Melanoma: What else beyond Checkpoint Inhibitor pathway?

Jose Lutzky MD, FACP
Director, Mount Sinai Melanoma Program
Miami Beach, Florida
Clinical Associate Professor, Wertheim School of Medicine,
FIU, Miami, Florida
Jose Lutzky, MD
Melanoma: What Else Beyond Checkpoint Inhibitor Pathway?

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Consultant: BMS, Array, Novartis
Speakers Bureau: BMS, Novartis

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Melanoma therapy beyond approved CPIs

Better

Adjuvant

Therapy
Melanoma therapy beyond approved CPIs

More

CPIs
Melanoma therapy beyond approved CPIs

More

Targeted

Therapy
Melanoma therapy beyond approved CPIs

Better

T-cell

Activation
Melanoma therapy beyond approved CPIs

Tumor Microenvironment Modification
Melanoma therapy beyond approved CPIs

Metabolic Intervention
Melanoma therapy beyond approved CPIs

Adoptive

Cell

Therapy
Melanoma therapy beyond approved CPIs

New Strategies
Overall Survival: IO and Metastatic Melanoma

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<thead>
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<tbody>
<tr>
<td>1-year OS</td>
<td>46%</td>
<td>47%</td>
<td></td>
<td></td>
<td>71%</td>
<td>71%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year OS</td>
<td>24%</td>
<td>29%</td>
<td></td>
<td></td>
<td>55%</td>
<td>58%</td>
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<tr>
<td>3-year OS</td>
<td>22%</td>
<td>21%</td>
<td></td>
<td></td>
<td>58%</td>
<td>52%</td>
<td></td>
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<tr>
<td>5-year OS</td>
<td></td>
<td>18%</td>
<td></td>
<td></td>
<td></td>
<td>34%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Previously treated pts (ipi/gp100 vs. ipi vs. gp100). ** Previously untreated pts (ipi/DTIC vs DTIC).


Presented by Katy K. Tsai, MD
Adjuvant Ipilimumab in High-Risk Melanoma

5 deaths in ipilimumab arm from irAEs

Eggermont et al. NEJM 2016
Adjuvant nivolumab vs ipilimumab in High-Risk Melanoma
3 mg/kg IV q 2 weeks x 1 year

Weber et al. NEJM 2017
In the overall intention-to-treat population, the 12-month rate of recurrence-free survival was 75.4% (95% CI, 71.3 to 78.9) in the pembrolizumab group and 61.0% (95% CI, 56.5 to 65.1) in the placebo group.
Other adjuvant trials with pending data

- **S1404**
  - IFN/ipilimumab vs. pembrolizumab
  - Accrued; results pending
  - Inclusion criteria: IIIA (N2a), IIIB, IIIC, IV

- **CheckMate 915**
  - nivolumab vs ipilimumab + nivolumab (attenuated)
  - Ongoing
  - Inclusion criteria: IIIB, IIIC, IIID, IV (AJCC 8th edition)
Adjuvant therapy of high risk BRAF V600 mutant melanoma

Long, GV et al. NEJM, 2017
# SAFETY SUMMARY

<table>
<thead>
<tr>
<th>AE Category, n (%)</th>
<th>Dabrafenib Plus Trametinib (n = 435)</th>
<th>Placebo (n = 432)</th>
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</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>422 (97)</td>
<td>380 (88)</td>
</tr>
<tr>
<td>AEs related to study treatment</td>
<td>398 (91)</td>
<td>272 (63)</td>
</tr>
<tr>
<td>Any grade 3/4 AE</td>
<td>180 (41)</td>
<td>61 (14)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>155 (36)</td>
<td>44 (10)</td>
</tr>
<tr>
<td>SAEs related to study treatment</td>
<td>117 (27)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Fatal AEs related to study drug</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to dose interruption</td>
<td>289 (66)</td>
<td>65 (15)</td>
</tr>
<tr>
<td>AEs leading to dose reduction</td>
<td>167 (38)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>114 (26)</td>
<td>9.7%/13.8%</td>
</tr>
</tbody>
</table>

AE, adverse event; SAE, serious adverse event.

<sup>a</sup> Most common AEs leading to treatment discontinuation in the dabrafenib plus trametinib arm were pyrexia (9%) and chills (4%).
(Neo-)adjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage III melanoma: Updated data from the OpACIN trial and first immunological analyses

Key eligibility criteria

- Histologically confirmed stage 3b metastatic cutaneous melanoma, palpable disease (no in-transit only) of the axilla or groin
- No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1
- Normal LDH
- Adults at least 18 years of age
- World Health Organization (WHO) Performance Status 0 or 1
- Presence of at least two of the defined HLA alleles that allow MHC tetramer analysis

Efficacy

- Pathological response rate was 80% in the neo-adjuvant arm.
- 5 patients relapsed, all relapses were early after post-surgery (median of 4.2 months).
- 2/10 (20%) patients in the neo-adjuvant arm relapsed (SD, only 2 courses due to grade 3 colitis, PD only 1 course due to grade 3 dermatitis).
- 3/10 (30%) patients relapsed so far in the adjuvant arm (one had 3 courses and two had 2 courses, stopped due to colitis, hypophysitis, and colitis, respectively).
- So far 9/20 (33%) patients recovered fully from irAEs, 11 patients have ongoing AEs (8 need only hormonal substitution, 3 have other ongoing irAEs: low-grade diarrhea, PNP, and rash + elevated ALT/AST).
- All patients are still alive; however two are progressive upon last line standard therapy.

