Lung Cancer Predictive Biomarkers
An Oncologist's Perspective

Eric Bernicker MD

HOUSTON Methodist CANCER CENTER

Weill Cornell Medical College

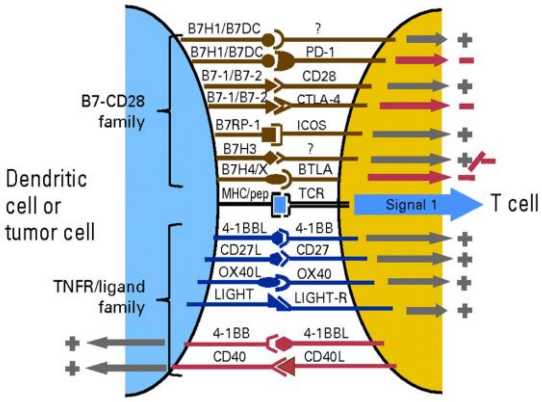
Disclosures

- Speakers bureau: Myriad
- Stock ownership: none

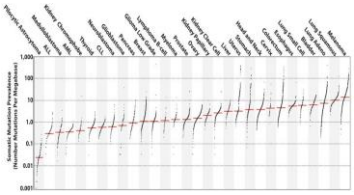
Which Got More Media Coverage ?

Immunotherapy and Lung Cancer

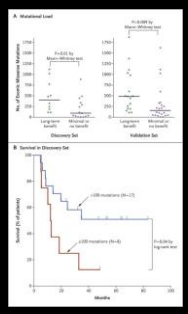
- The buzz is real
- Many patients do not respond but when they do, it can be prolonged
- Toxicities very different than standard cytotoxic agents
- Many questions remain: combination with XRT, chemo, targeted therapies; ? Adjuvant use; how long to treat. And: expense.



Mutational landscape of tumors



Mutational Landscape of Tumors According to Clinical Benefit from Ipilimumab Treatment.



Snyder A et al. N Engl J Med 2014;371:2189-2199.

The NEW ENGLAND JOURNAL of MEDICINE

Does the mutational landscape determine sensitivity to PD-1 blockade?

- Exomes of NSCLCs sequenced
- A median of 200 nonsynonomous mutations per sample were detected
- Higher somatic nonsynonymous burden was associated with clinical benefit to PD-1 blockade: 73% achieved a durable clinical benefit compared with 13% low mutation burden

Rizvi et al, Science 2015

PDL1 prevalence across tumors

Histology	n	PDL1 + (IC)	PDL1 + (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric Cancer	141	18	5
CRC	77	35	1
Pancreatic	83	12	4

Herbst et al, Nature, 2014

Is PD-L1 a prognostic biomarker?

- In NSCLC:
- 205 patients with advanced NSCLC treated with chemotherapy
- 55% women, 22% had Squamous as histology
- 25% strong positive, 50% weakly positive
- No statistical association between PD-L1 expression and OS

Sorenson et al, Annals of Oncology 2014

Is PD-L1 a prognostic biomarker?

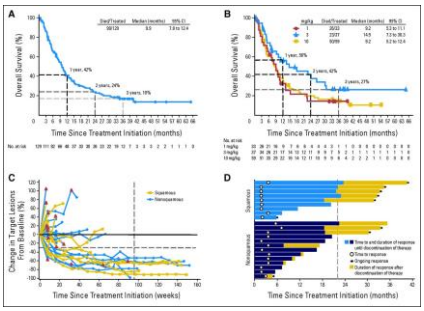
- In Renal cell carcinoma:
- Expression associated with adverse pathological features and decreased 3 year survival
- 24% of patients overexpressed PD-L1; worse disease progression free survival: 56% v 86% (Thompson et al, Cancer Research 2006)

Pathology of Non-responders

- Immunological ignorance: little or no tumor-infiltrating immune cells
- Non-functional immune response: immune infiltrate with minimal to no PDL1 expression
- Excluded infiltrate: immune infiltrate solely around the edge of the tumor cell mass

Herbst et al, Nature 2014

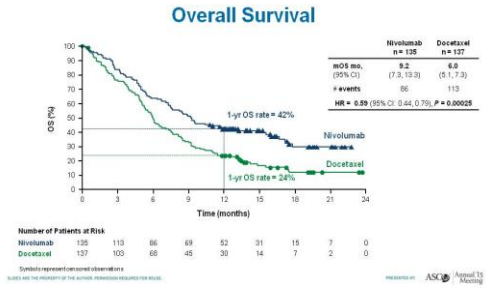
Clinical activity in patients with non–small-cell lung cancer (NSCLC) receiving nivolumab.



