RESEARCH ARTICLE

Trends in pancreatic cancer clinical trials in the United States

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Abstract

Trends in clinical trials for pancreatic cancer between 2011-2020 were tracked in the Pancreatic Cancer Action Network database originally designed to assist in identifying open trials for eligible patients. More than 125 trials specific for pancreatic cancer or including no more than one additional cancer type have been open each year, the majority for patients with a diagnosis of pancreatic adenocarcinoma (PAC). The trends indicate an active and progressive pancreatic cancer research community and include an increasing number of trials for previously treated patients, the emergence of trials for post-adjuvant or maintenance therapy, an increasing number of research-intensive phase 0 trials, increasing seamless phase I/II and II/III trials to improve efficiency, and an increasing number of phase III trials despite historical failures. Trials were analyzed by treatment type and included trials to optimize standard chemotherapy or radiation therapy, trials targeting tumor pathways, the stroma, or the immune system, biomarker-specified trials, and a miscellaneous category of trials testing tumor metabolism, complementary medicine approaches, or alternate energy sources. There was a dramatic increase in immunotherapy trials over this time. Several biomarker-specified trials were initiated, and FDA approval was obtained for biomarker-specified targeted agents, many in a tissue-agnostic setting, indicating an increase in a precision medicine approach to pancreatic cancer treatment. An increasing number of trials tested non-standard approaches, many which progressed to phase III. The trends suggest an encouraging trajectory of pancreatic cancer clinical research.

Key words: pancreatic neoplasms, clinical research

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1.0 Introduction

Pancreatic cancer stands out as a particularly deadly cancer in that the global number of deaths from the disease in 2020 (466,000) is estimated to be roughly equivalent to the number of cases (496,000).[1] Both incidence and mortality rates are increasing in the U.S. and many other highly developed nations, leading to the projection that pancreatic cancer will become third leading cause of cancer deaths in Europe[2] and second in the U.S.[3] by the end of the decade. The 5-year relative survival rate confirms the aggressive and deadly nature of the disease, with pancreatic cancer holding the distinction of having the lowest survival rate of those tracked in the U.S. at just 10%.[4]

The treatment of pancreatic cancer relies heavily on the effectiveness of systemic chemotherapies in that only approximately 15% of diagnoses have the potential to undergo surgery with curative intent.[5] The modest effectiveness of current standard therapies in widening the gap between incidence and mortality is reflected by the policy of organizations such as the National Comprehensive Cancer Network (NCCN) that pancreatic cancer patients should consider clinical trials as a treatment option at every decision point.[6] Clinical trials are recorded by the U.S. government at https://clinicaltrials.gov/, but do not necessarily reflect up-to-date information. To facilitate identifying appropriate clinical trials for individual patients, the patient advocacy organization the Pancreatic Cancer Action Network maintains a database of pancreatic cancer-specific clinical trials open in the U.S. that is updated monthly and can be accessed on-line or through the organization's Patient Services Help Line. Included trials target pancreatic histologies specifically, i.e. trials that enroll patients with pancreatic and no more than one other cancer type. The database has been useful in tracking the landscape of pancreatic cancer clinical trials in previous years.[7, 8] Herein we focus on the trends observed in pancreatic cancer clinical trials in the U.S. over the past decade to identify changes in clinical trial design and track the evolution of clinical research interests that may suggest progress against the disease, inform future trials, and encourage a concerted effort to improve outcomes in one of the world's deadliest cancers.

2.0 Clinical Trial Landscape

The total number of open therapeutic clinical trials in the U.S. directed at patients with a diagnosis of benign or malignant pancreatic tumors exceeded 125 every year since 2011 (Figure 1A), representing a robust interest in new therapies for a relatively rare cancer that ranks 11th in incidence.[4] The total number of trials peaked at 172 in 2015 and declined thereafter. Although the underlying reason for the decline cannot be ascertained from this data, an analysis of the pancreatic cancer clinical trial landscape in 2013 identified a disconnect between the number of pancreatic cancer patients available for clinical trial enrollment, and the number of patients needed to complete the ongoing clinical trials.[7] The decline in the number of open trials may represent a needed adjustment to increase the likelihood that open trials would accrue in a reasonable timeframe.

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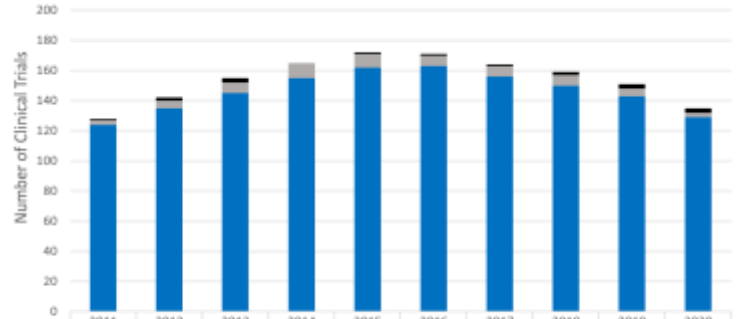
A.

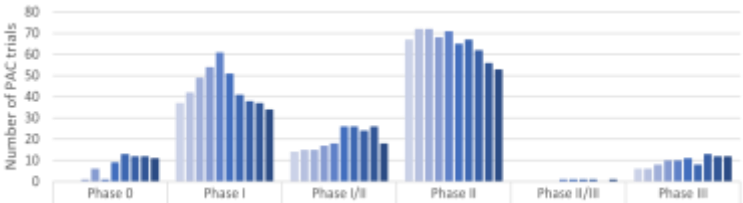


	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cyst	1	2	3	0	1	1	1	2	3	3
Other	3	5	7	10	9	15	16	7	5	3
PAC	124	135	145	155	162	148	146	150	143	129

B.

