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Advanced Pancreatic Cancer Clinical Trials: The Continued Underrepresentation of Older Patients

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Abstract

Objectives: Older patients make up the majority of patients with pancreatic cancer, with a median age of 71 years at diagnosis. However, older patients are underrepresented in clinical trials in pancreatic cancer. This study investigates trends in age distribution of patients enrolled in clinical trials for advanced pancreatic cancer over time, and examines outcomes and toxicity in older patient subgroups from two studies conducted by Eastern Cooperative Oncology Group (ECOG) in this disease.

Materials and Methods: 16,042 patients from 38 phase III clinical trials for locally advanced or metastatic pancreatic adenocarcinoma published between 1997 and 2016 were identified and included in this analysis. Outcomes and toxicity by age were examined in two of the trials, ECOG trials E2297 and E6201, which included a total of 1,146 patients.

Results: The median age across the trials was 62.7 years; median ages for individual trials ranged from 57 years to 66 years. Weighted linear regression showed no significant change in median age over time. Combined analysis of the two ECOG trials demonstrated higher rates of fatigue, thrombocytopenia, and infection in those ≥75 years compared with those <75 years, but despite this showed no difference in overall survival (OS) or progression-free survival (PFS) (OS: 5.7 vs. 5.6 months and PFS: 2.8 vs 3.5 months).

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Conflicts of Interest: None

Conclusions: Enrollment of older adults in phase III pancreatic cancer clinical trials has not increased over time, despite increasing number of older patients seen in clinic. Increased efforts are needed to enhance enrollment of older patients in clinical trials, and to promote trials specifically for older patients, in order to improve the evidence base for treating this patient population.

Introduction

Pancreatic cancer is a disease of older adults, with a median age at diagnosis of 71, and with 66.4% of new pancreatic cancers discovered in people aged 65 and over.¹ It is one of the deadliest malignancies; currently it is the third leading cause of cancer deaths in the United States, despite being only the eleventh most commonly diagnosed cancer in men and ninth in women.² The percentage of the US population over age 65 went from 12.7% in 2010 to 14.5% in 2016, and this percentage continues to rise.³ The incidence of pancreatic cancer is also increasing, paralleling the aging population: pancreatic cancer is projected to surpass colorectal cancer and become the second leading cause of cancer deaths by 2020.⁴

While advances have been made in the treatment of pancreatic cancer in recent years, unfortunately, clinical trials in this field have overwhelmingly underrepresented older patients. Concerns regarding increased toxicity from chemotherapy in the older population contribute significantly to underrepresentation of this group in trials.⁵

Numerous larger retrospective studies using cancer registries and databases have demonstrated that older patients with good functional status benefit from chemotherapy to a similar degree as younger patients.^{6,7} These studies carry limitations including their retrospective design and likely overrepresentation of a patient population seen in high-volume centers. Smaller studies using institutional databases from academic medical centers similarly show responses in older patients receiving chemotherapy for advanced pancreatic cancer that were similar to their younger counterparts.^{8,9} By contrast, a nationwide study in the Netherlands of 9,407 patients diagnosed with metastatic pancreatic cancer from 2005–2013 found worse OS in patients ages 75 and over who received chemotherapy compared to younger patients who received chemotherapy.¹⁰ In all of these retrospective analyses, there are undoubtedly numerous confounding variables that are not captured, and contribute to these conflicting results between studies. Overall, however, the majority of retrospective studies suggest similar outcomes from chemotherapy in older patients compared with those seen in younger patients.

Despite this evidence that older patients with pancreatic cancer benefit from chemotherapy, ageism in patient enrollment to clinical trials persists. Therefore generalizability of clinical trial results to older patients is challenging, and oncologists struggle with the appropriate treatment approach to the older patient population. This challenge will only increase with rising pancreatic cancer incidence and as the population ages.

In this report, we examine the rates of enrollment of older patients in phase III clinical trials of chemotherapy regimens for pancreatic adenocarcinoma, and investigate trends in age of clinical trial participants over time. We also examine outcomes and toxicity data in older

patient from two Eastern Cooperative Oncology Group (ECOG) trials of gemcitabine-based chemotherapy treatment of locally advanced and metastatic pancreatic cancer.

