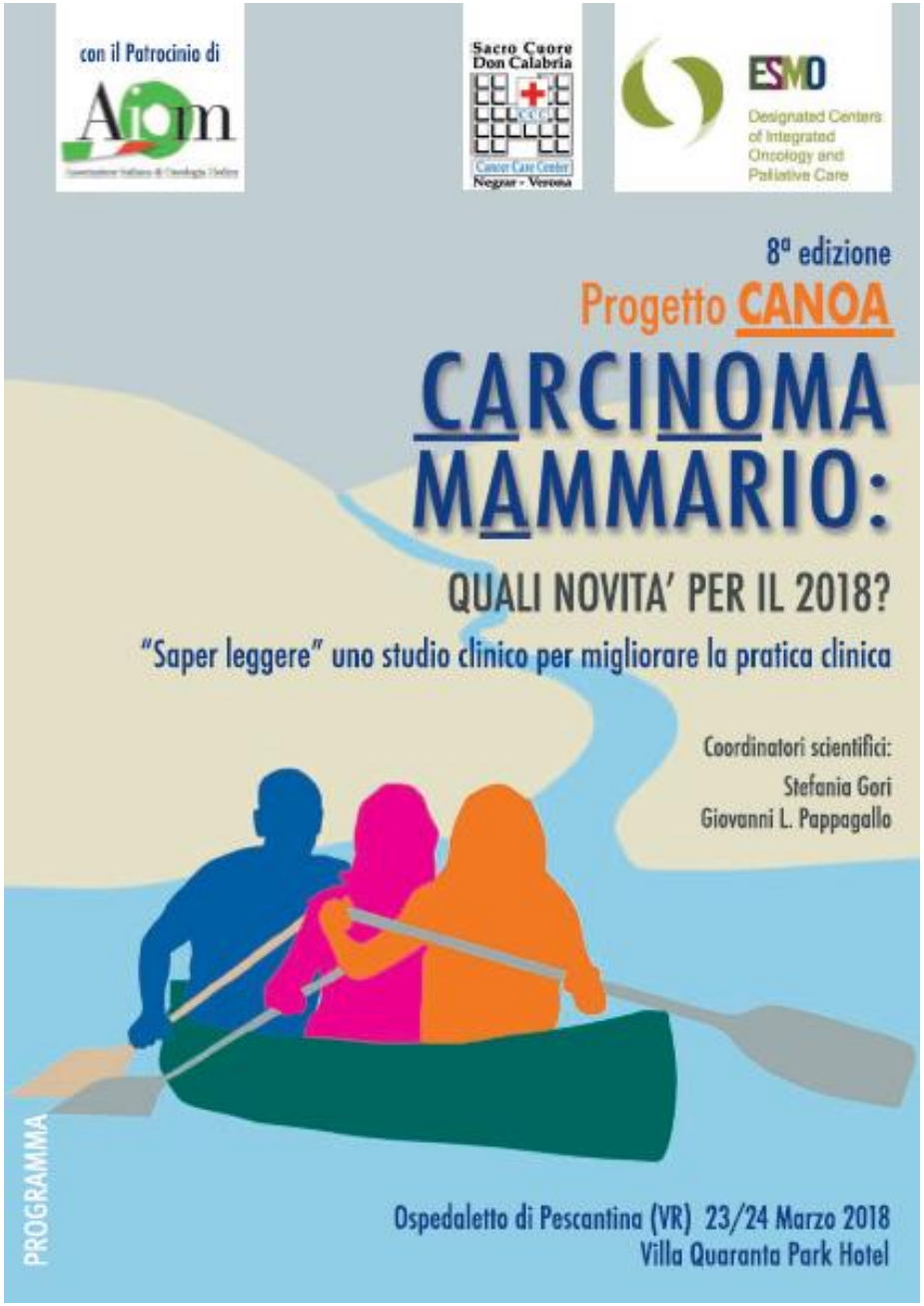

- *GRUPPO B*

Nelle pazienti BRCA mutate con carcinoma mammario metastatico pretrattate con chemioterapia, è opportuno considerare un trattamento con olaparib rispetto a chemioterapia?

