Dissecting Cross-resistance in Small Cell Lung Cancer

Benjamin Drapkin
Chabner Colloquium
November 18th, 2019
Systemic Therapy and Cross-Resistance in SCLC

• 240,000-300,000 cases annually world-wide.
• Usually metastatic at presentation.
• 9-11 month survival for metastatic disease.
• Only 1-2% resected (node-negative only).
• No clinical role for biopsy at relapse.
Systemic Therapy and Cross-Resistance in SCLC

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Tumor Burden

1st line therapy
Etoposide/Platinum (EP)
± Atezolizumab
60-70% ORR

2nd line therapy
Topotecan (or other single agent DNA dmg)
~5% ORR
20-30% ORR

* Other 2nd line:
Irinotecan, TMZ, Gemcitabine, Ifosfamide, Vinorelbine, Taxanes
Systemic Therapy and Cross-Resistance in SCLC

What makes SCLC tumors cross-resistant?

Model System Pre-Req’s:

- Retain molecular features of SCLC in patients.
- Recapitulate clinical responses to DNA damaging regimens.
- Capture diversity of SCLC cases (inter-tumoral heterogeneity).

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Biopsy

3 months
SCLC patient-derived xenograft (PDX) project at MGH

MGH Main Campus

Anna Farago

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Vashine Kamesan,
Nikita Thareja

Charlestown Navy Yard

Nick Dyson

Marcello Stanzione

Jun Zhong

Edmond Wong

Sarah Phat

David Myers
Approach to SCLC PDX development

Dearth of live tumor specimens

- Only N0 disease resected
- No clinical role for re-biopsy

1. Hann et al., Cancer Res 2008
Approach to SCLC PDX development

1. Hann et al., Cancer Res 2008
2. Hodgkinson et al., Nat Med 2014
Approach to SCLC PDX development

In collaboration with Daniel Haber and Shyamala Maheswaran
Approach to SCLC PDX development

1. Hann et al., Cancer Res 2008
2. Hodgkinson et al., Nat Med 2014
Intertumoral Heterogeneity

66 SCLC PDX models from 46 patients, initiated June 2014 – Dec. 2018
Genomic fidelity of PDX models

<table>
<thead>
<tr>
<th>Model</th>
<th>Source</th>
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<tbody>
<tr>
<td>MGH1504-1</td>
<td>CTC</td>
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<tr>
<td>MGH1512-1</td>
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<td>MGH1514-1</td>
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</tr>
<tr>
<td>MGH1528-1</td>
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Whole exome sequencing comparison of patient vs. PDX

- 7 matched PDX models
  - 2 biopsy-derived
  - 5 CTC-derived
- 3 genomes per model
  - Patient tumor biopsy (Pt Bx)
  - Initial PDX (PDX P0)
  - PDX after two passages (PDX P2)
Genomic fidelity of PDX models

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Genomic fidelity of PDX models

**Model** vs. **Source**
- MGH1504-1 CTC
- MGH1512-1 biopsy
- MGH1514-1 CTC
- MGH1515-1 CTC
- MGH1518-1 biopsy
- MGH1525-1 CTC
- MGH1528-1 CTC

**Integral Copy Number (iCN)**
- < 0.3
- 2.0
- > 6.0

**Mutations**
- missense
- nonsense
- indel
- splice
- silent
Genomic fidelity of PDX models

<table>
<thead>
<tr>
<th>Pt Bx</th>
<th>PDX P0</th>
<th>PDX P1</th>
<th>PDX P2</th>
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<tbody>
<tr>
<td>vs.</td>
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<tr>
<td>MGH1528-1</td>
<td>CTC</td>
<td>194</td>
</tr>
</tbody>
</table>

Integral Copy Number (iCN)

< 0.3  2.0  > 6.0
1. Intertumoral Heterogeneity: 66 PDX models biopsies, effusions and CTCs
2. Genomic Fidelity: alterations retained, and few changes with passaging
SCLC PDX Trial of Cisplatin/Etoposide (EP)

Hypothesis:
If PDX models of SCLC faithfully capture clinical response to EP, then models derived before EP should be more sensitive than models derived after.

SCLC Cell Line
Patient Treatment Hx.
- Chemo-naïve
- Post-relapse

Polley et al., JNCI 2016
SCLC PDX Trial of Cisplatin/Etoposide (EP)

Tumor Metrics

32 model panel treated with EP:

EP naïve (13) vs. Post-relapse (19)

- Treatment
- Response
- Best Response (% initial tumor volume)
- Time to Progression (TTP) (2x ITV)
SCLC PDX sensitivity to Platinum + Etoposide (EP) reflects patient treatment history

Tumor Metrics

- Treatment
- Response
- Best Response (% initial tumor volume)
- Time to Progression (TTP) (2x ITV)

32 model panel treated with EP:

- EP naïve (13) vs. Post-relapse (19)

Best Response (%ITV)

