Agenda

Welcome and introduction
Karl Mahler, Head of Investor Relations, Roche

The immunobiology of combinations and predictive biomarkers
Ira Mellman, Ph.D., Vice President, Cancer Immunology, gRED Genentech

ECC 2015 Roche cancer immunotherapy highlights:
- Atezolizumab phase II bladder and lung cancer data
  Daniel S. Chen, M.D., Ph.D., Cancer Immunotherapy Franchise Head Product Development, Genentech/Roche

- Atezolizumab regulatory update and further development program
  Cathi Ahearn, Lifecycle Leader atezolizumab lung and GU Cancers, Genentech/Roche

Q&A
## Strong newsflow yet to come in 2015

### Vienna, 25-29 Sep
- **atezolizumab**
  - NSCLC: POPLAR, BIRCH, P1b chemo combo update
  - Bladder: P2 (2L cohort)
- alectinib
  - NSCLC: P2 update
- CEA IL2v, IDO inh.: P1 update solid tumors

### Barcelona, 7-10 Oct
- **ocrelizumab**
  - RMS: P3 OPERA I/II
  - PPMS: P3 ORATORIO

### San Francisco, 18-21 Nov
- **atezolizumab**
  - mM: P1 vemurafenib combo
- cobimetinib + Zelboraf
  - BRAF+mM: coBRIM OS data

### San Antonio, 19-22 Nov
- **atezolizumab**
  - GBM: P1

### Orlando, 5-8 Dec
- **venetoclax**
  - CLL: P2 R/R p17del
  - Gazyva
  - NHL: P3 GADOLIN update
  - CLL: P3 GREEN update
- **atezolizumab + Gazyva**
  - r/r NHL

### San Antonio, 8-12 Dec
- **atezolizumab**
  - TNBC: P1b abraxane combo

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Presentations planned
The immunobiology of combinations and predictive biomarkers

Ira Mellman, Ph.D., Vice President, Cancer Immunology, gRED Genentech
Blocking PD-1/PD-L1 pathway

- PD-1/PD-L1 interaction inhibits T cell activation, attenuates effector function, maintains immune homeostasis
- Many tumors up-regulate PD-L1 and evade T cell killing
- Baseline expression of PD-L1 in tumors can be a readout of T cell activity
PD-L1 IHC: staining for TCs and ICs
Assay sensitivity critical in detecting both cell types

Immune cells (ICs)  Tumor cells (TCs)  Tumor and immune cells (TCs and ICs)

Predictive of benefit in bladder cancer (ORR/OS)¹
Predictive of benefit in lung cancer (ORR/PFS/OS)²

¹IMvigor 210 ECC 2015, ²POPLAR ECC 2015
PD-L1 expression patterns with SP142 are largely consistent in time and space

### Archival tissue vs. fresh biopsy

<table>
<thead>
<tr>
<th>PD-L1 cut-off</th>
<th>Number of paired metachronous biopsies with the same PD-L1 score, n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>9/11 (82%)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>9/11 (82%)</td>
</tr>
</tbody>
</table>

### Primary tumor vs. metastasis

<table>
<thead>
<tr>
<th>PD-L1 cut-off</th>
<th>Number of paired synchronous biopsies with the same PD-L1 score, n/N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>13/14 (93%)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>11/14 (79%)</td>
</tr>
</tbody>
</table>

Sample origin does not contribute to variability of SP142 assay
**Immune cell staining is more prevalent across indications**

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>RCC</th>
<th>UBC</th>
<th>NSCLC</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WO29074 (253) Phase II</td>
<td>GO 29023 (592) Phase II</td>
<td>POPLAR (287) Phase II</td>
<td>PCD4989g (413) Phase I</td>
</tr>
<tr>
<td>IC&gt;=1%</td>
<td>59%</td>
<td>68%</td>
<td>57%</td>
<td>58%</td>
</tr>
<tr>
<td>IC&gt;=5%</td>
<td>21%</td>
<td>33%</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>IC&gt;=10%</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>TC&gt;=1%</td>
<td>15%</td>
<td>22%</td>
<td>38%</td>
<td>14%</td>
</tr>
<tr>
<td>TC&gt;=5%</td>
<td>6%</td>
<td>15%</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>TC&gt;=50%</td>
<td>&lt;1%</td>
<td>4%</td>
<td>11%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**IC>1%**

- RCC: 59%
- UBC: 68%
- NSCLC: 57%
- TNBC: 58%

**IC>1%**

- RCC: 15%
- UBC: 22%
- NSCLC: 38%
- TNBC: 14%

**IC>1%**

- RCC: 2%
- UBC: 1%
- NSCLC: 11%
- TNBC: 3.5%

CRI, 2015
Adaptive expression of PD-L1 by tumor cells is inconsistent with PD-L1+ IC’s being predictors of response

Adaptive expression of PD-L1 by tumor cells is inconsistent with PD-L1+ IC’s being predictors of response

Adaptive expression of PD-L1 by tumor cells is inconsistent with PD-L1+ IC’s being predictors of response

Release of INFγ induces PD-L1 expression by surrounding tumor and immune cells

Adaptive expression of PD-L1 by tumor cells is inconsistent with PD-L1+ IC’s being predictors of response

But in the majority of tumors, PD-L1 is only expressed by infiltrating immune cells

Adaptive expression of PD-L1 by tumor cells is inconsistent with PD-L1+ IC’s being predictors of response

- Why can PD-L1 expression by immune infiltrating cells more predictive than PD-L1+ tumor cells?
- Do PD-L1+ myeloid cells, not tumor cells, regulate T cell function at baseline?
- What is the actual mechanism of PD-1-mediated suppression?