LE PROBLEMATICHE

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24 marzo 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

- ✓ **CONFIDENCE (verifica di affidabilità)**
- ✓ **DIRECTNESS (verifica di trasferibilità)**
- ✓ **RELEVANCE (verifica di rilevanza clinica)**

Robson M et al., NEJM 2017

CONFIDENCE – RISCHIO DI BIAS

Selection Bias

- *Generazione della sequenza di randomizzazione*.

al. Randomization was stratified according to previous use of chemotherapy for metastatic disease (yes vs. no), hormone-receptor status (hormone-receptor positive vs. triple negative), and previous use of platinum-based therapy (yes vs. no); this information was obtained locally at the time of trial registration with the use of an interactive voice or Web response system. All other clinical data and disease characteristics were collected at baseline with the use of a case-report form.

Robson M et al., NEJM 2017

- *Mascheramento dell'assegnazione*.

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

Robson M et al., NEJM 2017

CONFIDENCE – RISCHIO DI BIAS

Performance Bias

- **Open-label trial** → NO blinding

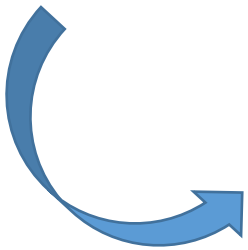
- **Without placebo control**

Robson M et al., NEJM 2017

CONFIDENCE – RISCHIO DI BIAS

Detection Bias

The primary end point was progression-free survival, which was defined as the time from randomization to objective radiologic disease progression (according to modified RECIST, version 1.1) or death from any cause. The primary analysis was based on blinded independent central review, which was performed by two main reviewers, with adjudication by a third reviewer in cases in which the two main reviewers disagreed. A

