
Nelle pazienti con carcinoma mammario HER-2 negativo ad alto rischio e portatrici di VP gBRCA1/2 che abbiano completato chemioterapia (neo)-adiuvante, è raccomandabile olaparib adiuvante (+ ormonoterapia adiuvante se HR-positivo)?

Sintesi delle evidenze e problematiche emerse dal lavoro di gruppo

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Terni

- **P**= pazienti con carcinoma mammario HER-2 negativo ad alto rischio e portatrici di VP gBRCA1/2
- **I**= olaparib (+ ormonoterapia adiuvante se HR+)
- **C**= nessun trattamento (+ormonoterapia adiuvante se HR+)
- **O**=IDFS, DDFS, OS, secondi tumori, qualità di vita e tossicità, fertilità

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ORIGINAL ARTICLE

# Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer

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## Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer

C.E. Geyer Jr. • J.E. Garber • R.D. Gelber • ... C. Campbell • A.N.J. Tutt • and the OlympiA Clinical Trial Steering Committee and Investigators ‡ • Show all authors • Show footnotes

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Alto rischio:

- precedente trattamento neoadiuvante: assenza di pCR per TNBC, assenza di pCR + CPS-EG score≥3 per HR+
- precedente trattamento adiuvante d'emblé ≥pN1 o ≥pT2 per TNBC, ≥pN2 per HR+

CPS + EG scoring system criteria

| | Score |
|---|---|
| **Clinical staging** | |
| I | 0 |
| IIA | 0 |
| IIB | 1 |
| IIIA | 1 |
| IIIB | 2 |
| IIIC | 2 |
| **Pathological staging** | |
| 0 | 0 |
| I | 0 |
| IIA | 1 |
| IIB | 1 |
| IIIA | 1 |
| IIIB | 1 |
| IIIC | 2 |
| **Tumor marker** | |
| ER[a] negative | 1 |
| NG[b] 3 | 1 |

CPS, clinical and pathologic stage; EG, estrogen receptor status and histolo grade.

[a] Estrogen Receptor.

