

# Advances in the management of pancreatic ductal adenocarcinoma

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**T**he incidence of pancreatic ductal adenocarcinoma (PDAC) is rising and PDAC is projected to become the third leading cause of cancer death in Canada.<sup>1</sup> Although risk factors for PDAC are known, the reason for its rising incidence is not. Overall survival for this disease at 5 years has improved recently; however, survival for other malignant diseases has improved more.<sup>2</sup> A 2018 retrospective study of patients in Alberta found that more than 40% of patients with advanced PDAC were not referred for specialist care.<sup>3</sup> Surgical resection remains the only opportunity to cure PDAC, and only 15%–20% of patients present with resectable disease.<sup>4</sup> However, PDAC is a heterogenous disease and several useful genomic classifiers<sup>5,6</sup> and RNA-based subtypes<sup>7–9</sup> have been identified that are beginning to inform treatment strategies for patients with nonresectable disease, with some showing survival benefit. We build on a previous review of the clinical presentation and surgical management of PDAC<sup>10</sup> to discuss evidence supporting the most recent clinical advances in treatment (Box 1). An approach to the treatment of PDAC by stage is presented in Figure 1.

## Who is at risk for pancreatic ductal adenocarcinoma?

Observational studies have shown that smoking,<sup>11</sup> obesity<sup>12</sup> and a prolonged history of diabetes<sup>13</sup> are associated with a higher risk of developing PDAC. A family history of pancreatic cancer in a first degree relative is reported in about 10% of patients,<sup>14</sup> and germline pathogenic variants in the *BRCA1*, *BRCA2* and *PALB2* genes can be found in 5%–7%.<sup>15,16</sup> Although reflex germline testing – using comprehensive gene panels for hereditary cancer predisposition syndromes – is now recommended by the National Comprehensive Cancer Network (NCCN) guideline<sup>17</sup> for all new diagnoses of PDAC to facilitate cascade testing of family members

### Box 1: Evidence used in this review

We identified articles for this review by searches of MEDLINE, Embase and Cochrane databases, and references from relevant articles, with various combinations of the search terms “pancreatic cancer,” “pancreas,” “PDAC,” “PDAC genetics” and “PDAC management and treatment.” We excluded articles that were reported only in the form of abstracts or meeting reports, and included articles published only in English between Jan. 1, 1980, and May 31, 2020.

