ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Survival analysis of the non-metastatic cohort of the Italian Association for Medical Oncology (AIOM) Guideline Application in Real world: multi-Institutional Based survey of Adjuvant and first-Line pancreatic Ductal adenocarcinoma treatment in Italy (GARIBALDI)

M. Reni[1*], M. Milella[2], F. Bergamo[3], M. Di Marco[4,5], E. Giommoni[6], G. G. Cardellino[7], L. Cavanna[8], M. Bonomi[9], F. Zustovich[10], S. Bozzarelli[11], F. Salmaso[12], M. Spada[13], G. Orsi[1], M. Macchini[1], J. Insolda[2], L. Procaccio[3], A. Santoni[14], I. De Simone[14], L. Caldirola[14], F. Galli[14] & C. Pinto[15]

[1]Medical Oncology Department, IRCCS Ospedale San Raffaele, Milan; [2]Section of Innovation Biomedicine, Department of Engineering for Innovation Medicine (DIMI), University of Verona and Verona University and Hospital Trust (AOUI), Verona; [3]Medical Oncology 1, Department of Oncology, Veneto Institute of Oncology IOV—IRCCS, Padova; [4]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna; [5]Medical Oncology Unit, IRCSS Azienda Ospedaliero Universitaria di Bologna, Bologna; [6]SODc Oncologia Medica AOU Careggi, Florence; [7]Dipartimento di Area Oncologica, ASUFC Udine, Udine; [8]Oncology and Hematology Department, Oncology Unit, Piacenza General Hospital, Piacenza; [9]Oncology Unit, ASST di Cremona, Cremona; [10]UOC Oncologia, AULSS 1 Dolimiti, Belluno; [11]IRCCS Humanitas Research Hospital, Milan; [12]Oncologia di Castelfranco Veneto, Castelfranco Veneto; [13]Fondazione Istituto G. Giglio di Cefalù, Cefalù; [14]Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; [15]AUSL-IRCCS Clinical Cancer Center of Reggio Emilia, Reggio Emilia, Italy

Available online XXX

Background: Non-metastatic pancreatic ductal adenocarcinoma (PDAC) presents a challenging scenario: the rarity of the disease, the limited number of completed prospective trials, and the shortcomings of comparability across series produce several controversial topics and unanswered questions. Guideline recommendations usually include all the different therapeutic options, *de facto* transferring to the multidisciplinary team the responsibility on the final decision. This secondary analysis of the GARIBALDI study was aimed to explore the correlation of center type, self-declared volume, and commitment with the overall survival (OS) in patients with non-metastatic PDAC.

Patients and methods: Treatment-naïve patients aged $\geq$18 years with a pathological diagnosis of non-metastatic PDAC, enrolled between July 2017 and October 2019, were analyzed. OS was defined as the time from treatment start to death. The impact of centers and clinical—demographic characteristics on OS was evaluated using Cox models.

Results: Overall, 402 patients enrolled in 41 centers were eligible for this analysis. The median age was 68.4 years (range 35.6-88.8 years), 49.5% were females, 93.5% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, 16.7% had prior cancer history, and the median CA 19-9 level was 171.5 IU/ml (first-third quartile 24.5-937.5 IU/ml). For 79.8% of patients treatment started within 1 month from diagnosis. Thirty six point six percent of patients underwent upfront surgery and 91.8% of these received a subsequent adjuvant chemotherapy; 14.2% received chemotherapy followed by surgery and 49.3% chemotherapy without surgery. The preferred chemotherapy schemes were gemcitabine (54.8%) for adjuvant chemotherapy and nab-paclitaxel + gemcitabine (55.3%) for upfront chemotherapy. The median follow-up was 57.6 months and 300 patients died. A statistically significant shorter OS was observed in both low- [hazard ratio (HR) 1.61, 95% confidence interval (CI) 1.12-2.32, $P = 0.0099$] and medium-commitment (HR 1.57, 95% CI 1.10-2.23, $P = 0.0120$) compared to high-commitment institutions, when adjusting for clinically relevant covariates.

Conclusion: The GARIBALDI study suggests that the volume and the academic brand are not associated with OS in patients with non-metastatic PDAC, while center commitment warrants further exploration.

Key words: pancreatic cancer, adenocarcinoma, non-metastatic, center volume, PDAC treatment

INTRODUCTION

Most patients affected by pancreatic ductal adenocarcinoma (PDAC) present a metastatic disease (50%-55%) at diagnosis.[1] Stage assessment is predominantly straightforward and therapeutic management includes limited options

*Correspondence to: Dr Michele Reni, Department of Medical Oncology, IRCCS Ospedale San Raffaele, Milan, Italy
E-mail: Reni.michele@hsr.it (M. Reni).

both in terms of strategy, which usually consists of systemic treatment only, and of available chemotherapy agents. Conversely, non-metastatic PDAC presents a more challenging scenario also due to drawbacks of diagnostic work-up generating a poorly reproducible surgical classification including heterogeneous definitions, which vary widely over time and among institutions, and subjective interpretation.[2,3] The rarity of the disease, the limited number of completed prospective trials, and the shortcomings of comparability across series produced several controversial topics and unanswered questions, such as the role and duration of neoadjuvant chemotherapy or the role and timing of (chemo)radiotherapy. In this context, guideline recommendations usually include all the different therapeutic options, *de facto* transferring to the multidisciplinary team the responsibility of the final decision.