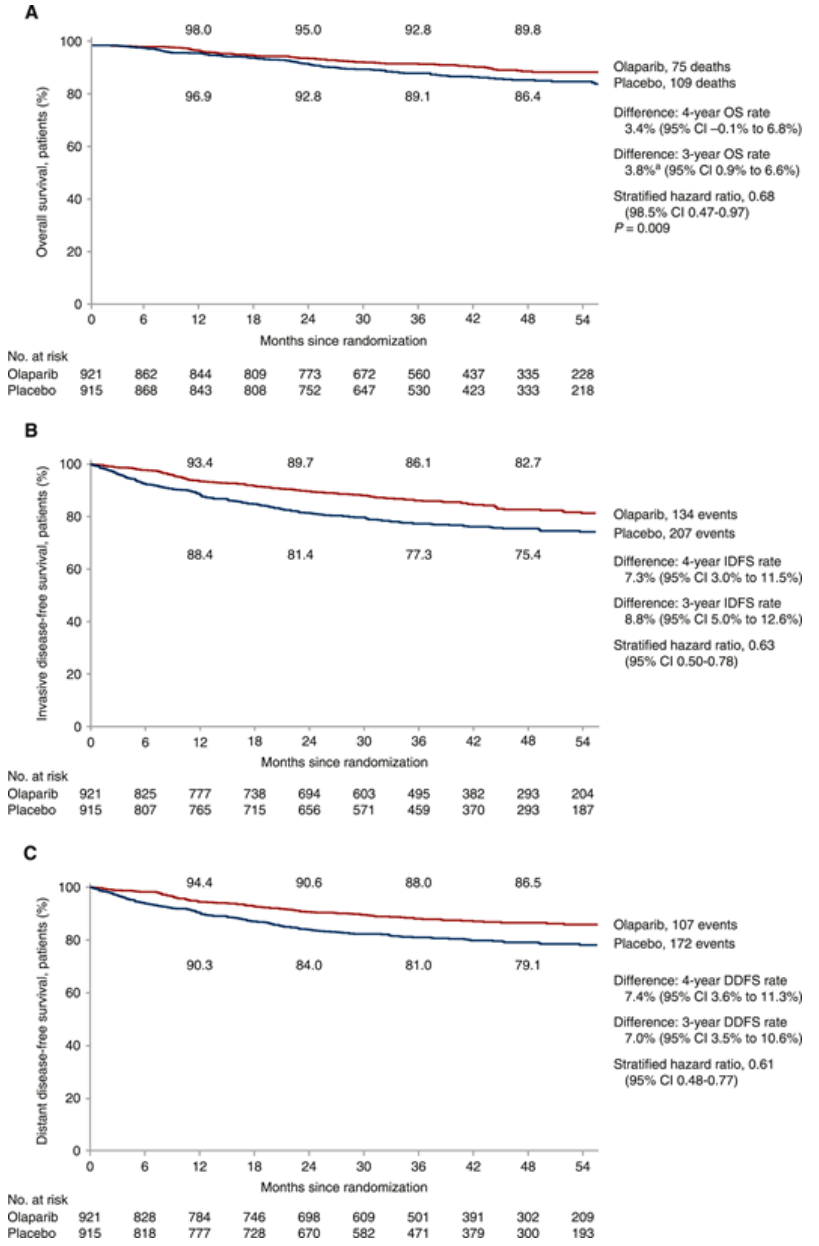
[b] Nuclear Grade

# Outcome di beneficio

Follow-up mediano: 3,5 anni

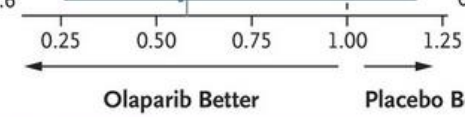
IDFS= 82.7% vs 75.4%, HR=0.63, 95%CI=0.50-0.78, p<0.0001

OS (HR 0.68; 98.5% CI 0.47-0.97; P = 0.009) with an absolute improvement in 4-year OS of 3.4% (89.8% olaparib; 86.4% placebo) in patients with high-risk EBC and gBRCA1/2pv




Geyer CE et al. AnnOncol 2022

| Subgroup | Olaparib | Placebo | 3-Yr Invasive Disease–free Survival | | Stratified Hazard Ratio for Invasive Disease or Death (95% CI) |
|---|---|---|---|---|---|
| | | | Olaparib | Placebo | |
| | *no. of patients with an event/total no.* | | % | | |
| All patients | 106/921 | 178/915 | 85.9 | 77.1 | 0.58 (0.46–0.74) |
| Timing of previous chemotherapy | | | | | |
| Neoadjuvant | 70/460 | 117/460 | 82.5 | 68.0 | 0.56 (0.41–0.75) |
| Adjuvant | 36/461 | 61/455 | 89.3 | 85.4 | 0.60 (0.39–0.90) |
| Previous platinum-based chemotherapy | | | | | |
| Yes | 34/247 | 43/239 | 82.0 | 77.0 | 0.77 (0.49–1.21) |
| No | 72/674 | 135/676 | 87.3 | 77.1 | 0.52 (0.39–0.69) |
| Hormone-receptor status | | | | | |
| HR+ and HER2– | 19/168 | 25/157 | 83.5 | 77.2 | 0.70 (0.38–1.27) |
| TNBC | 87/751 | 153/758 | 86.1 | 76.9 | 0.56 (0.43–0.73) |
| Germline *BRCA* mutation | | | | | |
| *BRCA1* | 70/558 | 126/558 | 85.0 | 73.4 | 0.52 (0.39–0.70) |
| *BRCA2* | 22/230 | 38/209 | 88.6 | 78.0 | 0.52 (0.30–0.86) |
| *BRCA1* and *BRCA2* | 0/1 | 0/3 | NC | NC | NC |
| Hormone-receptor status and timing of previous chemotherapy | | | | | |
| HR+ and HER2–, NACT | 13/104 | 20/92 | 86.0 | 67.0 | 0.52 (0.25–1.04) |
| HR+ and HER2–, ACT | 6/64 | 5/65 | 76.4 | 89.3 | 1.36 (0.41–4.71) |
| TNBC, NACT | 57/354 | 97/368 | 81.4 | 67.7 | 0.57 (0.41–0.79) |
| TNBC, ACT | 30/397 | 56/390 | 90.3 | 84.8 | 0.54 (0.34–0.83) |
| Previous platinum-based chemotherapy and timing of previous chemotherapy | | | | | |
| Yes, NACT | 26/169 | 39/169 | 81.8 | 70.1 | 0.66 (0.40–1.07) |
| Yes, ACT | 8/78 | 4/70 | NC | NC | NC |
| No, NACT | 44/291 | 78/291 | 83.1 | 66.8 | 0.51 (0.35–0.73) |
| No, ACT | 28/383 | 57/385 | 90.4 | 84.2 | 0.51 (0.32–0.79) |
| CPS+EG score in patients with previous NACT | | | | | |
| Score of 2, 3, or 4 | 55/398 | 96/387 | 84.3 | 68.9 | 0.51 (0.37–0.71) |
| Score of 5 or 6 | 11/22 | 10/15 | 50.0 | 17.9 | 0.44 (0.19–1.06) |
| Primary database | | | | | |
| Breast International Group | 95/810 | 160/806 | 86.0 | 76.7 | 0.58 (0.45–0.75) |
| NRG Oncology (United States) | 11/111 | 18/109 | 85.0 | 80.6 | 0.57 (0.26–1.18) |