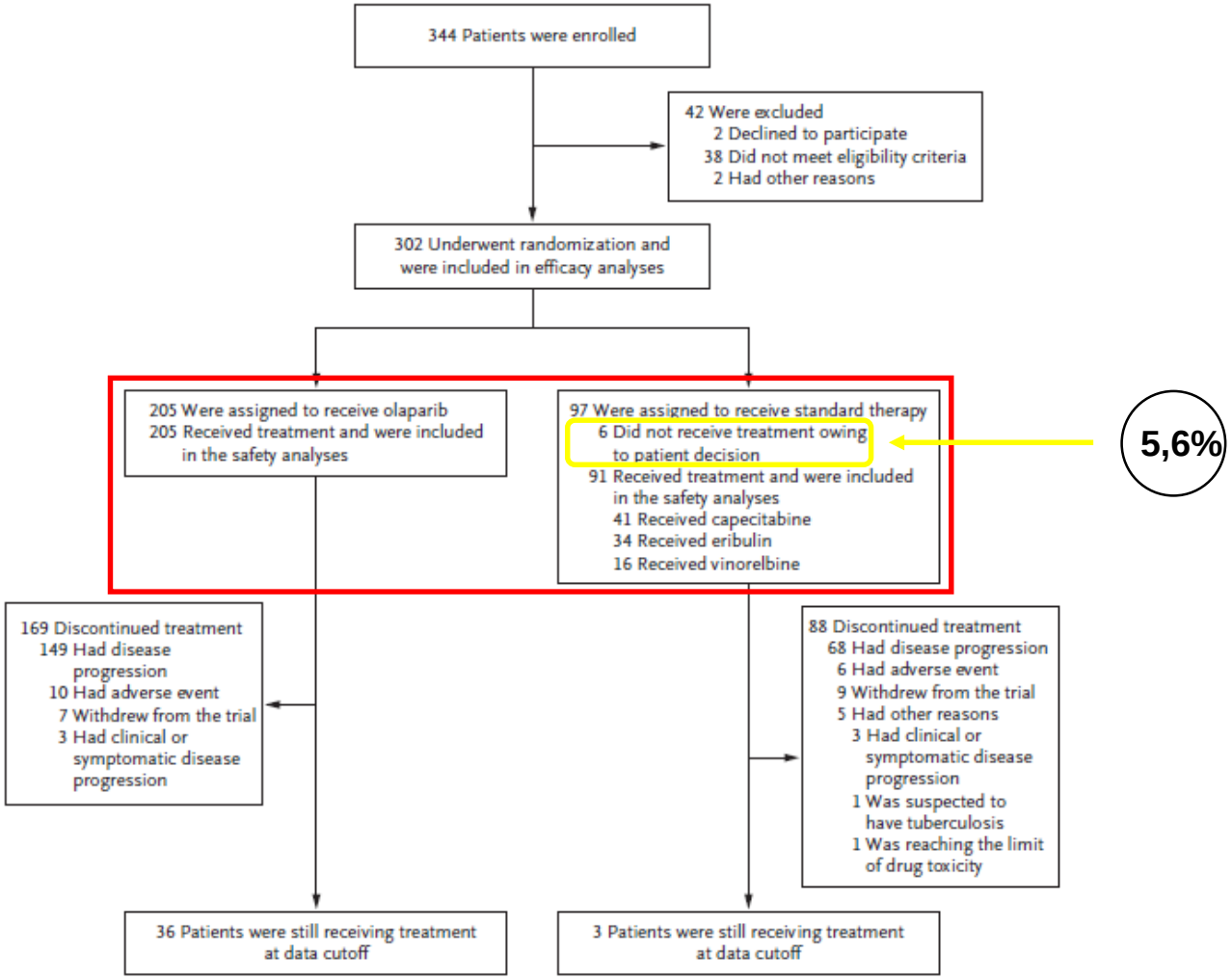


Computed tomography or magnetic resonance imaging was performed every 6 weeks until week 24 and then every 12 weeks thereafter. Overall

