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Cancer Clinical Trial Versus Real-World Outcomes for Standard of Care First-Line Treatment in the Advanced Disease Setting

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Abbreviations used:
APHINITY - A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2 (HER2)-Positive Primary Breast Cancer
BC – Breast cancer
CaP – Prostate cancer
CLEOPATRA – Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer
CRC – Colorectal cancer
ECOG – Eastern Cooperative Oncology Group
EGFR – Epidermal growth factor receptor
ePAD - Electronic castration-resistant Prostate cancer Australian Database
ER – Oestrogen receptor
FDG - Fluorodeoxyglucose
FIRSTANA - Cabazitaxel Versus Docetaxel Both With Prednisone in Patients With Metastatic Castration Resistant Prostate Cancer
FOLFOX – Fluorouracil, leucovorin and oxaliplatin
HER2 - Human epidermal growth factor receptor 2
MPACT - Metastatic Pancreatic Adenocarcinoma Clinical Trial
OS – Overall survival
PC – Pancreatic cancer
PDF - Portable Document Format
PET – Positron emission tomography
PFS - Progression-free survival
PR – Progesterone receptor
PS – Performance status
PSA – Prostate specific antigen
PSMA - Prostate Specific Membrane Antigen
PURPLE - Pancreatic cancer: Understanding Routine Practice & Lifting End results

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RAS – Rat sarcoma
RECIST – Response evaluation criteria in solid tumors
SBRT – Stereotactic body radiation therapy
SD – Standard deviation
TABITHA - Treatment of Advanced Breast Cancer in the HER2 Positive Australian Patient
TRACC - The Treatment of Recurrent and Advanced Colorectal Cancer
XELOX – Capecitabine, oxaliplatin

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Cancer Therapy and Prevention

Novelty and Impact:
In this novel study we examine data from a series of cancer registries, confirming previous data that trial patients are younger and fitter than consecutive routine care patients, but finding that real-world patients can have survival outcomes that match or exceed those reported in trials. We explore why real-world outcomes may improve after a new therapy becomes standard of care and how this should inform the statistical plan for further studies in this patient population.

ABSTRACT

Clinical trials have strict eligibility criteria, potentially limiting external validity. However, while often discussed this has seldom been explored, particularly across cancer types and at variable time frames post trial completion. We examined comprehensive registry data (January 2014 to June 2019) for standard first-line treatments for metastatic colorectal cancer (CRC), advanced pancreatic cancer (PC), metastatic HER2-amplified breast cancer (BC) and castrate-resistant prostate cancer (CaP). Registry patient characteristics and outcomes were compared to the practice-changing trial. Registry patients were older than the matched trial cohort by a median of 2-6 years (all p=< 0.01) for the CRC, BC and PC cohorts. The proportion of Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 patients was lower for CRC (94.1% vs 99.2%, p=0.001) and BC (94.9% vs 99.3%, p=0.001). Progression-free survival (PFS) for registry patients was similar to the trial patients or significantly longer (CaP, HR = 0.65, p=<0.001). Overall survival (OS) was also similar or significantly longer (CaP, HR 0.49, p=< 0.001). In conclusion, despite real-world patients sometimes being older or having inferior PS to trial cohorts, the survival outcomes achieved were consistently equal or superior to those reported for the same treatment in the trial. We suggest that this is potentially due to optimised use of each treatment over time, improved multidisciplinary care and increased post-progression options. We can reassure clinicians and patients that outcomes matching or exceeding those reported in trials are possible. The potential for survival gains over time should routinely be factored into future trial statistical plans.

INTRODUCTION

The randomised controlled trial is the gold standard of evidence-based medicine, with the randomisation process allowing for causal inference[1]. As new standards are defined these are adopted into routine care, with an anticipated positive impact on patient outcomes. The restrictive eligibility criteria for trials, however, often excludes patients who are elderly, of poor functional status and/or with comorbidities[2]. As a result, there is uncertain external validity,[3] a concept termed the efficacy-effectiveness gap[4]. To date there have been few studies exploring this, many of which are underpowered, and these have typically focused on patients treated soon after the new standard is adopted.

To our knowledge, no studies of the efficacy-effectiveness gap have been conducted using prospectively collected and comprehensive real-world data, or explored outcomes achieved several years after these new therapies have become well established. While important to document and understand what can be achieved in the real-world setting, exploring any gains over time if these are achieved, could usefully inform future trial statistical planning. In particular, the calculation of expected survival outcomes when a standard of care treatment becomes the control arm in a subsequent trial.

