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# Maintenance therapies in metastatic pancreatic cancer: present and future with a focus on PARP inhibitors

Pascal Hammel, Carole Vitellius, Émeric Boisteau, Mathilde Wisniewski, Elise Colle, Marc Hilmi, Christelle Dengremont, Sandra Granier, Anthony Turpin , Louis de Mestier and Cindy Neuzillet

**Abstract:** Metastatic pancreatic ductal adenocarcinomas (PDACs) are now more effectively controlled using chemotherapy combinations such as FOLFIRINOX and gemcitabine plus nab-paclitaxel (NabP) regimens with a subset of patients who achieve a sustained tumor stabilization or response. The next challenge is to design maintenance therapies that result in continued tumor control with minimal toxicity. Quality of life should always be a priority in these patients with prolonged survival. Gradually tapering off the intensity of chemotherapy by suppressing drug(s) in the combination is one option. Thus, maintenance with 5-fluorouracil or gemcitabine as single agents after FOLFIRINOX or gemcitabine-NabP induction, respectively, seems to be a promising approach to minimize neurotoxicity while maintaining efficacy. Another option is to introduce maintenance drug(s) with different anti-tumoral actions. The recent example of olaparib in patients with BRCA mutated PDAC provides a promising proof-of-concept of a switch maintenance strategy in this setting.

**Keywords:** chemotherapy, FOLFIRINOX, gemcitabine, maintenance, nab-paclitaxel, olaparib, pancreatic cancer, PARP, quality of life, toxicity

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) will become the second cause of cancer mortality in developed countries in the next few years.<sup>1,2</sup> Gemcitabine was the first available drug with modest efficacy in advanced PDAC.<sup>3</sup> After almost 15 years of failure to improve efficacy by combining this agent with other drugs, significant breakthroughs were made between 2011 and 2013 using more efficient but also more toxic chemotherapy regimens. Combinations of 5-fluorouracil (5-FU) and folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX), and then gemcitabine (Gem) plus nab-paclitaxel (NabP) were found to be superior to gemcitabine in large phase III randomized trials.<sup>4,5</sup> Cisplatin–gemcitabine–capecitabine–epirubin/docetaxel regimens (PEG, PEGF4, PEXG20, PAXG) were also developed by Reni *et al.*<sup>6–8</sup> Since these results were published, a significant subset of patients with

metastatic PDAC have achieved tumor control of more than 6 months, resulting in a paradigm shift. Indeed, the race to administer treatment lines with limited and short-term efficacy (i.e. gemcitabine or 5FU/platinum based) is no longer the ultimate goal. Instead the previously unimaginable objective of obtaining relief from chemotherapy and limiting therapeutic toxicity while still maintaining both tumor control and patient quality of life (QoL) has now become a focus of research (Figure 1).

## Concept of maintenance in PDAC with cytotoxic agents

Maintenance strategies had been developed in patients with tumors that are more chemosensitive than PDAC, such as in colorectal or lung cancers. These results have shown that continuing uninterrupted full-dose chemotherapy until progression

