Immuno-oncology in lung cancer

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I provided consultations or attended advisory boards for Astra-Zeneca, Eli Lilly Oncology, F. Hoffman-La Roche Ltd, Merck, Astellas and Pfizer, for which I received appropriate honoraria.
Immuno-oncology in lung cancer

Rationale
Magnitude of genomic derangement

Drugable targets in smokers and never smokers

Significantly mutated genes in squamous NSCLC

Nature 489:519-525, 2012
Evolution of NSCLC, from histology to molecular characteristics

Li T, et al. JCO, 2013
Lung cancer
Willam Coley (1862 – 1936)
Role of the immune system in cancer and the process of immunoediting

**Immunoediting** describes the contrasting role of the immune system in protecting against tumour development and promoting tumour growth.

**Elimination**
*Cancer immunosurveillance*
- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - e.g., T-cell activation without co-inhibitory signals

**Equilibrium**
*Cancer dormancy*
- Genetic instability
- Tumour heterogeneity
- Immune selection

**Escape**
*Cancer progression*
- Tumours avoid elimination through the outgrowth of tumour cells that can suppress, disrupt, or ‘escape’ the immune system

T-cell based immunomodulation

Prognostic roles of immune cells in NSCLC

- Similar to melanoma and RCC, lung tumours are recognised by the immune system, and initiate an immune response
- Certain immune cells are associated with a better prognosis/improved outcome, while others suggest an unfavourable prognosis and disease outcome

The T-cell antitumour response

1. Tumour antigens released by tumour cells

2. Tumour antigens presented to T cells

3. T cells are activated and proliferate

4. T cells recognize tumour antigens

5. T cells kill tumour cells

APC = antigen-presenting cell

Regulating the T-cell immune response

- T cell responses are regulated through a complex balance of inhibitory (‘checkpoint’) and activating signals.
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response.
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response.

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The image shows only a selection of the receptors/pathways involved:

**Activating receptors**
- CD28
- OX40
- CD137

**Inhibitory receptors**
- PD-1
- CTLA-4
- TIM-3
- LAG-3

**Antagonistic (blocking) antibodies**

**Agonistic antibodies**

*a*The image shows only a selection of the receptors/pathways involved.

LAG-3 = lymphocyte-activation gene 3

Multiple interactions regulate T-cell responses

Tumours use various mechanisms to escape the immune system

Immune escape mechanisms are complex and frequently overlapping

### Data suggesting immune recognition and response in selected tumour types

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Prognostic\textsuperscript{a} tumour infiltrating lymphocytes\textsuperscript{b}</th>
<th>Immune-related spontaneous tumour regression\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>Yes\textsuperscript{1}</td>
<td>Yes\textsuperscript{13} (rare)</td>
</tr>
<tr>
<td>CRC</td>
<td>Yes\textsuperscript{2}</td>
<td>Yes\textsuperscript{14}</td>
</tr>
<tr>
<td>Breast</td>
<td>Yes\textsuperscript{3,4}</td>
<td>No</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Yes\textsuperscript{5,6}</td>
<td>Yes\textsuperscript{15}</td>
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<tr>
<td>Renal</td>
<td>Yes\textsuperscript{7,8}</td>
<td>Yes\textsuperscript{16,17}</td>
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<tr>
<td>Prostate</td>
<td>Yes\textsuperscript{9}</td>
<td>No</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Yes\textsuperscript{10}</td>
<td>No</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Yes\textsuperscript{11}</td>
<td>No</td>
</tr>
<tr>
<td>Cervical</td>
<td>Yes\textsuperscript{12}</td>
<td>Evidence for cervical intraepithelial neoplasia 2/3\textsuperscript{18,19}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Covers correlation with improved overall or progression-free survival, disease stage, or therapy outcome

\textsuperscript{b}The type of lymphocyte dictates where there is a correlation with improved or worsened outcome

\textsuperscript{c}Based on PubMed search conducted in October 2013 using the terms ‘spontaneous regression’ and the tumour type

Potential investigational immunotherapeutic approaches as treatment options for lung cancer

Immunotherapy

Active
- Designed to act on the immune system itself

- Antigen dependent
  - Enhancing immune cell function
    - Cytokines
  - Therapeutic vaccines
    - GSK1572932A
    - TG4010
    - Belagenpumatumucel-L
    - Tergenpumatumucel-L
    - Racotumomab
    - Stimuvax
    - CIMAvax

- Antigen independent
  - Modulate T-cell function
    - Immuno-Oncology (I-O)
      - CTLA-4 inhibition
      - PD-1 inhibition
      - PD-L1 inhibition

Passive (adoptive)
- Designed to act at tumour; immune-based mechanism

- Antitumour mAbs
- Adoptive
  - Bavituximab
    - EGFR inhibition
  - Adoptive cell transfer

CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1

NSCLC tumor immunology and modulation by conventional therapies

Immuno-oncology in lung cancer

Vaccines
Mechanism of action of cancer vaccines

Mechanism of action of cancer vaccines

# Monovalent vaccine clinical trials in NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
<th>NSCLC stage</th>
<th>Patient (n)</th>
<th>Trial design</th>
<th>Endpoints</th>
<th>Secondary analysis/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC TAA + CFA</td>
<td>CFA +/- SCC TAA vs. Control</td>
<td>Stage I-II SCC¹</td>
<td>85</td>
<td>Phase III Randomized</td>
<td>Primary:</td>
<td>SCC TAA + CFA: 5-Y S = 75%, MOS = 106 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Survival (5-YS)</td>
<td>CFA Alone: 5-Y S = 53%, MOS = 71 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• OS</td>
<td>Control: 5-Y S = 34%, MOS = 38 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>LUD99-010</td>
<td>Recombinant MAGE-A3 protein +/- AS02B</td>
<td>Stage I-II (MAGE-A3+)</td>
<td>17</td>
<td>Phase II Non-randomized</td>
<td>Primary:</td>
<td>MAGE-A3 alone: (3/9) Abs to MAGE-A3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Immune resp.</td>
<td>(1/9) HLA-A2 restricted CD8+ resp.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MAGE-A3+ AS02B: (8/8) Abs to MAGE-A3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4/8) HLA-DR4 restricted CD4+ resp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1/8) HLA-A1 restricted CD8+ resp.</td>
</tr>
<tr>
<td>MAGE-A3 ASCI</td>
<td>Recombinant MAGE-A3 protein + AS15</td>
<td>Stage IB (122/182) Stage II (60/182) (MAGE-A3+)</td>
<td>182</td>
<td>Phase II Randomized (2:1) vax: placebo</td>
<td>Primary:</td>
<td>Hazard Ratio (favoring vax, arm):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• DFI</td>
<td>DFI = 0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary:</td>
<td>DFS = 0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Safety</td>
<td>OS = 0.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• DFS</td>
<td>Relative improvement in DFI and DFS (27%)</td>
</tr>
<tr>
<td>MAGRIT</td>
<td>Recombinant MAGE-A3 protein + AS15 (MAGE-A3+)</td>
<td>Stage IB-IIIA</td>
<td>2270 (expected)</td>
<td>Phase III Randomized (2:1) vax: placebo</td>
<td>Primary:</td>
<td>Pending</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• DFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary:</td>
<td>Validation of gene signature predictive of response</td>
</tr>
</tbody>
</table>

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## Multivalent vaccine clinical trials in NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
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<th>Secondary analysis/results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GVAX</strong></td>
<td>GM-CSF transduced, irradiated autologous tumor cells</td>
<td>Cohort A: IB–IIA (10/43) Cohort B: IIIA-IV (33/43)²</td>
<td>83</td>
<td>Phase I/II Non-randomized</td>
<td>Primary: • Safety • Feasibility • Immune resp. Secondary: • Tumor reg. • Disease prog. • Survival</td>
<td>• 80% vax. prod. success in cohort A • Immune resp. not associated with overall tumor reg. or surv. • Recurrences: 6/10 in cohort A</td>
</tr>
<tr>
<td><strong>Autologous Dendritic Cell (ADC)</strong></td>
<td>ADCs loaded with Her2/neu, CEA, WT1, MAGE-2, and survivin peptides</td>
<td>Stage IA–IIIA (13/16)³ Stage IIIB (3/16)⁴</td>
<td>16</td>
<td>Phase II Non-randomized</td>
<td>Primary: • Immune resp. Secondary: • Clinical tolerability</td>
<td>• TAA specific response in (7/12) surgical pts. • No recurrence in (9/12) surgical pts. at mean post-vax F/U of 18 months. • Well tolerated</td>
</tr>
</tbody>
</table>