Albeit the relationship between surgical center volume and operative mortality of patients with PDAC is well known,[4] whether the different volume of the center may impact on the overall outcome of patients is an unexplored topic.

The national, multicenter, prospective Guideline Application in Real world: multi-Institutional Based survey of Adjuvant and first-Line pancreatic Ductal adenocarcinoma treatment in Italy (GARIBALDI) collected data on the therapeutic management of treatment-naïve patients with PDAC in a real-world context to evaluate the agreement with national recommendations included in the Italian Association of Medical Oncology (AIOM) guidelines.[5] The aim of this secondary analysis was to explore the association between the oncology center volume, type, and commitment and the overall survival (OS) in chemo-naïve patients with non-metastatic PDAC.

PATIENTS AND METHODS

Forty-six centers, representative of different geographical and expertise areas, were selected for the GARIBALDI study, as previously described.[5] The institutions that accepted to participate in the survey were categorized based on: (i) self-declared volume (high volume with >50 patients with PDAC treated/year; medium volume with 25-50 patients treated/year; low volume with <25 patients treated/year); (ii) type (academic; general hospital); (iii) commitment (high commitment with >50 patients/year; medium commitment with 10-50 patients/year; low commitment with <10 patients/year). The commitment was calculated by dividing the total number of patients enrolled in the GARIBALDI study by the duration of participation in the study of the institution.

For the purpose of this secondary analysis, patients aged ≥18 years with a pathological diagnosis of non-metastatic PDAC, who were medical treatment naïve and received an active treatment in the participating centers, irrespective of chemotherapy regimen and performance status (PS) who were enrolled into the study between July 2017 and October 2019 and observed were considered.

The GARIBALDI study was approved by the ethics committees of all study sites, was conducted as per Good Clinical Practice (GCP) guidelines, and complied with the Declaration of Helsinki.

All patients provided written informed consent for study participation and data processing before any study-specific procedures.

Consenting patients were centrally registered by a web system, accessible 24 h a day at this address: https://GARIBALDI.aiom.it. Afterward, a unique identification number was assigned.

Data collected were pseudonymized in order to guarantee the protection of privacy as for D.Lgs. 196/2003 and Del n. 52, 24 July 2008 and for the General Data Protection Regulation 679/16—'European regulation on the protection of personal data'. Data collection was electronically done through a remote data entry and complied with GCP procedures, allowing integrity and transparency of data and maintaining memory of the changes done. Most of the monitoring activities were centralized by systematically checking each reported information for consistency, completeness, and accuracy by the coordinating data center that, if appropriate, issued data clarification forms.

The reverse Kaplan—Meier (KM) method was used to calculate the median follow-up. The follow-up completeness was defined as the ratio between the observed and potential follow-up, where the potential follow-up is the time from the start of follow-up to death or data snapshot, whichever comes first.

The OS was defined as the interval between the date of first administration of medical therapy and death from any cause. For alive patients at time of this analysis, survival data were right-censored to the date of last information available. Survival distributions were estimated by the KM method, described by means of median survival and 95% confidence intervals (95% CIs), and compared using the log-rank test.

Univariable and multivariable Cox proportional hazards models were estimated to evaluate the association between the institutions' characteristics described in the preceding text and the OS. All the multivariable models included demographical (age and sex) and clinical [body mass index (BMI), ECOG PS, baseline CA 19-9, prior cancer history, general practitioner as first physician, tumor stage, time from disease diagnosis to chemotherapy] prognostic characteristics. The hazard ratios (HRs) and 95% CIs were provided.

Continuous variables were summarized by mean, standard deviation, first quartile (Q1), median, third quartile (Q3), ranges (minimum and maximum), and number of missing values. Categorical variables were summarized by frequency and proportion of each subject in each category. The chi-square test was carried out to compare the distributions of categorical variables. Student's *t*-test and the Kruskal—Wallis test, as appropriate, were carried out to compare the distributions of continuous variables.

All analyses were done with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

During the period considered for this subgroup analysis, 402 non-metastatic patients were enrolled by 41 centers, each contributing with a median number of 7 patients (range