Here we examine data from a series of multi-site comprehensive advanced cancer registries, comparing the patient populations and examining the survival outcomes of a current standard first-line treatment versus the outcomes achieved in the clinical trial that defined this as a new standard. We aimed to determine the extent to which clinical trial results are reproduced in real-world practice, the extent to which this might vary across multiple tumour types and over time, and any factors that might predict the real-world performance of a new therapy. To our knowledge, this is the first multi-registry analysis of this kind.

METHODS

Data source

This retrospective observational study used data from four comprehensive, multi-site clinical registries enrolling consecutive patients at participating Australian sites. Comprehensive patient, tumour, treatment and outcome data had been collected over the course of the patient illness, including survival data. We selected four distinct disease types where longitudinal data was available from January 1st 2014 through to June 30th 2019. Individual site data was de-identified and combined using the BioGrid platform[6].

Data collection

Data was interrogated for patients with colorectal, pancreatic, HER2-amplified breast and castrate-resistant prostate cancer receiving a standard palliative intent first-line treatment. Outcomes for these patients were compared to those achieved in a practice-changing trial (Table 1).

COLORECTAL CANCER

Data was extracted across 25 sites from The Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry[5]. We included patients with metastatic colorectal cancer that were receiving first-line FOLFOX or XELOX plus bevacizumab with palliative intent (treatment intent is prospectively collected in the registry database). Data was compared to the intervention arms in the NO16966 trial[6], which enrolled patients from February 2004 to February 2005.

PANCREATIC CANCER

Data was extracted across 13 sites from the Pancreatic cancer: Understanding Routine Practice & Lifting End results (PURPLE) registry. We identified patients that received first-line gemcitabine and nab-paclitaxel for advanced pancreatic adenocarcinoma. The intervention arm from the MPACT study was used as the comparator, which enrolled patients from May 2009 to April 2012.

BREAST CANCER

Data was extracted across 22 sites from the Treatment of Advanced Breast Cancer in the HER2 Positive Australian Patient (TABITHA) registry[7]. We identified patients that received first-line treatment with a taxane (docetaxel or paclitaxel), trastuzumab and pertuzumab in combination. The intervention arm from the CLEOPATRA trial was used as the comparator, which enrolled patients from February 2008 to July 2010.

PROSTATE CANCER

Data was extracted across 16 sites from the Electronic castration-resistant Prostate cancer Australian Database (ePAD) registry. We identified patients receiving docetaxel as first-line treatment, having failed androgen deprivation therapy and/or a first-generation anti-androgen. The control arm in the FIRSTANA study[8] was used as the comparator, which enrolled patients from May 2011 to October 2013.

Statistical Plan

The primary objectives were to compare progression-free survival (PFS) and overall survival (OS) for registry patients to those receiving the identical treatment in an earlier clinical trial. Secondary objectives included examining differences in baseline characteristics between the two cohorts.

SAS Enterprise Guide and Graphpad Prism 8 software was used to interrogate the data. Descriptive statistics were used to describe baseline characteristics at commencement of treatment, percentages were used to describe categorical data, and medians (ranges) were used for continuous data. Fisher's exact test was used to determine statistical significance for categorical data between registry and trial cohorts, and the one-sample Wilcoxon signed rank test used to compare between medians. Treatment outcomes examined included discontinuation rates and reasons for discontinuation. Survival was measured from day 1 of treatment. PFS events were disease progression or death. A pre-specified subgroup analysis was performed on registry patients who appeared eligible for trial participation. The 'trial eligible' groups were formed by excluding registry patients in the primary analysis who did not meet inclusion criteria for the relevant clinical trial. The patient selection process is shown in the consort diagrams (See Supplementary data, S1-4). The survival analysis used the Kaplan-Meier method. Median time of follow-up was calculated using the reversed Kaplan-Meier analysis.

We combined the method of Liu et al[9] to extract the exact X- and Y-coordinates of the Kaplan-Meier curves from the Portable Document Format (PDF) files of the original papers with the Guyot et al[10] algorithm to reconstruct a close approximation of the original individual patient survival data, with minor modifications for improved accuracy. Hazard ratios were calculated using the Cox proportional hazards model, with the exact partial likelihood method to handle tied failure times. All data reconstruction and analyses code was implemented in R version 3.6.3.

