State of the art and new targets in the treatment of small cell lung cancer:

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Chair EORTC lung group
Disclosures

- None for this talk
- Ad boards for BI, MSD, Pierre Fabre, Biomarin
- Research grants from Roche
- Meeting support
US cancer deaths

Annual deaths (US)

Cancer type

- Non-small cell lung
- Colon & Rectum
- Breast
- Pancreatic
- Prostate
- Small cell lung
- Non-Hodgkin Lymphoma
- Liver & Intra-hepatic Biliary
- Ovarian
- Gastric
- Bladder
- Kidney
- Brain
- Myeloma
- Acute Myeloid Leukemia
- Melanoma
Cytotoxics

- Irinotecan – topo 1 inhibitor
- Topotecan – topo 1 inhibitor
- Amrubicin – topo 2 inhibitor

Amrubicin (AMR)

Doxorubicin (DXR)
Irinotecan East vs West – meta

- OS positive in both but magnitude greater in the eastern 40% v 15%
- Snap shot of world Tx

<table>
<thead>
<tr>
<th>Study name</th>
<th>Comparison Outcome</th>
<th>Outcome</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanna 2006</td>
<td>Blank</td>
<td>OS</td>
<td>0.900 0.715 1.132 -0.899 0.369</td>
<td></td>
</tr>
<tr>
<td>Hermes 2008</td>
<td>Blank</td>
<td>OS</td>
<td>0.710 0.533 0.946 -2.343 0.019</td>
<td></td>
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<tr>
<td>Lara 2009</td>
<td>Blank</td>
<td>OS</td>
<td>0.930 0.792 1.092 -0.884 0.377</td>
<td></td>
</tr>
<tr>
<td>Schmittel 2011</td>
<td>Blank</td>
<td>OS</td>
<td>0.750 0.543 1.036 -1.746 0.081</td>
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<tr>
<td>Zatloukal 2010</td>
<td>Blank</td>
<td>OS</td>
<td>0.810 0.650 1.010 -1.874 0.061</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.851 0.770 0.941 -3.151 0.002</td>
<td></td>
</tr>
</tbody>
</table>
Amrubinin not better than PE in first line

**PROGRESSION FREE SURVIVAL**

Median in Months (95% 2-sided CI)
- Amrub: 5.2 (3.0, 7.5)
- Amrub + Cisp: 6.9 (6.0, 7.5)
- Cisp + Etop: 5.8 (5.3, 7.8)

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>28</td>
<td>17 12 4 3 2 1 0 0</td>
<td>Amrub</td>
</tr>
<tr>
<td>28</td>
<td>30</td>
<td>24 18 5 1 1 1 1 1</td>
<td>Amrub + Cisp</td>
</tr>
<tr>
<td>28</td>
<td>30</td>
<td>23 14 3 1 0 0 0 0</td>
<td>Cisp + Etop</td>
</tr>
</tbody>
</table>

**OVERALL SURVIVAL**

Median in Months (95% 2-sided CI)
- Amrub: 11.1 (7.9, 14.5)
- Amrub + Cisp: 11.1 (7.3, 16.3)
- Cisp + Etop: 10.0 (9.2, 13.3)

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>28</td>
<td>26 22 14 12 5 2 0 0</td>
<td>Amrub</td>
</tr>
<tr>
<td>22</td>
<td>30</td>
<td>28 22 16 10 7 3 2 1</td>
<td>Amrub + Cisp</td>
</tr>
<tr>
<td>22</td>
<td>30</td>
<td>26 23 18 10 4 0 0 0</td>
<td>Cisp + Etop</td>
</tr>
</tbody>
</table>
Amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of extended-stage small cell lung cancer (ED-SCLC): JCOG0509 – Kotani Y et al

- aged 20 to 70, and ECOG PS 0–1:
- IP: I (60 mg/m²) iv on days 1, 8, and 15, and P (60 mg/m²) iv on day 1, every 4 weeks; or
- AP: A (40 mg/m²) iv on day 1–3, and P (60 mg/m²) iv day 1, 3 weeks
  - Dose of A was decreased from 40 mg/m² to 35 mg/m² due to increased FN