Scott N. Gettinger et al. JCO doi:10.1200/JCO.2014.58.3708

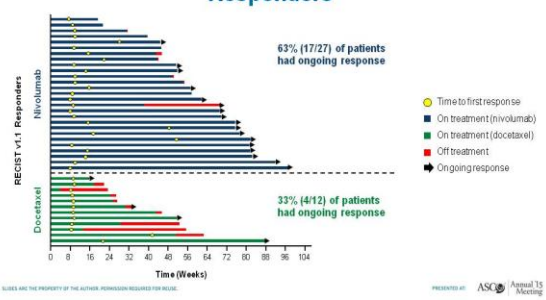
JOURNAL of CLINICAL ONCOLOGY ASCO

Checkmate 017 Results



Brahmer et al, ASCO 2015

Response Characteristics of Confirmed Responders



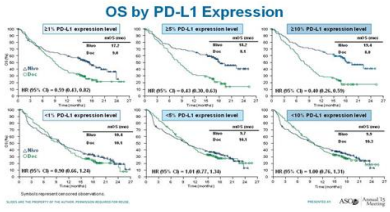
Spigel et al ASCO 2015

Biomarkers and response

- 53 NSCLC patients on a Phase 1 trial of MPDL3280A
- 30% pts were IHC 2 or 3+
- ORRs were associated with PD-L1 expression in ICs
- IHC 3+ 80% ORR (5/6)
- PD-L1 expression in TCs did not correlate with response

Soria et al Annals of Oncology 2014

PD-L1 Expression Predictive of Benefit to Nivolumab



Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting

Can We Characterize PD-L1 Expression and Therapeutic Response?

- SP142 IHC assay used to score IC and TC
- TC3 or IC3 : 20% of NSCLC
- TC2/3, IC2/3 40% of NSCLC
- TC1/2/3, IC1/2/3 65% of NSCLC
- IC3: high degree of immune infiltrates within tumor
- TC3: lower frequency of immune infiltrates, sclerotic tumor microenvironment

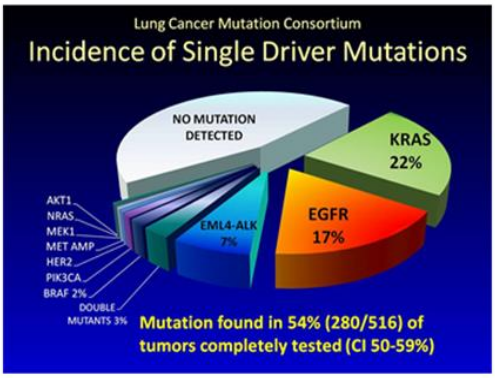
Gettinger et al 2015

SO…Do We Have a Predictive Biomarker or Not

- No, not yet
- We will need consensus on which antibody to use and when (initial biopsy, re-biopsy after frontline treatment)
- Each antibody cannot have it's own biomarker
- Correlate with histologic features? Immune infiltrates
- Blood-based testing?

And some PD-L1< 1% gain benefit

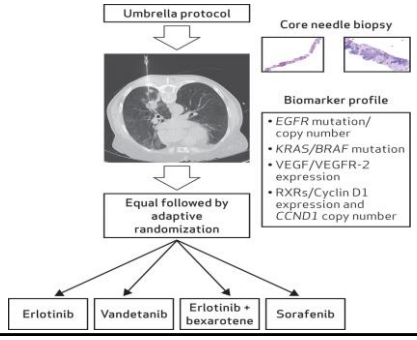
- If low-expressors have the same response to immune blockade as to Docetaxel, even if poor, it is a better tolerated therapy.
- We will need a better biomarker to discriminate for low-expressors, especially given the cost and the current emphasis on value.