RESULTS

Baseline demographics for the 975 patients commencing treatment from January 2014 to June 2019 are shown in Table 2.

Patient characteristics

COLORECTAL CANCER

As shown in Table 2, 396 TRACC registry patients treated with FOLFOX or XELOX plus bevacizumab were identified, with a median follow-up of 29.7 months. These were compared to 699 patients treated with FOLFOX4 or XELOX plus bevacizumab as part of the NO16966 study, where median duration of follow-up was 27.6 months.

Registry patients were older (median age 62 vs. 60 years, p=0.01) and less likely to be ECOG PS 0 – 1 (94% vs. 99%, p=<0.001). Gender and primary tumour location distribution were similar. There were more de novo metastatic patients in the registry (80% vs 64%, p=<0.001), and less prior adjuvant therapy (10% vs 24%,

p=<0.001). The number of metastatic sites was similar across the groups. Data such as tumour molecular information, primary tumour resection, co-morbidity, potential for resection of metastatic disease and time to recurrence for those with metachronous disease were available in the TRACC registry but are not reported here as these were not included in the trial publication.

PANCREATIC CANCER

As shown in Table 2, 225 registry patients were identified with a median follow-up of 23.8 months. These were compared to 432 patients in the gemcitabine/nab-paclitaxel arm of the MPACT study, with a median follow-up of 9.1 months.

The median age of registry patients was 6 years older than the trial cohort (p=<0.001). The proportion of patients who were ECOG PS 0-1, the primary tumour location and the rate of biliary stent insertion was similar. More registry patients had undergone a Whipple resection (12.4% vs 7.0%, p=0.045).

In terms of disease burden, registry patients were more likely to have only one metastatic site (55.5% vs. 8%, p=<0.001), less likely to have hepatic metastases (76.5% vs. 85%, p=0.01) and had a lower median CA19.9 level (691.0 vs. 2293.7 U/mL). In the MPACT trial, patients with locally advanced disease were excluded, whereas 18% of the registry patients had unresectable locally advanced disease. These were included in the registry analysis as they are managed similarly to metastatic patients in the real-world.

BREAST CANCER

195 TABITHA registry patients were identified. Median follow up for registry patients was 22.2 months. These were compared to 402 patients in the CLEOPATRA study[11] that were given trastuzumab, pertuzumab and docetaxel, where the median follow-up was 99.9 months (Table 2).

Registry patients were older (median age 58 vs. 54 years, p=0.003), less likely to be ECOG PS 0 -1 (94.9% vs. 99.3%, p=0.001) and more likely to have hormone receptor positive disease (57.4% vs. 45.8%, p=0.01). There were similar rates of prior adjuvant or neoadjuvant therapy (50.8% vs 45.8%, p=0.26). Notably 10% of TABITHA patients had brain metastases at baseline; an exclusion criterion for CLEOPATRA.

PROSTATE CANCER

159 registry patients were identified, with a median follow-up of 28.2 months. The comparator were the 391 control arm patients enrolled in the FIRSTANA study. A control rather than intervention arm was utilised as it was the most contemporary trial using the current standard of care treatment.

Registry and trial patients had a similar age and PS. The mean and median PSA level was higher (p=<0.001 for both) in the trial cohort, though the distribution of Gleason ≥7 disease was similar. Registry patients had a lower incidence of bone metastases (67% vs 91%, p=<0.0001).

Treatment outcomes

Figure 1 OS for the Registry vs Trial groups

Figure 2 PFS for the Registry vs Trial groups

COLORECTAL CANCER

The registry patients received first-line treatment for a median of 29.7 weeks, 2.6 weeks longer than NO16966 patients (p=<0.001). As seen in Figures 1-2, the PFS and OS for the registry cohort were superior to those in the trial groups (PFS 10.5 vs 9.4 months, HR=0.73, p=<0.001; OS 26.4 vs 21.3 months, HR 0.64, p=<0.001). 60% of registry patients received second-line therapy however this was not reported for NO16966 (Table 3).

Trial eligible patients

When TRACC registry patients not meeting NO16966 eligibility criteria (ECOG > 1 [n=24] or metastatic disease diagnosed within 6 months of completing adjuvant chemotherapy [n=11]) were excluded, the PFS (HR=0.69, p=<0.001) and OS (HR=0.58, p=<0.001) for the remaining 'trial eligible' registry patients was minimally changed compared to the trial.