PD-L1/PD-1 interaction may negatively regulate signaling by T cell receptors or co-stimulatory molecules (e.g. CD28)
New in-house data: PD-L1/PD-1 interaction regulates co-stimulatory molecule (CD28) signaling preferentially

Dendritic cell/macrophage

T cell

AACR 2015, manuscript in preparation
Significance of IC staining: Infiltrating cells positively and negatively regulate T cell function
PD-L1 expression by TCs in NSCLC is controlled by epigenetic regulation, and may not reflect immune regulation.

- **Sclerotic**
- **Desmoplastic**
- Regulated by methylation
- **Intrinsic PD-L1 regulation**

**PD-L1 TC3 tumors** exhibit a desmoplasic and sclerotic TME with low intra-epithelial and stromal IC.

**PD-L1 TC3 vs IC3 NSCLC tumors** have distinct tumor TME.

**PD-L1 IC3 tumors** represent immune-rich/CD8 high tumors.

**Adaptive PD-L1 regulation**
- Intra-epithelial/stromal IC
- Presence of $T_{eff}$ cells
- CD8 IHC
Strategic vision: Lead by developing best-in-class combination therapies

Cancer Immunotherapy targets and combinations may include the following:

- Immunotherapeutics
- Targeted therapies
- SoC chemotherapies
Several chemotherapeutics combine well with atezo pre-clinically

Unpublished data
Chemotherapy as immunotherapy
Creation of favorable immune profiles - mouse data

**Tumor CD8+ (T cells)**

**Tumor CD11b+Ly6C+ (MDSCs)**

**Tumor CD4+FoxP3+ (T regulatory cells)**

Unpublished data
MDSC=myeloid derived suppressor cells
Chemotherapy as immunotherapy

Creation of favorable immune profiles - patient data
Modulation of tumor immune status by chemotherapy may be transient

Return to the “equilibrium” inflammatory state

Optimal window for initiating immunotherapy combination

Hypothetical curve

CD8 staining images are illustrative
Combinations may help in maintaining tumor inflamed state

Hypothetical curve

Optimal window for initiating immunotherapy combination

Maintenance of inflamed state

Treatment (e.g. chemotherapy)

Response

Immunotherapy

CD8 staining images are illustrative
Summary

- PD-L1 expression in tumor microenvironment suppresses anti-cancer T cell responses
- Pre-clinical data points to an important role of ICs in regulating T cell function
- PD-L1 expression patterns reflect the biology of individual tumor types
- PD-L1 phenotypes appear remarkably stable in throughout lines of therapy and in primaries vs. mets: but assays must be optimized
- Pre-clinical data suggests chemotherapy alters tumor immune status to transiently increase inflammation
- Combinations of chemotherapy and atezolizumab may extend the inflammatory state for durable responses
ECC 2015 Roche cancer immunotherapy highlights: Atezolizumab phase II bladder and lung cancer data

Daniel S. Chen, M.D., Ph.D., Cancer Immunotherapy Franchise Head, Product Development, Genentech/Roche
High unmet need in urothelial bladder cancer
No new therapy with survival benefit in 30 years

**Advanced UC:**
- Median survival is short
- Durable responses not routinely observed
- High grade 3-4 toxicities with chemotherapy

**Vinflunine**: Only approved agent (EU) in 2L
- No survival benefit vs BSC in ITT
- ORR of 8.6% (vs 0% for BSC), median DoR: 7.4 mo
- Vinflunine was tested in a “pure” 2L population

Current therapy: Only few patients treated due to high toxicity and multiple comorbidities

BSC, best supportive care; HR, hazard ratio.

IMvigor 210: 2L bladder phase II study (cohort 2)

- **Study design**
  Locally advanced or metastatic UBC
  Transitional cell histology
  Progression during/following Pt-chemo
  ECOG PS 0-1
  Tumor tissue evaluable for PD-L1 testing
  No autoimmune disease or corticosteroid use

  Atezolizumab
  1200 mg IV q3w until loss of clinical benefit

  Response assessment
  q9 weeks
  (q12 weeks after 54 weeks)

- Co-primary Endpoints: ORR per RECIST v.1.1 (central independent review); investigator-assessed ORR per modified RECIST
- Key Secondary Endpoints: PFS, DOR, OS, Safety

- **PD-L1 expression and prevalence on immune cells**

  IHC status of treated patients in IMvigor 210 Study (n = 311)
  - Imvigor 201 enrolled an all-comer population
  - Ventana SP142 assay prospectively measured tumor-infiltrating immune cell (IC) PD-L1 expression
  - Tumor cell (TC) scoring conducted as an exploratory endpoint
IMvigor 210 efficacy: Objective response rate

