We are attending the 2017 American Society of Clinical Oncology (ASCO) conference from June 2nd to June 6th, 2017. As part of our coverage, we attended multiple oral presentations on June 2nd and our notes are below. Affected Companies include Jounce Therapeutics (NasdaqGS: JNCE), Bristol-Myers Squibb (NYSE: BMY), AstraZeneca (NYSE: AZN), Pfizer (NYSE: PFE), Roche (VTX: ROG.VX), Novartis (NYSE: NVS), and Merck (NYSE: MRK).

Session Notes: On the Shoulders of Giants: Historical Approaches to Immunotherapy in Solid Tumors

James Allison, PhD: Novel Approaches to Immunotherapy in Solid Tumors

- CTLA-4 outcompetes CD28, preventing co-stimulation. Why CTLA-4 has been a good cancer target.
- Necrotic cell death causes inflammation and allows APCs to come in, process, and present the antigens to cytotoxic T cells. Because started by cell death, anything that kills tumor cells can lead to antigen presentation. Preclinically, anti-CD28 antibodies allow tumors to grow quicker. Anti-CTLA-4 leads to remission.
- Median OS in melanoma – 9.5 months with Yervoy. 3-year OS rate of 21%.
- Why only 21%? – Other checkpoints occurring.
- CTLA-4 hardwired to prevent T cells from killing body. PD-L1 – upregulated by IFN-y. PD-1 works at T cell signaling vs. co-stimulation with CTLA-4.
- Very little activity with PD-1 in colorectal and prostate cancer.
- 2 year OS close to 60% for Ipi + nivo in melanoma.
- Reverse translation- needed for smarter clinical development.
- In CRPC, patients with responses have high mutation burden, with many non-synonymous. Although not all with high mutational burden respond.
- In CRPC, some responders with CTLA-4. Not just mutations. Infiltration also needed. Need T cells in.
- CTLA-4 can increase TILs in tumor area.
- VISTA – checkpoint induced on macrophages is induced after CTLA-4i treatment. Increases in prostate cancer.
- CTLA-4 responses often slow. PD-1 responses are quick. PD-1 targets TCR pathway, and CTLA-4 targets CD28 pathway. PD-1 does not expand clonal diversity, just number of T cells. CTLA-4 expands CD4 T cells. CTLA-4 can move T cells into tumor. PD-1 does not move T cells into tumors. PD-1 patients often relapse after response. CTLA-4 more rare to relapse after response.
- Mass cytometry analysis of MC38 TILs.
- Checkpoint blockade modulates MC38 infiltrating T cell population frequencies – ICOS+ upregulated in aCTLA-4 CD4 eff population.
- ICOS+ Th1-like CD4 eff correlate with outcome.
- ICOS is member of CD28/CTLA-4 superfamily – usually associated with Tfh or T reg.
- Following CTLA-4 – 2-10 fold increase in tumor and blood ICOS+.
- Contains essentially all tumor specific IFNy and TNFa Producing CD4 cells.
- Increase associated with longer survival.
- Pharmacodynamic marker or Ipi activity.
- Preclinically ICOS is essential for optimal efficacy of CTLA-4 blockade.
- Signaling via PI3K binding motif enhances tBet expression.
- Question is if can be targeted to increase efficacy of CTLA-4.
- Encouraging preclinical work in ICOS k/o and agonist. Great results. 30-fold increase in CD4 when given ICOS signaling.
- Future of immunotherapy - targeting multiple checkpoints to potentially cure patients.

For analyst certification and disclosures please see page 8
Suzanne Louise Topalian, MD: Novel Approaches to Immunotherapy in Solid Tumors

