Development and validation of a quantitative systems pharmacology model for prediction of preclinical efficacy of PARP inhibitors rucaparib and talazoparib combined with the ATR inhibitor gartisertib (M4344)

Abstract Number: 5699

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At the time the study was conducted

Disclosure Information

Nathalie Dupuy

Relevant financial relationships:

Employee of: Physiomics PLC

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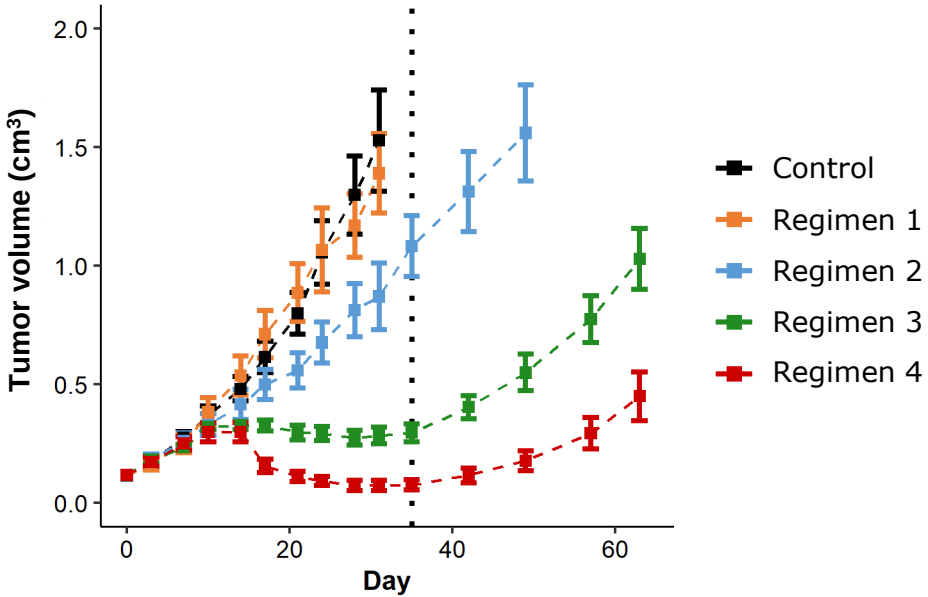
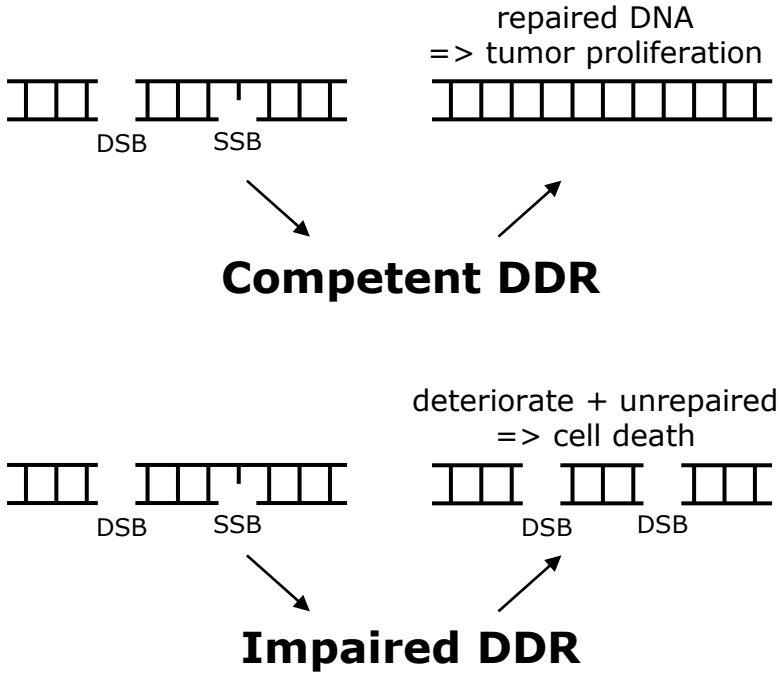
Stockholder in: Physiomics PLC

Computational model to capture the dose-response of agents targeting DDR





DDR. DNA damage response; DSB, double-strand break; SSB, single-strand break

Computational model to capture synthetic lethality induced by agents targeting DDR

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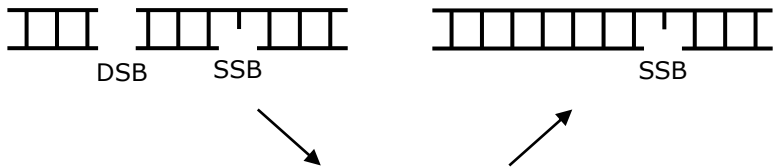
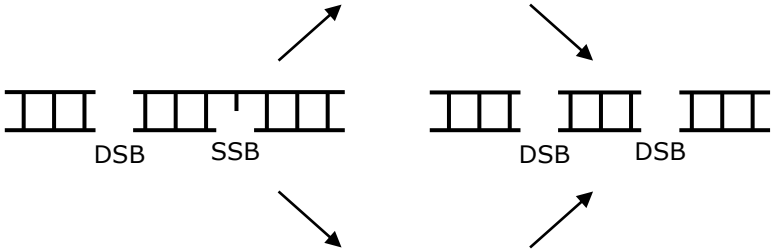
DNA damage repair is partially impaired
=> tumor proliferation



