Supplementary appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets in relapsed ovarian cancer: the SOLO2/ENGOT Ov-21 trial.

SOLO2 investigators

The table below lists the lead investigator for each site that participated in this study.

Country	Lead investigators
Australia	Clare Scott, Michael Friedlander, Linda Mileshkin
Belgium	Ignace Vergote, Hannelore Denys
Brazil	Roberto Hegg, Geraldo Queiroz, Rodrigo Pereira, Giuliano Borges, Elias Filho, Leonardo Costa, Fabio Franke
Canada	Diane Provencher, Marie Plante, Amit Oza, Stephen Welch, Holger Hirte, Paul Bessette, Allan Covens
China	Lingying Wu, Jihong Liu, Xiaohua Wu, Beihua Kong, Rutie Yin, Jianquing Zhu, Weiguo Lv, Yunong Gao, Xin Lu, Wei Li, Ying Cheng, Jing Wang, Ge Lou, Qi Zhou, Yueling Wang, Youguo Chen
France	Nicholas Pécuchet, Jacques Medioni, Anne Floquet, Salima Hamizi, Laurence Gladieff, Florence Joly, Alain Lortholary, Patricia Pautier, Isabelle Ray-Coquard, Jean-Pierre Lotz, Frédéric Selle, Marie-Christine Kaminsky, Béatrice Weber, Coraline Dubot, Thibault De La Motte Rouge, Manuel Rodrigues
Germany	Philipp Harter, Tjoung-Won Park-Simon, Barbara Schmalfeldt, Lars Hanker, Martina Gropp-Meier, Falk Thiel, Ahmed El-Balat, Toralf Reimer, Sabine Rothe
Israel	Jacob Korach, Ami Fishman, Limor Helpman, Ilan Bruchim, Ammon Amit
Italy	Sandro Pignata, Nicoletta Colombo, Maria Nicoletto, Francesco Cognetti, Giovanni Scambia, Roberto Sabbatini
Japan	Keiichi Fujiwara, Kenji Tamura, Mayu Yunokawa, Toshiaki Saito, Takayuki Enomoto, Koji Matsumoto, Hidemichi Watari, Masaki Mandai, Kazuhiro Takehara, Yasuyuki Hirashima
The Netherlands	Gabe Sonke, Roy Lalisang, Ingrid Boere, Petronella Ottevanger
Poland	Beata Śpiewankiewicz, Mariusz Bidziński, Tomasz Huzarski, Tomasz Byrski, Magdalena Miedzińska, Anna Słowińska, Wojciech Rogowski, Magdalena Sikorska
Russian Federation	Alla Lisyanskaya, Olga Mikheeva, Sergei Tjulandin
South Korea	Joo-Hyun Nam, Jae Weon Kim, Byoung-Gie Kim, Chel Hun Choi, Jae Hoon Kim

Spain	Andrés Poveda Velasco, María Jesús Rubio Pérez, José Alejandro Pérez-Fidalgo, César Mendiola Fernández, Alfonso Gómez De Liaño Lista, Ariadna Tibau Martorell, Belén Ojeda González, Maria Pilar Barretina, Ginesta, Miguel Beltrán Fabregat, Laura Vidal Boixader, Aleix Prat Aparicio, Antonio Casado Herraez, Nuria Laínez Milagro
United Kingdom	Fiona Nussey, Jonathan Ledermann, Sarah Williams, Susana Banerjee, Andrew Clamp, Christopher Poole, Christine Parkinson
United States of America	Richard Penson, Nathalie Mckenzie, Charles Leath III, Eva Chalas, Paul Celano, John Chan, Kian Behbakht, Susan Davidson, Marta Ann Crispens, Gustavo Rodriguez, Patrick Timmins, Thomas Morrissey, Daniel Kredentser, David O'Malley, James Hoffman, Jonathan Cosin, Scott Kamelle, Elizabeth Dickson-Michelson, Deborah Armstrong, David Warshal

Supplementary methods

Eligibility criteria

For each randomised patient, additional criteria that must have been met included:

- For the course of chemotherapy immediately before randomisation on the study, patients must have received at least four cycles of platinum-based chemotherapy. Patients were not allowed to receive bevacizumab or any investigational agent during this course of treatment. Furthermore, patients must have been randomised within 8 weeks of their last dose of chemotherapy (last dose is defined as the day of the last infusion).
- Patients must have had normal organ and bone marrow function measured within 28 days prior to randomisation, defined as: haemoglobin ≥10·0 g/dL with no blood transfusions in the past 28 days; absolute neutrophil count ≥1·5 x 10^9/L; platelet count ≥100 x 10^9/L; total bilirubin ≤1·5 x institutional upper limit of normal (ULN); aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2·5 x institutional ULN, unless liver metastases were present in which case AST/ALT ≤5 x ULN; serum creatinine ≤1·5 x institutional ULN.
- Patients must not have received previous treatment with a poly(ADP-ribose) polymerase inhibitor, including olaparib.
- With the exception of alopecia, patients must not have had any persistent toxicities (CTCAE grade 2 or higher) caused by previous cancer therapy.
- Patients must not have myelodysplastic syndrome or AML.