BATTLE trial at MDACC

- Previously treated patients with lung cancer
- Prior EGFR ok; not randomized to TKI arm
- Stable, treated brain metastases
- PS 0-2

BATTLE Trial Schema (MDACC)



Efficacy Result by Marker Groups

Disease Control by Treatment and Marker Groups Number of DC / Total Number of Patients (%)

Marker Group	Treatment				Total
	Erlotinib	Vandetanib	Erlotinib+ Bexarotene	Sorafenib	
EGFR	6/17 (35%)	11/27 (41%)*	11/20 (55%)*	9/23 (39%)	37/87 (43%)
KRAS/BRAF	1/7 (14%)	0/3 (0%)	1/3 (33%)	11/14 (79%)*	13/27 (48%)
VEGF/VEGFR-2	10/25 (40%)*	6/16 (38%)	0/3 (0%)	25/39 (64%)*	41/83 (49%)
RXR/Cyclin D1	0/1 (0%)	0/0 (NA)	1/1 (100%)*	1/4 (25%)	2/6 (33%)
None	3/8 (38%)	0/6 (0%)	5/9 (56%)*	11/18 (61%)*	19/41 (46%)
Total	20/58 (34%)	17/52 (33%)	18/36 (50%)	57/98 (58%)	112/244 (46%)

Kim et al Cancer Discovery 2011

BATTLE Trial : Efficacy

CUSTOM Trial: Design

- Recurrent or advanced NSCLC, SCLC or thymoma
- Archival tissue 73%; fresh tissue 27%
- Set of core mutations:
  AKT1, *BRAF*, *EGFR*,*ERBB2*, *HRAS*, *KIT*, *KRAS*, *NRAS*, *P DGFRA*, *PIK3CA*, and *PTEN*
- Gene amplification: *ERBB2*, *PIK3CA*, and *PDGFRA*.

CUSTOM Trial : Treatment Arms

- EGFR >>>erlotinib
- KRAS, HRAS, NRAS, or BRAF>>>Selumitinib
- PIK3CA, AKT1, or PTEN or amplification of PIK3CA >>MK2206, an AKT inhibitor
- Mutation or amplification of *ERBB2*>>Lapatanib
- KIT or PDGFRA>>>Sunitinib
- No actionable mutations>> SOC

CUSTOM Trial : Results

- KRAS mutations in 24.9%.
  - 110 pts, 11 enrolled on Selumetinib, 1 PR
- BRAF in 2% of NSCLC and 2% SCLC
- PIK3CA: 3.9% NSCLC, 8.5% SCLC
  - No responses in any of the enrolled patients
- KIT: 0% NSCLC
  - Felt to not be feasible to complete accrural; no responses seen
- ERBB2 in 2% of NSCLC, 0 in SCLC and TM
  - Slow accrual, arm shut; 0 responses to lapatanib

CUSTOM Trial: Lessons

- Feasible to enroll patients quickly: 647 patients in 20 months
- Certain targets not tested: ROS1 and RET
- Often long delay in getting genomic results
- Prior erlotinib was allowed but they had to be enrolled in other brackets: only 18% eligible patients put onto trial
- Lack of adaptive design hurt

Looking Deeper: MSKCC and hybrid-capture based NGS

- Adenocarcinomas of the lung: 11 genes initially tested: EGFR, ERBB2, KRAS, NRAS, BRAF, MAP2K1, PIK3CA, AKT1, ALK, ROS1, and RET
- Patients negative for the above eligible for NGS if little or no smoking history, stage IIIb/IV and good PS
- Goal: to see if a more sensitive assay could detect actionable mutations that would offer some patients targeted therapies

MSKCC NGS: Biopsy results

- 47 patients identified in 6 years
- 16/47 (34%): tissue exhaustion
- 84% of patients required more than > 2 biopsies (range: 2-6!!)
- Only 29% of samples were from the initial biopsy for diagnosis
- 71% obtained from surgery such as VATS or resection of a metastatic focus

LCMC 2.0: NGS in 617 Adenocarcinomas

Driver	Number (Percentage)
ROS	17 (3%)
RET	13 (2%)
EGFR	77 (13%)
ALK	20 (3%)
BRAF	18 (3%)
PIK3CA	4 (<1%)
HER-2	9 (2%)
MET amplification	12 (2%)
KRAS	135 (22%)
PTEN LOSS	15%
MET Expression	54 %

Kris et al ASCO 2015

NCCN Guidelines: Emerging Targeted Agents

Driver Mutation	Available Targeted Agents
BRAF V600E	Vemurafenib dabrafenib
MET amplification	crizotinib
ROS-1 rearrangements	crizotinib
HER-2 Mutations	trastuzumab (category 2B) Afatanib (category 2B)
RET rearrangements	Cabozantinib (category 2B)

