Best of ASCO 2016: Lung Cancer

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Disclosures

Consultant: Janssen Pharmaceuticals, Clovis Oncology, US Diagnostic Services, Astex Therapeutics, Exelixis, Immunogen, Pfizer, Teva, Medivation, Halozyme, Novartis
Grant/Research Support: Millennium, Polaris, Oncogenex, GlaxoSmithKline, Genentech, Aragon Pharmaceuticals, Janssen Biotech, Inc.
ASCO 2016 Highlights: My Tasks Today

- To summarize top abstracts from ASCO 2016
- To provide “my two cents”
  - I will try to define how the newly reported data fits into current clinical care

Abstracts: NSCLC/Metastatic


Abstract 9004: Local Consolidative Therapy (LCT) to improve progression-free survival (PFS) in patients with oligometastatic non-small cell lung cancer (NSCLC) who receive induction systemic therapy (IST): Results of a multi-institutional phase II randomized study. (Daniel Richard Gomez)

Abstract 9008: Primary analysis for alectinib versus crizotinib in ALK-inhibitor naïve ALK positive non-small cell lung cancer (ALK+ NSCLC) in randomized open-label phase III trial (J-ALEX study). (Hiroshi Nokihara)
Abstracts: Early Stage NSCLC & SCLC

Abstract 8500: Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer. (Zhongxing X. Liao)

Abstract 8504: CONVERT: An international randomised controlled trial of concurrent chemo-radiotherapy (cCTRT) comparing twice-daily (BD) and once-daily (OD) radiotherapy (RT) schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status (PS) (NCT00433563). (Corinne Faivre-Finn)

Abstract LBA8505: Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). (Charles M. Rudin)
**MET Exon 14 Alterations**

- MET mutations that lead to decreased MET degradation
  - deletions, insertions, or base substitutions
  - many disrupt splice sites flanking MET exon 14 → exon 14 skipping
  - increased MET receptor on the tumor cell surface


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**Distribution of genotypes among 933 patients with nonsquamous non–small-cell lung cancer (NSCLC).**

- KRAS (34%)
- EGFR (19%)
- ALK (3.9%)
- BRAF (3.8%)
- MET exon 14 (3.0%)
- PIK3CA (2.9%)
- ERBB2 (2.5%)
- NRAS (1%)
- RET (1%)
- ROS1 (1%)
- AKT (< 1%)
- HRAS (< 1%)
- MAP2K1 (< 1%)

Mark M. Awad et al. JCO doi:10.1200/JCO.2015.63.4600
**MET Exon 14-Altered Lung Cancers**

- **Incidence**
  - 3-4% of nonsquamous NSCLCs
  - 20-30% of sarcomatoid lung carcinomas

- **Clinicopathologic Features**
  - older patients
  - ↓ proportion of never smokers
  - patients should be screened regardless of these clinical features
  - 15-20% with concurrent MET amplification

- **Diagnosis**
  - DNA-based next-generation sequencing
  - RNA sequencing
  - IHC alone is insufficient

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**Study Design**

- **PROFILE 1001 Study**
  - open-label, multicenter phase I trial
  - MET exon 14 alteration cohort

- **Key Objectives**
  - to investigate the safety and antitumor activity of crizotinib

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*Presented by: Alexander Drilon MD*
### Patients

Patients with MET exon 14-altered lung cancers (n=21)

<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 (53–87)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14 (67%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Tumor histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Adenoidocarcinoma</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Prior treatments for advanced disease, n (%)</td>
<td>0 3 (14%) 1 12 (57%) 2 3 (14%) ≥3 3 (14%)</td>
</tr>
</tbody>
</table>

### Antitumor Activity

Response-Evaluable Population (n=18)

<table>
<thead>
<tr>
<th>Best overall response n (%)</th>
<th>Complete response (CR)</th>
<th>Partial response (PR)</th>
<th>Stable disease (SD)</th>
<th>Unconfirmed CR/PR†</th>
<th>Progression of Disease (PD)</th>
<th>Indeterminate ‡</th>
<th>Overall response rate (ORR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>8 (44%)</td>
<td>9 (50%)</td>
<td>5 (28%)</td>
<td>0</td>
<td>1 (6%)</td>
<td>44% (95% CI: 22–69), n=8/18</td>
</tr>
</tbody>
</table>

