ASCO 2019 update

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Disclosures

• Full time NHS Consultant

• Advisory
  • Boehringer Ingelheim
  • AstraZeneca
  • Roche
  • BMS
  • MSD
  • Pfizer
  • Lilly
  • Novartis
  • Takeda
Disclaimer

• Specifically tailored to current UK practice standards
Immunotherapy
Nivolumab in previously treated patients: 5 year survival data

Overall Study Population (n=129)

Patients with PD-L1 ≥50% (n=13)

Gettinger et al. JCO. 2018
5-Year Long-Term Overall Survival for Patients With Advanced NSCLC Treated With Pembrolizumab: Results From KEYNOTE-001


1David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica, CA, USA; 2Memorial Sloan Kettering Cancer Center, New York, NY, USA; 3Catalan Institute of Oncology Badalona, Badalona, Spain; 4Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Samsung Medical Center, Seoul, South Korea; 6Yale University, New Haven, CT, USA; 7The Angeles Clinic and Research Institute, Los Angeles, CA, USA; 8Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA, USA; 9Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; 10South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; 11University of California, San Francisco, San Francisco, CA, USA; 12Winship Cancer Institute of Emory University, Atlanta, GA, USA; 13Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology, Barcelona, Spain; 14Merck & Co., Inc., Kenilworth, NJ, USA; 15Westmead Hospital and the University of Sydney, Sydney, NSW, Australia

Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
KEYNOTE-001 (NCT01295827)

- Multicohort phase 1b study of pembrolizumab monotherapy in patients with treatment-naive or previously treated locally advanced NSCLC\textsuperscript{1,2}
  - Treatment-naive (N = 101): no prior therapy for advanced NSCLC; no \textit{EGFR} mutation or ALK translocation.
  - Previously treated (N = 449): \geq 1 line of prior therapy for advanced NSCLC.

- Current analysis provides 5-year OS and long-term safety outcomes in KEYNOTE-001.
  - Longest efficacy and safety follow-up of pembrolizumab for advanced NSCLC.

- At time of analysis (November 5, 2018)
  - Median follow-up: 60.6 mo (range, 51.8–77.9 mo).
  - Of 550 patients enrolled, 100 were alive at data cutoff.
  - 60 received \geq 2 years treatment (treatment-naive, n = 14; previously treated, n = 46).

Figure 3. Incidence of Immune-Mediated AEs at 3 Years (September 6, 2016) and at 5 Years (November 5, 2018) Follow-Up

Immune-mediated AEs were classified based on a list of preferred terms identified by the sponsor as having an immune etiology. Because there were changes in events included in this list between the 3- and 5-year analyses, certain events classified as immune-mediated at 3-years may not have been so-classified at 5-years.
• Pembrolizumab provided a clinically meaningful improvement in OS compared with rates that were achieved before the introduction of immunotherapies
  — 5-year OS in KEYNOTE-001 was 23.2% in patients with treatment-naive NSCLC and 15.5% in patients with previously treated NSCLC
  — 5-year OS rate in the United States between 2008 and 2014 was 5.5% in patients with metastatic NSCLC using standard-of-care cytotoxic chemotherapies\(^6\)
• 5-year OS rate with pembrolizumab monotherapy was at least 25% in patients with PD-L1 TPS ≥50%
  — The association between tumor PD-L1 expression and efficacy outcomes is consistent with data from randomized controlled trials (albeit with more limited follow-up) including KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042\(^2,4,7\)
• Among the 60 patients who received ≥2 years of pembrolizumab treatment, more than 85% had an objective response, the 5-year OS rate exceeded 75%, and 77% were alive at data cutoff
• Updated safety data are consistent with the known safety profile of pembrolizumab,\(^1,5\) with no evidence of cumulative immune-mediated toxicity or of late-onset grade 3–5 toxicity
• These 5-year data, which represent the longest follow-up to date of pembrolizumab treatment in patients with advanced NSCLC, continue to demonstrate the potential of pembrolizumab treatment to improve long-term outcomes for treatment-naive and previously treated patients with advanced NSCLC
Abstract 9012: IMpower150: Analysis of efficacy in patients with liver metastases: Study Design

Stage IV or recurrent metastatic nonsquamous NSCLC
Chemotherapy naive
Tumor tissue available for biomarker testing
Any PD-L1 IHC status

Stratification factors:
- Sex
- PD-L1 IHC expression
- Liver metastases
N = 1202

Maintenance therapy
(no crossover permitted)

R 1:1:1

Atezolizumab\(^{a,b}\) + Carboplatin\(^{a}\) + Paclitaxel\(^{a}\)
(ACP)
4 or 6 cycles

Atezolizumab\(^{a}\)

Treated with atezolizumab until PD per RECIST
v1.1 or loss of clinical benefit
and/or
Treated with bevacizumab until PD per RECIST
v1.1

Bevacizumab\(^{a}\) + Carboplatin\(^{a}\) + Paclitaxel\(^{a}\)
(BCP)
4 or 6 cycles

Bevacizumab\(^{a}\)

Co-primary objectives
- Investigator-assessed PFS in ITT-WT
- Investigator-assessed PFS in Teff-high WT
- OS in ITT-WT

This analysis explored: efficacy (PFS, OS, ORR, DOR) and safety of the ACP regimen in patients with liver metastases at baseline

Abst 9012 Socinski et al ASCO 2019
# IMpower 150

## Kaplan-Meier Estimates of Progression-Free Survival

**Rate of Progression-free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP</td>
<td>8.3 (3.9)</td>
</tr>
<tr>
<td>BCP</td>
<td>6.8 (6.0–7.1)</td>
</tr>
</tbody>
</table>

Median in the ACP group, 8.3 mo (95% CI, 6.9–10.7).