### KEY POINTS

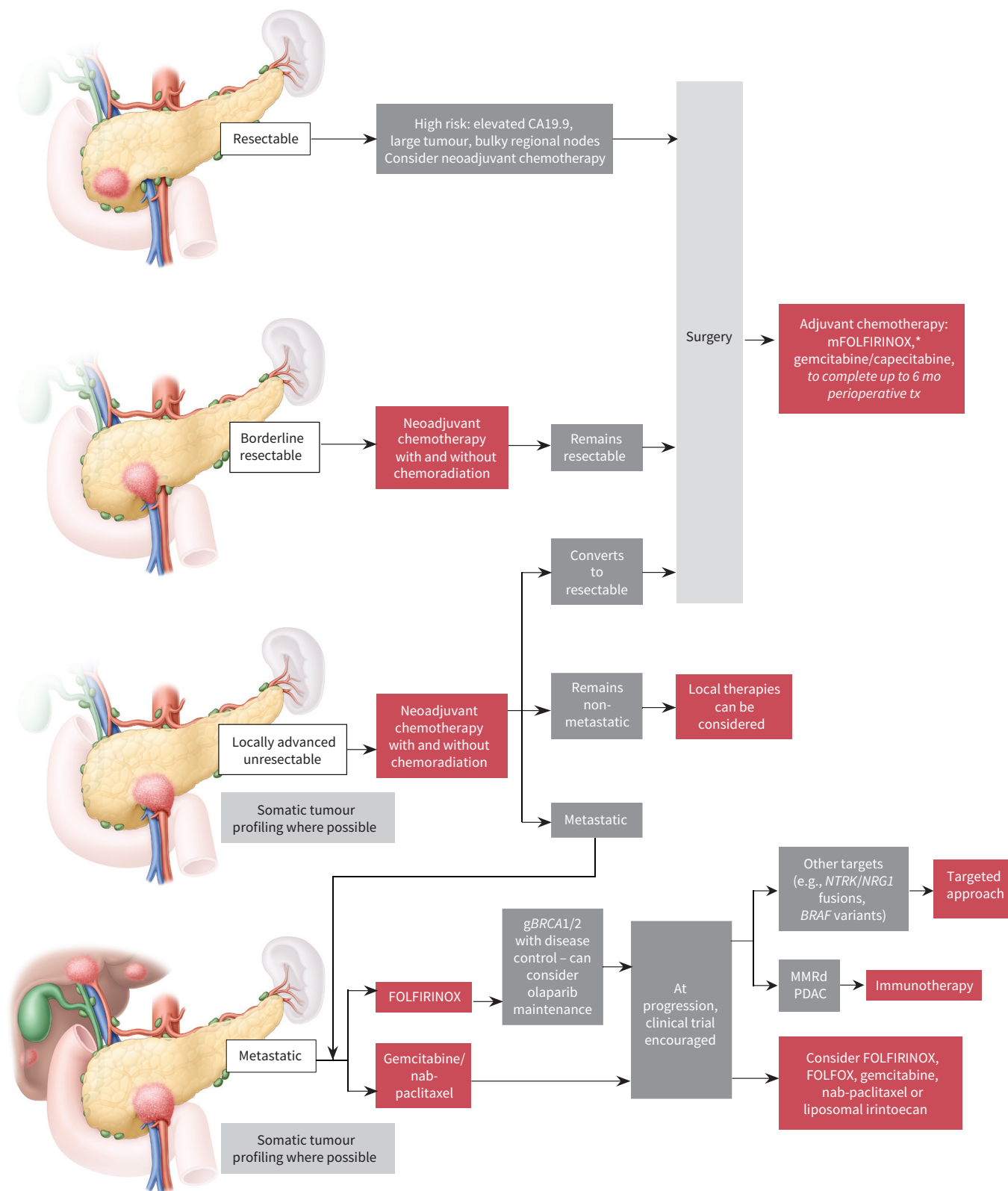
- Germline testing is now recommended for all patients with pancreatic ductal adenocarcinoma.
- In suitable patients, modified FOLFIRINOX is the adjuvant chemotherapy regimen of choice, after surgical resection.
- Neoadjuvant approaches for resectable disease are increasingly common and should be considered in patients with high-risk features such as an elevated carbohydrate antigen 19.9 level at diagnosis.
- Patients with borderline resectable or locally advanced pancreatic ductal adenocarcinoma (PDAC) should have induction combination chemotherapy when possible, before consideration of surgical resection or a local therapy.
- If resources allow, patients with advanced PDAC should have molecular profiling of their tumours to detect uncommon but therapeutically targetable somatic alterations.

and direct treatments in the advanced disease setting,<sup>18</sup> access to such testing is variable across Canadian jurisdictions.

Despite the rising incidence of PDAC, screening for the disease in the general population is not recommended by recent US Preventive Services Task Force guidance.<sup>19</sup> In high-risk patients with hereditary cancer predisposition syndromes, endoscopic ultrasonography or magnetic resonance imaging are accepted modalities for screening;<sup>20</sup> however, the impact of screening on mortality in this population is not yet clear.

