Lung Cancer Updates from ASCO 2016

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What is ASCO?

- ASCO is the American Society of Clinical Oncology that has an annual meeting each year where key research and clinical medicine highlights are presented by cancer researchers & clinicians to the global community.
- This was the 52nd Annual Meeting of the American Society of Clinical Oncology, held during June 3-7, 2016 in Chicago.
- It had 35,000 attendees- physicians, scientists, patients, advocates, survivors and Vice President Biden.
- The theme of this year’s meeting: Collective Wisdom: The Future of Patient-Centered Care and Research
- The meeting featured over 850 abstracts on lung cancer.

Major themes that emerged from the conference:

1. Immunootherapy is here to stay-
   - combinations will lead the way,
   - need to identify new biomarkers to select patients for therapy/identify those most likely to respond- such as mutational burden, genomic markers, immune microenvironment, cold or hot tumors,
   - we can convert ‘cold’ tumors to ‘hot’ tumors using rational combinations.

2. Continued development of Precision Medicine for lung cancer
   - Lung cancer is not one disease
   - the right drug for the right patient at the right time.
   - Evaluating treatment options for patients through innovative, new clinical trial design- Lung MAP, TAPUR, etc.
3. **First time in 30 years, exciting developments for Small Cell Lung Cancer patients:** Rova-T, immunotherapy combinations.

4. **Patient Engagement—** patients directly engaged in the planning and management of their care do better—through social media, mobile apps etc.

5. **Biosimilars appearing on the horizon:** First data on a biosimilar to be used to treat cancer: trastuzumab biosimilar for breast cancer showed encouraging results, and will open the door to others.

6. **Slow but steady validation of Liquid biopsies for disease monitoring/emergence of resistance.**

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**Advances in Immunotherapy for Lung Cancer**

- There was a lot of buzz around new advances in immunotherapies for lung cancer patients presented and shared at ASCO 2016.
- Before we delve into these, let’s understand how the immune system works—immune cells called T cells constantly patrol our body to identify ‘invaders’, they have a whole array of molecules on their surface that makes contact with the molecules on other cells to figure out if this cell is ‘foreign’ or ‘self’, and whether to prime themselves for an attack, call in reinforcements in the form of an army of fighter immune cells; OR, to move along.
- The immune system has checks and balances in place to ensure they only mount an attack against ‘foreign’ cells and spare the ‘self’ cells. These checks and balances are called ‘checkpoints’.
- Tumors overtake most of these checkpoints and hide as ‘normal’ cells, evading immune recognition.
- The first pathway is the CTLA4 or Cytotoxic T Lymphocyte Antigen 4 pathway
  - it works in the initial phase of immune recognition and priming, where the immune system is ‘deciding’ whether or not to mount an attack.
  - CTLA4 is an ‘off’ switch that downregulates the immune system.
  - We don’t want cancer cells to be able to turn the immune system ‘off’ and for the immune system to ‘tolerate’ cancer cells,
  - so we now have a potent anti-CTLA4 antibody, or a checkpoint inhibitor that prevents it from being turned off.
This drug is called ipilimumab, and was the first ever checkpoint inhibitor developed, tested and approved for cancer patients.
- Is approved for use in melanoma patients.
- There are other CTLA4 antibodies under development such as tremelimumab

- The second checkpoint that keeps the immune system is check is the PD1 pathway.
  - PD1 protein is expressed on immune cells during the second phase of immune activation, looks for its partners PDL1 and PDL2 expressed on immune cells, and usurped by tumor cells. PD1 binding to PDL1 and PDL2 inhibits immune activation.
  - Anti-PD1 antibodies or anti-PDL1 antibodies prevent interaction between PD1-PDL1 and allow the immune system to mount an attack, and present a prolonged anti-tumor response.
  - There are several anti-PD1 and anti-PDL1 antibodies under development, with two currently approved for use in lung cancer by the FDA: Nivolumab (Opdivo) and Pembrolizumab (Keytruda).

To learn more about immunotherapy, please read our article: Immunotherapy for Lung Cancer: Why You Should Be Excited.

**Monotherapy approvals, and testing in new settings:**

- Nivolumab is currently approved for both squamous and non-squamous non-small cell lung cancer in the second line setting.
- Pembrolizumab is also approved in the second line setting for NSCLC patients whose tumors test positive for PDL1.

- Now, the first question that comes to everyone’s mind when these facts are shared is, should these agents be used in the front line setting, upfront.

- Several clinical trials are addressing this, and the answer that is emerging right now, is- not outside a clinical trial.