**Rate of Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACP</td>
<td>14.7 (13.3–16.9)</td>
</tr>
<tr>
<td>BCP</td>
<td>19.2 (17.0–23.8)</td>
</tr>
</tbody>
</table>

Median in the ACP group, 14.7 mo (95% CI, 13.3–16.9).

## Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>HR</th>
<th>ABCP</th>
<th>BCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>425 (61)</td>
<td>0.55</td>
<td>8.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Female</td>
<td>267 (39)</td>
<td>0.73</td>
<td>8.2</td>
<td>6.8</td>
</tr>
<tr>
<td>65–74 years</td>
<td>375 (54)</td>
<td>0.65</td>
<td>8.0</td>
<td>6.8</td>
</tr>
<tr>
<td>75–84 years</td>
<td>248 (36)</td>
<td>0.52</td>
<td>9.7</td>
<td>6.9</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>282 (41)</td>
<td>0.78</td>
<td>9.7</td>
<td>6.8</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>404 (58)</td>
<td>0.64</td>
<td>7.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Current/previous smoker</td>
<td>598 (84)</td>
<td>0.58</td>
<td>8.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Never smoker</td>
<td>108 (16)</td>
<td>0.80</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>94 (14)</td>
<td>0.42</td>
<td>7.4</td>
<td>4.9</td>
</tr>
<tr>
<td>No liver metastases</td>
<td>598 (86)</td>
<td>0.63</td>
<td>8.3</td>
<td>7.0</td>
</tr>
<tr>
<td>ARAS mutant</td>
<td>80 (12)</td>
<td>0.50</td>
<td>8.1</td>
<td>5.8</td>
</tr>
<tr>
<td>ARAS WT</td>
<td>124 (18)</td>
<td>0.47</td>
<td>9.7</td>
<td>5.8</td>
</tr>
<tr>
<td>ARAS unknown</td>
<td>488 (71)</td>
<td>0.87</td>
<td>8.3</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Socinski et al NEJM 2018
A. With Liver Metastases
   ABCP vs BCP

   HR, 0.41
   (95% CI: 0.26, 0.62)

   Median, 8.2 mo
   (95% CI: 5.7, 10.3)

   Median, 5.4 mo
   (95% CI: 4.1, 6.0)

   No. at risk
   AUCB
   ABCP 52 44 42 29 16 11 10 6 6 3 1 1
   BCP 57 45 35 21 12 10 6 6 3 1 1

B. Without Liver Metastases
   ABCP vs BCP

   HR, 0.61
   (95% CI: 0.52, 0.73)

   Median, 7.0 mo
   (95% CI: 6.4, 7.0)

   Median, 8.4 mo
   (95% CI: 8.0, 10.3)

   No. at risk
   AUCB
   ABCP 349 308 294 233 169 155 124 84 66 52 34 23 12 6 6 1 1
   BCP 343 308 262 192 143 101 73 42 25 15 7 2 2 1 1

With Liver Metastases
   ACP vs BCP

   HR, 0.82
   (95% CI: 0.55, 1.21)

   Median, 5.4 mo
   (95% CI: 4.1, 6.0)

   No. at risk
   AUCB
   ACP 53 43 35 21 18 11 8 8 7 5 3 3 1 1
   BCP 57 45 35 21 12 10 6 6 3 1 1

Without Liver Metastases
   ACP vs BCP

   HR, 0.40
   (95% CI: 0.77, 1.03)

   Median, 5.9 mo
   (95% CI: 5.8, 7.1)

   Median, 6.9 mo
   (95% CI: 6.4, 7.9)

   No. at risk
   AUCB
   ACP 349 308 294 233 169 155 143 97 91 59 43 28 22 13 6 3 1
   BCP 343 308 262 192 143 101 73 42 25 15 7 6 2 3 1

PFS

Abst 9012 Socinski et al ASCO 2019
With Liver Metastases

**ABCP vs BCP**

- **Overall Survival (%)**
  - **Median, 13.3 mo**
    - (95% CI: 11.6, 26.1)
  - **HR, 0.52**
    - (95% CI: 0.33, 0.82)

**Without Liver Metastases**

**ABCP vs BCP**

- **Overall Survival (%)**
  - **Median, 9.4 mo**
    - (95% CI: 7.9, 11.7)
  - **HR, 0.82**
    - (95% CI: 0.66, 1.02)

