Session PO.CT02 - Phase I Clinical Trials: Part 2

CT050 / 7 - Expansion cohort of Phase I study of oral sapacitabine and oral seliciclib in patients with metastatic breast cancer and *BRCA1/2* mutations

April 1, 2019, 8:00 AM - 12:00 PM | Section 17

Presenter/Authors

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Disclosures

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Abstract

Introduction: Sapacitabine, a nucleoside analog, and seliciclib, a cyclin-dependent kinase 2/9 inhibitor, constitute a novel oral regimen aimed at augmenting DNA damage and impairing cell cycle checkpoints. The initial phase I cohort investigating this combination demonstrated a 25% response rate in *BRCA* carriers. Hence, we developed an expansion cohort to assess the safety and efficacy of this regimen in patients with metastatic breast cancer and *BRCA1/2* mutations.

Methods: We enrolled 20 patients with HER2-negative metastatic breast cancer and germline or somatic *BRCA1/2* mutations, who were treated with sapacitabine 50 mg twice daily for days 1-7 followed by seliciclib 800 mg twice daily for days 8-10 of a 21-day cycle. Baseline or archival biopsies underwent RAD51 immunohistochemistry to assess for functional homologous recombination proficiency. Available tissue was sent for whole exome and transcriptome sequencing, and pre- and post-treatment blood was submitted for cell-free DNA sequencing to assess for genomic correlates of response.

Results: Participants received a median of 2 prior lines of chemotherapy for metastatic disease. Of the 9 patients who received a prior platinum agent, 6 progressed on this therapy. In addition to chemotherapy, 7 patients received and progressed on a prior PARP inhibitor. The overall response rate for sapacitabine and seliciclib in this cohort was 10%, consisting of 2 patients with partial responses lasting 4.7 and 9.0 months, respectively. The clinical benefit rate (CR + PR + SD ≥ 6 months) was 30%, and durations of stable disease ≥ 6 months ranged from 7.4 to 11.7 months. For all patients, median PFS was 3.7 months. The most frequent grade 3/4 adverse events were neutropenia (25% of patients), transaminitis (20%), and rash (10%). No patients who progressed on prior PARP inhibitor therapy and 6 of 13 patients (46%) with no history of PARP inhibitor resistance experienced clinical benefit ($p = 0.052$ by Fisher's exact test). In contrast, 1 of 6 patients (17%) who progressed on prior platinum chemotherapy and 5 of 14 patients (36%) with no history of platinum resistance experienced clinical benefit ($p = 0.61$ by Fisher's exact test). Notably, the tumors of some resistant patients harbored *BRCA* reversion mutations. Additional genomic analyses and RAD51 immunohistochemistry will be presented.

Conclusions: The combination of sapacitabine and seliciclib was safe and led to durable clinical benefit in some patients with metastatic breast cancer and *BRCA1/2* mutations. Prior progression on PARP inhibitors predicted resistance to this combination, associated in some cases with *BRCA* reversion mutations. Based on these results, the combination of sapacitabine and the PARP inhibitor olaparib is now being investigated in patients with PARP-naïve metastatic HER2-negative breast cancer and germline *BRCA1/2* mutations.

Poster # CT050

Expansion of phase I study of oral sapacitabine and oral seliciclib in patients with metastatic breast cancer and *BRCA1/2* mutations

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BACKGROUND

- Sapacitabine, a nucleoside analog, and seliciclib, a cyclin-dependent kinase 2/9 inhibitor, augment DNA damage and impair cell cycle checkpoints.[1]
- The initial phase I cohort investigating this combination demonstrated a 25% response rate in *BRCA* carriers.[2]
- BRCA reversion alterations are a known mechanism of resistance to platinum and PARP inhibitors.[3,4]

STUDY OBJECTIVES

- The primary objective of this expansion cohort was to assess safety and efficacy in patients with metastatic breast cancer and *BRCA1/2* mutations.
- The secondary objective was to assess genomic correlates of response to this novel oral regimen.

METHODS

- This expansion cohort enrolled 20 patients with HER2-negative metastatic breast cancer and germline or somatic *BRCA1/2* mutations.
- Patients were treated with sapacitabine 50 mg twice daily for days 1-7 followed by seliciclib 800 mg twice daily for days 8-10 of a 21-day cycle.
- Baseline or archival biopsies underwent RAD51 immunohistochemistry to assess for functional homologous recombination proficiency.
- Available tumor tissue was sent for whole exome and transcriptome sequencing. Established pipelines were used to call genomic alterations, including large structural variants. Gene set enrichment analysis was performed using Hallmark gene sets.

REFERENCES

1. Shapiro G et al. *J of Clin Oncol*. 2012:30(15_suppl): 3053-3053.
2. Tolaney SM et al. *J of Clin Oncol*. 2016:34(15_suppl): 2503-2503.
3. Weigelt B et al. *Clin Cancer Res*. 2017;23(21):6708-6720.
4. Lin KK et al. *Cancer Discov*. 2019;9(2):210-219.

RESULTS

Patient Characteristics

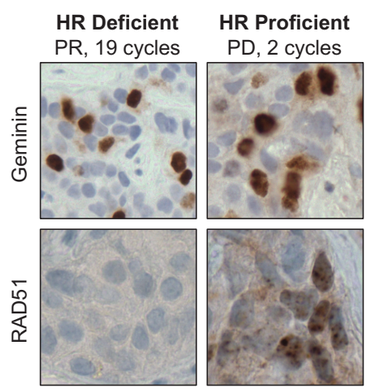
Characteristics	Patients n = 20
Median age (IQR), y	53 (43-62)
Female gender, n	20
Receptor status, n	
ER+, PR+, HER2-	6
ER+, PR-, HER2-	5
Triple negative	9
ECOG performance status, n	
0	10
1	9
2	1
BRCA carriers, n	
BRCA1	11
BRCA2	9
Prior metastatic chemotherapy*, n	
0	3
1-2	9
≥3	8
Progressed on prior therapy, n	
PARP inhibitor	7
Platinum agent	6

*Excludes targeted therapies (i.e. PARP & CDK4/6 inhibitors).

