection specimen
- A deep clinical response was observed in 61% of patients on the combo arm and 50% on the solo NIVO arm
- Nine participants on the MATISSE trial have demonstrated that organ preservation and durable complete remissions can be achieved in patients with CSCC after two rounds of neoadjuvant immunotherapy, without having to resort to surgery or radiotherapy

Uveal (Ocular) Melanoma Trial Data

Presentation: **The Evolving Management of Stage IV Melanoma**; from panel **The Changing Landscape of Uveal Melanoma**
Sophie Piperno-Neumann, MD (Institut Curie Paris)

- For HLA0201-positive patients, Tebentafusp (immunotherapy, bispecific fusion protein) is currently the systemic first-line treatment
- For patients who are HLA0201-negative, new agents are being developed to target the GNAQ and GNA11 mutations and towards the liver, a frequent metastasis site for ocular/uveal melanoma
- Studies: Augsburger, Khoja, Rantala, Nathan

- From a 2022 study by Paul Nathan et al.: one-year overall survival benefit for Tebentafusp was 73% (versus 59% in the control group), and 36% of patients in this study saw clinical benefit with Tebentafusp (check this latter fact)
- Additionally, the IMCgp100-102 study included six major uveal-melanoma specific genes, and found a correlation between circulating tumour DNA (ctDNA) reduction and the hazard ratio for death; the patients who had complete ctDNA removal saw longer survival rates
- In the following 202 study, ctDNA reduction was seen in 88% of patients who were treated with Tebentafusp
    - 37% of patients achieved ctDNA clearance, which was associated with the highest overall survival benefit

Abstract #3008: **A phase 1 study of the protein arginine methyltransferase 5 (PRMT5) brain-penetrant inhibitor PRT811 in patients (pts) with recurrent high-grade glioma or uveal melanoma (UM).**
Clinical trial: NCT04089449
Varun Monga, MBBS (University of Iowa)

- This study reports on the safety and efficacy of PRT811 during the dose-expansion phase for patients with recurrent high-grade glioma or uveal/ocular melanoma
    - PRT811 is a potent brain-penetrant PRMT5 inhibitor, PRMT5 being a protein that can facilitate cell cycle checkpoint activation
- Patients received 15-800mg of PRT811 orally daily, in order to determine the maximum tolerated or recommended phase II dose of PRT811 and evaluate dose-limiting toxicities
- All treatment-related adverse events observed were <grade 4
- Of the metastatic uveal melanoma patients in the study, 10% saw a confirmed partial response; 10% an unconfirmed partial response; and 40% had stable disease
- Overall, PRT811 demonstrated an acceptable safety profile, alongside clinical activity, for patients with metastatic uveal melanoma

Glossary of Terms

Drug acronyms:
IPI: ipilimumab
NIVO: nivolumab
PEMBRO: pembrolizumab

Other terms:
DMFS: distant metastasis-free survival
ORR: overall response rate

OS: overall survival
PFS: progression-free survival
RFS: relapse-free survival
TRAE: Treatment-related adverse events

Recent News Articles of Interest

- Re: KEYNOTE-716: **Data Support Adjuvant Pembrolizumab as Standard Care in Stage IIB/C Melanoma** in *Cancer Therapy Advisor*

- Re: KEYNOTE-942: **Personalized mRNA Vaccines May Transform the Treatment of Melanoma** in *The ASCO Post*

- Re: KEYNOTE-942: **Moderna and Merck cancer vaccine used with Keytruda reduces risk of deadly skin cancer spreading** in *CNBC*

- Re: KEYNOTE-942 **Moderna-Merck cancer jab blunts melanoma spread when dosed with Keytruda** in *Medical Marketing and Media*

- **Castle Biosciences Presents New Data Demonstrating the Ability of DecisionDx®-SCC to Identify Tumors Likely to Metastasize in Patients with Cutaneous Squamous Cell Carcinoma Deemed Low Risk by Traditional Staging** in *Business Wire*

- **Cancer Vaccine IFx-Hu2.0 Confers Immune Priming Effect in Previously Treated MCC and CSCC** in *OncLive*