## Phase II and III vaccine trials in NSCLC

<table>
<thead>
<tr>
<th>Agent and trial</th>
<th>Phase</th>
<th>Design and description</th>
<th>n</th>
<th>Results and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGE-A3 vaccine with A502 adjuvant</td>
<td>II</td>
<td>Randomized trial of vaccine or placebo post resection of stage IIB and II MAGE-A3+ NSCLC</td>
<td>182</td>
<td>Gene expression profile revealed a 43% reduction of recurrence in vaccine treated group (HR 0.57, 95% CI 0.36–1.2, P=0.99). Primary end point of disease-free interval was not significantly different between the two groups (HR 0.74, P=0.107)</td>
</tr>
<tr>
<td>Liposomal MUC-1 peptide vaccine (L-BLP-25)</td>
<td>II</td>
<td>Randomized trial of L-BLP-25 vs BSC in patients with stage IIIB or IV NSCLC with stable or responsive disease post chemotherapy or chemoradiation</td>
<td>171</td>
<td>Primary end point of median OS 17.2 months L-BLP-25 vs 13 months BSC (P=0.066); subgroup analysis: stage IIIB patients OS 30.6 months vs 13.3 months in BSC arm</td>
</tr>
<tr>
<td>Vaccinia/MUC-1 vaccine (TG4010)</td>
<td>II</td>
<td>Randomized trial of cisplatin and vinorelbine with TG4010 vs TG4010 as a single agent until disease progression followed by addition of vinorelbine and cisplatin in patients with MUC-1-positive advanced NSCLC</td>
<td>65</td>
<td>Primary end point of response was met only for the concurrent TG4010 and chemotherapy arm; response rate 29.5%</td>
</tr>
<tr>
<td>Vaccinia/MUC-1 vaccine (TG4010)</td>
<td>IIB</td>
<td>Randomized trial of gemcitabine and cisplatin vs the same combination with TG4010 in patients with stage 4 NSCLC</td>
<td>108</td>
<td>Patients with normal level of activated NK cells at baseline had an improvement in 6-month PFS and OS. Patients with high levels of active NK cells had increased toxic effects. Primary end point of 6-month PFS met only for the concurrent TG4010 arm (43%), but not significantly different from chemotherapy alone (35%)</td>
</tr>
<tr>
<td>Allogeneic whole cell NSCLC line vaccine with anti-sense TGF-β (Belagenpumatucel-L)</td>
<td>II</td>
<td>Randomized multi-dose trial in NSCLC with low volume stage II, IIIA, IIB, IV disease</td>
<td>75</td>
<td>Response rate 15%; OS, 441 days in advanced-stage disease setting</td>
</tr>
<tr>
<td>MAGE-A3 NCT00480025</td>
<td>III</td>
<td>Randomized phase III trial of patients with resected stage IIB–IIIA MAGE-A3+ NSCLC post resection or adjuvant chemotherapy</td>
<td>2,289</td>
<td>Primary end point: DFS</td>
</tr>
<tr>
<td>L-BLP-25 NCT00409188</td>
<td>III</td>
<td>Randomized trial comparing vaccine vs placebo in patients with unresectable stage III with stable or responding disease after chemoradiotherapy</td>
<td>1,464</td>
<td>Primary end point: OS not met</td>
</tr>
<tr>
<td>L-BLP-25 NCT01015443*</td>
<td>III</td>
<td>Randomized trial comparing vaccine vs placebo in patients with unresectable stage III with stable or responding disease after chemoradiotherapy</td>
<td>420</td>
<td>Primary end point: OS</td>
</tr>
<tr>
<td>L-BLP-25 NCT00828005†</td>
<td>II</td>
<td>BLP25 vaccine and bevacizumab after chemoradiotherapy for patients with unresectable stage IIIA/E NSCLC</td>
<td>55</td>
<td>Primary end point: safety</td>
</tr>
<tr>
<td>TG4010 NCT01383148</td>
<td>IIB/III</td>
<td>Randomized trial comparing platinum combination chemotherapy with or without vaccine in patients with stage IV NSCLC</td>
<td>1,000</td>
<td>Primary end point: OS</td>
</tr>
<tr>
<td>BeigenpumaturecHL NCT00576507</td>
<td>III</td>
<td>Randomized trial of vaccine or placebo in patients with stage IIA, IIB or IV NSCLC with stable or responding disease after initial chemotherapy</td>
<td>506</td>
<td>Primary endpoint: OS</td>
</tr>
</tbody>
</table>

Immuno-oncology in lung cancer
Differences in CTLA-4 and PD-1 blockade

CTLA-4 blockade (ipilimumab) vs. PD-1 blockade (nivolumab)

Activation (cytokines, lysis, proliferation, migration to tumour)

Ipilimumab blocks CTLA-4 and augments T-cell activation

**T-cell activation**

- CTLA-4
- T cell
- CD28
- B7
- MHC
- APC

**T-cell inhibition**

- CTLA-4
- T cell
- CD28
- B7
- MHC
- APC

**T-cell potentiation**

- Ipilimumab blocks CTLA-4
- T cell
- CD28
- B7
- MHC
- APC

Adapted from Weber J. Cancer Immunol Immunother 58:823, 2009
Randomized phase II study of Ipilimumab and CT in advanced NSCLC

First-line Stage IIIb/IV NSCLC 18 yrs of age or older ECOG PS 0/1

1:1:1

Randomize

Concurrent
IPI + Pac/Carbo

Phased
IPI + Pac/Carbo

Control
P + Pac/Carbo

(N = 204)

Induction Phase
(n = 203)

Maintenance Phase
(n = 73)

q3w

q12w

Follow-up phase

Follow-up phase

Follow-up phase

- Primary endpoint: irPFS
- Cx regimen: Pac 175 mg/m²/carbo AUC 6 prior to start of ipilimumab (10 mg/kg)

