Main focus of the meeting: the promise of immunotherapy as mono-therapy (i.e by itself) and in combination with other therapies (targeted therapy, radiation, and other immunotherapies). Lung cancer is one of the few cancers that has shown remarkable responses to immunotherapy, one reason being its high mutation burden, i.e. these tumors are a very high number of mutations (partly due to exposure to the carcinogens in tobacco/smoke). Recent studies have shown that tumors with higher mutational loads are more likely to respond to immunotherapy.

Below is a summary of the latest advances in immunotherapy presented at the meeting, and a general “state of the science” for lung cancer immunotherapeutics:

• Why is immunotherapy considered exciting in this disease state, and what advantages might it have over other existing types of treatment?
  • As we march into the era of personalized/precision oncology, it can’t get more personalized than using your own immune system to fight your cancer!
  • Immunotherapy is a game-changer, a breakthrough that oncology desperately needs. It is for the first time that we can begin to talk about long-lasting effects, even a cure. Even after you stop treatment, the immune system continues to recognize and attack tumors because it has been trained specifically to find these cancerous cells and mount an attack against them. Therefore, unlike other therapies, immunotherapies afford a sustained, durable response that continues even after the treatment is stopped.
  • It is a quantum leap forward, a moonshot, adding to our arsenal of agents that are active against even the most intractable cancers for which patients didn’t have many options, especially after their disease progressed upon treatment with the current standard of care therapies.
  • However, our excitement needs to be tempered down a little bit for a couple reasons:
    1. Immunotherapy doesn’t work in all patients, all the time. Approximately 70-80% cancer patients don’t respond, this however might also be due to the trial design- not conducting the study in the appropriately selected patient populations,
    2. In patients that it does work in, not all have dramatic, long-lasting effects. Effects are modest, but this must be considered in light of the fact that these patients don’t really have many options, so any positive effect is a good effect.
    3. We haven’t yet seen the long-term impact on overall survival and any other long term effects, if any,
    4. Cost- these therapies aren’t inexpensive, and now combinations of these therapies are beginning to be evaluated, so it will only get costlier. Are we
delivering enough value for the cost? Do 4/5/10 month additions in progression-free/ overall survival justify six-figure costs— ethical debate, vs. covering the costs of drug research and development, etc. etc.,

5. **Side effects**- we still do not completely understand all the concomitant effects of these therapies. Side effects are often mild, however, some side effects (especially those on combinations of immunotherapies) are serious enough to warrant hospitalization, and many patients also drop off of clinical trials due to these serious and/or life-threatening adverse events.

6. **Most patients present with psuedoprogression**- i.e. the disease appears to get worse before it gets better, because of the way the immune system works. Its mainly due to the infiltration of the tumor by immune cells causing an increase in tumor volume. Its a false alarm that the disease is progressing, when it isn’t. So physicians, patients and their caregivers need to be prepared for this to avoid discontinuing a potentially effective therapeutic regimen. However, there are also cases of real progression which need to be identified timely.

- **What subset of lung cancer is immunotherapy being evaluated against? Non-small cell lung cancer? Small cell?**
  - Yes, immunotherapies are being evaluated in both non-small cell (85% of all lung cancer patients) and small cell lung cancer (15% of all lung cancers).
  - NSCLC is further divided into squamous (accounts for 25% of all lung cancer patients) and non-squamous (accounts for 60% of all lung cancer patients).
  - Nivolumab (from Bristol Myers Squibb) has been evaluated in both squamous and non-squamous NSCLC, with FDA approval in the squamous setting.
  - Nivo has also been evaluated in the SCLC setting, both as mono therapy as well as in combination with Ipilimumab (anti-CTLA4 monoclonal antibody). Platinum-based chemotherapeutic agents are the preferred standard of care regimens and the Nivo+Ipi combo has shown positive response rates in platinum-refractory, relapsed SCLC pts.
  - Pembrolizumab (Merck anti-PD1) has been evaluated in the NSCLC and SCLC setting. Preliminary data for pembro mono therapy in 20 PDL1+ SCLC patients presented at the ASCO Annual Meeting demonstrate 35% overall response rates, demonstrating promise in a disease subtype that has not seen any change in the standard of care in the past 30 years, a disease that continues to have the lowest 5 year survival rates.

