# Olaparib and temozolomide in SCLC

Anna Farago, MD, PhD and Benjamin Drapkin, MD, PhD

March 16, 2018


HARVARD
MEDICAL SCHOOL


MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER

# Disclosures

Farago:

- Consulting fees from: PharmaMar, AbbVie, Takeda, Merrimack, Loxo Oncology
- Honorarium from: Foundation Medicine
- Research funding (to institution) from: AstraZeneca, AbbVie, Novartis, PharmaMar, Loxo Oncology, Ignyta, Merck, Bristol-Myers Squibb

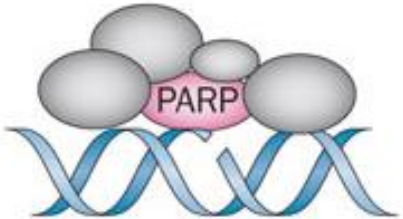
Drapkin:

- Research funding (to institution) from: AstraZeneca, AbbVie, Novartis

# Bedside to Bench… and Back

# PARP inhibition in SCLC

- PARP1 regulates base excision repair, homologous recombination, and non-homologous end joining. Inhibition of PARP enzymatic activity blocks PARP-mediated DNA repair.[1]
- PARP1 is highly expressed in SCLC compared to other cancers.[2, 3]
- SCLC cell lines are sensitive to PARP inhibitors. PARP sensitivity is not associated with *BRCA1/2* mutations or HR defects.[4,5]
- "Trapping" of PARP complexes to sites of DNA single stranded breaks by PARP inhibitors can cause failure of repair and induction of double strand breaks.[6]
- PARP inhibitors synergize with agents that increase prevalence of single stranded breaks in tumor models, including SCLC models.[7,8]



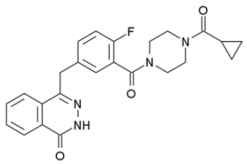


1. Sonnenblick et al., 2015
2. Byers et al., 2012
3. Cardnell et al., 2013
4. Stewart et al., 2017
5. George et al., 2015
6. Hopkins et al., 2015
7. Murai et al., 2014
8. Lok et al., 2016


Farago et al., Presented at AACR annual meeting 2017

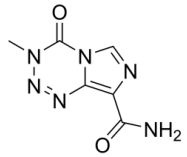
# Rationale for olaparib + temozolomide in relapsed SCLC

## Olaparib



- Catalytic inhibitor of PARP1 and PARP2
- Moderate PARP-trapping activity[1]
- FDA-approved as monotherapy for patients with *BRCA*-mutated advanced ovarian cancer and for patients with germline *BRCA*-mutated breast cancer

## Temozolomide



- Alkylating agent that induces single strand DNA breaks
- FDA-approved in newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma
- Single agent activity in SCLC[2]

- STOMP UK trial: Maintenance olaparib vs placebo following first-line chemotherapy. No PFS or survival benefit.
- SCLC second-line phase 2 study: temozolomide + veliparib vs temozolomide + placebo. Improved response rate with combo, but no significant difference in 4-month PFS.[4]


1. Hopkins et al., 2015
2. Pietanza et al., 2012
3. Pietanza et al., ASCO Abstract # 8512, 2016

# PARP inhibitors are not created equally

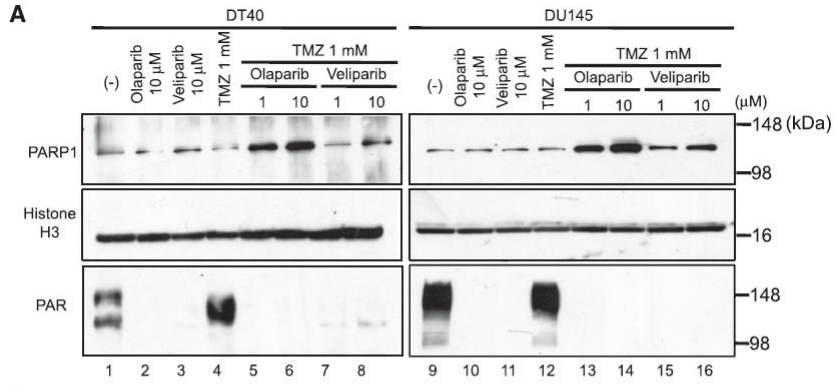
- PARP inhibitors have varying PARP trapping activity in vitro

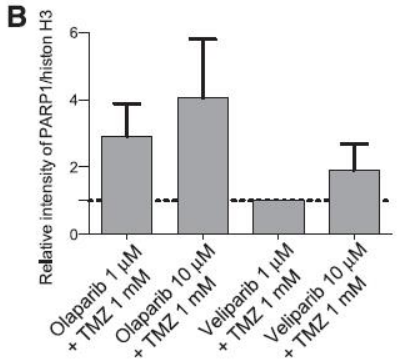
**Less PARP trapping** **More PARP trapping**