## How is pancreatic ductal adenocarcinoma diagnosed and staged?

Determining resectability is crucial in managing the patient with PDAC. The subjectivity of image interpretation has led to the development of templates for radiologists.<sup>21</sup> Nonmetastatic disease can be anatomically classified into 3 groups: resectable, borderline resectable and locally advanced unresectable pancreatic cancer, according to proximity and involvement of venous- or arterial vasculature. Determining these designations requires high-quality imaging, preferably using a dual-phase, thin-layer, pancreatic protocol computed tomography (CT).<sup>21</sup> A multidisciplinary approach in combination with the experience accrued in high-volume centres has proven to be critical, leading to changes in treatment recommendations in almost one-quarter of cases.<sup>22</sup>



**Figure 1:** Recommended approach to treatment of pancreatic ductal adenocarcinoma (PDAC). When possible, all cases discussed at the Multidisciplinary Cancer Conference, germline testing performed and clinical trials encouraged at all stages. Note: CA19.9 = carbohydrate antigen 19.9, FOLFIOX = 5-fluorouracil, leucovorin and oxaliplatin, mFOLFIRINOX = modified FOLFIRINOX (5-fluorouracil, irinotecan, leucovorin and oxaliplatin), MMRd = mismatch repair deficient, tx = treatment. \*In patients who are deemed suitable for this regimen. Original illustration by freelance medical illustrator Christine Kenney.

About 15%–20% of patients will meet imaging criteria for resectable PDAC,<sup>4,23</sup> defined by the NCCN guideline as tumours showing no arterial or venous involvement or less than 180° contact with the superior mesenteric vein or portal vein without vein contour irregularity.<sup>21</sup> In about 30% of new cases, vessel involvement and local involvement will preclude initial surgical attempts.<sup>24</sup> In addition, over half of patients present with metastatic disease for which median survival with chemotherapy remains less than 1 year.<sup>25,26</sup>

## What are the treatment options for patients with operable disease?

### Resection and adjuvant chemotherapy

Although surgical techniques have not changed substantially in the last decade, the role of perioperative combination chemotherapy is evolving (Table 1). Adjuvant gemcitabine was the standard of care for many years,<sup>29</sup> doubling survival compared

with surgery alone at 5 years (10.4% v. 20.7%). The European Study Group for Pancreatic Cancer (ESPAC)-4 trial evaluated the use of adjuvant gemcitabine versus gemcitabine and capecitabine combined, and was the first to show superiority of multiagent chemotherapy, increasing median overall survival (OS) to 28 months.<sup>28</sup> In 2018, results of the Canadian Cancer Trial Group and Unicancer-GI-PRODIGE Group phase III open-label clinical trial<sup>28,33</sup> transformed practice. In this study, patients aged less than 79 years with a postoperative level of carbohydrate antigen 19.9 (CA19.9) of 180 U/mL or less were randomly assigned to modified FOLFIRINOX (5-fluorouracil, irinotecan, leucovorin and oxaliplatin) or gemcitabine alone. Median OS was 54.5 months in the modified FOLFIRINOX group versus 35.0 months in the gemcitabine alone group (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.48 to 0.86,  $p = 0.003$ ), a surprisingly large difference for PDAC trials. However, the median age of patients enrolled in this study was 62 years, substantially

**Table 1: Select phase II and III trials of adjuvant or neoadjuvant treatment for resectable pancreatic ductal adenocarcinoma**

Author group (trial title)	Study type	Treatment arm	No. of patients	Specific inclusion	Primary outcome	DFS	p value	OS	p value
Conroy and colleagues <sup>25</sup> (PRODIGE24-CCTG PA6)	Phase III	Gemcitabine	493	ECOG 0–1; Age ≤ 76 yr; Baseline CA19.9 ≤ 180 U/mL	DFS	12.8	< 0.001	35	0.003
		FOLFIRINOX				21.6		54.4	
Tempero and colleagues <sup>27</sup> (APACT)	Phase III	Gemcitabine	866	ECOG 0–1; CA19.9 < 100 U/mL	DFS by independent reviewer	18.8	0.2	36.2	0.045
		Gemcitabine plus nab-paclitaxel				19.4		40.5	
Neoptomelos and colleagues <sup>28</sup> (ESPAC-4)	Phase III	Gemcitabine	730	WHO PS < 2	OS	13.1	0.08	25.5	0.032
		Gemcitabine plus capecitabine				13.9		28.8	
Oettle and colleagues <sup>29</sup> (CONKO-001)	Phase III	Observation	354	Karnofsky PS ≥ 50%	DFS	6.7	< 0.001	20.2	0.01
		Gemcitabine				13.4		22.8	
<b>Neoadjuvant trials</b>									
Motoi and colleagues <sup>30</sup> (Prep-02/JSAP-05)	Phase II/III	Gemcitabine/S1-surgery-S1	364	Resectable and BR; ECOG 0–1	OS	NR	–	36.7	0.015
		(Abstract)							
Versteijne and colleagues <sup>31</sup> (PREOPANC)	Phase III	Gemcitabine/radiation-surgery-gemcitabine	246	Resectable and BR	OS by intention to treat	8.1	0.03	16	0.096
		Surgery-gemcitabine				7.7		14.3	
Sohal and colleagues <sup>32</sup> (SWOG 1505) (Abstract)	Phase II	Modified FOLFIRINOX-surgery-modified FOLFIRINOX	102	Resectable	2-yr OS	10.9*	NR	22.4	NS
		Gemcitabine/nab-paclitaxel-surgery-gemcitabine/nab-paclitaxel				14.2*		23.6	