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

Randomized phase II study of Ipilimumab and CT in advanced NSCLC

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (n = 65)</th>
<th>Concurrency Ipilimumab (n = 71)</th>
<th>Phased Ipilimumab (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1 and 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Any adverse event, %</td>
<td>31</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Any treatment-related adverse event, %</td>
<td>43</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>Treatment-related non-hematologic adverse events, %</td>
<td>Fatigue</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>3</td>
<td>2</td>
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<tr>
<td></td>
<td>Diarrhea</td>
<td>14</td>
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<tr>
<td></td>
<td>Nausea</td>
<td>31</td>
<td>2</td>
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<tr>
<td></td>
<td>Vomiting</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy*</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral sensory neuropathy*</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Hematologic abnormalities, %†</td>
<td>Thrombocytopenia</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>89</td>
<td>6</td>
</tr>
<tr>
<td>Liver-function enzymes, %†</td>
<td>ALT</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>AST</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

**Ongoing phase III: Ipilimumab in squamous NSCLC**

- **Stage IV or recurrent squamous cell NSCLC**
  - ECOG PS ≤ 1 (N = 1100)

- **Double-blind study**
- **Primary endpoint: OS**
- **Secondary endpoints: OS in patients who receive 1 dose of ipilimumab/ placebo, PFS, RR**

**Randomization and Drug Allocation**

- **Treatment Group 1:**
  - Carboplatin AUC 6 + Paclitaxel 175 mg/m² q3w x 6 + Placebo

- **Treatment Group 2:**
  - Carboplatin AUC 6 + Paclitaxel 175 mg/m² q3w x 6 + Ipilimumab 10 mg/kg q3w x 4, then q12w starting at Wk 24
Immuno-oncology in lung cancer

PD-1 & PD-L1
Blockade of PD-1 binding to PDL1 (B7-H1) and PDL-2 (B7-DC) revives T cells

- PD-L1 expression on tumor cells is induced by γ-interferon
- In other words, activated T cells that could kill tumors are specifically disabled by those tumors
Role of PD-1 pathway in suppressing antitumour immunity

Recognition of tumour by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 upregulation on tumour

Priming and activation of T cells through MHC/antigen and CD28/B7 interactions with antigen-presenting cells

Tumour cell

Dendritic cell

Nivolumab is a PD-1 receptor blocking antibody
<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Target</th>
<th>Development Stage in NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Bristol-Myers Squibb</td>
<td>CTLA4</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>MedImmune</td>
<td>CTLA4</td>
<td>Phase I</td>
</tr>
<tr>
<td>Nivolumab (BMS-936558)</td>
<td>Bristol-Myers Squibb</td>
<td>PD-1</td>
<td>Phase III</td>
</tr>
<tr>
<td>Lambrolizumab (MK-3475)</td>
<td>Merck</td>
<td>PD-1</td>
<td>Phase III</td>
</tr>
<tr>
<td>BMS-936559</td>
<td>Bristol-Myers Squibb</td>
<td>PD-L1</td>
<td>Phase I</td>
</tr>
<tr>
<td>Medi-4736</td>
<td>MedImmune</td>
<td>PD-L1</td>
<td>Phase I</td>
</tr>
<tr>
<td>MPDL-3280A</td>
<td>Genentech</td>
<td>PD-L1</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Somme immune checkpoint inhibitors in NSCLC

Nivolumab phase I trial in squamous/nonsquamous NSCLC

Died/Treated - 88/129
Median, Mos (95% CI) - 9.6 (7.8-12.4)

1-yr OS: 42%
2-yr OS: 14%

Open circles indicate censored events, denoting the time to the last known alive date before the date of data analysis, for patients without a death.

Duration of response and overall survival with nivolumab monotherapy in NSCLC

NSCLC responders\(^a,b\) by histology

All treated subjects with NSCLC

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

\(^a\)Responses were assessed by modified RECIST v1.0

\(^b\)All efficacy analyses based on data collected as of September 2013


<table>
<thead>
<tr>
<th>Died/treated</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>94/129</td>
<td>9.90 (7.80, 12.40)</td>
</tr>
</tbody>
</table>

Median OS: 9.9 months (7.8, 12.4)

1 year OS rate 42% (48 patients at risk)

2 year OS rate 24% (20 patients at risk)
### Nivolumab: activity across NSCLC histology

<table>
<thead>
<tr>
<th>NSCLC histology</th>
<th>Dose (mg/kg)</th>
<th>ORR % (n/N)</th>
<th>Stable disease rate ≥24 week, % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>1</td>
<td>0 (0/18)</td>
<td>26.7 (4/15)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22.2 (4/18)</td>
<td>5.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>23.8 (5/21)</td>
<td>14.3 (3/21)</td>
</tr>
<tr>
<td>Squamous</td>
<td>All doses</td>
<td>16.7 (9/54)</td>
<td>14.8 (8/54)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>26.3 (5/19)</td>
<td>10.5 (2/19)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>18.9 (7/37)</td>
<td>5.4 (2/37)</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>All doses</td>
<td>17.6 (13/74)</td>
<td>6.8 (5/74)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5.6 (1/18)</td>
<td>5.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>22.2 (4/18)</td>
<td>5.6 (1/18)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>18.9 (7/37)</td>
<td>5.4 (2/37)</td>
</tr>
</tbody>
</table>