Conclusions

- Neo-adjuvant ipilimumab + nivolumab induces unexpected high frequency and depth of responses, but also a high percentage of grade 3 and 4 toxicities.
- At median follow up of 14 months none of the responders in the neo-adjuvant arm has relapsed.
- RNAseq based methods and mutational load do not seem to identify all patients with favorable outcome.
- Selective protein profiling (26 antibodies) of tumor (CD45lo) and margin areas (CD45hi) by the Nanostring™ microscope technique identified PD-L1 and B2M (absolute protein counts) as possible markers to identify patients benefitting from (neo)adjuvant ipilimumab + nivolumab; multi-parameter analysis might improve specificity.
Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-center, open-label, randomized, phase 2 trial
T cell checkpoint modulation

- **Single Agents**
  - **Agonists**
    - Anti-ICOS
    - Anti-GITR
    - Anti-OX40
    - Anti-41BB (CD 137)
    - Anti-CD27
  - **Antagonists**
    - Anti-LAG3
    - Anti-TIM3
    - Anti-VISTA

- **Combinations**
  - IDO + ipi/pembro/durva
  - TVEC+ ipi/pembro
  - pembro/ipi + IFN
  - pembro + JAK/STAT inhibitors
  - nivo + CD 137/TRAIL-R2 Ab/LAG-3
  - ipi + nivo + HDAC inhibitors
LAG-3 Inhibition (BMS-986016)

Figure 1. Role of LAG-3 in T-Cell Exhaustion and Anti-PD-1 Resistance

1. In therapy-naive patients, constitutive LAG-3 expression may limit the antitumor activity of PD-1 pathway blockade. Anti-LAG-3 combined with nivolumab may deepen or increase the durability of responses.

2. In patients exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression. Anti-LAG-3 combined with nivolumab may restore T-cell activation and tumor response.

Data presented by Paolo Ascierto, MD, ASCO 2017.
Initial efficacy of anti-lymphocyte activation gene-3 (anti–LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti–PD-1/PD-L1 therapy.

- Anti-LAG 3 (BMS-986016) in combination with nivolumab demonstrates encouraging initial efficacy, with a safety profile similar to nivolumab monotherapy
  - Treatment-related AEs of any grade occurred in 45% of patients (grade 3/4, 9%)
- These data provide first proof of principle that combining anti–LAG-3 and anti–PD-1 in IO-experienced patients overcomes tumor PD-L1 resistance and restores T-cell activity
- Greater and deeper response rate with LAG-3 expression ≥ 1% suggests that LAG-3 is a potential biomarker enriching for clinical benefit
- Evolving tumor biology provides confidence that this combination can overcome tumor immune escape mechanisms with the potential for broad applicability across lines of therapy and tumor types

Ascierto P et al. ASCO 2017
CA-170 Compound Overview

- Rationally designed, Oral small molecule
- Targets 2 separate and non-redundant immune checkpoint pathways:
  - **PD-L1** (Programmed Death Ligand 1)
  - **VISTA** (V-domain Ig-containing Suppressor of T-cell Activation) Myeloid suppressor cells and T-regs

**Anti-Tumor Activity Correlated with Tumor Types**

- **GROUP 1**
  - naïve to ICI therapy
  - approved PD(L)1 tumor type
- **GROUP 2**
  - naïve to ICI therapy
  - not approved PD(L)1 tumor type
- **GROUP 3**
  - received prior ICI therapy
  - all tumor types

Clinical Safety

- MTD and RP2D not established yet
- No DLT or IrAEs reported thus far for the dose range of 50 – 800 mg
- TEAEs and TRAEs predominantly Gr 1 or 2 and self-limiting

**Bang YJ et al. SITC 2017**
TIM-3 is a key immune checkpoint and a next-generation cancer immunotherapy target

TIM-3 negatively regulates T-cell activation and is a marker of exhausted T cells

PD-1 resistance is associated with increased TIM-3 expression in patient TILs

HNSCC=head and neck squamous cell carcinoma; NSCLC=non–small cell lung cancer; PD-1=programmed death 1; TIL=tumor-infiltrating lymphocyte; TIM-3=T-cell immunoglobulin and mucin-domain–containing-3; CE=control effusion; RE= resistant effusion; PT=primary tumor.