- So, let’s understand why. Currently the standard of care in the front line setting for NSCLC patients that do not have a targetable oncogenic driver like EGFR, ALK or ROS1 is platinum doublet chemo (carboplatin+paclitaxel) that is associated with a median progression-free survival of 4-6 months, and a median overall survival of 8-10 months. Additional improvements in OS can be achieved by adding maintenance therapy with pemetrexed and antibodies to Vascular Endothelial Growth Factor (VEGF) or Epidermal Growth Factor Receptor (EGFR), yet long term outcomes remain poor.

- To be approved in the first line setting, Nivolumab or Pembrolizumab have to produce better responses and perform better than the...
platinum doublets that typically have overall response rates in the range of 25-35%. It was relatively easier to show better responses than second-line chemotherapy- docetaxel- for the initial approvals of these agents in the second line, because the ORR with docetaxel in the second line is a measly 7%- a low bar to surpass.

- Now, early data emerging from the first line evaluation of Nivolumab and Pembrolizumab monotherapy show that the ORRs range in the 25% range in treatment naïve, PDL1 unselected patients, but responses jump up to 50-90% in PDL1 positive patients.
- Keynote-024 trial is looking at the response to Pembrolizumab vs chemo in the front line setting, in patients that have >=50% expression of PDL1 on their tumor cells. Is showing positive data already (not presented at ASCO), so might be the therapy of choice for this subset of patients.
- Similar results are emerging with Nivolumab monotherapy in the first line setting (this ongoing trial is a non-randomized, Phase 1 study testing Nivo in treatment-naïve patients).
- Therefore, it is increasingly becoming apparent that monotherapy with PD1 checkpoint inhibitors in the front line setting would be best served in a PDL1 positive population. We need larger, randomized clinical trials to confirm these early findings.

Immunotherapy + Chemotherapy Combinations in the 1st line:

- Now, what about PDL1 negative patients- do they get to benefit from PD1-PDL1 agents in the front line setting?
- To evaluate that another set of trials are ongoing that evaluate the combination of PD1 checkpoint inhibitors with platinum doublet chemotherapy agents.
- The rationale for the combinations is clear. Chemotherapy will kill cancer cells, causing the release of cancer antigens which get exposed to the immune system which is primed to mount a response to these antigens for a meaningful and deeper response.
- Early data from these studies show that Nivo+ platinum doublets show responses in the 33-47% ranges, and Pembro+carboplatin+pemetrexed show responses in the range of 58%, while Pembro+carboplatin+paclitaxel response is in the range of 28%- so the specific platinum doublet used may possibly impact response? Still early days here, small trials in a small cohort of patients, but very interesting.
- Keytruda combinations: with chemo in front line setting. Tested with 3 combos: carboplatin+ pemetrexed, carboplatin + paclitaxel, carboplatin+paclitaxel+ bevacizumab. Merck testing it regardless of PDL1 expression status. Showed an
ORR of 57 percent (n=42/74, 95% CI, 45-68), including one complete response and 41 partial responses. Median duration of follow-up was 12 months (range <1-21).

- Final readouts of these trials are expected around fall 2016, that’s when we find out whether adding immunotherapy to chemotherapies in the front line improve patient outcomes over chemo alone.

**Combinations of Immunotherapeutic Agents in Lung Cancer**

- Talking about combinations, there are several interesting clinical trials underway that are evaluating combinations of different immunotherapeutic agents.
- Let’s understand why combining these might be a good idea.
- Consider anti-CTLA4 drugs being combined with anti-PD1 drugs. As described above, the CTLA checkpoint is an ‘off’ switch that works in the first phase of immune activation, and the PD1 checkpoint is the ‘off’ switch that works in the second phase or the effector phase. Combining drugs that inhibit both these checkpoints together holds the potential to take the brakes off the immune system, and hit the gas pedal! This has the potential to effect rapid responses that are durable and long lasting. To test this hypothesis, Nivolumab (anti-PD1) and Ipilimumab (anti-CTLA4) are being tested in clinical trials for lung cancer right now, for both non-small cell as well as small cell lung cancer. This combination was recently approved for use in advanced melanoma patients.

**Nivolumab+ Ipilimumab in front line NSCLC:**

- Demonstrated clinical activity and manageable safety
- Currently approved for advanced melanoma
- Ipi+Nivo in front line: responses were seen in 27% of never-smokers and in 46% of smokers.
- Responses seen regardless of PDL1 expression, with higher magnitude of benefit in patients whose tumors expressed PDL1.
- Comparison to chemo. Tested combo every 12 weeks vs every 6 weeks vs nivo alone.
- Ipi+Nivo in 2\textsuperscript{nd} line: superior than standard chemo

**Other combinations of immunotherapeutics:**

- Combinations of checkpoint inhibitors with another set of immune activating signals are being tested for lung cancer, and early data on these combinations was presented at ASCO 2016.
- These immune activating signals or what are called the immune ‘agonists’, work in the opposite way of the checkpoints. These agonists work to rev up the immune system, stimulating these to mount an attack against tumors.
- Some of these agonists are molecules like OX40 which increase PDL1 expression, and decreases regulatory T cells that dampen immune responses.
- Early clinical trial data were presented at ASCO on a combination of an OX40 agonist (called MOXR916 produced by Genentech/Roche) and an anti-PD1
antibody in patients who’ve received multiple previous therapies. Data showed that OX40 agonists do indeed increase PDL1 expression, and a trend towards positive responses. It’s still early days, and hopefully fully fleshed out data will emerge by the next ASCO meeting.

