TEST ACCADEMICI PER LA VALUTAZIONE DELL'HRD E IMPATTO SU PRATICA CLINICA

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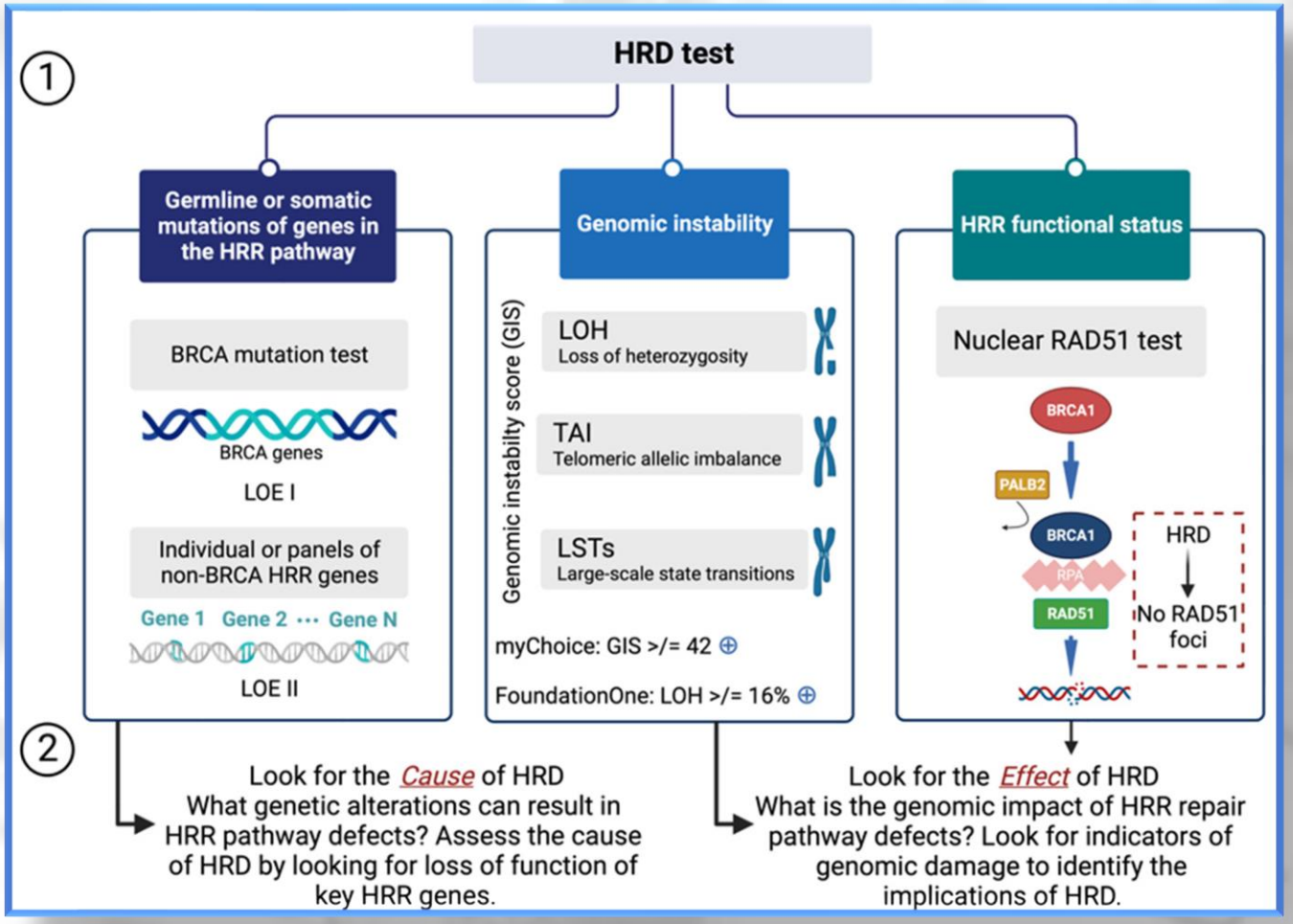
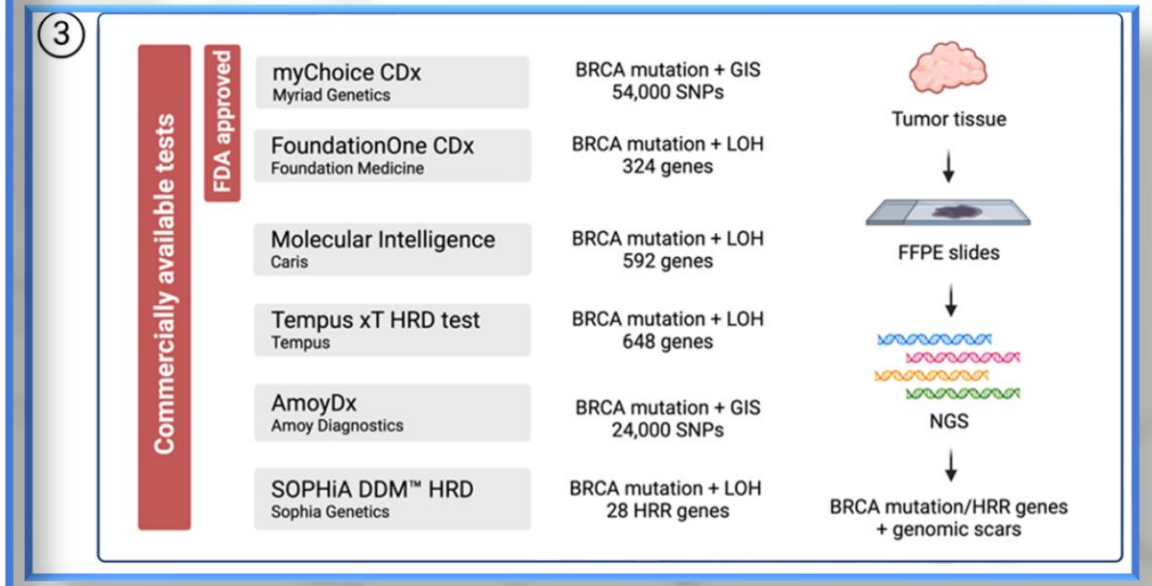
HRD tests: state of the art