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>IP</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>142</td>
<td>142</td>
</tr>
<tr>
<td>Male/Female</td>
<td>120/22</td>
<td>119/23</td>
</tr>
<tr>
<td>Age yrs, median (range)</td>
<td>63 (39–70)</td>
<td>63 (29–70)</td>
</tr>
<tr>
<td>Performance status: 0/1</td>
<td>78/64</td>
<td>80/62</td>
</tr>
<tr>
<td>Measurable lesion +/-</td>
<td>1/141</td>
<td>2/140</td>
</tr>
<tr>
<td>Metastasis (overlapped): lung/bone/brain/liver/others</td>
<td>9/25/32/35/68</td>
<td>14/31/41/45/64</td>
</tr>
</tbody>
</table>

FN, febrile neutropenia

Kotani et al. J Clin Oncol 30, 2012 (suppl; abstr 7003)
Key efficacy and safety data

- Median PFS: 5.7 (IP) vs 5.1 months (AP) (HR 1.44, 95% CI: 1.13–1.83)
- Grade 4 neutropenia (22.5% vs 79.3%) and Grade 3–4 febrile neutropenia (10.6% vs 32.1%) was higher in the AP arm, while Grade 3–4 diarrhoea (7.7% vs 1.4%) was higher in IP arm

Amrubinin not better than IP in first line

Kotani et al. J Clin Oncol 30, 2012 (suppl; abstr 7003)
2nd line: amrubicin not better than topo

**Sensitive Patients**

- **Amrubicin**: 225/168, Median OS 9.2 months, 95% CI 8.5-10.6
- **Topotecan**: 117/89, Median OS 9.9 months, 95% CI 8.5-11.5

HR=0.936, 95% CI [0.724, 1.211], P-value*=0.6164

**Refactory Patients**

- **Amrubicin**: 199/168, Median OS 6.2 months, 95% CI 5.5-6.7
- **Topotecan**: 96/86, Median OS 5.7 months, 95% CI 4.1-7.0

HR=0.766, 95% CI [0.589, 0.997], P-value*=0.0469

*Unstratified log-rank test*
### Maintenance chemotherapy

21 RCTs

PFS neg

OS +

Rossi et al

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Maintenance n/N</th>
<th>Follow-up n/N</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cullen 1986</td>
<td>12/16</td>
<td>14/16</td>
<td>0.48</td>
<td>0.28 - 0.81</td>
</tr>
<tr>
<td>Cullen 1986</td>
<td>25/29</td>
<td>29/32</td>
<td>0.47</td>
<td>0.28 - 0.81</td>
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<tr>
<td>Anonymous 1989</td>
<td>131/131</td>
<td>134/134</td>
<td>0.87</td>
<td>0.69 - 1.11</td>
</tr>
<tr>
<td>Byrne 1989</td>
<td>29/34</td>
<td>22/32</td>
<td>1.74</td>
<td>1.00 - 3.03</td>
</tr>
<tr>
<td>Ettinger 1990</td>
<td>24/25</td>
<td>21/25</td>
<td>1.57</td>
<td>0.87 - 2.82</td>
</tr>
<tr>
<td>Ettinger 1990</td>
<td>18/18</td>
<td>17/18</td>
<td>1.77</td>
<td>0.91 - 3.44</td>
</tr>
<tr>
<td>Giaccone 1993</td>
<td>209/219</td>
<td>206/215</td>
<td>1.04</td>
<td>0.68 - 1.28</td>
</tr>
<tr>
<td>Johnson 1993</td>
<td>55/72</td>
<td>53/79</td>
<td>0.46</td>
<td>0.32 - 0.67</td>
</tr>
<tr>
<td>Belth 1996</td>
<td>58/65</td>
<td>62/64</td>
<td>0.94</td>
<td>0.65 - 1.34</td>
</tr>
<tr>
<td>Sculler 1996</td>
<td>36/45</td>
<td>41/46</td>
<td>0.89</td>
<td>0.57 - 1.39</td>
</tr>
<tr>
<td>Schiller 2001</td>
<td>100/112</td>
<td>102/111</td>
<td>0.99</td>
<td>0.75 - 1.30</td>
</tr>
<tr>
<td>Hanna 2002</td>
<td>65/72</td>
<td>70/72</td>
<td>0.73</td>
<td>0.52 - 1.03</td>
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<tr>
<td>Han 2008</td>
<td>17/21</td>
<td>16/24</td>
<td>0.79</td>
<td>0.40 - 1.63</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>779/859</td>
<td>787/868</td>
<td>0.89</td>
<td>0.81 - 0.98</td>
</tr>
</tbody>
</table>

\[ \chi^2 \text{Het} = 40.37 \text{ df } = 12 \text{ (p=0.0001) } R^2 = 70.9\% \]

