Journal Scan

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SUMMARY

The goal of this new section in the BJMO is to provide a snapshot of pivotal studies published in recent issues of the most important international journals focusing on oncology. Importantly, the selection of the studies discussed here is the sole responsibility of the publisher and was not influenced by third parties. Do you miss an important study, or did you read a hidden jewel that deserves to be shared with your colleagues? Please let us know (editor@bjmo.be) and we will make sure to include it in the journal scan section of the next BJMO issue.

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TIVOZANIB DELAYS DISEASE PROGRESSION COMPARED TO SORAFENIB IN THE THIRD- OR FOURTH-LINE TREATMENT OF PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

TIVO-3 is a multicentre, randomised phase III trial comparing tivozanib (a potent and selective VEGFR inhibitor) with sorafenib as third- or fourth-line therapy in patients with metastatic renal cell carcinoma (mRCC). The study included 350 patients with histologically or cytologically confirmed mRCC who received at least two previous systemic treatments (including at least one VEGFR inhibitor), measurable disease according to RECIST 1.1, and an ECOG PS of 0-1. Patients were randomly assigned to receive tivozanib 1.5 mg orally once daily in 4-week cycles or sorafenib 400 mg orally twice daily continuously. After a median follow-up of 19 months, the study met its primary endpoint by demonstrating a statistically significant improvement in median progression-free survival (PFS) (median 5.6 *vs.* 3.9 months; HR[95%CI]: 0.73[0.56-0.94]; p= 0.016). At one year, 28% of patients on tivozanib was free of progression as compared to 11% in the sorafenib arm (18% *vs.* 5% at 2 years). Among the 26% of patients with prior immune checkpoint inhibitor therapy, the median PFS was 7.3 months with tivozanib as compared to 5.1 months with sorafenib (HR[95%CI]: 0.55[0.32–0.94]). Remarkably, the median overall survival (OS) with tivozanib was reported at 16.4 months, which is shorter than the 19.7 months median OS seen with sorafenib (HR[95%CI]: 0.99[0.76-1.29]; p= 0.95).[1] The most common grade 3 or 4 treatment-related adverse event (TRAE) was hypertension, which occurred in 20% of the patients in the tivozanib group and in 14% of the patients in the sorafenib group. Serious TRAEs occurred in 11% *vs.* 10% of patients, with gastrointestinal events being the most common in both groups. Adverse events (AEs) led to dose interruption in 48% *vs.* 63% of patients and to dose reduction in 24% *vs.* 38%.[1]

OLAPARIB FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER WITH DNA REPAIR GENE ABERRATIONS

Metastatic castration-resistant prostate cancer (mCRPC) is enriched in DNA damage response (DDR) gene aberrations. The phase II TOPARP-B trial aims to prospectively validate the association between DDR gene aberrations and response to the PARP inhibitor olaparib in mCRPC. In the study at hand, 711

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patients with mCRPC who were previously treated with one or two taxane chemotherapy regimens and had an ECOG status of 2 or less, were screened for DDR aberrations. In total, 161 patients had DDR gene aberrations of whom 98 were randomly assigned to receive 400 mg or 300 mg olaparib twice daily, given continuously in 4-week cycles until disease progression or unacceptable toxicity. Confirmed composite responses were observed in 25 of the evaluable patients who were treated with 400 mg of olaparib (54.3%) and 18 of the 46 patients who received 300 mg of olaparib (39.1%). Additionally, radiographic PFS (rPFS) activity was observed in 8 patients in the 400 mg cohort and 6 in the 300 mg cohort. Prostate-specific antigen declines of 50% (PSA50) were observed in 17 patients treated with the higher dose of olaparib and in 13 of those who received the lower dose. Patients in both cohorts also achieved circulating tumour cell (CTC) count conversion, 17 of whom were recipients of olaparib 400mg and 18 of whom received olaparib 300 mg. The toxicity profile observed in this study was considered to be consistent with previously reported data on olaparib and other PARP inhibitors. In both cohorts, the most common grade 3/4 AE was anaemia, which occurred in 31% of participants given 300 mg of olaparib and 37% of those treated with a 400 mg dose. Permanent discontinuation of treatment occurred in 18 (19%) of study patients overall.[2] The authors conclude that these findings place olaparib on the verge of becoming the first genetically targeted treatment in prostate cancer (PCa).