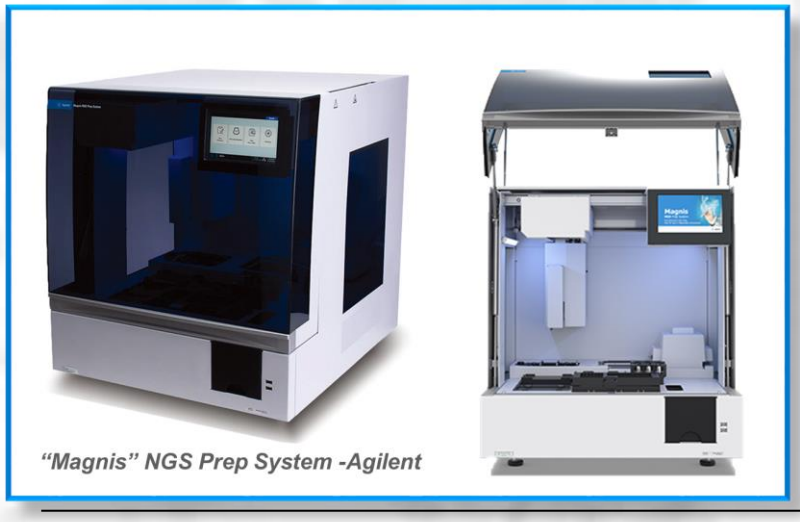
Mangogna et al., J. Pers. Med., **2023**

✓A library prep solution based on **hybrid-capture panel** was developed to detect in one single workflow both **SCNA (backbone-12Mb+ 2.37Mbp)** and **SNV (378 genes, 1,7Mb).**

✓Backbone was used to infer for **LOH, TAI, LST TD.**

✓**378** genes belong to the HR pathway (***BRCA1/2,, BRIP1 BARD1, PALB2, RAD51C/D***) MMR, PARPi resistance (***TP53BP1***) and actionable targets..

✓Pipeline analysis has been developed by our "Bio-informatic' team" and locally run on our servers.