Competent DDR
+ PARP inhibitor

Multiple DNA damage repairs are impaired
=> synthetic lethality

Innate DNA repair deficiency
+ PARP inhibitor



Competent DDR
+ PARP inhibitor + ATR inhibitor

ATR, ataxia telangiectasia and Rad3-related; DDR, DNA damage response; DSB, double-strand break; PARP, poly (ADP-ribose) polymerase; SSB, single-strand break

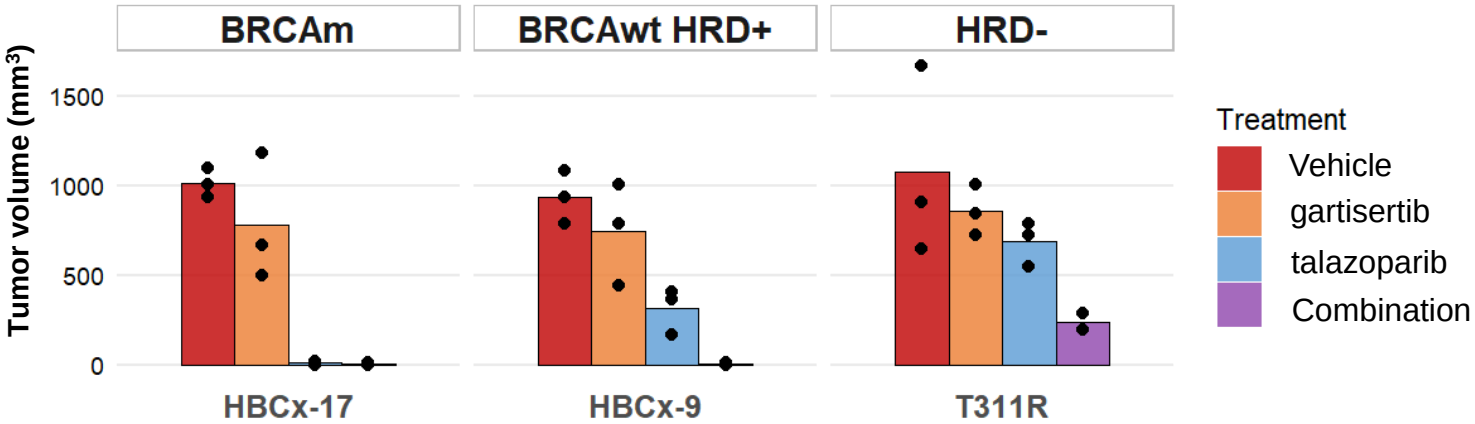
Model developed with a PDX panel of *in vivo* preclinical tumor growth inhibition (TGI) data

Preclinical work conducted by the healthcare business of Merck KGaA, Darmstadt, Germany

PARP inhibitors: rucaparib, talazoparib; **ATR inhibitor:** gartisertib (M4344)[1]

TGI efficacy at the end of treatment talazoparib + gartisertib

Representative data sets



Mouse TNBC PDX tumor models with various DNA repair deficiencies show distinct response profiles

1. Jo, U et al. *Mol Cancer Ther*. 2021;20(8):1431-41

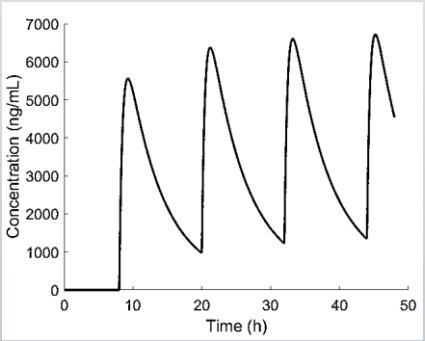
BRCAm, BRCA mutant; BRCAwt, BRCA wild-type; HRD, homologous recombination DNA-repair deficiency; PDX, patient-derived xenograft; TNBC, triple-negative breast cancer