Robson M et al., NEJM 2017

CONFIDENCE – RISCHIO DI BIAS

Attrition Bias

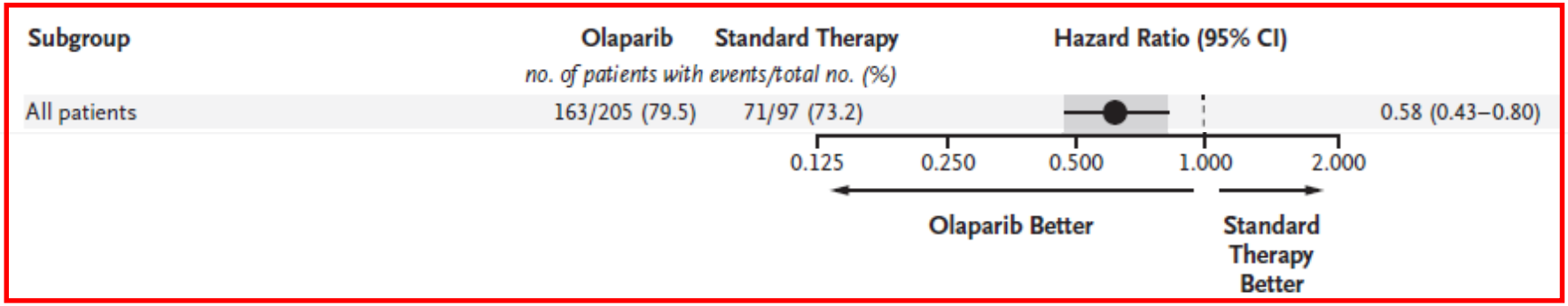


Robson M et al., NEJM 2017

CONFIDENCE – PRECISION

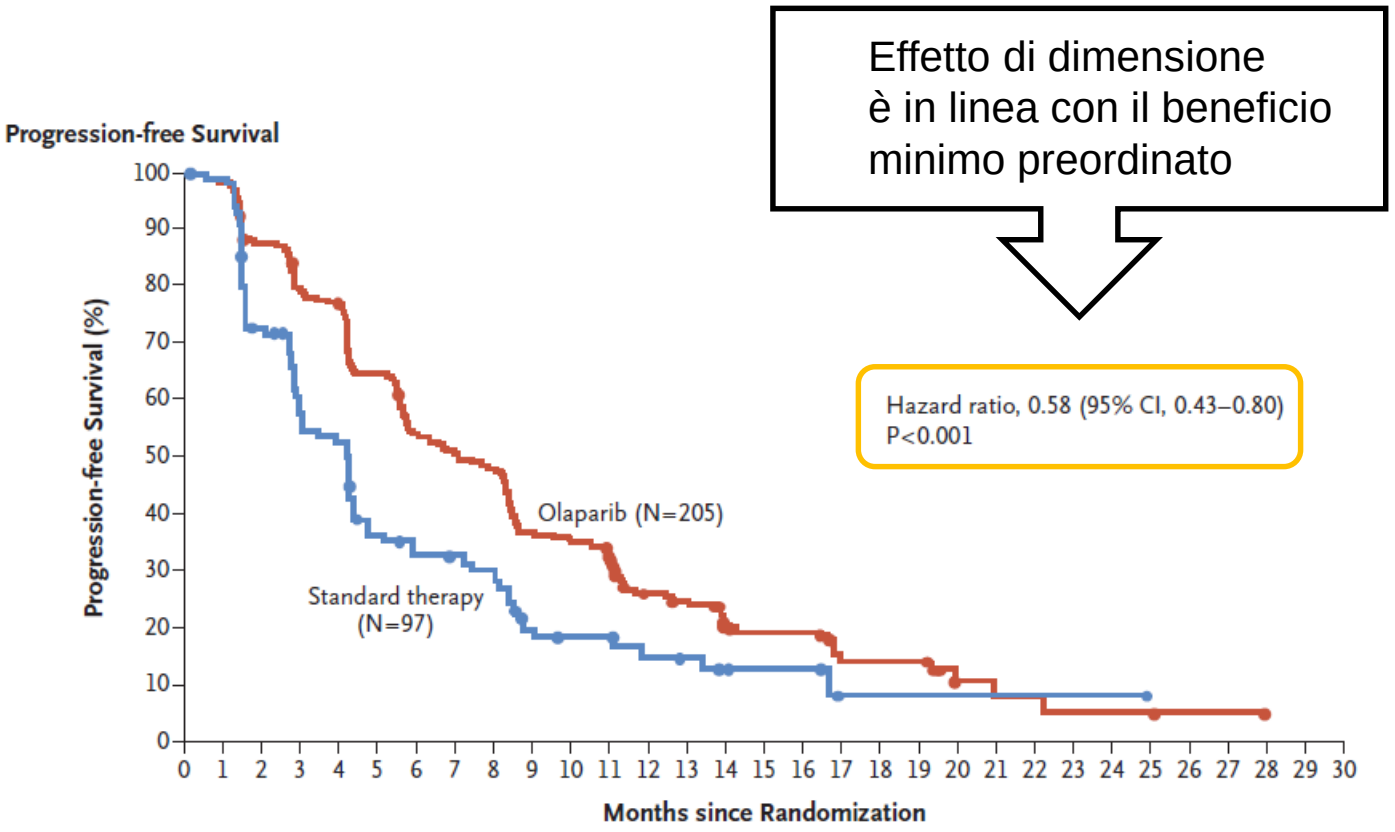
STATISTICAL ANALYSIS

We determined that a total of 230 progression-free survival events would give the trial 90% power (at a two-sided significance level of 5%) to show a statistically significant difference in progression-free survival between the olaparib group and the standard-therapy group, with a corresponding hazard ratio for disease progression or death of 0.635. Efficacy data were ana-