- Another abstract presented at ASCO looked at the combination of anti-PD1 antibody, Pembrolizumab, with another immune agonist- 4-1BB. Promising data but was seen in a small trial with no comparator arm.

**Combinations of Immunotherapy with Radiotherapy (RT):**
- For several years we have known about an interesting phenomenon with RT called the abscopal effect (ab-scopus, away from target) where we see tumor regression in lesions distant from the targeted site.
- Now RT also release antigens from dying cancer cells that can prime the immune system to mount an attack.
- Combining RT with immunotherapy therefore holds potential, as release of antigens combined with a primed immune system that has its ‘brakes’ removed will form the perfect storm to completely wipe out the tumor.
- This hypothesis is being tested in several clinical trials.
- A poster at ASCO demonstrated early data on the combination of a PD1 inhibitor by the company Regeneron, with RT.

**Combinations with Targeted Therapies**
- Immunotherapies are also being combined with targeted therapies in clinical trials. And some very encouraging early data is coming out.
- These combinations are one of the ways in which we can convert ‘cold’ tumors that do not respond to immunotherapies (because these tumors do not have enough immune cells in the tumor microenvironment, also called ‘immune deserts’) to ‘hot’ tumors. There is emerging data to support that some targeted therapies can increase the influx of immune cells (T cells) into the tumor microenvironment, and combining these with the immunotherapeutic agent makes sure that these cells mount an attack against the tumor.
- These combinations are fraught with toxicities and we need to be careful in determining doses, schedules- sequencing vs. simultaneous etc.
- e.g. anti-PDL1, Durvalumab with Osimertinib (Tagrisso).

**Several unanswered questions remain around combinations:**
- Is the combination better than monotherapy?
- Is it better to simultaneously administer the combination or should we sequence the drugs: Nivo→ Ipi, OR, Ipi→ Nivo?
- Can we re-administer after responders progress?
- If we do re-administer, should it be with just one agent alone (nivo maintenance)? And for what duration?
- What are predictive biomarkers of response for the combination?
- Can the combination be administered after single agent use?
New biomarkers for response to IO:

- 75-80% of patients do not respond to immunotherapies. We need new biomarkers to identify patients most likely to respond to these agents. These therapies are not inexpensive, and the side effect might be mild, but some patients can experience severe toxicities. So we need biomarkers to stratify patients.
- The current biomarker is PDL1 protein expression on tumor cells. Unfortunately, PDL1 is not the best biomarker as
  - its expression varies over time, and within tumors (temporal and spatial heterogeneity),
  - each pharma company has a different assay and antibody to test for PDL1 expression,
  - the definition of PDL1 positivity/cut-offs vary across these different tests.
  - The tissue being tested can affect measurement- fresh tissue vs. archival sample
  - The tumor microenvironment is a dynamic entity and the timing and location of the biopsy might impact readout
- The Blueprint Project, spearheaded by the International Association for the Study of Lung Cancer (IASLC) in collaboration with American Association for Cancer Research (AACR), the various pharma companies that manufacture PD1 and PDL1 antibodies (Bristol Myers Squib, Genentech, Merck and AstraZeneca), as well two diagnostic companies (Dako and Ventana), that manufacture the PDL1 tests, aims to harmonize PDL1 testing and identify similarities and differences across the different PDL1 assays.
- There are also several ongoing research initiatives to identify better biomarkers for response to immunotherapy.
- Potential new prognostic biomarkers, as well as biomarkers for response to immunotherapies that are beginning to be identified:
  a. Tumor Infiltrating Lymphocytes: higher the number of immune cells in your tumor microenvironment, greater your chances of response to immunotherapies.
  b. B-cell and T-cell gene signatures in the infiltrates (from mRNA...
sequencing) in the tumor microenvironment predicted improved overall survival.

c. Tumor mutational burden- number of mutations (including somatic, coding, base substitution and indel alterations) per Megabase of the genome.

i. Lung cancer in general has a higher mutational burden compared to other cancers.

ii. Within lung cancer, molecular subsets driven by a specific druggable oncogene had lower mutational burden, e.g. EGFR, ALK, ROS1, MET exon14.

iii. Interestingly subsets driven by BRAF and KRAS had higher mutational burdens.

iv. Mutational load is a good surrogate for response to immunotherapy, as higher mutational burden = more neoantigens to present to the immune system to mount a response against.

v. Data from Foundation Medicine presented at ASCO showed that patients with high mutational burdens stayed on immunotherapies longer.

