OVERVIEW

Metastatic castration-resistant prostate cancer (mCRPC) is a heterogeneous disease with high disease burden and poor outcomes despite androgen deprivation therapy. This activity by Neeraj Agarwal, MD, provides strategies for germline genetic testing and somatic testing to best inform treatment. Poly (ADP-ribose) polymerase (PARP) inhibitor therapy provides a unique approach to treatment. Dr. Agarwal reviews safety and efficacy findings from recent clinical trials for the two PARP inhibitors, olaparib and rucaparib, approved in the United States for mCRPC. He also shares observations regarding PARP inhibitors in combination with other therapies.

TARGET AUDIENCE

This activity was developed for medical oncologists and other healthcare professionals involved in the treatment of prostate cancer.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Discuss new and emerging data on PARP inhibitors in combination with other therapies for the treatment of advanced PC
- Identify patients who may benefit from the use of PARP inhibitors combinations for the treatment of advanced PC based on the latest evidence

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TESTING

In patients with castration-resistant prostate cancer (CRPC), the sequential use of available treatment options becomes standard of care.[1] Treatment is best informed through the use of germline genetic testing and somatic (tumor) testing to identify genomic alterations since alterations are common.[2-4] Among these alterations, 3% to 5% of men with metastatic CRPC (mCRPC) have germline mutations in DNA mismatch repair genes, while one-quarter have homologous recombinant repair (HRR) deficiency.[5,6] Men with germline or somatic mutations in an HRR gene, including *ATM, BARD1, BRCA1*, *BRCA2*, *BRIP1, CDK12, CHEK1, CHEK2*, *FANCL*, *PALB2*, *RAD51B, RAD51C, RAD51D*, and *RAD51L* are potential candidates for poly(ADP-ribose) polymerase (PARP) inhibitor therapy.[7]

Testing for both somatic and germline alterations is necessary since germline-only testing misses almost one-half of *BRCA1* and *BRCA2* alterations and most cases of mismatch repair gene defects.[8] Conversely, somatic testing may miss pathogenic germline variants.[8,9]

The 2019 Philadelphia Prostate Cancer Consensus Conference recommends large germline panels and somatic testing for metastatic prostate cancer.[10] Germline testing is recommended for men with metastatic disease or family history suggestive of hereditary prostate cancer. Priority genes to test for metastatic disease treatment include *BRCA2*, *BRCA1*, and mismatch repair genes, with broader testing, such as *ATM*, to determine eligibility for a clinical trial. Screening starting at age 40 years or 10 years before the youngest prostate cancer diagnosis in a family is recommended for *BRCA2* carriers, with consideration in *HOXB13*, *BRCA1*, *ATM*, and mismatch repair carriers.

Options for testing include focused panels, guidelines-based panels, comprehensive large panels, and reflex panels.[11] Focused and guidelines-based panels may be more appropriate for patients who prefer a smaller panel that encompasses genes relevant to their care and family history. Comprehensive panels may be more appropriate for men who need confirmation of clinical trial eligibility or who are more open to gaining genetic knowledge and are comfortable with uncertain genetic findings. Men who wish to proceed with stepwise testing may be more appropriate for reflex testing.

Finally, recent investigations demonstrate that, while genetic testing is not performed in one-third of men with metastatic prostate cancer,[12] men with prostate cancer value genetic testing and genetic counseling for personal and family implications.[13] Both investigations revealed lack of understanding among urologists and men with prostate cancer of the implications of positive genetic test results on female family members.[12,13]