† of the 5 patients; 2 awaiting confirmation, 3 cannot be confirmed
‡ this patient discontinued therapy in cycle 1, response imaging could not be performed but response available per protocol

Presented by: Alexander Drilon MD
Antitumor Activity

Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers
(n=16 with measurable disease at baseline and ≥1 response assessment scan)

- Partial response (PR), confirmed
- Stable disease (SD), includes 4 unconfirmed PRs
- Stable disease and 0% change from baseline

Duration of Therapy

- PR, confirmed
- SD
- Indeterminate
- Response assessment pending
- Response first achieved on study
- Off study

Median duration of treatment - 5.3 months (range 0.2–12.2)
Median duration of follow-up - 5.7 months (range 0.2–12.2)
Median progression-free survival - could not be calculated
Summary and Conclusions

- *MET* exon 14 alterations are actionable lung cancer drivers that can be detected in the clinic and should be screened for.
  - occur with a frequency comparable to ALK-rearranged lung cancers

- Crizotinib has clinically meaningful antitumor activity in patients whose lung cancers harbor a *MET* exon 14 alteration.
  - overall response rate of 44%; tumor shrinkage achieved in the majority of patients

- Adverse events were consistent with the known safety profile of crizotinib.

- Further study of crizotinib in this patient population is warranted.
  - PROFILE 1001 continues to accrue patients to this cohort.
  - accrual goal of up to 50 patients with *MET* exon 14-altered lung cancers

“*My Two Cents*”

- MET exon 14 alterations should now be assessed routinely in advanced NSCLC
  - Next generation sequencing assays are adequate

- Presence of MET exon 14 alterations predicts for response to MET inhibitors

- Recommended algorithm for MET exon 14 altered NSCLC:
  - Refer for clinical trial consideration
  - In absence of clinical trial, crizotinib is appropriate
Local Consolidative Therapy (LCT) Improves Progression-Free Survival (PFS) in Patients with Oligometastatic Non-Small Cell Lung Cancer (NSCLC) who do not Progress after Front Line Systemic Therapy (FLST): Results of a Multi-Institutional Phase II Randomized Study

Daniel Gomez, George Blumenschein, Jack Lee, Mike Hernandez, Ross Camidge, Robert Doebele, Laurie Gaspar, Don Gibbons, Jose Karam, Brian Kavanagh, Ritsuko Komaki, Alexander Louie, David Palma, Anne Tsao, William William, Jianjun Zhang, Stephen Swisher*, John Heymach*, on behalf of the MD Anderson Cancer Center Lung Cancer Moon Shot Initiative

*Co-senior authors

Trial Design

All patients had stage IV disease, three or fewer metastases, and no progression after initial treatment with chemotherapy

Crossover Allowed at Progression
CONSORT Diagram

74 Patients Enrolled into Step 1 (Induction Phase)

49 Patients Enrolled into Step 2 and Randomization

25 Patients Not Enrolled into Step 2 and Randomization

25 Patients Receiving LCT

24 Patients Receiving No LCT

At DSMC review in 1/2016, study closed due to observed efficacy in experimental arm after randomization of 49 patients

N=12 progression
N=5 refused randomization
N=4 lost to follow-up
N=3 further studies deemed ineligible
N=1 study closed prior to randomization

Patient Characteristics

• No statistically significant (p>0.05) differences between arms on gender, age, race, histology, or any of balanced factors

<table>
<thead>
<tr>
<th>Treatment regimens of LCT arm</th>
<th>N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypofractionated RT/SBRT</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Combination chemoRT &amp; hypofractionated RT</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Combination surgery &amp; RT</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>ChemoRT alone</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Progressed prior to local treatment</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
PFS Outcomes (updated data)

One patient inevaluable (24 in each group)

Median PFS times:

No-LCT arm: 3.9 months (95% CI 2.2-6.6 months)
LCT arm: 11.9 months (95% CI 5.4 months-NA)

Patterns of Failure

• Difference in patterns of failure trended towards significance (p=0.09)
  – Higher proportion of locoregional only failures in no-LCT arm (17% in no-LCT vs. 4% in LCT arm)
  – Higher proportion of metastatic only failures in LCT arm (40% in LCT vs. 25% in no-LCT arm)
  – Higher proportion of both locoregional and metastatic failures in no-LCT arm (29% in no-LCT vs. 8% in LCT arm)
**Time to New Site Failure (TNSF)**