Note: BR = borderline resectable, CA19.9 = carbohydrate antigen 19.9, DFS = disease-free survival, ECOG = Eastern Cooperative Oncology Group, NR = not reported, NS = not significant, OS = overall survival, PS = Performance Status, S1 = type of chemotherapy, WHO = World Health Organization.  
\*DFS is from time of surgery.

younger than the average patient with a diagnosis of PDAC (70 yr). As expected, toxicity was higher with modified FOLFIRINOX. The 2019 Nab-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone as Adjuvant Therapy in Subjects With Surgically Resected Pancreatic Adenocarcinoma (APACT) trial evaluated the combination of gemcitabine and nanoparticle albumin-bound (nab)-paclitaxel versus gemcitabine alone and did not find improvement in disease-free survival.<sup>27</sup>

In general, adjuvant chemoradiation has not been shown to improve survival in patients with PDAC;<sup>34</sup> however, it may be considered for certain patients with positive resection margins. A 2008 meta-analysis of 4 randomized controlled trials (RCTs) found a survival benefit of chemoradiation in this particular cohort compared with those patients with an R0 resection (i.e., no microscopic tumour present within 1 mm of the resection margin).<sup>35</sup>

### Neoadjuvant chemotherapy in resectable disease

Historically, neoadjuvant chemotherapy has been reserved for patients with borderline resectable or locally advanced unresectable pancreatic cancer. However, physicians increasingly accept that PDAC is a systemic disease and that higher cure rates are achieved with both surgery and combination chemotherapy. Despite this, a 2014 study in the United States on the impact of postoperative complications on the receipt of adjuvant chemotherapy found that just under 50% of patients who underwent resection for stage I-III PDAC did not receive adjuvant chemotherapy.<sup>36</sup> Given the importance of systemic treatment in providing an increased chance of cure, a chemotherapy-first approach may be optimal.

Theoretically, neoadjuvant chemotherapy may allow for better biological selection because 25% of patients experience a recurrence within 6 months of surgery.<sup>37</sup> These patients with early recurrences are unlikely to have benefited from a surgical approach. Neoadjuvant treatment could potentially downstage patients and increase the likelihood of a margin-negative resection. Many US centres practice this approach, although evidence from RCTs is not yet available. The NCCN guideline recommends a neoadjuvant approach only for patients with resectable disease and high-risk features such as elevated CA19.9, a large tumour or bulky regional nodes.<sup>17</sup> A summary of neoadjuvant chemotherapy trials<sup>30-32</sup> performed to date can be found in Table 1. Findings from the Alliance for Clinical Trials in Oncology (ALLIANCE A021806) are not yet available; however, they will inform outcome differences between neoadjuvant and adjuvant delivery of modified FOLFIRINOX. A Canadian phase II trial is also underway (Table 2).