Selected adverse events (≥1%) in patients with NSCLC treated with nivolumab

- Select adverse event defined as an event with potential immunological aetiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up
- Drug-related pneumonitis (any grade) occurred in 8 NSCLC patients (6%); 3 patients (2%) had grade 3-4 pneumonitis of which 2 cases were fatal

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-related select adverse event</td>
<td>41 (53)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Skin</td>
<td>16 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>6 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Nivolumab: change in tumour burden and response kinetics by number of prior therapies

Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Nivolumab: change in tumour burden according to **EGFR** and **KRAS** mutation status

Dashed horizontal lines denote 30% decrease for PR (in the absence of new lesions) and 20% increase for PD per RECIST v1.0

Baseline tumour measurements are standardised to zero; tumour burden is measured as the sum of the longest diameters of target lesions.
Horizontal lines denote 30% decrease for PR and 20% increase for PD per RECIST 1.1 Only patients with both baseline and on-study target lesion measurements are included.

Rizvi NA, et al. ASCO 2013. Abstract 8072
## Nivolumab plus CT: duration of response

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (10 mg/kg)</th>
<th>Nivolumab (5 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem/Cis n=12</td>
<td>Pem/Cis n=15</td>
</tr>
<tr>
<td>(Arm A)</td>
<td>(Arm B)</td>
<td>(Arm C)</td>
</tr>
<tr>
<td>Number of responders, n</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Ongoing responders, n (%)</td>
<td>2 (50)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Estimated median duration of response, weeks</td>
<td>NR</td>
<td>25</td>
</tr>
<tr>
<td>Response duration</td>
<td>12/18/33+/36+</td>
<td>13/14+/18+/24/27/29+/25/32/38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pac/Carb n=14</td>
</tr>
<tr>
<td>(Arm C5)a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; Pac = paclitaxel; Pem = pemetrexed

a Protocol was amended to include an extra arm for this combination;
b Time from first response to documented progression, death, or last tumour assessment;
c Estimated mean duration determined by Kaplan-Meier curves;
d+ indicates ongoing response
### Nivolumab plus CT: duration of response

<table>
<thead>
<tr>
<th>Treatment-related AE, n (%)</th>
<th>Nivolumab (10 mg/kg)</th>
<th>Nivolumab (5 mg/kg)</th>
<th>Total N=56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem/Cis n=12 (Arm A)</td>
<td>Pem/Cis n=15 (Arm B)</td>
<td>Pac/Carb n=15 (Arm C)</td>
</tr>
<tr>
<td>Any AE</td>
<td>0</td>
<td>5 (33)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>2 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>1 (7)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Colitis</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

Carb = carboplatin; Cis = cisplatin; Gem = gemcitabine; Pac = paclitaxel; Pem = pemetrexed

*Protocol was amended to include an extra arm for this combination*
Ongoing phase III: Nivolumab in squamous NSCLC

Stage IIIB/IV or recurrent squamous-cell NSCLC following RT or resection, previous Pt-containing chemotherapy ECOG PS ≤ 1 (N = 264)

- Primary endpoints: ORR, OS
- Secondary endpoints: PFS, ORR, and OS in PD-L1–positive vs PD-L1–negative subgroups, duration of OR, time to OR, proportion of patients exhibiting disease-related symptom progression as per Lung Cancer Symptom Scale

Treat until progression or unacceptable toxicity or withdrawal of consent

- Docetaxel 75 mg/m² IV q3w
- Nivolumab 3 mg/kg IV q2w
## Nivolumab development in NSCLC

<table>
<thead>
<tr>
<th>Setting</th>
<th>Population</th>
<th>Study</th>
<th>Design</th>
<th>Endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st-line</td>
<td>Treatment-naïve</td>
<td>CA209-012</td>
<td>Nivolumab monotherapy; nivolumab combined with platinum doublets; erlotinib; bevacizumab or ipilimumab</td>
<td>Safety; antitumour activity</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Treatment-naïve</td>
<td>CA209-026</td>
<td>Nivolumab vs investigator’s choice of chemotherapy</td>
<td>PFS in high PD-L1 expression tumours</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>2nd-line</td>
<td>Prior platinum, squamous histology</td>
<td>CA209-017</td>
<td>Nivolumab vs docetaxel</td>
<td>ORR/OS</td>
<td>Ongoing/ Accrual complete</td>
</tr>
<tr>
<td></td>
<td>Prior platinum, nonsquamous histology</td>
<td>CA209-057</td>
<td>Nivolumab vs docetaxel</td>
<td>OS</td>
<td>Ongoing/ Accrual complete</td>
</tr>
<tr>
<td>3rd-line and beyond</td>
<td>Squamous histology, ≥2 prior treatments</td>
<td>CA209-063</td>
<td>Nivolumab monotherapy</td>
<td>ORR</td>
<td>Ongoing/ Accrual complete</td>
</tr>
</tbody>
</table>
CA209-012/NCT01454102: ARMS A-F

