Molecular Targeted Therapy and Immunotherapy in Non-Small Cell Lung Cancer

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Thoracic/Head and Neck Medical Oncology
Professor
University of Washington
EGFR Targeting
Mutations in the EGFR Gene in Gefitinib-Responsive Tumors

EGFR Targeting in First Line: Highly effective in patients with EGFR mutations

- A number of phase II clinical trials showed high response rates, median PFS of +/- 1 year and survival +/- 2 years.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>EGFR TKI</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequist et al¹</td>
<td>USA</td>
<td>31</td>
<td>Gefitinib</td>
<td>55%</td>
<td>9 months</td>
<td>17 months</td>
</tr>
<tr>
<td>Tamura et al²</td>
<td>Japan</td>
<td>28</td>
<td>Gefitinib</td>
<td>75%</td>
<td>11.5 months</td>
<td>NR</td>
</tr>
<tr>
<td>Rosell et al³</td>
<td>Spain</td>
<td>113</td>
<td>Erlotinib</td>
<td>70%</td>
<td>14 months</td>
<td>28 months</td>
</tr>
</tbody>
</table>

1. Sequist L V et al. JCO 2008;26:2442-2449
IPASS

Advanced Adenocarcinoma
Non or light Smoker

Gefitinib
250mg/daily

Caboplatin AUC 5/6
Pacltaxel 200mg/m$^2$

Primary objective: Progression-Free Survival
Non-inferiority trial (95% CI upper limit HR<1.2)

No difference in overall survival: G 18.6 months and CP 17.3 months RR= 71% among mutation positive patients treated with gefitinib
EGFR Targeting Resistance

• Although first line therapy has a high response (55-80%) rate in patients with sensitizing EGFR mutations the time to progression is between 9-14 months

• 50-60% of tumors progressing after EGFR TIK have a T790M mutation (Pao et al. NEJM 2005;3552:786-92)
Second Line EGFR Inhibition

• Up to now no single agent second line EGFR inhibition has shown significant activity

• Afatinib: 7% RR and PFS of 3.3 months after progression on erlotinib or gefitinib
  (Miller VA Lancet Oncol 2012:528-538)

• Afatinib + Cetuximab showed activity at the expense of significant rash: RR 36%
  Janjigian et al. ASCO 2011 Abstract #7525
AZD 9291

- Irreversible oral EGFR TKI
- Preclinical models with activity against EGFR with sensitizing mutations and T790M
- Limited activity against EGFR wild-type
AZD 9291

- Phase I/II
- 232 patients (31/201)
- 100% prior EGFR oral TKI
- On the expansion cohort 92% tumors had del19 or L858R
- Median number of treatments: 3

Janne PA ASCO 2014 Abstract 8009
Safety

- Dose defined at 80mg/day
- Any grade 3: 24%
- Dose reduction: 2%
- Discontinuation: 4%
- Serious AE: 19%
- Grade 3 rash: 7/232 (3%) all cases above the recommended 80mg dose
- Hyperglycemia: only 3 cases none grade 3
Response rate* according to T790M (central test) status: immediate prior EGFR-TKI, # yes vs no

*Includes confirmed responses and responses awaiting confirmation; #TKI therapy is defined as being immediately prior if TKI was the last regimen taken prior to the study, with no subsequent therapy. Population: all dosed centrally confirmed T790M+ and T790M- patients with a baseline RECIST assessment and an evaluable response; T790M+ N=105 (from 107 T790M+ patients with response data, two patients not included as subgroup missing); T790M- N=50

Presented by: Pasi A. Jänne
Progression-free Survival According to Status with Respect to EGFR T790M.
CO-1686

• Potent oral inhibitor of key EGFR activating mutations and T790M
• “Designed to spare EGFR wild-type”
• Phase I/II
• 72 patients
• T790M (+)
• Median lines of therapy: 3
• Median lines of EGFR targeting: 2
• Prior history of diabetes: 10%

Sequist LV ASCO abstract 8010
Safety

- Rash 4% all grade 1
- Diarrhea no cases of grade 3
- Vomiting 3% grade 3
- Hyperglycemia:
  - Grade 1 (> ULN to <160): 19%
  - Grade 2 (160- <250): 11%
  - Grade 3 (250-<500): 22%
Progression-free survival (K-M estimate)