ATEZOLIZUMAB PLUS NAB-PACLITAXEL FOR METASTATIC TRIPLE NEGATIVE BREAST CANCER

The first issue of the Lancet Oncology in 2020 featured the updated efficacy results of the phase III IMpassion130 trial, evaluating nab-paclitaxel with or without atezolizumab as first-line treatment for 902 patients with locally advanced or metastatic triple negative breast cancer (TNBC).[3] After a median follow-up of approximately 18 months, the median OS was reported at 21 months for atezolizumab + nab-paclitaxel as compared to 18.7 months with nab-paclitaxel alone (HR[95%CI]: 0.86[0.72-1.02]; p= 0.078). Interestingly, an exploratory analysis revealed that the difference in OS between both arms was more pronounced in the subgroup of patients with PD-L1 immune cell-positive tumours, with a median OS of 25.0 and 18.0 months for the experimental and control arm, respectively (HR[95%CI]: 0.71[0.54-0.94]). The most common grade 3/4 AEs were neutropenia (8% in both arms), peripheral neuropathy (6% *vs.* 3%), decreased neutrophil count (5% *vs.* 4%), and fatigue (4% *vs.* 3%). Treatment-related deaths occurred in two (<1%) patients in the atezolizumab group (one case of autoimmune hepatitis related to atezolizumab and one septic shock related to nab-paclitaxel) and one (<1%) patient in the placebo group (hepatic failure). No new treatment-related deaths have been reported since the primary analysis.[3]

As such, this second interim OS analysis of IMpassion130 indicates no significant difference in OS between the treatment groups in the intention-to-treat population but suggests a clinically meaningful OS benefit in patients with PD-L1 immune cell-positive disease. However, this positive result could not be formally tested due to the prespecified statistical testing hierarchy.

OPTIMAL SEQUENCING OF ENZALUTAMIDE AND ABIRATERONE ACETATE PLUS PREDNISONE IN mCRPC

Abiraterone acetate plus prednisone and enzalutamide are both used for the treatment of metastatic castration-resistant prostate cancer. However, the optimal sequence for these two agents is subject to debate. In a phase II trial, reported in the Lancet oncology, *Khalaf et al.* randomised 202 patients with newly diagnosed mCRPC to receive abiraterone acetate (1000 mg orally once daily) plus prednisone (5 mg orally twice daily) until PSA progression followed by crossover to enzalutamide (160 mg orally once daily) (group A), or the reverse sequence (group B). Interestingly, at a median follow-up of 22.8 months, the time to second PSA progression was longer in group A than in group B (median 19.3 *vs.* 15.2 months; HR[95%CI]: 0.66[0.45–0.97]; p= 0.036). PSA responses to second-line therapy were seen in 26 (36%) of 73 patients for enzalutamide and three (4%) of 75 for abiraterone (χ^2 p<0.0001).[4] As such, enzalutamide showed activity as a second-line novel androgen receptor pathway inhibitor, whereas abiraterone acetate did not, leading to a longer time to second PSA progression for the sequence of abiraterone followed by enzalutamide than with the opposite treatment sequence. Therefore, these data suggest that using a sequencing strategy of abiraterone acetate followed by enzalutamide might provide the greatest clinical benefit.

SECOND-LINE PEMBROLIZUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA: KEYNOTE-240

KEYNOTE-240 is a randomised, double-blind, placebo-controlled, phase III trial designed to confirm the efficacy and safety of pembrolizumab plus best supportive care (BSC) *versus* placebo plus BSC in 413 patients with previously treated advanced HCC. Patients who had received prior immunotherapy, including anti–PD-1, anti–PD-1 ligand (PD-L1), or anti–PD-L2 agents, or previous systemic therapy

for HCC in the advanced setting other than sorafenib were excluded.[5] The median OS was 13.9 months in the pembrolizumab group *vs.* 10.6 months with placebo (HR[95%CI]: 0.781[0.611-0.998; p= 0.0238). The median PFS was 3.0 months for pembrolizumab and 2.8 months for placebo (HR[95%CI]: 0.718[0.570-0.904]; p= 0.0022) Results for OS and PFS were generally consistent in all subgroups. Although OS and PFS improved compared with placebo, they did not meet the prespecified boundaries of p= 0.0174 for OS (final analysis) and p= 0.002 for PFS (at the first interim analysis). The ORR was 18.3% for pembrolizumab and 4.4% for placebo in this final analysis.[5]

As such, KEYNOTE-240 did not meet its prespecified statistical dual endpoints of improving PFS and OS with pembrolizumab in the second-line treatment of advanced HCC. Nevertheless, the improvements in OS, PFS, ORR, and DOR with pembrolizumab in this randomised phase III study are consistent with those of KEYNOTE-224, supporting a favourable risk-to-benefit ratio for pembrolizumab in this population.

