As part of our ongoing coverage of the 2017 American Association for Cancer Research (AACR) meeting, we attended multiple oral presentations on April 4th and our notes are below. Affected companies include Viralytics (ASX: VLA.AX), NewLink Genetics (NasdaqGM: NLNK), Incyte (NasdaqGS: INCY), Corvus (NasdaqGM: CRVS), Amgen (NasdaqGS: AMGN), Bristol-Myers Squibb (NYSE: BMY), and Merck (NYSE: MRK).

Session Notes: Novel Immuno-oncology Agent Clinical Trials

**Brendan Curti: CT114 - The MITCI (Phase 1b) study:** A novel immunotherapy combination of intralesional Coxsackievirus A21 and systemic ipilimumab in advanced melanoma patients with or without previous immune checkpoint therapy treatment

**Companies Affected:** Viralytics, Merck, Bristol-Myers Squibb, Amgen

- CAVATAK – oncolytic virus – coxsackievirus A21 – non-enveloped RNA picornavirus “common cold virus”.
- Not genetically modified.
- Targeted to specific receptor over expressed on cancer cells (human ICAM-1).
- Rapid lytic cell infection.
- Destroys local and metastatic cells by oncolytic and immunotherapeutic activity.
- Potential application across a range of cancer types
- Generally well tolerated by patients
- Potential to combine with other immunotherapies.
- Treatment increases CD8 infiltration, increased PD-L1 expression, and other cytokines.
- In patients with disease control, many upregulations of immune checkpoints.
- CD122 upregulation – correlates with response to anti CTLA4
- 13 patients prior checkpoint therapy, 12 patients were checkpoint naïve.
- 69% M1c in prior checkpoint, 25% in checkpoint naïve.
- No DLTs reported, Grade 3+ events in these patients attributed to CVA21: none.
- BORR by ITT is 50% (11/22). 18% CR.
- If prior checkpoint, 36% ORR, with 1 CR (9%).
- If checkpoint therapy naïve, ORR of 64% with 27% CR rate.
- Having responses in injected and non-injected lesions.
- BORR of 64% (7/11) in CVA21+ipi, BORR of 60% (9/15) for CVA21 + pembrolizumab.
- Future development will be focused on patients with advanced melanoma who are refractory to prior checkpoint inhibition.
Hardev Pandha: CT115 - Phase 1b KEYNOTE 200 (STORM study): A study of an intravenously delivered oncolytic virus, Coxsackievirus A21 in combination with pembrolizumab in advanced cancer patients

Companies Affected: Viralytics and Merck

- Study conducted to determine if CVA21 given IV can track to malignant tumors, determine the safety of IV CVA21 single agent and in combo with pembro.
- TRAEs for CVA21 monotherapy very small. No SAEs.
- Dose escalation with CVA21 monotherapy increased systemic level of exposure.
- Tumor targeting of systemic CVA21 at day 8 high for melanoma, NSCLC, and iliac node bladder cancer.
- For CVA21 systemic monotherapy, only 1 PR (15 patients total), in castrate-resistant prostate cancer. 10 had SD.
- Data suggests secondary replication of virus. Detection of CVA21 viral RNA in tumor biopsies at study day 8.
- ADA development.
- Combo treatment of CVA21 and pembro well tolerated. 1 Grade 3 AE related to CVA21 – hyponatremia.
- 10 patients, No responses, but 3 still receiving treatment (days 44, 21, and 15).
- Opening expansion cohorts of NSCLC and bladder cancer.
- Biopsies on day 8 following IV administration. To see if virus getting to tumor.
- Increased systemic exposure. Get viral intratumoral replication. Robust intratumoral amplification of virus in NSCLC, bladder cancer and melanoma.
- In 2 patients shown, getting specific replication in tumor. Proof of principle.
- Low response rate with single agent CVA21 – 1 PR. Mostly SD. Goal is to create inflammatory tumor to respond to pembro.
- Viral wave of replication showing evidence of infecting tumor and spreading into blood stream.
- Peak viral RNA in blood stream typically late in week 1.
- See humoral immunity and ADAs.
- CVA21 IV: No SAE, good tumor targeting of virus, and minimal evidence of single agent activity, and secondary replication events suggested.
- With combo with pembro, maybe 1 Grade 3 SAE related to CVA21.
- Patients received multiple prior treatments.
- Big slug of IV virus, so in context of ADAs, could still have substantial virus not bound that can get to tumor. First 3 days of loading to tumor.