Centrally confirmed T790M+ Phase 1 and early Phase 2 expansion patients within therapeutic dose range (N=40)

Median PFS not reached; current estimate >12 months

K-M, Kaplan-Meier; PFS, progression-free survival
ALK Targeting
ALK Rearrangement in Cancer

Bang et al. ASCO 2010
FLUORESCENCE IN-SITU HYBRIDIZATION ANALYSIS:
Within a nucleus, split red and green signals indicate the presence of an ALK (2p22) gene rearrangement.
Response to ALK Inhibition

A Progression-free Survival

Probability of Progression-free Survival

- Crizotinib
- Chemotherapy

Months

Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI, 0.37–0.64)
P<0.001

No. at Risk
Crizotinib 173 93 38 11 2 0
Chemotherapy 174 49 15 4 1 0

B Progression-free Survival with Crizotinib vs. Pemetrexed or Docetaxel

Probability of Progression-free Survival

- Crizotinib
- Pemetrexed
- Docetaxel

Months

Hazard ratio for progression or death, 0.59 (95% CI, 0.43–0.80)
P<0.001 (vs. pemetrexed)

Hazard ratio for progression or death, 0.30 (95% CI, 0.21–0.43)
P<0.001 (vs. docetaxel)

No. at Risk
Crizotinib 172 93 38 11 2 0
Pemetrexed 99 36 2 3 1 0
Docetaxel 72 13 3 1 0

Second Line ALK Inhibition

- Ceritinib
- Phase I/II
- 130 patients
- Doses 50-750mg
- MTD: 750mg/day

Among those treated with at least 400mg/day
- Overall RR: 58%
- Previously treated with crizotinib: 56% RR
- PFS: 7 months

Shaw AT NEJM 2014;370:1189-1197
ROS-1 Targeting
Tumor Responses to Crizotinib in ROS1-Rearranged Non–Small-Cell Lung Cancer.


Median Progression-Free Survival: 19.2 months
# NCCN Guidelines Version 6.2015
Non-Small Cell Lung Cancer

## EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

<table>
<thead>
<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E mutation</td>
<td>vemurafenib(^1)</td>
</tr>
<tr>
<td></td>
<td>dabrafenib(^2)</td>
</tr>
<tr>
<td>MET amplification</td>
<td>crizotinib(^3,4)</td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>crizotinib(^5)</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>trastuzumab(^6) (category 2B)</td>
</tr>
<tr>
<td></td>
<td>afatinib(^7) (category 2B)</td>
</tr>
<tr>
<td>RET rearrangements</td>
<td>cabozantinib(^8) (category 2B)</td>
</tr>
</tbody>
</table>


Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC THERAPY FOR METASTATIC DISEASE

Metastatic Disease

Establish histologic subtype\(^a\) with adequate tissue for molecular testing (consider rebiopsy if appropriate)

Smoking cessation counseling

Integrate palliative care\(^b\) (See NCCN Guidelines for Palliative Care)

Adenocarcinoma

Large Cell

NSCLC not otherwise specified (NOS)

Squamous cell carcinoma

EGFR mutation testing\(^a\) (category 1)\(^a\)

ALK testing (category 1)\(^a\)

EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing\(^h\)

Consider EGFR mutation and ALK testing\(^i\) especially in never smokers or small biopsy specimens, or mixed histology\(^j\)

EGFR and ALK testing should be conducted as part of multiplex/next generation sequencing\(^h\)

SENSITIZING EGFR MUTATION POSITIVE

See First-Line Therapy (NSCL-17)

ALK positive

See First-Line Therapy (NSCL-18)

Both sensitizing EGFR mutation and ALK are negative or unknown\(^kk\)

See First-Line Therapy (NSCL-19)

SENSITIZING EGFR MUTATION POSITIVE

ALK positive

See First-Line Therapy (NSCL-17)

Both sensitizing EGFR mutation and ALK are negative or unknown\(^kk\)

See First-Line Therapy (NSCL-20)

\(^a\)See Principles of Pathologic Review (NSCL-A).


\(^h\)The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).


\(^j\)In patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bhma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIC). Curr Protoc Hum Genet 2008;Chapter 10:Unit 10.11.


