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ARTICLE

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Translational Therapeutics

Second-line therapy in pancreatic ductal adenocarcinoma (PDAC) patients with germline BRCA1-2 pathogenic variants (gBRCA1-2pv)

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BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) harbouring germline BRCA1-2 pathogenic variants (gBRCA1-2pv) is a distinct nosological entity. Information on second-line therapy (2LT) outcome in this setting is lacking.

METHODS: Data of gBRCA1-2pv metastatic PDAC patients treated with chemotherapy were collected. A primary analysis of 2LT RECIST response, median progression-free survival ($mPFS_2$) and overall survival (mOS_2), was performed. A secondary analysis addressed the impact of timing of platinum introduction on the outcome of patients receiving at least a first-line combination chemotherapy (1LT).

RESULTS: Eighty-four gBRCA1-2pv metastatic PDAC patients were enrolled. The primary analysis, including 43 patients, highlighted a significant improvement of $mPFS_2$ and a doubled response rate, in the platinum-based 2LT subgroup as compared to the platinum-free (8.8 versus 3.7 months, $p = 0.013$). Seventy-seven patients were included in the secondary analysis. Median PFS_1 of 3- and 4-drug platinum-based 1LT significantly outperformed both platinum-free combinations and platinum-based doublets (11.4 versus 6.4 versus 7.9 months, $p = 0.01$). Albeit still immature, data on mOS paralleled those on mPFS.

CONCLUSIONS: This study highlighted the beneficial role of platinum agents in gBRCA1-2pv PDAC patients also in second-line treatment setting. However, our data suggest that early use of 3- and 4-drug platinum-based chemotherapy combinations provides a survival outcome advantage.

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INTRODUCTION

Despite its overall rarity, pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related death throughout the world, with a 5-year overall survival (OS) rate drawing near 10% in 2020 [1]. Given its increasing incidence, PDAC is expected to rank second for cancer mortality by 2030 [2]. In most cases PDAC patients present with advanced stage disease ab initio, either metastatic (50–55%) or locally advanced (30–35%), for the most part amenable only to systemic therapeutic approaches [3]. Phase III and II randomised controlled trials (RCTs) demonstrated a significant improvement of survival outcome of metastatic PDAC with multidrug chemotherapy regimens, including Nab-paclitaxel plus Gemcitabine (AG), FOLinic acid, Fluorouracil, IRINotecan and OXaliplatin (FOLFIRINOX) and Cisplatin, Nab-Paclitaxel, Capecitabine and Gemcitabine (PAXG) [4–6]. Conversely, recommendations on second-line therapy are largely undefined [7, 8]. The PANCREOX and the CONKO-003 phase III RCTs reported either limited or no benefit from the addition of Oxaliplatin to Fluorouracil and Folinic acid upon failure of single-agent gemcitabine [9, 10]. Also, the more recent NAPOLI-1 RCT showed negligible survival advantage of the combination of liposomal Irinotecan (Nal-IRI) with 5-FU/LV in metastatic PDAC patients previously treated with gemcitabine-based chemotherapy (gemcitabine alone in 45% of cases) [11]. Noteworthy, 43% of these patients had received fluorouracil-based previous anticancer therapy, thus hampering the interpretation of the true magnitude of the OS benefit of combination over single agent fluorouracil in a fluorouracil-naive population [11]. Of note, no data from RCTs specifically addressing second-line therapy after first-line multidrug chemotherapy regimens (AG, FOLFIRINOX, PAXG) are currently available [8]. Therefore, clinical practice is based on real-word evidence, which endorses the options of either AG or gemcitabine alone after first-line FOLFIRINOX or 5-FU/LV either alone or combined with Oxaliplatin (FOLFOX) and/or Irinotecan/Liposomal Irinotecan after first-line AG-based therapy, according to patient PS [7, 8, 12].

GermlineBRCA1-2 pathogenic variants (gBRCA1-2pv)-related PDAC, which accounts for 5–9% of unselected patients, is emerging as a distinct clinical entity, benefitting from specific systemic treatments that exploit the defective homologous recombination (HR) system [13–16]. Several retrospective data support the use of platinum-based chemotherapy, inducing DNA double-strand breaks (DSB), in this setting [13, 17–19].

Intuitively, the scarce evidence on optimal second-line therapy for PDAC as a whole corresponds to a complete gap of knowledge in this rare subset of patients carrying gBRCA1-2pv, in which only anecdotal information is available [18, 20]. As the result of the germline test is not always available at the time of treatment start and since not all patients are suitable to receive upfront FOLFIRINOX chemotherapy, it is not unusual that metastatic PDAC patients with gBRCA1-2pv are initially treated with platinum-free therapy in clinical practice. Whether platinum salts could provide the same benefit also as second-line therapy or should be introduced as early as possible in the course of treatment is an unanswered issue. Keeping in mind the rarity of gBRCA1-2pv in PDAC, which is a considerable hindrance to prospective trials, retrospective information might be reasonably useful to shed light on this topic.

In this perspective, we explored second-line therapy outcome in PDAC patients harbouring gBRCA1-2pv through a multicentre survey, in an effort to provide useful insights on the therapeutic management of this specific PDAC subpopulation.