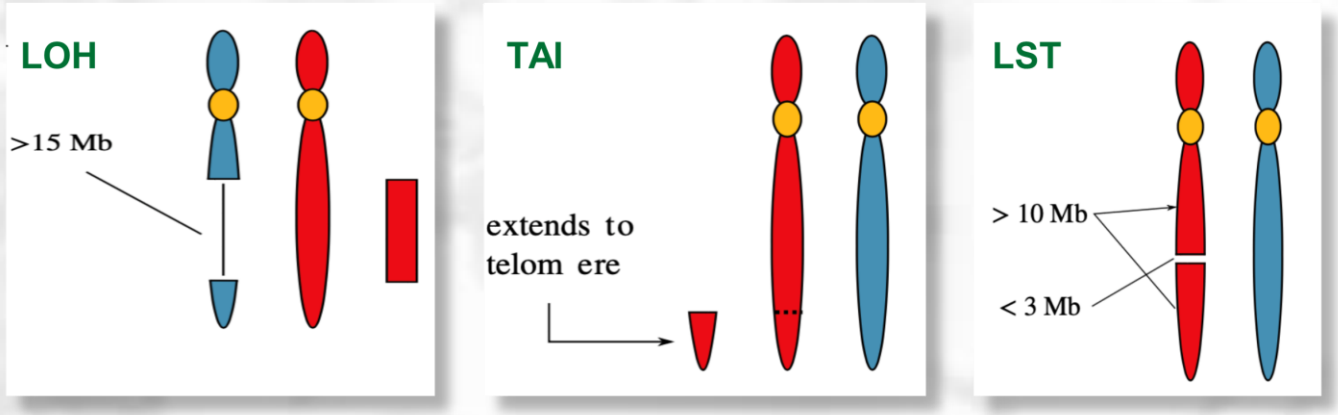
✓It works with 50-70 ng of both snap frozen and FFPE tumor biopsies, with low tumor purity **(< 30%).**

✓Libraries are prepared by a "walkaway" liquid handling solution to reduce manual biases. .

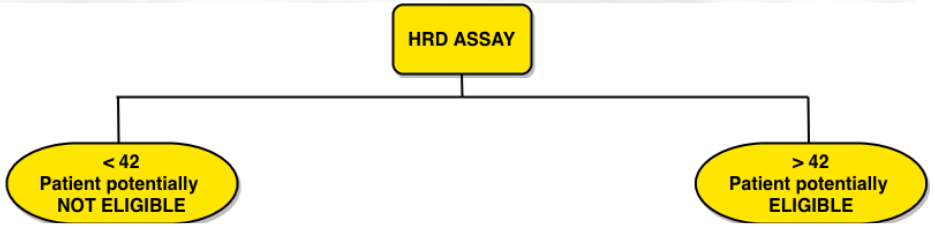
✓25 libraries are pooled and run at **200x** coverage on a benchtop sequencers (NextSeq550-Illumina).

✓ Turnaround time (TAT): 21 days

✓Data generated allows us to infer the HRD status through the conventional parameters:



- ✓ However, the designed "**backbone**" provides the opportunity to develop **new metrics**, such as **TD** to intercept those cases with HR defects not intercepted by conventional parameters.
- ✓ The **SNV** analysis allows to analyze the mutational profiles of *BRCA* genes, CDK12 as well as other genes involved in the resistance to PARPi (*TP53BP1*).


HRD ASSAY
< 42
Patient potentially
NOT ELIGIBLE
> 42
Patient potentially
ELIGIBLE

The Academic Response

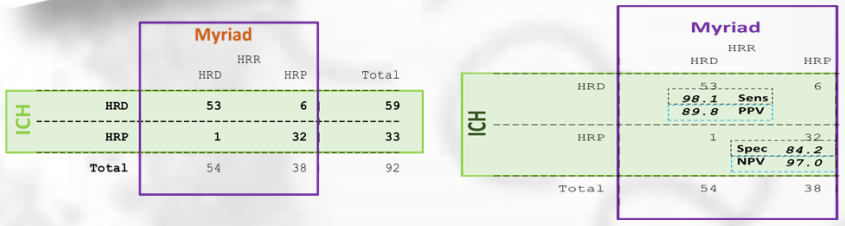
We have developed a roadmap of experiments based on retrospective and prospective cohort of cases aimed to test the performances of our “Academic test”, in comparison with results obtained with to the benchmark test.

1- Ability to call the same set HRD cases
2- Compare the prognostic role
3- Evaluate whether additional biological information retrieved by our analysis improve 1 and 2.
4- Prospective validation: we will include our assay in a randomised clinical trials to test the clinical utility of our assay compared to the commercial available one
5 transfer to other clinical center for external validation of the workflow