Discussion

- RNA based virus that binds ICAM-1. Overly expressed on cancer.
- Virus has rapid replication cycle. Once inside, can be translated and make viral proteins.
- Rapidly spreads throughout tumor.
- Triggers and causes pro-inflammatory state.
- Cancer cells and antiviral responses related.
- If healthy cell, and infected, stop cell growth, may commit suicide, could stop blood vessel formation – interferons big part of process.
- Biological processes underlying anti-viral defense are incompatible with efficient tumor evolution.
- Oncolytic viruses exploit cancer biology.
- When virus lands on normal cells, IFNs produced and stops process of virus.
- Cancer cells don’t have IFN capabilities.
- Viral oncolysis creates an environment that leads to a personalized in situ vaccine.
- Oncolytic viruses and immune checkpoint inhibitors: complementary therapeutics.
- Can resensitize patients who do not respond to checkpoints.
- Oncolytic viruses thrive on malignantly activated pathways.
  - Highly selective and well tolerated.
  - Infection of tumor cell leads to lysis and presentation of neo-epitopes.
  - Can turn cold tumors hot.
  - No additional toxicities.

**Lillian L. Siu:** CT116 - BMS-986205, an optimized indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, is well tolerated with potent pharmacodynamic (PD) activity, alone and in combination with nivolumab (nivo) in advanced cancers in a phase 1/2a trial

**Companies Affected:** Bristol-Myers Squibb, Incyte

- IDO enzyme inhibits T-cell function through local depletion of tryptophan and production of immunosuppressive kynurenine.
- High IDO expression associated with poor prognosis. Anti PD-1 treatment upregulates IDO1 expression in patients.
- BMS-986205 – potent and selective IDO1 inhibitor, with no significant inhibition of TDO or IDO2.
- Optimized preclinical PK profile supports QD dosing.
- Higher IC50 than epacadostat.
- Treatment restores human T-cell proliferation in the presence of tolerogenic dendritic cells in mixed lymphocyte reactions at single-digit nM concentrations.
- Phase I/IIa study conducted. First part – Single-agent dose escalation lead-in followed by combo with nivo.
- 2 drugs given together in expansion cohort.
- 44 patients in dose escalation, 11 in dose expansion. ECOG 0-1 for all patients.
- Selected dose expansion patients- 100 mg is dose expansion dose with 240 mg nivo.
- In expansion cohort, 10 patients continuing treatment with only 1 that discontinued. More patients remain on treatment is dose dependent manner to combo.
- BMS-986205 trough concentrations exceed levels predicted in vitro to inhibit IDO1.
- Mean serum kynurenine was substantially reduced at all BMS-986205 doses. Greater than 60% reduction was observed with both the 100 and 200 mg QD doses. Greater than reported previously with BID doses of epacadostat.
- Whole blood ex vivo assay showed greater than 90% inhibition at doses of 50 mg or higher.
- Intratumoral kynurenine reduced across all doses following treatment.
- Combo treatment well tolerated. MTD not yet reached, 2 patients discontinued treatment due to DLTs. No Grade 4 or 5 AEs reported.

**Yousef Zakharia:** CT117 - Interim analysis of the Phase 2 clinical trial of the IDO pathway inhibitor indoximod in combination with pembrolizumab for patients with advanced melanoma

**Company Affected:** NewLink Genetics

- IDO is an intracellular enzyme that regulates immune response by degrading tryptophan to kynurenine.
- IDO pathway activity results in a shift of tryptophan ration, causing kynurenine to increase, and causing a suppressive phenotype.
- Hijack IDO pathway, to cause overexpression in cancers. Correlated with worse prognosis.
- GDC-0919 and epacadostat – Direct IDO enzymatic inhibitors, block tryptophan metabolism.
- Indoximod – acts directly on immune cells to reverse IDO pathway – mediated suppression.
Available data suggest similar activity with both approaches.

Immune suppression of IDO linked to MDSC.

Rationale based on preclinical data from Allyson and Wolchok labs showing synergies with anti-PD1.

Indoximod – 1200 mg PO BID safe and being used in study.

Phase II is indoximod plus checkpoint inhibitors (ipi or pembro). Could switch checkpoint inhibitor after progression.

As of March 2017, 102 patients enrolled. 94 received pembro. 60 of 94 patients treated with pembro evaluable.

Half of patients had M1c status. ECOG 0-1.

Patients treatment naïve for checkpoint. 25% received prior systemic therapy.

52% ORR in 60 patients, 10% CR.

For cutaneous, non-ocular melanoma – 59% ORR, 12% CR, 80% DCR (n=51).

ORR with pembro monotherapy in this patient population is 33%.

Patients have durable response.

Spider plot shows some tumors are still regressing, ORR and CR rate could increase.

Majority of patients had response in first 12 weeks.

AE profile well tolerated. Similar to PD-1 single agent. Only 4 patients had SAE possibly related to indoximod. Grade 3 arthritis, gastritis, hearing impairment. Grade 2 interstitial nephritis.

Grade 3/4 at 55% in CLTA-4, nivo combo.