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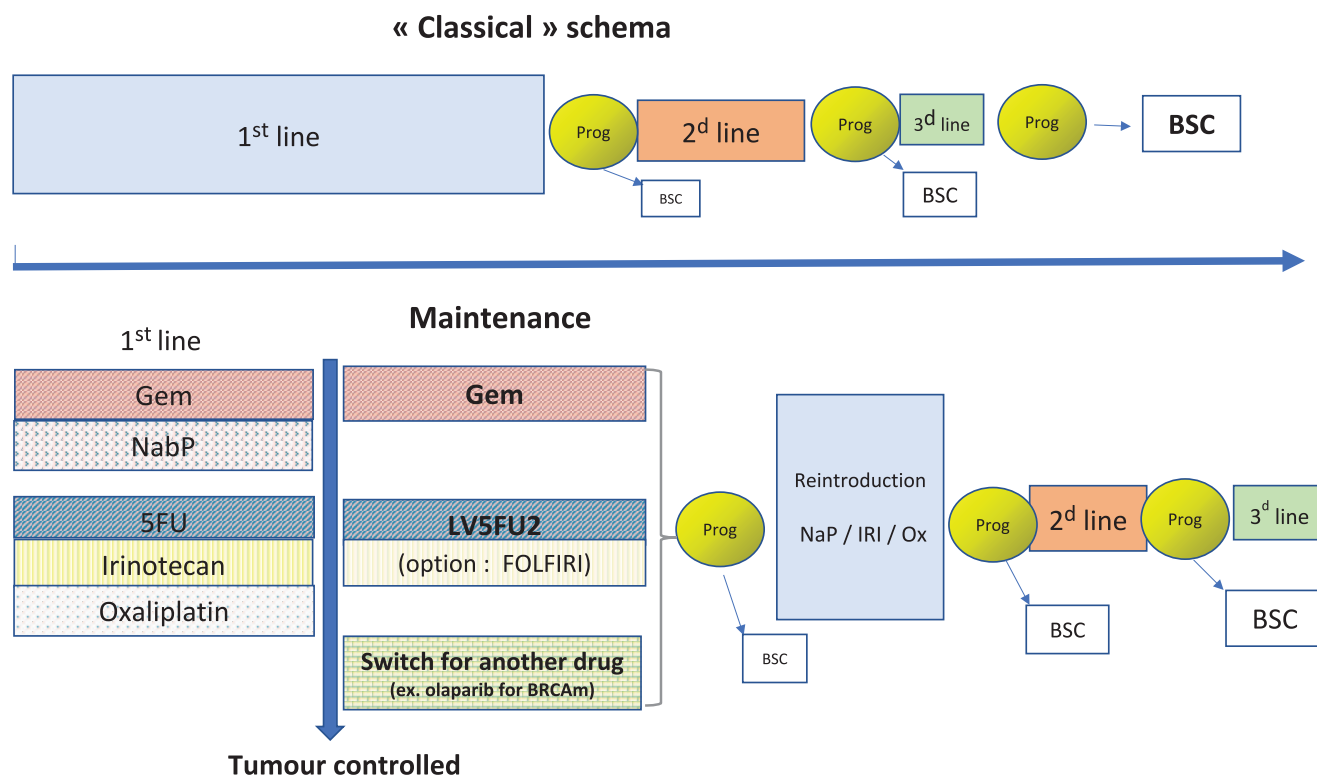
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**Figure 1.** Concept of maintenance therapy compared with the usual schemas of chemotherapy in metastatic pancreatic ductal adenocarcinoma (PDAC): after sustained tumor control has been obtained, lightened chemotherapy is continued while the neurotoxic drug [nab-paclitaxel (NabP) or oxaliplatin] is stopped, or another drug is proposed (e.g. olaparib for patients with gBRCAm). At progression, reintroduction of first-line drugs can be proposed depending on the patient's general status and remaining neurotoxicity.

Prog, tumor progression; BSC, best supportive care.

often leads to cumulative toxicity but not additional efficacy compared with therapeutic breaks or de-escalated chemotherapy regimens.<sup>9,10</sup> Two options have been explored in advanced PDAC, including reducing the number of chemotherapy drug(s) when sustained tumor control is achieved or introducing another drug(s) with different mechanisms of action, including targeted therapies, also known as “switch maintenance.”

Table 1 summarizes the studies on maintenance in PDAC patients.