Table 1. Demographics and other baseline characteristics

	Overall $n = 402$
Age (years)	
Mean (SD)	67.7 (9.6)
Median (Q1-Q3)	68.4 (61.2-75.2)
Min-max	35.6-88.8
Gender, *n* (%)	
Male	203 (50.5)
Female	199 (49.5)
BMI classes, *n* (%)	
Underweight	25 (6.4)
Normal weight	232 (59.5)
Overweight	103 (26.4)
Obese	30 (7.7)
Missing	12
ECOG PS, *n* (%)	
0	232 (58.0)
1	142 (35.5)
2+	26 (6.5)
Missing	2
First physician to see the patient, *n* (%)	
General practitioner	112 (28.2)
Emergency	90 (22.7)
Surgeon	74 (18.6)
Digestive	51 (12.8)
Internal medicine	47 (11.8)
Oncologist	8 (2.0)
Other/unknown	15 (3.8)
Missing	5
CA 19-9 at core biopsy, IU/ml	
Mean (SD)	2367.3 (19 417.3)
Median (Q1-Q3)	171.5 (24.5-937.5)
Min-max	0.0-350 933
Missing	46
CA 19-9 levels at core biopsy, *n* (%)	
CA 19-9 $\leq$ 200 IU/ml	128 (36.0)
200 IU/ml $<$ CA 19-9 $<$ 3150 IU/ml	116 (32.6)
CA 19-9 $\geq$ 3150 IU/ml	112 (31.5)
Missing	46
Prior cancer history, *n* (%)	
No	335 (83.3)
Yes	67 (16.7)
Disease status, *n* (%)	
Resectable	155 (39.0)
Borderline resectable	106 (26.7)
Unresectable	136 (34.3)
Missing	5
Tumor stage	
Tumor stage IA, *n* (%)	21 (5.7)
TNM (tumor—node—metastasis) staging, *n* (%)	
T1/N0	21 (100.0)
Tumor stage IB, *n* (%)	47 (12.8)
TNM staging, *n* (%)	
T2/N0	47 (100.0)
Tumor stage IIA, *n* (%)	32 (8.7)
TNM staging, *n* (%)	
T3/N0	32 (100.0)
Tumor stage IIB, *n* (%)	120 (32.7)
TNM staging, *n* (%)	
T1/N1	9 (7.6)
T2/N1	59 (49.6)
T3/N1	51 (42.9)
Missing	1
Tumor stage III, *n* (%)	147 (40.1)
TNM staging, *n* (%)	
T2/N2	25 (17.1)
T3/N2	11 (7.5)
T4/N0	16 (11.0)
T4/N1	52 (35.6)
T4/N2	4 (2.7)
T4/Nx	37 (25.3)
Tx/N0	1 (0.7)
Missing	1
No information about tumor stage	35

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; min-max, minimum-maximum values; *n*, number of patients; Q1-Q3, first-third quartile; SD, standard deviation.

1-90 patients), while 5 participating institutions did not contribute with any patient. The median age was 68.4 years (range 35.6-88.8 years), half of the patients were females, about one-third ($n = 133/390$; 34.1%) were overweight/obese, and 67 (16.7%) had prior cancer history. The majority of patients had a baseline ECOG score <2 ($n = 374$; 93.5%); the median CA 19-9 value at core biopsy was 171.5 IU/ml (Q1-Q3 24.5-937.5 IU/ml, 46 missing). Moreover, tumor stage at study entry was I for 68 patients (18.5%), II for 152 patients (41.4%), and III for 147 patients (40.1%); no information about tumor stage was collected for 35 patients. Out of 397 non-missing patients, 155 (39.0%) were classified at core biopsy as resectable, 106 (26.7%) as borderline resectable, and 136 (34.3%) as unresectable. The first physician to visit the patient was the general practitioner for 112 (28.2%) patients, the oncologist for 8 (2.0%) patients, and the surgeon for 74 (18.6%) patients, whereas for 5 patients this information was not collected (Table 1). Baseline patients' and tumors' characteristics and treatment are reported according to the center classifications in Supplementary Tables S1, S2, and S3, available at https://doi.org/10.1016/j.esmoop.2024.104001. A younger age and a higher CA 19-9 level in academic centers compared with general hospitals and different proportions of ECOG PS between the self-declared volume groups were detected. Moreover, the comparison according to the commitment highlighted statistically significant differences in terms of BMI classes, proportion of patients visited by the general practitioner as the first physician, and tumor stage.

The distribution of patients based on type of institution is reported in Table 2. Most patients were treated at an academic institution ($n = 250$; 62.2%) or in a self-declared high-volume center ($n = 262$; 67.4%). One single institution has reached the threshold of 50 enrolled patients to be classified as a high-commitment center, enrolling 90 patients (22.4%).

Table 2. Characteristics of recruiting centers

	Patients $n = 402$	Centers $n = 41$
Type of institution		
Academy	250 (62.2)	17 (41.5)
General hospital	152 (37.8)	24 (58.5)
Hospital self-declared expertise, *n* (%)		
<25 pancreatic patients/year	55 (14.1)	9 (23.7)
25-50 pancreatic patients/year	72 (18.5)	12 (31.6)
>50 pancreatic patients/year	262 (67.4)	17 (44.7)
Missing	13	3
Overall commitment, *n* (%)		
<10 pancreatic patients/year	162 (40.3)	29 (70.7)
10-50 pancreatic patients/year	150 (37.3)	11 (26.8)
>50 pancreatic patients/year	90 (22.4)	1 (2.4)

n, number of patients.