With Liver Metastases

**ACP vs BCP**

- **Overall Survival (%)**
  - **Median, 8.9 mo**
    - (95% CI: 6.5, 12.6)
  - **HR, 0.87**
    - (95% CI: 0.87, 1.32)

**Without Liver Metastases**

**ACP vs BCP**

- **Overall Survival (%)**
  - **Median, 17.0 mo**
    - (95% CI: 14.4, 19.2)
  - **HR, 0.84**
    - (95% CI: 0.68, 1.04)
In patients with NSCLC, presence of liver metastases represents a poor prognostic factor, with higher rates of PD due to new lesions vs those without liver metastases, which might be suggestive of more aggressive or dispersed disease in these patients.

Improved clinical outcomes with ABCP vs BCP were observed in patients with and without liver metastases.
- Higher ORR and durable DOR were also seen with ABCP vs BCP in patients with liver metastases.

Interaction tests suggested a trend towards improved PFS and OS favoring ABCP in patients with liver metastases; lack of statistical significance is likely due to small sample size.

Patients with liver metastases showed a greater survival benefit with ABCP vs BCP than patients without baseline liver metastases (OS HR, 0.52 vs 0.82).

ABCP was well tolerated regardless of baseline liver metastases status.
- The safety profile of ABCP in patients with liver metastases remained consistent with that observed in the ITT population; there were no new safety signals in this patient subgroup.

ABCP is an important new treatment option for patients with advanced nonsquamous NSCLC, particularly those with liver metastases.
Spatial and Temporal Heterogeneity of PD-L1 and its Impact on Benefit from Immune Checkpoint Blockade in Non-Small Cell Lung Cancer (NSCLC)

Lingzhi Hong1, Marcelo V. Negrao2, Seyyedeh Diba3, Alexandre Reuben4, Emily B. Roarty4, Ferdinandos Skoulidis5, Kyle G. Mitchell6, Carl M. Gray7, Tina Cascone7, Hai T. Tran7, Lauren Byers7, Boris Sepesi4, Warree Rinsurongkawong7, Jeff Lewis7, Don L. Gibbons7, Vassiliki Papadimitrakopoulou5, Bonnie S. Glisson1, George R. Blumenschein Jr1, P. Andrew Futreal8, Ignacio I. Wistuba1, Jack A. Roth1, Stephen G. Swisher9, George Simon7, J. Jack Lee7, John V. Heymach1, Jianjun Zhang1

1Department of Thoracic / Head and Neck Medical Oncology, 2Department of Biostatistics, 3Department of Thoracic and Cardiovascular Surgery, 4Department of Genomic Medicine, 5Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer center, Houston, TX

Abst 9017 Hong et al ASCO 2019
PD-L1 varies at different anatomic sites.

Fig 2. PD-L1 tumor proportion score (TPS) stratified by biopsy sites. LN: Lymph Node

PD-L1 changes over time with or without treatment

Fig 4. Changes of PD-L1 TPS in NSCLC patients treated with anticancer treatment. PD-L1 TPS (post-pre)= TPS of second biopsy - TPS of first biopsy.

Temporal heterogeneity impacts the predictive value of PD-L1 on ICI treatment

Fig 5. KM curves of PFS in metastatic NSCLC by different time points associated with PD-L1 expression TPS at 1% cutoff (A,C) and 50% cutoff (B,D). (A,B): New biopsy was defined as the biopsy was obtained within 90 days before initiating ICI treatment and patients did not receive other therapy between biopsy and ICI treatment. (C,D): Old biopsy was defined as the biopsy was obtained more than 90 days before initiating ICI treatment regardless of whether patients received other therapies between biopsy and ICI treatment.

- Liver and adrenal specimens had the highest PD-L1 expression, while specimens from brain and bone demonstrated the lowest expression.
- Prior treatment with ICIs is associated with lower PD-L1 expression.
- PD-L1 in LN biopsies may not be reliable to predict clinical benefit for ICIs in NSCLC.
- When PD-L1 is used to choose NSCLC patients for ICI treatment, new biopsy and PD-L1 staining should be strongly considered.
What does this mean for UK?

- We have access to 1\textsuperscript{st} line chemoIO across all PDL1 (KN189/IM150)
- We have access to 1\textsuperscript{st} line single agent IO for PDL1 high (KN24)
- We have access to IO single agent in subsequent lines (P/A/N)
- We have access to IO post CRT in PDL1 >1%

- Long term survival data is a game changer
- Need to ensure all eligible patients get access to IO at an appropriate timepoint in their illness.
- Remember “drop off”
- Set up pathways for tox identification and intervention
MET exon14 skipping mutations

- Abst 9004
- Abst 9005
- Abst 9006
Targeting \textit{MET}ex14-mutated NSCLC—Abstracts

• 9004—Wolf J et al. \textit{Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): Efficacy data from the phase II GEOMETRY mono-1 study.}

• 9005—Paik PK et al. Phase II study of \textit{tepotinib} in NSCLC patients with \textit{MET}ex14 mutations.