Test for overall effect \( Z = 3.33 \text{ (p=0.02) } \)

| 02 Interferon-alpha   |                 |               |             |             |
| Mattson 1992          | 62/91           | 66/87         | 0.70       | 0.50 - 0.98 |
| Kelly 1995            | 50/64           | 51/68         | 0.94       | 0.64 - 1.39 |
| Tummarello 1997       | 12/14           | 11/12         | 0.53       | 0.23 - 1.20 |
| Lebeau 1999           | 68/84           | 66/88         | 0.81       | 0.56 - 1.17 |
| Subtotal (95% CI)     | 190/253         | 184/235       | 0.78       | 0.64 - 0.96 |

\[ \chi^2 \text{Het} = 2.17 \text{ df } = 3 \text{ (p=0.64) } R^2 = 0\% \]

Test for overall effect \( Z = 2.39 \text{ (p=0.02) } \)

| 03 Interferon-gamma   |                 |               |             |             |
| Jett 1994             | 40/51           | 35/49         | 1.20       | 0.76 - 1.89 |
| Van Zandwijk 1997     | 56/65           | 54/62         | 1.03       | 0.71 - 1.49 |
| Subtotal (95% CI)     | 96/116          | 89/111        | 1.09       | 0.62 - 1.46 |

\[ \chi^2 \text{Het} = 0.27 \text{ df } = 1 \text{ (p=0.60) } R^2 = 0\% \]

Test for overall effect \( Z = 0.61 \text{ (p=0.54) } \)

| 04 Other biological agents |                 |               |             |             |
| Shepherd 2002           | 194/266         | 197/266       | 1.01       | 0.83 - 1.23 |
| Giaccone 2005           | 195/257         | 183/256       | 1.19       | 0.96 - 1.46 |
| Arnold 2007             | 53/53           | 52/54         | 1.01       | 0.60 - 1.69 |
| Pujol 2007              | 25/49           | 30/43         | 0.74       | 0.49 - 1.12 |
| Subtotal (95% CI)       | 467/625         | 462/621       | 1.05       | 0.92 - 1.20 |

\[ \chi^2 \text{Het} = 4.45 \text{ df } = 22 \text{ (p=0.22) } R^2 = 32.6\% \]

Test for overall effect \( Z = 0.75 \text{ (p=0.45) } \)

| Total (95% CI)          | 1522/1835       | 1522/1835     | 0.93       | 0.87 - 1.00 |

\[ \chi^2 \text{Het} = 55.51 \text{ df } = 22 \text{ (p=0.0001) } R^2 = 60.1\% \]

Test for overall effect \( Z = 1.95 \text{ (p=0.05) } \)
4-6 cycles of CT (cis 80 mg/m²/carbo AUC5 plus etop 100 mg/m² d1-3 q3w)
Maintenance sunitinib 150 mg/day loading then 37.5 mg/day/placebo

Primary endpoint: PFS

- 144 patients; 138 patients received CT;
- 95 randomised to maintenance; 85 received (44 sunitinib, 41 placebo)
- PFS on maint: 2.3 vs. 3.8 mths p v sunit (HR 1.53; 90% CI 1.03–2.27; p=0.037)
- OS: 6.9 v 9.0 mths p v sunitinib (HR 1.17; 90% CI 0.77–1.78; p=0.27)
- 40% crossover

- G 3/4 tox in ≥5% with sunitinib: fatigue, neuts, platelets and hyponatremia
### VEGF inhibitors – EORTC

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Target</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Phase III</td>
</tr>
<tr>
<td>IMC-1121b</td>
<td>VEGFR-2</td>
<td>Phase I</td>
</tr>
<tr>
<td>IMC-18F1</td>
<td>VEGFR-1</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>VEGF-A, PIGF</td>
<td>Phase III</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>B-RAF, C-RAF, VEGFR2, VEGFR2, PDGFR-β, Kit</td>
<td>Phase III</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR1, VEGFR2, PDGFR-β, c-Kit</td>
<td>Phase III</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>VEGF, EGFR</td>
<td>Phase III</td>
</tr>
<tr>
<td>Cediranib</td>
<td>VEGFR1, VEGFR2, VEGFR3</td>
<td>Phase II</td>
</tr>
<tr>
<td>Axitinib</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>Motesanib</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit</td>
<td>Phase I</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