PANCREATIC CANCER

The median duration of treatment, PFS and OS for registry and trial patients was similar to the matched trial cohort (PFS 5.1 vs 5.5 months, HR=1.15, p=0.15; OS 9.0 vs 8.7 months, HR=1.00, p=0.95). A similar proportion in each group received second-line therapy (Table 3).

Trial eligible patients

When PURPLE registry patients not meeting trial criteria (ECOG >2 [n=25], no tissue diagnosis [n=29] or locally advanced disease [n=40] were excluded the median PFS was 5.1 months (HR=1.16, p=0.19) and OS was 9.0 months (HR=1.03, p=0.82).

BREAST CANCER

The PFS for the TABITHA registry patients was 23.1 months versus 18.7 months for the matched CLEOPATRA cohort (HR=0.97, p=0.84), whereas OS was 52.2 months versus 56.5 months (HR=1.04, p=0.82). Registry patients received a shorter duration of taxane treatment (median 14.3 vs 24.0 weeks). The duration of exposure to the HER2-directed therapy was similar (Table 3).

Trial eligible patients

Excluding 30 registry patients (ECOG PS of >1 [n=10] and central nervous system (CNS) metastases [n=20] did not substantially impact PFS (HR=0.94, p=0.62) or OS (HR=1.08, p=0.68).

PROSTATE CANCER

Registry patients received less treatment than FIRSTANA patients (median exposure 22.5 vs 27.0 months, p=<0.001). Despite this, PFS (8.0 vs 5.3 months, HR=0.65, p=<0.001) and OS (36.9 vs 24.3 months, HR=0.49, p=<0.001) was superior in registry patients (Table 3).

Trial eligible patients

When registry patients not meeting trial criteria (ECOG score of >2 [n=3], prior chemotherapy (including upfront docetaxel) [n=4] and those who did not have histological or cytological confirmation of malignant disease [n=21]) were excluded, there was no change in median OS (HR 0.49, p=<0.001) but PFS was slightly shortened (7.7 vs 8.0 months, HR=0.71, p=0.002).

DISCUSSION

Here we report the first attempt at a uniform approach to comparing real-world versus trial outcomes across multiple and diverse tumour types. Despite observed age and ECOG PS differences that would be expected to negatively impact survival in the registry patients, survival outcomes achieved were similar or superior to the matched trial cohort. Notably, some years had elapsed since the comparator trials were reported and even more years from recruitment. Potentially, over this time many aspects of patient care have continued to evolve, including patient surveillance and imaging, therapy management, improved multidisciplinary care and the introduction of effective post-progression therapies. These may account for the observed survival gains.

Measuring real-world outcomes is essential to ensure the translation of benefits demonstrated in clinical trials into the real-world. Despite this acknowledged importance, there is limited previous data on this issue and

findings are inconsistent. Most reported analyses have only looked at single disease types with modest patient numbers and data on key prognostic factors are often incomplete. A recent paper[4] discussing the efficacy-effectiveness gap quoted several studies as evidence of inferior real-world outcomes. We note however that in three of these analyses there was no significant survival difference and in another similar outcomes were seen when examining the "trial eligible" cohort. Studies in breast cancer and glioblastoma patients reported that trial outcomes are in fact reflective of real-world results[12,13]. Based on the variable evidence from literature and acknowledging the possibility of publication bias, we would suggest that the outcomes may vary due to many reasons, including the time elapsed since the new therapy became available, disease type, the safety and efficacy of the new treatment and, treatment jurisdiction and location. Here we further explore a number of these issues.

For our registry cohort, notable changes in practice with respect to baseline imaging and surveillance following treatment of early-stage cancers when compared to the eras when the trials were conducted (trial patients were treated about 4 [prostate] and up to 12 [colorectal] years earlier than registry patients), could be impacting outcomes. Recent changes in practice across many solid tumour types include the increasing adoption of FDG PET, which is widely available in oncology practice, and can upstage a significant number of patients[14]. Specifically in prostate cancer the addition of PSMA PET scans were reported to upstage patients with otherwise localised disease in over 10% of cases[15]. More intensive surveillance of early stage colorectal cancer patients can bring forward detection of recurrence by 6-7 months[16,17]. Lead-time bias as a result of earlier detection of metastatic disease, may also mean fitter patients with less advanced disease are being treated, who potentially would derive more benefit from the initial first-line treatment.