### Perioperative radiation

The role of preoperative radiation remains uncertain in resectable PDAC. The Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC) trial<sup>31</sup> reported the outcomes of neoadjuvant chemoradiation (gemcitabine) compared with immediate surgery followed by adjuvant gemcitabine in patients with resectable or borderline resectable disease. More

than half of the enrolled patients had resectable PDAC. Overall survival did not improve. Preoperative chemoradiotherapy, however, was associated with better disease-free survival. Furthermore, in those patients who had surgery and started adjuvant chemotherapy, survival was improved in the neoadjuvant arm (35 v. 20 mo).

### Borderline resectable disease

Patients are considered to have borderline resectable PDAC if the tumour involves major arteries (e.g., celiac trunk, superior mesenteric artery or common hepatic artery) but to less than 180° circumference. The portal vein or superior mesenteric vein can be involved in borderline resectable PDAC, as long as the vessel contour is preserved.<sup>17</sup> Historically, blood vessel involvement was considered an exclusion criterion for curative surgery as negative margins were difficult to achieve<sup>39</sup> and the risk of micro-metastatic spread was higher.<sup>40</sup> However, several studies that evaluated neoadjuvant approaches have since challenged this convention, showing conversion to resectability and similar outcomes to upfront resectable PDAC.<sup>41-44</sup> A 2019 meta-analysis involving 313 patients with borderline resectable pancreatic cancer who received FOLFIRINOX (24 studies: 16 retrospective and 8 prospective) reported a median OS of 22.2 months.<sup>45</sup> Imaging after neoadjuvant treatment will not always show a radiographic response.<sup>46</sup> Therefore, resection should still be considered unless there is evidence of progression or a decline in performance status at follow-up.<sup>47</sup>

Strong evidence is lacking to support the use of combination chemoradiation for borderline resectable PDAC.<sup>48</sup> A 2018 study at an academic hospital in the US enrolled 48 patients in a single-arm, phase II clinical trial of FOLFIRINOX followed by either short-course or long-course radiation. Among the 32 (67%) patients who underwent resection, the median OS was 37.7 months, which suggests a benefit to this approach.<sup>49</sup> The role of stereotactic body irradiation in borderline resectable PDAC remains unclear. The ongoing ALLIANCE A021501 trial aims to compare FOLFIRINOX with or without stereotactic body irradiation in the preoperative management of borderline tumours (ClinicalTrials.gov, no. NCT02839343); however, the stereotactic body irradiation arm of this study was recently closed because of futility, with final results still pending.

### How should patients with locally advanced disease be managed?

About 30% of patients with PDAC have locally advanced unresectable disease with substantial vascular involvement at diagnosis,<sup>24</sup> which generally precludes them from undergoing surgery with curative intent. The Selective Chemoradiation in Advanced Localised Pancreatic Cancer (SCALOP) trial<sup>50</sup> and a 2009 qualitative systematic review<sup>51</sup> found subclinical metastases in as many as 50% of patients who were originally thought to have only locally advanced disease based on cross-sectional imaging. Induction chemotherapy, therefore, can buy time, allowing identification of those who are likely to progress and the selection of appropriate treatments.<sup>50,51</sup>

**Table 2: Select ongoing or completed Phase II and III trials in pancreatic ductal adenocarcinoma to answer specific questions**