Part 2 dose Expansion Cohorts

**Cohort A:**
- **anti-PD-1/L1 Treated Melanoma**
  - **A1**: TSR-022 MONOTHERAPY
    - Stage 1 (n=20) → Stage 2 (n=36)
  - **A2**: TSR-022 DL 1+ TSR-042
    - Stage 1 (n=29) → Stage 2 (n=15)
  - **A3b**: TSR-022 DL 2 + TSR-042
    - Stage 1 (n=29) → Stage 2 (n=15)

**Cohort B:**
- **anti-PD-1/L1 Treated NSCLC**
  - **B1**: TSR-022
    - Stage 1 (n=20) → Stage 2 (n=36)
  - **B2**: TSR-022 + TSR-042
    - Stage 1 (n=29) → Stage 2 (n=15)
  - **B3b**: TSR-022 DL 2 + TSR-042
    - Stage 1 (n=29) → Stage 2 (n=15)

**Cohort C:**
- **≥ 3rd line CRC**
  - **C1**: TSR-022
    - Stage 1 (n=20) → Stage 2 (n=36)
  - **C2**: TSR-022 + TSR-042
    - Stage 1 (n=20) → Stage 2 (n=36)
  - **C3b**: TSR-022 DL 2 + TSR-042
    - Stage 1 (n=20) → Stage 2 (n=36)
PEGylated IL-10 - Mechanism of Action

CD8+ T cells that recognize the tumor cell, become exhausted and undergo apoptosis, in the absence of a survival factor (IL-10).

AM0010

- Tumor recognizing CD8+ T cells are activated and proliferate
- AM0010 inhibits CD8+ T cell apoptosis and induces Granzymes and FasL
- Granzyme and FasL induces tumor cell death

Rationale for AM0010 + anti-PD-1

- Increased TCR signal
- Two complementary pathways activated

Rationale for AM0010 + Chemo

- Chemo induces immunogenic tumor cell death and AM0010 primes a sustained immune memory

Sequoia - Phase 3
PDAC 2nd Line (n=566)
FOLFOX + AM0010

Naing A. SITC Meeting 2017
AM0010 (Pegilodecakin) in IO Therapy

- Tumor antigen recognition by CD8+ T cells (TCR) induces IL-10R and PD-1 on CD8+ T cells
  - PD-1 is a negative feedback ("Immune Checkpoint")
  - IL-10 expands antigen activated CD8+ T cells (cytotoxic license)
- AM0010 (Pegilodecakin) induces
  - Phospho-STAT3 in intratumoral CD8+ T cells
  - Accumulation of immune checkpoint positive CD8+ T cells (PD-1+/Lag-3+)
  - Expansion of several hundred previously not detectable T cell clones / patient

- AM0010 induces objective tumor responses in monotherapy
  - 25% ORR in RCC
  - Long lasting response in RCC, ocular melanoma and CTCL (CR)
- AM0010 synergizes with anti PD-1
  - Tolerated with no significant increase in AE profile over either agent in monotherapy
  - ORR in RCC 44% (15 of 34 pts (2 CRs), 2x expected RR)
  - ORR in NSCLC 41% (11 of 27 pts, 2x expected RR)
Background

- BRAF/MEK inhibitor combination therapy is standard of care in BRAF V600-mutant locally advanced or metastatic melanoma,\(^1\) based on improved survival with manageable tolerability.\(^2,3\)

- **Binimetinib (BINI):** potent, selective allosteric, ATP-uncompetitive inhibitor of MEK1/2\(^4\) with shorter half-life than other MEK1/2 inhibitors; may provide more rapid resolution of toxicity upon interruption\(^5\)
  - MTD 45 mg BID

- **Encorafenib (ENCO):** ATP-competitive BRAFi with unique pharmacologic profile\(^6\)
  - Single agent MTD 300 mg QD\(^7\)
  - Dose able to be increased to 450 mg QD when combined with BINI\(^8\)

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\(^{5}\) Data on File. Array BioPharma Inc.
PFS: COMBO300 vs ENCO300 by Central Review

**Median PFS in months (95% CI)**

**COMBO300**

12.9 (10.1–14.0)

**ENCO300 (Parts 1 + 2)**

9.2 (7.4–11.0)

**HR (95% CI), 0.77 (0.61–0.97)**

P=0.029†

*Median duration of potential follow-up approximately 5 months longer than with COMBO300 due to longer duration in study of ENCO300 Part 1 patients.

