Characterization of Patients With Long-term Responses to Rucaparib in Recurrent Ovarian Cancer

Elizabeth M. Swisher,[1] Rebecca S. Kristeleit,[2] Amit M. Oza,[3] Anna V. Tinker,[4] Isabelle Ray-Coquard,[5] Ana Oaknin,[6] Robert L. Coleman,[7] Howard A. Burris,[8] Carol Aghajanian,[9] David M. O'Malley,[10] Alexandra Leary,[11] Stephen Welch,[12] Diane Provencher,[13] Geoffrey I. Shapiro,[14] Lee-may Chen,[15] Ronnie Shapira-Frommer,[16] Sandra Goble,[17] Lara Maloney,[17] Kevin K. Lin,[17] Iain A. McNeish[18]

[1]University of Washington, Seattle, WA, USA; [2]UCL Cancer Institute, University College London and UCL Hospitals, London, UK; [3]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [4]BC Cancer, Vancouver, BC, Canada; [5]Centre Léon Bérard, Université Claude Bernard, Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, Lyon, France; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]The Ohio State University, James Cancer Center, Columbus, OH, USA; [11]Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, Villejuif, France; [12]London Regional Cancer Centre, London, ON, Canada; [13]CHUM Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montreal, QC, Canada; [14]Dana-Farber Cancer Institute, Boston, MA, USA; [15]University of California San Francisco, San Francisco, CA, USA; [16]Sheba Medical Center, Tel Hashomer, Israel; [17]Clovis Oncology, Inc., Boulder, CO, USA; [18]Imperial College London, London, UK

Baseline patient characteristics of long- and short-term responders to rucaparib

- Final results from Study 10 Part 2 (n=54) and ARIEL2 (n=491) were pooled in this exploratory post-hoc analysis of long- and short-term responders to rucaparib
- Overall, 25% (138/545) of patients had a confirmed RECIST response to rucaparib
  - Thirty-eight responders (28%) had long-term confirmed responses (DOR ≥1 years), including 16 (12%) with DOR ≥2 years
  - Twenty-nine patients had short-term responses (DOR ≤20 weeks), including 16 with confirmed responses
- Baseline characteristics and prior number of chemotherapies were not significantly different between long- and short-term responders

	Long-term responders (n=38)	Short-term responders (n=29)
Median age (range), years	63 (33–82)	60 (44–83)
ECOG PS 0, n (%)	25 (65.8)	13 (44.8)
Median no. of prior chemotherapies (range)	2.5 (1–5)	2 (1–4)
Median no. of prior platinum-based therapies (range)	2 (1–4)	2 (1–3)
PFI from last platinum-based therapy, months, n (%)		
>24	4 (10.5)	1 (3.4)
>12–24	12 (31.6)	5 (17.2)
6–12	17 (44.7)	14 (48.3)
>2–<6	3 (7.9)	7 (24.1)
≤2	2 (5.3)	2 (6.9)

Long-term responders = confirmed RECIST response with DOR ≥1 year.
Short-term responders = confirmed or unconfirmed RECIST response followed by disease progression, resulting in DOR ≤20 weeks.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