Title (Clinical trial No.)	Study type	Treatment arm	Planned no. of patients	Specific inclusion	Question to be answered	Primary outcome
<b>Resectable or borderline resectable PDAC</b>						
ALLIANCE (A02180 PAC3)	Phase III	Perioperative modified FOLFIRINOX v. surgery and adjuvant modified FOLFIRINOX	344	Resectable PDAC	Is a neoadjuvant approach superior to surgery first followed by adjuvant?	OS
PANDAS-PRODIGE-44 (NCT02676349)	Phase II	FOLFIRINOX–surgery–adjuvant chemotherapy FOLFIRINOX–chemoradiotherapy (capecitabine/50.4Gy)–surgery–adjuvant chemotherapy	90	Resectable and BR; ECOG 0 or 1; Age 18–75 yr	Does additional conformal chemoradiation preoperatively improve R0 resection rates?	R0 resection rate
<b>Locally advanced PDAC</b>						
CROSSFIRE (NCT02791503)	Phase II	FOLFIRINOX and IRE; FOLFIRINOX and SABR	138	LAPC	Following FFX, which has better efficacy, IRE or SABR?	OS
CONKO-007 (NCT01827553)	Phase III	Induction chemotherapy with gemcitabine or FOLFIRINOX, followed by radiotherapy induction chemotherapy with gemcitabine or FOLFIRINOX alone	830	LAPC; ECOG ≤ 2	Does chemoradiotherapy postinduction chemotherapy compared with chemotherapy alone improve outcomes in LAPC?	OS
<b>Advanced or metastatic PDAC</b>						
CCTG PA.7 <sup>38</sup>	Phase II	Gemcitabine/nab-paclitaxel; Gemcitabine/nab-paclitaxel plus durvalumab plus tremelimumab	180	ECOG 0/1; Measureable disease	Does the addition of combination PD-L1 and CTLA-4 inhibition added to chemotherapy improve survival?	OS
PANCO03 (NCT03504423)	Phase III	Modified FOLFIRINOX; Modified FOLFIRINOX and CPI-613	500	Stage IV; ECOG 0/1	Does CPI 613, a drug targeting the mitochondrial tricarboxylic cycle, improve outcomes in metastatic pancreatic cancer?	ORR PFS
PASS-01 (NCT04469556)	Phase II	Modified FOLFIRINOX; Gemcitabine/nab-paclitaxel	150	Stage IV; absence of germline mutation	Is modified FOLFIRINOX superior to gemcitabine/nab-paclitaxel in the management of stage IV pancreatic cancer?	PFS

Note: BR = borderline resectable, CTLA-4 = cytotoxic T-lymphocyte-associated protein, ECOG = Eastern Cooperative Oncology Group, FFX = FOLFIRINOX, IRE = irreversible electroporation, LAPC = locally advanced pancreatic ductal adenocarcinoma, ORR = overall response rate, OS = overall survival, PD-L1 = programmed-death ligand 1, PDAC = pancreatic ductal adenocarcinoma, PFS = progression-free survival, SABR = stereotactic ablative radiation.

**Systemic treatments**

No standard recommendation exists for initial systemic treatment in patients with locally advanced unresectable pancreatic cancer. Most institutions have largely employed regimens used in metastatic disease to those with locally advanced unresectable disease, given the absence of good evidence in this subset. A 2016 systematic review and meta-analysis of FOLFIRINOX that involved 689 patients with locally advanced unresectable pancreatic cancer reported a median OS of 24.2 months.<sup>52</sup> Several of these patients received additional local therapy after chemotherapy, and one-quarter of patients had actually responded well to chemotherapy and had surgical resection. The phase II Nab-paclitaxel (Abraxane) Plus Gemcitabine in Subjects With Locally Advanced Pancreatic Cancer (LAPC): An International, Open-label, Multi-center, Phase 2 Study (LAPACT) trial evaluated gemcitabine–nab-paclitaxel in locally advanced unresectable

pancreatic cancer and found a 33.6% response rate. In this study, 16% of patients underwent surgery, with 7 achieving a microscopically margin-negative resection.<sup>53</sup> The addition of novel agents to further downstage patients to surgery is an area of active investigation (Table 2).

**Local treatments**

Patients with locally advanced unresectable PDAC may have considerable morbidity. Intractable abdominal pain and gastric outlet obstruction are the 2 most common reasons for hospital admission.<sup>54</sup> As many as one-third of patients with locally advanced unresectable pancreatic cancer will die of complications related to local progression, such as bleeding and perforation.<sup>55</sup> Chemoradiation or stereotactic body irradiation given after initial chemotherapy, with the aim of consolidating responses, have not shown to improve OS. Radiation dose delivery to pancreatic tumours is limited by their



proximity to luminal structures such as the small bowel and stomach; radiation to these organs can result in acute toxicity.<sup>56</sup> The Stanford group are currently enrolling patients in a phase III study of mFOLFIRINOX with and without stereotactic body irradiation in locally advanced unresectable pancreatic cancer (Table 2).

