Model selection for Targeted Therapies in Oncology drug Development

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Tumor Model 2016 Boston, USA
Outline:

• Employment of PDX models for Antibody Drug Conjugate (ADC) efficacy, PD marker studies and companion diagnostic development

• ADC+IO combination studies - the promise and challenges

• Future model needs in combination therapy
Most ADC compounds require specific target expression for efficient drug delivery.
PD marker (mitotic arrest) assessed in preclinical pancreatic PDX model:

- Pancreatic PDX tumors were treated with single dose ADC
- Increased phosphorylated H3 IHC (brown dots) indicated mitotic arrest
Companion Diagnostics is an important part in ADC clinical development:

- Lung
  - high
  - medium
  - low
  - negative

- Ovarian

<table>
<thead>
<tr>
<th>H score</th>
<th># of Patient Samples</th>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>50</td>
<td>10</td>
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<td>250</td>
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<td>300</td>
<td>60</td>
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IHC in NSCLC

IHC in Epithelial Ovarian Tumors
Correlation between target expression level and efficacy?

- Dose response assesses in 20 PDX models to determine minimal efficacious dose required for regression
- Target expression determined by validated companion diagnostic test
- Target negative models don’t respond
- Most PDX tumor models at cutoff (>50% 2-3+) respond to ADC at ≤ 3mg/kg
- Efficacy and expression level correlation not obvious
- Some outliers exist; likely due to intrinsic difference in payload sensitivity
PDX models that are resistant to SOCss can be used to demonstrate superior efficacy of new drugs:

**Adenocarcinoma NSCLC PDX 60257**

Treated with 3.0 mg/kg ADC on day 83

- 3.00 mg/kg ctrl conjugate
- 3.00 mg/kg ADC
- 20 mg/kg Paclitaxel (QW)
- 75 mg/kg Gemcitabine (Q2W)

PDX 60257
NSCLC, Adenocarcinoma
Target ++
Combination of ADC with SOC results in greater efficacy:

**LG 0551**

Day Post Tumor Implantation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tumor Volume (mm³)</th>
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<tbody>
<tr>
<td>1.5 mg/kg neg ctrl conjugate</td>
<td></td>
</tr>
<tr>
<td>1.5 mg/kg ADC</td>
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<tr>
<td>20 mg/kg paclitaxel</td>
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<tr>
<td>75 mg/kg gemcitabine</td>
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<tr>
<td>ADC + paclitaxel</td>
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<tr>
<td>ADC + gemcitabine</td>
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<tr>
<td>Paclitaxel + gemcitabine</td>
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</tbody>
</table>

**PDX LG0551**

NSCLC. Squamous cell carcinoma

Target +++
Potential Synergistic effect of combining Targeted Therapies with IO agents

Hans-Peter Gerber et al., Biochemical Pharmacology, Volume 102, 2016, 1–6
ICD: Immunologic Cell Death

- ICD constitutes a prominent pathway for the activation of the immune system against cancer
- Many conventional chemotherapeutic and targeted anticancer agents can were shown to induce ICD
- Combination of old and new agents with IOs are being tested in preclinical models to advise clinical trial design

Annu. Rev. Immunol. 31:51–72
Chemo + anti-PD-L1 combo increases T cell infiltration in mouse CT26 syngeneic model

Brown: CD3 staining
Challenges remain to combine targeted biologics with IO in preclinical models

- Targeted Biologics therapies are usually evaluated in human tumor xenograft models implanted in immunodeficient mice not suitable for IO efficacy studies
- IO agents are mainly tested in syngeneic mouse models with cell lines that lack expression of target antigens of interest

- Two common approaches:
  - Introduce target antigens into syngeneic cell lines
    - Issues: Not biologically relevant, exogenous target expression induces extra immunogenicity, need surrogate reagents
  - Implant xenograft models in humanized mice
    - Issues: Cost, engraftment consistency, not all models grow, still allogeneic
Potential synergy of combining ADC with anti-PD-L1

MDA-MB-231 xenograft model in humanized mice

Tumor volume (mm$^3$)

- Control IgG
- Anti-PD-L1
- ADC
- ADC + anti-PD-L1

Tumor regression

PD-L1 staining

ADC target staining

In vitro ADC IC$_{50}$ 127nM (not sensitive)
T cell infiltration and ICD markers assessed

Control
hIgG

Anti-PD-L1

ADC

ADC+
Anti-PD-L1
Enhanced cell death with ADC + anti-PD-L1 treatment in humanized mouse model

Brown: CD3 staining
Enhanced cell death with ADC + anti-PD-L1 treatment in humanized mouse model

Brown: CD3 staining
Most cells shown have fused nuclei
ICD marker calreticulin staining

Brown: Calreticulin staining

IgG1 control

Anti-PD-L1

ADC

Anti-PD-L1+ADC
ICD marker HMGB1 staining

Brown: HMGB1 staining

IgG1 control

Anti-PD-L1

ADC

Anti-PD-L1+ADC
What do we need for the future?

• Models that truly represent host-immune system interaction
  ❖ Do humanized model properly present the immune system?
  ❖ An autologous humanized model?

• Models that fully capture Tumor microenvironment of specific cancer types
  ❖ Orthotopic models
  ❖ Continuing development of GEMM models
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