MATERIALS AND METHODS

Study design and inclusion criteria

Clinical data of metastatic PDAC patients of any age carrying a germline pathogenic variant of BRCA1-2 genes completing any kind of chemotherapy regimen between October 2013 and November 2021 were retrospectively retrieved by medical records of 23 Italian Oncology Departments and collected in an electronic database.

Patients who progressed on first-line therapy and completed a second-line treatment by the time of database lock (November 15, 2021) were included in the primary analysis, that focused on second-line therapy outcome evaluation. Patients receiving single-agent chemotherapy as first-line and/or second-line treatment were excluded from this analysis, to minimise the potential confounding effect of poor performance status (PS) on therapy outcome evaluation.

Furthermore, a secondary analysis addressing the role of timing of platinum agent introduction was performed, including all stage IV patients who received a combination chemotherapy as first-line treatment with a minimum follow-up of 6 months from therapy start at the time of database lock, irrespective of receiving second-line treatment. This choice allows including into this secondary analysis all those patients who had the chance to receive a platinum compound during their therapeutic management. All patients enrolled in the study had signed a written informed consent for genetic test, authorising the use of clinical and genomic data for scientific research aims, in compliance with privacy policy.

Data collected included baseline patients and tumour characteristics (age, gender, type of germline BRCA pathogenic variant, ECOG PS, clinical stage according to AJCC/UICC TNM Eighth Edition, 2017, T site, presence/absence of liver metastases), carbohydrate antigen 19.9 (CA19.9), first- and second-line chemotherapy regimen, duration and outcome.

A descriptive analysis of outcome was performed, covering both Response Evaluation Criteria In Solid Tumours 1.1 (RECIST 1.1) best response and survival to first-line and second-line therapies. Progression-free survival 2 (PFS_2) and overall survival 2 (OS_2) were calculated from second-line therapy start to second disease progression or death without disease progression and to death or last follow-up visit, respectively. Overall survival (OS) was calculated from the date of first-line therapy start until the date of death or last follow up visit. Progression-free survival 1 (PFS_1) was calculated from first-line therapy start until the first documented disease progression. Information on CA19.9 response to first-line and second-line therapies was available for only a small subset of patients, therefore it was not included in the analysis.

Statistical analysis

The primary endpoint of the study was the descriptive analysis of RECIST response and survival outcomes, including OS_2 and PFS_2, related to second-line therapy in a cohort of stage IV PDAC patients carrying gBRCA1-2pv. The secondary endpoint aimed at investigating the impact on the outcome of the choice of recommending platinum-based chemotherapy early and of the type of platinum-based regimen (with 3–4 drugs including FOLFIRINOX [5], modified FOLFIRINOX (mFOLFIRINOX) [21], FOLinic acid, Fluorouracil, Oxaliplatin and IRInotecan (FOLFOXIRI) [22], PAXG [6], Cisplatin, Epirubicin, Capecitabine and Gemcitabine (PEXG) [23] and Cisplatin plus AG versus with 2 drugs, including Gemcitabine plus Oxaliplatin (GEMOX) [24] and FOLFOX [9]) as opposed to reserving this opportunity for a later time, in terms of OS, PFS_1 and probability of receiving a second-line treatment. Survival probabilities were estimated using the Kaplan–Meier methods. Due to the descriptive nature of the investigation, no statistical design or sample size calculation were performed. All analyses were carried out using Statistica 12.0 statistical package for Windows (Statsoft Inc., 2011, Tulsa, OK. 74104, USA).

All tests were two sided and P values <0.05 were considered statistically significant.

RESULTS

Patients and treatment characteristics

Clinical data of 84 PDAC patients with gBRCA1-2pv diagnosed with stage IV disease and treated with any type of chemotherapy in 23 Italian Oncology Departments between October 2013 and November 2021 were collected. Following the application of the aforementioned inclusion criteria, 43 patients were selected for the primary analysis of second-line therapy outcomes, as shown in the consort flow chart in Fig. 1. Characteristics of this subset of patients, alongside with the type of first-line and second-line chemotherapy regimens they received, are reported in Table 1. Twenty-two patients received a platinum-based first-line

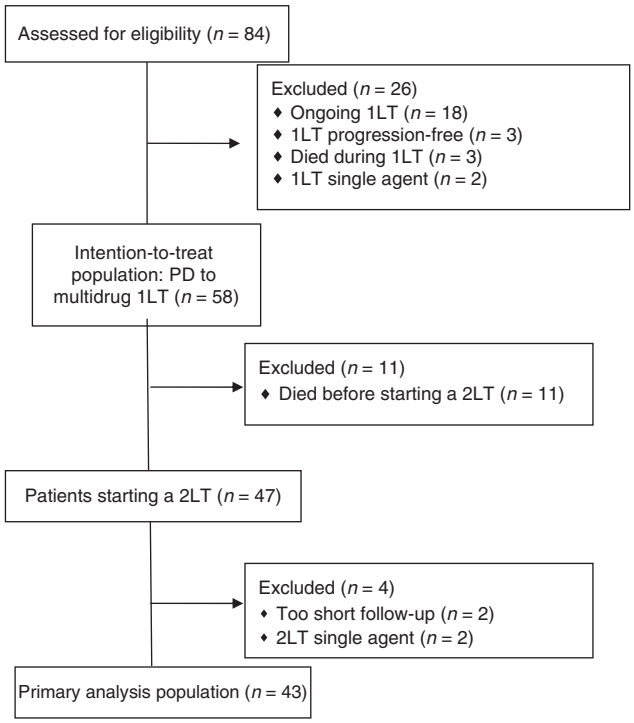

Fig. 1 Consort flow chart of patients' selection for the primary analysis. 1LT first-line therapy, PD progressive disease, 2LT second-line therapy.

chemotherapy, 12 (55%) of whom were also treated with Olaparib either as a maintenance therapy ($N = 8$) or as a subsequent line of therapy ($N = 4$). Three further patients of this group were randomised to either Olaparib or placebo in the context of POLO trial [15]. Among the 21 patients who did not receive platinum upfront, 6 (29%) received Olaparib either as maintenance therapy of a platinum-based second-line therapy ($N = 3$) or as subsequent line treatment ($N = 3$).