Median TNSF time 11.9 months in LCT arm vs. 5.7 months in no-LCT arm (p=0.0497)

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**“My Two Cents”**

- In oligometastatic (1-3 mets) NSCLC, local consolidative therapy after systemic therapy appears to improve PFS
  - Exploratory analysis: LCT increased time to development of new lesions
- Results of trial are intriguing but not yet practice changing
  - Population: highly heterogeneous (clinically and biologically)
  - Sample size: limited
  - Quality of life: unknown
  - Crossover design confounds overall survival endpoint
Alectinib versus Crizotinib in ALK Inhibitor Naïve ALK-Positive Non-Small Cell Lung Cancer: Primary Results from the J-ALEX Study

Hiroshi Nokihara, Toyoaki Hida, Masashi Kondo, Young Hak Kim, Koichi Azuma, Takashi Seto, Yuichi Takiguchi, Makoto Nishio, Hiroshige Yoshioka, Fumio Imamura, Katsuyuki Hotta, Satoshi Watanabe, Koichi Goto, Kazuhiko Nakagawa, Tetsuya Mitsudomi, Nobuyuki Yamamoto, Hiroshi Kuriki, Ryoichi Asabe, Tomohiro Tanaka, Tomohide Tamura

Presented by: Hiroshi Nokihara

J-ALEX Phase III Study Design

Key Entry Criteria
- Stage IIIb/IV or recurrent ALK-positive NSCLC
- ALK centralized testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- ≥1 measurable lesion assessed by investigator
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

Endpoints
- Primary - PFS assessed by IRF*
- Secondary - OS - ORR - PK - QOL - CNS PFS - Safety

Stratification factors:
Clinical stage (IIIb/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

*** Alectinib has high CNS penetration

*IRF Independent Review Facility

JapicCTI-132316
Safety Overview

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>100 (97.1%)</td>
<td>104 (100.0%)</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>27 (26.2%)</td>
<td>54 (51.9%)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>15 (14.6%)</td>
<td>27 (26.0%)</td>
</tr>
<tr>
<td>Discontinuation of study drug due to AEs</td>
<td>9 (8.7%)</td>
<td>21 (20.2%)</td>
</tr>
<tr>
<td>Dose interruptions due to AEs</td>
<td>30 (29.1%)</td>
<td>77 (74.0%)</td>
</tr>
</tbody>
</table>

Objective Tumor Response

ORR assessed by investigator in ITT population

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR [95%CI]</td>
<td>85.4% [78.6 - 92.5]</td>
<td>70.2% [61.4 - 79.0]</td>
</tr>
</tbody>
</table>

ORR* assessed by IRF

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=83)</th>
<th>Crizotinib (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR [95%CI]</td>
<td>91.6% [85.6 - 97.5]</td>
<td>78.9% [70.5 - 87.3]</td>
</tr>
</tbody>
</table>
Primary Endpoint: PFS by IRF (ITT Population)

HR = 0.34, p<0.001

Brain mets PFS 0.08

J-ALEX Trial: Adverse Events >20% (All grades & > Grade 3)

- Discontinuation rate for toxicity: 20.2% (crizotinib) vs. 8.7% (alectinib)
“My Two Cents”

- Alectinib is superior to crizotinib as frontline therapy of ALK-positive NSCLC
  - RR: 85% vs 70%
  - PFS HR = 0.34 (p<0.001)
    - mPFS: Not reached vs. 10 months
  - Time to progression for those with brain metastases: PFS was 92% better for alectinib
  - Toxicity profile favored alectinib
- Caveats: Japanese-only trial, cost (third party reimbursement)
- Bottom line:
  - Alectinib can be considered as frontline ALK-targeted therapy (particularly pts with brain mets)
  - However, its best to await definitive results of global ALEX trial

Abstracts: Early Stage NSCLC & SCLC

Abstract 8500: Bayesian randomized trial comparing intensity modulated radiation therapy versus passively scattered proton therapy for locally advanced non-small cell lung cancer. (Zhongxing X. Liao)

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Abstract LBA8505: Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). (Charles M. Rudin)
A Bayesian Randomization Trial of Intensity Modulated Radiation Therapy (IMRT) vs. 3-Dimensional Passively Scattered Proton Therapy (3DPT) for Locally Advanced Non-Small Cell Lung Carcinoma

(clinicaltrials.gov identifier NCT00915005)


Supported in part by NCI grants P01 CA021230 and U19 CA021239.