- The PD-1/L1 checkpoint: the tumors first line of defense against immune attack.
- Activation – cytokines, lysis, proliferate, and migrate. At same time, activated T cells express PD-1. If tumors expressing ligand for PD-1, T cells turned off.
- 16% 5-year OS in advanced NSCLC receiving Anti-DP-1 therapy. To put in context, historically, 4% would be living at 5 years.
- In most cases, don't know what causes immune related side-effects. Themes emerging. First, evidence that in some cases, admin of checkpoint blocker exacerbates preexisting autoimmune disorder undetected because presented at sub-clinical level.
- In other cases, organ specific injury.
- Patients who experience immune related side effects also more likely to have tumor regression.
- About 15% of colon cancers are MSI-high. – Lots of PD-L1 expression, and PD-1 expressed on TILs.
- 62% ORR in MSI high or MMR-deficient colon cancer vs. 0% on MMR-proficient colon cancer.
- Quality vs. quantity of tumor antigen.
- No significant difference on if virus associated + or – tumors.
- Classic Hodgkin lymphoma: Th1/Th17 dichotomy in EBV positive vs. negative tumors – Th1 – upregulation of IFN-y. for EBV(-) IL23R, IL13, IL1A, and IL17A were characteristic. High GITR expression in EBV(-).
- Moving therapies into earlier stages of disease. Looking at PD-1 therapy in neoadjuvant setting.
- 41% major pathologic response in lung cancers treated in neoadjuvant setting.
- Functional state, repertoire of T cells, and additional cells like myeloid cells all important.

Session Notes: Immunotherapy and Lung Cancer

Edward B. Garon, MD: Role of Checkpoint Inhibitors in First-Line Therapy and How to Sequence Immunotherapy

- Keyonte-024 – pembro or platinum therapy. Chemo arm could switch over to pembro at certain point. PFS is primary endpoint. Twice as likely not to progress on pembro arm. Even with cross over, OS still seen. Part of reason could be that some patients on chemo did not end up crossing over.
- Checkmate-026 – similar in design. (nivo vs. frontline chemo, cross over at time of progression). This study missed its endpoint and chemo looked possible better. OS also favored chemo in long-term.
  - Why possibly missed – randomization, therapy or evaluated patient population different. Don’t think randomization is to blame.
  - Main issues brought up were more women on pembro arm – do better on chemo. Also PD-L1 expression higher in chemo arm.
  - Efficacy quite similar across a range of studies with nivo and pembro.
  - Differences in study population – more patients received prior radiation in 026 study. – single center indicates that prior radiation causes better outcomes with PD-1. Also, now press release that PD-L1 durvalumab after chemo/radiotherapy, prolongs PFS.
  - Think patient selection is to blame. In Keynote-001 – 1% staining was selected. In this, PFS not better than what seen with standard first line therapy. Allowed enrichment. 50% PD-L1 cut point predicted outcomes.
  - In SCHNN – less of a difference in outcome between PD-L1 staining.
  - Is 50% correct cut point for Anti-PD1 – we don’t know.
  - Question is low cut point fail to enrich. If looking at OAK study with atezolizumab. Positive study.
  - Biomarker enriched outcomes. Outside of TC3 or IC3 group, not predictive.
  - Patients should be tested using 22C3 antibody. If 50% staining, should use pembro. If less than this, use chemo. If TC2/IC2 using SP42 antibody. At this point, consider any other option exploratory.
  - Tumor mutational burden associated with outcomes.
Cohort G in Keynote-021 got Chemo-PD1 combo approved. Like 024, could cross over after time of progression.

Increase PFS but no difference in OS at this point with combo.

Most striking benefit of chemo combo is patients with high PD-L1 expression. Between 1 and 49% staining, chemotherapy did better in cohort G. Hazards of looking in small patient numbers.

Conclusion limited by small number of patients and follow up time. OS unchanged. From speaker perspective, more patients have more toxicity for more time.

Metastatic NSCLC should be tested for PD-L1 using the 22C3 antibody. Greater than 50%, use PD1, less than use chemo. In terms of combo, up for debate.

Ben C. Creelan, MD, MS: What Is the Role of Immunotherapy in Patients With Mutations?