#### *Maintenance after FOLFIRINOX induction: results of the PANOPTIMOX study*

The first option was tested following induction chemotherapy with FOLFIRINOX and Gem-NabP combinations, which were established as first-line standards. Median progression-free survival (PFS) in the pivotal study with FOLFIRINOX (PRODIGE4/ACCORD 11) was 6.4 months.<sup>4</sup> This duration of oxaliplatin treatment is associated

with a high risk of permanent cumulative sensitive neuropathy, as observed in colorectal cancer. Indeed, grade 3 or higher neuropathy was reported in 17% of patients.<sup>4</sup> A similar rate of neuropathy was also observed with NabP (17%) in the study by von Hoff *et al.*<sup>5</sup>

Oxaliplatin neurotoxicity including cold-induced paresthesia or dysesthesia of the distal extremities usually resolves within a week following the first cycles (grade 1).<sup>18</sup> Chronic neuropathy develops with cumulative doses >540–600 mg/m<sup>2</sup>.<sup>19</sup> In the treatment of PDAC with FOLFIRINOX, this represents about six cycles/3 months of oxaliplatin at the recommended dosage of 85 mg/m<sup>2</sup>. Otherwise, neuropathy often limits taxanes' administration after 5–6 months of therapy (cumulative doses >1400 mg/m<sup>2</sup> with paclitaxel).<sup>20</sup>

Retrospective series have reported a median PFS (including reintroduction of induction chemotherapy) and overall survival (OS) of 10–14 months and 17–18 months, respectively, with

**Table 1.** Main publications of maintenance therapies in patients with PDAC.

Study	Study type	Maintenance treatment Induction chemotherapy	Population ( <i>n</i> patients)	Results
Reure <i>et al.</i> <sup>11</sup>	Retrospective	Capecitabine After 4–8 cycles of FOLFIRINOX	30	OS: 17 months. Survival rates: 73% at 1 year (95% CI 0.59–0.91) and 25% at 2 years (95% CI 0.13–0.50). PFS1: 5 months–PFS2: 10 months
Dahan <i>et al.</i> <sup>12</sup>	Phase II PANOPTIMOX	FOLFIRINOX continuous (A) <i>versus</i> LV5FU2 maintenance (B) <i>versus</i> Gem- irinotecan (C) After FOLFIRINOX	273	6-month PFS: 47% (A), 44% (B), 34% (C)—4-months RR: 35% (A), 41% (B), 17% (C) PFS: 6.3 months (A), 5.7 months (B), 4.5 months (C) OS: 10.1 months (A), 11.2 months (B), 7.3 months (C) Duration maintenance (B): 3.3 months (0.003–22.6)
Reni <i>et al.</i> <sup>13</sup>	Phase II PACT 12	Observation (A) <i>versus</i> sunitinib (B) 37,5mg/day After various chemotherapies combination (mainly Gem/platinum based)	56	A <i>versus</i> B: 6-month PFS: 3.6% (95% CI 0–10.6%) <i>versus</i> 22.2% (95% CI 6.2–38.2%; <i>p</i> < 0.01); 2 years OS: 7.1% (95% CI 0–16.8%) <i>versus</i> 22.9% (95% CI 5.8–40.0%; <i>p</i> = 0.11), Stable disease: 21.4% <i>versus</i> 51.9% ( <i>p</i> = 0.02).
Petrioli <i>et al.</i> <sup>14</sup>	Observational	Gem After three cycles of Gem-NabP	37 (>70years)	6-month DCR: 61% (95% CI 45–77) PFS: 6.4 months (95% CI 5.4–8.3) OS: 13.4 months (95% CI 11.1–16.7).
Relias <i>et al.</i> <sup>15</sup>	Retrospective OPTINAB	Gem After Gem-NabP when neuropathy occurred	27	Gem maintenance in seven patients with grade 3 neuropathy (median delay: 4.2 months) Mean duration maintenance: 2.8 months. Reintroduction NabP in 6/7 patients. PFS2: 2.2 months (range 1–4 months). DDR: 8,2 months (8–13) and 9.4 months with reintroduction of NabP OS: 11.7 months
Zhang <i>et al.</i> <sup>16</sup>	Phase II	S1 After six cycles of NabP plus S1	32	ORR (primary objective): 53.1% Disease control rate: 87.5% PFS: 6.2 months OS: 13.6 months
Golan <i>et al.</i> <sup>17</sup>	Phase III	Olaparib <i>versus</i> placebo After platinum-based chemotherapy	154 (gBRCA1/2 mutation)	PFS: 7.4 months <i>versus</i> 3.8 months (HR 0.53; 95% CI 0.35–0.82; <i>p</i> = 0.004—OS: 18.9 months <i>versus</i> 18.1 months (HR 0.91; 95% CI 0.56–1.46; <i>p</i> = 0.68 Anemia (11%), fatigue (5%), decrease appetite (3%), abdominal pain (2%), vomiting (1%), arthralgia (1%) (with olaparib)