Multi-disciplinary care is also evolving. For the subset of patients with oligometastatic disease, more patients with colorectal cancer are undergoing curative intent resection of liver or lung metastases[18]. Across many tumour types stereotactic body radiation therapy (SBRT) is increasingly being utilised, with benefits already demonstrated in prostate cancer[19] and pancreas cancer[20]. For patients with more extensive disease other interventions such as bone modifying agents in breast and prostate cancer are now a routine part of multi-disciplinary management. The improved management of chemotherapy-related nausea and vomiting[21] and the use of growth factors to reduce the risk of febrile neutropaenia[22] could also be expected to increase per protocol treatment delivery and may improve outcomes. Early incorporation of palliative care in the advanced disease setting is becoming more mainstream and may also provide a modest survival benefit[23].

Optimising the selection of patients and the application of the standard therapy option over time may also improve outcomes. Initial oxaliplatin-based treatment for patients with metastatic colorectal cancer is now of shorter duration, reducing the risk of neuropathy and allowing a later re-challenge. Initial therapy is now routinely followed by maintenance treatment with a fluoropyrimidine and bevacizumab until progression which provides a survival advantage[24,25]. Arguably strict trial protocols within the clinical trial context may lead to patients being taken off therapy despite receiving ongoing benefit, whereas in the real-world setting there is no limit on dose delays or dose reductions, treatment holidays are allowed, and patients can remain on treatment even if they fulfil RECIST criteria for disease progression if the clinician judges this likely to be helpful.

Changes in post-progression treatment would also impact the survival outcomes of the registry patients. For example, in colorectal cancer, better patient selection for EGFR inhibitors as well as the availability of additional lines of therapy such as regorafenib[26] and trifluridine/tipiracil[27] have demonstrated proven survival benefit. For prostate cancer patients, second-line treatment with abiraterone and enzalutamide is now routine, and cabazitaxel and lutetium PSMA therapy are now widely available. Multiple lines of therapy are increasingly being used in metastatic pancreatic cancer, with liposomal irinotecan now shown to provide a survival benefit[28]. The management of HER2-amplified metastatic breast cancer also continues to evolve[29].

Any improvement in outcomes over time as we report needs to be factored into the statistical plan for future studies where the intervention arm of a prior positive study becomes the control arm for the next study. In particular, it is important to ensure that trials are adequately powered to answer the hypothesis[30], which must be informed by expected outcomes in the control arm. As an extreme example the survival outcomes seen in NO16966 for oxaliplatin-based treatment plus bevacizumab (median OS 21.3 months), still a standard of care for many patients with metastatic colorectal cancer, was already substantially exceeded in the TRACC registry (median OS 26.4 months) and further gains over time should be anticipated. Underestimates of outcomes in control arm patients can mean that clinical trials are not sufficiently powered to address the study question.

One such example was observed in the APHINITY trial, where the effect on invasive disease-free survival (DFS) of adding adjuvant pertuzumab to standard-of-care trastuzumab plus chemotherapy was examined in HER2-positive breast cancer patients. The invasive DFS in the control arm was underestimated due to historical data being used for trial modelling[31]. A 3 year invasive DFS rate of 89.2% was assumed in the placebo arm, however the final DFS rate for this cohort was 93.2%. This underestimation then made it difficult for the experimental arm to be significantly superior to the control arm. Fortunately, the DFS in the experimental arm was also underestimated (predicted 91.8%, actual DFS rate of 94.1%). Both arms were underestimated, possibly reflecting the improved staging and management of patients with time as discussed above.

There are several limitations to our data. This was not collected with the same rigor as clinical trial data, so it is almost inevitable that there will be incomplete or inaccurate data in registries. Most challenging is the collection of adverse event data, which we have avoided analysing for this reason. The use of clinician-assessed versus RECIST-defined PFS data may also inflate PFS in the registry, if less strict criteria are used to define disease progression, as may less frequent imaging. However, for hard endpoints such as death dates, particularly where there is formal linkage with government funded state-wide cancer registries, the data is likely quite accurate.

Our data does provide reassurance that outcomes achieved in clinical trials can be reproduced in the real-world setting, utilising prospectively collected and comprehensive patient, disease and treatment data from four diverse tumour types. It also raises for the first time the possibility, particularly where some years have elapsed since the trial was reported, that PFS outcomes achieved in the real-world setting may even surpass those observed in the trial. We suggest this is in part due to more optimal application of the treatment over time and in part due to improved multidisciplinary care. Any improvement in first-line therapy outcomes would be expected, along with the uptake of salvage therapies that also extend survival, to improve OS expectations.