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BRAF V600E: Abst 8006

- Present in 1.5-2% of adenocarcinomas of lung
- Phase II trial of dabrafenib or dabrafenib+trametinib
- Dabrafeninb alone presented at ESMO2014 with a RR of 32%
- D+T: 24 patients evaluated for efficacy
- RR:63%
RET: Abstract 8007

• Rearrangements present in 1-2% of adenocarcinoma of the lung
• Tested by FISH or NGS
• Phase II of cabozantinib 60mg/day
• 16 patients on first stage
• Only one patient had >15 pack/year hxt
### Emerging Targeted Agents for Patients with Genetic Alterations

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<tr>
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<td>cabozantinib(^8) (category 2B)</td>
</tr>
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</table>

*Non-V600E mutations have variable kinase activity and response to these agents.

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Trials at SCCA

• First Line EGFR Targeting with CO-1686
• BRAF
• MET
Original Article

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

N Engl J Med
Volume 366(26):2455-2465
June 28, 2012
CheckMate-017

- 272 Patients
  Squamous Cell Carcinoma of Lung
  One prior platinum line
  PS 0-1

- Docetaxe 75mg/m² q 3 weeks
- Nivolumab 3mg/kg q 2 weeks (PD-1 antibody)

- PD-L1 status not used for inclusion
- Primary endpoint: Overall Survival

Brahmer J et al Published online on May 31, 2015
Results

• Former/current smoker: 92%
• No CNS metastases: 94%
• ORR: 20% (N) and 9% (D)
• Median follow-up: 11 months
• Median duration of response of nivolumab: not reached
• PFS at 1 year: 21% (N) and 6% (D)
### Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (N = 131)</th>
<th></th>
<th>Docetaxel (N = 129)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>76 (58)</td>
<td>9 (7)</td>
<td>111 (86)</td>
<td>71 (55)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (16)</td>
<td>1 (1)</td>
<td>42 (33)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (11)</td>
<td>1 (1)</td>
<td>25 (19)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (10)</td>
<td>0</td>
<td>18 (14)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (9)</td>
<td>0</td>
<td>30 (23)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (8)</td>
<td>0</td>
<td>26 (20)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (5)</td>
<td>0</td>
<td>9 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (5)</td>
<td>0</td>
<td>10 (8)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (4)</td>
<td>0</td>
<td>8 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (2)</td>
<td>0</td>
<td>12 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2)</td>
<td>0</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2)</td>
<td>0</td>
<td>28 (22)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (1)</td>
<td>0</td>
<td>15 (12)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>8 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>0</td>
<td>42 (33)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>14 (11)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
<td>29 (22)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
Results

• Median survival improvement: 3.2 months (9.2 months vs 6 months)
### Overall and Progression-free Survival According to PD-L1 Expression Level

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
<th>Unstratified Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>63</td>
<td>56</td>
<td>0.69 (0.45–1.05)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>54</td>
<td>52</td>
<td>0.58 (0.37–0.92)</td>
</tr>
<tr>
<td>≥5%</td>
<td>42</td>
<td>39</td>
<td>0.53 (0.31–0.89)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>75</td>
<td>69</td>
<td>0.70 (0.47–1.02)</td>
</tr>
<tr>
<td>≥10%</td>
<td>36</td>
<td>33</td>
<td>0.50 (0.28–0.89)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>81</td>
<td>75</td>
<td>0.70 (0.48–1.01)</td>
</tr>
<tr>
<td>Not quantifiable at baseline</td>
<td>18</td>
<td>29</td>
<td>0.39 (0.19–0.82)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>63</td>
<td>56</td>
<td>0.67 (0.44–1.01)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>54</td>
<td>52</td>
<td>0.66 (0.43–1.00)</td>
</tr>
<tr>
<td>≥5%</td>
<td>42</td>
<td>39</td>
<td>0.54 (0.32–0.90)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>75</td>
<td>69</td>
<td>0.75 (0.52–1.08)</td>
</tr>
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<td>33</td>
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<td>0.45 (0.23–0.89)</td>
</tr>
</tbody>
</table>
CheckMate 057

• Randomized phase III of nivolumab vs docetaxel in previously treated advanced “non-squamous” NSCLC
• One prior platinum doublet (maintenance allowed)
• No PD-L1 expression required but tissue submission was a requirement
• Nivolumab 3mg/kg Q2weeks vs docetaxel 75mg/m^2 Q3weeks
• Primary endpoint: Overall survival
Results