- 100,000 solid tumors exome sequencing. Published last month. NSCLC has very high mutational load.
- Also looked at intron sequencing for microsatellite instability – not much, but high tumor mutation burden.
- Mutation burden predictive across a range of tumors. Immune system may be pre programmed to fight these tumors.
- PD-1 biomarker thus far, should mutation burden be biomarker? In 026 study, high mutation burden group did very well vs. chemo. This is surrogate for neoantigens.
- Not all neoantigens are the same. Clonal vs. sub-clonal. No durable benefit in subclonal neoantigens. Subclonal can overtake original antigen and have escapes in all of them.
- Whole exome sequencing in multiple parts of tumor – great tumor heterogeneity. Subclonal mutation burden correlated to subregions sampled – higher recurrence risk.
- Driver mutations always clonal (ALK, RAS, EGFR).
- May have to sequence multiple regions of the tumor.
- Most Phase III studies exclude EGFR and ALK patients. In EGFR patients – favors docetaxel. PFS worse for PD-L1 subgroup. OS slightly favors docetaxel as well.
- If strongly PD-L1 positive – do just as well as docetaxel – small patient numbers.
- PD-L1 rarely expressed in EGFR patients.
- In erlotinib + atezolizumab – good ORR, but mature PFS data will be important.
- Checkmate-012 – nivolumab + erlotininb in EGFR acquired resistance cohort; ORR 15% (3/20).
- Checkmate 370 – ongoing. EGFRi +/- PD-1 inhibitor.
- KRAS – lump all together even though several mutation types. Seems to perform just as well as wild-type group in KRAS.
- STK11 driver mutation- frequently mutated with KRAS.
- PD-L1 expression less in STK11 patients, and worse outcome.
- Met ex 14 short variants: 2-4% of NSCLC.
- Median age of driver mutation is 72. Lots of prior tobacco use in these patients. These patients have more T cell infiltration and gene expression of inflammatory gene signatures. More PD-L1 expression, but less tumor mutation burden.
- Conclusion – Tumor mutation burden predictive of IO response across NSCLC histologies. With KRAS, currently lumping together, but some patients may do worse.
- Insufficient data to make conclusion about ALK.
Melissa Lynne Johnson, MD: Are All Immunotherapy Drugs the Same or Is One the Best?

- 5 PD-1/L1 inhibitors approved for cancer.
- Are these drugs interchangeable?
- All of these are mAbs. Fc portion determines effector function of antibody. PD-1/L1 based on steric hindrance of PD-1/L1 target.
- Different PD-1 inhibitors bind with different orientations to PD-1. Binding interface differs. Drugs are not carbon copies. Structural differences.
- Different IgG subtypes. Nivo and pembro IgG4, atezo, durva, and avelumab is IgG1.
- Avelumab has retained ADCC function whereas atezo and durva engineered to not. Do not know clinical manifestations of this.
- Some of PD-1 assays interchangeable but not all.
- No head to head trials between PD-1/L1 inhibitors. One retrospective experience comparing agents at Emory.
- 500 studies and abstracts dealing with agents.
- No stat-sig difference in AEs overall with PD-1/L1.
- Small but statistical difference in Pd-1 for immune related AEs - pneumonitis higher in PD-1 (p=0.01). No ORR difference in PD-1 vs. PD-L1. Earlier study showed immune AE correlated with good outcomes – this may be debated then. 4 randomized studies for 2nd line studies. Between 3 and 4 month difference in OS between trials.
- Avelumab seems to have more infusion reactions but less immune related AEs. May be due to ADCC aspect?
- So far agents seem to be very similar. Unknown how different at this time. Dosing schedule and costs could play role in treatment decisions.

Dickran Garo Kazandjian, MD: Pseudoprogression: Is It Real?

- PD-1s can be used past 1st progression – treatment past progression (TPP) in various indications.
- Limited data exist for NSCLC and pseudoprogression.
- TPP allowed if not rapid progression.
- In big study, 121 (23% of total) NSCLC patients who received TPP.
- Better ECOG for TPP subgroup.
- 77% of patients did not get TPP.
- 8% (10) of patients who received TPP had a response to treatment.
- 3 had ongoing responses of at least 12 months.
- Other study – 2% of patients in NSCLC were pseudoproversors and responded. All alive at 1 year.
- Traditional RECIST responses clinically meaningful.
- In RCC – conflicting perceptions on benefits of TPP.
- Different conclusions could be due to different approaches in data evaluations and definitions of clinical benefit.
- Overall – some patients may have benefit from TPP. Need to do better job figuring out which patients these are.
- Optimistic viewpoint – 2% - 10% receive benefit and may not have better treatment options.
- Pessimistic view – 90% - 98% not receiving benefit. Could benefit these patients more from receiving other therapies.
Session Notes: Biomarkers for Immunotherapy: An Illusion or a Reality?