†Nominal P-value.
## Selected AEs of Interest

<table>
<thead>
<tr>
<th>Event, %</th>
<th>COMBO300 n=257</th>
<th>ENCO300 (Parts 1+2) n=276</th>
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<tr>
<td><strong>Event, %</strong></td>
<td>All Grades</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td>Pyrexia*</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Rash†</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Transaminases increased‡</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Retinal pigment epithelial detachment‖</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Left ventricular dysfunction§</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Secondary skin neoplasms‖</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Dermatitis aciform</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity§</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>1</td>
<td>&lt;1</td>
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</table>

*Includes pyrexia, body temperature increased, and hyperthermia.
†Includes rash, rash generalized, rash erythematous, rash maculo-papular, dermatitis, rash follicular, rash macular, rash papular, rash pruritic, generalized erythema, rash vesicular, dermatitis psoriasiform, and rash pustular.
‡Includes alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatic function abnormal, and hepatic enzyme increased.
‖Includes chorioretinopathy, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, and subretinal fluid.
§Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, left ventricular failure, cardiac output decreased, and ventricular hypokinesia.
‖Includes basal cell carcinoma, Bowen's disease, keratoacanthoma, lip squamous cell carcinoma, neoplasm skin, squamous cell carcinoma, and squamous cell carcinoma of skin.
§Includes photosensitivity reaction, solar dermatitis, and sunburn.

18. Dummer R. ESMO 2017
6-thio-DG

Induction of Telomere Dysfunction Prolongs Disease Control of Therapy-Resistant Melanoma

Authors: Gao Zhang, Lawrence W. Wu, Ilgen Mender, Michal Barzily-Rokni, Marc R. Hammond, Omotayo Ope, Chaoran Cheng, Themistoklis Vasilopoulos, Sergio Randell, Norah Sadek, Aurelie Beroard, Min Xiao, Tian Tian, Jiuseng Tan, Umar Saeed, Eric Sugarman, Clemens Krepler, Patricia Brafford, Katrin Sproesser, Sengottuvelan Murugan, Rajasekharan Somasundaram, Bradley Garman, Bradley Wubbenhorst, Jonathan Woo, Xiangfan Yin, Qin Liu, Dennie T. Frederick, Benchun Miao, Wei Xu, Giorgos C. Karakousis, Xiaowei Xu, Lynn M. Schuchter, Tara C. Gangadhar, Lawrence N. Kwong, Ravi K. Amaravadi, Yiling Lu, Genevieve M. Boland, Zhi Wei, Katherine Nathanson, Utz Herbig, Gordon B. Mills, Keith T. Flaherty, Meenhard Herlyn, Jerry W. Shay
Target-Immuno Triplets: BRAF + MEK + PD1/L1

- Dabrafenib + Trametinib + Durvalumab
- Dabrafenib + Trametinib + Pembrolizumab
- Vemurafenib + Cobimetinib + Atezolizumab

Multiple Triplet Combinations Launching Into Phase III:
- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab

Ribas A. ASCO/SITC 2018
Cobimetinib (MEK inhibitor) + Atezolizumab (PDL-1 Ab) for BRAF WT Melanoma Phase I

Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

Wargo JA et al. CCR 2013

ribas a. ASCO/SITC 2018
IDO and TME Immunosuppression

Selvan, SR. Current Cancer Drug Targets, 2016
Incyte Corporation (Nasdaq: INCY) and Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that an external Data Monitoring Committee (eDMC) review of the pivotal Phase 3 ECHO-301/KEYNOTE-252 study results evaluating Incyte’s epacadostat in combination with Merck’s KEYTRUDA® in patients with unresectable or metastatic melanoma determined that the study did not meet the primary endpoint of improving progression-free survival in the overall population compared to KEYTRUDA monotherapy. The study’s second primary endpoint of overall survival also is not expected to reach statistical significance. Based on these results, and at the recommendation of the eDMC, the study will be stopped. The safety profile observed in ECHO-301/KEYNOTE-252 was consistent with that observed in previously reported studies of epacadostat in combination with KEYTRUDA.

Beatty et al. ASCO 2012
Gangadhar et al. ESMO 2016
The prevalence of somatic mutations across human cancer types.

Mutation = Neoantigen

High response rate and high mutational load in Desmoplastic melanoma

70% overall response rate
32% complete response rate

n=60 (out of 1058 cases Reviewed*)
2 slllc
3 M1a
20 M1b
35 M1c

*Retrospective Review

% Overall survival (OS), median not reached

Estimated 2 year OS 73% (CI 62-88).

Tumor Mutational Load
p=0.015

Non-Synonymous Mutations

Non-Desmoplastic Melanoma
Desmoplastic Melanoma

= Progressive Disease
= Response (RECIST 1.1)


High response rate to PD-1 blockade in desmoplastic melanomas. Nature 2018

Presented By Antoni Ribas at 2018 ASCO-SITC Clinical Immuno-Oncology Symposium
Adoptive T cell therapy can involve engineered (CAR, TCAR) or patient-derived (TIL, PBMC) T cells.
Engineered T-cell redirector

**IMCgp100 (ImmTAC gp100 & CD3)**

- UVEAL metastatic adjuvant
- CUTANEOUS metastatic
Personalized neoantigen vaccines in the treatment of melanoma
Innate Immune-Tumor Sensing