Table 3. Treatments administered

	Overall $n = 402$
Time from disease diagnosis to therapy start, *n* (%)	
Less than 2 weeks	158 (40.8)
Between 2 weeks and 1 month	151 (39.0)
More than 1 month	78 (20.2)
Missing	15
Time from last imaging evaluation to therapy start, *n* (%)	
Less than 4 weeks	121 (32.2)
Between 4 and 7 weeks	134 (35.6)
More than 7 weeks	121 (32.2)
Missing	26
Treatment received, *n* (%)	
Only surgery	12 (3.0)
Only chemotherapy (upfront chemotherapy)	198 (49.3)
Chemotherapy + surgery (upfront chemotherapy)	57 (14.2)
Surgery + chemotherapy (adjuvant treatment)	135 (33.6)
Chemotherapy scheme for upfront chemotherapy treatment, *n* (%)	
Nab-paclitaxel + gemcitabine	141 (55.3)
FOLFIRINOX	71 (27.8)
Gemcitabine	27 (10.6)
Other	16 (6.3)
Chemotherapy scheme for adjuvant treatment, *n* (%)	
Gemcitabine	74 (54.8)
FOLFIRINOX	30 (22.2)
Nab-paclitaxel + gemcitabine	5 (3.7)
Other	26 (19.3)
Radiotherapy received, *n* (%)	
No	268 (67.5)
Yes	129 (32.5)
Missing	5

Min-max, minimum-maximum values; *n*, number of patients; Q1-Q3, first-third quartile; SD, standard deviation.

Table 3 summarizes the treatment administered. Patients were treated mainly within 1 month from the pathological diagnosis ($n = 309/387$; 79.8%) and within 7 weeks from the last imaging evaluation ($n = 255/376$; 67.8%). Upfront surgery was carried out in 147 (36.6%) patients, while 57 (14.2%) patients received chemotherapy followed by surgery, and 198 (49.3%) chemotherapy without surgery.

General hospitals, self-declared low-volume centers, and low- or medium-commitment institutions less often recommended neoadjuvant therapy and adjuvant radiotherapy when compared with academic centers, self-declared medium- or high-volume centers, and high-commitment centers, respectively (Supplementary Tables S4, S5, and S6, available at https://doi.org/10.1016/j.esmoop.2024.104001).

Adjuvant chemotherapy was administered to 135 of 147 (91.8%) patients who were resected upfront and the preferred regimen was gemcitabine ($n = 74$; 54.8%) followed by chemotherapy treatment (FOLFIRINOX) ($n = 30$; 22.2%). No statistically significant difference was observed across institutions' categories in terms of administered regimens in the adjuvant setting, albeit a trend toward a more limited use of FOLFIRINOX was observed in general hospitals as opposed to academic institutions ($n = 7$; 12.1% versus $n = 23$; 29.9%, respectively) (Supplementary Tables S4, S5, and S6, available at https://doi.org/10.1016/j.esmoop.2024.104001). Upfront chemotherapy was administered to 255 patients (63.4%) mainly consisting of either nab-paclitaxel + gemcitabine ($n = 141$; 55.3%) or FOLFIRINOX ($n = 71$; 27.8%). While no significant difference in terms of regimen was observed based on institution's type and volume (Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.esmoop.2024.104001), the high-commitment institution never used the FOLFIRINOX regimen and had a statistically significant more frequent use of nab-paclitaxel + gemcitabine combination (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.104001).

The data snapshot date for the purpose of this analysis was 1 March 2024. Overall, the median follow-up is 57.6 months (95% CI 55.6-60.8 months), the follow-up completeness is 85.7%, and 300 (74.6%) patients died.

Although no statistically significant difference was found ($P = 0.1001$; Figure 1A), the median OS was longer in academic institutions as opposed to general hospitals (22.4 months, 95% CI 18.7-26.8 months versus 20.6 months, 95% CI 16.9-23.0 months, respectively).

Similarly, no statistically significant difference was found in terms of OS according to the volume centers ($P = 0.1171$; Figure 1B), but a clinically longer median OS was estimated in self-declared high-volume centers (23.7 months, 95% CI 19.3-26.9 months) compared with low-volume institutions (16.0 months, 95% CI 12.3-22.6 months) and medium-volume institutions (21.4 months, 95% CI 15.0-23.0 months).

Considering the commitment, a statistically significant difference between the three groups in terms of OS was not reached ($P = 0.0713$; Figure 1C), but a clinically not negligible difference in terms of median OS was observed between the high-commitment (27.4 months, 95% CI 18.1-35.5 months) and the low-commitment institutions (19.0 months, 95% CI 15.8-22.6 months). The median OS observed in the medium-commitment institutions was 22.4 months (95% CI 18.7-25.2 months).

As summarized in Table 4 and Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.104001, the univariable and multivariable analyses did not demonstrate any statistically significant increase in terms of risk of death in patients treated in a general hospital compared with