DCR, disease control rate; DDR, duration of disease control; Gem, gemcitabine; NabP, nab-paclitaxel; ORR, objective response rate; OS, overall survival.

oxaliplatin/irinotecan stop-and-go strategies after FOLFIRINOX induction chemotherapies in advanced PDAC.<sup>11</sup> The prospective phase II PRODIGE 35-PANOPTIMOX trial by Dahan *et al.*<sup>12</sup> has assessed three arms: (i) 12 cycles of FOLFIRINOX full-dose (arm A); (ii) 8 cycles of FOLFIRINOX and then maintenance using 5-FU plus leucovorin (LV5FU2) (arm B) with

FOLFIRINOX reintroduction at progression; and (iii) a sequential strategy alternating Gem and the 5-FU–irinotecan combination (FOLFIRI-3) (FIRGEM) (arm C). With the 6-month PFS rate as the main objective of the study, similar results were obtained in arms A and B (47% and 44%, respectively), with only 34% in arm C. Median OS was also not impaired with

maintenance therapy: 10.1 months and 11.2 months in arms A and B, respectively, and 7.3 months in arm C. It is important to note that the severe neurotoxicity rate was higher in the maintenance arm (B) probably because of a higher cumulative oxaliplatin dose following reintroduction in this study arm.<sup>12</sup> Indeed, the severe neurotoxicity rate was similar in the two groups with 6-month chemotherapy regimens. The difference was found after this period with more neurotoxicity in arm B than in arm A.<sup>12</sup> Although this was a non-comparative study, these results provide the first prospective evidence of continuation maintenance therapy with LV5FU2 in metastatic PDAC after FOLFIRINOX induction therapy. The full paper, including analysis of QoL and predictive factors of maintenance efficacy is pending. Some clinicians favor a pragmatic approach, with slower tapering of FOLFIRINOX doses, including a step using FOLFIRI for a few cycles before administering LV5FU2. However, more robust evidence of this FOLFIRI maintenance step is needed.

#### *Maintenance in PDAC using targeted agents with angiogenesis inhibitors*

In the prospective phase II study PACT-12 by Reni *et al.*<sup>13</sup> the authors tested the Folkman's induced dormancy theory, that is hypothesizing that blocking angiogenesis would prevent tumor progression and maintain stable disease. The biological rationale of this approach is that tumor cell proliferation is balanced by a high rate of apoptosis when angiogenesis is blocked. In this trial, 56 patients with controlled metastatic PDAC after 6 months of chemotherapy were randomized into observation or 37.5 mg of sunitinib daily continuously until progression. As reported previously, sunitinib toxicities included thrombocytopenia (12%), neutropenia (12%), hand-foot syndrome (12%) and diarrhea (8%). PFS at 6 months was 3.6% versus 22.2%, ( $p < 0.01$ ), 2-year OS was 7.1% versus 22.9% ( $p = 0.11$ ), and disease control was 21.4% versus 51.9% ( $p = 0.02$ ) in the observation and sunitinib arms, respectively. This study confirmed that targeting the VEGFR pathway, whose relevance has been shown to be limited in bulky and rapidly growing disease, could be valuable in maintaining tumor control once tumor growth has been slowed and optimal cytoreduction has been obtained.