Veliparib | Olaparib | Niraparib | Talazoparib

*Schematic only, not drawn to scale*

- Olaparib + temozolomide → greater PARP trapping than veliparib + temozolomide



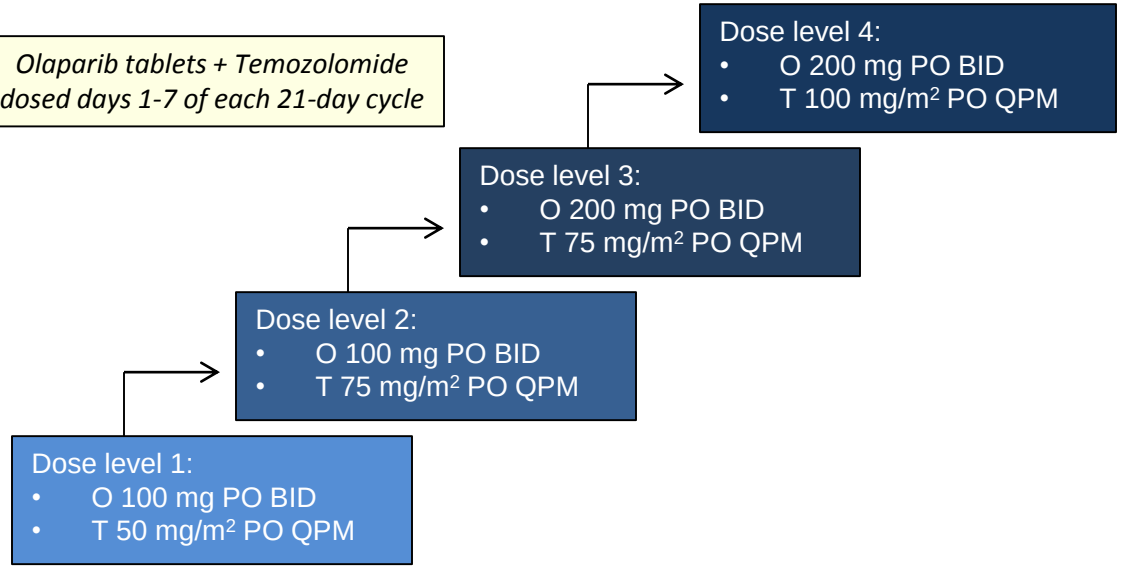

Murai et al., 2014
Hopkins et al., 2015
Murai et al., 2012

# Phase 1 study schema: olaparib tablets and temozolomide in SCLC

NCT02446704

- Histologically confirmed SCLC, not a candidate for potentially curative therapy
- Radiographic progression after one platinum based chemotherapy regimen (with any additional number of subsequent therapies allowed)
- ECOG PS 0-2
- Treated and stable brain metastases are allowed. Asymptomatic brain mets < 1 cm are allowed.

*Olaparib tablets + Temozolomide dosed days 1-7 of each 21-day cycle*




- Primary objective: Determine RP2D of combination olaparib and temozolomide
- Secondary objectives: Safety and tolerability, exploratory biomarker analyses
- Dose limiting toxicities (DLTs) monitored during cycle 1
- Disease assessment Q6 weeks, RECIST 1.1

Farago et al., Presented at AACR annual meeting 2017

# Phase 1 Patient characteristics

| | N=13 |
|---|---|
| Age, years, median (range) | 66.3 (39.2 – 85.2) |
| Sex, male/female (%) | 4 (31) / 9 (69) |
| ECOG performance status, n (%) | |
| 0 | 0 |
| 1 | 12 (92) |
| 2 | 1 (8) |
| Prior cancer therapies, n (%) | |
| 1 | 3 (23) |
| 2 | 4 (31) |
| 3 | 1 (8) |
| >3 | 5 (38) |
| Prior response to platinum-based therapy* | |
| Sensitive (%) | 8 (62) |
| Resistant (%) | 5 (38) |

* Based on time from completion of first-line therapy to start of second-line therapy.
Sensitive: ≥ 90 days
Resistant: < 90 days

Farago et al., Presented at AACR annual meeting 2017

# Phase 1 Treatment emergent adverse events related to study drugs

| Adverse Event Term, n (%) | Grade 1 | Grade 2 | Grade 3 | All Grades |
|---|---|---|---|---|
| Anemia | 4 (31) | 1 (8) | 3 (23) | 8 (62) |
| Nausea | 5 (38) | 3 (23) | 0 | 8 (62) |
| Thrombocytopenia | 2 (15) | 4 (31) | 2 (15) | 8 (62) |
| Neutropenia | 0 | 0 | 5 (38) | 5 (38) |
| Fatigue | 2 (15) | 2 (15) | 0 | 4 (31) |
| WBC count decreased | 1 (8) | 3 (23) | 0 | 4 (31) |
| Vomiting | 2 (15) | 0 | 1 (8) | 3 (23) |
| Diarrhea | 1 (8) | 1 (8) | 0 | 2 (15) |
| AST elevation | 2 (15) | 0 | 0 | 2 (15) |

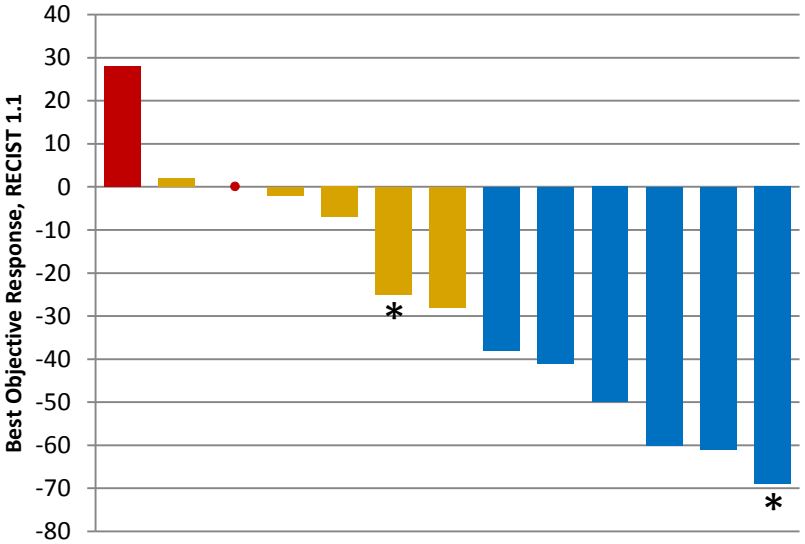
Listed are adverse events that were reported in at least 2 of the patients and that were deemed by the investigators to be possibly, probably, or definitely related to study drug(s). For each patient, only the highest grade of each AE is included.