As for the secondary analysis, 77 patients were included: 28 were treated with platinum-free first-line therapy, 49 with platinum-containing first-line chemotherapy regimens, 40 of whom receiving 3- and 4-drug combinations and 9 platinum-based doublets. Characteristics of these patients considered for the secondary analysis are detailed in Table 2.

Olaparib was administered as maintenance therapy of a platinum-based first-line chemotherapy in 23 out of 49 patients (47%), specifically in 19/40 (48%) patients previously treated with a triplet or quadruplet and 4/9 (44%) patients that received upfront platinum-based doublet (Chi-square test; $p = 0.87$). Among these 49 patients, 5 (10%) were enrolled in the POLO trial [15] (4 treated with platinum-based triplets/quadruplets and 1 with FOLFOX) and 4 (8%) received Olaparib as subsequent line treatment. Among the 28 patients who did not receive platinum upfront, 6 (21%) received Olaparib either as maintenance therapy of a platinum-based second-line therapy ($N = 3$) or as subsequent line treatment ($N = 3$).

Primary analysis: second-line therapy outcomes

RECIST best response was available for 21 out 22 patients receiving platinum-free second-line therapies, entailing 5 (24%) partial response (PR), 6 (28%) stable disease (SD) and 10 (48%) progressive disease (PD). Concerning the subgroup of 21 patients treated with platinum-based second-line chemotherapy, RECIST best responses were as follows: 10 (48%) PR, 5 (24%) SD, and 6 (28%) PD.

Survival outcomes (PFS_2 and OS_2) of second-line therapy in relation to different stratification variables (BRCA status, gender, age, platinum-free versus platinum-based second-line therapy and PFS_1) are reported in Table 3 and Fig. 2 (Kaplan–Meier). In the platinum-based second-line therapy group, 62% (95% confidence interval 95% CI 41–83%) and 28.6% (95% CI 9.3–47.9%) of patients were alive and free from disease progression at 6 months and at 1 year respectively, if compared to 45.5% (95% CI 24.7–66.3%) and 4.5% (95% CI 0–13.2%) of patients in the platinum-free second-line group. After a median follow-up of 35.2 months, 66.7% (95% CI 46.5–86.9%) of patients treated with platinum-based second-line therapy were alive at 1 year, as opposed to 43.6% (95% CI 22.9–64.3%) of patients receiving platinum-free chemotherapy regimens as second-line (median follow-up: 30.3 months).

Among the 19 patients experiencing disease progression to platinum-free second-line therapy, 12 (63%) received a third-line treatment, that was platinum-based in 50% of cases (6/12). Notably, the disease control rate in these 6 patients was 67% (i.e. 2 partial responses plus 2 stable disease) as opposed to none among the 6 who received a third-line platinum-free, with a median progression-free and overall survival from third-line chemotherapy start of 7.5 (interquartile (IQ) range 1.8–10.3) and 20.1 (IQ range 7.5–24.5) months, respectively, as opposed to 3.2 (IQ range 1.2–4.8) and 5.7 (IQ range 2.6–19) months, respectively, for platinum-free regimens. On the other hand, 17 out of 19 (85%) patients progressing to platinum-containing second-line therapy were further treated with a third line, which was platinum-based in 5 cases (29%) and platinum-free in 12. No difference in median progression-free [2.1 (IQ range 1.1–6.3) and 3.3 (IQ range 0.4–10.7) months, respectively] and overall survival [6.6 (IQ range 1.1–11.5) and 8.1 (IQ range 1.7–15.3) months, respectively] from third-line chemotherapy start was observed.

Secondary analysis: early platinum versus no early platinum?

Concerning survival outcomes of the 77 patients included in the secondary analysis, median PFS_1 ($mPFS_1$) of the 49 patients treated with platinum-based first-line regimens was 10.9 months (IQ range 7.7–20.1), as opposed to 6.4 months (IQ range 3.9–10.6) of the 28 patients receiving a platinum-free therapy ($p = 0.004$). The 40 patients treated with 3–4-drug platinum-based regimens had a $mPFS_1$ of 11.4 months (IQ range 7.9–21.0), with 14 (35%) patients progression-free at 7.6–91 months (median 18.5 months), significantly outperforming, not only the platinum-free subgroup ($p = 0.007$), but also the $mPFS_1$ [7.9 months (IQ range 3.5–9.2)] of the 9 patients receiving a platinum-based doublet ($p = 0.01$), all experiencing disease progression (Fig. 3a—Kaplan–Meier). No significant $mPFS_1$ difference was detected between platinum-based doublets and platinum-free regimens ($p = 0.86$—Fig. 3a—Kaplan–Meier). Six-month PFS_1 rates were 57.1% (95% CI 38.8–75.4%), 55.5% (95% CI 0–88%) and 85% (95% CI 74–96.1%) for first-line therapy containing no platinum salts, platinum-based doublets and platinum-based triplets/quadruplets, respectively. Accordingly, 1 year-PFS_1 rates were 14.3% (95% CI 1.3–27.3%) versus 11.1% (95% CI 0–96.1%) versus 53% (95% CI 0–31.6%) in the three subgroups.