### RECIST v1.1 Criteria by Independent Review\(^a\)

<table>
<thead>
<tr>
<th>PD-L1 subgroup</th>
<th>n</th>
<th>CR (%)</th>
<th>ORR (%)</th>
<th>95% CI</th>
<th>(P) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC2/3</td>
<td>100</td>
<td>8%</td>
<td>27%</td>
<td>19, 37</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>IC1/2/3</td>
<td>208</td>
<td>5%</td>
<td>18%</td>
<td>13, 24</td>
<td>.0004</td>
</tr>
<tr>
<td>All</td>
<td>311</td>
<td>4%</td>
<td>15%</td>
<td>11, 20</td>
<td>.0058</td>
</tr>
<tr>
<td>IC1</td>
<td>108</td>
<td>3%</td>
<td>10%</td>
<td>5, 18</td>
<td>N/A(^c)</td>
</tr>
<tr>
<td>IC0</td>
<td>103</td>
<td>1%</td>
<td>9%</td>
<td>4, 16</td>
<td>N/A(^c)</td>
</tr>
</tbody>
</table>

- IMvigor 210 met its co-primary endpoints in all subgroups tested
- ORR by independent review assessed (RECIST v1.1) and investigator (mRECIST) were concordant

\(^a\)Objective response evaluable population: all treated patients had measurable disease at baseline per Inv-RECIST v1.1.
\(^b\)\(P\)-value for \(H_0: \text{ORR} = 10\%\) versus \(H_a: \text{ORR} \neq 10\%\), where 10\% ORR is historical control, \(\alpha = 0.05\). \(^c\)No formal hypothesis testing conducted.

Data cutoff May 5, 2015. Follow up \(\geq 24\) weeks.

Additional unconfirmed responses - likely to mature in subsequent analyses
IMvigor 210: Changes in target lesions
Consistent with phase I data

Initial response profile of IMvigor comparable with Phase I data in PDL1-high subgroup
Atezolizumab in bladder cancer: Durable response

Phase 2 IMvigor 210 cohort 2

- Responses were durable with median DOR not reached in any subgroup
- Median follow-up time: 7 mo (range, 0-11 mo)
- Responses ongoing in 43/47 patients (92%)
IMvigor 210 efficacy: PFS and OS

Median OS not reached for PD-L1 IC2/3 subgroup

Median follow up: 7 mo (range, 0-11 mo), 142 events

Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>IC2/3, n = 100</th>
<th>IC0/1, n = 211</th>
<th>All, n = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo-OS, % (95% CI)</td>
<td>70% (60, 79)</td>
<td>56% (49, 63)</td>
<td>60% (55, 66)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (7.6, NE)</td>
<td>6.7 (5.7, 8.0)</td>
<td>7.9 (6.7, NE)</td>
</tr>
<tr>
<td>Median PFS, a mo (95% CI)</td>
<td>2.1 (2.1, 4.1)</td>
<td>2.1 (2.0, 2.1)</td>
<td>2.1 (2.1, 2.1)</td>
</tr>
</tbody>
</table>

NR, not reached; NE, not estimable. Data cutoff May 5, 2015. Follow up ≥ 24 weeks.
IMvigor 210 efficacy by prior chemotherapy

Subgroup analyses

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>IC2/3</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior systemic regimens, metastatic setting(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26% (12, 43)</td>
<td>12% (7, 19)</td>
</tr>
<tr>
<td>2</td>
<td>39% (17, 64)</td>
<td>18% (9, 30)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>20% (6, 44)</td>
<td>13% (6, 24)</td>
</tr>
<tr>
<td>Metastatic sites at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node only</td>
<td>38% (19, 59)</td>
<td>33% (20, 49)</td>
</tr>
<tr>
<td>Visceral</td>
<td>17% (9, 28)</td>
<td>10% (6, 14)</td>
</tr>
<tr>
<td>Liver</td>
<td>15% (4, 34)</td>
<td>6% (2, 13)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>19% (10, 31)</td>
<td>10% (6, 15)</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL</td>
<td>21% (7, 42)</td>
<td>9% (3,18)</td>
</tr>
</tbody>
</table>

- Median DOR was not yet reached in any of the subgroup populations

\(^a\) Per RECIST v1.1 (independent review). \(^b\) In patients with 0 prior regimens, ORR was 26% (11, 46) in IC2/3 patients (n = 27) and 20% (11, 31) in all-comer patients (n = 70). Data cutoff May 5, 2015. Follow up ≥ 24 weeks.
IMvigor 210: 2L bladder phase II study (cohort 2)
Atezolizumab - potential to change the SOC

• Atezolizumab efficacy
  – Co-primary endpoints of ORR in all subgroups met
  – Significant improvement over a historical 10% ORR (vinflunine 8.6% ORR, median DoR: 7.4 mo1)
  – Durable responses in heavily pretreated population; consistent with data from Phase I
  – Median duration of response not reached; consistent with Phase I data
  – Overall survival immature

• Atezolizumab safety
  – Atezolizumab well tolerated with low discontinuation rates
  – Superior safety over chemotherapy
  – No treatment related renal toxicity or treatment related deaths

1Bellmunt et al. J Clin Oncol. 2009
Atezolizumab in advanced or metastatic NSCLC

**BIRCH: Phase II PD-L1 selected***

- **Phase II atezolizumab in PDL1-selected advanced NSCLC**
- ECOG PS 0 or 1
- N = 667

- Cohort 1: n = 142
  - No prior chemo
  - PD

- Cohort 2: n = 271
  - 2L; 1 prior platinum chemo
  - Until loss of clinical benefit

- Cohort 3: n = 254
  - 3L+; >1 prior platinum chemo

- **Primary endpoint:** ORR (IRF-assessed by RECIST v1.1)
- **Secondary endpoints:** PFS, DoR, ORR (investigator-assessed by RECIST v1.1 and modified RECIST), OS, safety

Prevalence of screened patients with TC2/3 and/or IC2/3 tumors was 34%.