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Foundation	5	5	3	4	2	2	2	2	3	3
Industry/Pharma/Biotech	34	32	28	38	47	50	39	39	35	33
Institution/University	76	86	100	102	102	100	104	100	101	87
Government	9	12	14	11	11	11	11	9	4	6

C.



	Phase 0	Phase I	Phase I/II	Phase II	Phase II/III	Phase III
2011		37	14	67		6
2012		42	15	72		6
2013	1	49	15	72		8
2014	6	54	17	68		10
2015	1	61	18	71	1	10
2016	9	51	26	65	1	11
2017	13	41	26	67	1	8
2018	12	38	24	62	1	13
2019	12	37	26	56		12
2020	11	34	18	53	1	12

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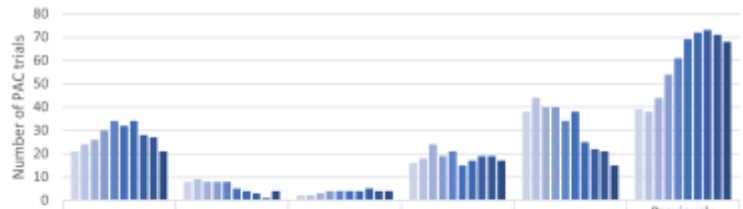

	Stage I and II	Adjuvant	Post-Adjuvant / Maintenance	Stage III, First Line	Stage IV, First Line	Previously Treated / Recurrent
2011	21	8	2	16	38	39
2012	24	9	2	18	44	38
2013	26	8	3	24	40	44
2014	30	8	4	19	40	54
2015	34	8	4	21	34	61
2016	32	5	4	15	38	69
2017	34	4	4	17	25	72
2018	28	3	5	19	22	73
2019	27	1	4	19	21	71
2020	21	4	4	17	15	68

Figure 1. U.S. Pancreatic Cancer Clinical Trial Landscape
Open clinical trials for individuals facing pancreatic cancer are tracked in a proprietary clinical trial database maintained by the Pancreatic Cancer Action Network.
(A) Open pancreatic cancer clinical trials by year. The total number of clinical trials that were open at any time within the designated calendar year is indicated on the x axis. Trials specifically for individuals diagnosed with premalignant cysts or IPMN are indicated in black, other histologies such as pancreatic neuroendocrine and adenosquamous in grey, and pancreatic adenocarcinoma in blue.
(B) Open pancreatic cancer clinical trials by sponsor. The total number of pancreatic adenocarcinoma clinical trials open within each year sponsored by the U.S. government (dark grey), an institution or university (light grey), the pharmaceutical or biotech industry (blue), or a private foundation or advocacy organization (black).
(C) Open pancreatic adenocarcinoma cancer clinical trials by phase. The total number of pancreatic adenocarcinoma clinical trials open within each year by clinical trial phase is indicated. Phase 0 studies include those indicated as pilot studies.
(D) Open pancreatic adenocarcinoma clinical trials by stage of disease. The total number of pancreatic adenocarcinoma clinical trials open within each year by disease stage is indicated.

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Clinical trials for individuals with a diagnosis of pancreatic adenocarcinoma (PAC) represented ≥ 94% of the total trials open in any year. Clinical trials for other histologies represented 2-6% of available trials and were focused on pancreatic neuroendocrine tumors except for a recent trial designated for the adenosquamous histology (NCT04116073). There were 1-3 therapeutic trials for individuals with mucinous cysts open most years, which primarily involve endoscopic ultrasound-guided injection of chemotherapeutic agents into cystic neoplasms (NCT01475331, NCT01643460, NCT03188991, for example). Trends in trials that specifically enrolled individuals with a diagnosis of PAC were further explored (Figures 1B-D, 2-5).

2.1 PAC trials by sponsor

The majority of PAC trials were sponsored by an academic institution or university, representing approximately 65% of trials open annually between 2011-2020, compared to 25% directly sponsored by Industry (pharmaceutical or biotechnology companies), 7% by the U.S. government, and 2-3% by non-profit Foundations (Figure 1B). The institution-sponsored trials are often investigator-initiated trials receiving drug(s) and in some cases funding from the pharmaceutical industry, indicating a substantial investment in clinical pancreatic cancer research by the private sector over and above their direct sponsorship of industry trials. Investigator-initiated institutional trials can also be supported by grants from the government, generally the National Cancer Institute (NCI). The NCI directly supports clinical research through the National Clinical Trials Network at more than 2,200 sites across the U.S. and including the Canadian Cancer Trials Group as well as through trials open at the NIH Clinical Center in Bethesda, MD.[9] Foundations, non-profit organizations set up to finance or complete projects, occasionally serve as sponsors of pancreatic cancer clinical trials, including the Pancreatic Cancer Research Team, Parker Institute for Cancer Immunotherapy, Proton Collaborative Group, and the Pancreatic Cancer Action Network (NCT03634332, NCT03214250, NCT02598349, NCT04229004, for example).

2.2 PAC trials by phase

The majority of PAC trials in any year between 2011 and 2020 have been phase II trials, with phase I trials slightly less abundant (Figure 1C). The number of research-intensive pilot/phase 0 trials markedly increased in the last 5 years, perhaps reflecting the realization that pancreatic cancer is a very complex and heterogeneous disease and a deeper understanding of the variability between patients is needed. Despite the many failures of previous phase III PAC trials,[10] the number of phase III trials open for pancreatic cancer patients has not diminished and in fact doubled between 2011 and 2019. As expected, the majority of the phase III trials are industry-sponsored, with 1 government, 1-3 Foundation, and 5-10 industry sponsored trials each year (data not shown).