• 9006—Guo R et al. \textit{MET inhibitor resistance} in patients with \textit{MET} exon 14-altered lung cancers.
**MET ex14 alterations in NSCLC**

- MET mutations can lead to decreased MET degradation
  - deletions, insertions, or base substitutions
  - disrupt splice sites flanking MET exon 14 \(\rightarrow\) exon 14 skipping
  - absence of JM domain, Cbl ubiquitination process inhibited
  - increased MET receptor on the tumor cell surface

Adapted from Drilon et al J Thorac Oncol 2016


Slides courtesy of Reckamp (Discussant) ASCO 2019
Patients with MET ex 14

- Older age, median 72.5y
  - increased comorbidities
  - may not undergo biopsy for additional testing
- Smokers and never smokers
- Sarcomatoid, pleomorphic histology
- Mutually exclusive with other driver alterations
- Over 100 different genomic variants


Slides courtesy of Reckamp (Discussant) ASCO 2019
# MET inhibitors in clinical trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Other Molecular Targets</th>
<th>IC$_{50}$ (nM)$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>MET (type la), ALK, ROS1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Capmatinib</td>
<td>selective MET (type Ib)</td>
<td>0.13</td>
</tr>
<tr>
<td>Tepotinib</td>
<td>selective MET (type Ib)</td>
<td>3</td>
</tr>
<tr>
<td>Savolitinib</td>
<td>selective MET (type Ib)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>MET (type II), VEGFR, RET, TIE2, AXL, FLT3, KIT</td>
<td>1.3</td>
</tr>
<tr>
<td>Merestinib</td>
<td>MET (type II), MST1R, FLT3, MERTK, TEK, ROS1, DDR, NTRK, AXL</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Type I—binds ATP-binding pocket in the active conformation; **Ib more highly specific**
Type II—binds ATP-binding pocket in the inactive conformation; potency is more variable
GEOMETRY mono-1: A phase II trial of capmatinib in patients with advanced NSCLC harboring MET exon14 skipping mutation

- Stage IIIB/IV NSCLC
- METΔex14 irrespective of MET GCN by central RT-PCR
- EGFR wt (for L858R and delE19) and ALK-negative
- PS 0–1
- ≥1 measurable lesion (RECIST 1.1)
- Neurologically stable or asymptomatic brain metastases allowed

Study methodology:
- Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
- Primary (ORR) and key secondary (DOR) endpoints based on BIRC including 2 parallel independent radiology reviewers (+ additional one for adjudication)
- Efficacy endpoints based on BIRC and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on MET mutated patients will be generated in Cohort 6 (2L; N=30) and Cohort 7 (1L; N=27)

Primary endpoint
- ORR by blinded independent central review (BIRC)
- Secondary endpoints
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Safety
### Best overall response (pretreated cohort 4)

*All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Cohort 4 (2/3L)</th>
<th>BIRC</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>0</td>
<td>1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td>28 (40.6)</td>
<td>28 (40.6)</td>
<td></td>
</tr>
<tr>
<td>Stable Disease</td>
<td>25 (36.2)</td>
<td>22 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>1 (1.4)</td>
<td>2 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>6 (8.7)</td>
<td>7 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>9 (13.0)</td>
<td>9 (13.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall response rate (ORR) %, (95% CI)</strong></td>
<td>40.6 (28.9, 53.1)</td>
<td>42.0 (30.2, 54.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease control rate (DCR) %, (95% CI)</strong></td>
<td>78.3 (66.7, 87.3)</td>
<td>76.8 (65.1, 86.1)</td>
<td></td>
</tr>
</tbody>
</table>

*not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks

BIRC, blinded independent review committee; CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD+non-CR/non-PD); ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; SD, stable disease
# Best overall response (treatment naive cohort 5b)

All responses confirmed per RECIST 1.1

Response rates consistent between BIRC and investigator assessment

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Cohort 5b (1L)</th>
<th>BIRC</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (3.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial Response</td>
<td>18 (64.3)</td>
<td>17 (60.7)</td>
<td></td>
</tr>
<tr>
<td>Stable Disease</td>
<td>8 (28.6)</td>
<td>10 (35.7)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (3.6)</td>
<td>1 (3.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall response rate (ORR) %, (95% CI)</strong></td>
<td><strong>67.9 (47.6, 84.1)</strong></td>
<td><strong>60.7 (40.6, 78.5)</strong></td>
<td></td>
</tr>
<tr>
<td>Disease control rate (DCR) %, (95% CI)</td>
<td><strong>96.4 (81.7, 99.9)</strong></td>
<td>**96.4 (81.7, 99.9)</td>
<td></td>
</tr>
</tbody>
</table>
**Duration of Response per BIRC**

Median DOR was 9.72 months in Cohort 4 (2/3L) and 11.14 months in Cohort 5b (1L)