BRCA mutation characteristics of long- and short-term responders to rucaparib

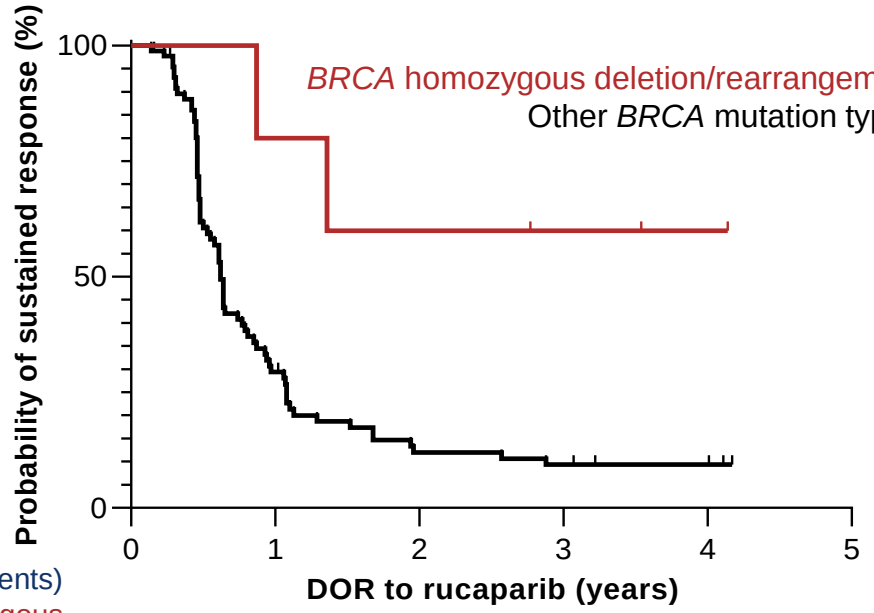
- Deleterious *BRCA* mutations were identified in 71% (27/38) of long-term responders and 52% (15/29) of short-term responders
- Distribution of *BRCA* germline and founder mutations, as well as fraction of *BRCA1* versus *BRCA2* mutations, were similar for long-term and short-term responders

	Long-term responders with *BRCA* mutations (n=27)	Short-term responders with *BRCA* mutations (n=15)
***BRCA* mutation origin, n (%)**		
Germline	22 (81.5)[a]	10 (66.7)
Somatic	5 (18.5)	5 (33.3)
Presence of *BRCA* founder mutation, n (%)		
Yes	8 (29.6)	2 (13.3)
No	19 (70.4)	13 (86.7)
***BRCA* gene with mutation, n (%)**		
BRCA1	17 (63.0)[a]	11 (73.3)
BRCA2	10 (37.0)	4 (26.7)
***BRCA* mutation type, n (%)**		
Homozygous deletion or rearrangement	4 (14.8)	0
Small insertion/deletion	21 (77.8)	9 (60.0)
Nonsense mutation	1 (3.7)	4 (26.7)
Missense, splice-site mutation	1 (3.7)	2 (13.3)

[a]One long-term responder with a germline *BRCA1* mutation also had a somatic *BRCA2* truncating rearrangement detected in the tumor.