Atezolizumab dosed at 1200 mg IV q3w in all cohorts.

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**POPLAR: randomized phase II in all-comer population**

- **Disease progression on a prior platinum therapy**
  - N = 287

- **Stratification Factors:**
  - PD-L1 IC expression (0 vs 1 vs 2 vs 3)*
  - Squamous vs non-squamous
  - Prior chemo regimens: 1 vs 2

- **R 1:1**
- **Atezolizumab until loss of clinical benefit**
- **Docetaxel until disease progression**

Atezolizumab dosed at 1200 mg IV q3w in all cohorts, docetaxel at 75 mg/m² IV q3w.

- **Primary endpoint:**
  - OS in ITT and PD-L1 expression subgroups
- **Secondary endpoints:**
  - PFS, ORR and DOR in ITT and PD-L1 expression, safety

Primary analysis conducted with 173 events, minimum follow-up 13 months

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*Tumor PD-L1 expression by IHC (TC2/3 and/or IC2/3); *archival or fresh tissue required for pre-dose testing
BIRCH: Objective response rate to atezolizumab
Primary endpoint met in all predefined subgroups

**Highest ORR in TC3 or IC3 patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>BIRCH</th>
<th>POPLAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1L Cohort 1</td>
<td>2L Cohort 2</td>
</tr>
<tr>
<td></td>
<td>TC3 or IC3</td>
<td>TC2/3 or IC2/3</td>
</tr>
<tr>
<td>n</td>
<td>65</td>
<td>139</td>
</tr>
<tr>
<td>ORR(^{a,b})</td>
<td>26%</td>
<td>19%</td>
</tr>
</tbody>
</table>

BIRCH:
- ORR data compared to historic controls for primary efficacy analyses (per data in 2013) using a hierarchical procedure

POPLAR:
- ORR data similar to BIRCH
BIRCH efficacy by overall survival
6 month landmark data comparable to POPLAR

Overall survival TC2/3 or IC2/3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>6-mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (1L)</td>
<td>82%</td>
</tr>
<tr>
<td>Cohort 2 (2L)</td>
<td>76%</td>
</tr>
<tr>
<td>Cohort 3 (3L+)</td>
<td>71%</td>
</tr>
</tbody>
</table>

Overall survival TC3 or IC3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>6-mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (1L)</td>
<td>79%</td>
</tr>
<tr>
<td>Cohort 2 (2L)</td>
<td>80%</td>
</tr>
<tr>
<td>Cohort 3 (3L+)</td>
<td>75%</td>
</tr>
</tbody>
</table>

*IRF Data cut-off May 28, 2015.*
POPLAR efficacy: OS in ITT population (n=287)

Statistical significance reached vs docetaxel

Median 12.6 mo (9.7, 16.4)

Minimum follow up = 13 months

HR$^a$ = 0.73 (0.53, 0.99)
P value = 0.040

Event/patient ratio: 60% (54% for atezolizumab, 66% for docetaxel)

$^a$Stratified HR.
Data cut-off May 8, 2015.
POPLAR: Overall survival by PD-L1 subgroups

Efficacy increasing with higher PD-L1 expression

Atezolizumab: Doubled likelihood of survival in PD-L1-high tumors (IC2/3 or TC2/3)

**Median OS (95% CI), mo**

<table>
<thead>
<tr>
<th>Subgroup (% of enrolled patients)</th>
<th>Median OS (mo) Atezolizumab n = 144</th>
<th>Median OS (mo) Docetaxel n = 143</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3 (16%)</td>
<td>0.49</td>
<td>15.5 (9.8, NE)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (37%)</td>
<td>0.54</td>
<td>15.1 (8.4, NE)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (68%)</td>
<td>0.59</td>
<td>15.5 (11.0, NE)</td>
</tr>
<tr>
<td>TC0 and IC0 (32%)</td>
<td>1.04</td>
<td>9.7 (6.7, 12.0)</td>
</tr>
<tr>
<td>ITT (N = 287)</td>
<td>0.73</td>
<td>12.6 (9.7, 16.4)</td>
</tr>
</tbody>
</table>

**Hazard Ratio**

- In favor of atezolizumab
- In favor of docetaxel

*Unstratified HR for subgroups and stratified HR for ITT; Data cut-off May 8, 2015.*
POPLAR: OS by PD-L1 expression subgroup
Atezolizumab increased OS by 7.7 mo in IC2/3 or TC2/3 subgroup

**TC3 or IC3 (n = 47)**
HR\(^a\) = 0.49 (0.22, 1.07)
P value = 0.068
Median 11.1 mo (6.7, 14.4)
Median 15.5 mo (9.8, NE)

**TC2/3 or IC2/3 (n = 105)**
HR\(^a\) = 0.54 (0.33, 0.89)
P value = 0.014
Median 7.4 mo (6.0, 12.5)
Median 15.1 mo (8.4, NE)