Median OS (mOS) of the 49 patients receiving platinum-based first-line chemotherapy was 26.3 months (IQ range 9.3–29.5), with 18 (37%) patients alive at 7.6–91.2 months (median follow-up 20.1 months), as opposed to 20.2 months (IQ range 12.5–33.4) of the 28 patients treated with platinum-free first-line therapy ($p = 0.54$), 6 (21%) of whom were alive at 11.1–80.3 months (median follow-up 35.2 months). Patients receiving platinum-based triplets and quadruplets ($N = 40$) had a mOS of 29.2 months (IQ range 9.2–31.8) [17 (42%) patients alive at 7.6–91.2 months (median follow-up 20.1 months)] significantly higher than 11.2 months (IQ range 9.3–18.5) of the 9 patients treated with 2-drug platinum-based first-line regimens ($p = 0.017$), of whom only 1 (11%) patient was alive at 20.7 months (Fig. 3b—Kaplan–Meier). Neither platinum-based triplets/quadruplets ($p = 0.19$) nor platinum-containing doublets ($p = 0.08$) had a

Table 1. Characteristics of the patients included in the primary analysis.

	Total ($N = 43$)	Platinum-based 2LT ($N = 21$)	Non-platinum-based 2LT ($N = 22$)
Age at 2LT start (years), median (range)	60 (30–75)	63 (47–75)	58 (30–74)
Gender, *N* (%)			
Female	23 (54)	11 (52)	12 (54)
Male	20 (46)	10 (48)	10 (46)
ECOG PS at 2LT start, *N* (%)			
0	22 (60)	13 (68)	9 (50)
1	13 (35)	6 (32)	7 (39)
2	2 (5)	0	2 (11)
NA	6		4
gBRCA PV status, *N* (%)			
gBRCA1	10 (23)	6 (28)	4 (18)
BRCA2	33 (77)	15 (72)	18 (82)
T site, *N* (%)			
Head/uncinate	14 (34)	8 (38)	6 (30)
Body	14 (34)	7 (33)	7 (35)
Tail	11 (27)	4 (19)	7 (35)
Diffuse	2 (5)	2 (10)	0
NA	2	0	2
Liver metastases at 2LT start, *N* (%)			
Yes	39 (91)	19 (90)	20 (91)
No	4 (9)	2 (10)	2 (9)
CA19.9 at 2LT start, *N* (%)			
0–37 U/ml	8 (23)	2 (12)	6 (32)
>37 U/ml	27 (77)	14 (88)	13 (68)
NA	8	5	3
CA19.9 U/ml, median (range)	530 (63–102,287)	1321 (86–102,287)	494 (63–302)
Regimen of 1LT, *N* (%)			
AG	21 (49)	17 (81)	4 (18)
(m)FOLFIRINOX/FOLFOXIRI	10 (23)	0	10 (45)
PAXG/PEXG	7 (16)	4 (19)	3 (14)
GEMOX	4 (9)	0	4 (18)
FOLFOX	1 (3)	0	1 (5)
Platinum based	22 (51)	4 (19)	18 (82)
Non-platinum based	21 (49)	17 (81)	4 (18)
Regimen of 2LT, *N* (%)			
AG	11 (25)	0	11 (50)
FOLFOX	15 (35)	15 (72)	0
FOLFIRI/5FU + NAL-IRI	10 (23)	0	10 (45)
FOLFIRINOX	3 (7)	3 (14)	0
GEMOX	3 (7)	3 (14)	0
Gemcitabine + Capecitabine	1 (3)	0	1 (5)

2LT second-line therapy, *PS* performance status, *NA* not available, *gBRCA* germline BRCA, *PV* pathogenic variant, *T* primary tumour, *CA19.9* carbohydrate antigen 19.9, *1LT* first-line therapy, *AG* Nab-paclitaxel plus Gemcitabine, *(m)FOLFIRINOX* (modified) FOLinic acid, Fluorouracil, IRINotecan and Oxaliplatin, *FOLFOXIRI* FOLinic acid, Fluorouracil, Oxaliplatin and IRInotecan, *PAXG* Cisplatin, Nab-Paclitaxel, Capecitabine and Gemcitabine, *PEXG* Cisplatin, Epirubicin, Capecitabine and Gemcitabine, *GEMOX* Gemcitabine plus Oxaliplatin, *FOLFOX* FOLinic acid, Fluorouracil and Oxaliplatin, *5-FU* Fluorouracil, *Nal-Iri* liposomal Irinotecan.

significant impact on OS if compared to no early platinum (Fig. 3b—Kaplan–Meier). In all, 82.1% (95% CI 67.9–96.3%), 33.3% (95% CI 2.5–64.1%) and 78.6% (95% CI 65.9–91.3%) of patients were alive at 1 year when receiving no early platinum, platinum-based first-line doublets and triplets/quadruplets, respectively. At 2 years, these rates decreased to 40% (95% CI 21.8–58.2%), 0% and 61.9% (95% CI 46.8–77%) in the three subgroups.