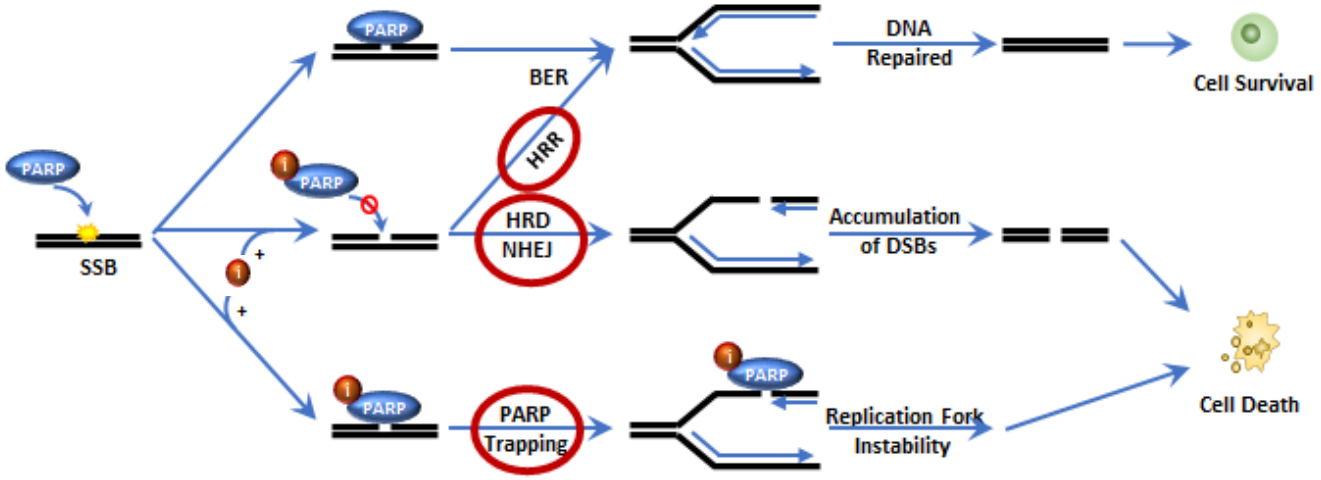
PARP INHIBITOR MECHANISM OF ACTION

In the presence of single-strand DNA damage, PARP is recruited, leading to activation of the base excision repair pathway and ultimately cell survival (Figure 1). In the presence of PARP inhibitors, an alternate mechanism for DNA repair, ie, HRR (BRCA1/2 pathway) is activated, also leading to cell survival. In the case of mutations in genes belonging to HRR (BRCAness or homologous recombination deficiency), the presence of PARP inhibitors leads to cell death due to accumulation of double-strand breaks and upregulation of the non-homologous end joining pathway, a process known as synthetic lethality. Alternatively, PARP inhibitors, eg, talazoparib (not approved for prostate cancer in the US), trap PARP at the site of damage, thereby preventing DNA replication and leading to replication fork instability and cell death regardless of DNA homologous recombination repair defect.

CLINICAL TRIALS OF PARP INHIBITORS

Among the various treatments for men with mCRPC, 2 PARP inhibitors are approved in the United States.[1] The indication for rucaparib is limited to men with deleterious germline or somatic mutations in *BRCA1* or *BRCA2* who have been treated with taxane-based chemotherapy and enzalutamide or abiraterone, while olaparib is indicated in a broader cohort of men with deleterious germline or somatic mutations in HRR genes who have progressed following treatment with enzalutamide or abiraterone.

Figure 1. PARP Inhibitors: Mechanism of Action



BER, base excision repair; DSB, double strand break; HRD, homologous recombination deficiency; HRR, homologous recombination repair; i, PARP inhibitor; NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase; SSB, single strand break.