**TC1/2/3 or IC3 (n = 195)**
HR\(^a\) = 0.59 (0.40, 0.85)
P value = 0.005
Median 9.2 mo (7.3, 12.8)
Median 15.5 mo (11.0, NE)

**TC0 and IC0 (n = 92)**
HR\(^a\) = 1.04 (0.62, 1.75)
P value = 0.871
Median 9.7 mo (8.6, 12.0)
Median 9.7 mo (6.7, 12.0)

\(^a\)Unstratified HR.
Data cut-off May 8, 2015.
POPLAR: PD-L1/PD-1 ligand and receptor family members predict clinical benefit in NSCLC

- **PD-L1**
  - Atezolizumab (PD-L1 high)
  - Atezolizumab (PD-L1 low)
  - Docetaxel (PD-L1 low)
  - Docetaxel (PD-L1 high)
  - OS HR: 0.46 (95% CI: 0.27 – 0.78)

- **B7.1**
  - Atezolizumab (B7.1 high)
  - Atezolizumab (B7.1 low)
  - Docetaxel (B7.1 low)
  - Docetaxel (B7.1 high)
  - OS HR: 0.44 (95% CI: 0.26 – 0.77)

- **PD-1**
  - Atezolizumab (PD-1 high)
  - Atezolizumab (PD-1 low)
  - Docetaxel (PD-1 low)
  - Docetaxel (PD-1 high)
  - OS HR: 0.43 (95% CI: 0.24 – 0.76)

- **PD-L2**
  - Atezolizumab (PD-L2 high)
  - Atezolizumab (PD-L2 low)
  - Docetaxel (PD-L2 low)
  - Docetaxel (PD-L2 high)
  - OS HR: 0.39 (95% CI: 0.22 – 0.69)

*Schmid et al., ECC 2015*
## POPLAR and BIRCH safety summary

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab n = 142</th>
<th>Docetaxel n = 135</th>
<th>All patients n = 659</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POPLAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median treatment duration</td>
<td>3.7 mo</td>
<td>2.1 mo</td>
<td>4.2 mo</td>
</tr>
<tr>
<td>All Grade AEs, any cause</td>
<td>96%</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>67%</td>
<td>88%</td>
<td>64%</td>
</tr>
<tr>
<td>Grade 3-4 AEs, any cause</td>
<td>40%</td>
<td>53%</td>
<td>38%</td>
</tr>
<tr>
<td>Treatment-related Grade 3-4 AEs</td>
<td>11%</td>
<td>39%</td>
<td>11%</td>
</tr>
<tr>
<td>Treatment-related Grade 5 AEs</td>
<td>1%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2%</td>
<td>0.2%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients withdrawing from treatment due to AEs</td>
<td>8%</td>
<td>22%</td>
<td>5%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>BIRCH</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety population</strong></td>
<td>Atezolizumab (n = 6): Cardiac failure, pneumonia, ulcer hemorrhage, pneumothorax, pulmonary embolism, embolism Docetaxel (n = 5): Sepsis (n = 2), death&lt;sup&gt;b&lt;/sup&gt; (n = 2), acute respiratory distress syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>POPLAR</strong> Grade 5 event terms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Atezolizumab (n = 6): Cardiac failure, pneumonia, ulcer hemorrhage, pneumothorax, pulmonary embolism, embolism Docetaxel (n = 5): Sepsis (n = 2), death&lt;sup&gt;b&lt;/sup&gt; (n = 2), acute respiratory distress syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety population includes patients who received any amount of either study treatment.</strong></td>
<td>Safety population includes patients who received any amount of either study treatment.</td>
<td></td>
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</tr>
<tr>
<td><strong>BIRCH</strong> Causes of atezolizumab withdrawal (all cohorts): pneumonitis (0.8%), pneumonia (0.5%), pneumonia aspiration (0.3%), septic shock (0.3%), cerebrovascular accident (0.3%), sudden death (0.3%), thrombocytopenia (0.3%).**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data cut-off May 8, 2015.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>One atezolizumab-related Grade 5 event (cardiac failure); three docetaxel-related \Grade 5 events (one each of sepsis, death and acute respiratory distress syndrome)  
<sup>b</sup>Cause unknown.  
<sup>c</sup>Data cut-off May 8, 2015.
BIRCH and POPLAR summary

Clinically meaningful efficacy in patients with advanced NSCLC

• **BIRCH**: Met pre-specified primary efficacy endpoint of ORR for all subgroups
  • 6-month OS rate is consistent with POPLAR results; more mature OS data are awaited
    • Median DOR was 7 mo in 3L+, not reached in 1L/2L in TC3 or IC3
    • Majority of responses still ongoing: > 61% in TC3 or IC3

• **POPLAR**: Significant OS improvement in patients receiving atezo vs docetaxel in all-comers
  • Improved OS correlated with increasing PD-L1 expression
  • Trend toward survival improvement in squamous and non-squamous NSCLC
    • Median DoR was 14.3 mo for atezolizumab
    • Majority of responses still ongoing: 57%
Atezolizumab combo with Pt-based chemotherapy in 1L NSCLC

