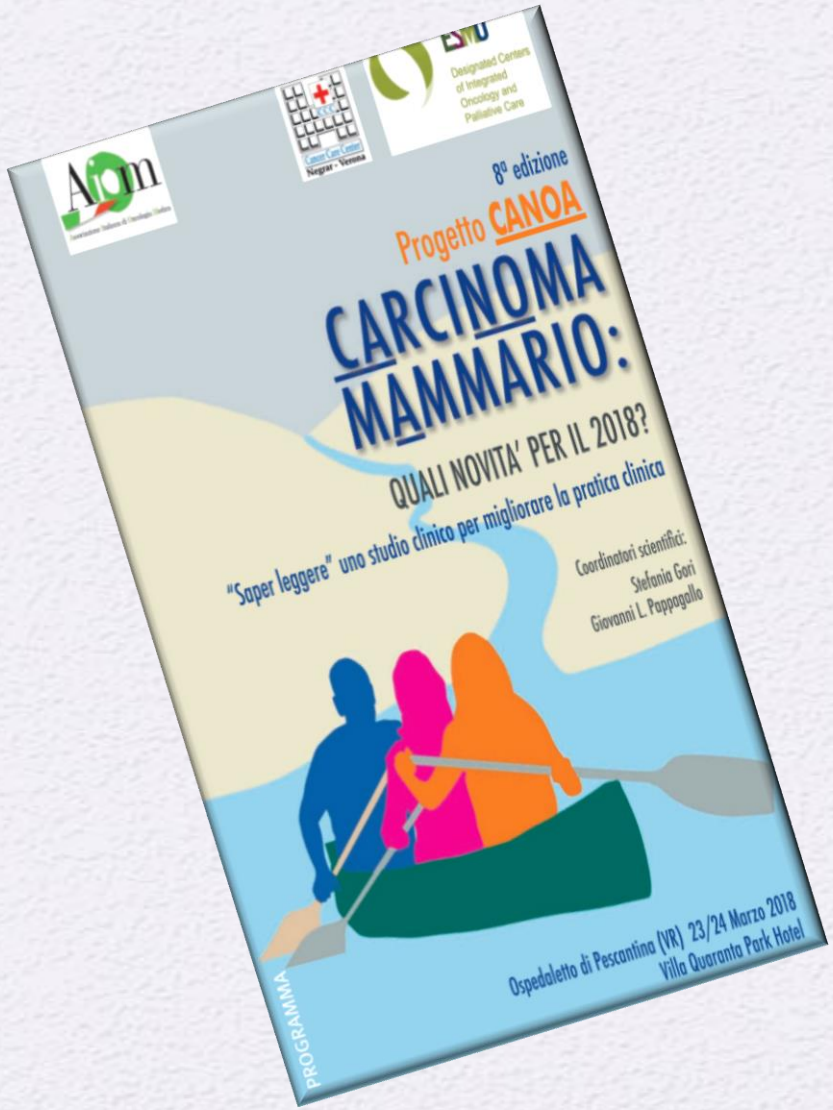

Nelle pazienti BRCA mutate con carcinoma mammario pretrattate con chemioterapia è opportuno considerare un trattamento con Olaparib rispetto a chemioterapia?

Take Home Message

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First THM

- The rationale behind the selected patient population was that a germline *BRCA* mutation would be a key determinant of the effectiveness of olaparib, despite the different clinical factors that are present in a broad patient population.

- Only deleterious or suspected pathogenic mutations:

  - Not C3 or Unknown Variants enrolled (90% benign mutations)

Limit (1)

- An open-label trial design was made necessary by the use of different treatments in the control group.
- All three treatments selected for the control group constitute standard chemotherapy options for such patients.
- Thus, to ensure robustness of the results of this open-label trial, the primary analysis was based on blinded independent central review for the intention-to-treat population.
- Olaparib as single agent treatment after progression:

  - Not mantainance study!!!

Limit (2)

- A second limitation of the study was the heterogeneity of the population in terms of hormonal-receptor status, previous use of chemotherapy, and previous use of platinum-based treatments.

- The trial was not powered to detect any differences in effect that are suggested by subgroup analyses, and thus any conclusions must be considered to be hypothesis-generating.

Second THM

- Median progression-free survival was significantly longer with oral olaparib monotherapy than with standard chemotherapy (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80).
- The risk of disease progression or death was 42% lower and the median progression-free survival was 2.8 months longer with olaparib than with standard therapy……

BUT…..