Olaparib

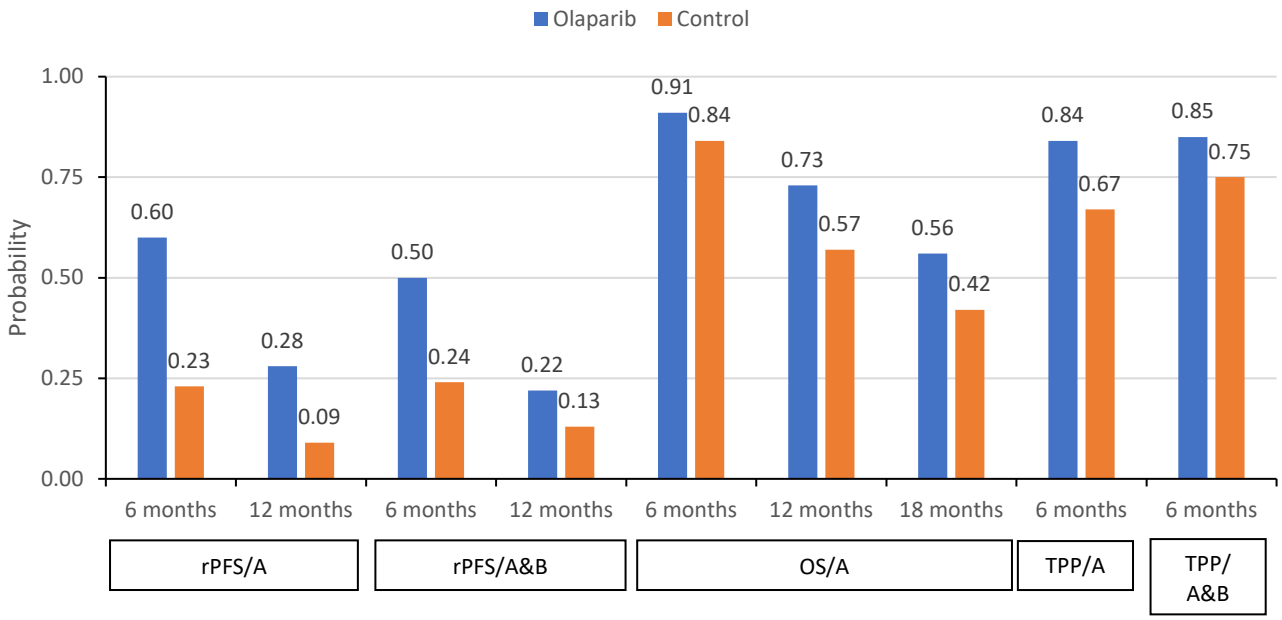
The safety and efficacy of olaparib were investigated in the phase 3, open-label PROfound study in men with mCRPC (N=387) who had an identified alteration in *BRCA1*, *BRCA2*, or *ATM* (cohort A) or 12 other prespecified genes with a direct or indirect role in HRR (cohort B).[14] Eligible patients experienced disease progression while receiving enzalutamide or abiraterone. Patients were randomized to olaparib 300 mg twice daily or either enzalutamide 160 mg once daily or abiraterone 1000 mg once daily in combination with prednisone 5 mg twice daily (control group). The median total duration of assigned treatment was 7.4 months and 3.9 months in the olaparib and control groups, respectively.

In cohort A (n=245), the imaging-based progression-free survival (rPFS) was significantly longer in the olaparib vs control group (hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.25 to 0.47; *P*<0.001) (Figure 2).[14] Similarly, in cohorts A and B combined, the median rPFS was significantly longer in the olaparib vs control group (5.8 months vs 3.5 months, respectively) (HR 0.49, 95% CI 0.38 to 0.63), indicating benefit with olaparib in men with alterations in genes other than *BRCA1*, *BRCA2*, or *ATM*. Subgroup analysis showed no impact on disease progression or death based on previous taxane use (yes vs no), presence of measurable disease at baseline (yes vs no), site of metastases (bone, visceral, other), age (<65 years vs ≥65 years), or PSA level (≥median vs <median).

In cohort A, the median time to pain progression was significantly longer in the olaparib vs control group (HR 0.44, 95% CI 0.22 to 0.91; *P*=0.02).[14] The median overall survival rates were 19.1 months vs 14.7 months, respectively (HR 0.69, 95% CI 0.50 to 0.97; *P*=0.02) in cohort A and 14.1 months vs 11.5 months, respectively, in cohort B.[15] Overall, 66% of patients in the control group crossed over to treatment with olaparib. A sensitivity analysis that adjusted for crossover to olaparib showed a lower risk for death in cohort A (HR 0.42, 95% CI 0.19 to 0.91) than cohort B (HR 0.83, 95% CI 0.11 to 5.98).[15]

In the PROfound study, the most common adverse events were (olaparib vs control): anemia (46% vs 15%), nausea (41% vs 19%), fatigue/asthenia (41% vs 32%), decreased appetite (30% vs 18%), and diarrhea (21% vs 7%).[14] Anemia was the most common grade ≥3 adverse event, occurring in 21% vs 5%, respectively. A new primary cancer was reported in 1

Figure 2. Efficacy Outcomes with Olaparib vs Control in the PROfound Study[14]



rPFS/A, imaging-based progression-free survival in cohort A; rPFS/A&B, imaging-based progression-free survival in cohorts A & B; OS/A, overall survival in cohort A; TPP/A, time to pain progression in cohort A; TPP/A&B, time to pain progression in cohorts A & B

patient in the olaparib group (glioma) and 2 in the control group (gastric, transitional-cell). Overall in the olaparib and control groups, 45% and 18% had a treatment interruption, 22% vs 4% dose reduction, and 18% vs 8% treatment discontinuation due to an adverse event, respectively. One treatment-related death was observed in each group.