- **Pazopanib**: VEGFR1, VEGFR2, VEGFR3, PDGFR-α, PDGFR-β, c-Kit, Phase I
- **CP-547,632**: VEGFR2, PDGF, Phase II
- **BIBF 1120**: VEGFR1, VEGFR2, VEGFR3, PDGFR, FGFR, Phase II
- **XL647**: EGFR, HER2, EphB4, VEGF, Phase II
- **AEE788**: EGFR, HER2, VEGF, Phase I
- **KRN951**: VEGFR1, VEGFR2, PDGFR, c-Kit, Phase I
- **ABT-869**: VEGF, PDGF, Phase I
- **OSI-930**: Kit, KDR, Phase I
- **BMS-690514**: pan HER, VEGF, Phase I
- **Thalidomide**: BFGF, Phase III
- **Lenalidomide**: BFGF, Phase I
- **Pomalidomide**: BFGF, Phase I
- **Cilengitide**: αvβ3, αvβ5, Phase I
- **TNP-470**: Methionine aminopeptidase, Phase I
- **AMG 386**: Angiopoietin, Tie2, Phase I
- **DMXAA**: Vascular disrupting agent, Phase II

**VEGF**, vascular endothelial growth factor; **PDGF**, platelet-derived growth factor.
Phase 2 sunitinib in SCLC – secondline with early PET for response

2nd line treatment: Sunitinib, to which he responded well and continued for 22 cycles.
Sudden death 20 months later – prob PE
After 4 weeks treatment with sunitinib
Case 2: Sunitinib Responder

- 70 years old Caucasian never smoker female.
- Presenting symptoms: breathlessness, cough and haemoptysis.
- PS = 1.
- History of malignant melanoma 20 years ago.
- Diagnosis: Pure SCLC, limited stage.
- 1\textsuperscript{st} line treatment: Concomitantchemoradiotherapy (6 cycles Carboplatin/Etoposide and 50 Gy radical radiotherapy) and PCI, with good response.
- Relapse: 2.5 years later.
- 2\textsuperscript{nd} line treatment: Sunitinib (10 cycles), with very good response.
- Sunitinib had to be discontinued after 10 months due to toxicities, followed by quick disease progression.
- Re-biopsy was performed
After 4 weeks treatment with sunitinib
Other news

- Pravastatin may stop the growth of tumour cells and make tumour cells more sensitive to chemotherapy – phase III in UK negative

- enoxaparin in SCLC (Fragmatic)

- ......new agents
• At least 17 members of PARP family (PARP-1 and 2 are activated by DNA damage)
• PARP-1 localizes to the site of DNA damage and recruits proteins that mediate repair
• Double knockout of PARP 1 & 2 results in embryonal lethality to mice

Dantzer et al, Biochemistry 2000; McCabe et al, Cancer Res 2006

Poly(ADP-ribose) sub-units

PARP-1 mediated SSB repair

Dantzer et al, Biochemistry 2000; McCabe et al, Cancer Res 2006
Parp inhibitors

- Olaparib
- Velaparib
- Niraparib
- BMN673 – PARP trap

Stabilizing the PARP DNA complex

2/18 in SCLC in phase I

Biomarker is the BRCA 1 and 2 mutation, brcaness or protein expression
Not helpful in SCLC
ECOG 2511 - 3 arm
Phase I/II PE +/- veliparib (ABT-888)

- Placebo-controlled first line randomized phase II study

Stratification:
1. Gender (M vs. F)
2. LDH ≤ upper limits of normal or > ULN

- 135 patients
- SCLC by histology
- Extensive stage disease
- ECOG PS: 0-1
- Adequate hepatic, renal and marrow function
- Eligibility criteria met

Experimental Arm (D):
- Veliparib pills (RP2D^2) bid po Days 1-7^1
- Etoposide 100 mg/m^2 in 500 ml NS Days 1-3
- Cisplatin 75 mg/m^2 in 250 ml NS Day 1
- Every cycle for 4 cycles

