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# PARP inhibitors as maintenance treatment for pancreatic cancer patients with germline *BRCA* mutations

Advancements in the treatment of pancreatic cancer during the last two decades have been limited mostly to the introduction of active, multi-drug chemotherapy regimens (such as FOLFIRINOX) or technologies aimed at improving the distribution of classic cytotoxic drugs (e.g. nab-paclitaxel). The introduction of novel approaches that have revolutionised systemic treatment in several types of solid tumours — targeted therapies and immunotherapy — have failed in the field of pancreatic cancer. Results of a single positive trial that evaluated the combination of gemcitabine and erlotinib, a targeted agent aimed at EGFR inhibition, are insignificant from clinical point of view because the improvement in overall survival was less than minimal. Immunotherapy, including both monotherapy and combinations of check-point inhibitors, lack the activity seen in other types of cancer. This is probably mostly due to the specific microenvironment of pancreatic cancer with abundant extra-cellular stroma that create a physical barrier impeding infiltration of immune cells. As a result, the modern treatment of pancreatic cancer still relies on classic cytotoxic drugs, mostly multidrug regimens. Without known predictive factors, we still cannot predict an optimal chemotherapy regimen for a specific patient. The decision between FOLFIRINOX and a combination of gemcitabine with nab-paclitaxel, the two most commonly used regimens in the first-line treatment, depends mostly on the experience of the physician and on local standards. Some retrospective analyses suggest additional benefit from platinum agents in patients with known germline mutations in *BRCA*-family genes. This is based on a deficiency in the homologous recombination repair (HRR) mechanism that is present in cells with *BRCA* mutations, leading to the impairment of the double-strain DNA break repair. Removal of DNA double-strain breaks, created by platinum agents mostly through binding purine bases, requires an efficient HRR mechanism. Combination of inadequate activity of HRR and the presence of platinum compounds may generate a critical amount of DNA damage that induces cell death through apoptosis or necrosis. An analogous effect in generating numerous double-strain DNA breaks in cancer cells with non-functional HRR can be achieved with PARP inhibitors. Blocking PARP protein, responsible for the repair of spontaneous single-strain DNA breaks, allows transformation of single-strain breaks into double-strain breaks when the cell enters its replication phase. Germinal mutations in *BRCA* genes are present in 7–10% of patients with pancreatic cancer, in many cases without familial history of *BRCA*-related cancers. Transferring the results of randomised clinical trials from the general population to patients with germinal *BRCA* mutations, we can assume that the optimal first-line chemotherapy regimen containing platinum agent is FOLFIRINOX. In the classic study published by Conroy in 2011 [1] treatment with FOLFIRINOX lasted at least six months in the absence of earlier disease progression. In clinical practice, achieving a full six months of intensive chemotherapy is difficult and often impossible due to cumulative toxicity. One of the possible solutions is the concept of induction and maintenance chemotherapy, which consists of a short, intensive period of FOLFIRINOX (preferably less than six months) with prompt de-escalation to a less intensive maintenance treatment. This approach was evaluated in the phase II PANOPTIMOX trial [2], which compared full six-month FOLFIRINOX and shortened four-month FOLFIRINOX with LV5FU2 maintenance until disease progression. The results show equivalence of the de-escalation strategy compared to the classic schedule, which is essential for patients poorly tolerating FOLFIRINOX. Unfortunately, despite improved tolerance, the de-escalation strategy failed to improve long-term outcomes, including progression-free survival and overall survival. The search for alternative maintenance strategies inspired the idea of using PARP inhibitors in pancreatic cancer patients with germline mutations in *BRCA* genes. This is based on the molecular mechanisms that provide pre-clinical evidence for the idea and the confirmed activity of PARP inhibitors as a salvage treatment in this population. The achieved results are both a breakthrough, because they provide proof that targeted agents offer significant activity in the treatment of pancreatic cancer, and a disappointment, because no effect on overall survival was seen.