Immunohistochemistry

Homologous Recombination Deficient:
+ g-H2AX, + geminin, - RAD51

9 baseline tumors
- 0/5 with no clinical benefit > 6 months
- 1/4 with clinical benefit > 6 months

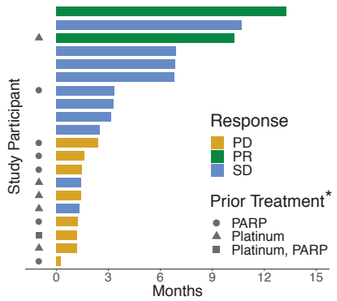


Overall Response Rate

Response Outcomes	n (%)
Response type	
PR	2 (10%)
SD	10 (50%)
PD	8 (40%)
Overall Response Rate	2 (10%)
Clinical Benefit Rate*	6 (30%)

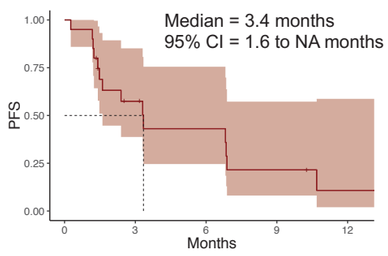
*CR + PR + SD > 6 months.

Duration of Response

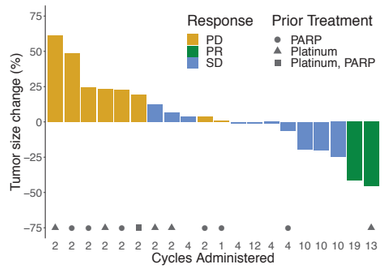


*Associated with lack of clinical benefit > 6 months (p = 0.02).

Progression Free Survival

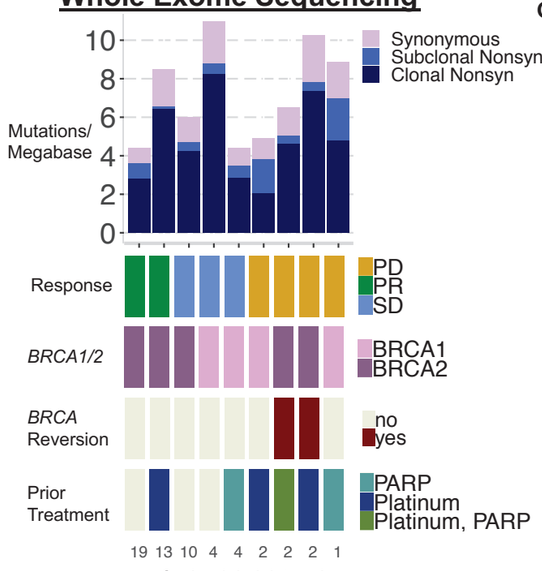


Tumor Size Change



PR confirmed with ≥ 2 scans.

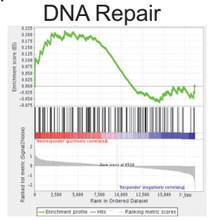
Whole Exome Sequencing



RNA Sequencing

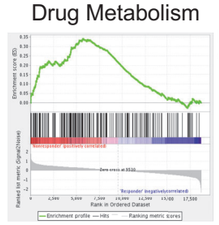
Gene Sets Enriched in Non-responders

DNA Repair



p = 0.3
q = 0.5

Drug Metabolism



p = 0.0
q = 0.0

n = 4 patients with no CB and 2 patients with CB

Adverse Events

Adverse event n* (%)	Grade 1-2	Grade 3
ALT or AST elevation	6 (30%)	4 (20%)
Neutropenia	1 (5%)	3 (15%)
Rash	1 (5%)	2 (10%)
Nausea	14 (70%)	1 (5%)
Vomiting	10 (50%)	1 (5%)
Diarrhea	6 (30%)	1 (5%)
Fatigue	8 (40%)	0 (0%)
Constipation	7 (35%)	0 (0%)
Decreased appetite	7 (35%)	0 (0%)

*n = number of patients.
Grade 4 AEs were neutropenia in 2 patients.

CONCLUSIONS

- The combination of sapacitabine and seliciclib was safe and led to durable clinical benefit in some patients with metastatic breast cancer and *BRCA1/2* mutations.
- Responses occurred in all 8 patients without prior progression on platinum or a PARP inhibitor (1 PR, 7 SDs), 3/6 patients who progressed on platinum (1 PR, 2 SDs), and 1/7 patients who progressed on a PARP inhibitor (1 SD).
- *BRCA* reversion alterations occurred in 2 patients with PD who progressed on platinum and/or a PARP inhibitor.
- Based on these results, an ongoing phase I/II study is investigating the combination of sapacitabine and the PARP inhibitor olaparib in patients with PARP-naïve metastatic HER2-negative breast cancer and germline *BRCA1/2* mutations.

FUTURE DIRECTIONS

- Whole exome sequencing of cell-free DNA from pre- and post-treatment blood will be assessed for *BRCA* reversion alterations.
- *BRCA* reversion alterations should be investigated prospectively as a response biomarker for novel *BRCA*-directed therapies.

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