Cost of Immunotherapy

• A poster presented at the meeting showed that more treatment-related adverse events or TRAEs were observed with docetaxel chemotherapy than with Nivolumab immunotherapy.

• The authors compared frequency and associated costs of TRAEs reported in the phase 3 clinical trials evaluating Nivolumab vs docetaxel in Stage 3b/4 squamous cell non-small cell lung cancer, and non-squamous NSCLC.

• They found that more TRAEs were observed with docetaxel than with Nivolumab and the cost of managing TRAEs was 15.8 and 10.7 times higher in the doc arm vs the nivo arm for the CheckMate 017 (Squamous trial) and CheckMate 057 (non-squamous) trials, respectively.
Points to consider about immunotherapies:

- Patients with autoimmune conditions are contraindicated for checkpoint inhibitor therapy. Immunotherapies *may reactivate these conditions*. Most patients with the following conditions are excluded from immunotherapy trials: Crohn’s disease, ulcerative colitis, irritable bowel disease, systemic lupus erythematosus, rheumatoid arthritis, scleroderma. Important to conduct more research in this space to determine whether these patients could be considered for immunotherapies, and at what doses and schedules to avoid re-activating their autoimmune disease.

- A poster presented at ASCO by Dr. Khan from UT Southwestern analyzed 210,509 patient records in the SEER database, found that 24.6% lung cancer patients have autoimmune diseases—rheumatoid arthritis (9%), psoriasis (4.4%), polymyalgia rheumatica (2.6%), Addison’s disease (1.9%), giant cell arteritis (1.4%) and ulcerative colitis (1.3%). Autoimmune diagnoses were more likely to occur in lung cancer patients who were older, female, and presented with earlier-stage disease and have improved clinical outcomes.

- Different spectrum of toxicities from current standards of care are seen with immunotherapies. These agents *may also stimulate autoimmune disease* as was seen in a paper published by the team at Johns Hopkins. They looked at patients treated with ipilimumab and Nivolumab seen between 2012-2016, and found 13 patients who had developed rheumatological immune related adverse events (IRAEs); 9 out of the 13 developed inflammatory arthritis, 4 developed synovitis. Other IRAEs included: pneumonitis, colitis, interstitial nephritis and thyroiditis.

- Response durations are different from targeted therapies where almost all patients with the biomarker (EGFR, ALK) respond, however development of resistance over time is inevitable. In contrast, fewer patients respond to immunotherapies, but those that do have beautiful, durable responses.

- The case of pseudoprogression:
Increasing evidence shows that pseudoprogression might not be a cause for concern in lung cancer as much as it is in melanoma and breast cancer, and that continued treatment with immunotherapies past disease progression may not be beneficial.

Data presented by a team from the FDA based on evaluation of anti-PD1 trial data showed that 71 patients received TPP (treatment past progression) with an anti-PD-1 and their best overall responses were progressive disease in 35 (49%), stable disease in 23 (32%), and partial response (PR) in 13 (18%); the partial response rate was similar in patients with and without TPP.

Among the TPP patients, 4 patients (5.6%) experienced additional tumor shrinkage.

We need better biomarkers to identify who this small segment of patients might be, that are likely to benefit from treatment beyond progression. We need definitive trials to be able to say one way or the other given the financial toxicity of these immunotherapeutic agents and the fact that pharma does not really have a lot of incentive in determining how long patients need to be on their drugs.

Summary: if a patient is clinically well and progression is not significant, it would be reasonable to continue immunotherapy. For true progression, it can be a challenge to convince patients to switch from immunotherapy.

Patients can be anxious to restart immunotherapy after stopping to address immune-related AEs (irAEs). Restarting inappropriately can be fatal, however, so patient expectations must be managed.

It is important to educate patients so that they report when they experience rash, diarrhea, or other symptoms. The patient may be reluctant to mention toxicities out of concern that the physician will stop therapy. However, stopping immunotherapy and administering steroids does not necessarily reduce their efficacy.

- **Is there a thing as too many PD1 and PDL1 inhibitors under development?**
  Dr. Richard Pazdur, the head of the Food and Drug Administration (FDA) has mentioned that too many companies are focused on the same approach of targeting the PD1 pathway. "People should ask themselves ... would we be better off spending those resources into looking at more novel drugs?" Pazdur told Reuters during ASCO. Having multiple inhibitors against the same target can be both a good and bad thing, given two agents have already received approval, and most new agents show similar responses. One way to differentiate these newer agents will be their use in combinations, and ability to elicit responses from non-responders, by converting ‘cold’ tumors to ‘hot’ tumors.