- TLR agonists
- STING agonists
  - Poly-ICLC (TLR3)
  - G100 (TLR4)
  - Imiquimod (TLR7)
  - SD-101 (TLR9)
  - CYT003 (TLR9)

Multiple TLR agonist clinical trials in combination with tumor vaccines and check-point blockade on-going
Modulation of the tumor microenvironment by intratumoral administration of IMO-2125

Cornfeld, MJ. SITC 2016
A Randomized Phase 3 Comparison of IMO-2125 with Ipilimumab versus Ipilimumab Alone in Subjects with Anti-PD-1 Refractory Melanoma

Diab A. ESMO 2016
Innate Immune-Tumor Sensing

- TLR agonists
- STING agonists

Virotherapy

- Talamogene laharparepvec (T-VEC)
- Coxsackievirus A21 (CVA21)
- JX-594
- ONCOS-102
- Pelareorep
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

Local Effect:
Virally-Induced Tumor Cell Lysis

OPTiM: Ph 3 T-VEC vs GM-CSF
- Improved Durable Response Rate (response for ≥6 months)
- 16% vs 2%, p<0.0001
- led to FDA approval 2015

Tumor-Specific Immune Response

Systemic tumor-specific immune response

Death of distant cancer cells

Kaufman et al. ASCO (2014), abstr LBA9008
T-VEC + Pembrolizumab in Stage IIIB-IV Melanoma

A phase 1b/3 Trial of Talimogene Laherparepvec With Pembrolizumab in Melanoma (KEYNOTE-034/MASTERKEY-265)

RECIST response = 46%, no increase in toxicity from pembrolizumab alone

Long et al. SMR 2015
Uveal melanoma is a “cold” tumor that primarily metastasizes to the liver.

TREATMENT

- Chemotherapy
- Targeted Rx
- Checkpoint Inhibitors
- TACE
- TAIE

Coxsackievirus A21 (CVA21)

Non-enveloped, single-stranded RNA virus

In general, CVA21 natural infection causes mild upper respiratory illness “common cold” Targets ICAM-1/CD54

Decreased PD-1 and PD-L1 expression in UM metastases. (A) Representative IHC for CD8, PD-1, and PD-L1 in UM and CM metastatic tissues. Quantification of CD8 (B), PD-1 (C), and PD-L1 (D) in UM and CM metastases as counts/mm² (B-C) and % positivity (D). Each dot represents a sample. Green, PD-L1-positive; Purple, PD-L1-negative. Statistical comparison between UM and CM cohorts was performed using non-parametric Mann-Whitney test (B-C) and Chi-square test (D).

CVA21 levels in tumor cells after IV administration in stage IV cancer patients

Liauw WS, Chern B, Shafren DR. Phase I, Open-Label, Cohort Study of CAVATAK (Coxsackievirus A21), Given Intravenously to Stage IV Patients Bearing ICAM-1 Expressing Solid Tumours; Poster presented at: EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; 6–9 November 2012; Dublin, Ireland
VLA-24 Study Design

- Phase 1b, open label for patients with metastatic uveal melanoma

- CVA21 intravenous infusion – max of 8 cycles (11 infusions) per subject

- Ipilimumab co-administered AFTER first 4 doses of CVA21 on Days 8, 29, 50 and 71

- On days where ipilimumab is given with CVA21, CVA21 will be given first.