Phase 1 trial: chemotherapy-based arms
Stage IIIB/IV NSCLC
N=220 (across all arms of trial)

**ARM A**
Squamous NSCLC
Cis 75 mg/m\(^2\) IV D1 Q3W x four cycles
Gem 1250 mg/m\(^2\) IV D1 and D8 Q3W x four cycles
Nivolumab 10 mg/kg D1 Q3W

**ARM B**
Nonsquamous NSCLC
Cis 75 mg/m\(^2\) IV D1 Q3W x four cycles
Pem 500 mg/m\(^2\) IV D1 Q3W x four cycles
Nivolumab 10 mg/kg D1 Q3W

**ARM C**
Any histology
Carbo AUC 6 IV D1 Q3W x four cycles
Pac 200 mg/m\(^2\) IV D1 Q3W x four cycles
Nivolumab 10 mg/kg D1 Q3W

**ARM D**
Nonsquamous NSCLC ≥4 cycles of platinum-doublet without PD
Maintenance: Bev 15 mg/kg IV D1 Q3W until PD or discontinuation due to toxicity
Nivolumab 5 mg/kg IV D1 Q3W

**ARM E**
Nonsquamous NSCLC with EGFR mutation
Erl 150 mg/day PO until PD or discontinuation due to toxicity
Nivolumab 3 mg/kg IV D1 Q2W

**ARM F**
Any histology
Nivolumab 3 mg/kg IV Q2W

Until PD or discontinuation due to toxicity

Protocol was amended to include Arm C5 to obtain further information regarding clinical safety and activity of nivolumab at 5 mg/kg in combination with paclitaxel and carboplatin.
CA209-012/NCT01454102: ARMS G-M

Phase 1 trial: chemotherapy-based arms
Stage IIIB/IV NSCLC
N=220 (across all arms of trial)

ARM G
Squamous NSCLC
IPI 3 mg/kg D1 Q3W x 4
Nivolumab 1 mg/kg IV D1 Q3W x 4, then 3 mg/kg Q2W

ARM H
Nonsquamous NSCLC
IPI 3 mg/kg D1 Q3W x 4
Nivolumab 1 mg/kg IV D1 Q3W x 4, then 3 mg/kg Q2W

ARM I
Squamous NSCLC
IPI 1 mg/kg D1 Q3W x 4
Nivolumab 3 mg/kg IV D1 Q3W x 4, then 3 mg/kg Q2W

ARM J
Nonsquamous NSCLC
IPI 1 mg/kg D1 Q3W x 4
Nivolumab 3 mg/kg IV D1 Q3W x 4, then 3 mg/kg Q2W

ARM K
Squamous NSCLC
pts completing ≥4 cycles of platinum-doublet chemotherapy without PD
Switch maintenance nivolumab 3 mg/kg IV Q2W

ARM L
Nonsquamous NSCLC
patients completing ≥4 cycles of platinum-doublet chemotherapy (bev) without PD
Switch maintenance nivolumab 3 mg/kg IV Q2W

ARM M
Any histology patients with untreated, asymptomatic brain metastases
Nivolumab 3 mg/kg IV Q2W

Until PD or discontinuation due to toxicity

www.clinicaltrials.gov
Lambrolizumab (MK-3475) in 2\textsuperscript{nd} line for NSCLC

**Objectives of Protocol:**
- Assess safety and efficacy in patients with previously treated NSCLC

**Eligibility Criteria for Protocol:**
- 2 prior systemic therapies
- ≥1 measurable lesion
- ECOG PS of 0-1
- Submission of a new tumor specimen for PD-L1 analysis

**Treatment:**
10 mg/kg IV Q3W until progression by irRC, intolerable toxicity, or consent withdrawal

**Patients:**
N = 38: 42% male, 45% aged ≥65 years, 58% with ECOG PS 1, 66% former/current smokers, 16% squamous, 11% treated brain metastases

**PD-L1 Status:** Assessed with a Merck proprietary IHC clinical trial assay; 61% positive (>0), 26% negative, 13% not evaluable; potential cut point determined by the Youden Index from a receiver operator characteristics curve
## Lambrolizumab (MK-3475) in 2nd line for NSCLC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>irRC, Investigator Review</th>
<th>RECIST v1.1, Independent Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ORR, n (%)</td>
<td>Median PFS, wk (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>38</td>
<td>9 (24%) [11%, 40%]</td>
<td>9.1 (8.3, 17.4)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>31</td>
<td>7 (23%) [10%, 41%]</td>
<td>9.1 (8.3, 17.0)</td>
</tr>
<tr>
<td>Squamous</td>
<td>6</td>
<td>2 (33%) [4%, 78%]</td>
<td>23.5 (2.7, NR)</td>
</tr>
</tbody>
</table>

Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1

<table>
<thead>
<tr>
<th>Score ≥ potential cut point</th>
<th>N</th>
<th>ORR, (%) [95% CI]</th>
<th>Median PFS, wk (95% CI)</th>
<th>N</th>
<th>ORR, (%) [95% CI]</th>
<th>Median PFS, wk (95% CI)</th>
<th>Median OS, wk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>score ≥ potential cut point</td>
<td>9</td>
<td>6 (67%) [30%, 93%]</td>
<td>—</td>
<td>7</td>
<td>4 (57%) [18%, 90%]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>score &lt; potential cut point</td>
<td>24</td>
<td>1 (4%) [0%, 21%]</td>
<td>—</td>
<td>22</td>
<td>2 (9%) [1%, 29%]</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

### MK-3475 Responders Have Prolonged Duration of Response

- **On therapy**
- **Off therapy**
- **Confirmed response**
- **Progression**
- **Therapy continuing**

IASLC, 15th WCLC, abst 2416, 2013
MPDL3280A in monotherapy in NSCLC: phase I trial

- Response in 12/53 patients (ORR: 23%)
  - 3 squamous
  - 9 nonsquamous
- PD rate: 40% (21/53)
- Rapid and durable responses

PD = progressive disease; ORR = objective response rate; NS = nonsquamous; S = squamous

*ORR includes investigator assessed unconfirmed and confirmed partial responses per RECIST v1.1

*patients experiencing ongoing benefit per investigator

Patients first dosed at 1-20 mg.kg by Oct 1 2012. Data cut off April 30 2013

MPDL3280A: activity across NSCLC patient subgroups

- **EGFR status** (n=53)
  - EGFR mutation positive: 11%; EGFR wildtype: 76%; Unknown: 13%

- **KRAS status** (n=53)
  - KRAS mutation positive: 19%; KRAS wildtype: 51%; Unknown: 30%

Efficacy?

Anti-PD-1 Nivolumab
- 129 NSCLC pts\(^1\) – ORR 17.1%, (21.7\%)\(^*\)
  - 50% responded in 8 weeks
  - Median OS 9.9 months

Anti-PD-1 MK-3475
- 38 NSCLC pts\(^2\) – ORR 21%, (24\%)\(^*\)
- 221 NSCLC pts (80% PD-L1+)\(^3\) – ORR 15%, (21\%)\(^*\)

Anti-PD-L1 MPDL3280A
- 175 pts\(^5\) (85 NSCLC – 53 evaluable – 85% PD-L1+) – ORR 23%

Anti-PD-L1 BMS 936559
- 207 pts\(^4\) (75 NSCLC – 49 evaluable) – ORR 10%

Anti-PD-L1 MEDI4736
- 26 pts\(^6\) (13 NSCLC) – ORR 15%

*including immune responders, irRECIST

\(^1\)Brahmer, et al. IASLC WCLC, 2013 \(^2\)Garon E, et al. IASLC WCLC, 2013 \(^3\)Garon E, et al. ASCO 2014 abstr 8020
\(^4\)Brahmer, et al. NEJM 2012 \(^5\)Horn L, et al. IASLC WCLC, 2013 abstr MO18.01
\(^6\)Soria JC, et al. European Cancer Congress 2013 abstr 3408
Toxicity?

Anti-PD-1 **Nivolumab** - 129 NSCLC pts\(^1\)
- 53% related AEs, 5% Gr 3-4
- Pneumonitis – 6%, Gr 3-4 3 pts (2%) – 2 deaths

Anti-PD-1 **MK-3475** - 221 NSCLC pts\(^2\)
- 48% related AEs - fatigue, 6% Gr 3-4
- Pneumonitis – Gr 3-4 3 pts (1%)

Anti-PD-L1 **MPDL3280A** - 85 NSCLC pts\(^4\)
- 66% related AEs, 11% Gr 3-4 - fatigue
- No Gr 3-5 pneumonitis

Anti-PD-L1 **BMS 936559** - 207 pts\(^4\)
- 61% related AEs, 9% Gr 3-4
- No pneumonitis

Anti-PD-L1 **MEDI4736** - 26 pts\(^5\) (13 NSCLC)
- 34% related AEs, no Gr 3-4
- No pneumonitis, no colitis

Tolerability of oncology therapies

Chemotherapy

**Target**
Rapidly dividing tumour and normal cells

**Adverse events**
Diverse due to non-specific nature of therapy

---

I-O therapies

**Target**
Immune system

**Adverse events**
Unique events can occur as a result of immune-system activity

---

Targeted therapies

**Target**
Specific molecules involved in tumour growth and progression

**Adverse events**
Reflect targeted nature

---

Different spectrum of AEs with each modality

---

Some AEs with I-O may present like those with other therapies

---

BUT – AEs may have different aetiologies
*e.g. diarrhoea/colitis, fatigue, rash/pruritus, endocrinopathies*

---

Require different management strategies

---

Predicting / Enriching for response?