There were no DLTs, SAEs or grade 4 or 5 AEs.

Data cut off: Feb 6, 2017

Farago et al., Presented at AACR annual meeting 2017

# Phase 1 Efficacy




| **Objective response rate**<br>all confirmed responses | **46%** |
|---|---|

| Best response | Dose level 1 | Dose level 2 | Dose level 3 | Dose level 4 | All dose levels (%) |
|---|---|---|---|---|---|
| Partial response | 2 | 1 | 2 | 1 | 6 (46) |
| Stable disease | 1 | 1 | 1 | 2 | 5 (38) |
| Progressive disease | 0 | 1 | 1 | 0 | 2 (15) |

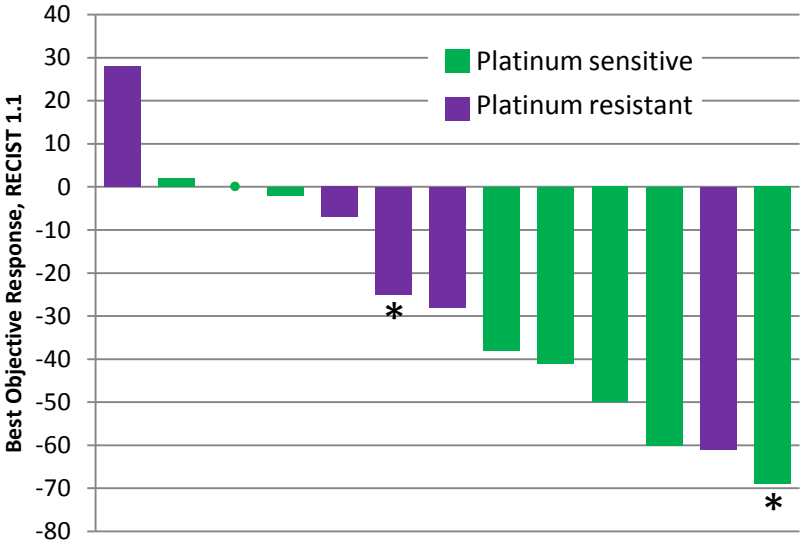
Shown are responses for all patient treated in the phase 1 portion (N=13)

• Patient with 0% response, progressive disease (new lesion)

* Patients still on treatment as of data cutoff, Feb 6 2017

Farago et al., Presented at AACR annual meeting 2017

# Phase 1 Efficacy by platinum sensitivity




| **Objective response rate**<br>all confirmed responses | **46%** |
|---|---|

| Best response | Dose level 1 | Dose level 2 | Dose level 3 | Dose level 4 | All dose levels (%) |
|---|---|---|---|---|---|
| Partial response | 2 | 1 | 2 | 1 | 6 (46) |
| Stable disease | 1 | 1 | 1 | 2 | 5 (38) |
| Progressive disease | 0 | 1 | 1 | 0 | 2 (15) |

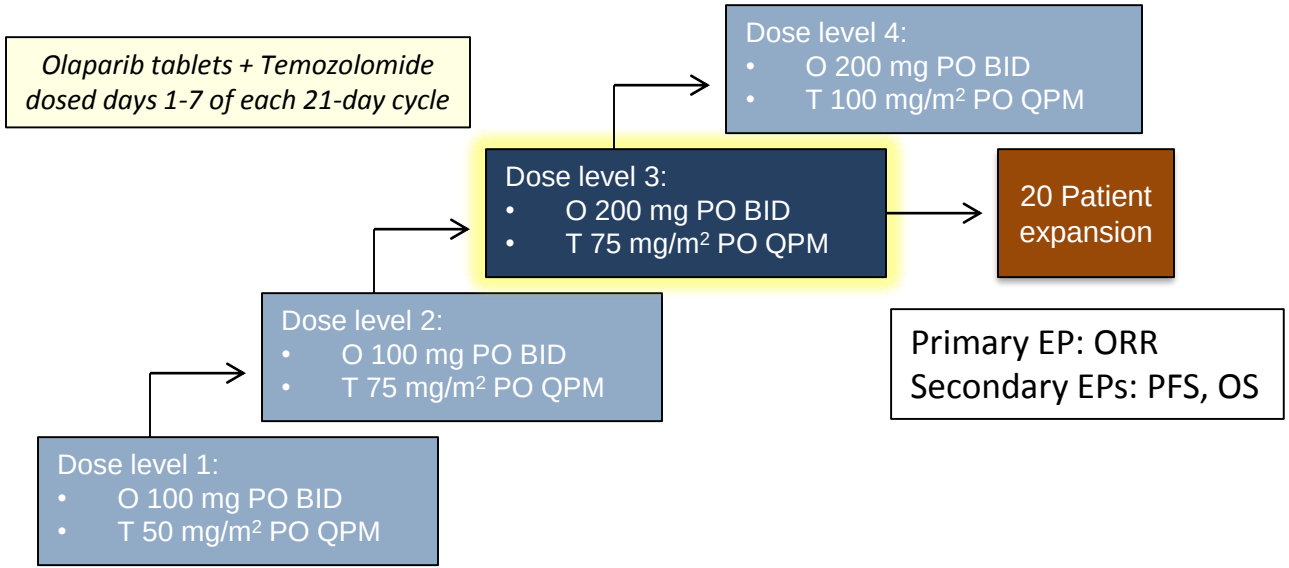
Shown are responses for all patient treated in the phase 1 portion (N=13)

• Patient with 0% response, progressive disease (new lesion)