# Adverse events (2)

| Adverse Event | Olaparib (N=911) | Placebo (N=904) |
|---|---|---|
| | *no. of patients (%)* | |
| Any adverse event | 835 (91.7) | 753 (83.3) |
| Serious adverse event | 79 (8.7) | 76 (8.4) |
| Adverse event of special interest† | 30 (3.3) | 46 (5.1) |
| MDS or AML | 2 (0.2) | 3 (0.3) |
| Pneumonitis‡ | 9 (1.0) | 11 (1.2) |
| New primary cancer§ | 19 (2.1) | 32 (3.5) |
| Grade ≥3 adverse event | 221 (24.3) | 102 (11.3) |
| Grade 4 adverse event¶ | 17 (1.9) | 4 (0.4) |
| Adverse event leading to permanent discontinuation of olaparib or placebo‖ | 90 (9.9) | 38 (4.2) |
| Adverse event leading to death** | 1 (0.1) | 2 (0.2) |

* Included are adverse events with an onset date on or after the date of the first dose and up to and including 30 days after the date of the last dose of olaparib or placebo. AML denotes acute myeloid leukemia, and MDS myelodysplastic syndrome.

† Included are adverse events of special interest with an onset at any date after the first dose of olaparib or placebo. One patient in the olaparib group had both pneumonitis and a nonmelanoma skin cancer and is counted in both the pneumonitis and new primary cancer categories.

‡ In the olaparib group, seven patients had pneumonitis, and two patients had radiation pneumonitis. In the placebo group, eight patients had pneumonitis, and three patients had radiation pneumonitis.

§ Detailed information on the numbers of patients in each group with specific new primary cancers is provided in Table S19.

¶ A total of 18 grade 4 adverse events were reported in 17 patients who received olaparib; one patient had both grade 4 anemia and decreased neutrophil count. In the olapar group, grade 4 adverse events included decreased neutrophil count (in 5 patients), anemia (in 4 patients), decreased lymphocyte count (in 3 patients), and AML, bipolar disorder, fatigue, febrile neutropenia, abnormal hepatic function, and a suicide attempt (in 1 patient each). In the placebo group, grade 4 adverse events included depressi (in 2 patients) and increased aspartate aminotransferase level and acute cholecystitis (in 1 patient each).

‖ The most common adverse events, occurring in at least 1% of the patients, that led to discontinuation of olaparib were nausea (2.0%), anemia (1.8%), fatigue (1.3%), and decreased neutrophil count (1.0%); there were no adverse events that occurred in at least 1% of patients that led to discontinuation of placebo.

** In the olaparib group, cardiac arrest led to death in one patient. In the placebo group, AML and ovarian cancer led to death in one patient each.

Olaparib adiuvante (+ ormonoterapia adiuvante se HR-positivo) rispetto a placebo in pazienti con carcinoma mammario HER2-negativo ad alto rischio e portatrici di VP gBRCA1/2, che abbiano completato chemioterapia (neo)-adiuvante

