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Clinical Benefit in Biomarker-Positive Patients With Locally Advanced or Metastatic Solid Tumors Treated With the PARP1/2 Inhibitor Pamiparib in Combination With Low-Dose Temozolomide

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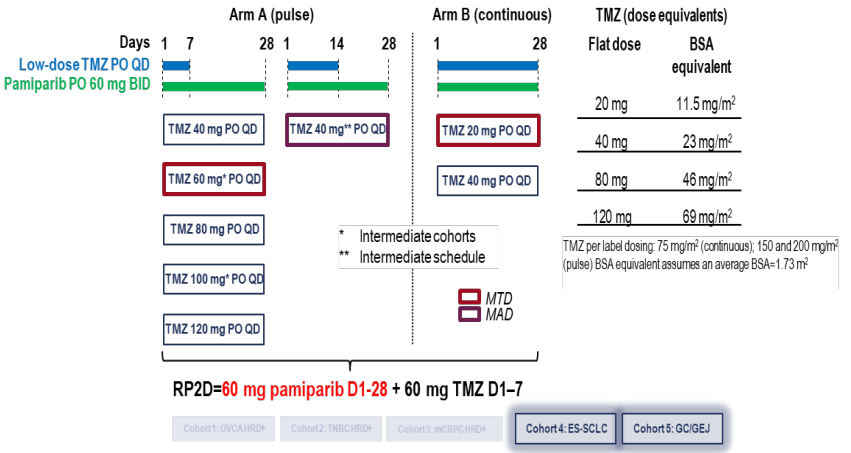
DISCLOSURE INFORMATION

Dr. Calvo reports grants and other from Boehringer-Ingelheim, Roche/Genentech, BMS, Novartis PsiOxus, Nanobiotix Janssen, Abbvie, PharmaMar, PUMA, Sanofi, Lilly, Pfizer, Merck, Nektar, Amcure, Amgen, AstraZeneca, Principia Bayer, CytomX, H3, Incyte, Kura, LOXO, Macrogenics, Menarini, Merck, Serono, Merus, Millenium, Rigontec, Tahio, and Tesaro outside of the submitted work.

Dr. Calvo reports other potential conflicts of interest from Janssen-Cilag, Seattle Genetics, Pierre Fabre, Cerulean Pharma, EUSA, Celgene, START, HM Hospitals Group, Oncoart Associated, International Cancer Consultants, Novartis, Nanobiotix, PsiOxus Therapeutics, Abbvie, AstraZeneca, Guidepoint Global, Roche/Genentech, GLG, Pfizer, Servier, Amcure, BeiGene, and NPO Foundation Intheos (Investigational Therapeutics in Oncological Sciences) all outside the submitted work.

Study Design and Patient Demographics



The study (BGB-290-103, NCT03150810) enrolled a total of 114 patients in dose-escalation and dose-expansion

The majority of the patients were white (75%) and were heavily pretreated (median prior therapies of three, range 1-10)

Median study follow-up time of 8.4 months (range 0.3-30.0)

data cutoff date: April 2020

Abbreviations: BID, twice daily; BSA, body surface area; ES-SCLC, extensive-stage small cell lung cancer; GC, gastric cancer; GEJ, gastroesophageal junction; HRD, homologous recombination deficiency; MAD, maximum administered dose; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; OVCA, ovarian cancer; PO, orally; QD, once daily; RP2D, recommended phase 2 dose; TMZ, temozolomide; TNBC, triple-negative breast cancer.

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Retrospective Biomarker Analysis

- Samples from dose-escalation and dose-expansion patients were included in the analysis
- Myriad myChoice HRD test performed in archival tissue samples obtained at baseline
  - *Genomic instability score (GIS, formerly HRD score) based on large-scale transitions, telomeric allelic imbalance, and loss of heterozygosity*
  - *GIS+ defined as GIS score ≥33*
- ctDNA NGS DNA-Seq performed in blood samples obtained at baseline
  - *Focus on 16 core DNA damage response (DDR) genes:*
    ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, CDK12, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L
  - *DDR+ defined as ≥1 mutation in one of 16 DDR genes*
- Correlation of DDR/GIS status with overall response rate (ORR) and disease control rate (DCR)

Abbreviations: ctDNA, circulating tumor DNA; DCR, disease control rate; DDR, DNA damage response; GIS, genomic instability score; HRD, homologous recombination deficiency; NGS DNA-Seq, next generation DNA sequencing; ORR, objective response rate.

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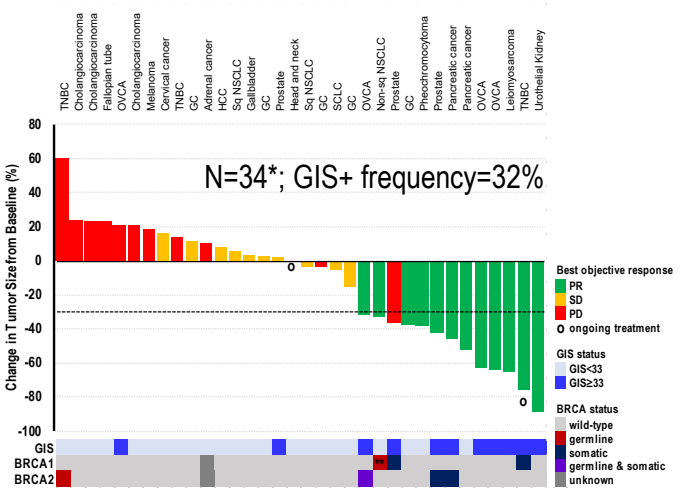
GIS+ Patients Had Better ORR and DCR than GIS− Patients, Irrespective of *BRCA* Mutation Status



*Patients with postbaseline tumor assessments and Myriad myChoice results.