An increase in combination phase I/II trials with a commensurate decrease in both phase I and phase II trials was observed from 2015 onward, suggesting recognition of the appeal of an efficient approach to expanding the cohort of pancreatic cancer patients treated if a therapeutic signal is observed. There are far fewer combined phase II/III trials; one randomized II/III trial opened in 2015 (NCT02436668), one in 2018 (NCT03512756), and the Pancreatic Cancer Action Network's Precision Promise[SM], a phase II/III platform trial opened in 2020 (NCT04229004). The latter represents a deliberate attempt to increase the efficiency and decrease the time for the development of new therapies for pancreatic cancer by

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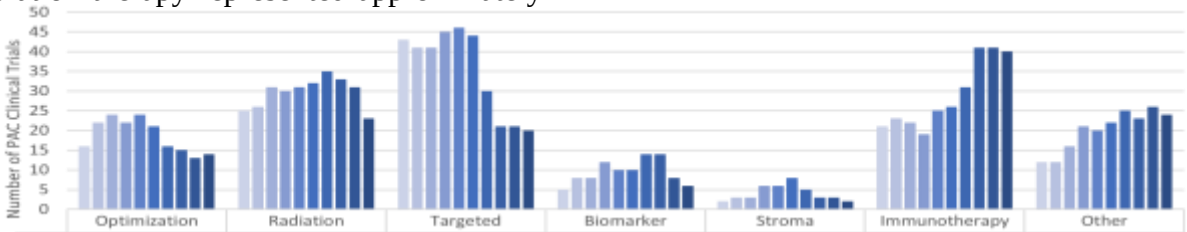
allowing multiple experimental therapeutic arms to be tested and compared to shared standard-of-care arms.

2.3 PAC trials by stage

There has been a marked increase in the number of trials for patients with previous treatments or recurrent disease over the past decade, increasing from 28-30% of the available trials in 2011-2013 to 49-53% in 2018-2020 with a related decrease in trials in the first line setting for metastatic disease (Figure 1D). Trials in the adjuvant setting have decreased over this time period and are balanced by a concomitant increase in trials in the post-adjuvant or maintenance setting. Both trends are consistent with improvement in overall survival in this population so that maintenance and 2nd+ lines of therapy have become of much greater importance and interest to the pancreatic cancer clinical research community.

3.0 Trends in treatment types

We examined changes in the treatment modality tested in PAC clinical trials. The number of trials focused on the optimization of standard chemotherapeutic agents and radiation therapy represented approximately one third of the PAC trials in any year, with declines in recent years. Novel therapies in the pancreatic cancer field have focused on targeting three major components within PAC tumors: therapies targeted to pathways altered within the tumor cells themselves, therapeutics that modulate the dense, fibrotic stroma that is characteristic of PAC, and therapeutic approaches to activating the endogenous immune response. Most notable is a marked increase in the number of trials focused on an immunotherapeutic approach to the disease, increasing from 12-17% % of the total PAC trials open in 2011-2014 to 27-31% of trials open between 2018 to 2020 (Figure 2). The number of PAC trials with targets that focused on molecular alterations within the tumor cells decreased over this time period from 35% in 2011 to 14-16% between 2018-2020, as did trials focusing on targets that modulate the stroma. The 'other' category of studies includes treatment with vitamins, diet, natural products, complementary medicine, alternate sources of energy, and the newly emerging area of cancer metabolism. A more thorough analysis of each of the treatment types follows.



	Optimization	Radiation	Targeted	Biomarker	Stroma	Immunotherapy	Other
2011	16	25	43	5	2	21	12
2012	22	26	41	8	3	23	12
2013	24	31	41	8	3	22	16
2014	22	30	45	12	6	19	21
2015	24	31	46	10	6	25	20
2016	21	32	44	10	8	26	22
2017	16	35	30	14	5	31	25
2018	15	33	21	14	3	41	23
2019	13	31	21	8	3	41	26
2020	14	23	20	6	2	40	24

Figure 2. Clinical trials by treatment type. The total number of open pancreatic adenocarcinoma clinical trials in the U.S. per year characterized by the treatment type: trials designed to optimize standard chemotherapies (optimization), radiation therapy (radiation), trials with agents that target pathways within the cancer cell (targeted), trials with a molecularly-identified eligibility requirement (biomarker), agents targeting the tumor stroma (stroma), immunotherapy, and a miscellaneous category that includes metabolism, natural products, vitamins, complementary medicine, and alternative energy sources (other).

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3.1 Immunotherapy trials

PAC has gained the reputation of being an exceptionally "cold" tumor and single agent checkpoint inhibitors have not been effective in PAC except in a small subset with microsatellite instability.[11] Hypotheses related to the influence of the dense desmoplastic stroma in excluding T-cells and the presence of abundant immunosuppressive myeloid-derived cells are being tested in clinical trials.[12] Most of the immunotherapy trials since 2015 are for patients with previously treated or recurrent PAC and the number of trials in the first-line metastatic setting are reduced relative to the earlier years (Figure 3A). This suggests that the earlier failures of immunotherapy in PAC resulted in a shift away from testing immunotherapy approaches in treatment-naïve metastatic patients in favor of those that have reached the limits of benefit from current standard treatments. There is also an increase in the number of immunotherapy trials for patients with stage I/II disease and in the post-adjuvant/maintenance setting (Figure 3A). Immunotherapy trials over the last few years have taken advantage of the phase 0 and phase I/II approaches to trial design (Figure 3B), perhaps signifying the realization of the need to better understand the molecular complexities of the immune response in PAC. Immunotherapy trials are primarily institution-sponsored (Figure 3C).