CONFLICT OF INTEREST

BT reports grants and personal fees from Amgen, AstraZeneca, BMS, Janssen, Pfizer, MSD, Ipsen, Bayer; grants from Astellas; personal fees from IQVIA, Roche, Sanofi, Tolmar and Novartis. AA reports research funding from Astellas, Amgen, AstraZeneca, Janssen and Mundipharma and honoraria from Janssen and Amgen. VW reports honorarium from Amgen, and research funding from Amgen, Novartis, Merck, Roche, Pierre Fabre and AstraZeneca. Other authors have no relevant disclosures/COI.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethics committee approval was granted (HREC/18/MH/28, HREC/16/MH/216, HREC/15/MH/8, HREC/15/MH/352).

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Figure 1 OS for the Registry vs Trial groups

(A) OS for TRACC vs NO16966
(B) OS for PURPLE vs MPACT
(C) OS for TABITHA vs CLEOPATRA
(D) OS for ePAD vs FIRSTANA

Figure 2 PFS for the Registry vs Trial groups

(A) PFS for TRACC vs NO16966
(B) PFS for PURPLE vs MPACT
(C) PFS for TABITHA vs CLEOPATRA
(D) PFS for ePAD vs FIRSTANA

Table 1

Metastatic patient population	Registry database	Comparator trial, Year published
Colorectal cancer	TRACC	NO16966, 2008[6]
Pancreatic cancer	PURPLE	MPACT, 2013[32,33]
HER2-amplified breast cancer	TABITHA	CLEOPATRA, 2012[11,34,35]
Castrate resistant prostate cancer	ePAD	FIRSTANA, 2017[8]

Table 2 Baseline characteristics of registry and trial patients

	TRACC (FOLFOX6 or XELOX +bevacizumab)	NO16966 (FOLFOX4 or XELOX +bevacizumab)
Number of patients	396	699
Median follow-up, months	29.7	27.6
Median age, years	62 (24-86)	60 (18-86)
Gender (%)		
Male	243 (61.4)	418 (60.0)
Female	153 (38.6)	281 (40.0)
Stage IV at diagnosis (%)	317 (80.1)	449 (64.0)
ECOG (%)		
0	195 (49.2)	405 (58.0)
1	177 (44.7)	289 (42.0)
≥2	23 (5.8)	1 (<0.1)
Unknown	1 (0.3)	0 (0.0)
Primary tumour site (%)		
Rectum	99 (25.0)	180 (26.0)
Colon	283 (71.5)	519 (74.0)
Occult or multiple primary	14 (3.5)	0 (0.0)
Number of metastatic sites (%)		
1	146 (36.9)	284 (41.0)
2	147 (37.1)	253 (36.0)
3	79 (19.9)	108 (15.0)
≥4	24 (6.1)	53 (8.0)
Prior adjuvant treatment (%)	40 (10.1)	164 (24.0)
	PURPLE (gemcitabine/nab-paclitaxel)	MPACT study (gemcitabine/nab-paclitaxel)
Number of patients	225	431
Median follow-up time, months	23.8	9.1
Median age (years)	68 (33-84)	62 (27-86)
Gender (%)		
Male	111 (49.3)	245 (57.0)
Female	114 (50.6)	186(43.0)
Stage		
Metastatic	185 (82.2)	431 (100.0)