- 10 patients

- 2-3 study sites
<table>
<thead>
<tr>
<th>Study phase</th>
<th>Institution/group</th>
<th>ClinicalTrials.gov ID</th>
<th>Disease site</th>
<th>Cohorts</th>
<th>Planned accrual</th>
<th>IT mechanism</th>
<th>Est. completion date</th>
<th>Primary outcome measure</th>
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<tr>
<td>II</td>
<td>Multi-institutional (CheckMate548)</td>
<td>NCT02667587</td>
<td>Newly diagnosed glioblastoma</td>
<td>Nivolumab + temozolomide + RT vs. placebo + temozolomide + RT</td>
<td>n = 320</td>
<td>anti-PD-1</td>
<td>May 2017</td>
<td>OS</td>
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<tr>
<td>III</td>
<td>Multi-institutional (CheckMate498)</td>
<td>NCT02617589</td>
<td>Newly diagnosed glioblastoma</td>
<td>Nivolumab + RT vs. temozolomide + RT</td>
<td>n = 550</td>
<td>anti-PD-1</td>
<td>October 2019</td>
<td>OS</td>
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<tr>
<td>II</td>
<td>Ludwig Institute for Cancer Research</td>
<td>NCT02336165</td>
<td>Newly diagnosed, recurrent glioblastoma</td>
<td>MEDI4736 vs. MEDI4736 + standard RT vs. MEDI4736 + bevacizumab</td>
<td>n = 108</td>
<td>anti-PD-1</td>
<td>July 2017</td>
<td>OS, PFS</td>
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<td>I/II</td>
<td>Northwestern University</td>
<td>NCT02530502</td>
<td>Newly diagnosed glioblastoma</td>
<td>RT + temozolomide + pembrolizumab → temozolomide + pembrolizumab</td>
<td>n = 50</td>
<td>anti-PD-1</td>
<td>March 2018</td>
<td>Dosage, PFS, OS</td>
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<td>I</td>
<td>H. Lee Moffitt Cancer Center</td>
<td>NCT02313272</td>
<td>Recurrent glioma</td>
<td>HFSRT + pembrolizumab + bevacizumab</td>
<td>n = 32</td>
<td>anti-PD-1</td>
<td>June 2017</td>
<td>Dosage</td>
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<tr>
<td>I/II</td>
<td>MD Anderson Cancer Center</td>
<td>NCT02696993</td>
<td>NSCLC BM</td>
<td>Nivolumab + SRS; nivolumab + WBRT; nivolumab + ipilimumab + SRS; nivolumab + ipilimumab + WBRT</td>
<td>n = 130</td>
<td>anti-PD-1; anti-CTLA-4</td>
<td>April 2020</td>
<td>Dosage; PFS</td>
</tr>
<tr>
<td>II</td>
<td>Grupo Español Multidisciplinar de Melanoma (GEM)</td>
<td>NCT02115139</td>
<td>Melanoma BM</td>
<td>Ipilimumab + WBRT</td>
<td>n = 66</td>
<td>anti-CTLA-4</td>
<td>October 2016</td>
<td>1-year survival rate</td>
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<tr>
<td>II</td>
<td>University of Michigan Cancer Center</td>
<td>NCT02097732</td>
<td>Melanoma BM</td>
<td>Ipilimumab → SRS → ipilimumab vs. SRS → ipilimumab</td>
<td>n = 40</td>
<td>anti-CTLA-4</td>
<td>May 2017</td>
<td>Local control rate</td>
</tr>
<tr>
<td>I</td>
<td>Thomas Jefferson University</td>
<td>NCT01703507</td>
<td>Melanoma BM</td>
<td>Ipilimumab + WBRT vs. ipilimumab + SRS</td>
<td>n = 24</td>
<td>anti-CTLA-4</td>
<td>November 2017</td>
<td>Dosage</td>
</tr>
<tr>
<td>I</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
<td>NCT01950195</td>
<td>Melanoma BM</td>
<td>Ipilimumab + SRS</td>
<td>n = 30</td>
<td>anti-CTLA-4</td>
<td>December 2016</td>
<td>Adverse events and safety</td>
</tr>
<tr>
<td>II</td>
<td>University Hospital, Lille</td>
<td>NCT02662725</td>
<td>Melanoma BM</td>
<td>Ipilimumab + SRS</td>
<td>n = 73</td>
<td>anti-CTLA-4</td>
<td>December 2015</td>
<td>OS</td>
</tr>
</tbody>
</table>

RT, radiation therapy; PD-1, programmed cell death protein 1; OS, overall survival; PFS, progression-free survival; HFSRT, hypofractionated stereotactic radiotherapy; IMRT, intensity-modulated radiation therapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; iRCC, immune-related response criteria; WBRT, whole brain radiation therapy; NSCLC, non-small cell lung cancer; BM, brain metastases; SRS, stereotactic radiosurgery; MM, metastatic melanoma; SBRT, stereotactic body radiation therapy.
Metabolic approaches in IO

- Adenosine (A2A receptor block)
- Arginine depletion
- Glutamine depletion
- IDO (tryptophan) inhibition
- Hypoxia inducible factor-1 (HIF-1) inhibition
- Oxidative phosphorylation (OXPHOS): metformin
- other
Metabolic switch to aerobic glycolysis is essential for effector T cell development and function.

Naïve/Quiescent T cell

- Glucose
- Glut1
- Glycolysis
- ATP
- Lactate

Activated T cell

- Glucose
- Glut1
- Glycolysis
- OxPhos
- ATP
- Lactate
- Pyruvate
- CO₂
- IFNγ
- Cytotoxicity
- CD40L
- Glutamine

Kaech S. Presented at SITC annual Meeting, Nov 2017
Role of epigenetic modification in immunotherapy of malignancy

A

Re-educated tumour cell

↑ CD80/CD86

↑ MHC

↑ ISGs

↑ MICA/MICB

↑ IFN signalling

↑ APM

↑ FAS

↑ CXCL9/CXCL10

<table>
<thead>
<tr>
<th>Up-regulated gene groups</th>
<th>Example genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN and IFN-related genes</td>
<td>IFNGR1, IFNGR2, STAT1, IFIT1, IFIT2</td>
</tr>
<tr>
<td>APM genes</td>
<td>TAP1, TAP2, LAMP7, LMP9, B2M</td>
</tr>
<tr>
<td>MHC class I/II genes</td>
<td>HLA-A, HLA-DRA</td>
</tr>
<tr>
<td>Co-stimulatory molecules</td>
<td>ICAM-1, CD80, CD86</td>
</tr>
<tr>
<td>Death receptors and stress-induced ligands</td>
<td>FAS, MICA, MICB, ULBPs</td>
</tr>
<tr>
<td>Chemokines</td>
<td>CXCL9, CXCL10</td>
</tr>
<tr>
<td>Immune checkpoints</td>
<td>PD-L1, PD-L2, CTLA-4</td>
</tr>
<tr>
<td>TAAs</td>
<td>MAGEA1, NY-ESO-1</td>
</tr>
</tbody>
</table>