Methods

Phase III clinical trials for advanced pancreatic adenocarcinoma from 1997–2016 were included. Phase III trials from 1997–2015 had been previously identified in a systematic review¹¹; trials from 2016 were added by searching clinicaltrials.gov, PubMed, and abstracts from meetings of American Society of Clinical Oncology (ASCO), including ASCO GI, European Society of Medical Oncology (ESMO), and the ESMO GI World Congress. A total of 41 eligible studies were identified. Of these, 2 abstracts and 1 paper were excluded from this analysis because authors did not report data on the ages of included participants, thus 38 studies were included in this analysis (listed in Table 1). The median ages, age ranges, and any age-related inclusion or exclusion criteria were recorded for each trial. The average median age of study participants and 95% confidence interval were calculated for all studies and for studies grouped by publication date: 2006 and earlier, 2007–2011, and 2012–2016. Weighted linear regression was used to calculate trend in median study age over time, with trend tested using the significance of the regression coefficient on time.

A subset of data from two sequential ECOG trials of gemcitabine-based chemotherapy treatment of locally advanced and metastatic pancreas cancer, E2297¹² and E6201¹³, was available. Toxicity profile and outcomes in patients ages <75 with those ages ≥75 years were compared. There were 322 patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine alone or gemcitabine plus 5-FU on protocol E2297. There were 824 patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine, gemcitabine FDR (fixed-dose rate infusion) or gemcitabine plus oxaliplatin on protocol E6201.

Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) were calculated along with their corresponding 95% confidence intervals. For the age analysis, a Cox model was used with study (E2297, E6201) and age as covariates to predict OS and PFS. Age <75 and ≥75 was compared for frequency and severity of toxicities for which data were available: fatigue, infection, neutropenia, anemia, and thrombocytopenia.

Results

A total of 16,042 patients were included in the 38 trials. The median sample size of the 38 phase III clinical trials was 349 patients (range 99–962). All studies were published between 1997 and 2016, with 14 studies before 2007, 12 studies between 2007 and 2011, and 12 studies between 2012 and 2016. Only six of the trials had criteria that explicitly excluded patients above a certain age; this age limitation ranged from >70 years to >79 years of age (see Table 1).

The median age of patients across the trials was 62.7 years (95% CI 62.2 – 63.2). Median age of individual trials ranged from 57 years to 66 years. Median ages and 95% confidence intervals for studies grouped by time periods were 61.7 (61.0 – 62.4) for studies from 1997–2006, 63 (61.8 – 64.2) for studies from 2007–2011, and 62.7 (61.2 – 64.2) for studies from

2012–2016. Only five of the 38 studies had median ages of 65 or greater, and no studies had a median age over 66. Weighted linear regression showed no statistically significant increase in median study age over time (beta coefficient= 0.05 years of age per calendar year; 95% CI (–0.07,0.17; $p=0.42$). Table 1 shows the median age of participants in each study, and Figure 2 shows the distribution of median study age versus year of publication.

For the two ECOG studies, 14% ($n=157$) of the study population was 75 or older; median ages of study participants were 65 years in E2297 and 63 years in E6201. There was no significant difference in either OS or PFS between patients over 75 years and under than 75 years of age. Median overall survival was 5.7 months in patients <75 years of age, versus 5.6 months in patients ≥75 years of age. Progression-free survival was 2.8 months in those <75 years of age, versus 3.5 months in those ≥75 years of age. Figures 3 and 4 show Kaplan-Meier plots for overall survival and progression-free survival by age groups. Rates of fatigue, infection, neutropenia, anemia and thrombocytopenia that were grade 3 were compared between those <75 and ≥75 years (Table 2). The older group experienced higher rates of fatigue (30% versus 17%; $p=0.004$), thrombocytopenia (25% versus 17%, $p=0.03$), and infection (9.5% versus 4.8%, $p=0.03$). Neutropenia and anemia were not significantly different in the two age groups.

Discussion

This report demonstrates the extent to which older patients are underrepresented in pancreatic adenocarcinoma clinical trials. While most of the studies did not explicitly exclude older patients, the median age of patients enrolled in these phase III clinical trials is almost a decade lower than the median age of patients diagnosed with pancreatic cancer (62.7 years versus 71 years). The median life expectancy of the general population currently in the United States is 78.8 years,¹⁴ and the percentage of the US population over 65 is increasing – this figure went from 12.7% in 2010 to 14.5% in 2016,³ and is expected to be nearly 20% by 2030.¹⁵ Correspondingly, the incidence of pancreatic cancer continues to rise,⁴ and the median age of patients with newly diagnosed pancreatic cancer can be expected to increase as well. Unfortunately, the present study shows that the median age of pancreatic cancer trial participants has not increased significantly over time.