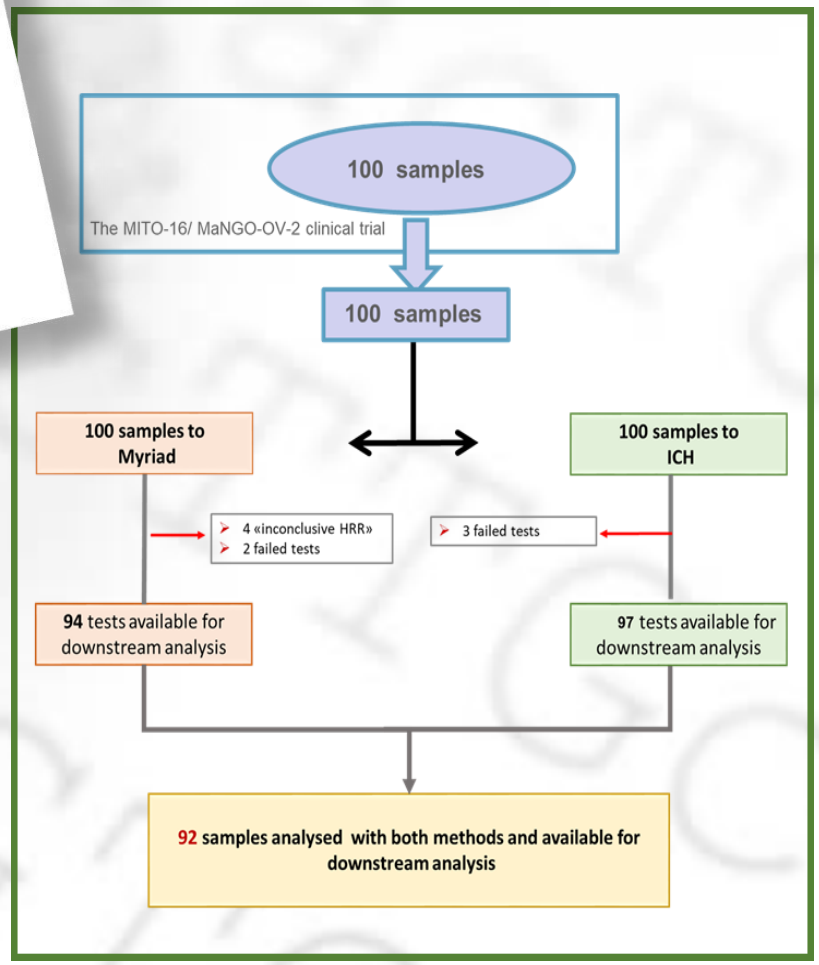
Results from step 1 and 2 are available for the discussion

The Academic Response

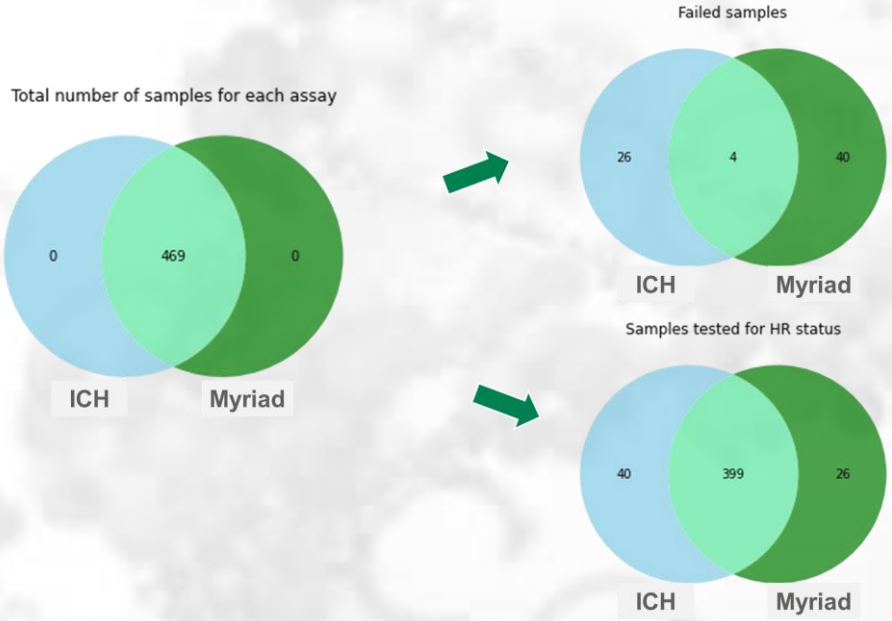
Publication



- **Agreement rate=** 0.92 (0.87-0.98)
- **K Cohen = 0.84 (0.72 – 0.96)**



The Academic Response



		Myriad		
		HRD	HRP	Total
ICH assay	HRD	214	23	237
	HRP	14	148	162
	Total	228	171	399