• Interim analysis with 93% of the events of the final analysis declared the superiority of nivolumab

• PD-L1 expression:

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>53%</td>
<td>55%</td>
</tr>
<tr>
<td>≥5%</td>
<td>41%</td>
<td>38%</td>
</tr>
<tr>
<td>≥10%</td>
<td>37%</td>
<td>35%</td>
</tr>
</tbody>
</table>

• 22% did not have enough tissue for evaluation
Results

• Median survival:
  12.2 months Nivolumab
  9.4 months Docetaxel p=0.0015; HR 0.73
• 1 year survival:
  51% Nivolumab
  39% Docetaxel
• Two subsets did not benefit in the subgroup analysis:
  EGFR mut (+) and never smokers
• ORR: 19% (N) and 12% (D) p=0.02
• Median duration of response:
  17.2 months (N) and 5.6 months (D)
Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, mo</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.92 (95% CI: 0.77, 1.11); P = 0.3932</td>
<td></td>
</tr>
</tbody>
</table>

1-yr PFS rate = 19% for Nivolumab and 8% for Docetaxel.

Number of Patients at Risk:
- Nivolumab: 292, 128, 82, 58, 38
- Docetaxel: 290, 156, 87, 58

Time (months):
- 12 months: 46, 35, 17, 7, 1
- 18 months: 18, 6, 2, 1
- 24 months: 1, 1
- 27 months: 0
Overall Survival

<table>
<thead>
<tr>
<th></th>
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<th>Docetaxel (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mo</td>
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<tr>
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1-yr OS rate = 51%
1-yr OS rate = 39%
OS by PD-L1 Expression

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>Nivo mOS (mo)</th>
<th>Doc mOS (mo)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1%</td>
<td>17.2</td>
<td>9.0</td>
<td>0.59 (0.43, 0.82)</td>
</tr>
<tr>
<td>≥5%</td>
<td>18.2</td>
<td>8.1</td>
<td>0.43 (0.30, 0.63)</td>
</tr>
<tr>
<td>≥10%</td>
<td>19.4</td>
<td>8.0</td>
<td>0.40 (0.26, 0.59)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>10.4</td>
<td>10.1</td>
<td>0.90 (0.65, 1.24)</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>9.7</td>
<td>10.1</td>
<td>1.01 (0.77, 1.34)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>9.3</td>
<td>10.3</td>
<td>1.00 (0.76, 1.31)</td>
</tr>
</tbody>
</table>
Toxicity

• Treatment related SAEs: 7% (N) and 20% (D)
• Treatment AEs leading to discontinuation: 5% (N) and 15% (D)
• Immune toxicity of nivolumab (%G3-4): hypothyroidism 7%(0); diarrhea 8 % (1); AST 3% (0); ALT 3% (<1); pulmonary 3% (1); rash 9% (<1)
ADENOCARCINOMA, LARGE CELL, NSCLC NOS
FIRST-LINE THERAPY

PS 0-1 →
- Doublet chemotherapy (category 1)
- Bevacizumab + chemotherapy (if criteria met)

PS 2 →
- Chemotherapy

PS 3-4 →
- Best supportive care

Tumor response evaluation:
- Response or stable disease
- Progression

4-6 cycles (total)

Tumor response evaluation:
- Progression

SUBSEQUENT THERAPY

If not already given:
- Docetaxel
- Pemetrexed
- Erlotinib or Gemcitabine
- Ramucirumab + docetaxel
- Nivolumab

Erlotinib (if not already given)

Best supportive care

See NCCN Guidelines for Palliative Care

Continuation maintenance
- Bevacizumab (category 1)
- Pemetrexed (category 1)
- Bevacizumab + pemetrexed
- Gemcitabine (category 2B)

Switch maintenance
- Pemetrexed or Erlotinib

Close observation

Progression

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

References:
- See Systemic Therapy for Advanced or Metastatic Disease (NSCLC).
- See Emerging Targeted Agents for Patients With Genetic Alterations (NSCLC).
- Bevacizumab should be given until progression.
- Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
- Erlotinib versus docetaxel as second-line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. Lancet Oncol 2013; 14:981-988.
- If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
- Erlotinib may be considered for PS 3 and 4 patients with sensitizing EGFR mutations.
- If not already given, options for PS 0-2 include erlotinib, nivolumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.
Who Benefits?
Is there a Biomarker?