Robson M et al., NEJM 2017

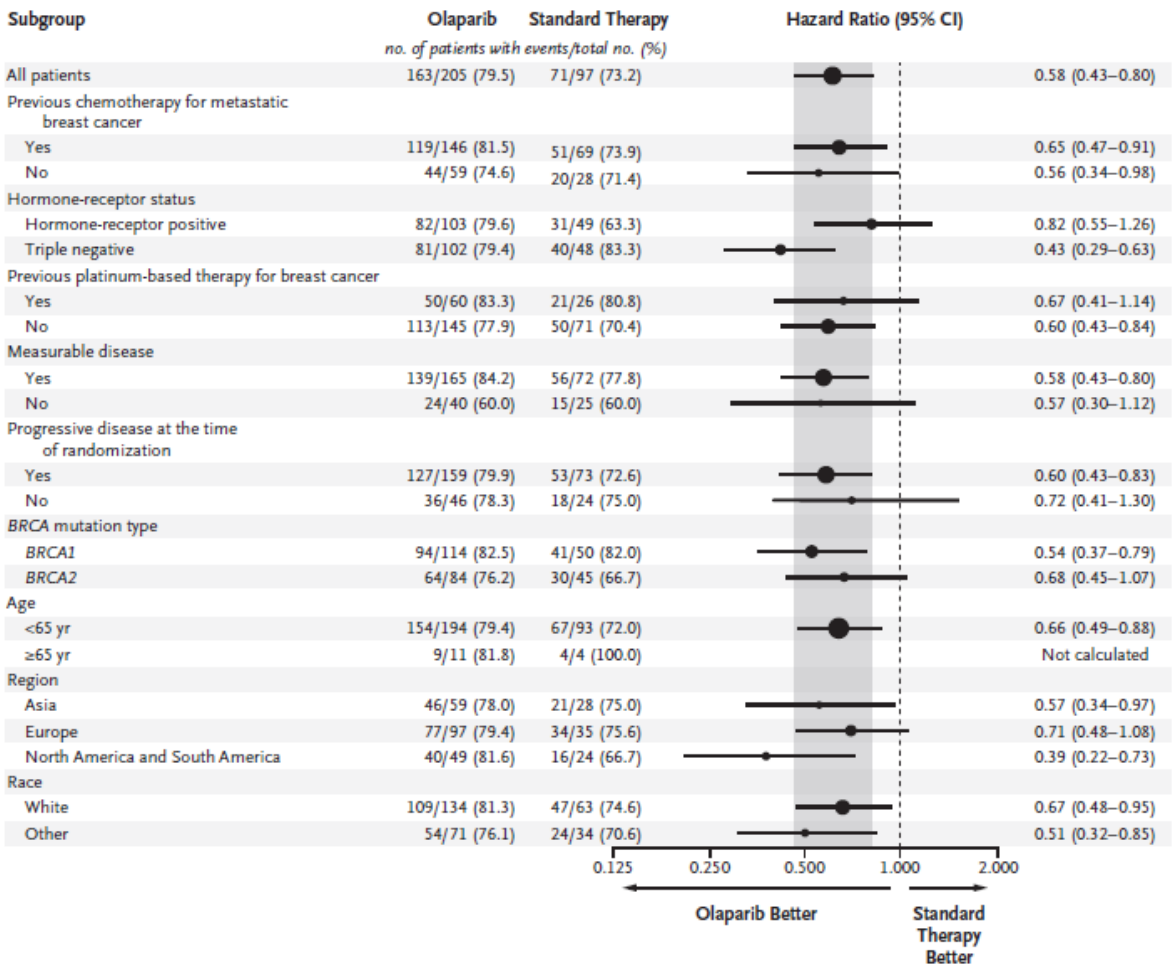
- Analysis after 234 of 302 patients (77,5%) had events.



Robson M et al., NEJM 2017

CONFIDENCE

Analisi di sottogruppo



Robson M et al., NEJM 2017

DIRECTNESS

QUESITO STRUTTURATO: il metodo PICO

P opulation	Pazienti con carcinoma mammario metastatico, BRCA mutate e HER2 negative, pretrattate con chemioterapia
I nterverntion	Olaparib
C omparison	Monochemioterapia (capecitabina, eribulina o vinorelbina)
O utcomes	- PFS, time to second progression or death, OS and ORR (beneficio) - Safety and tolerability, global HRQoL (danno)

DIRECTNESS – Population

- Stratificazione delle pazienti in base a:

✓ precedente utilizzo di chemioterapia nel setting metastatico (sì *vs* no)

✓ stato recettoriale

(HR+ *vs* TNBC)

✓ precedente utilizzo di sali del platino (sì *vs* no)

→eterogeneità

→incremento del beneficio con miglior selezione delle pazienti?

