New Developments in Palliative Chemotherapy

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Figure 6 Population pyramids for 2006 and 2041 (M1F1)
# Rankings of Likely Death: Ireland 2014

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Cases / yr</th>
<th>Deaths / yr</th>
<th>% Death</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal</td>
<td>388</td>
<td>369</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>518</td>
<td>483</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>2378</td>
<td>1828</td>
<td>77</td>
<td>3</td>
</tr>
<tr>
<td>Brain / CNS</td>
<td>379</td>
<td>265</td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>Stomach</td>
<td>565</td>
<td>312</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Bladder</td>
<td>438</td>
<td>213</td>
<td>49</td>
<td>6</td>
</tr>
<tr>
<td>Breast</td>
<td>2919</td>
<td>694</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Prostate</td>
<td>3364</td>
<td>527</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>968</td>
<td>159</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>
Misfortune Strikes
The Passing of Time

- Curative Care
- Palliative Care
- Hospice
- Death and Bereavement Care

% focus vs. Time
Palliative Chemotherapy

• Maintain / Improve Quality of Life
• Prolong life

though cure is not possible
The Balance Within Life

The Person

- Spirit
- Body
- Reproduction
- Sexuality
- Home Environment
- Financial Environment
- Emotional Support Systems
- Co-morbidities
- Tumour
Shades of Objectives

PERSON:
• Live longer
• Quality of Life
• Dignity

STATE:
• Cost-effectiveness
• Standards of care

MEDICAL STAFF:
• Maintain quality of life
• Minimise toxicity
• Prolong survival
• Progression-free survival
• Minimise disease-related toxicity
• Balance between all the various factors
ALEKSANDR
SOLZHENITSYN
Winner of the Nobel Prize in Literature
CANCERWARD
The most moving of Solzhenitsyn's novels. - Clifton Fadiman
The Consultation

- Doc, is it treatable?
- How long do I have?
- What are the toxicities?
- How do I receive it?
- Can I drive?
- Should I stop smoking?
- What about medicinal cannabis?
- How successful is the treatment?
- I had a normal CXR last year. How can that be right?
Generalists and Specialists

Breadth of knowledge expertise

- Creating synergy between groups needed to achieve success

Specialists have focused depth of knowledge

Generalists have breadth of knowledge, but less depth
Seeking Wisdom:

• To understand the essence/meaning of something **you need depth** - what truly is this thing/idea.

  IMMERSION

• To understand the context of something **you need breadth** - how does this fit with everything else.

  COMTEMPLATION

• Thus to fully appreciate and 'know' something is to understand it well (depth) and understand how it interrelates and is connected with everything else you know (breadth).

=> WISDOM is the sum of deep understanding about a domain of knowledge and the breadth of appreciation of how it relates to all (or as much as you can be aware of) other things.
The Selection Process

- The Person
- Performance Status
- Co-morbidities
- Mindset (once news processed)
- Form of cancer
- Their family / external supports
- Location
- Prior life experiences
Disease or Treatment Related Symptoms?

*(indirect retrospective contrast)*

Nausea
Vomiting
Stomatitis
Diarrhoea
Fatigue
Infection

Erlotinib
Placebo (BR21)
Docetaxel

Legend:
- Orange: Erlotinib
- Blue: Placebo (BR21)
- Green: Docetaxel
Survival in trials of supportive care versus supportive care plus chemotherapy (only trials using regimens based on cisplatin).
Survival in trials of supportive care versus supportive care plus chemotherapy (only trials using regimens based on cisplatin).

Chemotherapy and BSC > BSC alone

Chemotherapy and Palliative Care > Chemotherapy alone

=>
• focus on optimising symptom control
• Chemotherapy in appropriate individuals

• LOGIC: If people are maintained in an optimal state, they are likely to want to live longer, and have the capacity to live longer
Advanced Disease – CancerCare Ontario population based study (de novo Stage IV NSCLC 2005-9)

-23% of stage IV NSCLC patients received CT in SEER Analysis (1991-6)
  - increase over time
  - referral to oncologist, age, comorbidity → CT

-30% of IIIB/IV pts in BC received CT
  - only 54% referred to oncologist, 37% PS 3 or 4