In general, the complexity of immunotherapy trials has increased over time. Trials from 2011 and 2012 tested a vaccine or an immune modulating agent alone or in combination with gemcitabine (NCT01072981, NCT01472198, NCT01417000, NCT00726037, and NCT01272791 for example). In 2013-2015, phase II trials with combination immunotherapies that included a checkpoint inhibitor appeared, generally as institutional investigator-initiated trials (NCT01896869 and NCT02243371, for example). The complexity of the combinations showed marked increases from 2016 onwards (NCT02754726, NCT02826486, NCT03336216 for example). These trends are likely to indicate an acknowledgement of the need to address the immunological complexity of PAC if we are to hope for a significant benefit for the majority of PAC patients.

3.2 Tumor, stroma, and biomarker-specified targeted trials

There has been a decrease in the number of PAC trials that test drugs that target a tumor-specific molecular pathway in recent years ('Targeted', Figure 2). This decrease is somewhat misleading, however, in that agents that target pathways believe to regulate the immune response became classified as immunotherapy treatment type but are more broadly considered targeted agents. In addition, the targeted category is somewhat compensated by an increase in biomarker-driven trials ('Biomarker'), studies in which targeted therapies are tested in a subset of patients with appropriate molecular indicators.

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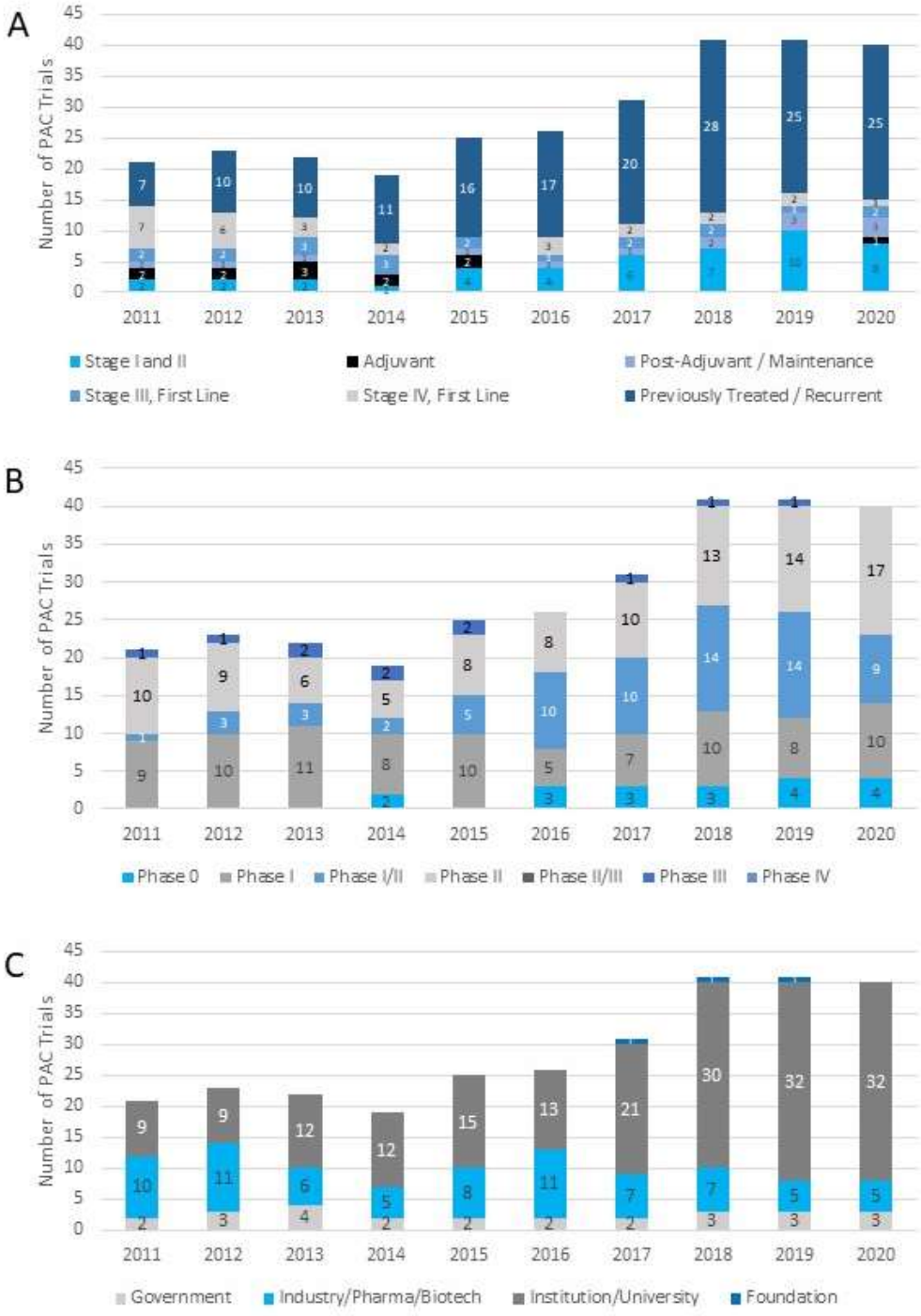

Figure 3. Immunotherapy trials. The total number of pancreatic adenocarcinoma immunotherapy clinical trials open annually in the U.S. by stage (Panel A), phase (Panel B), and sponsor (Panel C).