A retrospective analysis was conducted involving 46 consecutive men with progressive mCRPC treated with olaparib at 3 US medical centers prior to its approval by the US Food and Drug Administration for prostate cancer.[16] Twenty-three men had pathogenic mutations in *BRCA1*, *BRCA2*, or *ATM*. Of these, 57% of the mutations were of germline and 44% of somatic origin. Thirteen of the 23 men achieved a >50% decline in the PSA level from baseline (PSA_{50}), the primary efficacy endpoint. A PSA_{50} was achieved by 76% of those with *BRCA1/2* mutations but none with an *ATM* mutation.

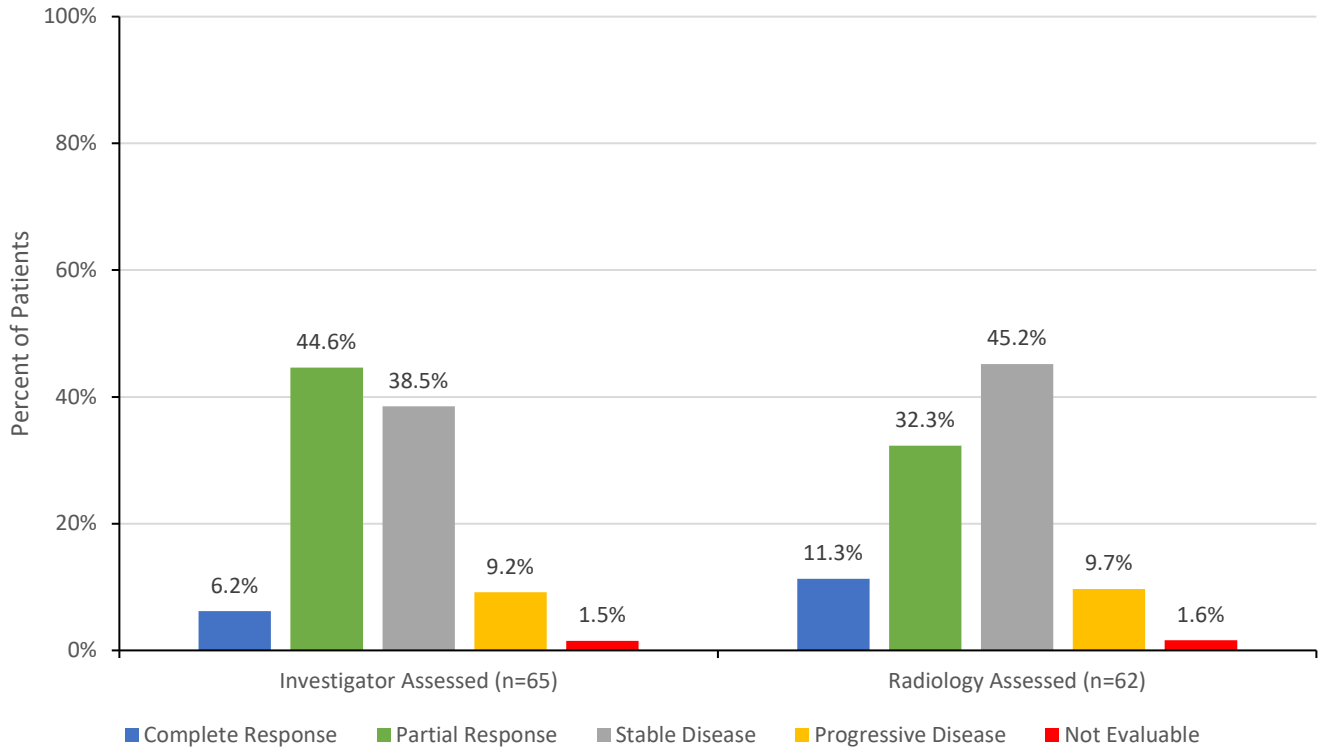
Rucaparib

The safety and efficacy of rucaparib were investigated in the phase 2, single-arm TRITON2 study in men with mCRPC and established *BRCA1* or *BRCA2* gene mutation (N=115).[17] Eligible patients experienced disease progression after 1 or 2 lines of abiraterone, enzalutamide, or apalutamide for prostate cancer and 1 prior taxane-based chemotherapy for castration-resistant disease.

All patients were treated with rucaparib 600 mg twice daily. The median treatment duration was 8.1 months.

The independent radiology review and investigator-assessed objective response rates (ORRs) were 43.5% and 50.8%, respectively (Figure 3).[17] The radiologic ORRs were similar for patients with a germline or somatic *BRCA* alteration and for patients with a *BRCA1* or *BRCA2* alteration. Subgroup analysis also showed no impact on radiologic ORR by

Figure 3. Response Rates to Rucaparib[17]



presence of liver metastases (yes vs no) or age (<65 years vs 65-74 years vs ≥75 years).