QSP model of a virtual tumor

Pharmacokinetic model

Compartment model

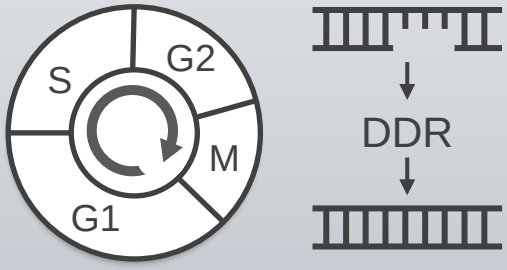
Drug plasma concentration over time



Pharmacodynamic model

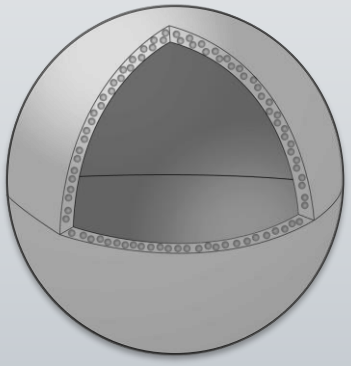
Cell population model

Cell cycle + DDR
Drug mode of action



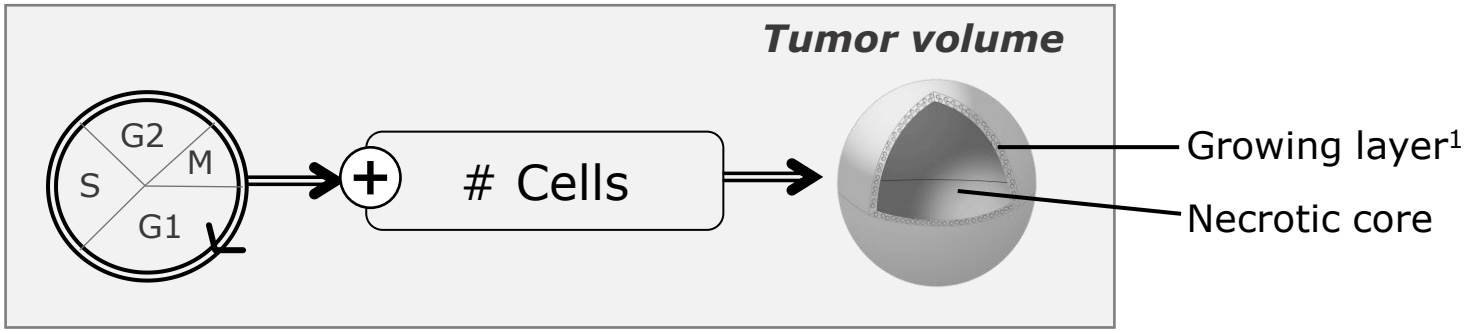
Tumor volume over time

Number of cells extrapolated to spherical tumor volume



DDR, DNA damage repair; QSP, quantitative systems pharmacology

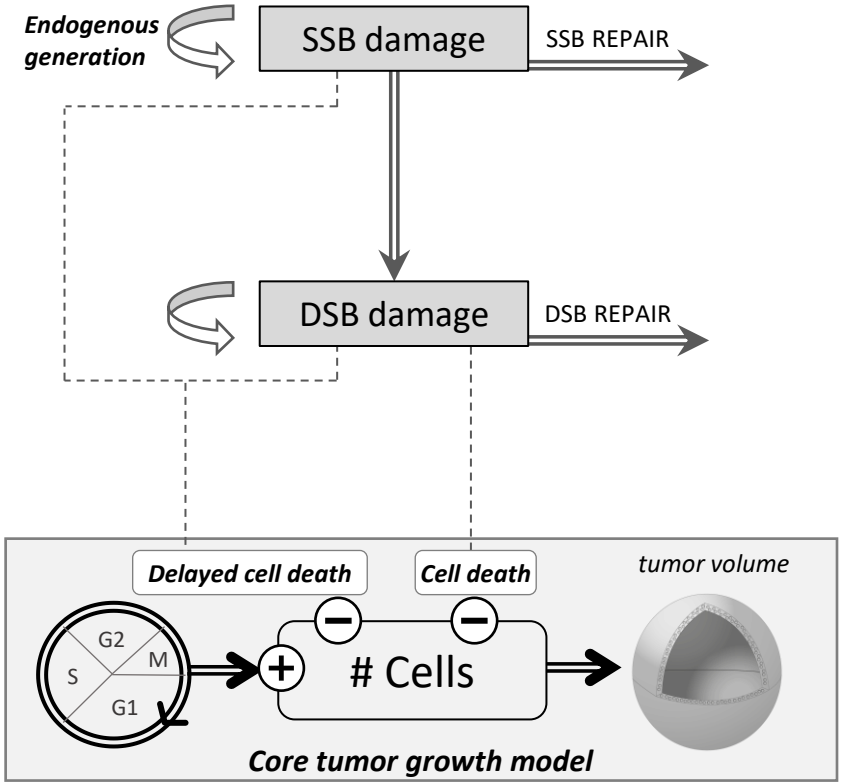
Core model tracks cell populations



1. Mayneord, WV. On a Law of Growth of Jensen's Rat Sarcoma. *The American Journal of Cancer*. 1932;16(4):841–6

Model implements DNA damage accumulation leading to cell death

- Endogenous generation of DNA damage: SSB and DSB
- SSB converted into DSB
- DSB more deleterious than SSB
- Delayed cell death[1] => damage accumulation leading to cell death after several generations