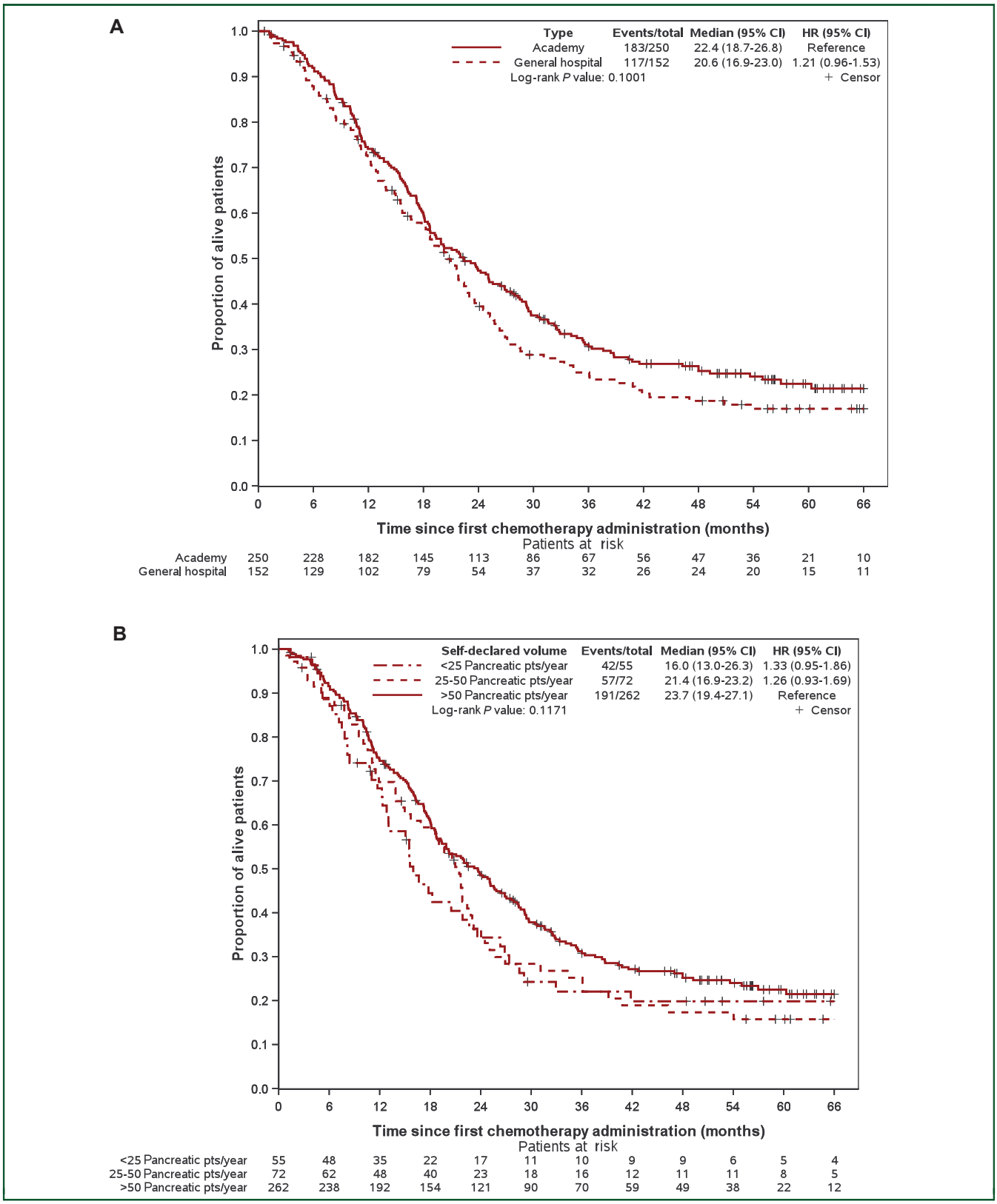

Figure 1. Kaplan–Meier curve of overall survival. Kaplan–Meier curve of overall survival according to (A) the type of institution, (B) the pancreatic self-declared expertise of the hospital, and (C) the centers' commitment.
CI, confidence interval; HR, hazard ratio; pts, patients.

patients treated in an academic institution (unadjusted HR 1.21, 95% CI 0.96-1.53, $P = 0.1008$; adjusted HR 1.23, 95% CI 0.93-1.62, $P = 0.1517$) as well as in patients treated in self-declared medium-volume centers (unadjusted HR 1.26, 95% CI 0.93-1.69, $P = 0.1309$; adjusted HR 1.15, 95% CI 0.80-1.65, $P = 0.4477$) or self-declared low-volume centers