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The presented results were published on 2nd July 2019 in "The New England Journal of Medicine" by Golan et al. [3]. The POLO study was a randomised, double-blinded, phase 3 trial that compared maintenance olaparib (300 mg orally twice daily) with placebo in patients with metastatic pancreatic cancer with known germline mutation in *BRCA1* or *BRCA2* genes, who received at least four months of platinum-based first-line treatment without progression. Recruited patients were randomised in a 3:2 ratio to olaparib or placebo. No cross-over after progression was allowed. The primary endpoint was progression-free survival (PFS), with overall survival (OS) as one of the secondary endpoints. Among 3315 patients screened for eligibility, 247 (7.5%) had *BRCA* mutations, and only 154 patients (4.6% of all screened patients) underwent randomisation. Most of the patients (86% in the olaparib arm and 81% in the placebo arm) received FOLFIRINOX as the first-line treatment. The study met the primary endpoint with median PFS of 7.4 months in patients receiving olaparib as compared to 3.8 months in patients receiving placebo (hazard ratio [HR] for progression or death 0.53; 95% confidence interval [CI] 0.35–0.82; p = 0.004). The achieved result remained significant in all analysed subgroups and was independent of the type of mutation (*BRCA1 vs. BRCA2*). Available results in term of OS are immature (46% of events), but an interim analysis showed no statistically significant difference between both arms (with median OS 18.9 months in the olaparib arm *vs.* 18.1 months in the placebo arm; HR 0.91; 95% CI 0.56–1.46; p = 0.68). In the placebo arm, 14.5% of patients received PARP inhibitor after progression. The response rate was 20% among patients receiving olaparib and 10% among patients receiving placebo, with a median duration of response of, respectively, 24.9 months and 3.7 months. Adverse events grade 3 or higher were seen in 40% of patients in the olaparib arm and in 23% of patients in the placebo arm, with serious adverse events seen in, respectively, 24% and 15% of patients. The most common adverse events in the olaparib group were anaemia and fatigue. Patients receiving olaparib required treatment with interruptions or dose reductions due to adverse events. The rate of patients who discontinued the treatment due to toxicity was 5% in the olaparib arm and 2% in the placebo arm. No treatment-related deaths were seen in either arm. Quality of life analysis showed no significant difference between the olaparib and placebo arm.

The results of the POLO study bring important changes to a certain sub-population of patients with pancreatic cancer. The application of olaparib as a maintenance treatment for patients with known *BRCA* mutations nearly doubled the progression-free survival. This validates PARP inhibitors as an interesting treatment option, justifying evaluation of *BRCA1*/*BRCA2* in all patients with pancreatic cancer as a standard. Additionally, results of the POLO study are the first to show clinically significant improvement with targeted therapies in patients with pancreatic cancer. Unfortunately, several aspects of the study limit its popularity. Firstly, the proportion of patients who qualified for the treatment was more than limited — only 4.5% of all screened patients. Secondly, despite the significant improvement in PFS, we currently cannot confirm that olaparib improves the most important endpoint in oncology — overall survival. Thirdly, treatment with olaparib was associated with a significantly higher rate of at least grade 3 adverse events and serious adverse events, albeit without a negative effect on the quality of life. Nevertheless, the POLO study is one of the most important trials dedicated to patients with metastatic pancreatic cancer in recent years, proving the potential of targeted therapies guided by a proper biomarker. We can expect further trials aimed at expanding the role of PARP inhibitors in the treatment of patients with pancreatic cancer, searching for biomarkers other than *BRCA* germline mutations.

## When less is more — optimising systemic treatment for elderly and/or frail patients with gastroesophageal cancers

One of the most fascinating aspects of the annual American Society of Clinical Oncology Congress is the fact that some studies presented only as abstracts often influence clinical practice without the publication of full results. While many presented trials are dedicated to narrow and limited subgroups without greater impact on daily clinical practice, some results affect wide groups of patients and provide evidence to revise daily clinical decisions, especially when dedicated to less systematised areas of modern oncology. One such challenge, with growing significance as the populations of Western countries age, is providing care for elderly and/or frail cancer patients. Frailty syndrome is defined as a state of limited functional reserve, mostly due to a decreased capacity of more than one organ system, which impairs adaptation to stressogenic situations (from physical and psychical perspectives). Despite the fact that frailty syndrome and older age often co-exist, even separately they are demanding and difficult to assess because some elderly patients have sufficient functional reserve and some younger patients are extremely vulnerable due to frailty syndrome. As both elderly and frail patients are

underrepresented in clinical trials, it is important to notice results of trials dedicated solely to this population.

One such study, the phase 3 GO2 trial, was given as an oral presentation and abstract at the 2019 Congress of American Society of Clinical Oncology by Hall et al. [4]. It was a randomised, phase 3 trial that compared different variants of doses of CAPOX in patients with gastroesophageal cancer, who were ineligible to the EOX regimen due to age and/or frailty syndrome. Comparison included three different variants of doses of CAPOX: level A — with oxaliplatin 130 mg/m$^2$ on day 1 and capecitabine 625 mg/m$^2$ on days 1–21 of every 21-day cycle; level B — with 80% of doses from level A; and level C — with 60% of doses from level A. The primary endpoint was a comparison of PFS, with OS as one of secondary endpoints. Additionally, the trial included evaluation of composite endpoint (called Overall Treatment Utility; OTU), which included treatment benefit evaluated by a physician, tolerability of treatment, quality of life, and assessment of treatment by the patient. The trial included 514 patients, randomised in a 1:1:1 ratio to all three treatment arms. Median age was 76 years in arm A and arm B and 77 years in arm C. In each arm about 1/3 of patients had performance status (ECOG) 2 or worse, and nearly 80% of patients in each arm had frailty syndrome. Median PFS was 4.9 months in arm A, 4.1 months in arm B and 4.3 months in arm C, which met a prespecified non-inferiority margin for comparison of arm B to arm A (HR 1.09; 95% CI 0.89–1.32) and for comparison of arm C to arm A (HR 1.10; 95% CI 0.90–1.33). Median OS was 7.5 months in arm A, 6.7 months in arm B, and 7.6 months in arm C. In arm C, lower rate of non-haematological adverse events grade 3 or higher was noted (37% in arm C compared to 56% in arm A) as well as better results in terms of combined endpoint OTU. No subgroup benefited from higher doses of chemotherapy.