- Kaplan-Meier median [95% CI] (months): 9.72 [5.55, 12.98]
- Event-free rate at 12 months [95% CI]: 31.8% [14.8, 50.3]

Median DOR per investigator was 8.31 months [95% CI: 4.34, 12.06] in Cohort 4 and 13.96 months [95% CI: 4.27, NE] in Cohort 5b

n is the number of events, N is the number of patients

Abst 9004 Wolf et al ASCO 2019
**Progression-free survival per BIRC**

**Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5b (1L)**

Kaplan-Meier median [95% CI] (months): 5.42 [4.17, 6.97]
Event-free rate at 12 months (95% CI): 25.8% (15.9, 36.9)

Kaplan-Meier median [95% CI] (months): 9.69 [5.52, 13.86]
Event-free rate at 12 months (95% CI): 49.7% (29.3, 67.1)

**Median PFS per investigator was 4.80 months (95% CI: 4.11, 7.75) in Cohort 4 and 11.14 months (95% CI: 5.52, 15.24) in Cohort 5b**

$n$ is the number of events, $N$ is the number of patients
BIRC neuro-radiologist review confirms activity against brain metastases

- 13 evaluable patients with brain metastasis at baseline by BIRC [3.3 brain lesions/patient (range 1–8)].

- 54% (n=7/13) had intracranial response*: o 4 patients had complete resolution of all brain lesions o The other 3 responding patients had: ➢ complete resolution in 3 lesions, -50% reduction in 1 lesion, stabilization in remaining 4 lesions (total of 7 lesions) ➢ Complete resolution in 2 lesions, stabilization in 1 remaining lesion (total of 3 lesions) ➢ Complete resolution in 1 lesion, stabilization in 3 remaining lesions (total of 4 lesions)

- Intracranial responses were as fast as responses in extracranial lesions.

- Intracranial disease control achieved in 12/13 patients.

* All responses were confirmed at next staging

73 year old, female patient with multiple brain metastases treated with WBRT and pembrolizumab (PD-L1 85%).
- Progression after 3 cycles, both systemic and intracranial [3 new metastases and progression on pre-existing lesions].
- Feb 2018: start of capmatinib.
- Brain response since first CT scan; complete resolution of all lesions by 2nd post baseline CT scan at 12 weeks.
- Systemic PR; patient still ongoing and in response after 15+ months.
CT images courtesy Dr. Johan Vansteenkiste (University Hospitals KU Leuven), informed consent by the patient.
Tumor shrinkage by MET alterations

- Deep responses and DOR were observed independently of type of MET mutation (SNV, Indel) leading to METΔex14 or co-occurrence of MET amplification.

- MET mutations could be detected by both RT-PCR and NGS
  - High concordance (99%) between NGS and RT-PCR in detection of METΔex14 in tumor tissue

---

1. 73 tissue samples, Cohort 4-53 (including 1 patient with a noncanonical METΔex14 rearrangement and no canonical variants), Cohort 5b=20.
2. SNV, Single nucleotide variant in MET leading to Ex14 skipping; Indel, Insertion or deletion leading to METEx14; AMP_NGS, amplification detected by FM NGS panel ≥ 6 GCN; AMP_FISH, MET FISH copy number
### Safety summary

**Favorable and manageable safety profile**

<table>
<thead>
<tr>
<th>Most common adverse events - treatment related (≥10%, all grades), n (%)</th>
<th>All Patients N = 334</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Any</td>
<td>282 (84.4)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>139 (41.6)</td>
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<tr>
<td>Nausea*</td>
<td>111 (33.2)</td>
</tr>
<tr>
<td>Increased blood creatinine†</td>
<td>65 (19.5)</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>63 (18.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46 (13.8)</td>
</tr>
<tr>
<td>Decreased appetite*</td>
<td>42 (12.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38 (11.4)</td>
</tr>
</tbody>
</table>

- Safety determined in the largest dataset of MET dysregulated† NSCLC patients (N=334).
- Median treatment exposure time: 14.9 weeks
- Capmatinib was well tolerated with few Grade 3/4 events [only 15 patients (4.5%) had Grade 4 events]
- Dose adjustment due to treatment related AE: 73 (21.9%)
- Discontinuation due to treatment related AE: 37 (11.1%)
  - Most frequent (≥ 1%): peripheral edema (n=6, 1.8%), pneumonitis (n=5, 1.5%) and fatigue (n=5, 1.5%)
- Serious treatment related AEs: 43 (12.9%)

* Capmatinib administered in fasting conditions; food restriction removed in new cohorts 6 and 7
† Capmatinib is known to inhibit creatinine transporters
‡ MET mutated/amplified
Conclusions

- Capmatinib has demonstrated clinically meaningful efficacy in advanced NSCLC patients harboring $MET\Delta ex14$ mutations.
  - Responses were rapid, deep with meaningful duration regardless of the line of therapy.
    - **Cohort 5b (1L):** ORR 67.9%, mDOR 11.14 months
    - **Cohort 4 (2/3L):** ORR 40.6%, mDOR 9.72 months
  - The higher ORR in treatment-naive $MET\Delta ex14$ mutated patients highlights the importance of early molecular testing.