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Targeted trials showed a trend away from trials for first-line metastatic disease and are now predominantly for patients who were previously treated or have recurrent disease (Figure 4A). The pathways, agents, and approaches taken vary widely within this category. The activation of the RAS/MEK/ERK pathway through KRAS, BRAF, or other signal transduction mediators is a key driver of pancreatic carcinogenesis[13] and agents targeted to this pathway are investigated in many clinical trials represented by this category. Trials using MEK inhibitors in combination with gemcitabine were open in 2011 (e.g., NCT01231581), whereas in 2020 trials with MEK/ERK inhibitors were more likely to be investigating a combination of inhibitors of other pathways such as autophagy or DNA repair (e.g., NCT04132505, NCT03825289, NCT04005690). The recent approval of sotorasib for KRAS G12C mutant non-small cell lung cancer provides hope that agents targeted to the more common KRAS G12D, G12V or G12R alterations in pancreatic cancer[13] are forthcoming.

Biomarker trials reflect a maturation of the field and an increased acknowledgement of the value of precision medicine in PAC. These trials were primarily investigator-initiated phase II studies for previously-treated PAC (Figure 4 A-C). The majority of trials are for the use of PARP inhibitors in individuals with alterations in DNA repair pathways, with early phase I/II trials in 2011 having a broader definition of eligibility (e.g., NCT01489865 and NCT01296763) than later trials that focused on those with sporadic and/or germline BRCA mutations (e.g., NCT02184195, NCT02042378). Large, tissue agnostic basket trials have provided pancreatic cancer patients with rare alterations the opportunity to participate in clinical research that would not otherwise be possible due to the low prevalence of many molecularly-targeted alterations in pancreatic cancer. The NCI's MATCH trial (NCT02465060)[14] and ASCO's TAPUR trial (NCT02693535)[15] have both included pancreatic cancer patients, with TAPUR results on Olaparib efficacy in pancreatic cancer patients with germline or somatic BRCA1/2 inactivating mutations recently reported.[16]

Trials that have as their primary purpose a targeting of elements of the tumor stroma that is characteristic of PAC are tracked in the "stroma" category (Figure 4 A-C). There was considerable excitement but subsequent disappointment about this approach that is reflected in the peak of trials in 2016 and subsequent decline. Based on strong preclinical data,[17] a modified form of the hyaluronic acid (HA)-degrading enzyme hyaluronidase was tested clinically with promising results in early phase trials (NCT01839487)[18]. However, a subsequent randomized phase II (NCT01959139)[19] and a phase III trial conducted in patients with high HA levels and classified as a biomarker-driven trial (NCT02715804)[20] failed to meet the primary endpoint. The complexity of PAC and the possibility that, although the stroma may be a physical barrier that impedes drug delivery, it may also have protective effects in restraining tumor growth, are areas where additional research is needed if we hope to realize therapeutic benefit from targeting the PAC stroma.

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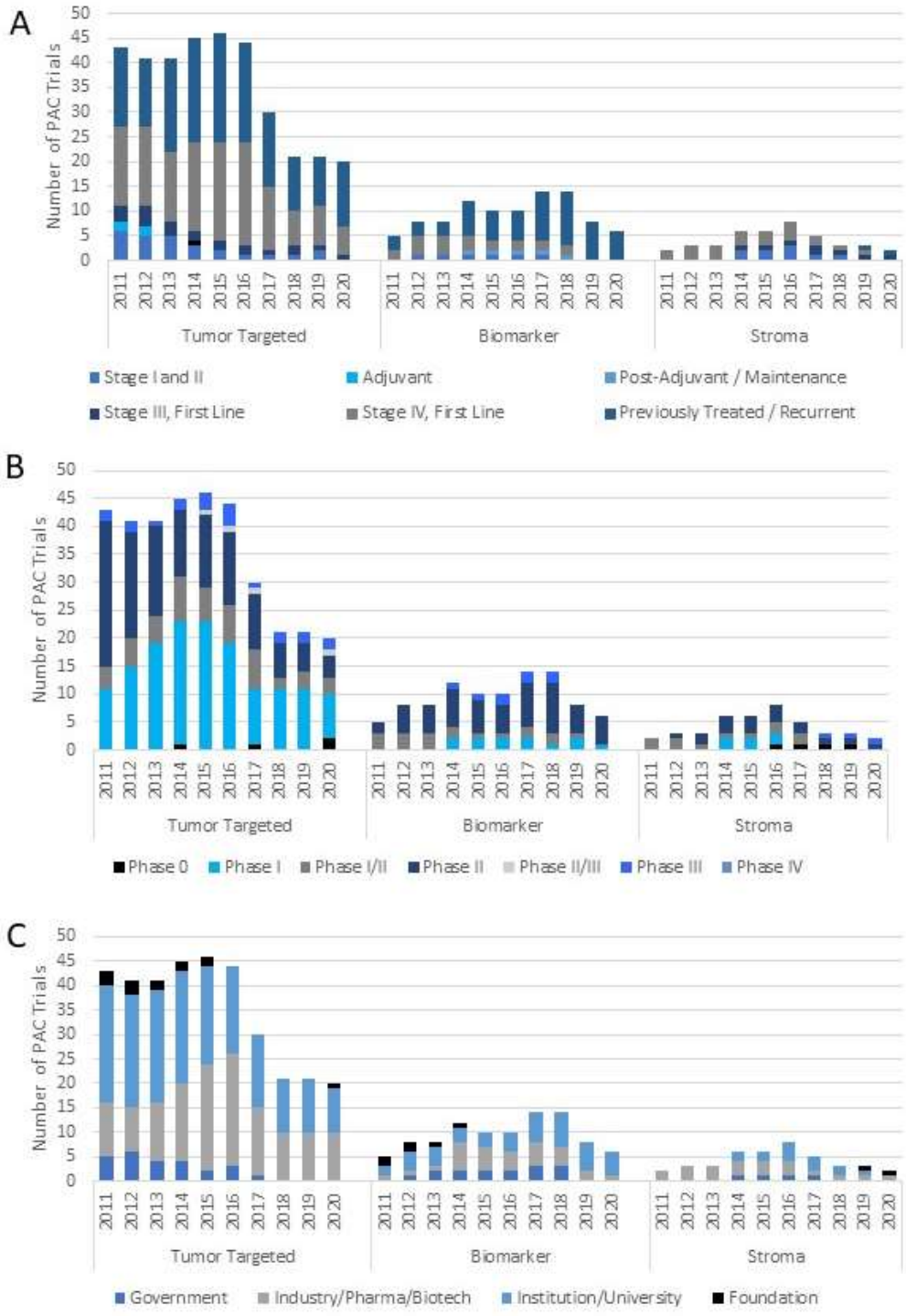