Table S1. Prior treatment in the metastatic and/or adjuvant or neoadjuvant setting

n (%)	Olaparib 300 mg bd (N=205)	Standard therapy (N=97)
Endocrine therapy in HR+ patients[1]		
Metastatic	66 (66.0)	28 (59.6)
Adjuvant/neoadjuvant	70 (70.0)	35 (74.5)
Lines of chemotherapy for metastases		
0 line	68 (33.2)	31 (32.0)
1 line	80 (39.0)	42 (43.3)
2 lines	57 (27.8)	24 (24.7)
Platinum therapy for breast cancer		
Metastatic	43 (21.0)	14 (14.4)
Adjuvant/neoadjuvant	15 (7.3)	7 (7.2)

Robson M et al., NEJM 2017

DIRECTNESS – Comparison

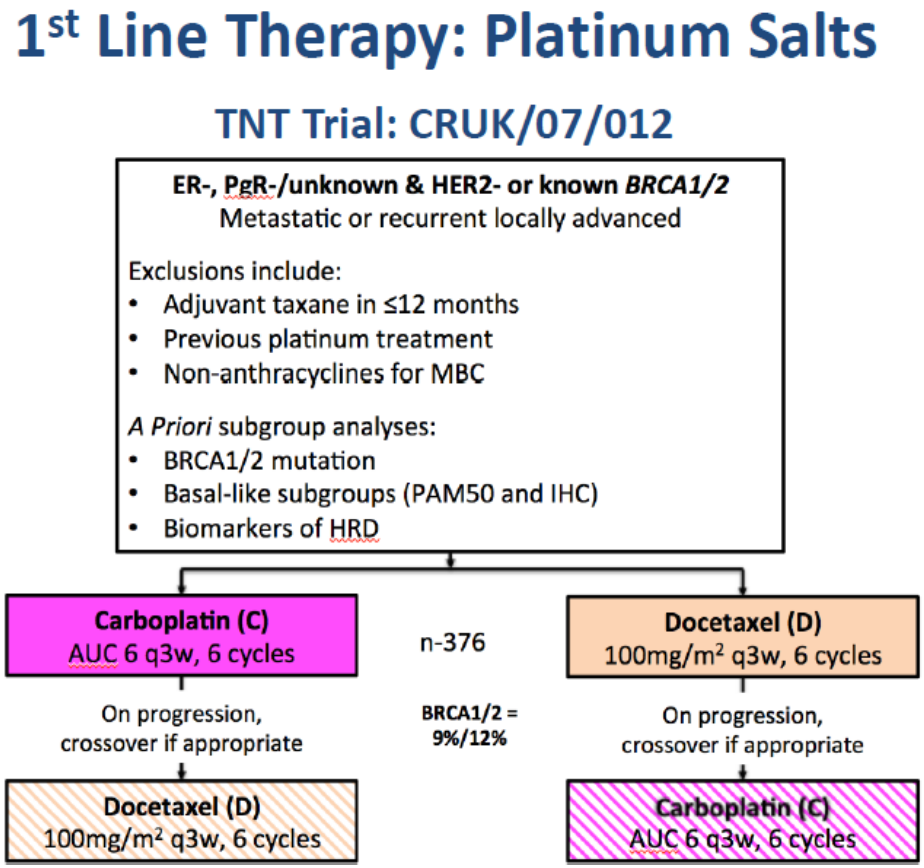
- Uso di differenti trattamenti nel gruppo di controllo

Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tab lets (300 mg twice daily) or standard therapy with one of the following three prespecified chemotherapy regimens: capecitabine administered orally at a dose of 2500 mg per square meter of body-surface area daily (divided into two doses) for 14 days, repeated every 21 days; eribulin mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8, repeated every 21 days; or vinorelbine administered intravenously at a dose of 30 mg per square meter on day 1 and day 8, repeated every 21 days. The assigned treatment