Hypothesis

Proton therapy will

– Reduce irradiated lung volume, hence reduce radiation pneumonitis (RP)

– Achieve same local control (LC) with same biological effective radiation dose (Proton relative biological equivalence=1.1)
Primary Objective

Protocol Failure (Dual endpoints):
- Radiation Pneumonitis grade > 3 (CTCAE 3.0)
  - IMRT = 15%
  - 3DPT = 5%

- Local failure (PET, CT, biopsy):
  - IMRT = 3DPT
  - 15% at 6mo & 25% at 12mo.

Randomized and Treated According to Randomization Analysis
Baseline Characteristics

- Demographics (age, gender, ECOG, smoking status, histology, stage) no difference.
- Target Volumes:

<table>
<thead>
<tr>
<th>Target Volumes (cc)</th>
<th>IMRT</th>
<th>3DPT</th>
<th>Total</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Median</td>
<td>66.10</td>
<td>77.7</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(5.75-686.59)</td>
<td>(1.9-673.7)</td>
<td>(1.9-686.59)</td>
</tr>
<tr>
<td>ITV</td>
<td>Median</td>
<td>257.655</td>
<td>329.7</td>
<td>292.7</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(42.91-1316.24)</td>
<td>(30-1384)</td>
<td>(30-1384)</td>
</tr>
<tr>
<td>PTV</td>
<td>Median</td>
<td>429.35</td>
<td>524.9</td>
<td>480.31</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(103.92-1776.08)</td>
<td>(76-1906)</td>
<td>(76-1906)</td>
</tr>
</tbody>
</table>
- RT dose 74 Gy: IMRT vs. 3DPT = 63% vs. 75.4% (p<0.001)

Protocol Failure - Randomized and Treated According to Protocol

Protocol Failure (Dual endpoints):
- RP grade > 3 (CTCAE 3.0)
  - IMRT = 15% vs. 6.5%
  - 3DPT = 5% vs. 10.5%
- Local Failure at 12 month (PET, CT, biopsy):
  - IMRT = 3DPT = 25% vs. 10.7%
Overall Survival

**Cox Regression Analysis for OS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>p-value</th>
<th>95% CI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>0.012</td>
<td>1.01</td>
<td>1.06</td>
</tr>
<tr>
<td>RT Dose</td>
<td>0.62</td>
<td>0.036</td>
<td>0.39</td>
<td>0.97</td>
</tr>
<tr>
<td>GTV</td>
<td>1.002</td>
<td>0.02</td>
<td>1.00</td>
<td>1.003</td>
</tr>
</tbody>
</table>

**“My Two Cents”**

- Proton beam RT is no better than standard IMRT
  - Primary endpoint not met
    - Pneumonitis numerically worse with protons
    - No significant differences in treatment failure rates
    - Trend for worse survival with proton beam
      - IMRT 29.5 months vs. Proton 26.1 months
- Results dispel prevailing notion that proton beam RT is superior to standard RT
- Lack of clear benefits of proton beam RT do not justify its higher cost in this patient context
CONVERT trial

Concurrent ONce-daily VErsus twice-daily RadioTherapy: A 2-arm randomised controlled trial of concurrent chemoradiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited-stage small cell lung cancer and good performance status

Conrine Faivre-Finn1, Michael Snee2, Linda Ashcroft3, Weibke Appel3, Fabrice Barlesi4, Adi Bhatnagar5, Andrea Bezjak6, Felipe Cardenal7, Pierre Faumet8, Susan Hardin9, Cecile Le Pechoux11, Rhona McMenamin12, Nazia Mohammed13, Mary O’Brien14, Jason Pantarotto15, Veerle Surmont16, Jan Van Meerbeeck16, Paul Lorigan17, Fiona Blackhall1