#### *Maintenance after Gem-NabP induction*

A prospective observational study with Gem-NabP by Petrioli *et al.*<sup>14</sup> treated 36 older patients

in good condition (PS 0–1), median age 77 years old (71–86), with metastatic (78%) or locally advanced (22%) PDAC. Three cycles of Gem-NabP<sup>5</sup> were administered with a dose reduction in vulnerable patients or patients older than 80. Patients without progressive disease then received gemcitabine single agent 1000 mg/m<sup>2</sup> weekly for 3 or 4 weeks as maintenance therapy until disease progression or unacceptable toxicity. After induction treatment with Gem-NabP, a partial response, stable disease, or progressive disease was observed in 18 (50%), 13 (36%), and 5 patients (14%), respectively. Overall, 31 patients (86%) received a median of 3 (2–9) cycles of gemcitabine maintenance therapy. The 6-month disease control rate (main objective of study) was 61% (95% CI 45–77). Median PFS was 6.4 months and median OS was 13.4 months. These results were comparable with those of the pivotal trial (6.7 months and 8.5 months, respectively). During the maintenance period, grade 3 hematological toxicity only occurred in six patients (19%). Grade 2 neuropathy, which affected 17% of patients during Gem-NabP induction did not worsen during gemcitabine maintenance.

In a retrospective study by Relias *et al.*<sup>15</sup> a “stop-and-go” strategy (OPTINAB) included the reintroduction of NabP after neurotoxicity had resolved. NabP was suspended if grade 3 neuropathy occurred and then only reintroduced if biochemical or imaging progression developed. In this series of 27 treated patients, 7 (25%) developed a grade 3 peripheral neuropathy after a mean 4.2 months (2–4) and gemcitabine alone was continued for a mean 2.8 months. Neuropathy improved and regressed to grade 1 or less after 29 days. After NabP was reintroduced at tumor progression, tolerance was acceptable in all patients except one in whom neuropathy rapidly worsened and NabP was stopped. These six patients continued NabP with a mean second PFS of 2.2 months (1–4). Disease control in this sub-group of patients lasted a mean 9.4 months and average OS was 11.7 months.

Zhang *et al.*<sup>16</sup> tested a first-line treatment of advanced PDAC with a NabP and S-1 combination followed by S-1 maintenance therapy. In this phase II study, 120 mg/m<sup>2</sup> of NabP was administered on days 1 and 8, and 80–120 mg/day of S-1 depending on body surface area, twice a day on days 1–14 every 3 weeks. Patients with controlled tumors (stable disease + partial or complete response) after six cycles then received the same schedule of S-1 maintenance therapy until disease



progression or unacceptable toxicity. The objective response rate (primary objective) in the intention-to-treat population of 32 patients was 53.1%, and the disease control rate was 87.5%. Median PFS and OS were 6.2 months and 13.6 months, respectively. Toxicity was mainly hematologic (grade 3/4 neutropenia: 27.6%).

### Maintenance in PDAC with cytotoxic agents: lessons, next steps

Overall, the above-mentioned studies show that maintenance therapy by tapering of initially effective induction chemotherapy is feasible with acceptable toxicity. In addition, OS was not decreased with LV5FU2 maintenance following a limited period of FOLFIRINOX induction therapy compared with standard treatment,<sup>12</sup> or with Gem maintenance following limited Gem–NabP induction compared with pivotal trials.<sup>14,15</sup> Moreover, survival with S-1 maintenance therapy following S-1–NabP induction therapy was promising.<sup>16</sup> While these strategies could be directly applicable further comparisons of their efficacy, toxicity, and QoL are needed to those of standard treatment especially for NabP-based regimens. Another potential interest of early oxaliplatin or NabP interruption before reaching severe neurotoxicity is to allow reintroduction of these drugs when tumor progression occurs during maintenance therapy. However, the most appropriate strategy at progression remains to be defined: rechallenge or switch? Finally, biomarkers are needed to help determine the treatment strategy, possibly including those related to the type, duration, and extent of initial response.