- Capmatinib also demonstrated efficacy in patients with brain metastases.

- As with other molecular drivers, tumors harboring $MET\Delta ex14$ mutations have low TMB.

- Efficacy of capmatinib seems independent of type of MET genetic alteration leading to $MET\Delta ex14$ or co-occurrence of MET amplification.

- Capmatinib was well-tolerated with a manageable safety profile.

**Capmatinib is a potent and selective MET inhibitor that represents a new potential treatment option in this rare but challenging patient population of advanced NSCLC harboring $MET\Delta ex14$ mutations.**

Orphan Drug Designation and Breakthrough Therapy Designation granted to capmatinib.
Tepotinib

- Tepotinib is a highly selective, ATP-competitive, reversible, potent MET tyrosine kinase inhibitor (TKI)
  - $IC_{50}$ ~1.7 nM
  - At 1 μM, only MET is inhibited out of a panel of over 300 kinases
- No MTD reached at 1400 mg QD; RP2D is 500 mg QD
- Preclinical brain penetration
  - High binding to rat brain tissue ($f_{ub\ br} = 0.4\%$)
  - The $K_{p,u,u}$ (ratio of free brain vs plasma concentration) in rats was 0.25, i.e. 25% of free tepotinib levels in brain, relative to levels found in plasma
- Complete brain and systemic response lasting almost 1 year in patient with NSCLC harboring MET-RB1 translocation treated with tepotinib as compassionate use (Dr Marie Florescu, MD, and Dr Raafat Alameddine at CHUM Montreal, Canada)


$f_{ub\ br}$, unbound brain fraction; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; QD, once daily; RB1, retinoblastoma gene; RP2D, recommended phase 2 dose.
VISION study design

VISION is a single-arm, phase II trial of tepotinib in patients with NSCLC harboring MET alterations (NCT02864992)

Study Design

- Stage IIIIB/IV NSCLC
  - All histologies (including squamous and sarcomatoid)
  - Exclusion of active brain metastases or brain as only measurable lesion
- Tissue- or blood-based MET alterations (central lab testing)
  - METex14 skipping mutations detected:
    - Plasma, LBx (DNA based)
    - Tissue, TBx (RNA based)
  - MET amplification only
- 1st, 2nd, 3rd line of therapy
  - Prior anti-MET therapy was not allowed
  - Prior immunotherapy was allowed
  - N = up to 120

Selected Endpoints

Primary endpoint
- Objective response rate (ORR) by independent review

Secondary endpoints
- ORR by investigator assessment
- Duration of response
- Objective disease control
- Progression-free survival
- Overall survival
- Safety
- Health-related quality of life

Cohort A
METex14 skipping mutations
- Tepotinib 500 mg QD (21 day cycles until progressive disease [PD])

Cohort B
MET amplification
- Tepotinib 500 mg QD (21 day cycles until PD)

The trial aims for an ORR based on independent review in the range of 40–50% with a lower limit of the corresponding exact 2-sided 95% confidence interval (according to Clopper–Pearson) to exceed an ORR of 20%.

We now report interim data including ORR assessed by independent review and select secondary endpoints.
### Efficacy: Best overall response (IRC/Investigator)

Efficacy analysis includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason.

<table>
<thead>
<tr>
<th>Tepotinib 500 mg QD</th>
<th>Liquid biopsy (L+)</th>
<th>Tissue biopsy (T+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRC (n=48)</td>
<td>Investigator (n=47)</td>
</tr>
<tr>
<td><strong>BOR by RECIST 1.1, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>24 (50.0)</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8 (16.7)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (14.6)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>9 (18.8)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td><strong>ORR, * n (%)</strong></td>
<td>24 (50.0) [35.2, 64.8]</td>
<td>26 (55.3) [40.1, 69.8]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mDOR, months</strong></td>
<td>12.4 [5.8, ne]</td>
<td>17.1 [7.1, ne]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DCR, † n (%)</strong></td>
<td>32 (66.7) [51.6, 79.6]</td>
<td>31 (66.0) [50.7, 79.1]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ORR, objective response rate: confirmed complete response/partial response.
†DCR, disease control rate: confirmed complete response/partial response or stable disease lasting at least 12 weeks.
L+, METex14-skipping mutation-positive in ctDNA; T+, METex14-skipping mutation-positive in tissue.
BOR, best overall response; CI, confidence interval; IRC, independent review committee; mDOR, median duration of response; ne, not estimable.