DOR to rucaparib in patients with *BRCA* homozygous deletion or rearrangement

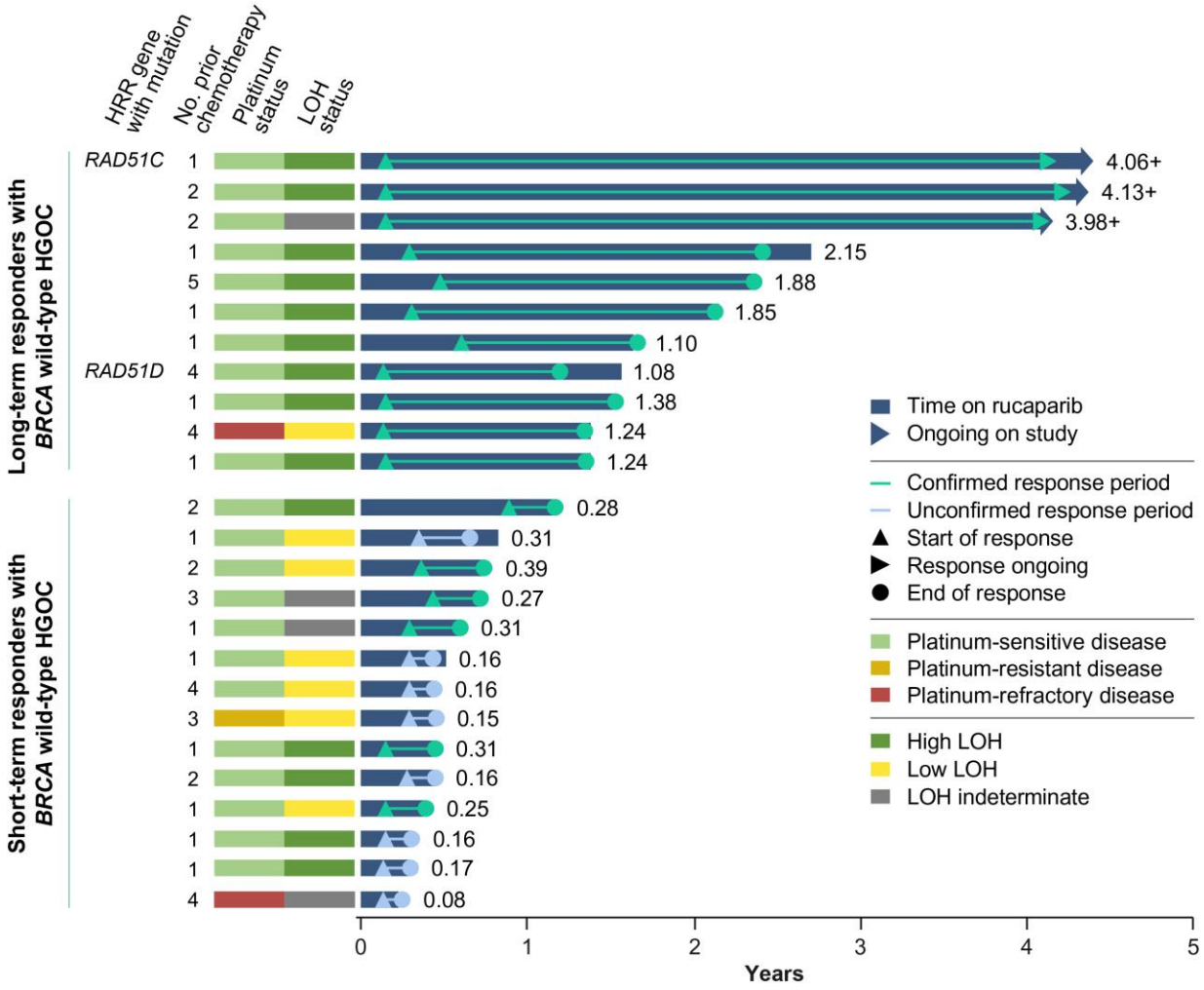
- *BRCA* homozygous deletion or rearrangement was detected in 15% (4/27) of long-term versus 0% (0/15) of short-term responders
- In an expanded analysis of HGOC with *BRCA* mutations and a confirmed response to rucaparib (n=95), *BRCA* homozygous deletion or rearrangement was associated with significantly longer DOR than other mutation types



Patients at risk (events)						
BRCA homozygous deletion/rearrangement	5 (0)	4 (1)	3 (2)	2 (2)	1 (2)	0 (2)
Other *BRCA* mutation type	90 (0)	23 (58)	9 (71)	7 (73)	4 (73)	0 (73)

DOR, duration of response; HGOC, high-grade ovarian cancer; HR, hazard ratio; NR, not reached.

Time on rucaparib and genomic/clinical characteristics of long- and short-term responders with *BRCA* wild-type HGOC



- High LOH was seen in 9/11 (82%) long-term responders with *BRCA* wild-type ovarian cancer
  - *RAD51C/D* mutations (n=2) were also observed
- Only 5/14 (36%) short-term responders with *BRCA* wild-type ovarian cancer had high LOH

Values shown represent DOR to rucaparib in years; ongoing responses are indicated with a +.
DOR, duration of response; HGOC, high-grade ovarian cancer; HRR, homologous recombination repair; LOH, loss of heterozygosity.

Conclusions

- Overall, 28% of patients with recurrent HGOC and a confirmed response to rucaparib had a response ≥1 year, including 12% with a response lasting ≥2 years
- The majority (71%) of the long-term responders to rucaparib harbored a deleterious *BRCA* mutation, particularly homozygous deletion or rearrangements which would not be susceptible to somatic reversion mutations
- Most long-term responders with *BRCA* wild-type ovarian cancer (82%) had tumors with high genome-wide LOH, a genomic scar indicative of homologous recombination deficiency
  - In 2 patients with a long-term response, high genome-wide LOH was observed in the context of a deleterious *RAD51C/D* mutation

HGOC, high-grade ovarian cancer; LOH, loss of heterozygosity.