More than 25% of patients with PDAC are old and/or frail thus not eligible for combination chemotherapies, and only Gem can be given.<sup>21,22</sup> A subset of these patients may achieve an appreciable and sustained tumor control with acceptable toxicity. Therapeutic breaks, or maintenance with reduced dosage of Gem or other drugs in the future may be envisaged. In these patients, supportive care remains of course a priority.

### Maintenance in PDAC with targeted agents: the example of PARP inhibitors

#### *BRCAness mutations in PDAC*

Targeting of biological abnormalities is needed to identify new maintenance therapies in PDAC patients. However, targeted therapies, alone or combined with gemcitabine, have failed to

improve clinical outcomes in patients with progressive PDAC. An unstable genotype with numerous structural variations is present in about 10–15% of PDAC.<sup>23,24</sup> This genomic instability co-segregates with inactivation of DNA maintenance genes (*BRCA1*, *BRCA2*, or *PALB2*) or a mutational signature of DNA damage repair deficiency. A germline mutation in *BRCA* genes (gBRCAm) is identifiable in about 5–7% patients with PDAC and somatic mutations in genes involved in DNA repair such as *BRCA2*, *BRCA1*, *PALB2*, *ATM*, and *RAD51* may also be identified. Recently, the prevalence of homologous recombination (HR) DNA damage repair deficiencies was re-evaluated, showing an enlarged spectrum of double-strand break (DSB) repair deficient genes called “BRCAness” signature genes, which affect up to 17.4% of PDAC.<sup>23–28</sup>

The presence of DSB repair or mismatch repair in these canonical HR genes leads to activation of CD8-positive T-cell lymphocytes or overexpression of regulatory molecules such as cytotoxic T-cell lymphocyte antigen 4 or programmed cell death 1, due to the high frequency of somatic mutations and the burden of tumor-specific neoantigens, at a lesser degree than microsatellite unstable tumors.<sup>23</sup> PARP repairs single-strand DNA breaks through the base excision repair pathway and PARPi act by catalytic inhibition of the PARP1 protein.<sup>29</sup> Single-strand DNA breaks remain when PARP function is altered, then irreparable DSB occur during replication in tumor cells lacking HR proteins, leading to cell death through synthetic lethality principle.<sup>27</sup>

#### *PDAC and germinal BRCA mutations: the example of olaparib*

The potential efficacy of olaparib as a single agent in patients with gBRCAm and PDAC, even with pre-treatment, was suggested by the results of a phase II trial by Kaufman *et al.*<sup>30</sup> The response rate, median PFS and OS were 21.7%, 4.6 months and 9.8 months, respectively. The efficacy of olaparib was prospectively assessed in the phase III POLO study. A total of 3315 patients with PDAC were screened in 10 countries in this study and 154 gBRCAm patients with controlled tumors after receiving platinum-based induction chemotherapy, mainly FOLFIRINOX, for  $\geq 16$  weeks (one third received  $>6$  months induction chemotherapy) were randomized: 92 to receive olaparib and 62, a placebo.<sup>17,31</sup> PFS, the primary endpoint of the study, was significantly longer in the

olaparib arm than in the placebo arm (median 7.4 months *versus* 3.8 months, respectively; HR 0.53; 95% CI 0.35–0.82;  $p=0.004$ ).<sup>17</sup> The rate of grade  $\geq 3$  adverse events, mainly anemia and fatigue, was 39.6% in the olaparib group and 23.3% in the placebo arm, and 5.5% and 1.7% of patients, respectively, discontinued treatment due to an adverse event. The QoL was not impaired in patients receiving olaparib compared with those with placebo, which is an important goal for any maintenance therapy.<sup>32</sup> Although there was no difference in OS between the olaparib and placebo arms in the first study by Golan *et al.*<sup>17</sup> those results were based on an interim analysis at 46% maturity and the role of the reintroduction of effective chemotherapies or even olaparib, even though cross-over was not allowed, may have biased the OS results. It is important to note that the median sustained response in the subgroup of 18 patients receiving olaparib (23.1%) who achieved a tumor response was significant (24 months *versus* 3.7 months in the placebo arm). In addition, the longer secondary PFS (median, 13.2 months *versus* 9.2 months, respectively; HR 0.76; 95% CI 0.46–1.23;  $p=0.26$ ) suggests that there was a sustained benefit with post-protocol chemotherapies following olaparib.<sup>17</sup>