Figure 4. Tumor, stroma, and biomarker-specified clinical trials. The total number of open U.S. pancreatic adenocarcinoma clinical trials in the indicated years that test agents that are targeted to tumor-specific pathways (tumor targeted), that have a molecularly identified eligibility requirement (biomarker), or that are targeting the tumor stroma (stroma). Trials are stratified by stage of disease (panel A), phase of trial (panel B), or trial sponsor (Panel C).

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3.3 Studies on standard and non-standard therapies

Trials to optimize chemotherapeutic agents, for example by modifications that improve their bioavailability or test alternative delivery methods or combinations, are primarily investigator-initiated phase II studies being tested in all stages of disease (Figure 5A-C). Notable recent government-sponsored studies include investigations of standard therapies in the neoadjuvant setting (NCT02562716), comparing chemotherapy in the neoadjuvant and adjuvant settings (NCT04340141), and testing chemotherapeutic combinations in older patients (NCT04233866).

The number of studies addressing radiation therapy have remained relatively constant in recent years, with a decline in 2020 that is particularly pronounced and may have been disproportionately impacted by the requirement for daily in-person hospital visits during the COVID-19 pandemic (Figure 2, 5A-C). In addition, the long-standing NCI RTOG trial (NCT01013649) stopped accrual in 2018 and initial results focusing on the chemotherapy portion of the trial were presented in early 2020.[21] Although an analysis of the National Cancer Database suggests a benefit of adjuvant radiation therapy,[22] radiation therapy for resectable pancreatic cancer remains controversial and discussions are turning to exploring biomarkers for response to radiation. Radiation therapy trials over the past decade were predominantly for resectable tumors or in the post-adjuvant/maintenance setting, with a recent broadening of trial eligibility to include patients with localized disease that were previously treated or had recurrent disease (Figure 5A). Radiation therapy is an area of research that has taken advantage of the pilot/phase 0 approach in recent years and is primarily sponsored by academic institutions, perhaps leading to innovations in patient selection or therapy sequencing in the future (Figure 5B-C).

The ‘other’ category of studies includes trials that focus on alternative sources of energy for cancer destruction, as well as those that employ complementary medicine approaches including natural products and vitamins. The trending increase in the number of studies in this area reflects the innovation that is being applied to the treatment of pancreatic cancer (Figure 2). These trials are predominately for previously treated patients and several approaches have reached phase III trials (Figure 5 A-C). Phase III trials include novel technologies such as irreversible electroporation (NCT03899636) and tumor treating fields (NCT03377491), and modifications such as post-surgical rinse to reduce recurrence (NCT02757859). In addition, the newly emerging area of cancer metabolism (NCT03504423, NCT03512756 for example) is classified as “other” but is an area that is likely to grow and become recognized as a distinct area of therapeutic development.