Interestingly, older patients do not seem to view their age as an important factor in the decision about whether or not to enroll in clinical trials.⁵ The main reason older patients accept or decline cancer treatment is physicians' recommendations;¹⁶ this implies that action to address the under-treatment and clinical trial under-enrollment of older adults needs to come from physicians themselves. Without clinical trial data that reflect the true demographic of those suffering from pancreatic cancer, oncologists are unable to make well-informed, evidence-based treatment decisions for their older patients. As a result, clinicians understandably may continue to be reluctant to treat these patients aggressively, and hesitant to enroll them in clinical trials, which will only perpetuates the problem.

This is not a newly recognized problem: there have been multiple papers calling for increased accrual of older patients to cancer clinical trials, and recommending methods to do so, for over 15 years.^{5,17–21} An ASCO statement published in *Journal of Clinical Oncology*

in 2015 made recommendations to improve evidence generation in older adults with cancer, in response to a critical need identified by the Institute of Medicine.²² The statement proposes a multipronged approach that includes increasing older adults' access to clinical trials by using trial designs that allow for better data collection and analysis in older patients, encouraging clinicians to increase recruitment of older adults to clinical trials, and using less stringent eligibility criteria.²¹ Even without a strict upper age limit, age-related factors such as a suboptimal performance status, previous cancers, certain comorbid diseases, and hepatic and renal function exclude many older patients from clinical trials. Thus, when designing clinical trials, we need to carefully examine inclusion and exclusion criteria to relax them wherever it is safe to do so. Allowing ECOG Performance Status 0–2 rather than 0–1 would likely have a significant impact on the percentage of older patients who would be eligible for a trial. It is also important to consider that pancreatic cancer itself may affect performance status and physical fitness, particularly in older patients.

Our separate analysis of the two ECOG studies demonstrates similar efficacy of gemcitabine-based chemotherapy in older patients ages 75 and over compared with their younger counterparts, although with higher rates of fatigue, infection, and thrombocytopenia. There have been subgroup analyses of a few of the other 36 phase III clinical trials of advanced pancreatic adenocarcinoma. Similar to our analysis these showed a clinical benefit from chemotherapy in older and younger patients alike. In the subgroup analysis of the GEST study, Imaoka et al found gemcitabine to confer a similar overall survival among patients ≥70 years and <70 years (8.5 months vs. 8.9 months respectively; $p=0.275$), compared with 4.2 months in patients of all ages who received supportive care only. In their study, grade 3 thrombocytopenia was more common in older patients, however rates of other toxicities were similar in all age groups.²³ Subsequent analyses of the MPACT trial demonstrated improved overall survival with *nab*-paclitaxel plus gemcitabine versus gemcitabine alone in the older patient (≥65 years) subgroup. However, the magnitude of the benefit was lower in the older patients cohort: 9.6 vs. 6.8 months ($p<0.001$) for patients <65 years old; 7.7 vs. 6.5 months ($p=0.048$) for patients ≥65 years old.^{24–26}

The paucity of data on the efficacy and tolerability of more toxic chemotherapy regimens in older adults is even more pronounced. The landmark trial that established FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) as standard-of-care first-line therapy excluded patients older than 75, thus the authors limit the recommendation to patients younger than 76 years.²⁷ Despite this, some clinicians have elected to treat their fit older patients with this regimen, and several small retrospective studies of older patients treated with FOLFIRINOX in Europe have found similar or better median survival rates compared with previously published results in younger patients, albeit with higher toxicity.^{28,29} In these studies, toxicities were managed with dose reductions and GCSF; these dose reductions did not significantly impact OS. The recent phase III NAPOLI-1 study led to the approval of 5FU + liposomal irinotecan (Nal-IRI) in second line treatment of metastatic pancreatic cancer. A post-hoc subgroup analysis by patient age demonstrated similar benefit among older patients and their younger counterparts with similar toxicity profile and rates of dose modifications.³⁰

Current National Comprehensive Cancer Center (NCCN) guidelines for untreated metastatic pancreatic adenocarcinoma recommend either a clinical trial (preferred option), FOLFIRINOX, or combination of gemcitabine plus nab-paclitaxel as the preferred first-line treatment for all patients with good functional status, and do not make specific recommendations based on age.³¹ The NCCN does however recommend a comprehensive geriatric assessment to derive a complete assessment of a patient's fitness for therapy, to help guide individual treatment decisions.³² Several tools have been developed in recent years to assess risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score,³³ and the Cancer and Aging Research Group (CARG) Chemotherapy Toxicity Calculator.^{34,35} Since health status and fitness is especially heterogeneous in older patients, and chronological age can differ markedly from functional age, these tools can help clinicians move toward making better decisions about treatment and clinical trial enrollment based on the latter.