The confirmed prostate-specific antigen (PSA) response rate (defined as ≥50% decrease from baseline) was 54.8%.[17] More patients with a *BRCA2* vs *BRCA1* alteration (59.8% vs 15.4%, respectively) experienced PSA response. The median progression free survival rates were 9.0 months (radiologic) and 8.5 months (investigator).

In the TRITON2 study, the most common adverse events were: fatigue/asthenia (62%), nausea (52%), anemia (44%), increased ALT/AST (33%), decreased appetite (28%), constipation (27%), and thrombocytopenia (25%).[17] Anemia was the most common grade ≥3 adverse event, occurring in 25%. Overall, 64% had either a treatment interruption or dose reduction and 8% a treatment discontinuation due to an adverse event. One treatment-related death due to acute respiratory distress syndrome occurred.

PARP Inhibitor Combinations

With Chemotherapy

The common occurrence of anemia observed with cytotoxic chemotherapy as well as PARP inhibitors makes their combined use challenging. Moreover, the limited benefit with the combination in other cancers has dampened interest in the mCRPC setting.[18]

With Androgen Deprivation Therapy

An interaction between androgen receptor signaling and synthetic lethality with PARP inhibition has been conceptualized.[19,20] This was explored in a murine xenograft model showing a decrease in tumor burden with the combination of bicalutamide and olaparib.[19] Further supportive evidence was provided by a phase 2 study in men with disease progression on docetaxel unselected for mutational

status.[21] The study demonstrated a significant increase in rPFS with the combination of olaparib and abiraterone vs abiraterone alone (13.8 months vs 8.2 months) (HR 0.65, 95% CI 0.44 to 0.97; *P*=0.034).Grade ≥3 anemia was observed in 21% vs 0%, respectively. One treatment-related death (pneumonitis) occurred in the olaparib group.