- Patients with tumor with (-) expression of PD-L1 have lower response. However a few do respond and there is no established method to define PD-L1 status
- Smokers may have higher response rate
- Patients with SCCa have higher benefit or larger gain vs current available therapies
mutation rates across cancer

https://www.genome.gov/Multimedia/Slides/TCGA1/TCGA1_Lawrence.pdf
Tumors With High Somatic Mutation Rate Respond Better to a PD-1 Antibody

• In the initial reports of phase I of PD-1/PD-L1 antibodies only 1 of 33 patients with metastatic colorectal cancer responded. Investigators from Johns Hopkins hypothesized and proved that this patient had a mismatched repair-deficient tumor

• Nonpolyposis colorectal cancer: inherited germline defect in 1 of 4 mismatch-repair genes

• Patients with metastatic, treatment refractory tumors in 3 cohorts:
  A. Mismatch repair deficient colorectal cancer
  B. Mismatch repair proficient colorectal cancer
  C. Mismatch repair deficient other than colorectal cancer (ampullary or cholangiocarcinoma 4; endometrial 2; small bowel 2; gastric 1)

Le Dt et al Published on line at NEJM.org on May 30, 2015
Mismatch-deficient tumors:
Mean of 1782 somatic mutations

Mismatch-proficient tumors:
Mean of 73 somatic mutations
Safety and Efficacy of First-line Nivolumab (Anti-programmed Death-1 [PD-1]) and Ipilimumab in Non-small Cell Lung Cancer (NSCLC)

Naiyer Rizvi,¹ Scott N. Gettinger,² Jonathan Goldman,³ Matthew D. Hellmann,¹ Laura Q. Chow,⁴ Rosalyn Juergens,⁵ Hossein Borghaei,⁶ Julie Brahmer,⁷ Yun Shen,⁸ Christopher Harbison,⁹ Faith Nathan,⁹ Neal E. Ready,⁹ Scott J. Antonia¹⁰

¹Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²Yale Cancer Center, New Haven, CT, USA; ³University of California, Los Angeles, Los Angeles, CA, USA; ⁴University of Washington, Seattle, WA, USA; ⁵Juravinski Cancer Centre at McMaster University, Hamilton, ON, Canada; ⁶Fox Chase Cancer Center, Philadelphia, PA, USA; ⁷The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; ⁸Bristol-Myers Squibb, Princeton, NJ, USA; ⁹Duke University Medical Center, Durham, NC, USA; ¹⁰H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

*Current affiliation: Columbia University Medical Center, New York, NY, USA
CheckMate 012: Previously Presented Advanced NSCLC Cohorts

<table>
<thead>
<tr>
<th></th>
<th>ASCO 2015 (n = 52)</th>
<th>ESMO 2014 (n = 56)</th>
<th>CMSTO 2014 (n = 24)</th>
<th>CMSTO 2014 (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>23</td>
<td>33–47</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Estimated mDOR, 6 wks</td>
<td>NR</td>
<td>23.9–NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1-yr OS rate, %</td>
<td>74</td>
<td>50–87</td>
<td>65</td>
<td>44</td>
</tr>
<tr>
<td>Treatment-related AEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>71</td>
<td>93</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>19</td>
<td>45</td>
<td>58</td>
<td>44</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Treatment-related deaths, n</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