**ORR : 17,1 – 24 %**

- **Tissue:**
  - IHC for T cells and PD-L1
  - Gene signature for immune responsiveness, immunoscore

- **Blood markers, imaging**

- **Clinical factors**
Clinical factors for response?

- **Histology?** – SCLC more likely to respond?
  - Nivolumab 14/76 RR - 33% SCLC, 12% non-SCLC
  - MK-3475 9/38 RR – 33% SCC, 23 non-SCLC

- **Smoking? Mutation status?**
  - 85 pts, with MPDL3280A

\[\text{ORR} (%)\]

- [EGFR mutation]: 17% (1/6)
- [EGFR wildtype]: 23% (9/40)

## Planned and ongoing lung cancer trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment</th>
<th>Patient population</th>
<th>Status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plus various (including ipilimumab)</td>
<td>NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td>Monotherapy</td>
<td>Advanced or recurrent NSCLC</td>
<td>Ongoing*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Monotherapy</td>
<td>Advanced or metastatic NSCLC</td>
<td>Ongoing*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monotherapy</td>
<td>Squamous NSCLC</td>
<td>Ongoing*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monotherapy</td>
<td>Stage IV first line or PDL-1+ NSCLC</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monotherapy</td>
<td>Following platinum failure</td>
<td>Ongoing*</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monotherapy</td>
<td>Advanced or metastatic NSCLC</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Monotherapy and plus chemotherapy</td>
<td>NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Monotherapy</td>
<td>PDL-1+ NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Monotherapy</td>
<td>Locally advanced NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>Combination</td>
<td>Advanced or metastatic NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Monotherapy</td>
<td>NSCLC and brain metastases</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td>2/3</td>
<td>Monotherapy</td>
<td>Prior-treated NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ipilimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plus erlotinib or crizotinib</td>
<td>Extensive disease SCLC</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plus chemotherapy</td>
<td>Neoadjuvant NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plus pembrolizumab</td>
<td>Locally advance or metastatic NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Monotherapy</td>
<td>Limited disease SCLC</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Plus carboplatin and etoposide</td>
<td>Extensive disease SCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Plus etoposide and platinum therapy</td>
<td>Newly diagnosed extensive disease SCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Plus paclitaxel and carboplatin</td>
<td>Squamous NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MPDL3280A1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Plus Tarceva</td>
<td>NSCLC</td>
<td>Not yet open</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Monotherapy</td>
<td>PDL-1+ locally advanced NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Plus docetaxel</td>
<td>Locally/advanced disease post-platinum NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monotherapy</td>
<td>Locally/advanced disease post-platinum NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Plus gefitinib</td>
<td>NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Plus MED14763</td>
<td>Advanced NSCLC</td>
<td>Recruiting</td>
<td></td>
</tr>
</tbody>
</table>

* And not recruiting

Implications of the adaptive immune resistance mechanism for combinatorial immunotherapy of cancer

Will immunotherapy obsolete CT/targeted therapy?
No – CT/targeted therapy primes tumour immunity

Tumours with increased mutations are more likely to have increased T cells

Immunotherapy – The beginning of the end for cancer

Transforming cancer into chronic disease

“Immunotherapies will likely become the treatment backbone in up to 60% of cancers over the next 10 years compared with < 3% today.”

Andrew Baum, MD

Open questions

→ Anti-PD1 vs anti-PD-L1 (schedule)

→ Augment the efficacy (combination therapy, sequencing, maintenance)

→ Combination therapy (CT, targeted agents, immunotherapy)

→ Duration of therapy (1 year, 2 years, indefinitely)

→ Toxicity (pneumonitis)

→ Treat beyond progression

→ What to do after acquired resistance

→ PD-L1 as a predictive biomarker or other biomarkers
Summary

→ Anti-tumour immune response through vaccination is appealing, but achieving objective response is quite rare.
  ▪ Nevertheless cancer vaccines remain a valid treatment that need further development
  ▪ New formulations/vaccine vectors, new antigens and application together with checkpoint blockade will likely rejuvenate cancer vaccine strategies

→ Immune-checkpoint blockade (CTLA-4, PD-1, PG-L1 antibodies) has demonstrated clear evidence of objective responses and survival.
  ▪ Probably and like several trials are seeking, we will need to combine conventional therapy with immune checkpoint blockade
  ▪ Unanswered safety and efficacy questions

→ Immunotherapies and combination immunotherapies will be the wave of the future.
  ▪ Key: improve responses
pelo doente,
para o doente
e com o doente com cancro do pulmão