A complete list of eligibility criteria is available in the study protocol at Lancet.com.

Sensitivity analysis: adjustment for informative censoring

Our analyses of PFS show that, in the olaparib group, the median from the BICR analysis (30·2 [IQR 8·4–not calcuable] months) was higher than the median from the primary endpoint of investigator assessment (19·1 [IQR 8·3–33.2] months). This discrepancy in the point estimates may have been driven by informative censoring, whereby some patients who had progressed according to investigator assessment had not yet been shown to progress by BICR because scans were performed every 12 weeks only and then submitted for BICR. To determine the potential impact of informative censoring on the BICR results, we performed a sensitivity analysis that adjusted conservatively for informative censoring, where potential informatively censored patients (patients who had progressed according to the investigator, but not according to BICR) were assumed to have an event at the next scan (+12 weeks).

Study oversight

Alongside the Declaration of Helsinki and Good Clinical Practice guidelines, this study was carried out in accordance with the AstraZeneca policy on bioethics.[21]

Supplementary results

Duration of treatment

The median total duration of treatment with olaparib was 19.4 (IQR 8·2–25.5) months mean 17·5 ± standard deviation [SD] 9·8 months) compared with 5.6 (IQR 3·7–11.0) months in the placebo group (mean 9·0 ± SD 8·1 months). At the primary analysis, in total, 106/195 (54·4%) of patients in the olaparib group had undergone a dose interruption and 59/195 (30·3%) of patients required a dose reduction, compared with 23/99 (23·2%) and 6/99 (6·1%), respectively, in the placebo group. The median relative dose intensity, defined as the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation, was 98·4% (IQR 84·7–99·9; mean 91·2% ± SD 13·5) for olaparib-treated patients and 99·4% (IQR 98·1–100; mean 97·3% ± SD 5·6) in the placebo group. The median daily dose, defined as the total dose divided by the actual duration of treatment (the total duration of treatment excluding any dose interruptions), was 597·6 (IQR 541·3–600·0) mg (mean 568·2 ± SD 53·1 mg) for olaparib-treated patients and 598·4 (IQR 593·0–600·0) mg (mean 592·1 ± SD 16·9 mg) in the placebo group.

Sensitivity analysis: adjustment for informative censoring

In the full analysis set, 27/196 (13·8%) patients in the olaparib group and 14/99 (14·1%) patients in the placebo group were classified as having been informatively censored. For patients with informative censoring, the distribution of censoring times was spread evenly from randomisation. When potential informatively censored patients are assumed to have had an event at the next scan (+12 weeks), PFS by BICR was still significantly longer with olaparib than placebo (HR 0·26 [95% CI 0·19–0·35], p<0·0001; median 19·6 [IQR 8·0–not calcuable] months vs 5·5 [IQR 2·8–8·4] months). The results of this sensitivity analysis demonstrate the robustness of the primary PFS data.

Supplementary table 1: Adverse events of special interest

Event	Olaparib (n=195)		Placebo (n=99)	
	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events of special interest				
Elevated ALT	10 (5·1%)	0	4 (4·0%)	1 (1·0%)
Elevated AST	4 (2·1%)	0	4 (4·0%)	0
Secondary malignancies*	7 (3·6%)	7 (3·0%)	5 (5·1%)	5 (5·1%)
AML*	2 (1·0%)	2 (1·0%)	1 (1·0%)	1 (1·0%)
CMML*	1 (0·5%)	1 (0·5%)	0	0
Gastric cancer*	2 (1·0%)	2 (1·0%)	0	0
Hepatic neoplasm*	1 (0·5%)	1 (0·5%)	0	0
Invasive ductal breast carcinoma*	0	0	1 (1·0%)	1 (1·0%)
MDS*	1 (0·5%)	1 (0·5%)	3 (3·0%)	3 (3·0%)
Hypertension	5 (2.6%)	0	1 (1.0%)	0
Tachycardia	1 (0.5%)	0	1 (1.0%)	0
Elevated blood creatinine	21 (10.8%)	0	1 (1.0%)	0
Insomnia	0	0	1 (1.0%)	0
Anxiety	12 (6.2%)	0	5 (5.1%)	0

Data are number of patients (%). ALT=alanine aminotransferase increased. AML=Acute Myeloid Leukemia. AST=Aspartate aminotransferase increased. CMML=Chronic myelomonocytic leukaemia.

MeDS=Myelodysplastic syndrome. *The incidence of secondary malignancies is given for the long-term follow-up period.