*Based on a March 2015 DBL; †Based on a September 2014 DBL. Nivolumab plus ipilimumab (x4 cycles) was followed by nivolumab 3 mg/kg Q3W as maintenance therapy until disease progression or unacceptable toxicity. *Time from first response to documented progression, death within 100 days of last nivolumab dose, or last tumor assessment (for censored data).
<table>
<thead>
<tr>
<th></th>
<th>Nivo 1 + ipl 1 Q3W (n = 31)</th>
<th>Nivo 1 Q2W + ipl 1 Q6W (n = 40)</th>
<th>Nivo 3 Q2W + ipl 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + ipl 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Treatment-related AEs, %</td>
<td>77</td>
<td>29</td>
<td>73</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>13</td>
<td>10⁺</td>
<td>8</td>
<td>8⁺</td>
<td>5</td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of doses (range)</td>
<td>4 (1–42)</td>
<td>7 (1–26)</td>
<td>13 (1–26)</td>
<td>8 (1–25)</td>
<td>8 (1–62)</td>
</tr>
<tr>
<td>Median duration of therapy, wks (range)</td>
<td>12.0 (3.0–92.0)</td>
<td>16.0 (2.0–59.0)</td>
<td>28.7 (2.0–52.0)</td>
<td>18.0 (2.0–53.0)</td>
<td>16.0 (2.0–129.6)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of doses (range)</td>
<td>NC</td>
<td>3 (1–9)</td>
<td>3 (1–5)</td>
<td>2 (1–9)</td>
<td>NA</td>
</tr>
<tr>
<td>Median duration of therapy, wks (range)</td>
<td>11.6 (3.0–24.0)</td>
<td>17.6 (6.0–59.0)</td>
<td>35.7 (12.0–60.0)</td>
<td>15.0 (6.0–54.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Results for Nivo 3 Q2W are reported based on a March 2015 DBL; ⁺Increased AST, rash, and pneumonitis (n = 1 each); ²Autoimmune hepatitis (n=2), increased ALT, and increased AST (n = 1 each); ³Transaminase, encephalopathy, facial nerve disorder, rash, and pneumonitis (n = 1 each); ⁴Increased lipase, increased ALT, increased AST, cardiac failure, hyperglycemia, and pneumonitis (n = 1 each); ⁵Median number of ipilimumab doses was not calculated as patients received a maximum of 4 doses.

• There were no treatment-related deaths
## Summary of Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Nivo 1 + Ipi 1 Q3W (n = 31)</th>
<th>Nivo 1 Q2W + Ipi 1 Q6W (n = 40)</th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</th>
<th>Nivo 3 Q2W* (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, % (95% CI)</strong></td>
<td>13 (4, 30)</td>
<td>25 (13, 41)</td>
<td>39 (24, 57)</td>
<td>31 (17, 48)</td>
<td>23 (13, 37)</td>
</tr>
<tr>
<td><strong>Confirmed DCR, % (95% CI)</strong></td>
<td>55 (36, 73)</td>
<td>58 (41, 73)</td>
<td>74 (57, 87)</td>
<td>51 (35, 68)</td>
<td>50 (36, 64)</td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Partial response</td>
<td>13 (41)</td>
<td>25 (41)</td>
<td>39 (57)</td>
<td>31 (55)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Unconfirmed partial response</td>
<td>3 (10)</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>8 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>42 (36, 71)</td>
<td>NC</td>
<td>34 (44, 76)</td>
<td>NC</td>
<td>27 (21, 34)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>35 (30)</td>
<td>30 (28)</td>
<td>13 (10)</td>
<td>26 (18)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>6 (5)</td>
<td>10 (9)</td>
<td>8 (7)</td>
<td>15 (13)</td>
<td>12 (10)</td>
</tr>
<tr>
<td><strong>PFS rate at 24 wks, % (95% CI)</strong></td>
<td>55 (36, 71)</td>
<td>NC</td>
<td>63 (44, 76)</td>
<td>NC</td>
<td>41 (27, 54)</td>
</tr>
<tr>
<td><strong>Median PFS, mos (95% CI)</strong></td>
<td>10.6 (2.1, 16.3)</td>
<td>4.9 (2.8)</td>
<td>8.0 (4.2)</td>
<td>8.3 (2.6)</td>
<td>3.6 (2.3, 6.6)</td>
</tr>
<tr>
<td><strong>Median OS, mos (95% CI)</strong></td>
<td>NR (11.5)</td>
<td>NR (8.9)</td>
<td>NR</td>
<td>NR</td>
<td>22.6 (14.9)</td>
</tr>
<tr>
<td><strong>Median length of follow-up, mos (range)</strong></td>
<td>16.6 (1.8–24.5)</td>
<td>6.2 (0.4–13.1)</td>
<td>8.4 (0.9–12.3)</td>
<td>7.7 (1.1–12.2)</td>
<td>14.3 (0.2–30.1)</td>
</tr>
</tbody>
</table>