Phase Ib study design

1L NSCLC
\( n=37 \)

4-6 cycles

- C: atezolizumab 15mg/kg IV q3w + carboplatin q3w + paclitaxel q3w
- D: atezolizumab 15mg/kg IV q3w + carboplatin q3w + pemetrexed q3w
- E: atezolizumab 15mg/kg IV q3w + carboplatin q3w + nab-paclitaxel q1w

Maintenance

- atezolizumab
- atezolizumab +/- pemetrexed
- atezolizumab

Treat to PD or loss of clinical benefit

Treat to PD or loss of clinical benefit

Treat to PD or loss of clinical benefit
Atezolizumab combo with Pt-based chemotherapy in NSCLC: phase Ib safety and efficacy update

**Disease control rate by chemo combo**

**Summary of responses by RECIST v1.1**

Data preliminary*: 25 patients per arm for final analysis

<table>
<thead>
<tr>
<th></th>
<th>Arm C cb/pac n=8</th>
<th>Arm D cb/pem n=17</th>
<th>Arm E cb/nab n=16</th>
<th>All n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>4 (50)</td>
<td>13 (76.5)</td>
<td>9 (56.3)</td>
<td>26 (63.4)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (25)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>4 (50)</td>
<td>13 (76.5)</td>
<td>5 (31.3)</td>
<td>22 (53.7)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>4 (50)</td>
<td>1 (5.9)</td>
<td>4 (25)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>0 (0)</td>
<td>2 (11.8)</td>
<td>2 (12.5)</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

Historic ORR for platinum-based chemo doublets: 20-30%

*High ORR and DCR: supporting potential synergy between atezolizumab and chemotherapy*

*Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015*
Atezolizumab PhIIb chemo combination efficacy
Encouraging depth and duration of response

Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015; SLD, sum of longest diameters; *PD for reasons other than new lesions
Conclusions from phase Ib atezolizumab chemo combinations

- High response rate (63% for the combined NSCLC cohort) supporting potential synergy between atezolizumab and chemotherapy

- Low rates of discontinuation, AEs were similar to chemotherapy

- No unexpected toxicities in combination with standard first-line chemotherapy, no pneumonitis or other respiratory AEs of concern

Several phase III studies in monotherapy and combinations in NSCLC are underway
ECC 2015 Roche cancer immunotherapy highlights: Atezolizumab regulatory update and further development program

Cathi Ahearn, Lifecycle Leader Atezolizumab
Genentech/Roche
Establishing atezolizumab represents the early portion of Roche’s CIT strategy

**2016**
- **Launch rapidly**
- **Leverage Dx**
- **2L+ bladder**
- **2L+ NSCLC**

**2017**

**2018**

**2025**

**Lead scientific understanding**
*Identify and target the biological mechanisms of CIT responsiveness across tumor types*

**Broaden across indications**
*Earlier treatment settings, broader patient population*

**Differentiate through portfolio**
*Atezo+NME-based combinations*
# Atezolizumab strategy in bladder cancer
## Rapid launch in a setting of high unmet need

### Fast-to-market strategy

**Phase II IMvigor 210**
- **Metastatic Bladder**
  - Cohort 1 (n=100): Cis-Ineligible
  - Cohort 2 (n=311): Prior platinum

- **Atezolizumab 1200 mg IV Q3 weeks**
  - 1° Endpoint: ORR
  - Cohort 2 data at ECC 2015
  - Cohort 1 data expected in 2016

**Filing: US Early 2016, EU 1H 2016**

### Development program in bladder cancer

**Phase III IMvigor 211**
- **2L+ Bladder**
  - n=767

- **atezolizumab 1200 mg IV Q3 weeks**
  - Chemotherapy

**Confirmatory Phase 3**
- 1° Endpoint: OS
- Data expected 2017

**Phase III IMvigor 010**
- **Adjuvant Bladder (MIBC) Dx–sel monotherapy, n=440**

- **atezolizumab 1200 mg IV Q3 weeks**
  - Observation

**Improve long-term outcomes**
- 1° Endpoint: DFS
- Data expected 2019
Atezolizumab lung cancer strategy

Market entry in PD-L1-selected relapsed/refractory NSCLC

**Fast-to-market strategy**

**BIRCH**
- Phase II
  - PD-L1-selected mNSCLC $n=667$
  - Atezolizumab 1200 mg IV Q3 weeks
- 1° Endpoint: ORR
- First presentation: ECC 2015

**POPLAR**
- Phase II
  - All comers 2/3L mNSCLC $n=287$
  - Atezolizumab 1200 mg IV Q3 weeks
  - Docetaxel 75 mg/m² IV Q3 weeks
- 1° Endpoint: OS
- OS data: ECC 2015

**OAK**
- Phase III
  - All comers 2/3L mNSCLC $n=1225$
  - Atezolizumab 1200 mg IV Q3 weeks
  - Docetaxel 75 mg/m² IV Q3 weeks
- Confirmatory Phase 3
  - 1° Endpoint: OS
  - Data expected 2016

Filing: US Early 2016, EU 1H 2016

mNSCLC = metastatic Non Small-Cell Lung Cancer
## Broaden in lung cancer: Ongoing phase 3 programs