Among the 26 out of 28 (93%) patients who experienced disease progression to platinum-free first-line chemotherapy, 22 (85%) received a second-line therapy. Moreover, 24 of the 40 (60%) patients treated with 3–4-drug platinum-based first-line therapy had PD and 19 out of these 24 (80%) patients received a second-line therapy. Lastly, PD was reported in 8 of the 9 (89%) patients that received a 2-drug platinum-based first-line

Table 2. Characteristics of the patients included in the secondary analysis.

	Non-platinum-based 1LT[a] (*N* = 28)	Platinum-based 3- and 4-agents 1LT[b] (*N* = 40)	Platinum-based 2 agents 1LT[c] (*N* = 9)
Age at diagnosis (years), median (range)	61 (38–75)	57 (35–72)	66 (51–72)
Gender, *N* (%)			
Female	19 (68)	17 (42)	4 (44)
Male	9 (32)	23 (58)	5 (56)
ECOG PS at diagnosis, *N* (%)			
0	20 (71)	23 (60)	3 (33)
1	7 (25)	15 (40)	4 (44)
2	1 (4)	0	2 (23)
NA	0	2	0
Liver metastases at diagnosis, *N* (%)			
Yes	22 (79)	31 (77)	7 (78)
No	6 (21)	9 (23)	2 (22)
gBRCA PV status, *N* (%)			
gBRCA1	7 (25)	9 (23)	3 (33)
gBRCA2	21 (75)	31 (77)	5 (56)
gBRCA 1 + 2	0	0	1 (11)

1LT first-line therapy, *PS* performance status, *NA* not available, *gBRCA* germline BRCA, *PV* pathogenic variant.
[a]25 patients were treated with Nab-paclitaxel plus gemcitabine (AG) [4], 2 with AG-based therapy within a clinical trial [25, 26], 1 with Nab-Paclitaxel plus Fluorouracil and Irinotecan (Nab-FOLFIRI) within a clinical trial [27].
[b]22 patients received FOLinic acid, Fluorouracil, IRINotecan and OXaliplatin (FOLFIRINOX) [5], modified FOLFIRINOX (mFOLFIRINOX) [21] or FOLinic acid, Fluorouracil, Oxaliplatin and IRInotecan (FOLFOXIRI) [22], 14 PAXG [6], 2 Cisplatin, Epirubicin, Capecitabine and Gemcitabine (PEXG) [23], 2 Cisplatin plus AG.
[c]5 patients were treated with Gemcitabine plus Oxaliplatin (GEMOX) [24], 4 with FOLFOX [9].

therapy, of whom 6 (75%) were treated with a second-line therapy.

DISCUSSION

The primary analysis of this multicentre survey demonstrated that platinum-based second-line therapy significantly delayed disease progression when compared to platinum-free chemotherapy regimens in PDAC patients harbouring gBRCA1–2pv. Indeed, despite the younger age, the median PFS_2 of patients receiving a platinum-free second-line therapy was superimposable with that reported in RCTs, including either platinum-based combinations (FOLFOX in [9], OFF in [10]) or platinum-free regimens (Nal-IRI + 5FU/LV in [11], FOLFIRI in [20]) in second-line treatment of PDAC patients, regardless gBRCA1-2 status. Similar $mPFS_2$ was also reported in many phase II trials or retrospective analyses on second-line therapy in PDAC [8]. Conversely, in our study $mPFS_2$ was longer than expected in the platinum subgroup. These figures parallel those previously reported by our group in first-line treatment of gBRCA1-2pv PDAC patients with platinum-based chemotherapy and platinum-free regimens [19].

OS_2, results are consistent with those reported for PFS_2, endorsing the benefit of platinum-based therapy use. Indeed, it must be noticed that median OS_2 in the platinum subgroup remarkably exceeded the median OS_2 to second-line treatment described in RCTs on unselected PDAC patients, ranging between 5.9 and 6.5 months [9–11, 20], that is comparable to the OS_2 reported for the platinum-free second-line therapy subgroup in our survey. To this regard, the lack of a statistically significant difference between the two subgroups seems to be due to the favourable outcome observed in the 6 patients that, after failing a platinum-free therapy, were treated with a platinum-containing third-line therapy that yielded a further sizeable benefit and shaped the tail of the Kaplan-Meier overall survival curve thus masking, in a sort of cross-over effect, the true impact of second-line platinum.

No significant differences in terms of second-line treatment survival outcomes were reported in relation to gBRCApv subtype, gender or age in our study.

Lastly, objective response rate (ORR) was doubled with platinum-based second-line therapy if compared to platinum-

Table 3. Survival outcomes of second-line therapy.