- **If a lung cancer is likely to respond to a targeted drug because it has the right mutation, would there be any reason to skip the targeted drug and go right to immunotherapy?**
  - No reason right now to skip targeted therapy if a molecular test or an FDA approved companion diagnostic has shown the presence of its targeted underlying lesion in the tumor. Moreover, these decisions need to be first evaluated in randomized, controlled clinical trials before translating into clinical practice.

- **What is Opdivo (Nivolumab) and why the hype behind it?**
  - Opdivo or Nivolumab is an anti-PD (Programmed Death)-1 humanized monoclonal antibody.
• PD1 is a protein expressed on immune cells called T cells. PD-1 binds its ligand, PDL1 (or Programmed Death Ligand 1) that's expressed by cancer cells to mask themselves and avoid recognition by the immune system. Many current immunotherapies currently under development target the PDL1 protein rather than PD1.

• PD1 interacting with its ligand PDL1 is a checkpoint used by the immune system to determine whether to mount a response or not. Nivolumab, therefore is a checkpoint inhibitor-Kind/Class of immunotherapy.

• Nivolumab has been evaluated in phase 3 trials in both squamous (25% of all lung cancers) and non-squamous (60% of all lung cancers) non-small cell lung cancer (NSCLC). Both trials tested it against docetaxel chemotherapy in advanced, metastatic patients, and Nivolumab showed better overall survival benefits against docetaxel chemo in both settings.

• It has received approval from the US FDA (March 5, 2015, 3 months ahead of schedule) for the treatment of patients with metastatic SQUAMOUS non-small cell lung cancer (based on the results of the CheckMate-017 trial), with progression on or after platinum-based chemotherapy. Nivolumab demonstrated an OS rate of 42% vs 24% for docetaxel, with a median overall survival of 9.2 months vs 6 months on docetaxel, and median progression-free survival (mPFS) of 3.5 mo vs 2.8 mo for Docetaxel. Given these unprecedented positive data, nivo needs to be moved into the frontline setting for these patients, and studies to this effect are ongoing.

• In April, 2015, a phase 3 study evaluating Nivolumab (3mg/kg intravenously every two weeks) versus docetaxel (75 mg/m2 intravenously every three weeks) (Check-Mate-057) in 582 previously treated patients with advanced NON-SQUAMOUS NSCLC was stopped early because an assessment by the independent Data Monitoring Committee (DMC) concluded that the immunotherapeutic demonstrated superior overall survival (27%) vs the docetaxel chemotherapy, and the study met its end-point of overall survival. Detailed data on this study were presented at the recent ASCO Annual Meeting in Chicago, May 29-June 2, 2015. Nivo demonstrated a 19% overall response rate (ORR) vs 12% with docetaxel. Median duration of response was 17.2 months versus 5.6 months in the nivolumab and control arms, respectively. Fifty-two percent of the nivolumab responses are still ongoing compared with 14% of the docetaxel responses. One-year PFS favored nivolumab at 18.5% versus 8.1% for the control arm.

• Bristol Myers Squibb that is developing the immunotherapy agent has applied to the US FDA for approval in this new non-squamous setting.

• Biomarker for response: Till very recently, it was believed that the presence/ expression of PDL1 may serve as a biomarker of response and prognosis for patients treated with anti-PD1 therapies, and that PDL1 expression might help to stratify patients that are more likely to respond to anti-PD1 therapy. This is important because these therapies are expensive and not without concomitant side effects, therefore they are best used for patients that are most likely to respond. However, data presented at the ASCO Annual Meeting suggests that PDL1 might not after all be a great biomarker for anti-PD-1 sensitivity and response, and is not ready for translation into the clinic. However, it is, at the present moment the only biomarker for response to anti PD1 immunotherapies, and in some cases, PDL1 expression does correlate with improvement in progression-free and overall survival. However, more work is needed for appropriate biomarker refinement and standardization.
Each drug manufacturer in the PD1 space is developing their own independent assay to measure PDL1 expression and there’s no consistency. Further, PDL1 expression does not uniformly predict for response to all anti-PD1 immunotherapies.