All immune related AEs similar to that expected with PD-1 monotherapy.

Headaches symptom was not hypophysitis – investigating side effect, but low Grade. Don’t know if drug related, or if IDO class.

Data support Phase III development of indoximod.

Leisha Emens: CT119 - CPI-444, an oral adenosine A2a receptor (A2aR) antagonist, demonstrates clinical activity in patients with advanced solid tumors

Company Affected: Corvus

Adenosine signaling suppresses immunity in the tumor microenvironment. – PD-1/L1 antibodies are effective immunotherapies with response rates of 20-30%.

Novel agents that enhance response or overcome resistance to immunotherapy are a high priority.

The adenosine pathway is a potential new immunotherapy target.

Adenosine binds multiple immunity targets, and suppresses immunity at tumor site.


Phase I/Ib study of CPI-444 as single agent and combo with anti-LD-L1 in patients with incurable cancers.

Step 1: Dose selection phase.

Drug tested at 4 distinct dosing schedules. Tested in several incurable cancers – NSCLC< melanoma, RCC, TNBC others.

Step 2: Cohort expansion by disease type. 14 patients each – NSCLC, mel, RCC, TNBC, others.

Potential expansion to 26 and 48.

In step 1: n = 47 (33 single agent)

Step 2: n=66 (26 single agent).

Median number of prior regimens is 2.

Median duration of treatment 9 weeks. Range up to 40+.

No grade 3/4 AEs with single agent CPI-444.

Disease control rate of 38% for all patients. No sign difference between single agent and combo.
■ Median follow up time is between 4 and 44 weeks. 23/37 with disease control remain on study.
■ Doesn’t seem like much activity relative to rest of cancer development.
■ Patients with stable disease.
■ Response with single agent CPI-444 in RCC patient. Combo caused response in NSCLC and melanoma.
■ Tumor regression observed in RCC, NSCLC, TNBC, SCCHN, and CRC.
■ Two responses in patients with resistant/refractor disease.
■ Single patient – refractory NSCLC (2 prior chemo and nivolumab) – received single agent CPI-444 and had disease regression.
■ Other patient – regression in nivolumab resistant lung cancer – 1 prior chemo, responded to nivolumab, then progressed.
  ◦ Received combo and had regression of disease.
■ Serial biopsies of liver mets fromPD-1 refractory RCC patient treated with single agent CPI-444.
■ Inflammation and CD8+ T cell infiltration after progression on PD-1 therapy increased with single agent CPI-444 therapy.
■ CPI-444 well tolerated as a single agent and in combo with atezo.
■ Most common Grade 1/2 toxicities: nausea, fatigue, pruitis.
■ irAEs of hemolytic anemia (Grade 3), meningoencephalitis (Gr4), and pancreatitis (Gr2) seen with combo therapy.

Session Notes: Mechanisms of Primary and Acquired Resistance to Immunotherapy

Padmanee Sharma: - From the clinic to the lab: Investigating response and resistance mechanisms to immune checkpoint therapy

Company Affected: N/A

■ Proposed integration of immunotherapy CT and laboratory interrogation, mirroring the TCGA project
■ Suggested mice experiments were good for hypothesis testing for hypotheses generated in patients.
■ Rethinking the CT
  ◦ Phase I and II to gauge biomarker. These trials are small, allowing access all tumors, which can be brought to the lab to test various parameters.
  ◦ Gave example of anti-CTLA treated… a So-called “Window of opportunity trials”.
    • IHC pre- vs post treatment
    • After gene expression studies in treated patients ICOS most differentially expressed gene in CTL.
    • T cells expressing ICOS were effector T cells…and the frequency of ICOS expression of increases of time while patients were on treatment.
    • Suggested ICOS can now be used as biomarker.
    • Retrospective look in anti-CTLA treated melanoma. Those that had hi expression ICOS had better outcomes.
■ Showed mice melanoma model were loss of Icos impaired anti-tumor responses.
■ ICOS pathway targeted in as adjuvant for anti-CTLA therapy
■ In prostate cancer, Anti-Ctla-4 plus hormonal therapy to make the tumor hot.
■ Tested immune infiltration in the treat vs, pre-treatment
■ Inhibitory pathways increased were PDL-1, PD-1 and VISTA. In particular, Vista and PD-L1 in were expressed on CD-8 and macrophages.
- In melanoma treated with ipi. They see an M1 signature compared to M2. Did not see that in Prostate cancer ipi-treated suggesting different mechanism for different cancer types.

Questions

- Q. Are you going to partner with company to test to develop combo trials in the way you describe. A. Yes. Currently parenting with BMS and Janssens.
- Q. What should be the base therapy for these combination trials. A. Anti-CTLA-4 should be the baas and anti-PD-1 should be used later.

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