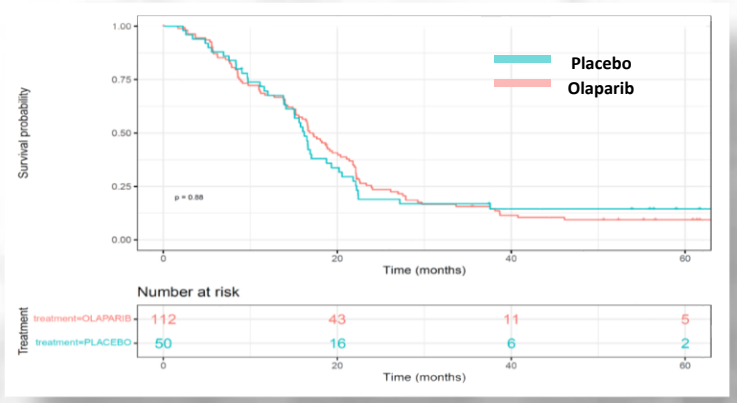
- ✓ **Dropout rate= ICH 6,4%; Myriad= 9,4%**
- ✓ **Agreement Rate = 90.73%**
- ✓ **Sensitivity = 93.86% (95% CI: 89.91%- 96.60%)**
- ✓ **Specificity = 86.55% (95% CI: 80.50% -91.28%)**
- ✓ **Cohen's K = 0.809 (95% CI from 0.751 to 0.868)**