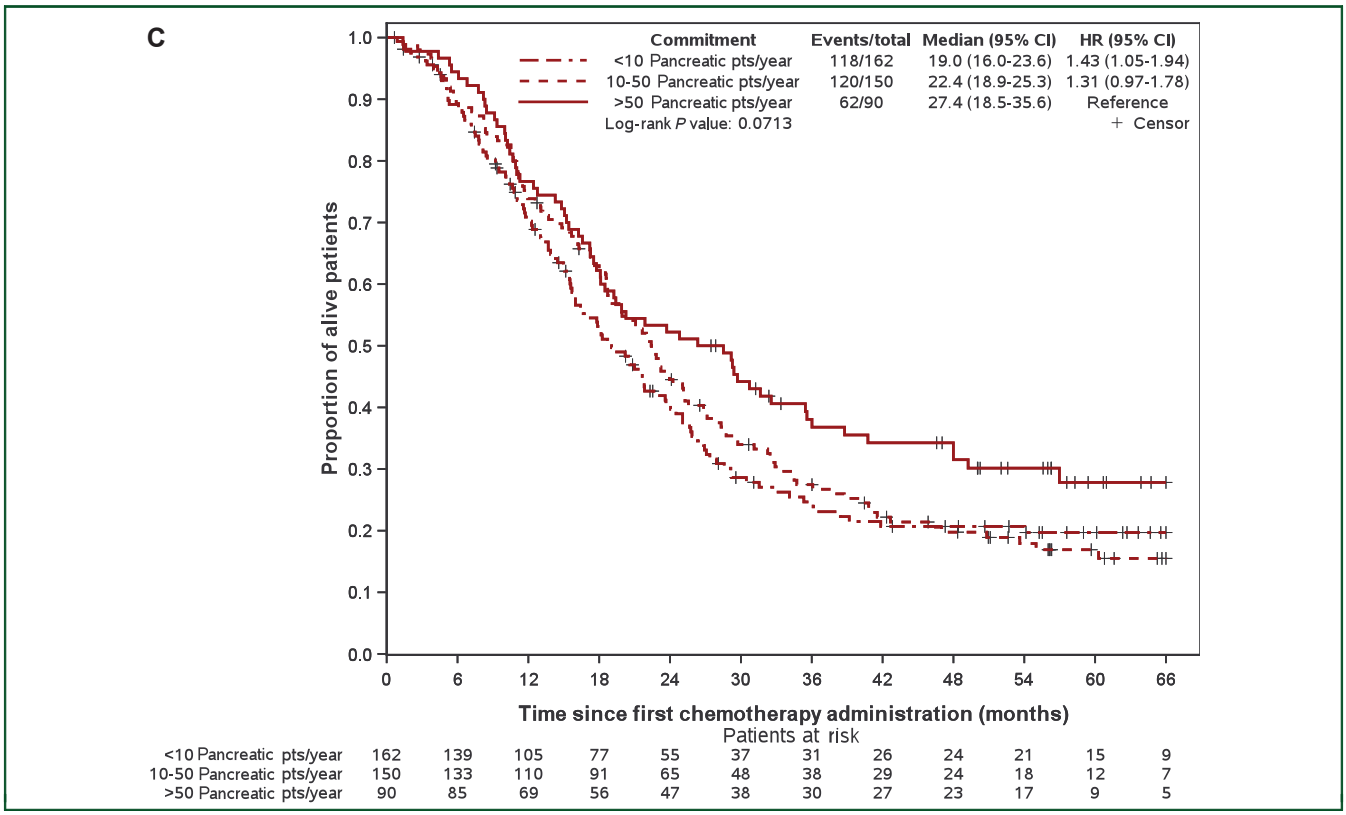

Figure 1. **Continued.**

Table 4. **Impact of recruiting centers' characteristics and demographic and clinicopathological characteristics on overall survival**

	Type of institution (n = 306)		Hospital self-declared volume (n = 296)		Overall commitment (n = 306)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
General hospital versus academy	1.23 (0.93-1.62)	0.1517				
Hospital self-declared volume (ref. >50 pancreatic patients/year)				0.2463		
<25 pancreatic patients/year			1.38 (0.93-2.05)	0.1098		
25-50 pancreatic patients/year			1.15 (0.80-1.65)	0.4477		
Overall commitment (ref. >50 pancreatic patients/year)						0.0182
<10 pancreatic patients/year					1.61 (1.12-2.32)	0.0099
10-50 pancreatic patients/year					1.57 (1.10-2.23)	0.0120
Age (1-year increase)	1.02 (1.01-1.04)	0.0034	1.02 (1.01-1.04)	0.0033	1.02 (1.01-1.04)	0.0044
Male versus female sex	1.02 (0.78-1.34)	0.8584	1.05 (0.80-1.38)	0.7065	1.00 (0.77-1.31)	0.9735
BMI class (ref. normal weight)		0.3472		0.5080		0.3018
Underweight	1.23 (0.68-2.23)	0.4970	1.18 (0.64-2.18)	0.5926	1.25 (0.69-2.25)	0.4637
Overweight	1.03 (0.75-1.43)	0.8434	1.00 (0.72-1.39)	0.9909	1.09 (0.79-1.51)	0.6007
Obese	1.58 (0.93-2.68)	0.0882	1.49 (0.86-2.56)	0.1527	1.63 (0.96-2.77)	0.0713
ECOG PS (ref. 0)		0.3726		0.4282		0.2540
1	0.98 (0.74-1.30)	0.8970	0.94 (0.71-1.27)	0.7026	0.99 (0.74-1.31)	0.9276
2+	1.42 (0.84-2.41)	0.1858	1.36 (0.79-2.35)	0.2625	1.53 (0.90-2.58)	0.1146
Baseline CA 19-9 (IU/ml) (ref. up to 200)		<0.0001		<0.0001		<0.0001
>200, <3150	1.32 (0.94-1.84)	0.1092	1.30 (0.92-1.84)	0.1312	1.29 (0.92-1.80)	0.1420
≥3150	2.42 (1.72-3.42)	<0.0001	2.46 (1.73-3.50)	<0.0001	2.34 (1.66-3.29)	<0.0001
Prior cancer history	1.09 (0.76-1.55)	0.6450	1.13 (0.79-1.63)	0.5034	1.07 (0.76-1.52)	0.6916
Visited by a general practitioner as first physician	0.90 (0.66-1.22)	0.4900	0.92 (0.68-1.26)	0.6228	0.93 (0.69-1.26)	0.6522
Tumor stage at core biopsy (ref. IA)		0.0002		0.0002		<0.0001
IB	1.99 (0.68-5.85)	0.2090	2.60 (0.77-8.83)	0.1254	2.10 (0.71-6.22)	0.1787
IIA	5.10 (1.69-15.35)	0.0038	6.31 (1.81-22.04)	0.0039	5.62 (1.85-17.06)	0.0023
IIB	3.95 (1.42-11.01)	0.0086	5.08 (1.56-16.49)	0.0068	3.94 (1.41-11.05)	0.0091
III	5.04 (1.81-14.08)	0.0020	6.39 (1.97-20.75)	0.0020	5.46 (1.94-15.34)	0.0013
Time from disease diagnosis to therapy start (ref. <2 weeks)		0.2068		0.2000		0.1501
Between 2 weeks and 1 month	1.31 (0.97-1.77)	0.0827	2.60 (0.77-8.83)	0.1254	1.33 (0.98-1.81)	0.0658
More than 1 month	1.07 (0.75-1.53)	0.7185	6.31 (1.81-22.04)	0.0039	1.03 (0.72-1.47)	0.8775