In addition to increasing enrollment of older adults in regularly accruing trials for patients of all ages, more effort should be placed on designing trials specifically for older patients. There have been such studies in metastatic colorectal cancer: the FOCUS2 trial and AVEX trial investigated reduced-dose and better tolerated chemotherapy regimens, respectively, in older patients. These trials demonstrate feasibility and utility of designing clinical trials focused on an older patient population.^{36,37} However, thus far there have been no studies testing chemotherapy regimens specifically in older adults with advanced pancreatic cancer. There is currently one ongoing trial of a modified version of FOLFIRINOX being tested in patients 70 years and older in the French phase II PAMELA-70 study [[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02143219) identifier: NCT02143219].³⁸

The design of clinical trials for older patients should reflect the unique characteristics of this population. Geriatric assessment tools, such as the aforementioned CRASH tool and CARG Chemotherapy Toxicity score, can be used in several ways. First, these tools can be used as part of eligibility criteria to ensure that older patients are selected for trials in a systematic way. Second, the geriatric assessment variables can be incorporated as variables in study analyses to help determine what factors predict better outcomes and better tolerance of chemotherapy in older patients. A current limitation of the CRASH and CARG tools is that they were developed and validated in cohorts of older patients with all types of cancers, at all stages of disease.^{33,35} Inclusion of these tools in studies of advanced pancreatic cancer will help elucidate their applicability in informing treatment decisions for this patient population, and help define patient characteristics that predict better outcomes. Studies in older adults should also evaluate outcomes other than overall survival that may be especially important to older adults, such as quality of life and maintenance of independence.³⁹ In the FOCUS2 trial in metastatic colorectal cancer, a baseline comprehensive health assessment was performed, and variables from this assessment were analyzed as predictors of an "overall treatment utility" composite measure, intended to better capture meaningful outcomes in the older patient population.³⁶ This type of study design that uses variables pertinent to older patients is needed in advanced pancreatic cancer clinical trials as well.

There are several limitations of the present study. The two ECOG studies were selected for analysis based on data availability, and only a subset of the data from these studies was

available. These two studies are older (published in 2002 and 2009), however the baseline characteristics of patients in these trials were similar to those in more recent studies (slight male predominance, large majority moderately or poorly differentiated tumors, and >90% metastatic disease rather than locally advanced). Gemcitabine-based chemotherapy regimens remain the mainstay of treatment in older adults, thus the data from these trials are still relevant. Outcomes by age group from the two ECOG studies presented here were initially analyzed for a previously drafted manuscript (data unpublished); the Kaplan Meier plots, overall survival, progression-free survival were available and thus are presented here, but corresponding *p*-values from those analyses were not. Additionally, only five toxicities were examined from these studies; these included neutropenia, anemia, and thrombocytopenia, which are among the most frequent and more relevant toxicities, and the most common indications for dose reductions of gemcitabine.⁴⁰

This study demonstrates that despite mounting evidence that older adults with advanced pancreatic cancer benefit from chemotherapy, with manageable toxicities, they continue to be underrepresented in clinical trials. This is a disservice to these patients and to the advancement of clinical research in this field. As clinical researchers, we need to ensure that older patients have access to trials, and focus on design of studies targeting specifically this patient population.

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Figure 1.
Flow Diagram Outlining the Methodology

Figure 2.
Median Age of Subjects Enrolled in Phase III Pancreatic Cancer Clinical Trials Over Time

Figure 3.
Kaplan-Meier Plot of Overall Survival by Age

Figure 4.
Kaplan-Meier Plot of Progression-Free Survival by Age

Table 1:

List of phase III clinical trials examined

Author	Year	Journal	n	Median Age	Age Range	Ages Excluded	Title
Burris	1997	J Clin Oncol	126	61.5	36–79	-	Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial
Bramhall	2001	J Clin Oncol	414	63	29–89	-	Marimastat as First-Line Therapy for Patients With Unresectable Pancreatic Cancer: A Randomized Trial
Colucci	2002	Cancer	107	61	33–75	> 75 yrs	Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma
Berlin	2002	J Clin Oncol	322	65	28–85	-	Phase III Study of Gemcitabine in Combination With Fluorouracil Versus Gemcitabine Alone in Patients with Advanced Pancreatic Carcinoma: Eastern Cooperative Oncology Group Trial E2297
Bramhall	2002	Br J Cancer	239	62	32–85	-	A double-blind placebo-controlled, randomized study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer
Moore	2003	J Clin Oncol	277	66	Not reported	-	Comparison of Gemcitabine Versus the Matrix Metalloproteinase Inhibitor BAY 12–9566 in Patients With Advanced or Metastatic Adenocarcinoma of the Pancreas
Rocha Lima	2004	J Clin Oncol	360	62	32–82	-	Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate
Van Cutsem	2004	J Clin Oncol	688	62	29–89	-	Phase III Trial of Gemcitabine Plus Tipifarnib Compared With Gemcitabine Plus Placebo in Advanced Pancreatic Cancer
Louvet	2005	J Clin Oncol	313	63	22–77	> 75 yrs	Gemcitabine in Combination With Oxaliplatin Compared With Gemcitabine Alone in Locally Advanced Metastatic Pancreatic Cancer
Oettle	2005	Ann Oncol	565	63	22–82	-	A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer
Reni	2005	Lancet Oncol	99	61	25–69	> 70 yrs	Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomized controlled multicenter phase III trial
Abou-Alfa	2006	J Clin Oncol	349	63	30–85	-	Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer
Heinemann	2006	J Clin Oncol	195	65	37–85	-	Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer
Stathopoulos	2006	Br J Cancer	130	64	31–84	-	A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer
Moore	2007	J Clin Oncol	569	64	36–92	-	Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer
Ciuleanu	2009	Eur J Oncol	303	57	27–80	-	A randomized Phase III trial of glufosamide compared with best supportive care in metastatic adenocarcinoma previously treated with gemcitabine
Cunningham	2009	J Clin Oncol	533	62	26–83	-	Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer

Author	Year	Journal	n	Median Age	Age Range	Ages Excluded	Title
Poplin	2009	J Clin Oncol	824	63	29–96	-	Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E2601: A Trial of the Eastern Cooperative Oncology Group
Van Cutsem	2009	J Clin Oncol	607	62	20–85	-	Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer
Dahan	2010	Gut	202	63	39–84	-	Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomized strategic phase III trial (FFCD 0301)
Colucci	2010	J Clin Oncol	238	63	35–75	-	Randomized Phase III Trial of Gemcitabine Plus Cisplatin Compared With Single-Agent Gemcitabine As First-Line Treatment of Patients With Advanced Pancreatic Cancer
Philip	2010	J Clin Oncol	743	64	Not reported	-	Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma
Kindler	2010	J Clin Oncol	602	64	26–88	-	Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer
Conroy	2011	New Engl J Med	342	61	25–76	> 75 yrs	FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer
Kindler	2011	Lancet Oncol	630	62	26–88	-	Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma
Goncalves	2012	Ann Oncol	104	62.5	40–85	-	BAYPAN study: a double blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer
Heinemann	2013	Gut	274	64	32–78	> 75 yrs	Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer
Von Hoff	2013	New Engl J Med	861	63	27–88	-	Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine
Ueno	2013	J Clin Oncol	832	65	Not reported	> 79 yrs ^a	Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study
Rougier	2013	Eur J Cancer	546	61	34–88	-	Randomized, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer
Oettle	2014	J Clin Oncol	160	63	37–83	-	Second-line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial
Middleton	2014	Lancet Oncol	962	63	55–69	-	Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced metastatic pancreatic cancer (TeloVac): an open-label, randomized, phase 3 trial
Fuchs	2015	Ann Oncol	800	62	31–85	-	A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial
Deplanque	2015	Ann Oncol	348	62	31–84	-	A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer
O'Neil	2015	Ann Oncol	160	63	29–87	-	A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer

Author	Year	Journal	n	Median Age	Age Range	Ages Excluded	Title
Wang-Gillam	2016	Lancet	417	63	55–70	-	Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based chemotherapy (NAPOLI-1)
Gill	2016	J Clin Oncol	108	66	38–82	-	PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy
Van Cutsem	2016	J Clin Oncol (abstract)	693	65	27–87	-	Evofosfamide (TH-302) in Combination With Gemcitabine in Previously Untreated Patients with Metastatic or Locally Advanced Unresectable Pancreatic Ductal Adenocarcinoma

^aProtocol amended to exclude those > 79 years old after four of the first eight patients who were over 79 years of age experienced serious side effects.

Table 2.

Combined Grade 3+ Toxicities By Age From E2297 And E6201

Toxicity Type	Toxicity Rates (%)		P-Value
	75 Years	<75 Years	
Fatigue *	29.7	16.8	0.004
Neutropenia	27.7	21.6	0.11
Thrombocytopenia	25.0	17.1	0.03
Infection	9.5	4.8	0.03
Anemia	8.8	11.3	0.48

E2297 Had 321 Cases (Out Of 322) Assessable For Toxicity; E6201 Had 802 Cases (Out Of 824) Assessable For Toxicity. 14% Of Total Study Population (N=157) Was 75 Years Old.

* Fatigue Only Assessed In E6201