The Academic Response

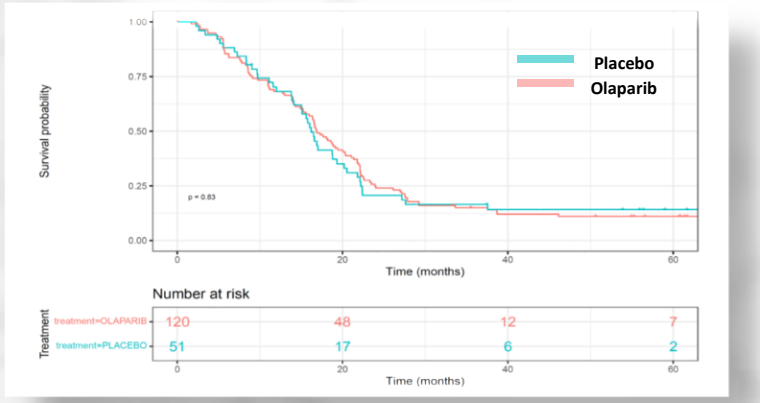
HUMANITAS

Myriad

HRP

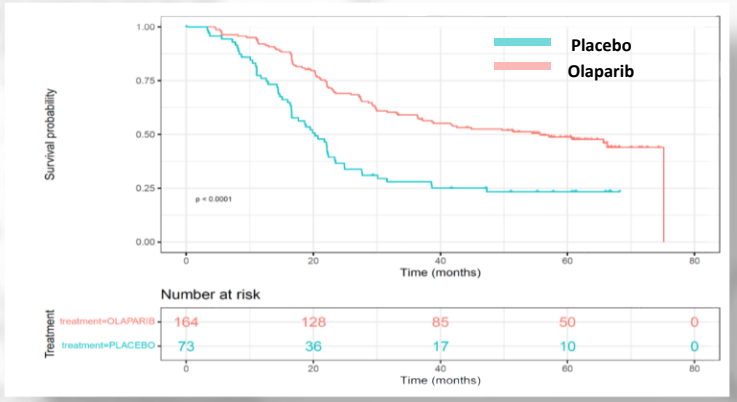


HR (Olaparib vs Placebo): 0,973 (0,71-1,477); *p=0,88*

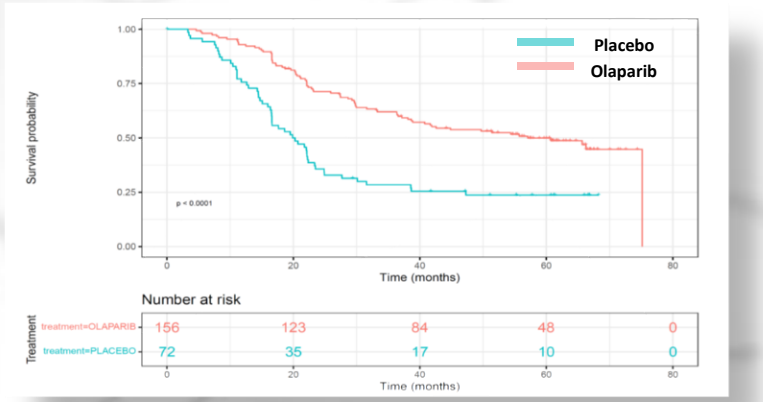


HR (Olaparib vs Placebo): 0,963 (0,72-1,48); p=0,83

HRD



HR (Olaparib vs Placebo): 0,44 (0,31-0,0,62); p<0,0001



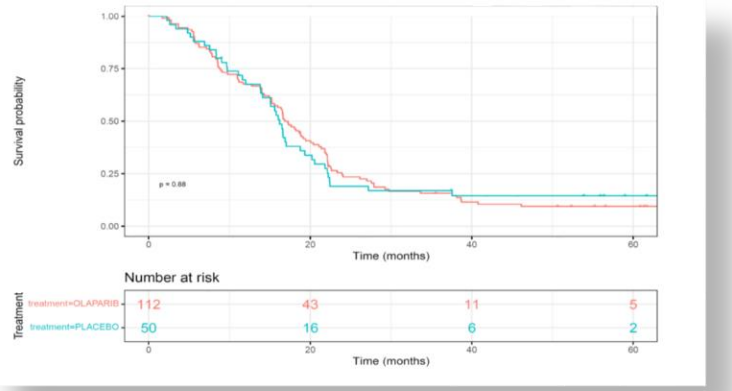
HR (Olaparib vs Placebo): 0,419 (0,294-0,595); p<0,0001

The Academic Response

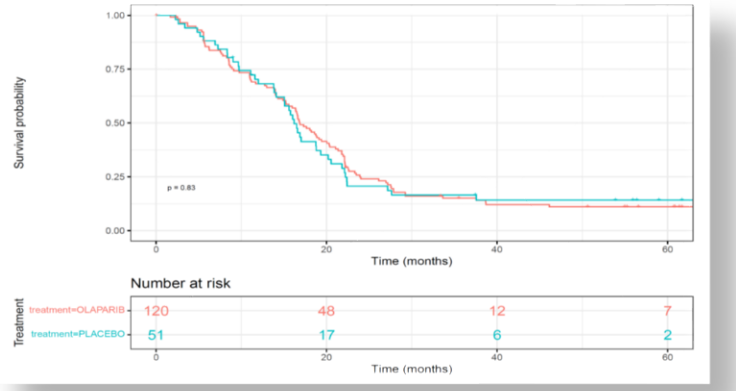
HUMANITAS

Myriad

HRP
***BRCA*$^{+/+}$**

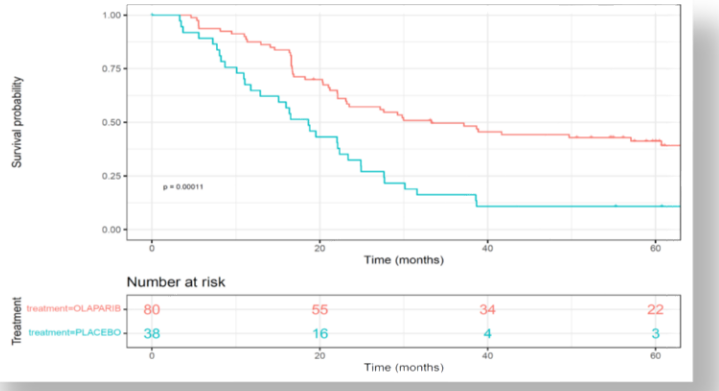


HR (Olaparib vs Placebo): 0,97 (0,677-1,39); p=0,88

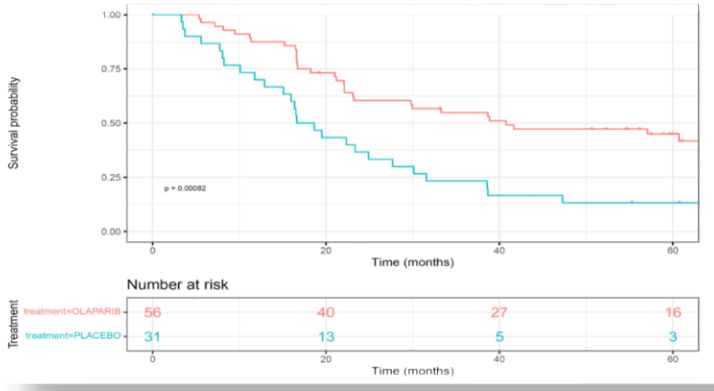


HR (Olaparib vs Placebo): 0,96 (0,674-1,375);p= 0,83

HRD
***BRCA*$^{+/+}$**



HR (Olaparib vs Placebo): 0,42 (0,27-0,66); p<0,00011



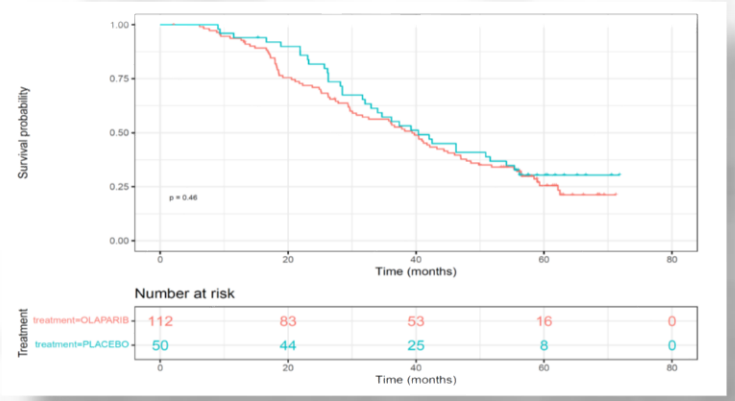
HR (Olaparib vs Placebo): 0,42 (0,25-0,71); p= 0,00082