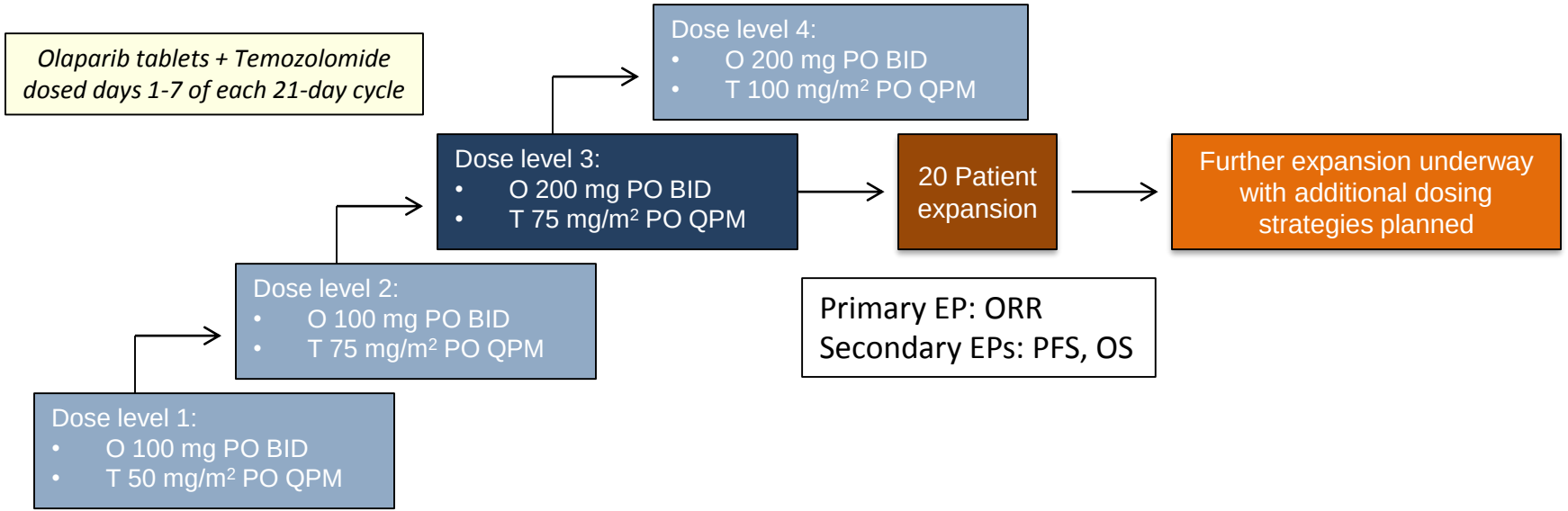
* Patients still on treatment as of data cutoff, Feb 6 2017