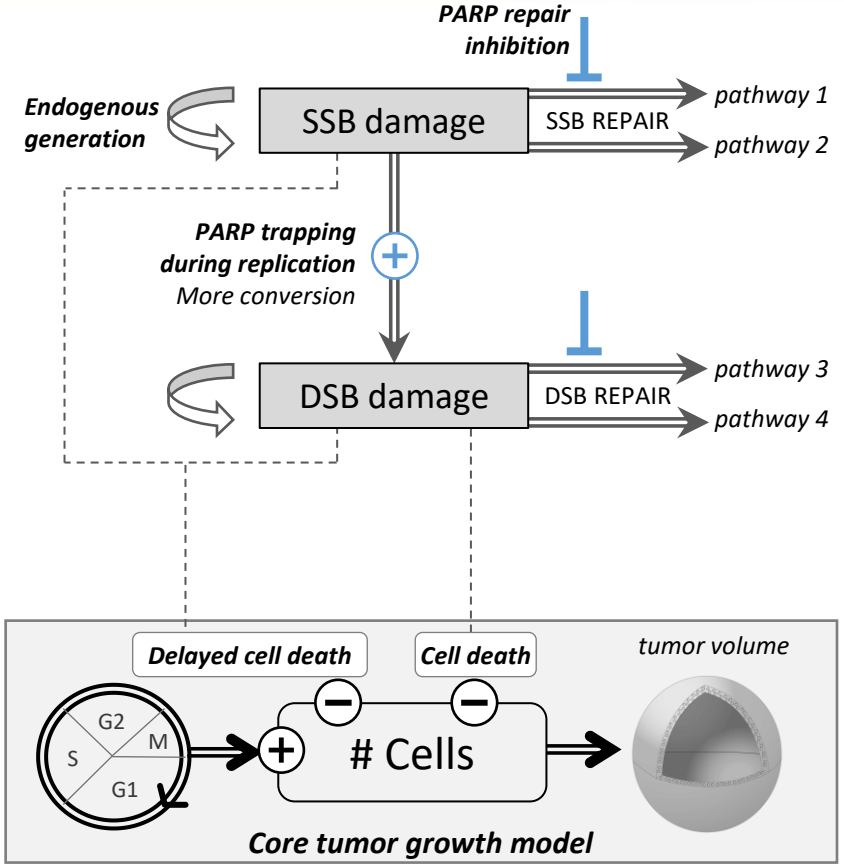
1. Cardilin, T *et al*. *Cancer Chemother Pharmacol*. 2019;83(6):1159-73

DSB, double-strand break; SSB, single-strand break

Model incorporates redundant DNA repair pathways, PARP inhibitor only partially impairs DDR

PARP is involved in the repair of[1]
- SSB
- DSB
- DNA replication damage

Model abstraction of PARP inhibitor mechanisms
- catalytic inhibition
- PARP-DNA trapping

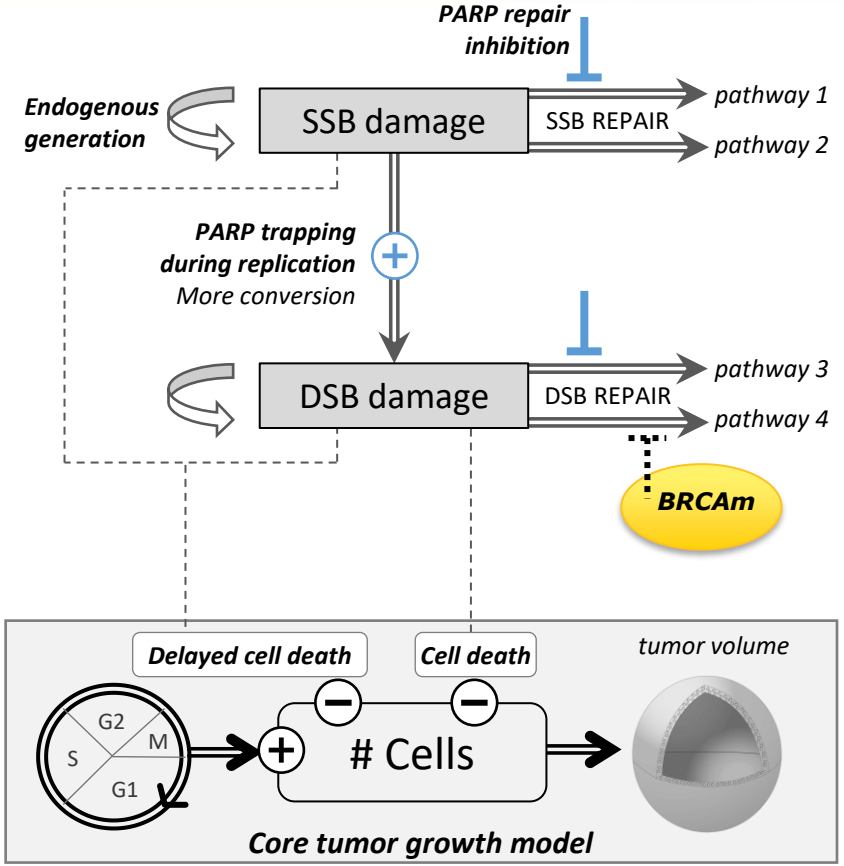


1. Pommier, Y *et al*. *Sci Transl Med.* 2016; 8(362):362ps17

DDR, DNA damage repair; DSB, double-strand break; PARP, poly (ADP-ribose) polymerase; SSB, single-strand break