The Academic Response

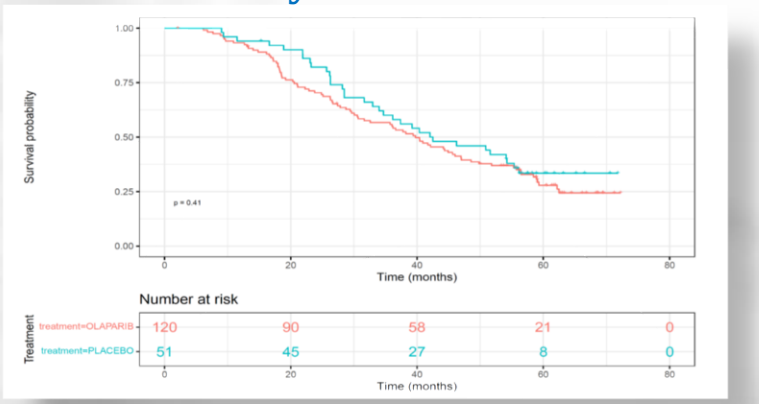
HUMANITAS

Myriad

HRP

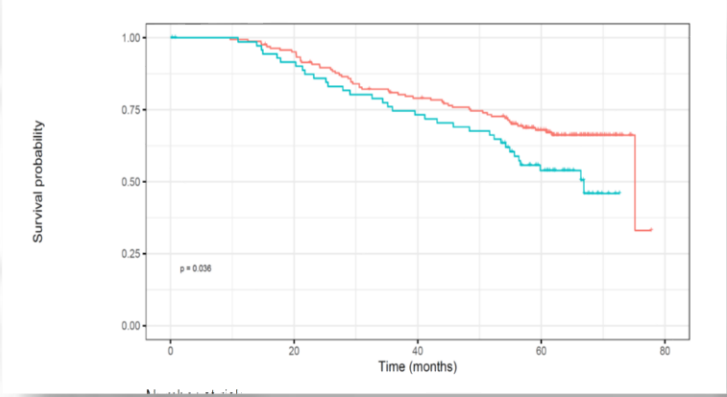


HR (Olaparib vs Placebo): 1,161 (0,77-1,7); *p=0,46*

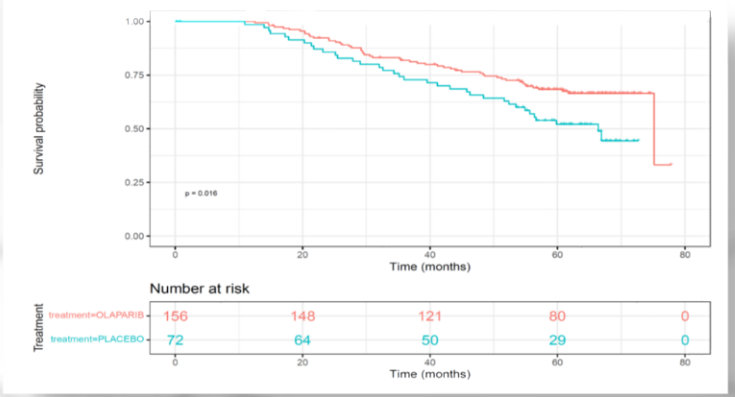


HR (Olaparib vs Placebo): 1,182 (0,78-1,78); *p=0,41*

HRD



HR (Olaparib vs Placebo): 0,63 (0,4-0,97); *p=0,036*



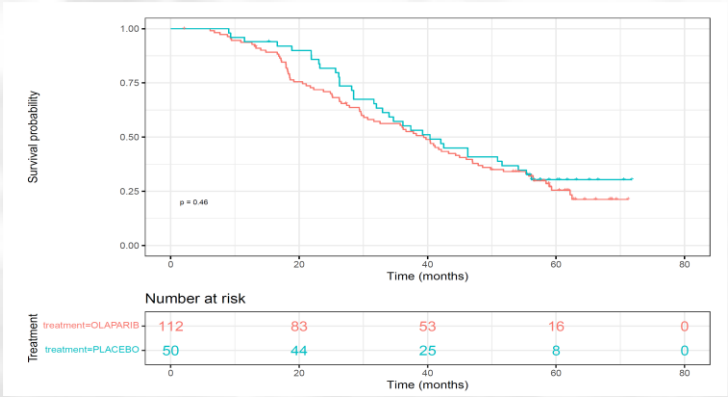
HR (Olaparib vs Placebo): 0,59 (0,38-0,9*) p=0,016*