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Treatment arms</th>
<th>Primary completion*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1L Combination studies – All comers (PD-L1 subgroup analysis)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMpower150</td>
<td>Non-squamous</td>
<td>Atezo + Carbo + Pac</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=1200</td>
<td></td>
<td>Atezo + Carbo + Pac + Avastin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbo + Pac + Avastin</td>
<td></td>
</tr>
<tr>
<td>IMpower130</td>
<td>Non-squamous</td>
<td>Atezo + Carbo + Nab-pac</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=550</td>
<td></td>
<td>Carbo + Nab-pac</td>
<td></td>
</tr>
<tr>
<td>IMpower131</td>
<td>Squamous</td>
<td>Atezo + Carbo + Pac</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=1200</td>
<td></td>
<td>Atezo + Carbo + Nab-pac</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbo + Nab-pac</td>
<td></td>
</tr>
<tr>
<td><strong>1L Monotherapy studies – PD-L1 Selected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMpower110</td>
<td>Non-squamous</td>
<td>Atezo Cis or Carbo + Pem</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMpower111</td>
<td>Squamous</td>
<td>Atezo Cis or Carbo + Gem</td>
<td>2017 (PFS)</td>
</tr>
<tr>
<td>n=400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant Monotherapy study– PD-L1 Selected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMpower010</td>
<td>Adj. NSCLC</td>
<td>Atezo Best supportive care</td>
<td>Post 2018 (DFS)</td>
</tr>
<tr>
<td>n=845</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Outcome studies are event driven, timelines may change, OS endpoint included for all studies

Atezo=atezolizumab; Carbo=Carboplatin; Pac=Paclitaxel; Nab-pac= Nab-paclitaxel; Cis=Cisplatin; Pem=Pemetrexed; Gem=Gemcitabine
Roche atezolizumab lung cancer strategy
Complete offering across all lines of treatment

- Leverage diagnostics to rapidly launch atezolizumab
- Broaden into 1L via first in class combinations
- Personalize cancer immunotherapy

Hypothetical timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>2L+ Dx+ mono</td>
</tr>
<tr>
<td>2017</td>
<td>1L Dx+ mono, 1L all-comers with chemo, chemo+Avastin</td>
</tr>
<tr>
<td>2018+</td>
<td>Adjuvant mono, Combinations with targeted tx, immune tx</td>
</tr>
</tbody>
</table>
Roche’s CIT strategy: Expanding the utility of cancer immunotherapy

- Lead scientific understanding
  Identify and target the biological mechanisms of CIT responsiveness across tumor types

- Broaden across indications
  Earlier treatment settings, broader patient population

- Differentiate through portfolio
  Atezo+NME-based combinations

- Launch rapidly
  Leverage Dx

- 2L+ bladder
- 2L+ NSCLC
Roche cancer immunotherapy program
Industry-leading portfolio with 7 internal NMEs

- **43** CI studies (including 2 adjuvant studies)
- **18** Monotherapies
- **25** Combinations
- **34** Atezolizumab studies
- **4** Pre-clinical NMEs

**Phase I**
- **8** Monotherapies
- **16** Combinations

**Phase II**
- **5** Monotherapies
- **2** Combination

**Phase III**
- **5** Monotherapies
- **7** Combinations

- **Solid tumours**
- **Haem**
- **Melanoma**
- **Triple Negative Breast**
- **Colorectal**
- **Non-Small Cell Lung**
- **Myeloma**
- **Renal**
- **Bladder**
2014-2016: Launch atezolizumab rapidly in PDL1-selected patients

*Evaluate tumor: Is the tumor inflamed?

Y
Inflamed

N
Non-Inflamed

PDL1-selected

Atezo
2016-2018: Broaden indications and leapfrog competition into 1L All-comers

*Evaluate tumor: Is the tumor inflamed?

Y: Inflamed

- PDL1+
  - Atezo + Chemo / SOC

- PDL1-
  - Atezo + Chemo / SOC

N: Non-Inflamed

- T Cells at Periphery (Excluded Infiltrate)
  - Atezo + Chemo / SOC

- No T Cells (Immunologic Ignorance, Immune Desert)
  - Atezo + Chemo / SOC
2018-2020+: Aim for personalized cancer immunotherapy through combinations

*Evaluate tumor: Is the tumor inflamed?*

- **Yes (Inflamed):**
  - High PDL1 expression
  - Low/No PDL1 expression
  - No identified target
  - T Cells at Periphery
  - No Effectors
  - MHC Loss
  - No Identified target

- **No (Non-Inflamed):**
  - How do we kill cancer cells that do not express MHC?