Model can include innate DNA repair deficiency, leading to synthetic lethality with PARP inhibition

Model abstraction of synthetic lethality: combined with PARP inhibition, cells with HRD, such as *BRCA* mutations, have no DSB repair pathway to fall back on[1]



1. Lord, CJ *et al*. *Annu Rev Med*. 2015;66:455-70

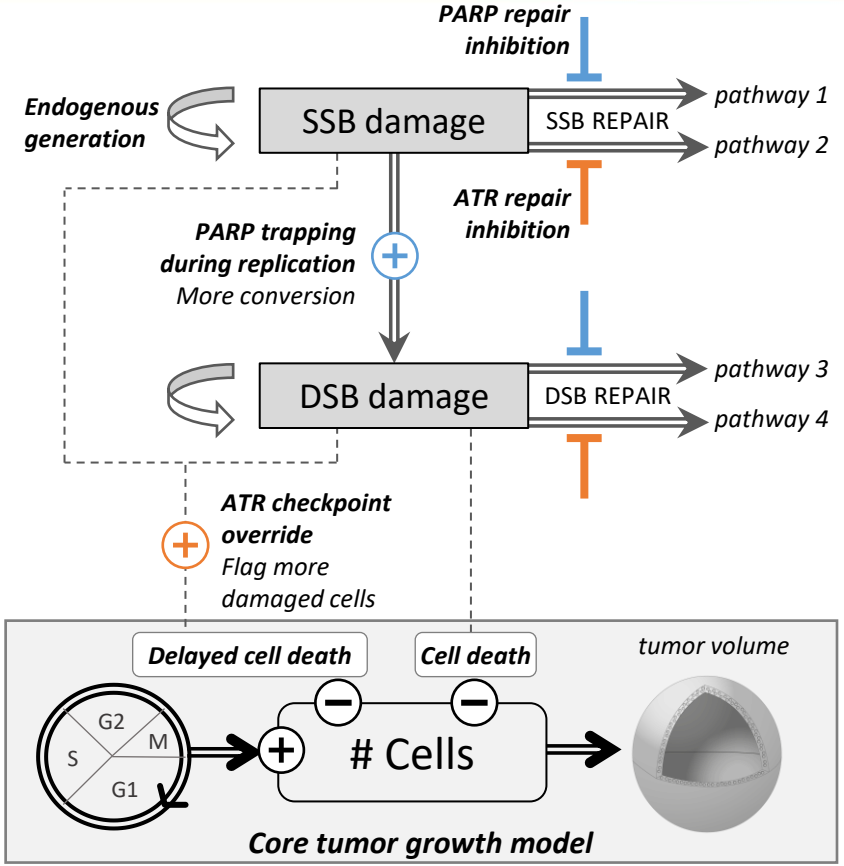
BRCAm, breast cancer mutation; DSB, double-strand break; HRD, homologous recombination DNA-repair deficiency; SSB, single-strand break

Model includes ATR involvement in other repair pathways to reflect synergy of PARP+ATR inhibition

ATR has a role in coordinating[1]
- DDR pathways
- cell cycle checkpoints

in response to SSB, DSB, and replication stress

Model abstraction of ATR inhibitor mechanisms combine synergistically with PARP inhibition



1. Weber, AM *et al*. *Pharmacol Ther*. 2015 May;149:124-38

ATR, ataxia telangiectasia and Rad3-related;
DSB, double-strand break; PARP, poly (ADP-ribose) polymerase;
SSB, single-strand break

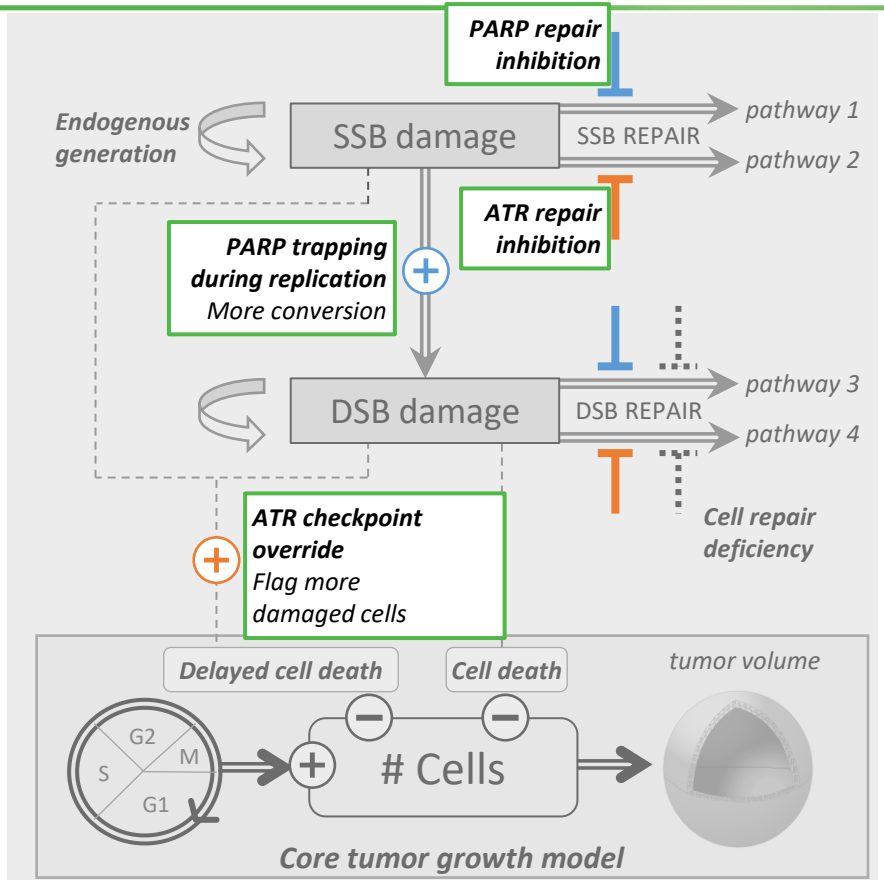
Calibrated drug model parameters are always fixed across data sets