- Your microbiome might impact your response to immunotherapies.

- **Choosing Nivolumab or Pembrolizumab:** Factors taken into account while making a clinical decision to administer Nivo or Pembro include the patient’s lifestyle, distance from the clinic etc.
• Pembro administration: 2mg/kg IV over **30 mins** every 3 weeks,
• Nivo: 3mg/kg over **60 mins** every 2 weeks.
• **Use of PD-L1 testing:** Currently, nivolumab does not require PD-L1 testing, which makes it easier to administer. However, pembrolizumab is given every 3 weeks, compared with every 2 weeks with nivolumab, which can be a factor for patients in rural areas that have long travel times to reach the clinic.

**Anti-PDL1 Checkpoint Inhibitors Under Development for Lung Cancer:**

- **Atezolizumab:**
  - Anti-PDL1 antibody being developed by Genentech/Roche
  - Approved by the FDA recently for urothelial carcinoma
  - Ph3 trial in NSCLC- OAK - completed accrual

- **Durvalumab**
  - Also known as MEDI-4736
  - Being developed by AstraZeneca

**Advances in Targeted Therapies for Lung Cancer:**

**EGFR-mutated NSCLC:**

- First ever liquid biopsy gene test was approved by the FDA on June 3, 2016- the Cobas EGFR Mutation Test v2.
  - Lung tumors shed cancer DNA into patients’ blood. The approved test detects exon 19 deletion and exon 21 (L858R) substitution **EGFR** mutations harbored by NSCLC tumors in patient blood samples. Patients with these tumor mutations may benefit from erlotinib.
  - “However, if such mutations are not detected in the blood, then a tumor biopsy should be performed to determine if the NSCLC mutations are present,” the FDA advised. “In so far as the test provides positive results, it may benefit patients who may be too ill or are otherwise unable to provide a tumor specimen for EGFR testing.”
  - The FDA’s approval of the cobas® EGFR Mutation Test v2 was based on findings from a clinical trial in which participants had previously confirmed positive EGFR exon 19 deletion or L858R mutations using the cobas® EGFR Mutation Test v1.
The test is manufactured by Roche Molecular Systems (Pleasanton, Calif.) for Astellas Pharma Technologies, and is distributed by Genentech.

- **Two new drugs active against Leptomeningeal (LM) disease:**
  - a complication of epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC), where cancer cells spread to the cerebrospinal fluid (CSF) and metastases grow in the spinal and meningeal spaces.
  - LM is a devastating disease often associated with advanced lung cancer.

1. **Osimertinib (Tagrisso)**
   - Data from a trial in Asia showed that AstraZeneca drug crossed the blood-brain barrier and caused decrease in central nervous system lesions in patients with leptomeningeal disease, with accompanying neurological improvement.
   - Irrespective of T790M mutation status of patients, osimertinib demonstrated activity through assessments with MRI imaging intracranial response.
   - Osimertinib is being evaluated in several combinations- with immunotherapies (durvalumab), with targeted therapies- savolitinib (MET inhibitor), selumetinib, navitoclax etc.

2. **AZD3759:**
   - a new third generation EGFR inhibitor developed by AstraZeneca.
   - This oral drug was designed to achieve high concentrations in the brain, cerebrospinal fluid and plasma, and shows anti-tumor activity in brain mets and leptomeningeal disease.

- Treating patients with EGFR mutation–positive lung cancer and brain metastases at diagnosis: Experts would treat patients with symptomatic brain metastases with surgery, stereotactic radiosurgery, or whole-brain radiation therapy. For asymptomatic patients, an EGFR tyrosine kinase inhibitor (TKI) is preferred, since this is thought to delay treating the brain directly, which carries a risk of cognitive impairment.

**ALK-rearranged non-small cell lung cancer:**

- **Brigatinib:**
  - a second-generation ALK inhibitor, was reported at the meeting to be highly active in ALK-translocated NSCLC.
  - In the clinical trial, 72% of crizotinib-resistant patients had objective responses to brigatinib.
  - The median duration of responses in this group was 14.5 months, and longer in patients who had not received crizotinib previously.
Most encouragingly, patients with brain metastases had a similarly high rate of responses to brigatinib (67%).
Will be in market later this year/earlier this year in the second line setting.
Is being evaluated in the first line setting in ALK inhibitor-naïve patients, vs. crizotinib in the ALTA-1L trial.