Variable	*N*	$mPFS_2$ (mo—IQ range)	*P* value	mOS_2 (mo—IQ range)	*P* value
2LT					
Platinum	21	8.8 (3.3–13.2)	**0.013**	13.5 (8.6–18.2)	0.82
No platinum	22	3.7 (1.8–9.1)		7.2 (3.0–27.4)	
Germline BRCA pv			0.81		0.17
1	10	2.9 (2.0–9.0)		6.0 (5.3–13.5)	
2	33	6.9 (2.7–10.2)		13.5 (6.3–25)	
Gender			0.84		0.57
Male	20	7.4 (3.0–11.0)		14.1 (5.9–24.0)	
Female	23	6.4 (2.1–10.2)		12.9 (5.3–25.0)	
Age at 2LT start (years)			0.28		0.21
≤65	35	6.5 (2.7–10.3)		13.5 (6.0–25.0)	
>65	8	3.4 (1.9–9.1)		9.3 (2.1–16.0)	
Previous PFS_1 (mo)			**0.01**		0.58
≤6	14	9.7 (2.5–16)		12.7 (7.2–28.0)	
>6	29	4.3 (2.2–9.0)		12.9 (5.3–24.0)	

$mPFS_2$ median progression-free survival 2, *mOS_2* median overall survival 2, *mo* months, *IQ* interquartile, *2LT* second-line therapy, *pv* pathogenic variant, *PFS_1* progression-free survival 1.
Statistically significant *p*-values are in bold.

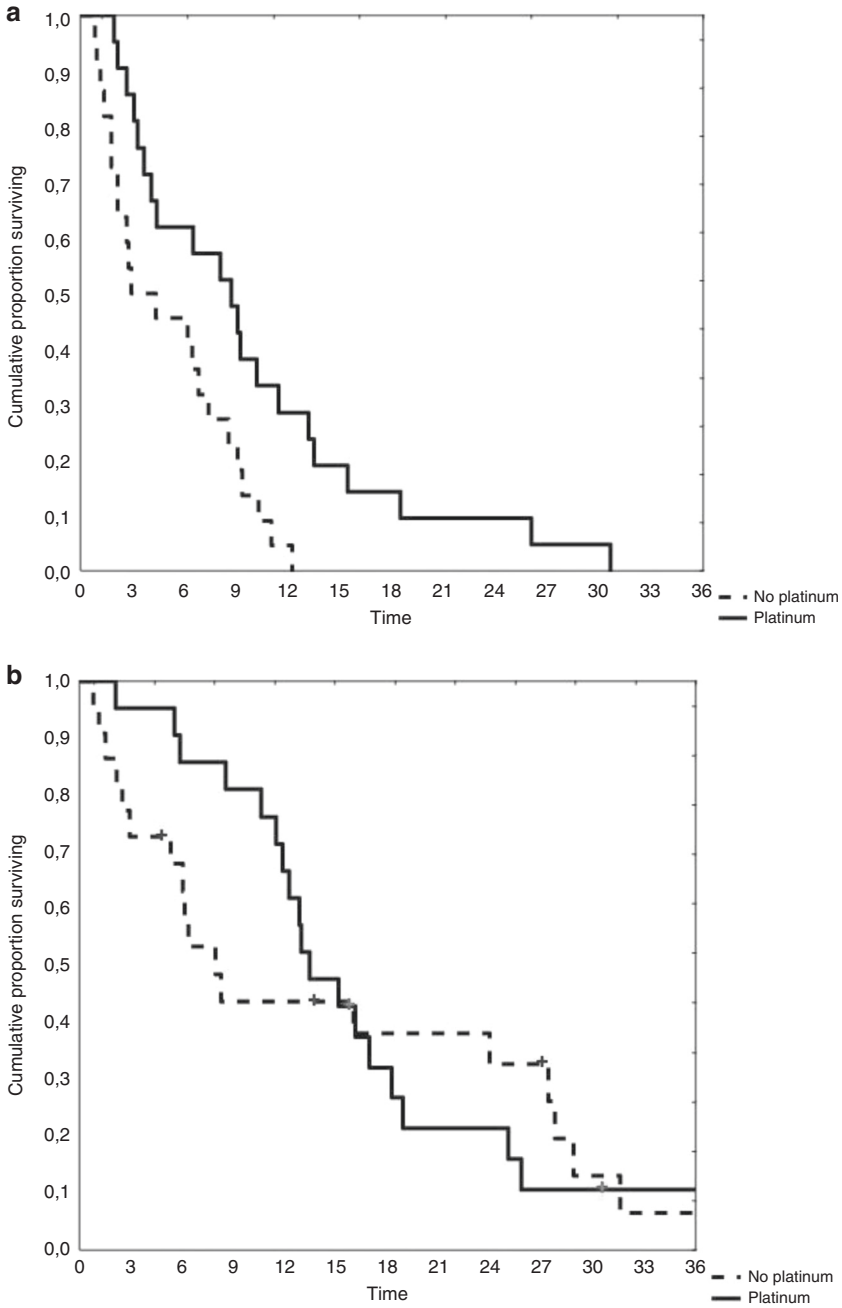

Fig. 2 Survival outcome for primary analysis. Kaplan-Meier curves for progression-free survival$_2$ (**a**) and overall survival$_2$ (**b**) of platinum-free versus platinum-based second-line therapy.

free chemotherapy (48% versus 24%, respectively) and higher to that reported in the literature on second-line therapy in PDAC, both in RCTs (11–16% in [9, 11, 20]) and in non-randomised trials (0–23 %) [7]. Even in third-line, platinum-based chemotherapy yielded a 67% disease control rate (DCR) rate versus null for platinum-free regimens in patients who received a platinum-free second-line therapy.