Farago et al., Presented at AACR annual meeting 2017

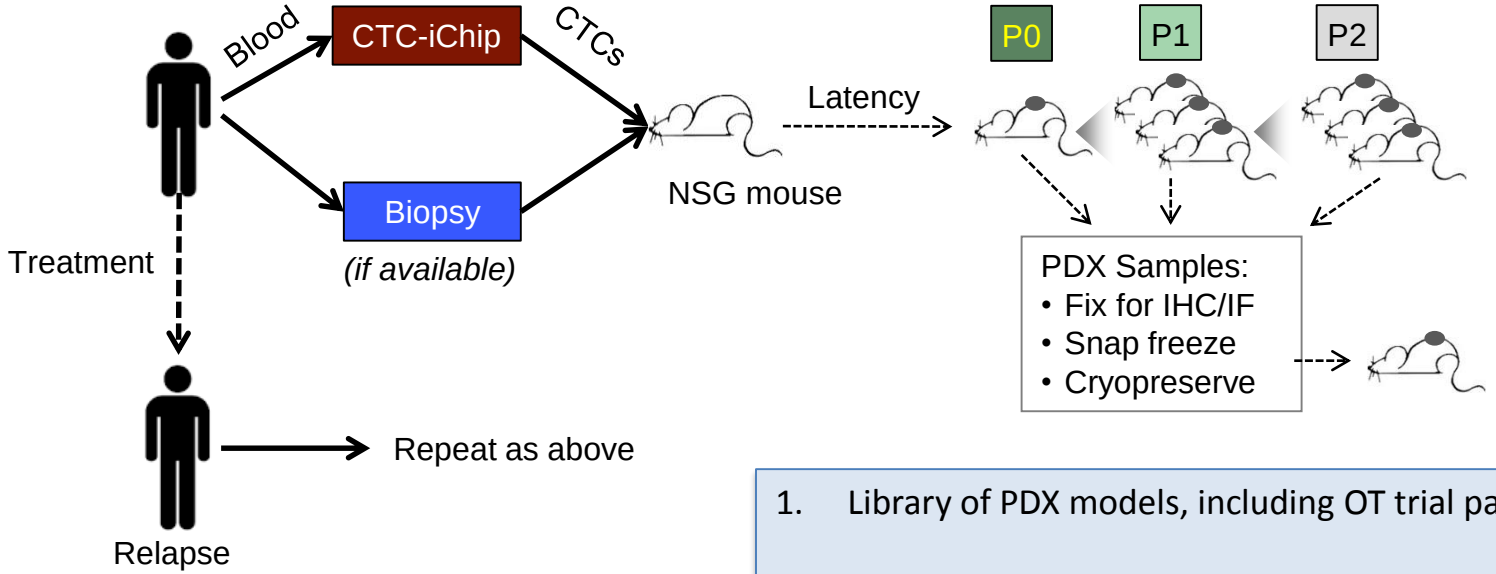
# Phase 2 expansion



# Phase 2 expansion



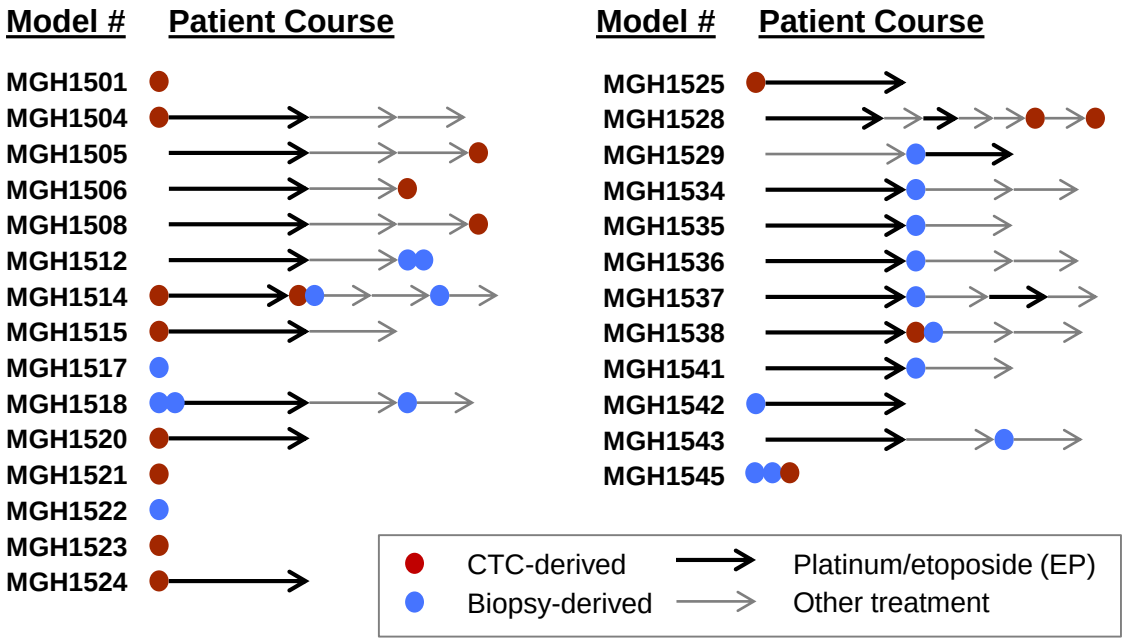
# New patient-derived xenograft (PDX) models of SCLC




1. Library of PDX models, including OT trial patients
2. Model responses mirror patient responses
3. Molecular determinants of sensitivity to OT

*In collaboration with Shyamala Maheswaran and Daniel Haber*

# Library of SCLC PDX models




| **PDX Take Rate** (P0 / attempts, monitored 365 days) | |
|---|---|
| CTC (iChip) | **38%** (16/42) |
| CTC (RosetteSep/Ficoll) | 1/4 |
| Biopsy (Bx.) | **89%** (16/19) |
| Effusions (Eff.) | 1/3 |

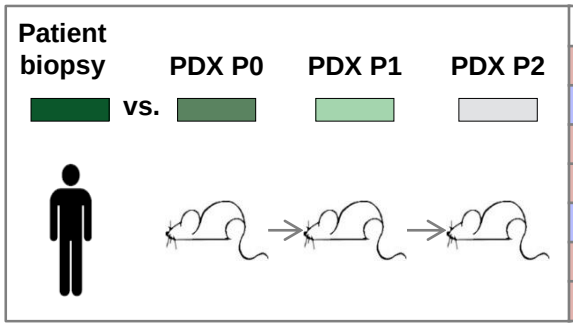
| **Pathologic Fidelity** | |
|---|---|
| Model H&E + IHC c/w SCLC | 32/34 models |
| Model H&E ≈ Patient | 14/14 models |
| Model IHC ≈ Patient | 12/13 models |

Models initiated June 2014 – June 2016
34 models from 27 patients

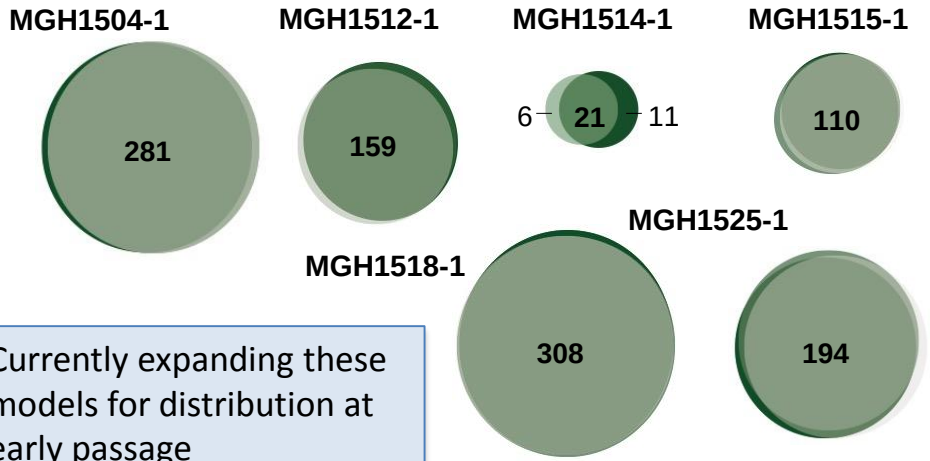
Update as of December 2017
44 models from 32 patients