0% 100% 200%

Days 0 14 28 42 56 70 84

Best Response

+50% 0% -100%

Naïve Patients Relapsed Patients

Platinum-Sensitive Platinum-Resistant

p = 0.002

p = 0.03
Olaparib + temozolomide (OT) in relapsed SCLC

Rationale for combination

- High PARP1 expression in SCLC (see IHC figure)
- Sensitivity to PARP inhibitors \textit{in vitro}
- Sensitivity to DNA alkylating agents
- OT synergy \textit{in vitro} in multiple tumor models

Byers et al., Cancer Discovery 2012
Sonnenblick et al., 2015
Byers et al., 2012
Cardnell et al., 2013
Stewart et al., 2017
George et al., 2015
Lok et al., 2016
Hopkins et al., 2015
Murai et al., 2014
Pietanza et al., 2012
Phase I/II trial of Olaparib/Temozolomide in relapsed SCLC

48 patients with evaluable response
ORR: 41.7%
mPFS: 4.2 mo (95% CI 2.8-5.7)
mOS: 8.5m (95% CI 5.1-11.3)
PDX models from OT trial patients recapitulate clinical response and resistance.

2 OT-naïve PR models
PDX models from OT trial patients recapitulate clinical response and resistance

2 OT-naïve PR models
1 OT-naïve SD model
PDX models from OT trial patients recapitulate clinical response and resistance

2 OT-naïve PR models
1 OT-naïve SD model
3 OT-relapse models
including 2 serial models

Best percent change compared to baseline
Best response
Confirmed PR
Unconfirmed PR
SD
PD

Baseline  Nadir  Progression

OT-naïve

OT-relapse

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER
PDX models of OT trial patients define co-clinical trial response categories

32 model panel treated with OT:

<table>
<thead>
<tr>
<th>Model</th>
<th>%ITV</th>
<th>Days</th>
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<tbody>
<tr>
<td>MGH1518-3</td>
<td>+100%</td>
<td>0</td>
</tr>
<tr>
<td>MGH1528-2</td>
<td>0%</td>
<td>42</td>
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<tr>
<td>MGH1543-1</td>
<td>-100%</td>
<td>84</td>
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<tr>
<td>MGH1514-5</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>MGH1528-1</td>
<td>100%</td>
<td>42</td>
</tr>
<tr>
<td>MGH1518-1B</td>
<td>0%</td>
<td>84</td>
</tr>
</tbody>
</table>

Best Response (%ITV)

- Post-relapse
- SD
- PR

Resistant → Sensitive
Molecular and functional fidelity of SCLC PDX models to their corresponding patients

- Genomic alterations are retained from patients, and stable with passaging.
- PDX sensitivities to first-line cisplatin/etoposide (EP) reflect clinical history.

Drapkin et al., Cancer Disc. 2018

- Olaparib/Temozolomide (OT) is active in SCLC following relapse.
- PDX models derived from OT trial patients recapitulate OT sensitivity.
- These trial patient models can be used to divide panel into sensitive and resistant cohorts.

Farago et al., Cancer Disc. 2019
Transcriptional profiles of EP and OT sensitivity are highly correlated

**Discovery Set**
32 models

- **RNAseq**

**Drug-gene expression: EP vs. OT**

- **EP vs. OT**

  - Cor. EP TTP (r) vs. Cor. OT TTP (r)
  - FDR <10%

- **EP TTP (days)** vs. **OT TTP (days)**

- **r = 0.68**

- **r = 0.56**
Low Basal Interferon-Stimulated Gene (ISG) expression marks EP/OT cross-resistance
Low Basal Interferon-Stimulated Gene (ISG) expression marks EP/Topotecan cross-resistance

**Basal ISG Signature** (24 genes)

![Graph showing Basal ISG Signature](image)

- **EP TTP (days)**
- **OT TTP (days)**
- **Mean ISG expression**

- **Discovery Set**
  - 32 models
  - RNAseq

- **Discovery Set**
  - 13/32 models
  - Topo

**EP TTP (days)**

- **Topotecan TTP (days)**

![Graph showing EP TTP vs Topotecan TTP](image)
STING expression may underly the basal ISG signature
Basal ISG expression represents capacity for interferon induction with DNA damage

![Graph showing Basal ISG Signature with MGH1518-1B and MGH1518-3](image)

**OT TTP (days)**

- **EP TTP (days)**
  - +1.5
  - 0
  - -1.5

**OT TTP (days)**

- Pre-EP
- Post-OT

**MGH1518-1B**

- +100%
- 0%
- -100%
- +100%

**MGH1518-3**

- +100%
- 0%
- -100%
- +100%

**Days + OT:**
- total STING
- pY-STAT1
- total STAT1
- GAPDH

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**Marcello Stanzione**

**Massachusetts General Hospital**

**Cancer Center**
Marker vs. mediator of cross-resistance

**DNA Dmg.** → **STING** → **IFN** → T-cell Independent Cytotoxicity

**Significance & Next Steps**

- STING silencing is a cross-resistance mechanism
- ± STING/IFN in sensitive vs. resistant models
- Low STING/ISG expression are biomarkers for cross-resistance
- Assess in patient tumors
Thank You!

Nick Dyson and Anna Farago

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