- Case in point is the differential results for Nivolumab in the two phase 3 studies in NSCLC: PDL1 expression was not linked to survival in the squamous cell lung cancer population while stronger overall survival was observed in the PDL1-positive population subset in the non-squamous non-small cell lung cancer subtype, demonstrating a 60% reduction in the risk of death in patients that expressed the highest levels of PDL1. So, **PDL1 status was a clear prognostic indicator of survival in the treatment of non-squamous NSCLC patients with Nivo, but was irrelevant in the treatment of squamous pts.**

**Which immunotherapeutics are in the pipeline for lung cancer?**

- Anti-PD1 and PDL1 therapies currently under development:
  - **Anti-PD1:** nivolumab (Opdivo, BMS) pembrolizub (Keytruda, Merck & Co), pidilizumab (CureTech), AMP-224
  - **Anti-PDL1:** BMS, MPDL3280A (Atezolizumab/Genentech/Roche), MEDI4736 (AstraZeneca/Mediimmune), Avelumab (Merck-Serono)
- CAR-T cell therapies: Kite Pharma, Novartis, Juno Therapeutics, Bellicum

**Which one is better?** Can’t really say at this moment, because data in all these studies is premature, its still early days, the patient populations assessed are not exactly the same, the trial designs differ, the biomarkers used for patient stratification vary (the antibodies used in these tests have all been independently developed by these pharma cos), so absolute comparison should probably be avoided.

- Among PD1-directed therapies, the head-to-head competition is between Nivo and Pembro. Differences between these two are mainly in the use of the PDL1 biomarker. Generally speaking, Pembro has demonstrated better PFS (Progression Free Survival) benefit in patients with higher levels of PDL1, while Nivo also works in patients that do not express PDL1 (some patients). MPDL3280A (which is an antiPDL1) from Roche also works only in PDL1+ pts, so, compared to these two, Nivo might be applicable in a larger population. Pembrolizumab from Merck comes with its own companion diagnostic to check for PDL1 status.

**Are there immunotherapy combinations being tested, and what is the rationale?**

- Yes, combinations are beginning to be tested in lung cancer. These were initially tested in melanoma (skin cancer) which like lung cancer is one of the few cancers that responds to immunotherapy exceptionally well.
- Results from a Ph 3 trial evaluating a Nivolumab + Ipilimumab combination in melanoma patients, presented at the ASCO Annual Meeting demonstrated that the combination effected superior overall survival than either immunotherapeutic alone.
- The rationale for this combination is that Ipi which is an anti-CTLA4 monoclonal antibody works at the activation phase of the immune system, while Nivo, an anti-PD1 antibody works at the effector stage of the immune response, therefore the combination of the two holds potential for a durable, sustained immune response in a fashion that takes the breaks off the immune system, and maintains that momentum so that the body’s own defense mechanism can mount a potent response against cancer. Plus, combinations afford rapid onset of response that is durable.
• Some data also points to the fact that CTLA4 blockade by Ipilimumab causes the release of certain immunomodulatory molecules called cytokines that increase the expression of PDL1, therefore sequential therapy with an anti-PDL1 after an anti-CTLA4 might hold potential.

• One word of caution for combinations is the accompanying toxicity which is greater than that seen with either therapy alone (in the nivo+ipi combo in melanoma, 36% patients dropped off due to serious adverse effects). However, this might be offset by the fact that these combinations will need to be used for shorter time periods.

• Another word of caution- COST, the combination together would cost upwards of $300,000 per year, that too by conservative estimates.