Results of the GO2 study provide valuable insights into clinical management of elderly and/or frail patients with gastroesophageal cancers. In this group, lower doses of chemotherapy were associated with a reduced rate of adverse events and maintained activity with PFS and OS comparable to standard dosing. Additionally, probably due to the lower rate of non-haematological adverse events, the lowest doses of chemotherapy achieved the best results in a combined endpoint that evaluated, among others, quality of life. Implementation of these results into daily practice may be challenging, especially in health care systems with limited financing, such as in Poland, due to difficulties with evaluation of frailty syndrome. Proper evaluation of frail patients, especially when frailty coexists with older age and other comorbidities, requires competences not common among oncologists and additional time, a resource that is scarce for most practicing oncologists in Poland. Nevertheless, even including the aforementioned difficulties, the improvement of quality of life obtained with decreased intensity of chemotherapy highly valuable and is extremely important in more vulnerable populations, including elderly and frail patients.

## Molecular subgroups of low-grade gliomas and effectiveness of PCV chemotherapy — a new predictive factor?

Treatment of primary central nervous system tumours in one of the most demanding fields in oncology. Proper diagnostics, surgical treatment, radiotherapy, and possible systemic treatment not only significantly impacts overall survival, but also defines quality of life. This includes glioblastoma multiforme, a disease characterised by uniquely unfavourable prognosis, which usually requires multimodality treatment, as well as low-grade gliomas in which maintenance of functional capabilities and quality of life is nearly as important as improvement in overall survival. From this perspective, personalisation of treatment and adjustment of intensity according to treatment aims is more than crucial. For low-grade (G2) gliomas with unfavourable prognostic factors — age over 40 years and age under 40 years with subtotal tumour resection, since 2016 and publication of NRG Oncology/RTOG 9802 trial results, standard postoperative treatment consists of radiotherapy and subsequent 48-week PCV (procarbazine, lomustine, vincristine) chemotherapy [5]. The addition of PCV chemotherapy to standard radiotherapy prolonged median OS by nearly six years, increasing rate of 10-year PFS from 21% to 51%. Still, the chemotherapy is intensive, long, and associated with high risk of adverse events, mostly haematological. New analysis of data from the NRG Oncology/RTOG 9802 study, which assessed the newest molecular subgroups of low-grade gliomas, gives the opportunity for further optimisation of treatment in this group of patients.

The report was presented at an oral session and as an abstract on 2019 Congress of American Society of Clinical Oncology by Bell et al. [6]. The analysis included 106 (46%) of 251 patients with grade 2 gliomas, who participated in the NRG Oncology/RTOG 9802 study and who had tumour sample sufficient to evaluated state of IDH1/2 mutation and 1p/19q co-deletion. Mutations

in IDH were present in 75% of analysed patients, with 41% of patients having IDH mutations without 1p/19q co-deletion and 35% of patients having both IDH mutation and 1p/19q co-deletion. In a single-factor analysis no benefit from PCV chemotherapy was seen in patients without IDH mutation, and strong benefit from PCV chemotherapy was seen in patients with IDH mutation without simultaneous co-deletion (HR for PFS 0.32; $p = 0.003$; HR for OS 0.38; $p = 0.013$) as well as in patients with IDH mutation and 1p/19q co-deletion (HR for PFS 0.13; $p < 0.001$; HR for OS 0.21; $p = 0.029$).

Despite the fact that the analysis is post-hoc and include only a limited population, it seems that the role of IDH as a predictive factor for benefit from postoperative PCV chemotherapy in grade 2 gliomas with unfavourable risk factor is strong and promising. Evaluation of IDH mutation, included currently in the standard WHO classification of gliomas, can be a good argument in the discussion with patients in favour of chemotherapy. Implementation of IDH evaluation provides a very rare opportunity for personalised treatment within the current standard of care.

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