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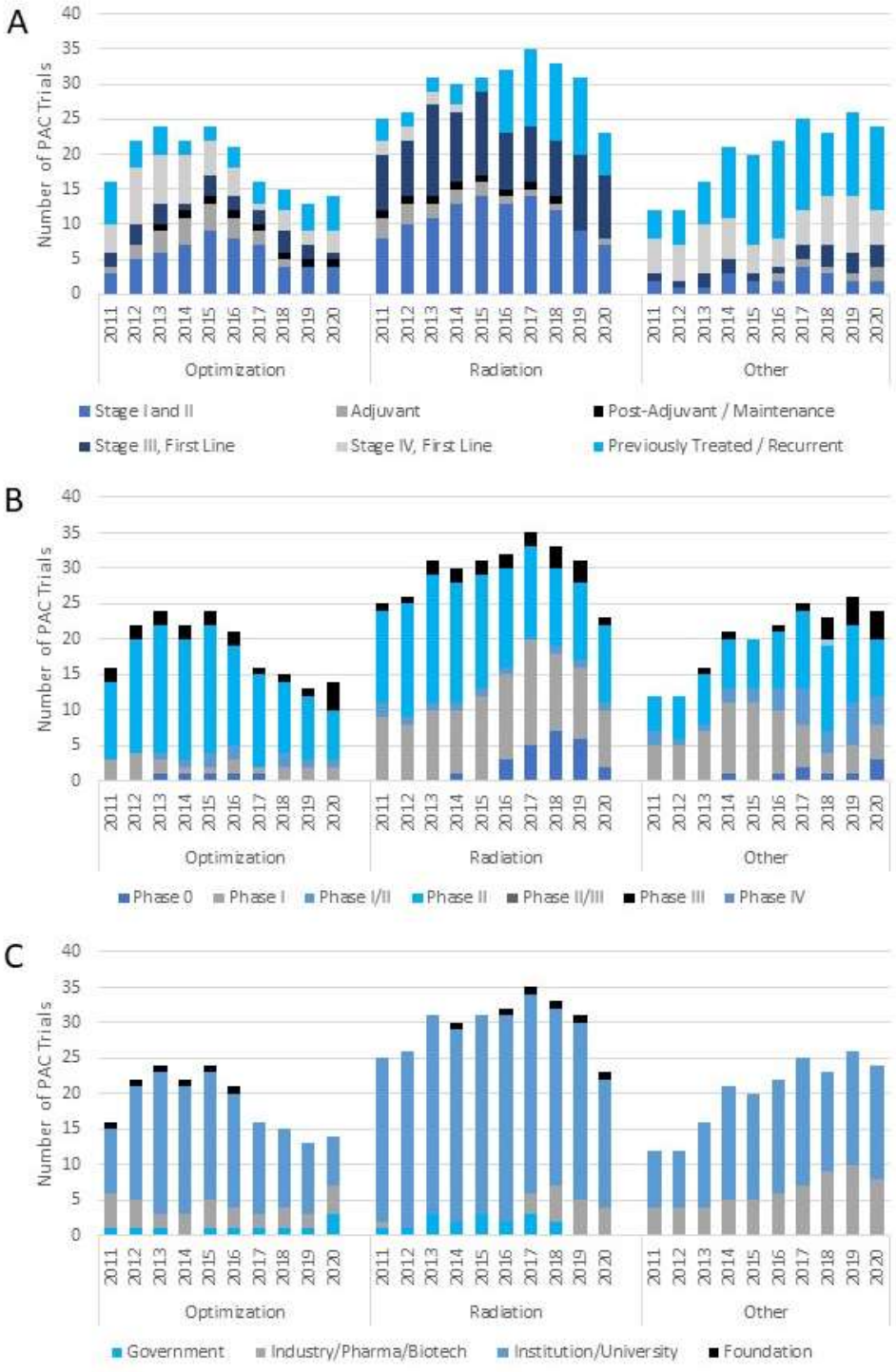

Figure 5. Standard and non-standard therapy clinical trials. The total number of open U.S. pancreatic adenocarcinoma clinical trials in the indicated years that aim to optimize standard chemotherapeutic agents (optimization), test radiation therapy approaches (radiation), or represent a non-standard approach that includes metabolism, complementary medicine, and alternative energy sources (other). Trials are stratified by stage of disease (panel A), phase of trial (panel B), or trial sponsor (Panel C).

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4.0 Advances in the treatment of pancreatic adenocarcinoma

Advances in the treatment of PAC in the U.S. depend primarily on clinical research leading to FDA approval for new treatment entities, although successful clinical trials with agents that are off patent have also changed the standard-of-care and are insurance reimbursed. Progress has historically been painfully slow. An evaluation of trial results for chemotherapy-naïve metastatic PAC up to 2015 revealed that less than 10% of phase III trials for this population resulted in a clinically meaningful change in treatment of these patients.[10] Gemcitabine became the standard-of-care for metastatic PAC in 1996, FOLFIRINOX was added based on trial results from France in 2010, and the combination of gemcitabine and nab-paclitaxel was FDA approved in 2013 (Table 1). However, over the past 5 years there has been a flurry of clinical research activity that has resulted in FDA approval of new treatments for sub-populations of pancreatic cancer patients or evidence for the efficacy of chemotherapeutic agents in specific disease states. Initial trials focused on more effective treatments for newly diagnosed stage IV patients. With FOLFIRINOX and gemcitabine plus nab-paclitaxel now both considered effective standard-of-care options for these patients, research efforts resulted in the first FDA approval of a second line treatment of 5-FU + nal-irinotecan for metastatic PAC patients who received gemcitabine in the first line.[23] There have also been accepted clinical advances resulting in the widespread use of gemcitabine-based or FOLFIRINOX-based regimens for adjuvant treatment for earlier stage PAC.[24, 25] The relative benefit of chemotherapy or radiation therapy in the preoperative versus postoperative setting and the agents of choice for neoadjuvant therapy for those diagnosed with resectable or borderline resectable disease remains a topic of debate. The results of clinical trials from Asia[26, 27] and Europe[28] support the practice in many U.S. institutions of up-front neoadjuvant therapy as the results from U.S. clinical research, in particular NCI-sponsored trials (NCT02562716, NCT04340141), are awaited.

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TABLE 1 Approved treatments for PAC in the U.S.