Case study

- 64 year old smoking female
- Stage II adenocarcinoma 7 years ago: resection and adjuvant chemotherapy
- 6 years later: new mediastinal nodes
- Bx confirms adenocarcinoma, EGFR and ALK negative
- Concomitant chemo/XRT puts her into remission
- 6 months later, new pleural lesion with rib destruction: biopsy

Case Study

- Foundation One NGS on the biopsy: FLT 3 and PDGFRA mutation
- Started on Sorafenib: hand-foot issues as well as diarrhea
- 2 months later: first CT shows no new disease and 50% decrease in the pleural/rib nodule
- Therapy is continued

Crizotinib in MET-Amplified Lung Cancer

- Data from a phase I Crizotinib trial
- MET amplification determined by FISH
- Low, intermediate or high (MET/CEP7 ratio <2.2, <5, >%)
- 12 patients evaluable for response
- 4 PRs: low (0); Intermediate (1); High (3)
- Median duration of response : 35 weeks
- 75% patients had AEs, generally grade 1: diarrhea, nausea, edema

Camidge et al, ASCO Proceedings, 2014

RET Fusions in NSCLC

- 1-2 % of patients with adenocarcinoma, higher in patients who are never smokers and lack other driver mutations.
- Younger patients with early nodal spread and poorly differentiated histology
- Drilon et al published their experience with cabozantinib in 3 patients
- 2 PRs and 1 stable disease (8 months) in the first 3 patients treated
- All 3 remain on therapy
- Falchook reported on a patient treated with Vandetanib and had a 75% decrease and remains on therapy

HER-2 and Lung Cancer

- 1-2% of patients, adenocarcinoma and often never smokers. 69% women.
- Exon 20 insertions
- Trastuzumab seems to offer a benefit with 50% response rate (PRs) and DCR of 82%.
- Afatanib effective although numbers are small (DCR of 100% in 3 patients)

Mazieres et al, JCO 2013

BRAF Targeted Therapy in NSCLC

- Dabrafenib monotherapy has a ORR of 32%
- Combination therapy with Trametinib tested BRAF mutated lung cancer
- 64% female, 73% former smokers; all had failed frontline chemo.
- ORR 63%, all PRs.
  DCR 88% at 12 weeks
- 27% needed a dose reduction for serious Aes
- Ongoing trials

So where do we stand with genomics?

- Tissue remains a frustrating issue: CTCs or cell-free DNA to the rescue?
- Almost all trials have been done second line or the benefit has heavily been with known drivers already tested for; EGFR, ALK and ROS1
- Tumor heterogeneity and acquired resistance remain significant issues
- Drop in expense does not yet mean that this should be standard
- We need better drugs and a better understanding of clonal evolution and the microenvironment

A Cautionary Tale

- Non-smoking 52 year old male presented with right hilar mass and rib metastases
- Initial biopsy: Adenocarcinoma. ALK, EGFR and ROS-1 negative
- Remission with 4 cycles of pemetrexed, carboplatin and bevacizumab.
- After 2 cycles of Bev Maintenance: rapid relapse in liver.
- Received anti-PD-L1 on trial. Well tolerated: however he progressed.
- NGS on liver : RET fusion

A Cautionary Tale

- Placed on Cabozanitinib
- Brief response that lasted 3 months then again with progressive disease
- Frustrating lesson that even with Immunotherapy and precision medicine, we still have more to learn to help all of our patients

Circulating factors with biomarker potential

Biomarkers	Strengths	Limitations
Classic protein biomarkers	Inexpensive, standardized Widely available	Small % of tumors produce markers
Circulating tumor cells	Unique to tumors Can be enumerated; Molecular characterization	Low cell yield limits dynamic range and sensitivity Higher cost
Circulating tumor DNA	Unique to tumors Wide dynamic range seems to correlate with tumor burden	Individual tumors might not have detectable levels of DNA

From Neal et al, Nat.Rev.Clin.Oncol 2015

Summary

- Genomics and immunotherapy have already made significant improvements in the care of patients with advanced lung cancer
- Much work remains to be done
- We need to continue to enroll patients in meaningful clinical trials.
- Multidisciplinary teams of specialists will be necessary to improve our therapeutics and make sure that we are offering patients the best chance of response as well as value

Targeted agents and companion biomarkers