#### *PDAC and BRCA mutation: other PARP inhibitors and remaining questions*

There are several steps needed to confirm the effectiveness of maintenance therapies. First, it must be determined whether patients with PDAC that harbor DNA damage response and repair germline mutations other than BRCA 1/2, or sporadic PDAC and somatic BRCA/BRACness mutations, are sensitive to PARPi. In addition, resistances to PARPi caused by primary or secondary mutations in the BRCA genes, in example by restoring the function of HR repair genes and those in the DNA-binding domains of PARP1 or by amplification of the mutation-carrying BRCA2 allele with increased RAD51 loading and PARPi resistance, must be better understood.<sup>33,34</sup> The characteristics of tumors in gBRCAm patients (~30%) with rapid progression under olaparib must also be better defined to propose the optimal therapeutic management. Moreover, studies are needed to determine whether olaparib and other PARPi should be used in settings other than metastatic PDAC (adjuvant treatment, etc.) and whether combining PARPi with other drugs, such as platinum salts or checkpoint inhibitors could improve tumor control considering the previously described

immunological characteristics of these tumors.<sup>33</sup> O'Reilly *et al.*<sup>35</sup> recently reported the results of a randomized phase II trial in 56 patients showing that the cisplatin–Gem combination was an effective regimen in patients with advanced PDAC (metastatic: 84%) with the germinal BRCA 1/2 (94%) or PALB2 (6%) mutations. However, concurrent administration of veliparib did not improve the response rate (74.1% *versus* 65.2%,  $p=0.55$ ) or the disease control rate, PFS, or OS (100% *versus* 78.2%,  $p=0.02$ ; 10.1 months *versus* 9.7 months,  $p=0.73$ ; 15.5 months *versus* 16.4 months,  $p=0.6$ , respectively). Nevertheless, no conclusion can be drawn on the potential efficacy of veliparib in a maintenance setting because the drug was administered as induction therapy without a previous selection for good PARPi candidates (platinum responders). Moreover, whether the efficacy of veliparib differs from other PARPis in that setting remains to be defined. On the other hand, rucaparib appears to be a promising maintenance therapy in platinum-sensitive PDAC patients with germline gBRCA/PALB2 mutations.<sup>36</sup>

At present, the patient population eligible for olaparib maintenance therapy is small due to the low rate of gBRCAm patients with metastatic PDAC who are fit to receive platinum-based chemotherapy and without tumor progression during this induction treatment. Moreover, access to rapid genetic screening is still an important issue.

#### **Future options for maintenance therapy, role of immunotherapy**

Other drugs being currently tested for maintenance therapy include nimotuzumab (anti-EGFR), fluzoparib (PARPi), pembrolizumab (anti-PD-1), paricalcitol (analog vitamin D), durvalumab (anti-PDL-1), vaccines (CV301, OSE-21), and nivolumab (anti-PD-1) (see Table 2).

The lack of efficacy of immunotherapies is mainly due to the low immunogenicity and non-inflamed phenotype of PDAC tumors. The abundant stroma generates a hypoxic microenvironment and drives the recruitment of immunosuppressive cells through cancer-associated fibroblast activation and transforming growth factor  $\beta$  secretion.<sup>37</sup> The aim of the therapeutic strategy is to combine checkpoint inhibitors with other drugs, such as vaccines, oncolytic viruses, MEK inhibitors, cytokine inhibitors, and hypoxia- and stroma-targeting agents to increase immunogenicity as well as to recruit and activate effector T cells.