Median Age | 68
--- | ---
Female/Male | 46%/54%


Presented By Natasha Leighl at 2015 ASCO Annual Meeting
Molecular Classification of NSCLC

- SCLC
- NSCLC
- Squamous
- Non-squamous (adenocarcinoma)

- KRAS 25%
- EGFR 13%
- No Known Genotype
- RET
- NTRK1
- FGFR
- MET amp
- PIK3CA
- MET Exon 14
- ALK 4%
- HER2
- ROS1

PD1 / PDL-1

Presented by Alice Shaw at 2017 ASCO Annual Meeting
Metastatic Lung Cancer
ALK Mutated

- Presented with malignant effusion 7/15
  
  Alimta-carboplatin x 6 cycles: good response
  ALK Mutation detected; crizotinib started 1/16

  Stable disease; treatment well tolerated over next 12 mths

Headaches / ataxia 8/17

Radiation therapy 8/17

What next in 10/17?
Primary endpoint: PFS, investigator-assessed

- Crizotinib (N=151)
  - Patients with events, n (%): 102 (68)
  - Median PFS, months (95% CI): 11.1 (9.1–13.1)
  - HR (95% CI): 0.47 (0.34–0.65)
  - P-value (log-rank test): P<0.0001

- Alectinib (N=152)
  - Patients with events, n (%): 62 (41)
  - Median PFS, months (95% CI): NR (17.7–NR)

- Patients at Risk:
  - Crizotinib: 151, 132, 104, 84, 65, 46, 35, 16, 5
  - Alectinib: 152, 135, 113, 109, 97, 81, 67, 35, 15, 3

No. at Risk

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Presented By Alice Shaw at 2017 ASCO Annual Meeting
Secondary endpoint: Time to CNS progression (by IRC, ITT)

- A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted.
- For each patient, the first event of CNS progression, non-CNS progression or death was counted.

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>68 (45)</td>
<td>18 (12)</td>
</tr>
</tbody>
</table>

**Cause-specific HR**
(95% CI) 0.16 (0.10–0.28)$
P-value (log-rank test) P<0.0001

Cumulative incidence of CNS progression

- **Crizotinib**
  - 12 month CIR: 41.4% (95% CI, 33.2–49.4)
- **Alectinib**
  - 12 month CIR: 9.4% (95% CI, 5.4–14.7)
Metastatic Breast Cancer (ER+/Her2+) in a young 35yr old woman

Perjeta-Herceptin-Docetaxel
Addition of Perjeta: median survival 56 mths vs 40 mths

Progressive disease (7/15) despite initial response on 4/17 scan

TDM-1 vs Her2
30.9 months vs. 25.1 months

TDM1: 7/15 until 7/16
New hip lesion / more liver disease
Metastatic Breast Cancer (ER+/Her2+) in a young 35yr old woman

- She was not eager for orthopaedic intervention; tolerated radiation therapy
- Switched to vinorelbine – herceptin; poorly tolerated
- Switched to taxol-herceptin 9/16 (in view of poor tolerance of vinorelbine)
- Progressive disease 7/17; change to CMF-herceptin 3/7/17
Glioblastoma Multiforme in a 48yr old male

- GBM diagnosed. Good post-op recovery
- STUPP (radiation/tem. -> tem.)
- Debulking over 2 further episodes
- Immunotherapy (expanded access Nivo-Ipi)
- Deterioration:
  - ? Treatment related colitis
  - ? Steroid-resistant cerebral oedema
- Avastin commenced 6/16; dramatic physical improvement
- VP shunt insertion for hydrocephalus
Glioblastoma Multiforme in a 48yr old male

• New lesion lesion:
  – ? Nature

• Biospy of liver
• Addition of temozolomide 9/16
• Ongoing response within liver / stability in brain
## Nomenclature

<table>
<thead>
<tr>
<th>Anti-PD1</th>
<th>Anti-PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
<td><strong>Atezolizumab</strong></td>
</tr>
<tr>
<td>(BMS-936558)</td>
<td>(MPDL3280A)</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td><strong>Durvalumab</strong></td>
</tr>
<tr>
<td>(MK3475)</td>
<td>(MED14736)</td>
</tr>
<tr>
<td></td>
<td><strong>Avelumab</strong></td>
</tr>
<tr>
<td></td>
<td>(MSB0010718C)</td>
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</table>
PD-L1 as a biomarker: NSCLC