At best of our knowledge, overall, these findings represent the first evidence of a positive effect of platinum-based therapy in the specific setting of second (and third?)-line treatment of metastatic PDAC patients with gBRCA1-2pv, in line with the benefit demonstrated with platinum salts in the earlier phase of treatment [19]. Previously, Wattenberg et al. reported a PFS of 2.5 months for 5 PDAC patients with gBRCA1-2 pv, all receiving a platinum-based chemotherapy either as second-line (4) or third-line (1) treatment [18]. More recently, a median Time to Treatment Progression of 7.3 months and a mOS of 10.6 months were described for a subset of 4 gBRCA1-2pv PDAC patients receiving a second-line with 5-FU plus Irinotecan with (3) or without (1) the PARP-Inhibitor Veliparib as part of a randomised phase II trial [20]. Nonetheless, these data did not allow drawing any sound conclusion on second-line therapy outcome in gBRCA1-2pv-related PDAC, due to the limited number of patients and the lack of a comparison between platinum-free and platinum-based treatments.

The secondary analysis performed in our study in order to define the role of timing of platinum agent introduction in gBRCA1-2pv PDAC patients treatment revealed a positive impact of platinum-based triplets and quadruplets on extending PFS to first-line therapy. Specifically, 3- and 4-drug chemotherapy regimens including a platinum salt significantly outperformed

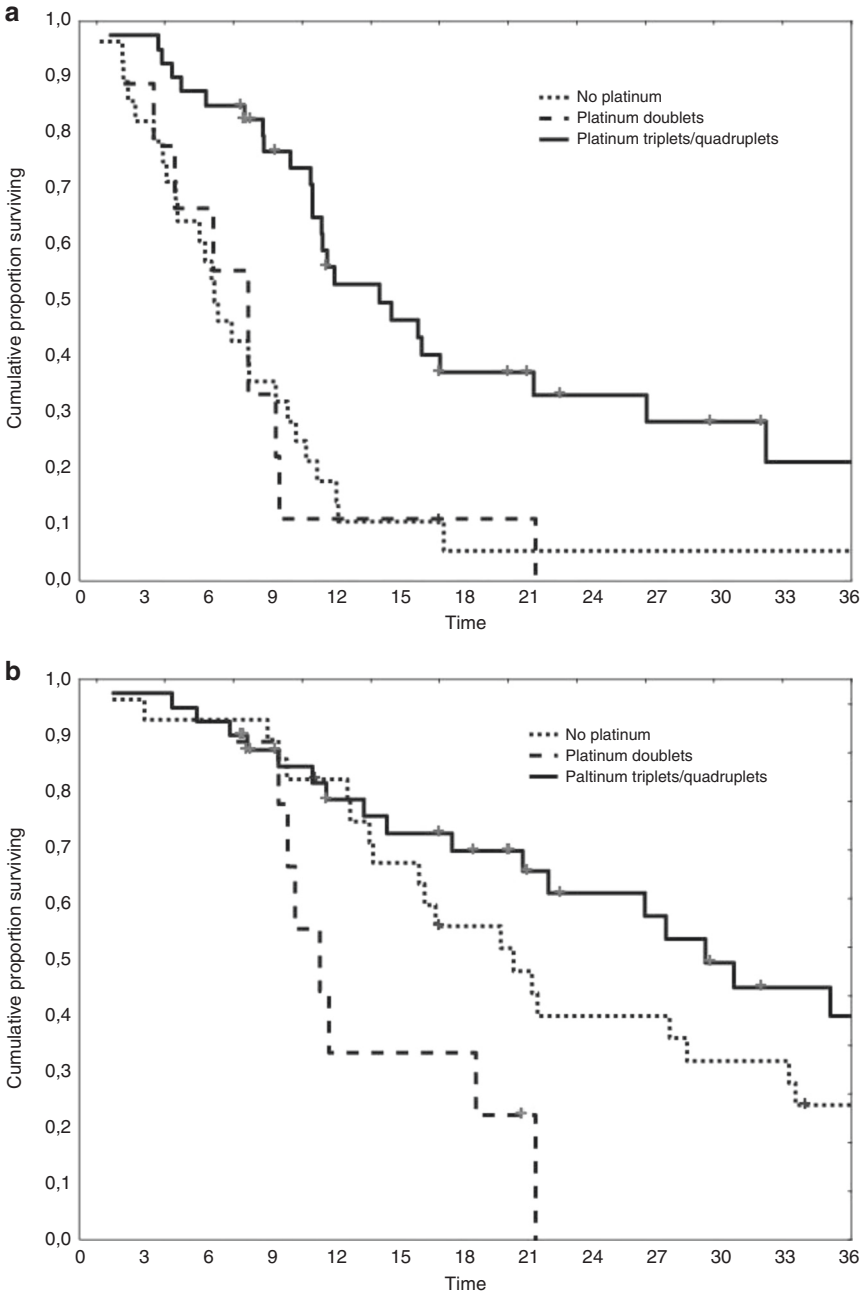

Fig. 3 Survival outcome for secondary analysis. Kaplan-Meier curves for progression-free survival$_1$ (**a**) and overall survival (**b**) of early platinum-containing (triplets/quadruplets and doublets) versus no-early platinum upfront therapy.

both platinum-free combinations and platinum-based doublets in terms of PFS, also allowing for a greater proportion of patients to be alive and free from disease progression at 6 and 12 months. On the contrary, no PFS difference was detected between platinum-based doublets and no-early platinum chemotherapy subgroups. Although this result might be partially affected by the unbalanced allocation of unfavourable prognostic factors, namely the higher median age and percentage of patients with ECOG PS > 1 and gBRCA1pv in the platinum-based doublet subgroup, it is consistent with a previous report of our group prompting a greater benefit of platinum salt-containing triplets and quadruplets over other types of regimens in this subset of patients [19]. Furthermore, the proportion of patients receiving Olaparib as maintenance therapy of a first-line platinum-containing treatment was comparable between the triplet/quadruplet and the doublet subgroups, thus minimising a potential bias related to the proven effect of this drug on disease progression delay [15].