- **Alectinib:**
  - Very exciting results from a head-to-head comparison of Alectinib vs Crizotinib in a Japanese trial- J-ALEX looking at ALK-inhibitor naïve NSCLC patients, as in patients who’ve never been exposed to targeted therapies for ALK-fusions (but have been treated with chemotherapies).
  - Median PFS (progression-free survival) was not reached in the Alectinib arm, while on crizotinib median PFS was 10.2 months.
  - In terms of side effect profiles, only constipation (36%) was an adverse event with >30% frequency in patients on Alectinib, while in the Crizotinib arm nausea (74%), diarrhea (73%), vomiting (59%), visual disturbance (55%), dysgeusia (52%), constipation (46%), ALT elevation (32%), and AST elevation (31%) were seen in >30% pts. Grade 3-4 adverse events occurred with greater frequency in the crizotinib arm (ALC arm: 27% vs CRZ arm: 51%).
  - Alectinib has great CNS activity.
  - Global study of alectinib will be presented at ASCO next year

- **Lorlatinib:**
  - Highly brain-penetrant ALK and ROS1 tyrosine kinase inhibitor
  - Active against most known resistance mutations.
  - Will most probably be given breakthrough therapy designation by the FDA soon.
  - Should see in market in 2018.
  - Currently in Ph I/II trials in heavily pre-treated patients with brain mets
  - Hypercholesterolemia was the most common treatment related adverse event, which can be treated with crestor/Lipitor.
  - Can be salvage therapy for patients that fail ceritinib, alectinib, crizotinib, and even brigatinib.

**ROS1-rearranged NSCLC:**
- Crizotinib approved by the US FDA in 2016
- Several agents under development- Entrectinib (Ignyta), Lorlatinib (Pfizer), Briagtinib (Ariad),

**MET Amplification in NSCLC:**
- Crizotinib under clinical trial evaluation

**RET-rearranged lung cancer:**
- Vandetanib in clinical trials
- Fusion partners in RET might dictate response to targeted therapies.

**BRAF-mutated lung cancer**
- Another relatively rare subtype of adenocarcinoma,
- Seen in 2-3% of patients
- A specific mutation, the BRAF V600E mutation is most common, also seen in melanoma, and has approved treatments with of dabrafenib (BRAF inhibitor, Tafinlar) and trametinib (MEK inhibitor, Mekinist).
- Dabrafenib+Trametinib showed an objective response rate of 63% in BRAF-mutant lung cancer, with a median duration of 9 months.
- Another agent vemurafenib (Zelboraf), a mutant BRAF inhibitor, is also an option, but the combination works better based on this early data.

**Small Cell Lung Cancer**

**First-ever molecularly targeted therapy for SCLC: Rova-T (Rovalpituzumab Tesirine)**
- SCLC accounts for approximately 15% of all lung cancers and is particularly aggressive — about two-thirds of patients have extensive-stage disease when they are first diagnosed, and the median survival for these patients is less than a year.
- Substantial therapeutic advances for this disease have lagged far behind other cancers, with no new drug being approved for SCLC in the past three decades.
- Rova-T is the first molecularly targeted drug to show antitumor efficacy in SCLC
- Delta-Like Protein 3 (DLL3) is expressed in 80% of all SCLC tumors.
- Rova-T is an antibody drug conjugate or an ADC- it combines a monoclonal antibody that targets DLL3 and a cellular toxin, basically it is a Trojan horse that uses the DLL3 antibody to steer it to SCLC tumors that express the DLL3 protein, where it delivers its payload, the toxin that specifically kills these cells.
- Results of first-in-man trial that tested Rova-T in patients with recurrent or refractory SCLC with >1 prior treatments were presented at ASCO.
- Patients with higher expression of the DLL3 protein, responded better
- Overall response rates were 18%
- In patients with >50% expression od DLL3 in their tumors ORR was 70% in the third line setting that currently has no therapies approved for patients.
- Manageable toxicity.
- Still early days as this was an early phase trial in a few patients, therefore the results will be considered preliminary until confirmed in larger scale studies that are currently underway.
- Important for SCLC patients to test if their tumors express DLL3 and enquire about clinical trials for Rova-T, such as the Phase II trial TRINITY, currently underway at Memorial Sloan-Kettering Cancer Center under the leadership of Dr. Charles Rudin.