PARP inhibitor

4 parameters
- inhibition of SSB / DSB repair
- PARP trapping
- two clearances of effect

ATR inhibitor

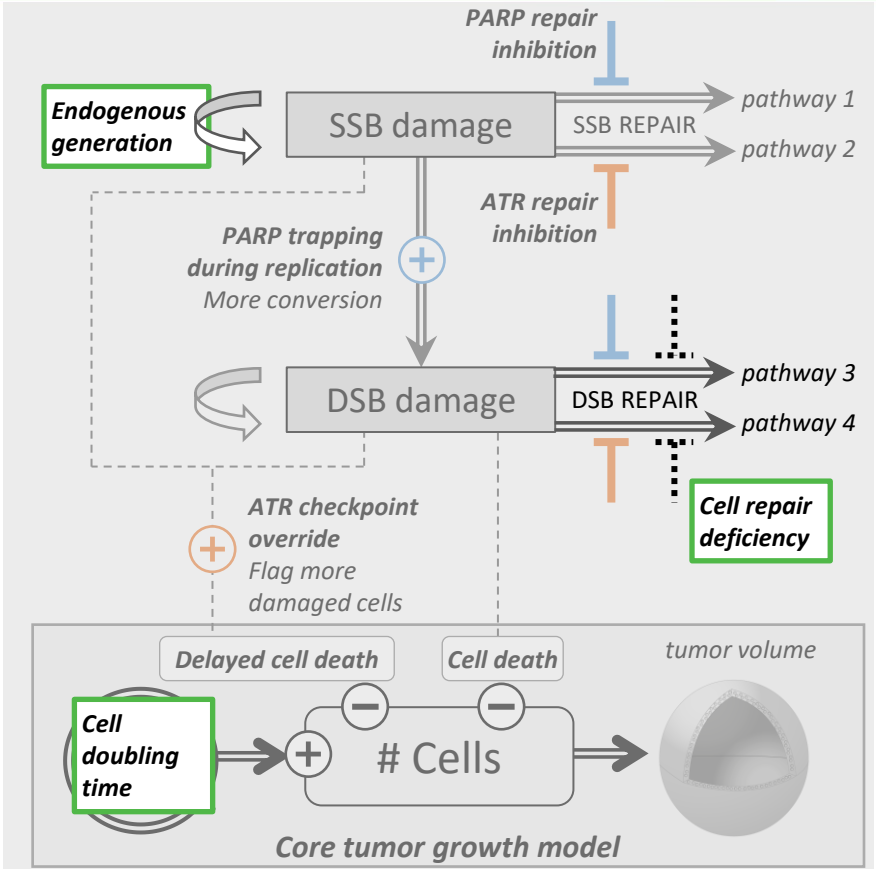
3 parameters
- inhibition of SSB / DSB repair
- checkpoint override
- clearance of effect



ATR, ataxia telangiectasia and Rad3-related;
DSB, double-strand break; PARP, poly (ADP-ribose) polymerase;
SSB, single-strand break

Model parameters characterising cancer cells are specific to tumor models

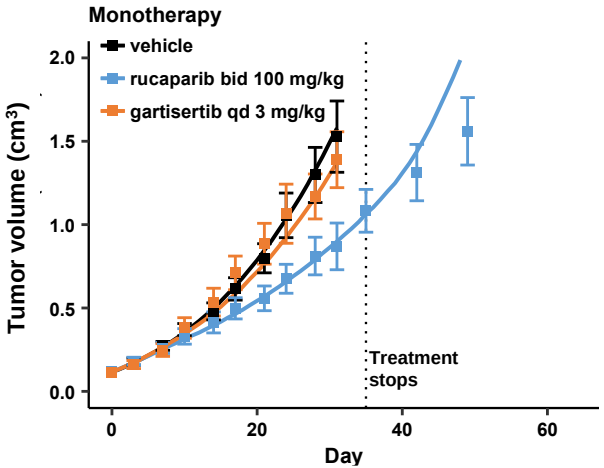
- Endogenous SSB generation is calibrated and fixed for a tumor model
- Cell doubling time & repair deficiencies vary across data sets