**Table 2.** Active trials of maintenance therapy in metastatic pancreatic cancer.

Drug	Target	Induction chemo	Maintenance schema	Phase	ClinicalTrials.gov identifier
Nimotuzumab	EGFR	G + nimotuzumab + S1	Nimo + S1 <i>versus</i> placebo + S1	IV	NCT02945267
Fluzoparib	PARP1/2	FOLFIRINOX + Fluzoparib	Fluzoparib	Ib-II	NCT04228601
Pembrolizumab Paricalcitol	Anti-PD1 Analog of 1,25-dihydroxyergocalciferol		Pembrolizumab with paricalcitol or placebo	II	NCT03331562
Rucaparib	PARP (germline or somatic BRCA1/2 or PALB2 mutation)	Platinum-based chemo	Rucaparib	II	NCT03140670
Durvalumab CV301	PDL-1 CEA-MUC-1-TRICOM vaccine		MVA-BN-CV301 (prime) FPV-CV301 (boost) Durvalumab-capecitabine	I/II	NCT03376659
OSE-21 vaccine Nivolumab	Vaccine PD-1	FOLFIRINOX	OSE-21 vaccine alone or with nivolumab, or FOLFIRI	II	NCT03806309

Otherwise, neoadjuvant strategies can favorably remodel the PDAC microenvironment by depleting regulatory T- and myeloid-derived tumor cells and decreasing stroma activation.<sup>38</sup> In a series by Murakami *et al.*<sup>39</sup>, 84 patients with borderline/resectable PDAC received either neoadjuvant treatment with chemoradiotherapy before surgical resection or frontline resection. Analysis of resected specimens showed that the damage-induced molecular patterns of neoadjuvant treatment could favorably influence PDAC immunomodulation.

Two prospective trials are ongoing in France to test various maintenance strategies in metastatic PDAC.<sup>40</sup> The TEDOPaM-PRODIGE 63 phase II study is evaluating maintenance therapy in patients with locally advanced or metastatic PDAC that has been controlled with eight cycles of FOLFIRINOX, using a polyantigenic HLA2-restricted vaccine OSE2101, alone or combined with nivolumab, with the reintroduction of FOLFIRI at progression, *versus* the continuation of FOLFIRI (Table 2). The MAZEPPA randomized phase II study is evaluating maintenance therapy with olaparib or selumetinib (MEK 1/2 inhibitor) plus durvalumab (anti-PDL-1) according to BRCAness and KRAS somatic status in patients with tumors controlled by FOLFIRINOX induction chemotherapy. One alternative to maintenance therapy is sequential drug administration, for example in the FUNGEMAX-PRODIGE 61 phase II trial which compares three arms: nano-liposomal irinotecan (Nal-IRI) plus 5-FU/folinic acid, Gem-NabP and

sequential treatment with Nal-IRI plus 5-FU/folinic acid for 2 months, then Gem-NabP for 2 months.

In the near future, in addition to clinical follow-up, imaging assessment and measurement of conventional serum tumor markers such as CA 19.9, the monitoring of circulating tumor DNA, tumor cells or extra-cellular vesicles will help guide maintenance therapies in patients with PDAC.<sup>41-43</sup> This confirms the importance of carefully designing ancillary studies as well as those for treatment.

### Conclusion

Owing to the availability of more effective first-line chemotherapy combinations, a significant subset of patients with metastatic PDAC may be candidates for maintenance therapies. While continuing with lower doses of chemotherapy is one strategy, administration of different drugs will also be a future option. In the small population of patients with gBRCAm PDAC, the POLO study paved the way for targeted maintenance therapy. These results can stimulate further studies and the design of innovative maintenance therapy trials, based on targetable biological abnormalities whenever possible,<sup>44</sup> to maintain both QoL and increase OS.

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**Conflict of interest statement**

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