• However, we are still in the early days of testing immunotherapy combinations and many unanswered questions remain:
  • what is the optimal dosing of each immunotherapeutic in the combo,
  • optimal sequence of the drugs or is concurrent therapy better?,
  • optimal duration of combo therapy?,
  • potential effects of prior treatments that patients might have received on the efficacy and safety of immunotherapy combinations,
  • PK/PD of the combo (pharmacokinetics/pharmacodynamics),
  • effects/ toxicity of checkpoint blockade on subsequent therapy upon disease progression?
  • patient specific characteristics that might impact treatment benefit such as age, comorbidities, brain metastases etc.

• Do the same immunotherapy treatments work on both smokers and never-smokers with lung cancer, or do these groups need different immunotherapies?
  • Yes, they work in both subsets, but studies have shown that the underlying genomic mutational landscape impacts a patient’s response to immunotherapy, i.e. a higher mutational burden, (i.e. more mutations in the genome) is correlated with a higher response to immunotherapy. Smokers’ genomes are typically associated with higher mutational loads due to exposure to carcinogens in cigarette smoke, and therefore may respond better than non-smokers, an example being the promising effects of immunotherapies seen in squamous cell lung cancer and small cell lung cancer, both of which disproportionately affect smokers. A recent study in the journal Science by researchers at Memorial Sloan-Kettering Cancer Center found a specific genetic signature that correlated with better response to Pembrolizumab, this genetic signature is that often seen in tumors that have smoking-associated genomic alterations.

• Are there specific tissue tests to predict who will best respond to immunotherapies?
  • Yes, and no. PDL1 expression has been used so far to identify patients most likely to respond to immunotherapies, however, it hasn’t been consistently proven to work every time. PDL1 is the cognate ligand for the PD1 receptor and strategies to boost the immune response against cancer have also exploited targeting PDL1.
  • Immunotherapies need effective and reliable biomarkers of response and prognoses.
  • Further, biomarker refinement and standardization are critical right now for these to be implemented in clinical decision making.
• One potential biomarker is mutational burden. Recent data demonstrates that higher the number of mutations in a tumor, higher its favorable response to immunotherapy. Lung cancer, both non-small cell and especially small cell, present with very high mutational loads and therefore the exceptional responses to immunotherapy.

Other Takeaways from the 2015 ASCO Annual Meeting

Cost of drugs: On the first day of the meeting, an oncologist from Memorial Sloan Kettering Cancer Center, Leonard Saltz, presented a talk on the skyrocketing costs of breakthrough cancer drugs, and presented an example of the cost of two immunotherapies (both manufactured by Bristol Myers Squib): Nivolumab (Opdivo) and Ipilimumab: a whopping ~$300,000. Dr. Saltz said “the unsustainably high prices of cancer drugs is a big problem, and it’s our problem... Cancer-drug prices are not related to the value of the drug. Prices are based on what has come before and what the seller believes the market will bear.” This talk has been picked up by media outlets everywhere and has initiated a lot of discussion on the cost of oncology care, an important discussion that needs to happen.

Small Cell Lung Cancer (SCLC):
• It has traditionally been the most aggressive subset of lung cancer for which there has been no new treatment option for the past 30 years.
• The current standard of care is platinum-based chemotherapy that works remarkably well for a few months, after which invariably most patients develop resistance.
• It was encouraging to see that new treatments are being evaluated in this subset of the disease and some positive data is coming out, e.g. SCLC is responsive to immunotherapy.
• **Reasons:** SCLC is predominantly a smokers’ disease, smoking causes multiple mutations in the genomes of these tumors, resulting in a high ‘mutational burden’ in SCLC. And a high mutational burden is a predictive biomarker of response to immunotherapy, as in, higher the number of mutations in a tumor, greater the likelihood for immunotherapy to be active against it.

• Immunotherapy has been shown to work in the platinum-refractory patients as well, i.e. patients who had stopped responding to platinum-based chemo.

• Combinations of immunotherapy have been evaluated in clinical trials in these patients and have shown promising results.