B

Immune gene

Re-educated immune gene

- Epigenetic drugs

mRNA

+ Epigenetic drugs

Dunn J. and Rao S. Molecular Immunology 2017
Role of epigenetic modification in immunotherapy of malignancy

<table>
<thead>
<tr>
<th></th>
<th>Tumour cell</th>
<th>T cell</th>
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<tr>
<td>BET inhibitors</td>
<td>✔️ ▼ PD-L1</td>
<td>✔️ ▲ Persistence/function</td>
</tr>
<tr>
<td>EZH2 inhibitors</td>
<td>✔️ ▲ Chemokines</td>
<td>?</td>
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<tr>
<td>HDM inhibitors</td>
<td>✔️ ▲ Silenced genes</td>
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</table>
Table 1
Current clinical trials combining checkpoint inhibitors and epigenetic drugs in various cancer types.

<table>
<thead>
<tr>
<th>ClinicalTrials.gov identifier</th>
<th>Recruitment status</th>
<th>Phase</th>
<th>Cancer type</th>
<th>Immune checkpoint inhibitor/s</th>
<th>Epigenetic drug/s</th>
<th>Other drugs</th>
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<tbody>
<tr>
<td>NCT02437136</td>
<td>Recruiting</td>
<td>lb/II</td>
<td>NSCLC and melanoma</td>
<td>Pembrolizumab</td>
<td>Entinostat</td>
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<tr>
<td>NCT02936752</td>
<td>Not yet recruiting</td>
<td>lb</td>
<td>MDS following DNMTI-failed therapy</td>
<td>Pembrolizumab</td>
<td>Entinostat</td>
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<tr>
<td>NCT02546986</td>
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<td>II</td>
<td>Advanced/metastatic NSCLC</td>
<td>Pembrolizumab</td>
<td>Oral azacytidine</td>
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<tr>
<td>NCT02909452</td>
<td>Recruiting</td>
<td>I</td>
<td>Advanced solid tumours</td>
<td>Pembrolizumab</td>
<td>Entinostat</td>
<td></td>
</tr>
<tr>
<td>NCT02697630</td>
<td>Not yet recruiting</td>
<td>II</td>
<td>Metastatic uveal melanoma</td>
<td>Pembrolizumab</td>
<td>Entinostat</td>
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<tr>
<td>NCT02538510</td>
<td>Recruiting</td>
<td>I/II</td>
<td>Recurrent unresectable/metastatic HNSCC and SGC</td>
<td>Pembrolizumab</td>
<td>Vorinostat</td>
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<tr>
<td>NCT02658090</td>
<td>Recruiting</td>
<td>I/II</td>
<td>Stage IV NSCLC</td>
<td>Pembrolizumab</td>
<td>Vorinostat</td>
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<tr>
<td>NCT02619253</td>
<td>Recruiting</td>
<td>I/II</td>
<td>Advanced renal or urothelial cell carcinoma</td>
<td>Pembrolizumab</td>
<td>Vorinostat</td>
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<tr>
<td>NCT02395627</td>
<td>Recruiting</td>
<td>II</td>
<td>Hormone resistant BC</td>
<td>Pembrolizumab</td>
<td>Vorinostat</td>
<td>Tamoxifen</td>
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<tr>
<td>NCT02901899</td>
<td>Not yet recruiting</td>
<td>II</td>
<td>PR recurrent OC</td>
<td>Pembrolizumab</td>
<td>Guadecitabine</td>
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<tr>
<td>NCT02900560</td>
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<td>PR epithelial OC</td>
<td>Pembrolizumab</td>
<td>Oral azacytidine</td>
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<td>NCT02512172</td>
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<td>I</td>
<td>MSS advanced CRC</td>
<td>Pembrolizumab</td>
<td>Romidepsin with/without oral azacytidine</td>
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<tr>
<td>NCT02260440</td>
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<td>II</td>
<td>Chemo-refractory metastatic CRC</td>
<td>Pembrolizumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02845297</td>
<td>Recruiting</td>
<td>II</td>
<td>Relapsed/refractory AML</td>
<td>Pembrolizumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02816021</td>
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<td>II</td>
<td>MM</td>
<td>Pembrolizumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT01928576</td>
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<td>NSCLC</td>
<td>Nivolumab</td>
<td>Azacytidine with/without entinostat</td>
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<td>NCT02518958</td>
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<td>I</td>
<td>Advanced solid tumours or lymphomas</td>
<td>Nivolumab</td>
<td>RRx-001</td>
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<tr>
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<td>II</td>
<td>AML</td>
<td>Nivolumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02599649</td>
<td>Recruiting</td>
<td>II</td>
<td>MSS</td>
<td>Lirilumab and nivolumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02550463</td>
<td>Recruiting</td>
<td>II</td>
<td>MDS</td>
<td>Nivolumab and/or lirilumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02664181</td>
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<td>Advanced NSCLC</td>
<td>Nivolumab</td>
<td>Decitabine</td>
<td>Oral THU</td>
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<tr>
<td>NCT02795923</td>
<td>Not yet recruiting</td>
<td>II</td>
<td>NSCLC</td>
<td>Nivolumab</td>
<td>Oral decitabine</td>
<td>Tetrahydrodouridine</td>
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<tr>
<td>NCT02543620</td>
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<td>I</td>
<td>Metastatic unresectable HER2-negative BC</td>
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<td>Entinostat</td>
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<tr>
<td>NCT02635061</td>
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<td>lb</td>
<td>Unresectable NSCLC</td>
<td>Nivolumab and ipilimumab</td>
<td>ACY-241</td>
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<td>NCT02890329</td>
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<td>Relapsed/refractory MDS or AML</td>
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<td>Decitabine</td>
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<tr>
<td>NCT02608437</td>
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<td>lb</td>
<td>MM</td>
<td>Ipilimumab</td>
<td>SGI-110</td>
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<tr>
<td>NCT02032810</td>
<td>Recruiting</td>
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<td>Unresectable stage III/IV melanoma</td>
<td>Ipilimumab</td>
<td>Panobinostat</td>
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<tr>
<td>NCT02508870</td>
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<td>MDS</td>
<td>Atezolizumab</td>
<td>Azacytidine</td>
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<tr>
<td>NCT02708680</td>
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<tr>
<td>NCT0281197</td>
<td>Recruiting</td>
<td>II</td>
<td>MSS-CRC, PR-OC, ER-positive and HER2-negative BC</td>
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<td>Azacytidine</td>
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<td>NCT02281084</td>
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<td>NCT02775903</td>
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<td>MDS, AML</td>
<td>Durvalumab</td>
<td>Azacytidine</td>
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<tr>
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<td>Advanced solid tumours and NSCLC</td>
<td>Durvalumab</td>
<td>Mocetinostat</td>
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<tr>
<td>NCT02915523</td>
<td>No yet recruiting</td>
<td>lb/II</td>
<td>Refractory/recurrent epithelial OC</td>
<td>Avelumab</td>
<td>Entinostat</td>
<td></td>
</tr>
</tbody>
</table>