Other local therapies under evaluation for the treatment of locally advanced unresectable disease include irreversible electroporation, a nonthermal, locally destructive technique that generates direct current through the tumour.<sup>57</sup> Retrospective studies investigating the safety and efficacy of irreversible electroporation for locally advanced unresectable pancreatic cancer have reported mixed results, and a 2019 systematic review reported treatment-associated morbidity in 1 in 3 patients.<sup>58</sup> The multicentre, prospective Percutaneous Irreversible Electroporation in Locally Advanced and Recurrent Pancreatic Cancer (PANFIRE-2) study, in which patients with locally advanced unresectable pancreatic cancer either received induction gemcitabine-based chemotherapy or FOLFIRINOX, followed by irreversible electroporation,<sup>59</sup> reported that OS from diagnosis was 17 months for both groups. Randomized controlled trials are needed to determine the role of irreversible electroporation; a feasibility study is currently enrolling patients at the University Health Network in Toronto (ClinicalTrials.gov, no. NCT03257150).

### What progress has been made in the treatment of metastatic disease?

Patients with advanced PDAC should be encouraged to enrol in clinical trials of treatment. First-line standard regimens include modified FOLFIRINOX<sup>25</sup> and gemcitabine–nab-paclitaxel.<sup>26</sup> Gemcitabine–nab-paclitaxel is funded only as a first-line treatment in most Canadian provinces and not if other treatments have been tried, which limits treatment sequencing options. The only second-line regimen to show improved patient survival is the combination of liposomal irinotecan/5-fluorouracil (NAPOLI-1 trial), which is not currently publicly funded in Canada.<sup>60</sup> Although no RCT comparing modified FOLFIRINOX and gemcitabine–nab-paclitaxel has yet been done, a multicentre North American trial (Pancreatic Adenocarcinoma Signature Stratification for Treatment, PASS-01) is now accruing (ClinicalTrials.gov, no. NCT04469556). This study aims to establish predictive biomarkers for these 2 regimens (Table 2). A recent study showed that a basal-like RNA subtype of PDAC is more resistant to chemotherapy and, in particular, to FOLFIRINOX.<sup>61</sup>

The presence of a germline pathogenic variant in *BRCA1*, *BRCA2* or *PALB2* is currently the only molecular biomarker that can direct physicians to use platinum-based regimens such as modified FOLFIRINOX. In patients with these biomarkers, the tumour is likely to be deficient in homologous recombination repair, meaning it is unable to repair double-strand DNA breaks. Platinum regimens such as FOLFIRINOX or cisplatin and gemcitabine should be considered,<sup>18</sup> because platinum exploits this tumour weakness. The 2019 Pancreas Cancer Olaparib Ongoing (POLO) trial led to Health Canada's approval of olaparib, an inhibitor of poly-(ADP-ribose) polymerase, as a maintenance approach in patients with a confirmed germline pathogenic variant in

*BRCA1* or *BRCA2* who have shown disease control after 4 months of a platinum regimen. In this international phase III trial, 154 patients were randomly assigned to maintenance olaparib versus placebo (3:2), and patients receiving the active treatment showed better disease-free survival but no difference in OS and no improvement in quality of life.<sup>18</sup> Although olaparib was approved by Health Canada, its use is not publicly funded at present and patients must pay for the treatment.