Multivariable Cox proportional hazards models.
BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; *n*, number of patients.

(unadjusted HR 1.33, 95% CI 0.95-1.86, $P = 0.0915$; adjusted HR 1.38, 95% CI 0.93-2.05, $P = 0.1098$) compared with those treated in self-declared high-volume centers. Conversely, a worse OS was detected both in patients treated in low-commitment centers (unadjusted HR 1.43, 95% CI 1.05-1.94, $P = 0.0237$; adjusted HR 1.61, 95% CI 1.12-2.32, $P = 0.0099$) and medium-commitment centers (unadjusted HR 1.31, 95% CI 0.97-1.78, $P = 0.0824$; adjusted HR 1.57, 95% CI 1.10-2.23, $P = 0.0120$) compared with those treated in high-commitment centers.

In all multivariable models, older age, worse stage, and a higher baseline CA 19-9 value were significantly correlated to a worse OS, while no correlation was found for ECOG PS, sex, BMI class, time interval between disease diagnosis and treatment start, prior cancer history, and being visited first by a general practitioner.

Since a significantly better OS was observed in the high-commitment centers but all the patients included in that category were enrolled and treated in a single center, we decided to repeat all the above-mentioned analyses after removing this center. No differences in terms of results were observed (data not shown).

DISCUSSION

The GARIBALDI study showed no OS difference in multivariable analyses between academic centers and general hospitals and between patients treated in self-declared high- and low-volume centers. These results were also confirmed after excluding the single center defined as a high-commitment center. On the contrary, a statistically significant longer OS was observed in high-commitment over both low- and medium-commitment institutions, when adjusting for clinically relevant covariates. Accordingly, data do not endorse the conclusion that patients with PDAC should be necessarily addressed to academic or high-volume institutions for receiving a proper oncological treatment and suggest that focusing on pure numbers or on academic nature of the center may be trivial.

Studies focusing on the impact of institution's volume or brand on survival of patients affected by various types of cancer are heterogeneous in terms of histology, stage of disease, and treatment modality analyzed[6-13] and results are conflicting. In particular, rare diseases such as glioblastomas, gastroenteropancreatic neuroendocrine tumors, and bone tumors, which require a complex multidisciplinary approach, did not benefit from a clinically relevant reduction in the risk of death when treated in medium- and high-volume centers.[14-16] A similar observation was reported on PDAC patients as well.[17] Our figures parallel these results and seem reassuring for patients affected by a poor prognosis disease because they could receive treatment close to their home with a benefit in terms of quality of life and without financial toxicity. Nevertheless, the significant difference in OS observed in the high-commitment institution raises some concerns. In fact, this OS benefit is unlikely related to a better patient selection as suggested by the multivariate analysis, the large number of patients suggesting a consecutive enrolment, and the prospective registration design. Noteworthy, a statistically significant correlation between enrolment rate and OS was previously reported in the adjuvant chemotherapy setting for resected PDAC.[18] Accordingly, brand and volumes cannot be considered synonymous of a better treatment quality and the reasons behind this phenomenon warrant further speculation. When comparing the overall treatment strategy, a significantly larger use of neoadjuvant versus adjuvant chemotherapy, of nab-paclitaxel + gemcitabine versus FOLFIRINOX, and of adjuvant radiotherapy versus no adjuvant radiotherapy was observed in the high-commitment versus the other institutions. However, unless ascribing the observed difference in OS to the superiority of these strategies, which is not supported by scientific evidence up to date, treatment outcomes are more likely related to other factors including a real multidisciplinary interaction based on a deeper and wider disease knowledge, on a better internal organization, and on the availability of a complete team of disease-devoted specialists. Furthermore, a more positive attitude of the attending physicians, the presence of a PDAC oncologist, and the attitude to confront and interact in a network based on a hub and spoke model may also be beneficial.

The GARIBALDI study has several strengths. Firstly, data were collected prospectively. Secondly and different from other studies in this setting, the study period was very short thus avoiding the confounding bias of learning curves and treatment changes over time. Thirdly, the sample's characteristics are representative of PDAC and inclusive in terms of access to the cure, census, and education. Furthermore, the involved centers were selected by using geographical and volume criteria to reflect the national context. Finally, the originality of assessing the enrolment rate instead of brand and volume allowed to critically challenge the topic of center quality.