Control Arm (E):
- Placebo bid po Days 1-7^1
- Etoposide 100 mg/m^2 in 500 ml NS Days 1-3
- Cisplatin 75 mg/m^2 in 250 ml Day 1
- Every cycle for 4 cycles

Long-Term Follow-Up

Phase II Accrual Goal = 150
Cycle = 3 weeks (21 days)
IV doses are based on actual weight

Study Chair: Taofeek Owonikoko MD PhD
Randomized phase II study of temozolomide with or without veliparib

Recurrent SCLC after 1 or 2 prior regimens
No chemotherapy or radiotherapy in prior 3 weeks
ECOG PS ≤1

Double blind

50
Veliparib 40mg PO BID × 7 days
Temozolomide 200mg/m²/d × 5 days
28 day cycle

50
Placebo 40mg PO BID × 7 days
Temozolomide 200mg/m²/d × 5 days
28 day cycle

Study Chair: Cathy Pietanza MD

Participating Sites:
MSKCC
SKCCC at JHU
MDACC
Seidman CC
Temozolomide – old (alkylating agent, cross BBB, - new - SCLC has aberrantly methylated *MGMT*

- Overall RR 20% (95% CI 11–32%)
- 13% in refractory cohort
- Of 13 patients with brain metastases
  - 4/13 with CR in brain; 1/13 with PR
  - ORR 38% in the CNS
Startup

- Randomised trial of olaparib as maintenance chemotherapy in ext SCLC post 4-6 chemotherapy - STOMP
- Same design as French and UK NSCLC
- BMN 673
Aurora Kinases

- Antimitotic agents ABC oral
  - A MLN8237 – 2 responses
  - B AZD1152 - alisertib

- 38% neutropenia, 39% alopecia
- $10/47 = 21\%$
- 3/11 responses in refractory 27%
- 7/36 19% in sensitive

- Alisertib + weekly paclitaxel
- C-Myc amplification and sensitivity
Models for Hedgehog activity in cancer - Hh sonic – required for lung development, upregulated in SCLC and inhibition delays recurrence in primary SCLC models – no mutation in sclc

Type-1  
Cancers with mutations in Hh signaling

Type-2  
Cancers with autocrine requirement for Hh

Type-3  
Cancers with paracrine requirement for Hh

BCC medulloblastoma  
glioblastoma myeloma  
SCLC  
pancreatic, colon cancer
E1508: a randomized phase II study of chemotherapy +/- vismodegib or (IGF-1R mAb) A12
T cell mediated immune rejection of tumours

Therapeutic intervention

Tumour vaccine
e.g. MAGE or intrinsic (unknown)

Presentation of tumour-specific/associated Ag

Activation of Tumour-specific T cells

CD137
CD28
IL-2
IL-15

Co-stimulatory T cell Signals

Agonists

Other immunosuppressive factors environment

T regulatory cells
Myeloid suppressor cells
IL-10, TGFbeta

Negative Regulatory signals
(immune check-points)

CTLA-4
PD1
B7-1

Antagonists

e.g. MAGE or intrinsic (unknown)
Sequential Ipilimumab Improves Irpfs In ED SCLC 1st Line Therapy With Paclitaxel / Carboplatin  

Reck M et al., Ann Oncol. 2013 Jan;24(1):75-83

Being repeated as Ideate (CA 184-156), sequential ipi, Stimuli – limited stage
Immunotherapy and SCLC

- Is it logical?? – very highly mutated – as is melanoma

- Phase 2 randomized study, ipi TC v TC PFS 5.7m vs 4.6m, HR = 0.72, P = 0.05, no improvement when used concurrently Reck et al Ann Oncol 2013.

- nivolumab (anti -PD1) v N + ipilimumab (CTL 4) followed by nivo maintenance
Ongoing studies

- Parp inhibitors/Temozolamide
- Aurora kinases/hedgehog/immuno
- 2 studies French & Italian: recruiting
  
  *Poster at meeting 2nd line paclitaxel weekly + bev*

- NGR-hTNF in Combination With Doxorubicin in Patients Affected by Metastatic Small Cell Lung Carcinoma (NGR007): MolMed

- Secondline +/- valproic acid
  
  *Old drugs new indication*

- CE + anti-NCAM – anti CD 56 BB 10901 Immunogen
  NORTH study – closed toxicity
Small-cell lung cancer sequencing project

Candidate *driver* genome alterations in SCLC
Some SCLC genes....