Concerning overall survival, firm conclusions cannot be drawn, due to the immature follow-up and the limited number of events, especially among the 40 patients treated with platinum-based triplets and quadruplets, 42% of whom were still alive by the time of database lock. Notwithstanding, OS of this subgroup was significantly prolonged compared to that reported for patients treated with platinum-based doublets and despite the lack of statistical significance, it numerically exceeded by 9 months survival of patients not receiving upfront platinum salts. Moreover, the proportion of patients who were alive at 2 years from therapy start with platinum-containing first-line triplets and quadruplets as opposed to the no-early platinum

subgroup was increased by >20%, hinting at a possible survival benefit of these combinations that might become evident with longer follow-up.

The proportion of patients receiving a second-line treatment after disease progression to first-line therapy was comparable across the three subgroups. However, it should be highlighted that a lower percentage of patients (60%) experienced disease progression with platinum-based 3- and 4-drug combinations as opposed to platinum-containing doublets (89%) and platinum-free regimens (93%).

The results of this multicenter survey need to be interpreted cautiously due to several drawbacks, including the retrospective and non-randomised nature of the investigation, the relatively limited sample size, alongside with the lack of a comparison with an internal control of wild-type PDAC patients. Additionally, the follow-up immaturity, especially of those patients included in the secondary analysis, hampers conclusive speculations on the impact platinum-based chemotherapy had on overall survival of this cohort.

Keeping in mind these limitations, we can conclude that our study has relevant implications for the management of PDAC patients harbouring gBRCA1-2pv, as it is the first to report the beneficial role of platinum salts not only as upfront therapy but also in second- and third-line treatment setting. Moreover, our findings suggest that early platinum use provides a survival outcome advantage and raise the concern that platinum-based doublets should not be considered as a standard first-line treatment approach in this biologically distinct subgroup of patients. Overall, our findings endorse the need to screen for BRCA1-2 germ-line mutations all patients with PDAC, due to the relevance of this test to drive therapeutic recommendations that have a considerable impact on outcome.

DATA AVAILABILITY

Data are available upon reasonable request.

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AUTHOR CONTRIBUTIONS

GO, MM and MR: conception of the study; data acquisition, analysis and interpretation. AC, GT, SL, MM, MDM, GG, EV, MS, SB, SN, MGR, AMM, IGR, IG, SDL, BM, AB, LS, LP, CP, AS, UP, MN, EG, IB, ET, KB, LF, MMV: data acquisition. SC: data interpretation. All authors: manuscript drafting, revision and final approval.

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COMPETING INTERESTS

GT reports advisory board for BMS, AZ, MSD, Merck, Servier. SL reports consulting or advisory role for Amgen, Merck, Serono, Lilly, Astra Zeneca, Incyte, Daiichi-Sankyo, Bristol-Myers Squibb, Servier, MSD; Speakers' Bureau for Roche, Lilly, Bristol-Myers Squibb, Servier, Merck, Serono, Pierre-Fabre, GSK, Amgen; research funding for Amgen, Merck, Serono, Bayer, Roche, Lilly, Astra Zeneca, Bristol-Myers Squibb. LS reports speakers' and consultant's fee from MSD, Astra-Zeneca, Servier, Bayer, Merck, Amgen, Pierre-Fabre. AS reports advisory board or invited speaker for Pierre Fabre, Lilly, Merck, Viatris. MN reports travel expenses from Celgene, speaker honorarium from Accademia della Medicina; honoraria from Medpoint SRL for editorial collaboration; consultant honoraria from EMD Serono, Basilea Pharmaceutica, Incyte and MSD Italia. SC reports travel expenses and personal honoraria for the following companies: Speaker for Amgen, Bayer, Eli Lilly, Servier; Advisory Boards for Amgen, Eli Lilly, Bayer, Baxter, Merck Sharp & Dohme (MSD), Servier; Consultant for Amgen, Baxter, Eli Lilly, Celgene, Novartis, MSD; Research grant for Celgene, Eisai. MM reports personal honoraria as speaker or consultant for Astrazeneca, MSD, Boehringer Ingelheim, Pfizer, EUSA Pharma, Merck-Serono, Novartis, Roche, Ipsen, Mylan. MR reports advisory boards for Astra-Zeneca, PANAVANCE, Viatris, SOTIO, Servier, MSD, Lilly, Celgene, Shire, Baxter, Sanofi and a research grant from Astra-Zeneca. All remaining authors have declared no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Before testing, all patients signed an informed consensus statement that was revised and approved by a local ethics committee and allowed for genetic testing and data collection, analysis and elaboration. Data were irreversibly anonymised before entering into the database.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

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