Drapkin et al., Cancer Discovery 2018

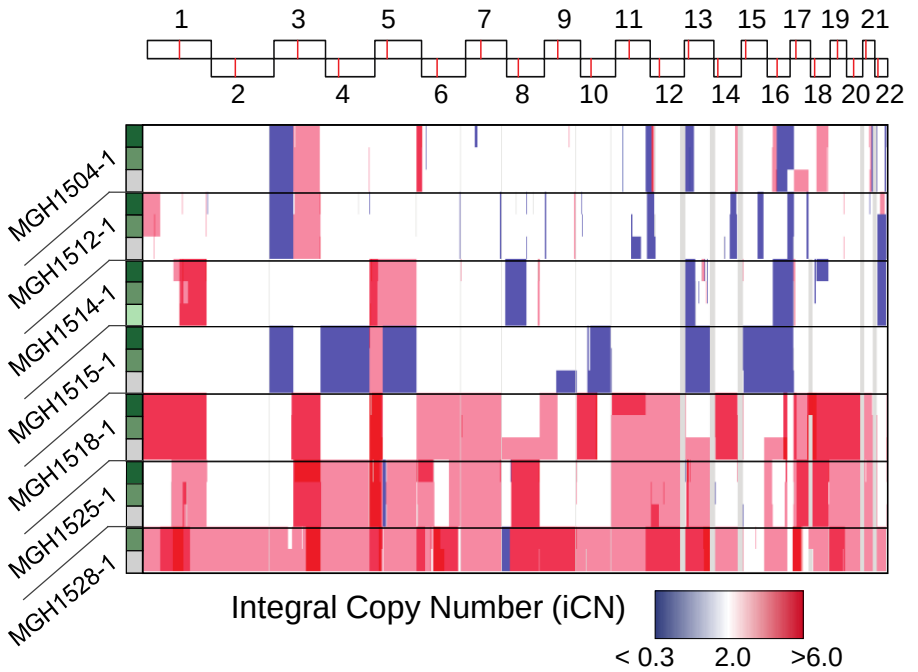
# Comparative whole exome sequencing between tumor biopsy and xenografts shows genomic fidelity of PDX models




| Model | Source |
|---|---|
| MGH1504-1 | CTC |
| MGH1512-1 | biopsy |
| MGH1514-1 | CTC |
| MGH1515-1 | CTC |
| MGH1518-1 | biopsy |
| MGH1525-1 | CTC |
| MGH1528-1 | CTC |




Currently expanding these models for distribution at early passage



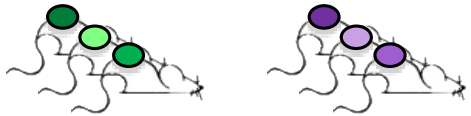

*In collaboration with Roman Thomas and Julie George*

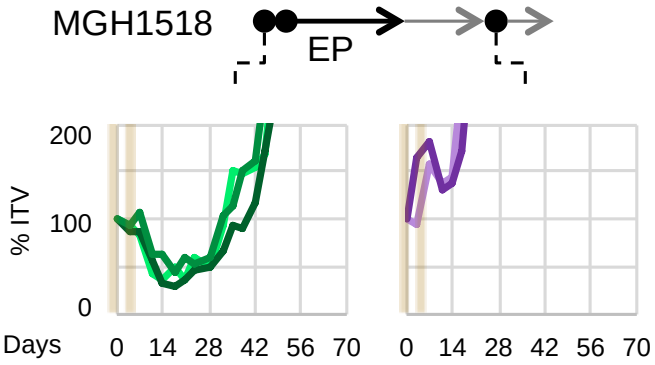
Drapkin et al., Cancer Discovery 2018

# Sensitivity of the PDX library to first-line chemotherapy

30 PDX trial with EP

Naïve (12) vs. Relapsed (18)