**How do we boost T Cell function?**

- *Improving understanding of immune biology/cytokines, collagen targets*
- *Improving understanding of immune biology*

**How do we (re)activate T Cells?**

- *Atezo + Other CIT (aTIGIT, IDOi, TCBs, IL2v)*
- *Atezo + aOX40 (or aCD40, vaccine)*
- *Atezo + TCBs (or IFN)*
- *Atezo + Avastin (or A2V)*
- *Atezo + Chemo/SOC (or IFN)*

**How do we deepen Atezo responses?**

- *Atezo* + CIT (aTIGIT, IDOi, TCBs)
- *Atezo + Other CIT (aCSF1R, TCBs, IL2v)*
- *Atezo + Chemo/SOC*
The wonderful world of combinations!
Tidal wave of combination data coming

- **Cancer Immunotherapy targets and combinations may include the following:**

  - **Priming & activation**
    - anti-CEA-IL2
    - anti-FAP-IL2
    - anti-OX40
    - anti-CTLA4
    - anti-CD27
    - anti-41BB
    - anti-cytokine

  - **Antigen presentation**
    - anti-CD40
    - INFα
    - oncolytic viruses
    - neo-epitope vaccines

  - **Antigen release**
    - Pro-inflammatory
      - EGFRi
      - ALKi
      - BRAFi
      - MEKi
      - Chemo
      - BTKi
      - HDAC

  - **Cancer cell killing**
    - anti-PD1
    - anti-PD-1
    - anti-CSF-1R
    - IDOi
    - anti-TIGIT
    - anti-TIM
    - anti-LAG3
    - A2Ai
    - IDO/TDOi
    - TDO

  - Immuno-suppression

  - T cell trafficking

  - T cell infiltration
    - anti-VEGF
    - anti-Ang2/VEGF

  - T cell infiltration

  - Immunotherapeutics
  - Targeted therapies
  - SoC chemotherapies
Roche cancer immunotherapy at ECC 2015

### Phase I

- **aPDL1**
  - Solid tumors
- **aPDL1 + chemo**
  - Solid tumors
- **aPDL1 + Tarceva**
  - NSCLC
- **aPDL1 + Zelboraf**
  - Melanoma
- **aPDL1 + cebimetinib**
  - Solid tumors
- **aPDL1 + Avastin**
  - Solid tumors
- **aPDL1 + Gazyva**
  - R/R FL / aNHL
- **aPDL1 + Avastin + chemo**
  - Solid tumors
- **aPDL1 + lenalidomide**
  - MM
- **aPDL1 + Zelboraf + cobi**
  - Melanoma
- **aCD20/CD3 TCB**
  - Solid tumors
- **aCEA-IL2v FP**
  - Solid tumors
- **aOX40**
  - Solid tumors
- **aCEA/CD3 TCB**
  - Solid tumors

### Phase II

- **aPDL1**
  - Solid tumors
- **aCSF-1R**
  - Solid tumors
- **aPDL1 + ipilimumab**
  - Solid tumors
- **aPDL1 + IFN-alfa**
  - Solid tumors
- **aPDL1 + aCD40**
  - Solid tumors
- **aPDL1 + aOX40**
  - Solid tumors
- **aPDL1 + aCSF-1R**
  - Solid tumors
- **aPDL1 + aCEA-IL2v FP**
  - Solid tumors
- **aPDL1 + IDO**
  - Solid tumors
- **aOX40**
  - Solid tumors
- **aCEA/CD3 TCB**
  - Solid tumors
- **aPDL1 + Zelboraf**
  - Melanoma
- **aPDL1 + Tarceva**
  - NSCLC
- **aPDL1 + Avastin + chemo**
  - 1L Renal
- **aPDL1 + chemo**
  - 1L non sq NSCLC
- **aPDL1 + Avastin + chemo**
  - 1L non sq NSCLC
- **aPDL1 + chemo**
  - 1L sq NSCLC
- **aPDL1 + Avastin**
  - 1L TNBC
- **aPDL1 + lenalidomide**
  - MM
- **aPDL1 + chemo**
  - 1L RCC
- **aPDL1 + Avastin**
  - 1L RCC
- **aPDL1**
  - Adjuvant MIBC (Dx+)
- **aPDL1**
  - Adjuvant NSCLC (Dx+)

### Phase III

- **aPDL1**
  - Solid tumors
- **aPDL1**
  - 2/3L NSCLC
- **aPDL1**
  - 2/3L Bladder
- **aPDL1 + Avastin + chemo**
  - 1L non sq NSCLC
- **aPDL1 + chemo**
  - 1L non sq NSCLC
- **aPDL1 + chemo**
  - 1L sq NSCLC
- **aPDL1**
  - 1L squamous NSCLC (Dx+)
- **aPDL1**
  - 1L squamous NSCLC (Dx+)
- **aPDL1 + chemo**
  - 1L RNCC
- **aPDL1 + Avastin**
  - 1L RCC
- **aPDL1**
  - Adjuvant MIBC (Dx+)
- **aPDL1**
  - Adjuvant NSCLC (Dx+)

**Status as of Sept 28, 2015**
### Cancer immunotherapy newsflow in H2 2015

**Vienna, 25 -29 Sep**
- atezolizumab
  - NSCLC: POPLAR final, BIRCH, P1b chemo combo update;
  - Bladder: P2 (2L cohort)
- CEA IL2v, IDO inh.: P1 update solid tumors

**San Francisco, 18-21 Nov**
- atezolizumab
  - mM: P1 vemurafenib combo

**San Antonio, 19-22 Nov**
- atezolizumab
  - GBM: P1

**Orlando, 5-8 Dec**
- atezolizumab + Gazyva
  - r/r NHL

**San Antonio, 8-12 Dec**
- atezolizumab
  - TNBC: P1b abraxane combo

Planned presentations
Doing now what patients need next