Limits (3)

- Since platinum agents were not included as treatment options in the control the trial cannot address the relative benefits of olaparib and platinum-based chemotherapy in patients with breast cancer and a germline *BRCA* mutation.
- It is worth noting, however, that the response rate of 59.9% and the median progression-free survival of 7.0 months that were observed with first-, second-, or third-line olaparib in this trial are similar to the response rate of 68.0% and the median progression-free survival of 6.8 months that were observed with first-line single-agent carboplatin in a similar population.

Third THM

- Although no significant difference in overall survival was observed between olaparib treatment and standard therapy, this trial was not powered to assess differences in overall survival between treatment groups.
- Analysis of overall survival is also likely to be confounded by subsequent treatment, and more patients in the standard-therapy group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy after they had disease progression while receiving the assigned treatment

Fourth THM

- The response rate in the olaparib group was approximately double the rate in the standard-therapy group (59.9% vs. 28.8%).
- The median time to the onset of a response was similar with olaparib and with standard therapy; this finding is an important consideration for symptomatic or rapidly progressing patients.

Fifth THM

- Fewer grade 3 or higher adverse events and adverse events leading to discontinuation occurred with olaparib than with standard therapy.
- In the olaparib group, the most common adverse event was grade 1 or 2 nausea, and the most common grade 3 or higher adverse event was anemia.
- The safety profile of olaparib was similar to that reported in other studies of olaparib monotherapy.

Sixth THM

- There was a small significant difference between treatment groups in the adjusted mean QLQ-C30 score across all time points, and a clinically meaningful decrease in the QLQC30 score was delayed in the olaparib group

Hypothesis- Generating

1) Maintenance study
2) Comparison with platinum-derived drugs
3) Only TNBC
4) Delay of CT in HR+

STRUTTURAZIONE DEL QUESITO CLINICO

Popolazione (descrizione del paziente oggetto del quesito clinico)	Nelle pazienti BRCA mutate con carcinoma mammario pretrattate con chemioterapia
Intervento terapeutico (descrizione del trattamento oggetto del quesito clinico)	è opportuno considerare un trattamento con Olaparib
Confronto (descrizione dell'alternativa tera-peutica cui si intende confrontare il trattamento oggetto del quesito)	rispetto a chemioterapia?
Outcome (elenco dei parametri di beneficio e di danno ritenuti essenziali / importanti per la valutazione del trattamento oggetto del quesito)	*Outcome di beneficio:* ***- essenziali*** *PFS* *G3-4 Toxicity* *QoL* ***- importanti*** RR
	Outcome di danno: ***- essenziali*** Anemia G3-4 ***- importanti*** *Nausea G1-2*

STRUTTURAZIONE DEL QUESITO CLINICO

Outcome di beneficio

descrizione dell'outcome *PFS*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐ 6 X7 ☐8 ☐9
descrizione dell'outcome *< gradi 3-4 tossicità*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐ 6 x7 ☐8 ☐9
descrizione dell'outcome *RR*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 X 6 ☐7 ☐8 ☐9
descrizione dell'outcome *QoL*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 X 7 ☐8 ☐9
descrizione dell'outcome	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9
descrizione dell'outcome	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9

Outcome di danno

descrizione dell'outcome *anemia G3-4*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 X 7 ☐8 ☐9
descrizione dell'outcome *nausea G1-2*	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐ 3 X4 ☐5 ☐6 ☐7 ☐8 ☐9
descrizione dell'outcome	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9
descrizione dell'outcome	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9
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descrizione dell'outcome	*rilevanza per la decisione terapeutica* ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9

Legenda – rilevanza outcome

Rating	*Importanza*	*Incluso in*
7 8 9	Outcome importanti ed essenziali	Tabelle sulla qualità delle prove: SI Raccomandazione : SI
4 5 6	Outcome importanti ma non essenziali	Tabelle sulla qualità delle prove: SI Raccomandazione : NO
1 2 3	Outcome non importanti	Tabelle sulla qualità delle prove: NO Raccomandazione : NO

RACCOMANDAZIONE:

Nelle pazienti BRCA mutate (HER2-) con carcinoma mammario pretrattate con chemioterapia il trattamento con PARP inibitore può essere preso in considerazione

Forza Raccomandazione				Bilancio Beneficio/Danno		
Positiva Forte	Positiva Debole	Negativa Debole	Negativa Forte	Favorevole	Incerto	Sfavorevole
	X			X		

Qualità delle Evidenze

La qualità delle evidenze è stata giudicata MODERATA per i seguenti motivi:

Si tratta di un open-label design. L'outcome PFS soffre di eterogeneità e gli obiettivi nella sottopopolazione chemiotrattata non erano stati prefissati. Non possiamo stabilire un confronto tra Olaparib e platino perché non è stato inserito nel braccio di confronto. L'outcome OS risulta negativo ma non era stato pre-pianificato