### What are emerging targeted treatments for PDAC?

Ninety percent of PDAC harbour an oncogenic *KRAS* mutation for which a target drug has not been successfully developed until recently. A specific *KRAS* variant at codon 12 (G12C), which is found in 1%–2% of PDAC cases, has shown promise as a putative drug target. In 2019, the CodeBreak 100 trial reported disease control in 9 of 11 patients who received a G12C-targeting drug.<sup>64</sup> This study opens an avenue for more *KRAS* inhibitors, which could transform future treatment. Furthermore, DNA copy number changes in mutant *KRAS* may influence the aggressiveness of some tumours and frequent tumour hypoxia may hamper treatment responses in PDAC.<sup>62,63</sup> Several other uncommon somatic targets that may be highly targetable are among the *KRAS* wild-type PDAC, which accounts for about 5%–10% of cases.<sup>65,66</sup> Gene fusions involving *NTRK*,<sup>67</sup> *NRG1*,<sup>68,69</sup> *RET*<sup>69</sup> and *ALK*<sup>70</sup> are important to identify in this PDAC subtype. In addition, alterations in *BRAF* have been reported in *KRAS* wild-type PDAC.<sup>65,66,71</sup> In 2020, the Know Your Tumor registry trial reported a survival advantage when patients were matched to treatments, thus underscoring the importance of somatic tumour profiling.<sup>72</sup>

The characteristic desmoplastic stroma that envelops pancreatic tumour cells may also promote tumourigenesis and inhibit systemic treatment response. Several stroma-targeting agents have not been successful in clinical trials, although others are currently under investigation.<sup>73</sup> The large, phase III HALO 109–301 trial, which evaluated the addition of PEGPH20 (a biologic) to gemcitabine–nab-paclitaxel, failed to show any benefit of this drug in tumours with high expression of hyaluronic acid, despite promising phase II data.<sup>74</sup>

Pancreatic ductal adenocarcinoma is considered an immunologically “cold” tumour, with few tumour-infiltrating lymphocytes and a low tumour mutational burden.

Combining chemotherapy with immune checkpoint inhibitors has been postulated to prime the immune system and induce anti-genicity. However, the randomized Canadian Cancer Trials Group (CCTG) PA.7 trial reported in 2020 that there was no benefit of adding tremelimumab and durvalumab to gemcitabine–nab-paclitaxel as first-line treatment in patients with metastatic disease.<sup>38</sup> Median OS was 8.8 months compared with 9.8 months in the experimental arm ( $p = 0.7$ ).

Other strategies to elicit an immune response include vaccines and adoptive cell therapy; however, these have not shown efficacy in PDAC. Importantly, PDAC that are DNA mismatch repair deficient are “hot” tumours, which are highly immunogenic. These represent less than 1% of such tumours; hot tumours can arise from deleterious

germline pathogenic variants in the mismatch repair genes, otherwise known as Lynch syndrome, or because of somatic alterations in these genes.<sup>75</sup> DNA mismatch repair deficiency has become the first tumour-agnostic biomarker for which pembrolizumab (a programmed death receptor-1 immune checkpoint inhibitor) was approved.<sup>76</sup> Of 86 patients in a landmark study, 8 had previously treated advanced PDAC, of which 5 responded to pembrolizumab, with 2 complete responses.<sup>76</sup> However, the 2020 KEYNOTE-158 trial, which included 22 patients with DNA mismatch repair deficiency PDAC, reported that only 4 patients had a documented response (1 complete and 3 partial responses, objective response rate 18.2%).<sup>77</sup> Despite the robust DNA mismatch repair deficiency biomarker, Canadian patients have limited access to programmed death receptor-1 inhibitors and must often rely on enrolment in clinical trials for access.

## Conclusion

Progress in improving outcomes for patients with PDAC has been slow, although recent major scientific breakthroughs have accelerated physicians' understanding of this deadly disease. Canadian patients have limited access to new drugs that could improve outcomes and an awareness of treatment options is lacking. The role of neoadjuvant chemotherapy in resectable PDAC is now being defined. Both germline and somatic profiling will identify additional patients who may benefit from a personalized approach for tumours that are susceptible to treatment that could extend survival. Ongoing research into the understanding of the complex interplay between tumour, stroma and tumour microenvironment are needed to better select agents targeting these compartments. Canadian physicians should refer patients with PDAC to specialist care, encourage enrolment in clinical trials and support collaborative research into new treatment modalities.

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