Among limitations, the topic of GARIBALDI study, which was the assessment of adherence to guidelines, may have excluded non-compliant centers. However, the therapeutic choices are limited for this disease and treatment heterogeneity is accordingly limited.

Also, the GARIBALDI population may not be representative of the Italian landscape because over 60% of patients were treated at an academic institution or in a self-declared high-volume center and because participation itself of the center in the trial represents a selection bias. However, due to the difficulty in involving small and non-academic centers in prospective trials, the GARIBALDI study may be also considered a success in this perspective. Furthermore, data suggest that patients treated in academic and high-volume centers do not seem to have any survival benefit when the analyses were repeated by excluding the confounding effect of the single high-commitment center. Accordingly, we reckon that the GARIBALDI population is a reliable proxy of the national situation.

Overall, the GARIBALDI study is hypothesis-generating and suggests identifying quality indicators and testing their correlation with outcomes. Also, educational programs

focusing on this orphan disease are warranted. Finally, the design of a hub and spoke model based on center quality may allow improving the survival figures in PDAC.

ACKNOWLEDGEMENTS

AIOM sponsored the study and played the role of not-for-profit sponsor. Celgene Italia supported the study with an unrestricted economical grant for costs related to data collection and management, generation of electronic case report form for remote data entry, data quality control, central and local monitoring, and statistical analysis. Celgene Italia had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

FUNDING

This study was sponsored by AIOM (Italian Association for Medical Oncology) and funded by Celgene Italy with an unrestricted economical support (no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

1. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *J Am Med Assoc*. 2021;326(9):851-862.
2. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. *Ann Oncol*. 2017;28(11):2786-2792.
3. Halperin DM, Varadhachary GR. Resectable, borderline resectable, and locally advanced pancreatic cancer: what does it matter? *Curr Oncol Rep*. 2014;16:366.
4. Balzano G, Zerbi A, Capretti G, et al. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *Br J Surg*. 2008;95:357-362.
5. Reni M, Giommoni E, Bergamo F, et al., GARIBALDI Study Group. Guideline Application in Real world: multi-Institutional Based survey of Adjuvant and first-Line pancreatic Ductal adenocarcinoma treatment in Italy. Primary analysis of the GARIBALDI survey. *ESMO Open*. 2023;8(1):100777.
6. Bajaj A, Martin B, Bhasin R, et al. The impact of academic facility type and case volume on survival in patients undergoing curative radiation therapy for muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys*. 2018;100(4):851-857.
7. Atallah C, Oduyale O, Stem M, et al. Are academic hospitals better at treating metastatic colorectal cancer? *Surgery*. 2021;169(2):248-256.
8. Uhlig J, Sellers CM, Khan SA, Cha C, Kim HS. Hepatocellular carcinoma: impact of academic setting and hospital volume on patient survival. *Surg Oncol*. 2019;31:111-118.
9. Sui W, Hall ME, Barocas DA, et al. Association between surgical volume and survival among patients with variant histologies of bladder cancer. *Urology*. 2022;159:100-106.
10. Lin SM, Ku HY, Chang TC, Liu TW, Chang CS, Hong JH. Outcomes for cervical cancer patients treated with radiation in high-volume and low-volume hospitals. *Int J Radiat Oncol Biol Phys*. 2018;102(1):184-193.
11. D'Rummo KA, TenNapel MJ, Shen X. The impact of radiotherapy facility volume on the survival and guideline concordance of patients with muscle-invasive bladder cancer receiving bladder-preservation therapy. *Am J Clin Oncol*. 2019;42(9):705-710.
12. Wright JD, Huang Y, Ananth CV, et al. Influence of treatment center and hospital volume on survival for locally advanced cervical cancer. *Gynecol Oncol*. 2015;139(3):506-512.
13. Rosander E, Holm T, Sjövall A, Hjern F, Weibull CE, Nordenvall C. The impact of hospital volume on survival in patients with locally advanced colonic cancer. *BJS Open*. 2022;6(6):zrac140.
14. Koshy M, Sher DJ, Spiotto M, et al. Association between hospital volume and receipt of treatment and survival in patients with glioblastoma. *J Neurooncol*. 2017;135(3):529-534.
15. Baeg K, Harris C, Naparst MS, et al. Effect of treatment center volume on outcomes in gastroenteropancreatic neuroendocrine tumor patients. *BMC Cancer*. 2021;21(1):146.
16. Malik AT, Alexander JH, Khan SN, Scharschmidt TJ. Is treatment at a high-volume center associated with an improved survival for primary malignant bone tumors? *Clin Orthop Relat Res*. 2020;478(3):631-642.
17. Ladekarl M, Rasmussen LS, Kirkegård J, et al. Disparity in use of modern combination chemotherapy associated with facility type influences survival of 2655 patients with advanced pancreatic cancer. *Acta Oncol*. 2022;61(3):277-285.
18. Conroy T, Castan F, Lopez A, et al. Five-year outcomes of FOLFIRINOX vs gemcitabine as adjuvant therapy for pancreatic cancer: a randomized clinical trial. *JAMA Oncol*. 2022;8:1571-1578.