**Immunotherapy combinations (Nivolumab+Ipilimumab) in SCLC**
• Are being tested in advanced, previously treated SCLC patients with progressive disease.
• Trial data presented at ASCO 2016 compared Nivo alone vs. Nivo+Ipi (2 separate doses: N3+ I1, N1+I3)
• Higher rate of responses was seen in the combination arms than was seen with nivolumab alone: Nivo alone Objective Response Rate= 10%, Combination ORR= 20%
• Responses were observed independent of platinum sensitivity and PDL1 expression.
• The immunotherapeutic regimens are active in patients who are particularly difficult to treat, with responses observed in those who were resistant to initial standard chemotherapy and in patients who had two or more prior treatments.
• Responses also lasted longer. Durable responses seen with some patients remaining in response for greater than 18 months- unprecedented for SCLC.
• However, these improvements came with a higher burden of toxicities (side effects) seen in combination arms.
• In summary, immunotherapy combinations demonstrate durable objective response rates and manageable toxicities in small cell lung cancer.
• Two large phase III clinical trials are planned to further demonstrate the efficacy of the combination in SCLC.

Patient Engagement in their care, improves outcomes:
• In an unprecedented move, ASCO provided an oral presentation spot to an abstract discussing a mobile application used by lung cancer patients.
• This app, MoovCare is a symptom-reporting, web-based application that allows for earlier detection of relapse among patients with advanced lung cancer, resulting in improving survival by 7 months, according to the authors.
• A company based in Jerusalem called Sivan Innovation is developing the app,
MoovCare.

- French physician Dr. Fabrice Denis conducted a Ph 3 randomized trial. Median age of patients in the trial was 65 years (so it was not a ‘younger’ cohort) and most patients had Stage III or IV lung cancer.
- Patients on one arm of the trial were asked to provide weekly assessments on 12 symptoms through the app (can also be entered by caregivers) that are reported to the oncologist, and those on the other arm had standard follow-up and underwent CT scans every 3-6 months.
- For the app submissions, an algorithm assessed specific changes in symptoms and triggered email alerts for the doctor, who would then confirm the need of anticipated exams or visits to adapt cancer treatment, including supportive care options.
- For 121 evaluable patients receiving care at 5 medical centers, the median overall survival of those who used the app was 19 months as compared with 12 months for those who received standard follow-up for lung cancer after surgery. At 1 year, 75% of patients were still alive in the Web application group, compared with 49% in the standard follow-up group. The study was stopped at planned interim analysis because of these results.
- The study showed that there was no difference in progression-free survival, but patients using the app experienced: Fewer scans, less exposure to imaging procedures, personalized care, lower costs of care, improved quality and length of life.
- It took oncologists only 15 minutes per week to follow 60 patients, and automation decreased the frequency of patient phone calls to the office.
- This app will be available in the United States in January 2017, according to the developers and the French investigator, Dr. Denis.

**Biosimilars for Cancer:**

- Biologics are drugs produced by living organisms that have complex structures, and are more difficult to copy, such as vaccines, interleukins, antibodies.
- Biosimilars are drugs similar to the biologics, not the exact same, as in biosimilars mimic the effects of a biologic, but are not exactly identical.
- Data on a new biosimilar to trastuzumab for breast cancer was presented. Ph3 clinical trial conducted in 500 HER2+ breast cancer patients in Asia, Latin America, Africa showed the biosimilar was similar in efficacy and safety profile to trastuzumab, and did not trigger an immune response- low immunogenicity
- Benefits: Improved patient access, lower costs
- As patents for the original biologics expire, several new biosimilar agents enter clinical development, and can be a potential answer to the question around costs of drugs such as immunotherapies.
- Biosimilars to bevacizumab for non-small cell lung cancer, and rituximab are under evaluation, and hold promise.
Liquid Biopsies
- Barriers with traditional tissue biopsy: require invasive procedures, including surgery, and some patients may not be candidates because of poor health or because of a tumor’s location in the body. In addition, after the initial testing and analyses of biopsy samples, not enough additional tissue may be left for comprehensive molecular profiling, or it may not be of sufficient quality for profiling.
- A tumor’s molecular profile changes over time, in response to treatment. Also varies between patients, and in the same patient—concepts of inter- and intra-tumoral heterogeneity.
- Need for minimally-invasive methodology to get a window into the tumor, especially when tissue biopsy is insufficient for genotyping or cannot be obtained safely.