SUPERIOR OVERALL SURVIVAL WITH FIRST-LINE OSIMERTINIB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

The first issue of the New England Journal Of Medicine in 2020 featured the OS results of the pivotal phase III FLAURA trial.[6] In FLAURA, 556 patients with previously untreated advanced non-small cell lung cancer (NSCLC) with an *EGFR* mutation (exon 19 deletion or L858R allele) were randomised to receive either osimertinib (80 mg once daily) or one of two other EGFR-TKIs (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily, with patients receiving these drugs combined in a single comparator group). The median OS (secondary endpoint in this trial) was reported at 38.6 months with osimertinib, which was 7 months longer than the 31.8 months median OS seen with the comparator TKI (HR[95%CI]: 0.80[0.64-1.00]; p= 0.046). At one year, this difference translated into a 19% difference in OS rate (28% *vs.* 9%). AEs of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group, despite a longer duration of exposure in the osimertinib group. As such, these findings further support osimertinib as the standard of care first-line treatment for patients with advanced NSCLC.[6]

RAMUCIRUMAB PLUS ERLOTINIB AS FIRST-LINE TREATMENT FOR *EGFR*-MUTATED ADVANCED NSCLC

Preclinical data suggest that the combination of vascular endothelial growth factor receptor (VEGFR) inhibitors with EGFR tyrosine kinase inhibitors could result in longer duration of responses. However, early trials combining erlotinib with the VEGFR inhibitor bevacizumab failed to reveal significant improvements in OS (despite other evidence of increased efficacy). The phase III RELAY trial evaluated the combination of erlotinib and ramucirumab *vs.* erlotinib alone in 449 patients with stage IV NSCLC, with an *EGFR* exon 19 deletion (ex19del) or exon 21 substitution (Leu858Arg) mutation (ECOG PS: 0-1, no central nervous system metastases). The median PFS proved to be longer for the combination arm than with erlotinib alone (19.4 *vs.* 12.4 months; HR[95%CI]: 0.59[0.46-0.76]; p< 0.0001). Grade 3/4 TEAEs were reported in 72% patients in the ramucirumab plus erlotinib group as compared to 54% in the placebo plus erlotinib group. The most common grade 3/4 TEAEs in the combination arm were hypertension (24%; grade 3 only) and dermatitis acneiform (15%).[7]

Based on these results, the authors conclude that the RELAY regimen could provide a viable alternative for osimertinib in the first-line treatment of *EGFR*-mutated NSCLC. However, whether the ramucirumab-erlotinib combination also provides an OS benefit (as was the case for osimertinib) remains to be seen. In addition to this, also the toxicity profile of this combination will have to be balanced to that of osimertinib.

PROMISING DATA WITH LORLATINIB IN PATIENTS WITH *ROS1*-MUTATED ADVANCED NSCLC

Lorlatinib is a potent, brain-penetrant, third-generation tyrosine kinase inhibitor (TKI) that targets *ALK* and *ROS*. In the most recent issue of the Lancet oncology, results were published of a phase I/II study evaluating lorlatinib in patients with advanced NSCLC. The study included a total of 364 patients, of whom 69 were found to be *ROS1* mutated (21 TKI naïve, 40 previously treated with crizotinib only, 8 received one non-crizotinib ROS1 TKI or two or more ROS1 TKIs). Among TKI naïve patients, an overall response rate (ORR) of 62% was reported, while patients who previously received crizotinib as their only TKI had an ORR of 35%. Intracranial responses were achieved in seven of 11 (64%) TKI-naïve patients and 12 of 24 (50%) previous crizotinib-only patients. The most common grade 3/4 TRAEs were hypertriglyceridemia (19%) and hypercholesterolemia (14%). Serious treatment-related adverse events occurred in five (7%) of 69 patients.[8]

The authors conclude that lorlatinib shows clinical activity in patients with advanced *ROS1*-positive NSCLC, including those with CNS metastases and those previously treated with crizotinib. The latter is of particular importance given the fact that crizotinib-refractory patients have very few treatment options.

HELICOBACTER PYLORI TREATMENT IN FAMILIAL GASTRIC CANCER

Helicobacter pylori infection and a family history of gastric cancer are the main risk factors for gastric cancer. In a study reported in the New England Journal of Medicine, *Choi et al.* evaluated the effect of eradicating *H. pylori* on the incidence of gastric cancer in persons with a family history of gastric cancer in first-degree relatives. The study at hand randomly assigned 1,838 first-degree relatives of patients with gastric cancer and a *H. pylori* infection to receive either eradication therapy (lansoprazole [30 mg], amoxicillin [1000 mg], and clarithromycin [500 mg], each taken twice daily for 7 days) or placebo. During a median follow-up of 9.2 years, gastric cancer developed in 10 participants (1.2%) in the treatment group and in 23 (2.7%) in the placebo group, corresponding to a 55% risk reduction (HR[95%CI]: 0.45[0.21- 0.94]; p= 0.03). Among the 10 participants in the treatment group in whom gastric cancer developed, 5 (50.0%) had persistent *H. pylori* infection. Gastric cancer developed in 0.8% of participants (5 of 608) in whom *H. pylori* infection was eradicated and in 2.9% of participants (28 of 979) who had persistent infection (HR[95%CI]: 0.27[0.10-0.70]).[9]

In brief: among persons with a *H. pylori* infection who had a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduces the risk of gastric cancer.

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