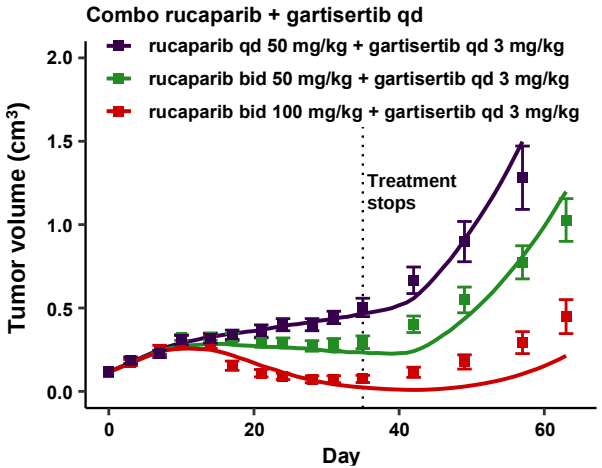


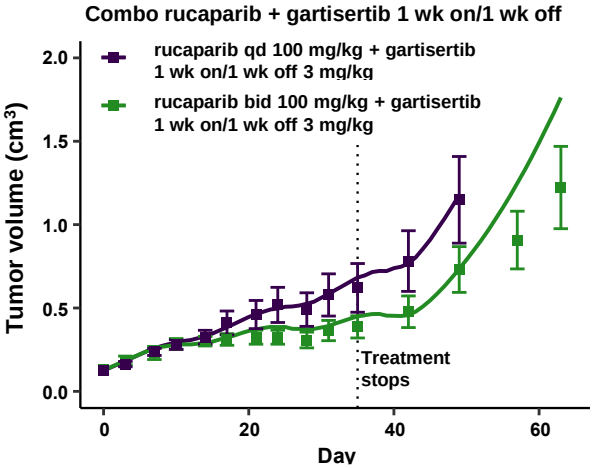
ATR, ataxia telangiectasia and Rad3-related;
DSB, double-strand break; PARP, poly (ADP-ribose) polymerase;
SSB, single-strand break

Parameters for PARPi and ATRi calibrated with TGI data in HBCx-9 model (BRCAwt HRD+) (1/2)

- 2 data sets for rucaparib (PARPi) + gartisertib (ATRi)
- Example fit (lines) using a representative data set (markers)



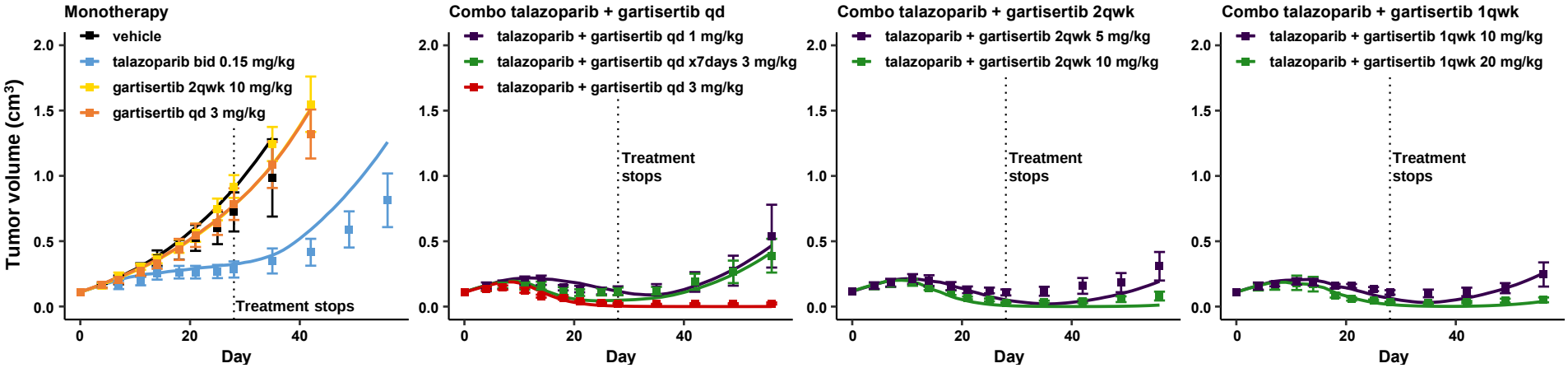




1 wk on/1 wk off, 1 week on 1 week off; ATRi, ATR inhibitor; bid, twice daily; combo, combination; BRCAwt, BRCA wild-type; HBCx, human breast cancer xenograft; HRD, homologous recombination DNA-repair deficiency; PARPi, PARP inhibitor; qd, daily dosing; TGI, tumor growth inhibition