1. The University of Manchester, Institute of Cancer Sciences, Manchester, UK; 2. St James Hospital, Leeds, UK; 3. MAHSC-CTU, The Christie NHS Foundation Trust, UK; 4. Royal Preston Hospital, UK; 5. CHU de Marseille, France; 6. Southamton General Hospital, UK; 7. Canadian Cancer Trials Group, Princess Margaret Cancer Centre, Toronto, Canada; 8. GEC-PC, Institut Català d’Oncologia, Barcelona, Spain; 9. GIPF, Institut de Cancérologie de la Loire, France; 10. Addenbrookes Hospital, Cambridge, UK; 11. Institut Gustave Roussy, Villejuif, France; 12. Freeman Hospital, Newcastle-upon-Tyne, UK; 13. Beatson Cancer Centre, Glasgow, UK; 14. Royal Marsden Hospital, Surrey, UK; 15. Ottawa Health Research Institute, Canada; 16. Universitat Gens, Belgium; 17. Weston Park Hospital, Sheffield, UK

Presented by: Prof C Faivre-Finn

Study design

multinational, phase III randomised study

RTP after randomisation
RT started on D22 cycle 1
- 3DCRT or IMRT
- No ENI
- QA programme

Chemotherapy
4 to 6 cycles
- Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1
- Etoposide 100mg/m2 D1-3

Stratification factors
- Centre
- No. of cycles chemo: 4 vs.6
- PS: 0-1 vs. 2

Limited Stage Small Cell
Registration Randomisation

RT 45Gy/30F/19D
Twice-daily (BD) thoracic RT

RT 66Gy/33F/45D
Once-daily (OD) thoracic RT

Chemotherapy
Restage
No PCI
Study objectives

- Primary endpoint
  - Overall survival

- Secondary endpoints
  - Compliance with chemotherapy and RT treatments
  - Toxicity (CTCAE v3.0)
  - Local progression free survival
  - Metastatic progression free survival
  - Exploratory translational objectives (archival tissue, blood samples, germline DNA and CTCs - for Manchester patients only)

The study enrolled 547 patients with histologically or cytologically proven SCLC recruited from 73 centers in 7 European countries and Canada between 2008 and 2013.

Statistical assumptions

- A survival benefit of 12% at 2 years (from 44% in the BD arm to 56% in the OD arm) was considered to be clinically significant

- Total number of events/patients required
  - 5% significance level, 2-sided test, 80% power
  - Hazard ratio 0.70
  - 253 events were required
  - 26 patients (5%) were added to allow for ineligible patients/lost to follow-up
  - 532 patients were required

- A planned interim analysis was carried out for the IDMC 12 months after the first patient was randomised (safety, deliverability and accrual)

- All results are reported on an intention-to-treat basis
Overall survival

Primary objective-survival at 2 years
Trail hypothesis
• Expected survival BD arm 44%
• Projected survival OD arm 56%

Median follow-up: 45 months

<table>
<thead>
<tr>
<th>Overall survival (n=543)</th>
<th>BD</th>
<th>OD</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>30 (24-34)</td>
<td>25 (21-31)</td>
<td>p=0.15</td>
</tr>
<tr>
<td>1-year</td>
<td>83% (78-87)</td>
<td>76% (71-81)</td>
<td></td>
</tr>
<tr>
<td>2-year</td>
<td>56% (50-61)</td>
<td>51% (45-55)</td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>43% (37-49)</td>
<td>39% (33-45)</td>
<td></td>
</tr>
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</table>

Progression free survival

<table>
<thead>
<tr>
<th>Time to progression (N=543)</th>
<th>BD</th>
<th>OD</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall progression (n)</td>
<td>182</td>
<td>190</td>
<td>p = 0.26</td>
</tr>
<tr>
<td>Median (months; 95% CI)</td>
<td>15 (13-19)</td>
<td>14 (12-17)</td>
<td></td>
</tr>
<tr>
<td>Local progression (n)</td>
<td>175</td>
<td>186</td>
<td>p = 0.21</td>
</tr>
<tr>
<td>Median (months; 95% CI)</td>
<td>21 (16-28)</td>
<td>18 (16-22)</td>
<td></td>
</tr>
<tr>
<td>Metastatic progression (n)</td>
<td>176</td>
<td>182</td>
<td>p = 0.24</td>
</tr>
<tr>
<td>Median (months; 95% CI)</td>
<td>20 (16-25)</td>
<td>17 (14-22)</td>
<td></td>
</tr>
</tbody>
</table>
### Acute Toxicity