Karen L. Reckamp, MD: Incorporating Biomarkers into clinical practice Challenges and Opportunities.

- In the atezolizumab setting high levels of PDL1 in the tumor and immune cells correlates with higher overall response and better outcomes, however this is not a requirement for benefit.
- KeyNote-024. pembrolizumab vs. chemo in advanced NSCLC with >50% PDL1 expression saw a benefit
- CheckMate-026 study nivolumab vs. chemo in non-squamous NSCLC with at least 5% PDL1 expression saw no clinical benefit in PFS.
- Clearly PDL1 expression adds value; responses are much higher, at least in the first line setting.
- FDA recently approved carboplatin plus pemetrexed combo with pembrolizumab in first line non-squamous NSCLC. Patients without PDL1 expression saw improved RR and PFS 13mos. vs. 9 mos. and no difference in OS. Have to take into account that it was small study and PDL1 status has not been updated to date.
- **What about emerging biomarkers?** Small clinical trials have identified potential biomarkers and have highlighted the complexity and dynamics of the immune system.
  - Looking at the life cycle for immunotherapies offers a shot at identifying new biomarkers. The presenter showed example of immunogram and the identification of patients with high immunogenicity that would otherwise have been labeled as non-responders.
  - Tumor mutation burden, which associates with clinical benefit.
  - Blood tests. Circulating tumor DNA (ctDNA) tumor volume is key, but also fluctuates overtime with treatment.
- Types of biopsies can give you differing responses fresh biopsies vs. archival.
- Biggest complication is tumor heterogeneity. Recent study of 100 patients with early stage NSCLC looking ~300 tumor regions, found significant somatic mutation and copy number variations in genes involved in different pathways depending on where you looked. This highlights the complexity of the problem.
- PDL1 expression across assays show significant differences between assays and inter assay variability.
- One of the biggest challenges are patients who don’t respond. Presenter suggested that one of the best groups to look at where de novo non-responders, EGFR mutant patients (these have lower response rate to immunotherapy).
- Tumor vs. immune cell testing. Tumor cell testing is still the gold std, less variability than immune cell testing.
- Blood based testing, ctDNA, of biomarker is still under review and needs validation.
- Tumor mutational burden as a marker is still not ready for primetime.

Vamsidhar Velchiti, MD: Biomarkers for Immune-Related Toxicities

- Immune related adverse events are problem in immunotherapy, especially in the combination therapy setting.
- There needs to be a better understanding of central tolerance.
- Identifying candidate biomarkers for prediction of AE.
  - Immune cell phenotyping.
  - Circulating cytokine assays. IL-17.
  - T cell and B cell sequencing; characterize diversity of immune response in patients treated with immunotherapy as a way to predict toxicity.
  - Identifying genes that stratify irAE in patients with high tumor mutational burden.
- Microbiome ad irAEs.
  - Certain bacterial strains associated with resistance to colitis. Further studies should shed light onto the role the microbiome and irAE.
- Moving on, incorporating these putative biomarkers into CT will be useful.
**Roy S. Herbst, MD, PhD: Future Strategies for Personalized Immunotherapy**