| Esito | Effetto assoluto anticipato (95% CI) | | Effetto relativo (95% CI) | № dei partecipanti (studi) | Certo |
|---|---|---|---|---|---|
| | Rischio con placebo | Rischio con olaparib adiuvante (+ ormonoterapia adiuvante se HR-positivo) | | | |
| **Invasive disease-free survival (IDFS)**<br>valutato con: tempo intercorso dalla data della random a uno dei seguenti eventi: ipsilateral invasive breast tu mor, locoregional invasive disease, distant recurrence, c ontralateral invasive breast cancer, second primary inv asive cancer, or death from any cause<br>follow up: mediana 3.5 anni | **Bassa** | | **HR 0.63**<br>(0.50 a 0.78)<br>[ipsilateral invasive breast tumor, locoregional invas ive disease, distant recurrence, contralateral invasiv e breast cancer, second primary invasive cancer, or d eath from any cause] | 1836<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| | 226 per 1.000 | **392 per 1.000**<br>(313 a 475) | | | |
| **Distant disease-free survival (DDFS)**<br>follow up: mediana 3.5 anni | **Bassa** | | **HR 0.61**<br>(0.48 a 0.77)<br>[distant disease] | 1836<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| | 190 per 1.000 | **363 per 1.000**<br>(278 a 451) | | | |
| **Overall survival (OS)**<br>follow up: mediana 3.5 anni | **Bassa** | | **HR 0.68**<br>(0.47 a 0.97)<br>[morte per ogni causa] | 1836<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| | 119 per 1.000 | **235 per 1.000**<br>(127 a 368) | | | |
| **Qualità della vita**<br>valutato con: European Organization for Research and Treatment of Cancer QLQ-C30 Global Health Status and Quality of Life scale<br>follow up: mediana 2.5 anni | global health quality did not decline during the 12 months of treatment with either olaparib or placebo. Any differences between the trial groups were not considered to be clinically significant | | | (1 RCT) | ⨁⨁⨁◯<br>Moderata [a] |
| **Secondi tumori** | 23 per 1.000 | **12 per 1.000**<br>(6 a 25) | **RR 0.53**<br>(0.26 a 1.08) | 1826<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| **Dicontinuazione precoce del trattamento**<br>follow up: mediana 3.5 anni | 207 per 1.000 | **259 per 1.000**<br>(219 a 306) | **RR 1.25**<br>(1.06 a 1.48) | 1815<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| **Eventi avversi di grado >=3**<br>follow up: mediana 3.5 anni | 113 per 1.000 | **243 per 1.000**<br>(195 a 301) | **RR 2.15**<br>(1.73 a 2.67) | 1815<br>(1 RCT) | ⨁⨁⨁⨁<br>Alta |
| **Eventi avversi seri (SAE)**<br>follow up: mediana 3.5 anni | 84 per 1.000 | **87 per 1.000**<br>(64 a 117) | **RR 1.03**<br>(0.76 a 1.39) | 1815<br>(1 RCT) | ⨁⨁⨁◯<br>Moderata [b] |

Aggiungi esito

# Evidence to decision

- Valore preferenze: all'interno dello studio non c'è l'esito della fertilità molto importante soprattutto per le pazienti triplo negative giovani

- Bilancio beneficio/danno:

In considerazione del vantaggio osservato in termini di iDFS, DDFS, OS, secondi tumori, tenuto conto dell'impatto non detrimentale in termini di qualità di vita e dell'impatto in termini di tossicità, il Panel ha giudicato il bilancio beneficio/danno a favore di olaparib in pazienti con mutazione germinale BRCA1/2 affetti da neoplasia mammaria HER2-negativa (a recettori positivi o negativi) ad alto rischio di recidiva.

Risorse: costo farmaco (circa 2700 euro al mese) e del test (circa 800 euro)

Equità di accesso ridotta per disponibilità del test

Accettibilità ottima

Fattibilità:CPS+GP score spesso non disponibile

| CRITERI | SUMMARY OF JUDGEMENTS | | | | | | | IMPORTANCE FOR DECISION |
|---|---|---|---|---|---|---|---|---|
| PROBLEM | No | Probably no | Probably yes | **Yes** | Varies | Don't know | | |
| DESIRABLE EFFECTS | Trivial | Small | Moderate | **Large** | Varies | Don't know | | |
| UNDESIRABLE EFFECTS | Trivial | **Small** | Moderate | Large | Varies | Don't know | | |
| CERTAINTY OF EVIDENCE | Very low | Low | Moderate | **High** | No included studies | | | |
| VALUES | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability | | | | |
| BALANCE OF EFFECTS | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | **Favors the intervention** | Varies | Don't know | |
| RESOURCES REQUIRED | **Large costs** | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know | |
| CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES | Very low | Low | Moderate | High | No included studies | | | |
| COST EFFECTIVENESS | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | No included studies | |
| EQUITY | **Reduced** | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know | |
| ACCEPTABILITY | No | Probably no | Probably yes | **Yes** | Varies | Don't know | | |
| FEASIBILITY | No | Probably no | **Probably yes** | Yes | Varies | Don't know | | |

| **Qualità globale delle evidenze** | **Raccomandazione clinica** | **Forza della raccomandazione** |
|---|---|---|
| MODERATA | ***In pazienti con carcinoma mammario HER2-negativo ad alto rischio e mutazione germinale BRCA (che abbiano completato chemioterapia [neo]-adiuvante), un trattamento adiuvante con olaparib (+ terapia ormonale se HR+) dovrebbe essere utilizzato rispetto a nessun trattamento (+ terapia ormonale se HR+).*** | Forte a favore |