Unresectable locally advanced	40 (17.7)	0 (0.0) (excluded)
ECOG (%)		
0	69 (30.6)	69 (16.0)
1	131 (58.2)	328 (76.1)
≥2	25 (11.1)	32 (7.4)
Pancreatic tumour location (%)		
Head	105 (46.6)	191 (44.0)
Tail	56 (24.9)	132 (31.0)
Body	50 (22.2)	105 (24.0)
Unknown	14 (6.2)	3 (1.0)
Number of metastatic sites (%)		
1	125 (55.5)	33(8.0)
2	77 (34.2)	202 (47.0)
3	19 (8.4)	136 (32.0)
>3	4 (1.7)	60 (14.0)
Liver metastases (%)	172 (76.4)	365 (85.0)
CA 19.9 level U/ml (median)	691.0	2293.7
Previous therapy (%)		
Biliary stent	40 (17.7)	80 (19.0)
Resection (Whipple procedure)	28 (12.4)	32 (7.0)
	TABITHA (docetaxel OR paclitaxel/trastuzumab/pertuzumab)	CLEOPATRA (docetaxel/trastuzumab/pertuzumab)
Number of patients	195	402
Median follow-up (months)	22.2	99.9
Female (%)	194 (99.5)	402 (100.0)
Age (median, years)	58.0 (range 27-95)	54.0 (range 22–82.0)
Sites of disease (%)		
Visceral	-	314 (78.1)
Non-visceral	-	88 (21.9)
Bone only	18 (9.2)	-
Liver	72 (36.9)	-
Brain	20 (10.3)	-
ER/PR profile		
HR+ (ER+, PR+ or both)	112 (57.4)	189 (47.0)
HR- (ER- and PR-)	81 (41.5)	212 (52.7)
Unknown	2 (1.0)	1 (0.2)
ECOG (%)		
0	132 (67.7)	274 (68.2)
1	53 (27.2)	125 (31.1)
≥2	8 (4.1)	3 (0.7)
Unknown	2 (0.5)	-
Prior neoadjuvant or adjuvant therapy (%)		
Yes	99 (50.8)	184 (45.8)
No	96 (49.2)	218 (54.2)
	ePAD (docetaxel)	FIRSTANA (docetaxel)
Number of patients	159	391
Median follow-up time (months)	28.2	Not reported
Age (median, years)	69.0 (49-84)	69.0 (41-87)
Metastatic at diagnosis	62 (39.0)	-
ECOG status		
0-1	151 (95.0)	374 (95.7)
2	5 (3.1)	17 (4.3)
Unknown	3 (1.9)	0 (0.0)
Gleason score		
≤6	10 (6.3)	42 (10.7)
≥7	120 (75.5)	309 (79.0)
Unknown	29 (18.2)	40 (10.2)
PSA		
Mean (SD)	46.9 (104.3)	252.82 (625.20)
Median (range)	13.8 (0.01 - 93)	73.92 (2.4-6 - 862.0)

Metastases, No. (%)		
Bone	109 (68.6)	356 (91.0)
Liver	8 (5.0)	35 (9.0)

Table 3 Summary of survival outcomes across registry and trial cohorts

Colorectal cancer		
Cohort	**TRACC**	**NO16966**
Median treatment duration (weeks)	29.7	27.1
PFS (months)	10.5 (95% CI 9.2-11.2)	9.4
OS (months)	26.4 (95% CI 22.8-28.8)	21.3
Interval metastatic disease resection (%)	46 (11.6)	59 (8.4)
Cohort	**TRACC (trial eligible, n=361)**	**NO16966**
PFS (months)	10.8 (95% CI 9.7-11.6)	9.4
OS (months)	26.8 (95% CI 23.3-30.0)	21.3
Pancreatic cancer		
Cohort	**PURPLE**	**MPACT**
Duration of treatment (weeks)	14.9	15.6
PFS (months)	5.1 (95% CI 2.2-5.9)	5.5
OS (months)	9.0 (95% CI 6.8-9.9)	8.7
Second-line therapy (%)	76 (33.7)	164 (38.0)
Cohort	**PURPLE (trial eligible, n=139)**	**MPACT**
PFS (months) (trial eligible)	5.1 (95% CI 4.1-5.8)	5.5
OS (months) (trial eligible)	9.0 (95% CI 6.7-10.7)	8.7
Breast cancer		
Cohort	**TABITHA**	**CLEOPATRA**
Median HER2+ directed treatment duration (months)	21.9	18.1
Median chemotherapy duration (weeks)	14.3	24.0
PFS (months)	23.1 (95% CI 16.2-27.7)	18.7
OS (months)	52.2 (95% CI 43.1-NR)	56.5
Cohort	**TABITHA (trial eligible, n=167)**	**CLEOPATRA**
PFS (months)	24.0 (95% CI 17.5-27.7)	18.7
OS (months)	51.7 (95% CI 40.0-NR)	56.5
Prostate cancer		
Cohort	**ePAD**	**FIRSTANA**
Median treatment duration, weeks	22.5 (4.8 – 72.6)	27.0 (3.0 – 147.0)
Median PFS (months)	8.0 (95% CI 7.0-8.8)	5.3 (composite)
PSA Response (%)	79 (49.4)	242 (68.4)
Median OS (months)	36.9 (95% CI 31.4-45.8)	24.3 (22.18-27.60)
Reason for treatment discontinuation		
Toxicity	40 (25)	133 (34.4)
Progressive Disease	52 (32.5)	139 (35.9)
Cohort	**ePAD (trial eligible, n=126)**	**FIRSTANA**
PFS (months)	7.7 (95% CI 6.7-8.7)	5.3 (composite)
OS (months)	36.9 (95% CI 31.4-45.8)	24.3 (22.18-27.60)