• Basic research into the biology of SCLC has identified some **new drug targets** that were presented at the meeting: DNA repair pathway- PARP, Cyclin Dependent Kinases (CDK), topoisomerases, polokinases, microtubule inhibitors

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**Targeted Therapies**

**New drugs for other segments of the lung cancer pie:**

• Lung cancer is not one disease, it is a heterogenous collection of several subtypes, each of which has a different underlying ‘driver’ mutation. Targeted therapies against these driver mutations have been shown to halt disease progression, e.g. Erlotinib (Tarceva) in EGFR+ pts, Crizotinib (Xalkori) in ALK+ patients etc.

• Because several known cancer-causing mutations occur in multiple types of tumors, cancer is increasingly defined not just by the organ in which it originated but by the mutations that drive its growth.

• 1-2 % of NSCLC patients present with **RET fusions**. Data presented at the ASCO meeting suggested that a drug active in medullary thyroid cancer, **cabozantinib** might be effective in this lung cancer subtype, with a median duration of response of 8 months, median progression-free survival of 7 months, overall survival of 10 months.

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**EGFR (Epidermal Growth Factor Receptor) TKIs (Tyrosine Kinase Inhibitors):**

• EGFR is a protein that is mutated in a subset of non-small cell lung cancer (NSCLC). Mutated EGFR can be easily identified by a lab test, and we have targeted therapies that are effective against the various mutations in EGFR.

• Patients with EGFR mutations that receive EGFR-directed targeted therapy usually develop resistance to these treatments over time- 60% of patients develop resistance to these therapies in a year. Therefore, the need for newer, more effective EGFR-targeted agents.

• Several are under development. The top two contenders are third-generation EGFR inhibitors from AstraZeneca and Clovis, its a David Goliath story. Data on these two drugs was presented in the same session.

• **Rociletinib** or **CO-1686**, Clovis’ EGFR inhibitor demonstrated a median progression-free survival (PFS) of 8 months in heavily pretreated EGFR+ NSCLC patients compared to the 13.5 month PFS with the AZ drug, **AZ9291**.

• In terms of side effects, the AZ drug was related to “interstitial lung disease-like” side effects vs. Clovis’ drug that’s associated with hyperglycemia or high blood sugar, caused by insulin resistance mediated by the drug. Both these side effects are manageable, AZ9291 by adjusting the dose, and CO1686 by commonly prescribed medication. Interestingly, the Clovis drug is active in T790M-ve patients as well, which may be attributed to a false nega-
tive, i.e. these patients were actually T790M+ but were falsely diagnosed as T790M negative due to imperfections in the testing (assay sensitivity issues) or tumor heterogeneity, etc. Also, an interesting phenomenon noted was that patients develop resistance to the Clovis drug over time and in 50% of these patients that were originally T790M+ became T790M negative.

• The study on Rociletinib also evaluated the ability to detect the T790M mutation in plasma DNA. Patients with T790M positive disease identified by plasma had response rates similar to those identified by biopsy/tissue-based molecular testing. This is very interesting that it shows up in plasma DNA despite tumor heterogeneity. Secondly, non-invasive detection is any time better than getting multiple biopsies.

• Rociletinib was active in T790M negative patients. Further evaluation in this patient population is ongoing.

• AstraZeneca is currently also investigating AZD9291 as first line therapy for EGFRm NSCLC patients, and in combination with MEDI4736 (anti-PDL1 immunotherapy), selumetinib (MEK inhibitor) and AZD6094 (MET inhibitor) in NSCLC. n

• Several other EGFR TKIs are under development. Preclinical and phase 1 data on a new EGFR inhibitor AZD3759 in NSCLC were presented in a poster. This new inhibitor presents with excellent blood brain barrier penetration and is effective against brain metastases. Further clinical evaluation is underway in the Asian market by AstraZeneca.