Year	Treatment	Population	Approval	Reference
1996	Gemcitabine	Metastatic, 1st line	FDA	[29]
2005	Gemcitabine + erlotinib	Metastatic, 1st line	FDA	[30]
2010	FOLFIRINOX	Metastatic, 1st line		[31]
2013	Gemcitabine + nab-paclitaxel	Metastatic, 1st line	FDA	[31]
2015	5-FU + nal-irinotecan	Metastatic, post gemcitabine	FDA	[23]
2016	Gemcitabine + capecitabine	Post-surgery adjuvant		[24]
2017	Pembrolizumab	Microsatellite instability (MSI-Hi) or deficient mismatch repair (dMMR)	FDA tissue agnostic	[32]
2018	Modified FOLFIRINOX	Post-surgery adjuvant		[25]
2018	Larotrectinib	NTRK fusions, refractory	FDA, tissue agnostic	[33]
2019	Entrectinib	NTRK fusions, refractory	FDA, tissue agnostic	[34]
2019	Olaparib	Germline BRCA1/2, maintenance	FDA	[35]
2020	Pembrolizumab	High tumor mutation burden (TMB)	FDA, tissue agnostic	[36]

The approval of targeted therapies for molecularly indicated subtypes of PAC and other solid tumors in recent years is notable and evidence of the impact of research efforts in pancreatic cancer specifically and in molecularly identified, tissue agnostic cancer types in general (Table 1). Although NTRK-fusions (<1%),[37] MSI-Hi/dMMR alterations (~1%),[38] and germline BRCA1/2 mutations (5-10%)[39] are found only rarely in pancreatic cancer, the existence of FDA-approved treatment options for these individuals justified NCCN guideline changes to recommend genetic testing for inherited mutations of all pancreatic cancer patients and biomarker testing of tumor tissue of all advanced pancreatic cancer patients seeking treatment.[6] This realization was not initially apparent to the field, and the difficulty and risk in obtaining sufficient primary tissue samples and the presence of activating KRAS alterations in >90% of PAC cases initially limited attempts at the application of precision medicine approaches to pancreatic cancer. However, efforts from several groups, including the International Cancer Genome Consortium,[40] Memorial Sloan Kettering,[41] the NCI The Cancer Genome Atlas,[42] and the Pancreatic Cancer Action Network[43] all indicated there are individuals with alterations in driver genes for which targeted therapies were indicated in other cancer types. In many cases, these studies were retrospective and there was insufficient opportunity to determine if treatment with molecularly indicated therapies resulted in a survival benefit for pancreatic cancer patients. The Pancreatic Cancer Action Network's Know Your Tumor® (KYT) program was designed to provide biomarker testing of tumor tissue for patients throughout the U.S. and follow treatment outcomes as a real-world study. After 5 years, more than 1000 patients, and by aggregating the results of treatment with all targeted therapies, it was concluded that approximately 27% of all pancreatic cancer patients harbored molecular alterations that indicated treatment

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with a specific therapy.[44] Moreover, these individuals had an overall survival one year longer than individuals with alterations who did not receive targeted therapy or those with no molecular alterations (2.58 vs 1.51 and 1.32 years mOS respectively). The low prevalence of specific alterations, combined with the relatively low incidence of PAC (11th most common cancer type in the U.S.), makes a traditional clinical trial approach for approval for these targeted therapies in PAC virtually impossible. The flexibility of the FDA in supporting tissue-agnostic approvals of targeted therapies for biomarker-identified cancers plays an important role in pancreatic cancer patients realizing the benefits of this research.

In addition to the benefit provided by new drug approvals, there has been improvement in overall survival with standard-of-care chemotherapies over time. For example, the mOS after treatment with gemcitabine reported in phase III trials between 1993-2000 was 5.5 months, between 2001-2006 6.2 months, and 2007-2012 8.1 months.[10] Similarly, the mOS for the clinical trial of gemcitabine plus nab-paclitaxel was 8.5 months for the trial that completed enrollment in 2012,[45] whereas the mOS for the gemcitabine/nab-paclitaxel control arm of the RESOLVE trial that completed enrollment in 2018 was 10.8 months.[46] This presumably reflects the increased experience of medical oncologists and improvements in supportive care measures to the substantial benefit of pancreatic cancer patients.

5.0 Conclusions

The trends in pancreatic cancer clinical research over the past decade are encouraging. Pancreatic clinical trials are not necessarily more numerous but are displaying trends indicating progress. These trends include:

- Increasing number of trials for previously treated patients
- Emergence of trials for post-adjuvant or maintenance therapy
- Increasing research-intensive phase 0 trials
- Increasing seamless phase I/II and II/III trials to improve efficiency
- Increasing number of phase III trials despite historical failures
- Dramatic increase in immunotherapy trials
- Biomarker-specified trials and FDA approval for biomarker-specified targeted agents
- Improved overall survival with standard-of-care chemotherapies
- Increases in non-standard approaches, many progressing to phase III trials

As we contemplate the future of pancreatic cancer clinical research, we must consider the impact of the SARS-CoV-2 pandemic. COVID-19 necessitated extremely rapid changes in the delivery of healthcare in the U.S. and galvanized the use of telemedicine for cancer care. Oncology clinical trials also had to adapt with decentralized and remote trial coordination.[47] The experience will almost certainly lead to a reduced willingness to travel for specialized healthcare treatment or clinical trials in the future. This can be seen as an advantage for diseases such as pancreatic cancer. The relatively low incidence means that the average oncologist sees few pancreatic cancer patients each year. Yet organizations such as the Pancreatic Cancer Action Network encourage seeing a specialist to ensure accurate diagnosis and treatment from those most experienced with the disease. Systems are being developed to facilitate access to specialists without physical travel, and such systems are likely to improve the dissemination of best practices throughout the U.S. With careful planning and capitalization on systemic changes, the clinical trial system can benefit, and in turn benefit the patients of the future. Pancreatic cancer clinical research is encouraged to

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continue to take calculated but bold steps towards the day when a diagnosis of pancreatic cancer is no longer the poster child for a terminal disease.

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