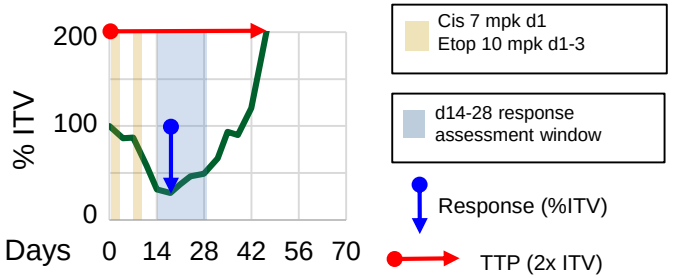



PDX population trial approach

1. Dosing regimen that distinguishes serial models

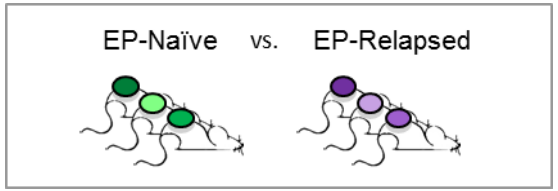
2. Apply regimen across PDX panel

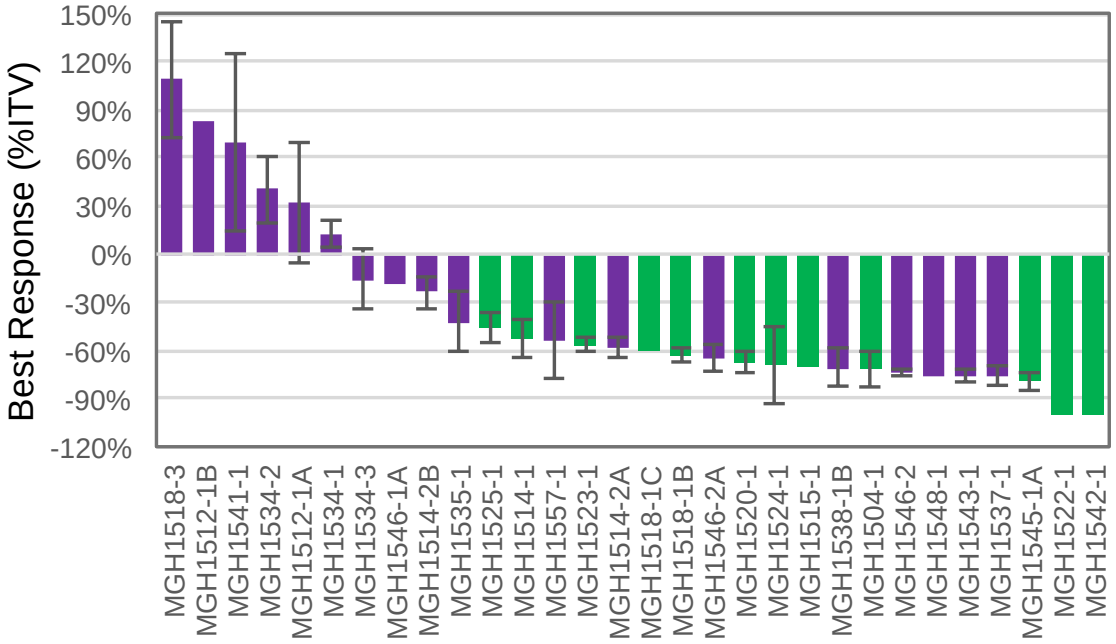
Tumor Metrics

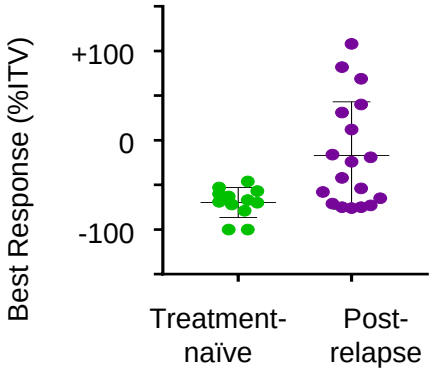


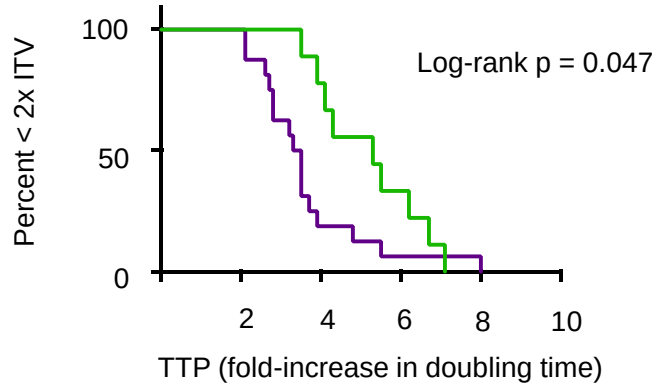

Drapkin et al., Cancer Discovery 2018

# PDX model response to EP reflects patient treatment history



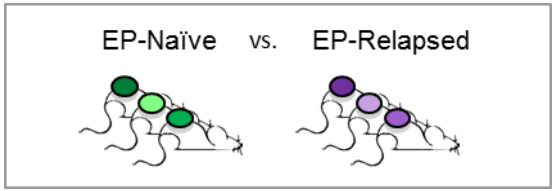



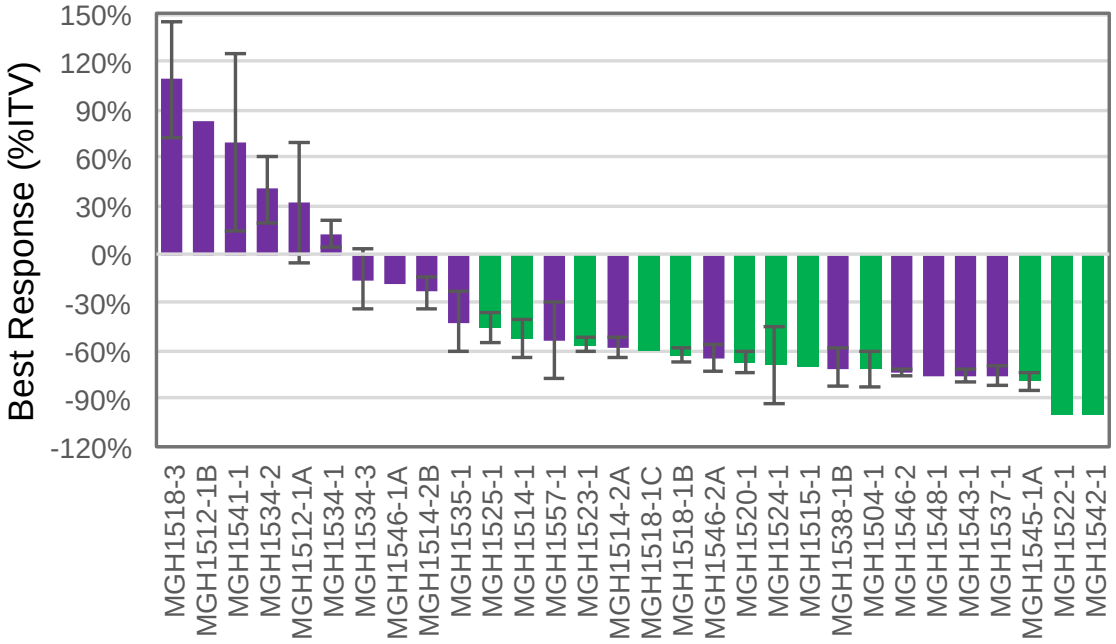



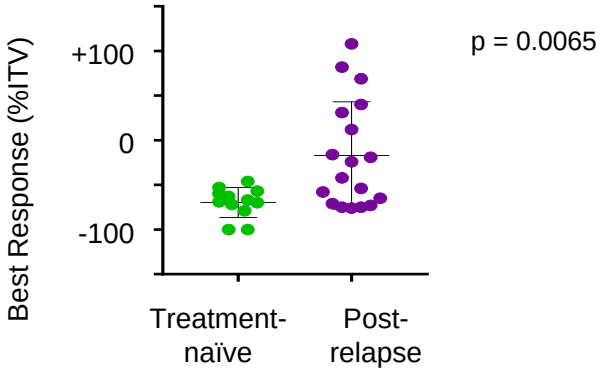




Drapkin et al., Cancer Discovery 2018

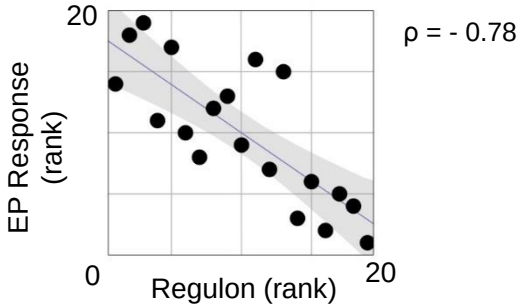
# PDX model response to EP reflects patient treatment history