Liquid Biopsy platforms such as Guardant Health
- Cancer cells as well as DNA from dying cancer cells, are shed into the bloodstream. These are referred to as circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA).
- Guardant Health, based in Redwood City, CA, USA have a liquid biopsy test, Guardant360, for lung cancer that they presented data on at the ASCO Annual Meeting.
- Researchers used >15,000 blood samples from patients diagnosed with 50 different types of cancer to see if a liquid biopsy test from Guardant Health (which paid for the study) called Guardant360, would flag known mutations that drive cancer.
- Looked at 70 different cancer-related genes in the circulating tumor DNA or ctDNA in the blood.
- The blood test detected known mutations in 83% of the samples. Basically similar frequency of detection, and similar mutation profile distribution patterns as seen with traditional tumor biopsies.
- In a second component of the study, researchers analyzed the DNA in tumor tissue samples from nearly 400 lung and colorectal cancer patients taken during a traditional surgical biopsy and compared that with the patients’ liquid biopsies. Mutations detected in the tumor DNA matched those found in the liquid biopsies in 87% of the cases. Higher concordance was observed if the two biopsies were done within 6 months of each other.
- However, in some cases, the liquid biopsy platform was not able to detect resistance mutations at similar frequencies to a traditional biopsy.
- Liquid biopsies have great potential, but tissue remains the gold standard, and it is still early days for this technology. We need more data to validate the liquid biopsy multiplex gene platforms, and there is still work to do to better understand how best to use liquid biopsies and what role they might eventually play in patient care.
- But at this point, based on the study’s findings, the evidence suggests that liquid biopsies could be an alternative when traditional tumor biopsies “are not practical, accessible, or feasible.”
Main utility right now: disease monitoring, and tracking emergence of disease resistance.

More research is needed before liquid biopsies are used routinely in cancer care, said Richard Schilsky, M.D., of the University of Chicago, during the press briefing. The current study, Dr. Schilsky noted, was not a randomized trial, and there’s no evidence yet that the liquid biopsies under development or that are commercially available improve patient outcomes.

“Just because a test can be done, doesn’t mean it should be done,” he said. “The burden is on all of us to demonstrate true clinical utility of the tests that are out there.”

Plasma, Urine Tests can detect EGFR T790M mutations

- EGFR T790M is one of most common resistance mutations that emerges when patients stop responding to first-line EGFR inhibitors. Seen in ~60% EGFR TKI resistant patients.
- Data presented at ASCO demonstrated that testing for T790M mutations with plasma and urine assays can complement testing done from biopsy tissue in patients with EGFR tyrosine kinase inhibitor (TKI)-resistance.
- These results were obtained from the clinical trial of the EGFR inhibitor rociletinib (manufactured by Clovis Oncology) whose development has now been stopped. It was observed that response to rociletinib was similar whether T790M mutation status was tested with biopsy or plasma or urine.
- Rociletinib clinical development has been discontinued, but the mutation testing results are still broadly applicable.
- The sensitivity of the urine analysis was 81.1%.
- The response rates to rociletinib were not substantially different based on the sample type.
- It did appear to be more difficult to find the mutation with plasma and urine testing in patients with M1a/M0 disease—meaning metastases only in the lung—than in those with M1b (distant metastases) disease.
- Dr. Heather Wakelee, from Stanford University, who presented the data at ASCO shared that “T790M plasma, tissue, and urine tests complement one another. Each test identifies cases missed by the other tests. EGFR mutation detection from plasma and urine should be considered viable approaches, particularly when tumor tissue is not available”.

Cool Stuff:

Artificial Intelligence- based drug discovery and patient stratification for clinical trials
• A company based in Boston called Berg presented some interesting data on their proprietary platform called Interrogative Biology that merges systems biology with artificial intelligence/machine learning algorithms.
• They collect data on genomics, proteomics, metabolomics and lipidomics from normal and cancer cells; then add clinical info, and analyze all data through their AI platform to identify markers for cancer cells, and specific targets.
• These markers help identify patients most likely to respond to drugs against the selected targets.
• Helps design targeted clinical trials.
• Through their platform they’ve developed a molecule BPM31510 based on differences in cancer and normal cells. They found that Warburg effect or glucose metabolism is most often dysregulated between cancer cells and normal cells.
• They attempted to target this dysregulated metabolism through BPM31510 that tries to reverse the Warburg effect.
• According to the company, BPM31510 is the first drug developed using artificial intelligence.
• Encouraging data from Ph 1 trial in solid tumors, entering Ph2 in pancreatic cancer.
• Berg is now evaluating other disease types to target, both as monotherapy as well as combinations, and is looking at NSCLC as a potential target.

For more information on what’s happening in the lung cancer research and clinical medicine space, sign up for the Bonnie J. Addario Lung Cancer Foundation’s Patient Portal at lungcancerfoundation.org/portal. We feature stories on the latest drugs approved for lung cancer, new clinical trials, new diagnostics and therapeutics you might benefit from, as well as inspiring stories of patients who’ve fought lung cancer bravely.

If you have questions about information we have here, navigating the complex path of cancer treatment, or anything else, get in touch with us at portal@lungcancerfoundation.org. Your message will be delivered directly to Danielle Hicks (Director of Patient Services and Programs), Michele Zeh (Patient Navigation and Services Coordinator), and Guneet Walia, PhD (Director of Research and Medical Affairs). They are always happy to hear from you!

Bonnie J. Addario Lung Cancer Foundation
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