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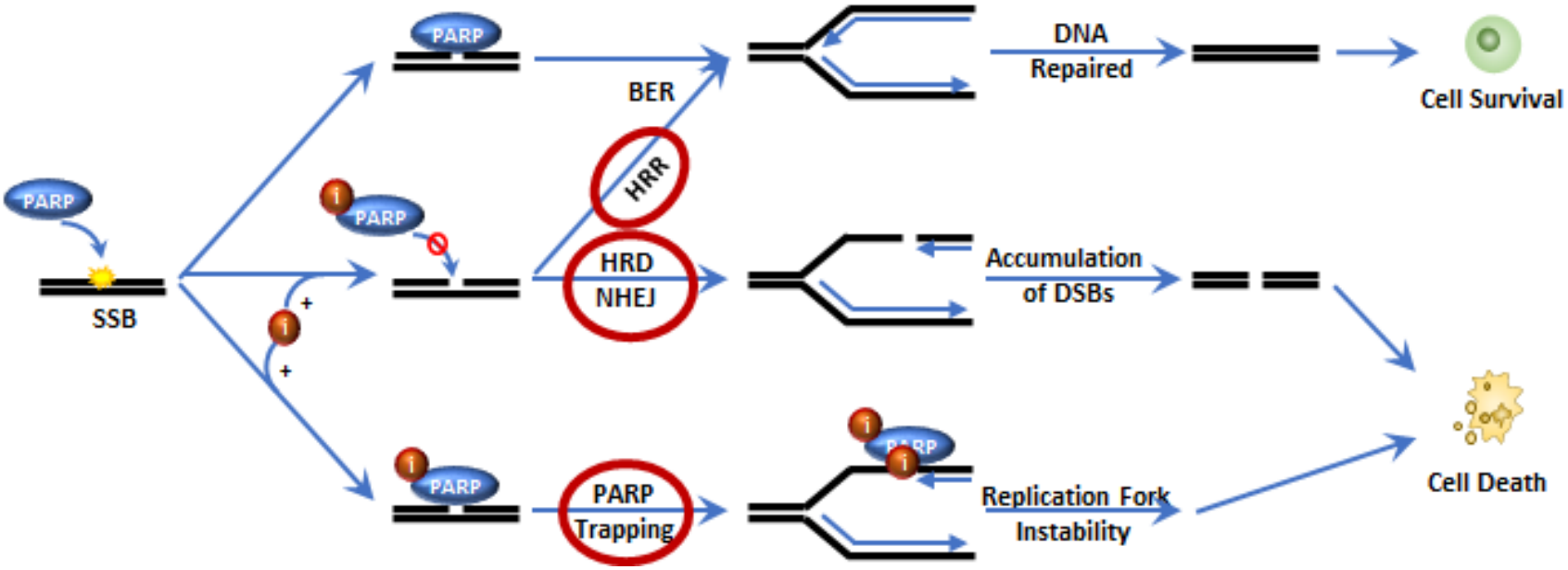

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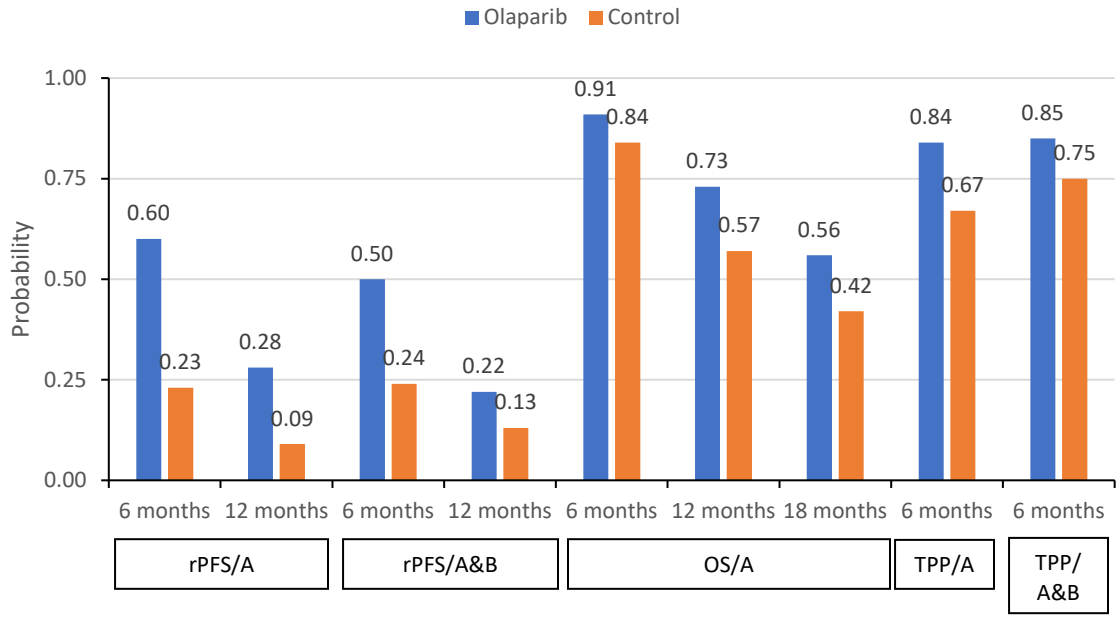

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