The Academic Response

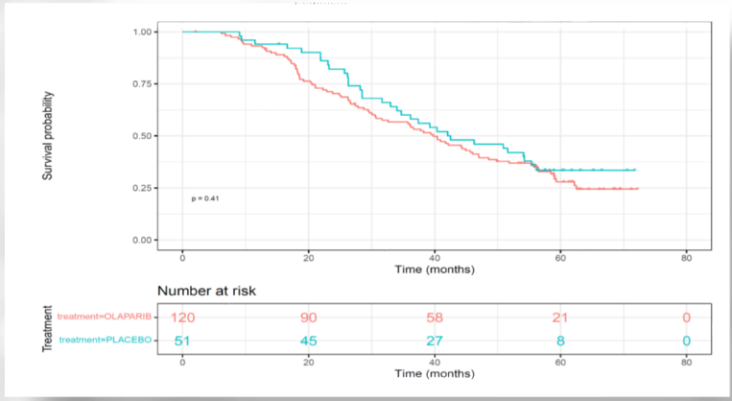
HUMANITAS

Myriad

HRP
BRCA+/+

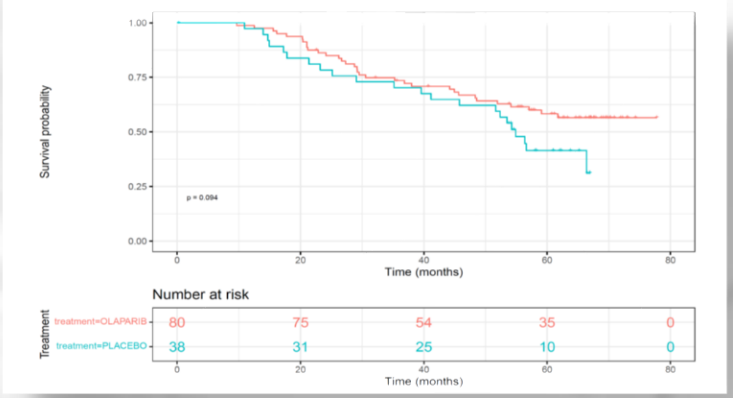


HR (Olaparib vs Placebo): 1,161 (0,86-1,7*); p=0,46*

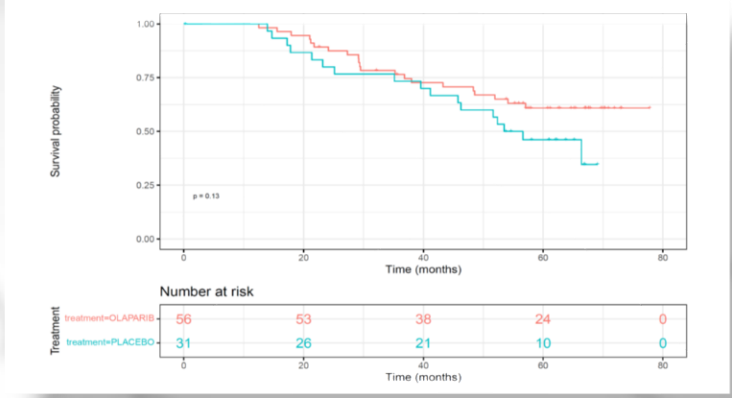


HR (Olaparib vs Placebo): 1,182(0,78-1,7);p=0,41

HRD
BRCA+/+



HR (Olaparib vs Placebo): 0,632 (1,089-1,5); *p=0,094*



HR (Olaparib vs Placebo): 0,61 (0,32-1,16); p=0,13

TAKE HOME MESSAGE

- ✓A high level of concordance of the ICH assay with the HRD status collected with benchmark test was reported.
- ✓This high concordance was paralleled with a very low failure rate, therefore suggesting the feasibility of ICH assay.
- ✓FTO analysis revealed a possible patent infringement with Myriad MyChoice assay.
- ✓We are still working on the possibility to introduce novel metrics in the analysis to improve the selection of case eligible for PARPi therapy (TD) or to predict intrinsic resistance to PARPi treatment.

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