** The gBRCA1 mutation reported for the nonsquamous NSCLC patient was non-pathogenic.

GIS (formerly HRD score) measures LST+TAI+LOH; GIS+ = GIS score ≥33

ORR

	*BRCA1/2*mut (N=7)	*BRCA1/2*wt (N=27)	Total (N=34)
GIS+	**100.0%** (5/5) (90% CI, 0.55-1.00)	**66.7%** (4/6) (90% CI, 0.27-0.94)	**81.8%** (9/11) (90% CI, 0.53-0.97)
GIS−	50.0% (1/2) (90% CI, 0.03-0.97)	9.5% (2/21) (90% CI, 0.02-0.27)	13.0% (3/23) (90% CI, 0.04-0.30)

DCR

	*BRCA1/2*mut (N=7)	*BRCA1/2*wt (N=27)	Total (N=34)
GIS+	**100.0%** (5/5) (90% CI, 0.55-1.00)	**83.3%** (5/6) (90% CI, 0.42-0.99)	**90.9%** (10/11) (90% CI, 0.64-1.00)
GIS−	50.0% (1/2) (90% CI, 0.03-0.97)	57.1% (12/21) (90% CI, 0.37-0.75)	56.5% (13/23) (90% CI, 0.38-0.74)

Abbreviations: *BRCA*, breast cancer gene; DCR, disease control rate; GC, gastric cancer; GIS, genomic instability score; HCC, hepatocellular carcinoma; HRD, homologous recombination deficiency; LST, large-scale transitions; LOH, loss of heterozygosity; mut, mutation; NSCLC, non-small cell lung cancer; ORR, objective response rate; OVCA, ovarian cancer; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; Sq, squamous; TAI, telomeric allelic imbalance; TNBC; triple-negative breast cancer; wt, wild-type.

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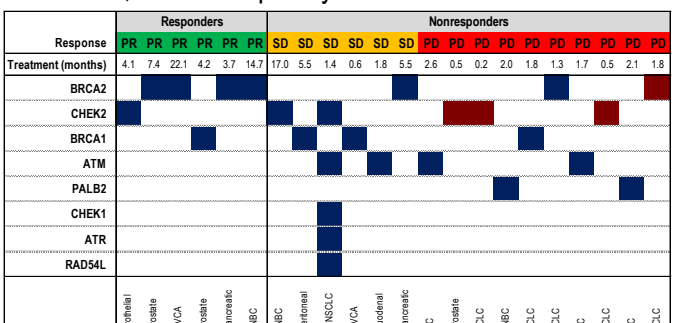
DDR+ Patients Had Better ORR than DDR− Patients, but Responses were Associated with *BRCA* Mutations

N=86*; DDR+ frequency=26%



*Patients with postbaseline tumor assessments and ctDNA data.

DDR panel: ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, CDK12, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L

DDR+ = ≥1 mutation in one of 16 DDR genes

5 patients were GIS+ and DDR+

ORR

	***BRCA1/2*mut** (N=14)	***BRCA1/2*wt** (N=72)	**Total** (N=86)
DDR+	**38.5%** (5/13) (90% CI, 0.17-0.65)	**11.1%** (1/9) (90% CI, 0.06-0.43)	**27.3%** (6/22) (90% CI, 0.12-0.47)
DDR−	100.0% (1/1) (90% CI, 0.05-1.00)	12.7% (8/63) (90% CI, 0.06-0.22)	14.1% (9/64) (90% CI, 0.08-0.23)

DCR

	***BRCA1/2*mut** (N=14)	***BRCA1/2*wt** (N=72)	**Total** (N=86)
DDR+	**61.5%** (8/13) (90% CI, 0.35-0.83)	**44.4%** (4/9) (90% CI, 0.17-0.75)	**54.5%** (12/22) (90% CI, 0.35-0.73)
DDR−	100.0% (1/1) (90% CI, 0.05-1.00)	65.1% (41/63) (90% CI, 0.54-0.75)	65.6% (42/64) (90% CI, 0.55-0.76)

Abbreviations: *BRCA, breast cancer gene; CNV, copy number variants; ctDNA, circulating tumor DNA; DCR, disease control rate; DDR, DNA damage response; GC, gastric cancer; GIS, genomic instability score; mut, mutation; ORR, objective response rate; OVCA, ovarian cancer; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SD, stable disease; SNV, single nucleotide variants; TNBC; triple-negative breast cancer; wt, wild-type.*

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Conclusions

- In this limited subset of patients treated with pamiparib in combination with different doses of LD TMZ, GIS+ patients derived superior benefit, irrespective of *BRCA1/2* mutation status, compared with DDR+, GIS−, and DDR− patients
- Responses in the DDR+ subpopulation were primarily associated with *BRCA1/2* mutations
- GIS status, which is a global measure of genomic instability, appears to be a robust biomarker to predict response to pamiparib + LD TMZ
- As previously shown, mutations in DDR genes other than *BRCA1/2* have limited utility in predicting the response to PARP inhibitors
- A new cohort, cohort 6, is currently evaluating the antitumor activity of pamiparib + LD TMZ in patients with GIS+ NSCLC, head and neck, esophageal, and soft tissue sarcoma tumors

Abbreviations: *BRCA*, breast cancer gene; DDR, DNA damage response; GIS, genomic instability score; LD, low dose; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; TMZ, temozolomide.

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