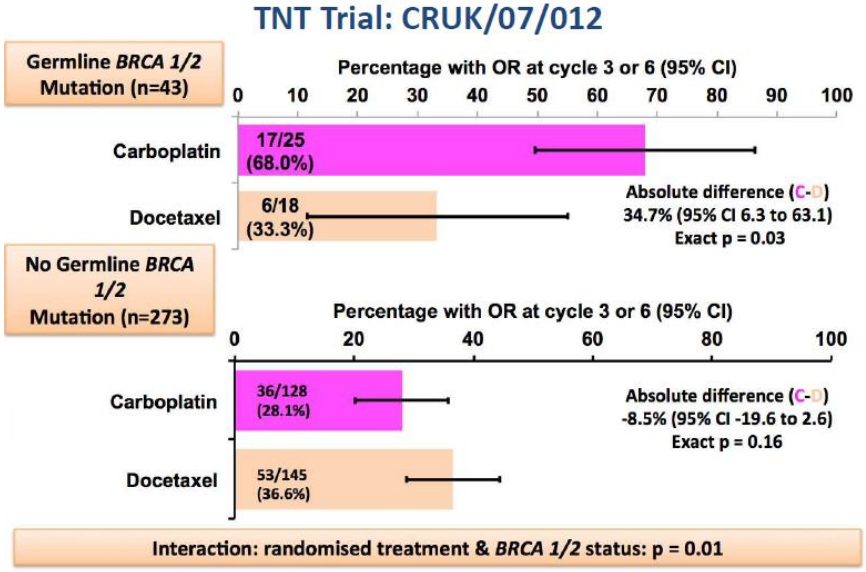
Robson M et al., NEJM 2017

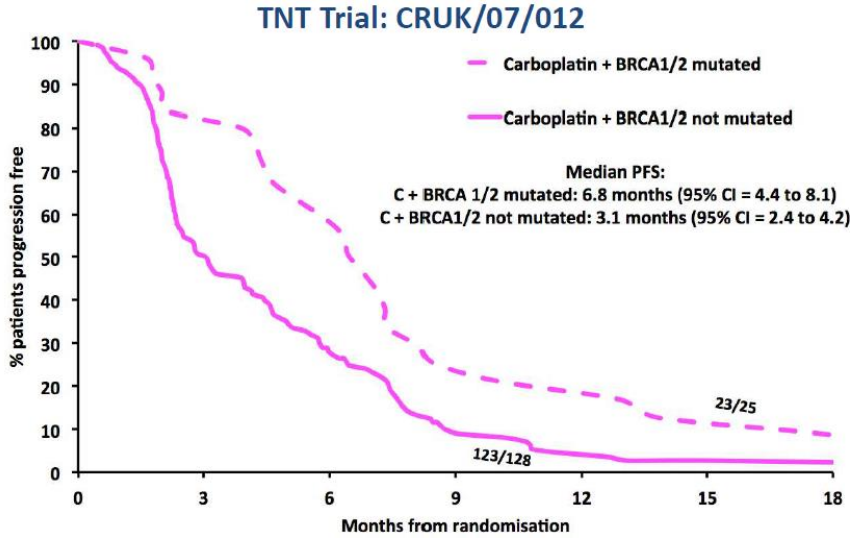
DIRECTNESS – Comparison

- Mancanza di un braccio con sali del platino



Tutt M et al., SABCS 2014





Tutt M et al., SABCS 2014

DIRECTNESS – Outcomes di beneficio

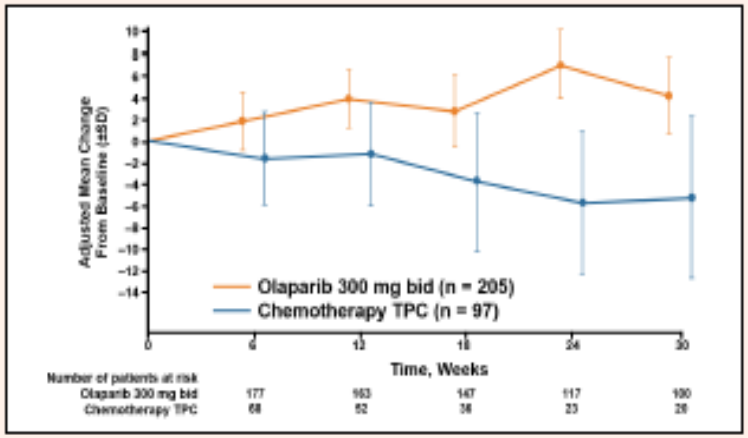
- **Incremento in PFS e TTP**.
- Nessun vantaggio in OS → possibile influenza dei trattamenti successivi ed endpoint NON pre-pianificato.
- La proporzione di risposte obiettive è stata del 59.9% nel gruppo olaparib e 28.8% nel gruppo sottoposto a terapia standard (**RADDOPPIATA**).

Robson M et al., NEJM 2017

DIRECTNESS – Outcomes di danno

Global Health Status/Quality of Life

- Global health status/QoL score increased in the olaparib group (mean change 3.9 [±1.2]) and decreased in the chemotherapy TPC group (-3.6 [±2.2])
  - Difference 7.5; 95% CI 2.48-12.44; P = .0035



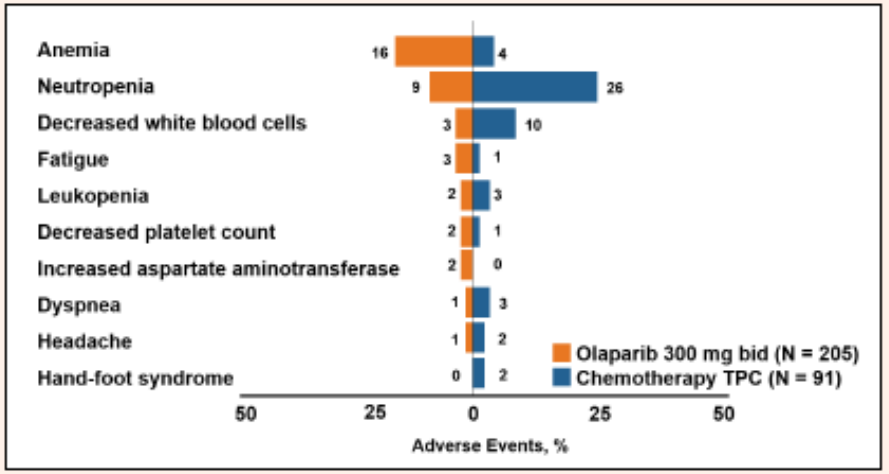


Figure 6. Grade ≥3 Adverse Events in ≥2% of Patients in Either Arm

Abbreviation: TPC, treatment of physician's choice

- Grade ≥3 adverse events was 36.6% in the olaparib arm and 50.5% in the standard therapy group

- Scarse conoscenze sugli effetti collaterali a lungo termine (segnalati casi di leucemie secondarie al trattamento nelle pazienti trattate con carcinoma ovarico), ma *corto follow-up*.

Robson M et al., NEJM 2017

RELEVANCE

- HR for PFS = 0.58 (95% CI 0.43 to 0.80)
- mPFS: 7 mesi nel gruppo olaparib *vs* 4.2 mesi nel gruppo sottoposto a terapia standard → PFS raddoppiata →Δ = 2.8 mesi → *clinicamente rilevante* in considerazione delle scarse opzioni terapeutiche disponibili in questo setting di pazienti.

Robson M et al., NEJM 2017

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Grazie a tutti per l'attenzione

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TRIAL OVERSIGHT

This trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics. The trial was designed in collaboration between the principal investigator and AstraZeneca. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. An external independent data and safety monitoring committee performed two interim reviews of the safety data. The manuscript was written with medical-writing support, which was funded by AstraZeneca, with critical review and input from the authors. The authors had access to the data and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Robson M et al., NEJM 2017