<table>
<thead>
<tr>
<th>AE CTCAE v3.0</th>
<th>Arm</th>
<th>0</th>
<th>1-2</th>
<th>3-5</th>
<th>p 0,1,2 vs 3,4,5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea</strong></td>
<td>BD</td>
<td>70 (28.4)</td>
<td>66 (25.1)</td>
<td>172 (64.9)</td>
<td>171 (65.1)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>BD</td>
<td>146 (55.3)</td>
<td>155 (59.0)</td>
<td>105 (39.7)</td>
<td>95 (36.1)</td>
</tr>
<tr>
<td><strong>Mucositis</strong></td>
<td>BD</td>
<td>173 (65.5)</td>
<td>169 (64.5)</td>
<td>88 (33.4)</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>BD</td>
<td>21 (8.0)</td>
<td>212 (80.3)</td>
<td>216 (82.4)</td>
<td>31 (11.7)</td>
</tr>
<tr>
<td><strong>Neuro-motor</strong></td>
<td>BD</td>
<td>250 (94.3)</td>
<td>12 (4.5)</td>
<td>1 (0.4)</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Neuro-sensory</strong></td>
<td>BD</td>
<td>245 (93.5)</td>
<td>15 (6.0)</td>
<td>2 (0.8)</td>
<td>4 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE CTCAE v3.0</th>
<th>Arm</th>
<th>0</th>
<th>1-2</th>
<th>3-5</th>
<th>p 0,1,2 vs 3,4,5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>BD</td>
<td>39 (14.7)</td>
<td>41 (15.7)</td>
<td>194 (72.9)</td>
<td>184 (70.8)</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>BD</td>
<td>31 (11.7)</td>
<td>43 (16.5)</td>
<td>38 (13.7)</td>
<td>47 (18.1)</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>BD</td>
<td>203 (76.6)</td>
<td>214 (82.0)</td>
<td>NA</td>
<td>52 (23.4)</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>BD</td>
<td>132 (49.6)</td>
<td>119 (45.8)</td>
<td>89 (33.5)</td>
<td>87 (33.4)</td>
</tr>
</tbody>
</table>

* 2 grade 5 (1 peripheral arterial ischemia and 1 septic shock)
* 1 grade 5

---

### “My Two Cents”

- Once daily (66 Gy x 6 weeks) is no better than BID (45 Gy x 3 weeks) in limited stage SCLC
  - Median survival: 25 vs 30 months (p=0.15)
  - Two year survival: 51% vs 56%
- Toxicity profiles were comparable
- In clinical practice, both approaches are reasonable
  - BID more inconvenient, but treatment completed sooner
- Phase III CALGB 30610/RTOG 0538 is still accruing (slowly)
  - Once daily (70 Gy x 7 weeks) versus BID (45 Gy x 3 weeks)
Safety and efficacy of single agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC)

Rudin CM1, Pietanza MC1, Bauer TM2,3, Spigel DR2,3, Ready N4, Morgensztern D5, Glisson BS6, Byers LA6, Johnson ML2,3, Burris HA III2,3, Robert F7, Strickland DR7, Zayed H8, Govindan R5, Dylla SJ5, Peng SL8

1 Memorial Sloan Kettering Cancer Center, New York, NY; 2Tennessee Oncology, PLLC., Nashville, TN; 3Medical Oncology, Sarah Cannon Research Institute, Nashville, TN; 4Duke University Medical Center, Durham, NC; 5Washington University School of Medicine in St. Louis, St. Louis, MO; 6The University of Texas MD Anderson Cancer Center, Houston, TX; 7The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; 8AbbVie Stemcentrx LLC, South San Francisco, CA

Delta-like Protein 3 (DLL3): a novel target in neuroendocrine tumors

- An atypical inhibitory Notch ligand
- Induced by the key neuroendocrine transcription factor, ASCL1
- Aberrant cell surface expression in >80% of small cell lung and large cell neuroendocrine cancers
  - On both cancer stem and tumor cells but not normal adult tissues
- Not prognostic, and does not predict response to chemotherapy

Saunders et al., Sci Transl Med 2015
**Rovalpituzumab Tesirine (Rova-T™, SC16LD6.5)**

A delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC)

- **Anti-DLL3 mAb** (SC16)
  - Drug-to-antibody ratio = 2
  - Cathepsin B - cleavable linker
  - Pyrrolobenzodiazepine (PBD) dimer toxin (D6.5 / SC-DR002)