- iRAE will become important as we move forward with combination therapies.
- Heterogeneity of the tumor; PDL1 expression, not perfect but it is a piece of the puzzle. Keynote 024 changed the way we look at PDL1. Pembrolizumab signal better than chemo; 45% response rate, but how about remaining non-responders; this is where new biomarkers come into effect.
- The PDL1 cutoff makes a difference as lower 5% cut off saw no difference compared to chemo.
- Keynote 21, clear PFS benefit no OS advantage. Waiting for updated results later during the meeting.
- Building future combination trials.
  - Different categories of tumors based of PDL1 and TIL profile.
  - The majority of patients are PDL1/TIL negative. A way to work around this may be to inflame the tumor.
  - Quantitative measurements of markers will become more and more relevant and are now being integrated into clinical trial settings. Examples include CD3+ marker.
  - Groups are actively collaborating with one another to integrate other markers.
- Comparing responder to refractory patients. Sequencing and immune profiling
  - Beta2 Ig loss is a potential resistance mechanism that may emerge.
- Moving forward with respect to therapies:
  - Combos with: targeted therapies, cell based therapies, vaccines. Basically, an all of the above strategy.
- Looking at the tumor microenvironment.
  - Proposed VEGF as a marker. Its expressed by suppressor cells in the tumor microenvironment.

**Session Notes: Novel Targeted Agents and Immunotherapy in Breast Cancer**

**Sherene Loi, MD, PhD: Novel Therapeutic Agents for HER2-Amplified Breast Cancers**

- HER2 positive becoming highly curable disease. In trastuzimab treated patients, DFS is increasing. We are awaiting APHINITY trial data during the meeting.
- What is the future for Her2 positive disease. Evaluating:
  - N2 disease.
  - Patient with residual disease
  - Stage 4
  - Brain metastasis
  - Targetable oncogenic mutations.
- Studies thus far have shown that patients with HER2 positive tumors require HER2 inhibitor maintenance. Highlighted lapatinib as potential therapy in this area.
- In disease with brain metastasis tucatinib has shown greater potency over other HER2 antagonist. Tucatinib may lower diarrhea associated with other TKI treatments. The presenter commented that the reason may be that it is better metabolized or reaching the CNS better than other drugs.
- PI3K are frequently mutated in HER2 positive diseases and is associated with poor outcomes. PI3K inhibitors may emerge in the residual disease setting. Identification these of cells will be critical moving forward.
- CDK4/6 inhibition. Studies have identified CDK4/6 as mechanism of resistance in HER2 positive BC. Look for results coming from trials evaluating CDK4/6i in this setting.
■ Immunotherapies. TILs have been shown as a prognostic biomarker. HER2 triggers innate and adaptive immunity.
■ In advance disease TILS are exhausted and less TILs in infiltrate in metastasis.
■ Presenter highlighted the Panacea trial. The trial evaluates the addition of anti-PD-1 therapy in trastuzumab resistant HER2 positive disease, still waiting for readout from this study.
■ In low immunity settings, the presenter highlighted as potential avenues of treatment:
  ◦ CAR-T
  ◦ Radiation therapies
  ◦ HER2 treatment plus chemo
  Among others.
■ Current drugs in development:
  ◦ ADCs. Mm302, was stopped for futility.
  ◦ Her3 Monoclonal antibody therapy, rationale being enhance inhibition the HER pathway.
■ Combination therapy is highly likely in HER2 positive setting.

**Risk to an Investment**

Investors should consider the risk of any investment. These stocks can have high risk and high volatility. Clinical stage assets may not be successful in clinical trials or may fail to gain regulatory approval. If products are launched, it is possible that revenues will not meet investor expectations, or that the products will face unexpected competition. The revenues of approved products may also not meet investors expectations, and approval in one disease does not always correlate with success and approval in another disease. Overall market conditions may also affect the value of the underlying securities.
Analyst Certification

The research analyst denoted by an “AC” on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an “AC” on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC (“LSC”) research analysts.

LSC has not provided investment banking and other broker-dealer services to any of the companies that are the subject of this report within the past twelve months. LSC does not expect to receive or intend to seek compensation for investment banking services from any of the companies that are the subject of this report in the next three months. LSC does not make a market in the securities of any of the companies that are the subject of this report.

Neither the research analyst(s), a member of the research analyst's household, nor any individual directly involved in the preparation of this report, has a financial interest in the securities of the any of the companies that are the subject of this report. Neither LSC nor any of its affiliates beneficially own 1% or more of any class of common equity securities of any of the companies that are the subject of this report.

LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC does not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with each issuer that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC’s judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request.

No part of this report may be reproduced in any form without the express written permission of LSC. Copyright 2017.