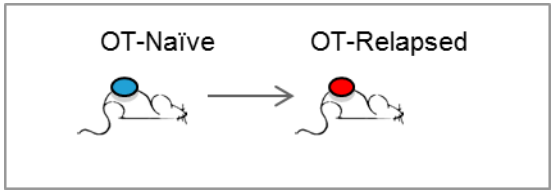

MYC regulon vs. EP response



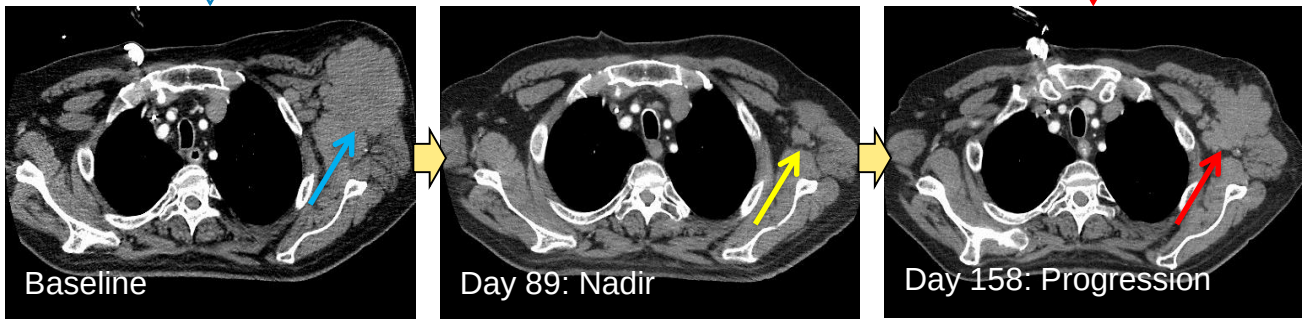

*In collaboration with Camilla Christensen and Ruben Dries*

Drapkin et al., Cancer Discovery 2018

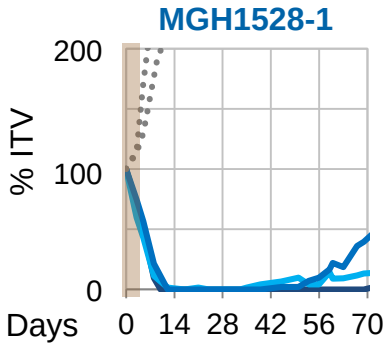
# Serial PDX models derived before and after olaparib + temozolomide (OT)

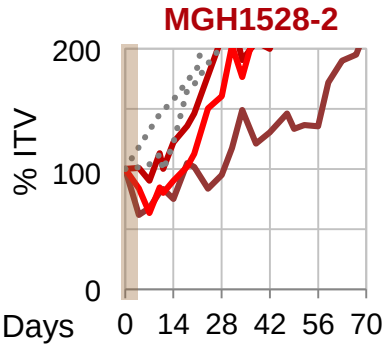


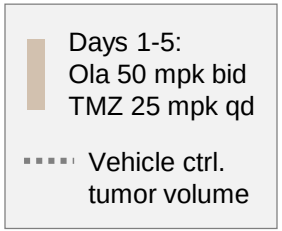

MGH1528 Clinical Course:


MGH1528 CTC-derived models




Drapkin et al., Cancer Discovery 2018

# Conclusions

- OT is tolerable and shows promising clinical activity
  - Phase I with 6/13 responses from pre-treated SCLC patients
  - Phase II expansion underway with additional dosing strategies planned
- Efficient generation of SCLC PDX’s from biopsies, effusions or CTCs
- Genomic alterations retained, and few changes with passaging
- PDX responses reflect patient clinical course
  - Sensitivity to EP reflects donor patient history
  - Sensitivity to OT reflects trial patient responses
- Ongoing experiments to assess biomarkers and mechanism of OT activity in PDX models.

# Acknowledgements


**Nick Dyson**
**Marcello Stanzione**
Sarah Phat
David Myers
Jun Zhong
Peter Igo
Vashine Kamesan
Roxana Azimi
Jane Bailey Grinnell

*Dyson Lab*
Ioannis Sanidas
Ana Guarner-Peralta
Badri Krishnan
Katerina Fella

*Haber/Maheswaran Lab*
Daniel Haber
Shyamala Maheswaran
Joseph Licausi

*MGH Cancer Center*
Mari Mino-Kenudson
Aaron Hata
Cyril Benes
Lee Zou

*MGH Thoracic Oncology*
Alice Shaw
Lecia Sequist
Jerry Azzoli
Rebecca Heist
Justin Gainor
Zosia Piotrowska
Jennifer Temel
Inga Lennes

*Dana Farber*
**Camilla Christensen**
**Ruben Dries**
Kwok-Kin Wong

*University of Cologne*
**Roman Thomas**
**Julie George**
Martin Peifer
Nima Abedpour

*Funding*
U24 for SCLC
V Foundation
Lung Cancer Research Foundation
ASCO YIA
Novartis-MGH Alliance