Parameters for PARPi and ATRi calibrated with TGI data in HBCx-9 model (BRCAwt HRD+) (2/2)

- 2 data sets for talazoparib (PARPi) + gartisertib (ATRi)
- Example fit (lines) using a representative data set (markers)



1qwk, once weekly; 2qwk, twice weekly; ATRi, ATR inhibitor; BRCAwt, BRCA wild-type; combo, combination; HBCx, human breast cancer xenograft; HRD, homologous recombination DNA-repair deficiency; PARPi, PARP inhibitor; qd, daily dosing; TGI, tumor growth inhibition

Model captures heterogeneity in responses due to different genetic backgrounds

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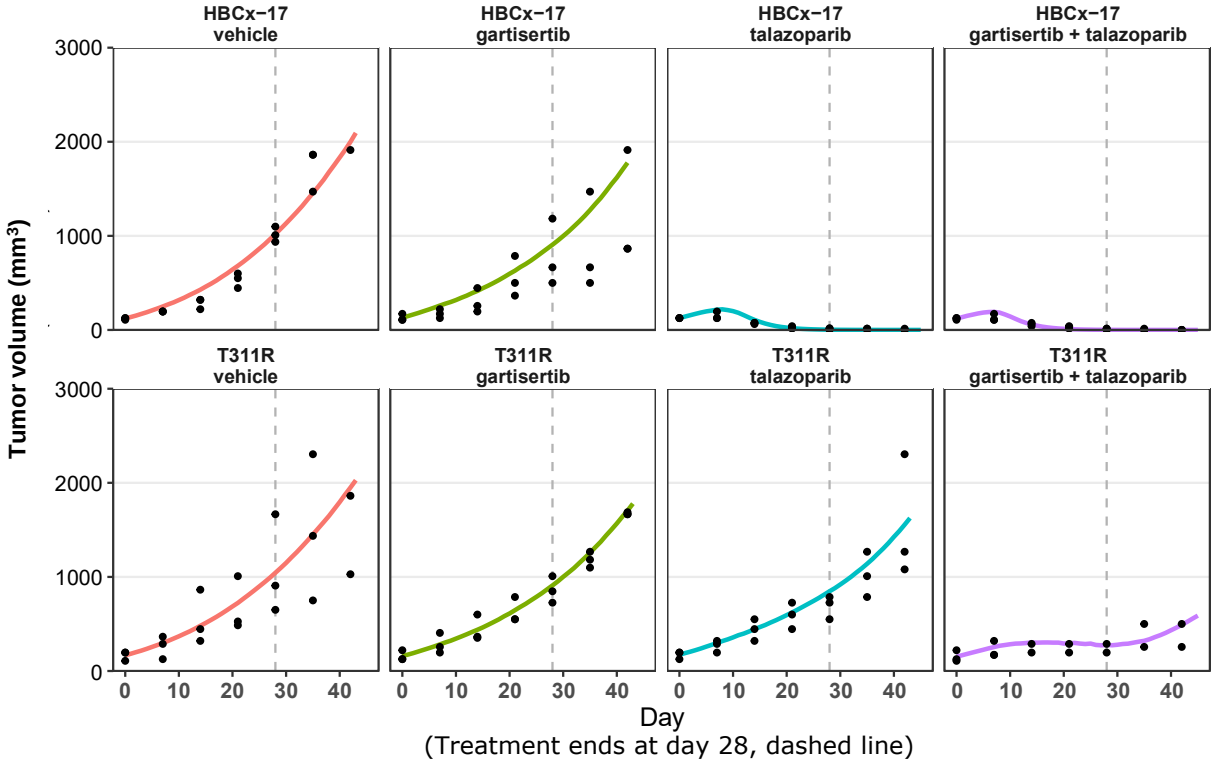

BRCA mutant tumor model HBCx-17

⟺ ***SSB endogenous generation***

↑ ***DSB repair deficiency***

HRD-tumor model T311R

↓ ***SSB endogenous generation***

↓ ***DSB repair deficiency***

⟺ ↑ ↓

Relative to HBCx-9 tumor model (BRCAwt HRD+)

BRCAwt, BRCA wild-type; DSB, double-strand break; HBCx, human breast cancer xenograft, HRD, homologous recombination DNA-repair deficiency; SSB, single-strand break

Conclusion

- **Computational model captures**
  - Synthetic lethality induced by
    - Talazoparib or rucaparib PARP inhibition + innate DNA repair deficiencies
    - Combined inhibition with talazoparib or rucaparib (PARPi) + gartisertib (ATRi)
  - Heterogeneity in tumor growth inhibition observed across multiple TNBC PDX models treated with talazoparib (PARPi) and gartisertib (ATRi)
- **Model is a framework that can help investigate**
  - Novel therapeutic strategies to address shortcomings with single agents (e.g., PARPi monotherapy)
  - Clinical dosing regimen optimization in populations stratified by genetic background

ATRi, ATR inhibitor; PARPi, PARP inhibitor; PDX, patient-derived xenograft; TNBC, triple-negative breast cancer

Teamwork!

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