- Median DOR was not reached in any arm
- Unconventional immune-related responses were observed in arms Nivo 3 Q2W + Ipi 1 Q12W (n = 2), Nivo 3 Q2W + Ipi 1 Q6W (n = 1) and Nivo 3 Q2W (n = 3)
- PFS: progression-free survival
- OS: overall survival
- DOR: duration of response

*Results for Nivo 3 Q2W are reported based on a March 2015 DBL
Atezolizumab (MPDL3280A) combined with platinum-based chemotherapy in non-small cell lung cancer (NSCLC): a phase Ib safety and efficacy update

D. Ross Camidge,1 Stephen V. Liu,2 John Powderly,3 Neal E. Ready,4 F. Stephen Hodi,5 Scott N. Gettinger,6 Giuseppe Giaccone,2 Bo Liu,7 Jeffrey Wallin,7 Roel Funke,7 Daniel Waterkamp,7 Rebecca S. Heist8

1University of Colorado, Aurora, CO; 2Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC; 3Carolina BioOncology Institute, Huntersville, NC; 4Duke University Medical Center, Durham, NC; 5Dana-Farber Cancer Institute, Boston, MA; 6Yale Cancer Center, New Haven, CT; 7Genentech, Inc., South San Francisco, CA; 8Massachusetts General Hospital, Boston, MA
## Summary of safety data

One event of Grade 5 candidemia after prolonged neutropenia in Arm D was assessed by the investigator as related to atezolizumab.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm C – cb/pac (n=14)</th>
<th>Arm D – cb/pem (n=24)</th>
<th>Arm E – cb/nab (n=20)</th>
<th>All NSCLC patients (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>14 (100)</td>
<td>24 (100)</td>
<td>19 (95.0)</td>
<td>57 (98.3)</td>
</tr>
<tr>
<td>Any grade 3/4 AE</td>
<td>11 (78.6)</td>
<td>16 (66.7)</td>
<td>18 (90.0)</td>
<td>45 (77.6)</td>
</tr>
<tr>
<td>Any treatment-related grade 3/4 AE</td>
<td>10 (71.4)</td>
<td>13 (54.2)</td>
<td>17 (85.0)</td>
<td>40 (69.0)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>5 (35.7)</td>
<td>10 (41.7)</td>
<td>8 (40.0)</td>
<td>23 (39.7)</td>
</tr>
<tr>
<td>Any grade 5 AE</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Any treatment-related grade 5 AE</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td>0 (0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Treatment interruptions due to an AE</td>
<td>2 (14.3)</td>
<td>8 (33.3)</td>
<td>16 (80.0)</td>
<td>26 (44.8)</td>
</tr>
<tr>
<td>Atezolizumab withdrawals due to an AE</td>
<td>0 (0)</td>
<td>1 (4.2)</td>
<td>1 (5.0)</td>
<td>2 (3.4)</td>
</tr>
</tbody>
</table>

Data cut-off: 10 Feb 2015; median treatment exposure was 5.5 cycles in Arm A, 5.5 cycles in Arm D and 6.0 cycles in Arm E.
Summary of response by RECIST v1.1 (response-evaluable patients*)

- Data are preliminary; ~25 patients will be included in each arm for final analysis

<table>
<thead>
<tr>
<th></th>
<th>Arm C – cb/pac (n=8)</th>
<th>Arm D – cb/perm (n=17)</th>
<th>Arm E – cb/nab (n=16)</th>
<th>All NSCLC patients (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response, n (ORR %)</td>
<td>4 (50.0)</td>
<td>13 (76.5)</td>
<td>9 (56.3)</td>
<td>26 (63.4)</td>
</tr>
<tr>
<td>[95% CI for ORR]</td>
<td>[15.7–84.3]</td>
<td>[50.1–93.2]</td>
<td>[29.9–80.3]</td>
<td>[46.9–77.9]</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (25.0)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>4 (50.0)</td>
<td>13 (76.5)</td>
<td>5 (31.3)</td>
<td>22 (53.7)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>4 (50.0)</td>
<td>1 (5.9)</td>
<td>4 (25.0)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>0 (0)</td>
<td>2 (11.8)</td>
<td>2 (12.5)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Missing or not evaluable, n (%)</td>
<td>–</td>
<td>1 (5.9)</td>
<td>1 (6.3)</td>
<td>2 (4.9)</td>
</tr>
</tbody>
</table>

*Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015
Thank you!