<table>
<thead>
<tr>
<th>Detection antibody</th>
<th>Nivolumab (Roche)</th>
<th>Pembrolzumab (Merck)</th>
<th>Atezolizumab (Roche)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>28-8</td>
<td>22C3</td>
<td>SP142</td>
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<tr>
<td>IHC Platform</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
</tr>
<tr>
<td>Tested cells</td>
<td>Lung (TC)</td>
<td>NSCLC (TC)</td>
<td>NSCLC (IC and TC)</td>
</tr>
<tr>
<td>PD-L1 Prevalence</td>
<td>TC &gt;=5% 46%</td>
<td>TC &gt;=50% 25%</td>
<td>TC or IC &gt;=50% 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC or IC &gt;=5% 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC or IC &gt;=1% 68%</td>
</tr>
</tbody>
</table>

- Anti-PDL1/PD1 therapies show efficacy in previously treated NSCLC regardless of histology or biomarker status

- PD-L1 expression may identify patients with greater response rates
Kaplan–Meier Curves for Overall Survival.
NSCLC Stage IV (Squamous), 2nd line Nivolumab vs Docetaxel

<table>
<thead>
<tr>
<th></th>
<th>Median Overall Survival</th>
<th>1-Yr Overall Survival</th>
<th>No. of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (N=135)</td>
<td>9.2 (7.3–13.3)</td>
<td>42 (34–50)</td>
<td>86</td>
</tr>
<tr>
<td>Docetaxel (N=137)</td>
<td>6.0 (5.1–7.3)</td>
<td>24 (17–31)</td>
<td>113</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.59 (0.44–0.79) P<0.001

No. at Risk
Nivolumab 135 113 86 69 52 31 15 7 2 0
Docetaxel 137 103 68 45 30 14 7 2 0

CHECKMATE-017

Advanced Stage NSCLC, PDL1 >50%

Overall Survival

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60 (0.41-0.89)</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

OS, %

Time, months

No. at risk

0 3 6 9 12 15 18 21

154 136 121 82 39 11 2
151 123 106 64 34 7 1

Data cut-off: May 9, 2016.

Presented By Edward Garon at 2017 ASCO Annual Meeting
PFS by Tumor Mutation Burden (TMB) Subgroup
CheckMate 026: Nivolumab vs. platinum doublet in first-line NSCLC

High TMB

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Median PFS, months</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>47</td>
<td>9.7</td>
<td>(5.1, NR)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>60</td>
<td>5.8</td>
<td>(4.2, 8.5)</td>
</tr>
</tbody>
</table>

HR = 0.62 (95% CI: 0.38, 1.00)

Low/medium TMB

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Median PFS, months</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>111</td>
<td>4.1</td>
<td>(2.8, 5.4)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>94</td>
<td>6.9</td>
<td>(5.5, 8.6)</td>
</tr>
</tbody>
</table>

HR = 1.82 (95% CI: 1.30, 2.55)
OAK: 1-2 prior lines of systemic therapy (non-IO) for advanced NSCLC

OS Post-PD in Atezolizumab Arm: By Post-PD Treatment

18-mo OS
- 37%
- 20%
- 9%

Overall Survival Post-PD (%)

Time since First Reported PD (months)

No PD per RECIST v1.1
- n = 93, 22%

PD per RECIST v1.1
- n = 332, 78%

Atezolizumab
- n = 425

Continued Atezo Post-PD
- n = 168, 51%
- mOS 12.7 mo (9.3, 14.9)

Other anti-cancer NPT Post-PD
- n = 94, 28%
- mOS 8.8 mo (6.0, 12.1)

No anti-cancer NPT Post-PD
- n = 70, 21%
- mOS 2.2 mo (1.9, 3.4)


Presented By David Gandara at 2017 ASCO Annual Meeting
The Impact

• Cognitive function
• Energy
• Fertility
• Financial well-being
• Neurological
• Nutrition
• Physical

• Hope
Life-giving vs Death-bringing Sword