---

**Subject Baseline Characteristics (n=74)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, years (range)</td>
<td>61 (38-81)</td>
</tr>
<tr>
<td>Female</td>
<td>32 (43%)</td>
</tr>
<tr>
<td>Baseline ECOG: 0 / 1 / 2</td>
<td>21 (28%) / 50 (68%) / 3 (4%)</td>
</tr>
<tr>
<td>Extensive Disease at Presentation</td>
<td>56 (76%)</td>
</tr>
<tr>
<td>Response to 1st line therapy</td>
<td>39 (53%)</td>
</tr>
<tr>
<td>Sensitive¹</td>
<td>23 (31%)</td>
</tr>
<tr>
<td>Resistant²</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Refractory³</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Not evaluable Treatment-Free Interval (before 2nd line)</td>
<td>4.1 months (0.2-89.1)</td>
</tr>
<tr>
<td>Hx CNS mets (Per Investigator)</td>
<td>21 (28%)</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Lines of Therapy: 1 / 2</td>
<td>39 (53%) / 35 (47%)</td>
</tr>
<tr>
<td>Prior treatments</td>
<td>71 (96%)</td>
</tr>
<tr>
<td>Platinum/Etoposide</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Platinum/Other</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Platinum/Etoposide/Other</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Topotecan</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>61 (82%)</td>
</tr>
<tr>
<td>ABT-888</td>
<td>16 (22%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Tumor DLL3 Expression</td>
<td>42/48 (88%)</td>
</tr>
<tr>
<td>≥ 1% of tumor cells</td>
<td>32/48 (67%)</td>
</tr>
<tr>
<td>≥ 50% of tumor cells</td>
<td>24/48 (50%)</td>
</tr>
</tbody>
</table>
Adverse Event Profile in SCLC Subjects (n=74)

<table>
<thead>
<tr>
<th>Adverse Event PT</th>
<th>Grade 3+</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>28 (38%)</td>
<td>65 (88%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (4%)</td>
<td>26 (35%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6 (8%)</td>
<td>23 (31%)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>2 (3%)</td>
<td>20 (27%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>0 (0%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (11%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Appetite Loss</td>
<td>0 (0%)</td>
<td>12 (16%)</td>
</tr>
</tbody>
</table>

Highest Related TEAE Terms ≥ 15%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Group Grade</th>
<th>Grade 3+</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>9 (12%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>Serosal Effusions</td>
<td>2</td>
<td>8 (11%)</td>
<td>26 (35%)</td>
</tr>
<tr>
<td>Skin Reaction</td>
<td>3</td>
<td>6 (8%)</td>
<td>36 (49%)</td>
</tr>
</tbody>
</table>

RECIST Confirmed Responses per Investigator

- Objective Response Rate (ORR = PR+CR)
  - 18% for 60 evaluable DLL3
  - 39% for 26 evaluable DLL3

- Clinical Benefit Rate (CBR = SD+PR+CR)
  - 68% for 60 evaluable DLL3
  - 89% for 26 evaluable DLL3

Response-Evaluable Subjects Active Doses (0.2-0.4 mg/kg)
Best Responses per Investigator by DLL3

- % Change from Baseline
- DLL3 Expression
  - Not Available
  - DLL3 : 0%
  - DLL3 : 1-49%
  - DLL3 ≥ 50%

Confirmed Responses Comparable in 2nd & 3rd Line

- Second Line
  - ORR: 13% 29% 72% 86%
  - CBR: 32 14 32 14
- Third Line
  - ORR: 25% 50% 64% 92%
  - CBR: 28 12 28 12
SCLC Kaplan-Meier Overall Survival

**DLL3 Status** | **Overall Survival**
---|---
≥ 50% | 5.8 mo | 32%
All | 4.6 mo | 18%

**“My Two Cents”**

- Rova-T has encouraging single-agent activity in SCLC
  - Entirely new drug class
  - Clinically meaningful responses, some durable
  - Warrants further clinical testing
- First biomarker-directed therapy in SCLC
  - 67% = DLL3-high
- Issues:
  - Validation of drug-target engagement
  - Dose limiting thrombocytopenia
    - Need to explore mechanism (off target binding?)
    - Limits combinability with cytotoxics
thank you