Note: All information on current clinical trials was obtained from ClinicalTrials.gov. Abbreviations: NSCLC: non-small cell lung cancer; MDS: myelodysplastic; DNMTI: DNA methyltransferase inhibitor; HNSCC: head and neck squamous cell carcinoma; SGC: salivary gland cancer; BC: breast cancer; PR: platinum resistant; OC: ovarian cancer; MSS: microsatellite stable; CRC: colorectal cancer; AML: acute myeloid leukaemia; MM: metastatic melanoma; TNBC: triple-negative breast cancer.
Autophagy

Amavaradi RK. 2018

inhibit mTOR and autophagy

Cancer Growth

mTOR

DQ661

PPT1

Lysosome

Autophagy

Recycling & Cancer Cell Survival
• Higher gut microbiome diversity is associated with improved response to anti–PD-1 immunotherapy in patients with metastatic melanoma

• *Compositional* differences in the gut microbiome are associated with responses to anti–PD-1 immunotherapy

• *Antibiotics* compromise the efficacy of PD-1 blockade in mouse tumor models and cancer patients

• Metagenomic analyses of fecal samples *predicts* response to PD-1 at 3 months in cancer patients

• Gut microbiome effects on response to immunotherapy are *transferable*

V. Gopalakrishnan et al. Science 2018;359:97-103;
Bertrand Routy et al. Science 2018;359:91-97
Antibiotics compromise the efficacy of PD-1 blockade in mouse tumor models and cancer patients.

Bertrand Routy et al. Science 2018;359:91-97
The intestinal microbiota influences the efficacy of PD-1 blockade

The enrichment of specific microbial taxa in intestines correlates with response to PD-1 blockade in cancer patients. FMT from responders into tumor-bearing mice improved responses to anti–PD-1 therapy and correlated with increased antitumor CD8+ T cells in the tumors. Mice receiving FMT from nonresponders did not respond to anti–PD-1 therapy, and tumors had a high density of immunosuppressive CD4+ T_{reg} cells.
THE FUTURE IS BRIGHTER