Abst 9005 Paik et al ASCO 2019
# Efficacy: ORR by line of therapy (IRC/Investigator)

Consistent ORR across treatment lines

<table>
<thead>
<tr>
<th>Tepotinib 500 mg QD</th>
<th>Liquid biopsy (L+)</th>
<th>Tissue biopsy (T+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRC (n=48)</td>
<td>Investigator (n=47)</td>
</tr>
<tr>
<td>First line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* n/N (%) (95% CI)</td>
<td>10/17 (58.8) [32.9, 81.6]</td>
<td>12/17 (70.6) [44.0, 89.7]</td>
</tr>
<tr>
<td>Second line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* n/N (%) (95% CI)</td>
<td>8/15 (53.3) [26.6, 78.7]</td>
<td>7/14 (50.0) [23.0, 77.0]</td>
</tr>
<tr>
<td>≥Third line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* n/N (%) (95% CI)</td>
<td>6/16 (37.5) [15.2, 64.6]</td>
<td>7/16 (43.8) [19.8, 70.1]</td>
</tr>
<tr>
<td>≥Second line</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR,* n/N (%) (95% CI)</td>
<td>14/31 (45.2) [27.3, 64.0]</td>
<td>14/30 (46.7) [28.3, 65.7]</td>
</tr>
<tr>
<td>mDOR, months (95% CI)</td>
<td>12.4 [5.6, ne]</td>
<td>ne</td>
</tr>
</tbody>
</table>

Efficacy analysis includes patients having ≥2 post-baseline assessments or who discontinued treatment for any reason.

*ORR, objective response rate: confirmed complete response/partial response.

L1, METex14-skipping mutation-positive in ctDNA; T+, METex14-skipping mutation-positive in tissue.

CI, confidence interval; IRC, independent review committee; mDOR, median duration of response; ne, not estimable.
# Safety: Treatment-related adverse events

<table>
<thead>
<tr>
<th>Tepotinib 500 mg QD (N=87)</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related AE, n (%)</td>
<td>71 (81.6)</td>
<td>17 (19.5)</td>
</tr>
<tr>
<td>Treatment-related AEs reported in ≥5% patients, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>42 (48.3)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (23.0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (20.7)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>11 (12.6)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (9.2)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Amylase increase</td>
<td>7 (8.0)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>6 (6.9)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>AST increased</td>
<td>5 (5.7)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>5 (5.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

- No grade 4 or grade 5 treatment-related AEs
- Other relevant treatment-related AEs (any grade) include:
  - lipase increased (4.6%)
  - fatigue (3.4%)
  - vomiting (3.4%)
- Treatment-related AEs led to permanent discontinuation in 4 patients:
  - two patients due to peripheral edema
  - one patient due to interstitial lung disease
  - one patient due to diarrhea and nausea

Data cut-off: February 18, 2019

*AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.*
Conclusions

- Tepotinib has shown durable clinical activity in patients with NSCLC harboring METex14 mutations, detected by liquid biopsy or tissue biopsy:
  - Liquid biopsy (L+): ORR was 50.0% and 55.3% by IRC and investigator assessment
  - Tissue biopsy (T+): ORR was 45.1% and 54.9% by IRC and investigator assessment
  - mDOR was > 1 year in all groups (12.4 to 17.1 months)
- Promising and consistent activity was observed across treatment lines
- Patients with brain metastases at baseline benefitted equally from treatment
- The safety profile of tepotinib was favorable
- Study is ongoing and includes a cohort of patients with high MET amplification

L+, METexon14-skipping mutation-positive in ctDNA; T+, METexon14-skipping mutation-positive in tissue.
AE, adverse events; IRC, independent review committee.
Acquired resistance involves on target and bypass pathways

Off-target Acquired Resistance
- EGFR (36%)
- G12S
- KRAS
- RASA1
- S742*

Paired tumor biopsies (n=14)

Off-target Resistance
- KRAS (G13V 9%)

Post-progression cfDNA (n=11*)

Unknown 50%
Unknown 91%

Slides courtesy of Reckamp (Discussant) ASCO 2019
Abst 9006 Guo et al ASCO 2019
Conclusions

In MET exon 14-altered lung cancers

• MET protein expression can affect response to MET TKI therapy
  • The presence of MET protein may select patients more likely to respond

• Acquired resistance to MET TKI therapy
  • On-target acquired resistance include MET kinase domain mutation and HGF amplification
  • Off-target acquired resistance include RAS and EGFR bypass pathway activation
## MET TKI preliminary efficacy in MET ex14 NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>MET testing</th>
<th>n</th>
<th>Brain metastases (n)</th>
<th>ORR % (95% CI)</th>
<th>DOR (months)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capmatinib</td>
<td>Tissue RT-PCR</td>
<td>97</td>
<td>1L—3</td>
<td>1L—67.9 (47.6, 84.1)</td>
<td>1L—11.1 (5.55, NE)</td>
<td>1L—9.7 (5.5, 13.86)</td>
</tr>
<tr>
<td>(Wolf J et al ASCO 2019)</td>
<td></td>
<td></td>
<td>2/3L—11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/3L—69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid (DNA based NGS)</td>
<td>73</td>
<td>Liquid—8</td>
<td>Liquid—50 (35.2, 64.8)</td>
<td>Liquid—12.4 (5.8, NE)</td>
<td>Liquid—9.5 (6.7, NE)</td>
</tr>
<tr>
<td>(Paik et al ASCO 2019)</td>
<td></td>
<td></td>
<td>Tissue—51</td>
<td>1L—58.8 (32.9, 81.6)</td>
<td>Tissue—15.7 (9.0, NE)</td>
<td>Tissue—10.8 (6.9, NE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥3L—35</td>
<td>2L—53.3 (26.6, 78.7)</td>
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<tr>
<td>Crizotinib</td>
<td>Tissue-local Prospective central tissue &amp; liquid ctDNA</td>
<td>65</td>
<td>na</td>
<td>32 (21-45)</td>
<td>9.1 (6.4, 12.7)</td>
<td>7.3 (5.4, 9.1)</td>
</tr>
<tr>
<td>(Drilon A et al WCLC 2018)</td>
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<td></td>
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</tr>
<tr>
<td>Savolitinib</td>
<td>Tissue</td>
<td>29</td>
<td>5</td>
<td>54.8</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>(Lu S et al AACR 2019)</td>
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</tbody>
</table>