Figure 1 OS for the Registry vs Trial groups

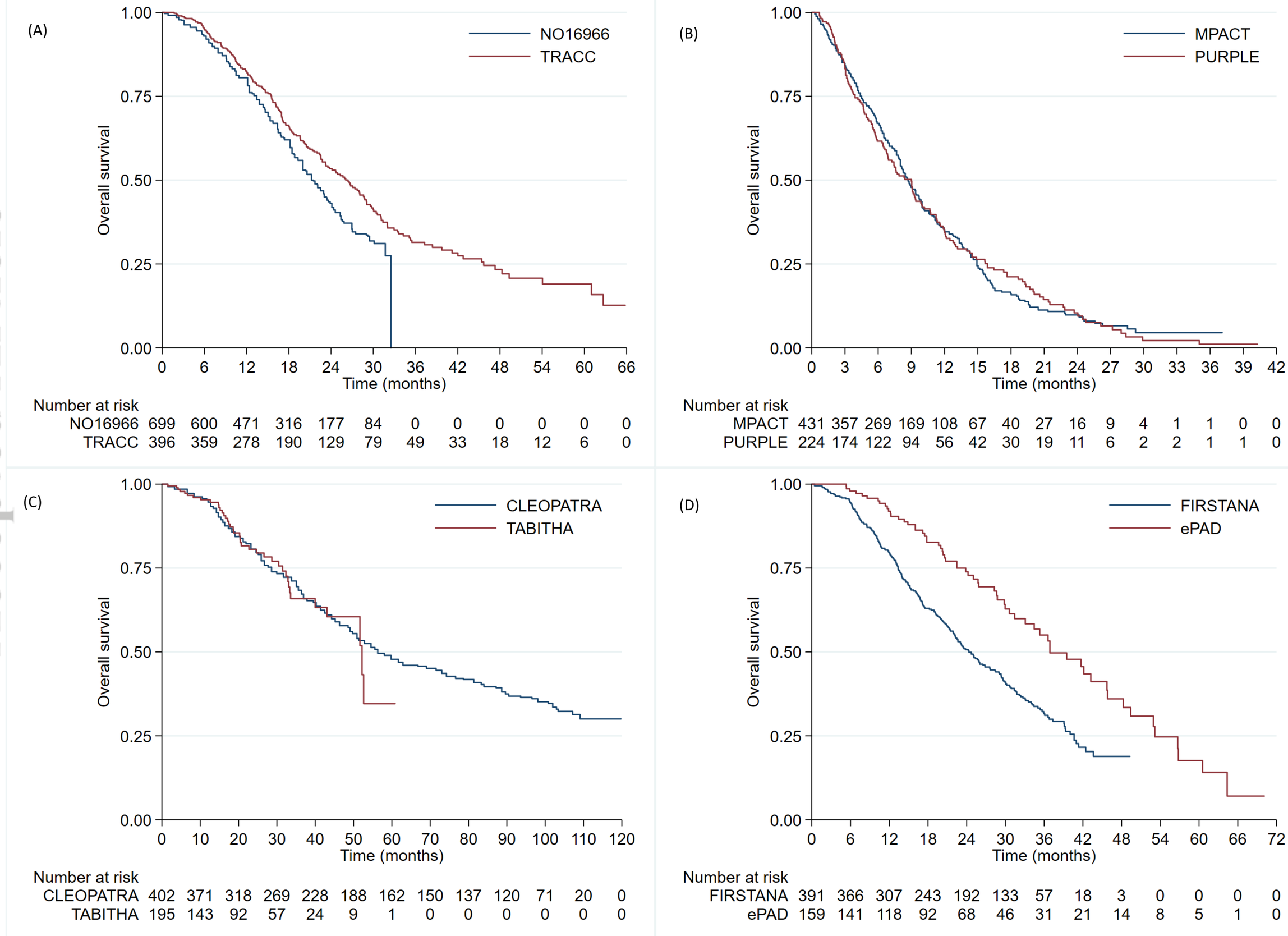

Figure 2 PFS for the Registry vs Trial groups