• Unanswered questions:
  • Additional clinical investigation will also be required to determine the ideal sequence of the various EGFR TKIs, and how best to prevent or manage the different mechanisms of resistance to the EGFR TKIs. Need randomized clinical trials to evaluate these.
  • If 3rd gen agents begin to be used in the frontline setting, would there be a role for the 1st/2nd gen agents? Yes and no. New pathways of resistance to these new inhibitors are beginning to be identified, e.g. new EGFR mutations are being identified in resistant tumors (C797S, which confers resistance to third-generation TKIs, so it is important to sequence for C797S mutation in patients with acquired resistance to third-generation TKIs to determine further treatment strategies), NSCLC to small cell transformations. One recent study has shown that using an EGFR inhibitor in combination with an EGFR directed monoclonal antibody (Cetuximab) is effective against the most resistant clone in these resistant tumors.
  • Though the T790M mutation remains the most common resistance mechanism, other resistance mechanisms are emerging: MET amplification, HER2, transformation to small cell lung cancer, and these need to be studied further.

ALK rearranged Lung Cancer

• Alectinib for ALK+ NSCLC patients: Alectinib is a highly selective ALK inhibitor that is five times more potent than crizotinib (Xalkori), and is active in both Crizotinib-naive and Crizotinib-refractory patients.

• One benefit over Crizotinib is that Alectinib crosses the blood-brain barrier very effectively and is very effective against central nervous system (brain) metastases, that are commonly seen in patients that progress on crizotinib. Only 2% of current drugs pass the BBB, which is both a good and a bad thing, Erlotinib (Tarceva) concentrations in the CNS are typically 1-10% of what they are in the blood, while Crizotinib (Xalkori) is only 0.3%.

• Phase 2 data on Alectinib was presented at the ASCO Annual Meeting that demonstrated that the drug was well tolerated and achieved a robust treatment response, including excellent intracranial activity, in ALK+ NSCLC pts who had progressed on crizotinib; most had also failed prior chemo and had CNS mets. Alectinib treatment resulted in an overall response rate of almost 50% in patients with advanced ALK-positive NSCLC whose disease
had progressed after crizotinib. A phase 3 trial of first-line alectinib vs crizotinib and an expanded access program are ongoing.

**ALK/ ROS Rearrangements**

- Alice Shaw presented a poster on **PF-06463922**, a selective, brain-penetrant ALK/ROS1 tyrosine kinase inhibitor (TKI) with potent activity against de novo fusions as well as resistance mutations, including **ALKG1202R**, that arise during treatment with other TKIs. PF-06463922 was well tolerated and had clinical activity in patients with ALK+/ROS1+ NSCLC, most of whom had CNS metastases and received ≥ 1 prior tyrosine kinase inhibitors. Further evaluation is ongoing.

**New drug targets in LC**: MET exon splice mutations and NF1 mutations

**Survivorship Issues**

**Obesity is a major unrecognized risk factor for Cancer:**

- Obesity is associated with worsened prognosis after cancer diagnosis and also negatively affects the delivery of systemic therapy, contributes to morbidity of cancer treatment, and may raise the risk of second malignancies and comorbidities.

**Early Initiation Of Palliative Care Improves Patient Well-Being:**

- Recent research has shown that palliative care services not only improve physical symptoms and emotional and mental well-being for patients with advanced cancer, but can also extend life. However, palliative care is often offered too late in the course of the disease—typically in the last 2 months of life, after all curative treatments have been exhausted.
- Discussion during a session at the meeting pointed to the fact that early palliative care with chemotherapy is typically better for ambulatory lung cancer patients than chemo alone. These patients typically end up receiving lesser chemo in the last 14 days of life 17.5% relative to 24% in the patients who didn't receive palliative care.
- The ENABLE study conducted in community centers, NCI and the VA hospitals that compared early palliative care vs late PC showed that at 1 year there was a 15% survival difference- 63% vs 48% with just a 3 mo diff in palliative care administration.
- Compared with patients who received standard cancer care only, patients who also received palliative care services had improvements in several aspects of quality of life—spiritual well-being, quality of life at the end of life, symptom severity, and satisfaction with care—at 4 months after diagnosis.