Slides courtesy of Reckamp (Discussant) ASCO 2019
What does this mean? We have a new AM!

- Currently: EGFR, ALK, ROS1 + PDL1 = reimbursed therapies within NHS
- BRAF V600E – not reimbursed in NHS – but result known with NGS
- Actionable but not reimbursed: ?KRAS/NTRK/RET/cMET/Her2/TMB
- METex14 = definitely actionable
- Switch to NGS. Do we need RNA to pick up fusions?
- SMP2 will pick up METex14
- MATRIX has a criz arm for these patients
The Molecular and Histologic Landscape of Resistance to Osimertinib Identified by Tumor Tissue Analysis in EGFR-Mutant Lung Cancers

Adam J. Schoenfeld, Joseph M. Chan, Hira Rizvi, Romel Somwar, Daisuke Kubota, Yahya Daneshbod, Jason Chang, Michael Offin, Maria E. Arcila, Mark G. Kris, Dana Pe’er, Natasha Rekhtman, Gregory J. Riely, Marc Ladanyi, Helena A. Yu

Memorial Sloan Kettering Cancer Center, New York, NY

Abstract # 9028
• EGFR mut patients with NGS on tissue before therapy and after resistance to either 1st line or later line EGFRi (osimertinib)

• 27 1st line osi patients

• 35 pts received osi after failure of 1st line TKI

Abst 9028 Schoenfeld et al ASCO 2019
A) First line osimertinib
Conclusions

- By evaluating tissue rather than plasma, we observed a high rate of histologic transformation, including squamous cell transformation.
- Early progressors and 1st line osimertinib may have different resistance patterns than treatment after prior TKIs, with off-target resistance emerging earlier and on-target resistance mutations later.
What does this mean?

• Tissue Bx post PD in mutEGFR is important

• Exclude phenotypic change

• Facilitate NGS – elucidation of resistance pathways and potential new trials
Mesothelioma
Randomized phase 2 study of maintenance pemetrexed versus observation for patients with malignant pleural mesothelioma without progression after first-line chemotherapy:
Cancer and Leukemia Group B (CALGB) 30901 (Alliance)

Arkadiusz Z. Dudek1, Xiaofei Wang2, Lin Gu2, Thomas E. Stinchcombe3, Robert Kratzke4, Everett E. Vokes5, Hedy L. Kindler5
1HealthPartners Inc, Minneapolis, MN, 2Alliance Statistics and Data Center, Duke University, Durham, NC, 3Duke Cancer Institute, Duke University, Durham, NC,
4University of Minnesota/Masonic Cancer Center, Minneapolis, MN, 5University of Chicago Comprehensive Cancer Center, Chicago, IL
• Patients were treated initially with pemetrexed plus either cisplatin or carboplatin for 4-6 cycles at the discretion of the treating physician.
• Patients who achieved at least stable disease were randomized 1:1 to pemetrexed or observation
• Patients were stratified by:
  • First-line regimen (cisplatin vs. carboplatin)
  • Histologic subtype (epithelioid vs. other)
  • Number of cycles received (6 vs. < 6)

• Patients received either:
  • Pemetrexed 500 mg/m² iv Q 21 days or observation
• CT scans were obtained:
  • Q 2 cycles x 6 months, then Q 3 cycles x 6 months, then Q 4 cycles until disease progression
**Progression-free survival**

- **Observation:** 3.0 mo
- **Pemetrexed:** 3.4 mo
- **HR:** 0.99
- **95% CI:** 0.51-1.90
- **p:** 0.97

**Overall survival**

- **Observation:** 11.8 mo
- **Pemetrexed:** 16.3 mo
- **HR:** 0.86
- **95% CI:** 0.44-1.71
- **P:** 0.67
Conclusions

• Although the study closed prematurely, the results do not suggest a benefit to maintenance pemetrexed in MPM patients who have stable or responding disease after completion of first-line pemetrexed and platinum.
  • Maintenance pemetrexed is well-tolerated.

What does this mean?
  • Don’t give maintenance pem in meso
Thank you

@DrRiyazShah

riyaz.shah@nhs.net