- **Hot spot mutations**
  - *TP53, RB1, PIK3CA, CDKN2A, PTEN*
  - RAS family regulators (*RAB37, RASGRF1, RASGRF2*)
  - Chromatin modifiers (*EP300, DMBX1, MLL2, MED12, etc.*)

- **Hot spot mutations** *PLUS q-score*
  - *RUNX1T1, CDYL, RIMS2*

- **Gene families and pathways**
  - PI3K pathway, Notch and Hedgehog, glutamate receptor family, DNA repair/checkpoint, SOX family, histones

- **Focal amplifications**
  - *MYC, SOX2, SOX4, KIT*

- **Recurrent translocations and fusion genes**
  - Recurrent: *RLF–MYCL1*
  - Kinase fusions

Rudin et al., *Nat Genet* 2012
Proteomic analysis of SCLC

Higher in SCLC:
- cKit
- IGFBP2
- LKB1
- AMPK
- TSC2
- p16
- p21
- Cyclin D1
- Rb
- PARP1
- E2F1
- TS
- EZH2
- DNA repair
- Apoptosis

Higher in NSCLC:
- EGFR
- Her2
- cMet
- Axl
- VEGFR2
- PI3K
- Akt
- mTOR
- p70S6K
- S6
- Ras
- Raf
- MEK
- MAPK
- Src
- STAT
- E-cadherin
- B-catenin
- PTCH
- Notch3

Byers et al., Cancer Discovery, 2012
SCLC – biomarker search

*N* = 60 patients

- **BRAF mutation**: 1 positive (*V600E* mutation), 46 wild type and 13 invalid.
- **EGFR mutation**: 31 wild type and 29 invalid.
- **KRAS mutation**: 35 wild type and 25 invalid.
- **ALK gene rearrangement**: 58 with no rearrangements detected and 2 invalid.
- **MET gene amplification**: 40 no amplification, 18 invalid.
exon 15 (including codon V600) (CE-SSCA)
capillary electrophoresis-single strand conformation analysis
A Case with Positive V600E BRAF Mutation

- 55 years old Caucasian male smoker.
- Presenting symptoms: increasing shortness of breath on exertion and dry cough.
- PS = 1

- A history of squamous cell carcinoma 6 months before the new diagnosis, treated by right lobectomy.

- Biopsy diagnosis: *Pure SCLC, limited stage.*

- Treatment: Radical chemoradiotherapy (4 cycles of Carboplatin/Etoposide and radiotherapy 36Gy in 12 fractions) and PCI.
- Sudden death 9 months from MI.
- Review pathology – mixed pathology in resected specimen
Case 2 sunitinib: Whole Exome Sequencing of initial sample

- **68 somatic mutations** (50 substitutions and 18 indels) were detected in the relapsed sample that did not occur in the germline. 28 out of the 68 were predicted to alter protein sequences.

- 311 germline variants and 2 somatic mutations were enriched in the relapsed sample due to LOH and predicted to alter protein sequences.

- When compared to the Cancer Gene Census (CGC), a set of 5 genes in the CGC list were found to contain missense or splice site mutations that are either somatic or enriched in carcinoid cells due to LOH. These genes are:
  - **MEN1**: essential splice site
  - **PDGFRA** (a RTK target for sunitinib): missense
  - **BCL6**: missense
  - **MLH1**: missense
  - **BRCA2**: missense

- **MLH1, BCL6, BRCA2 and PDGFRA** were predicted to be neutral with regard to the protein function.

- **REPEAT biopsy …….**
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- **REPEAT biopsy ……. ATYPICAL CARCINOID**
Heterogeneity in SCLC

- SCLC - atypical carcinoid
- Adeno mutated – SCLC
- Squamous – SCLC – with bRAF
Words of warning

- One swallow does not make a summer
- Amrubicin in refractory
- Paclitaxel weekly + bevacuzimab

- Never smoking SCLC – think carcinoid
- Unexpected stable disease
- Sunitinib works for carcinoid

- Remember heterogeneity.
- Small biopsies are giving erroneous leads…….