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Original Research

Evaluating management of progressive disease for control arm patients in trials of first line PD-1 or PD-L1 inhibitor-based treatment for metastatic solid tumours

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Abstract ***Introduction:*** First-line trials evaluating programmed cell death protein 1/programmed-death ligand 1 inhibitors (PDI) are often preceded by FDA approvals of PDI in second-line settings; however, many control-arm patients in these first-line trials do not receive PDI at disease progression. We performed a systematic analysis of trials evaluating upfront use of PDI in metastatic solid tumours to (1) quantify the number of control-arm patients that receive PDI upon disease progression and (2) the timing difference between FDA approval for a PDI in the second-line setting and (3) enrolment period for the same drug in a first-line trial.
Methods: Using the Drugs@FDA website, we evaluated all approvals for first-line and second-line PDI in metastatic solid tumours through December 2021. From corresponding trials, we calculated the timing difference between second-line approval of a PDI and start/end of accrual of first-line trials and management of disease progression for control-arm patients.
Results: 25/32 approvals for upfront PDI were preceded by approval of a PDI in the second-line of the same disease and included in this analysis. First-line trials start of accrual preceded approval of a PDI by a mean of 4 months, median 6 months and ended accrual by a mean and median of 14 after second-line approval. A mean of 51% of control-arm patients received subsequent therapy, with a mean of 33% of these patients receiving a PDI.
Conclusion: This analysis shows that many control-arm patients in the included trials did not receive a PDI with already established efficacy at any point during their recorded treatment. This underscores a need to standardise the approach to disease progression for control-arm patients to reflect evolving standards of care. This analysis is limited by a lack of individual

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patient-level data, heterogeneity of included trials and exclusion of first-line PDI trials that did not meet their primary endpoint.

1. Introduction

Since 2015, programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, jointly referred to as PDI in this article, have received FDA approval as first-line treatment in many different solid tumours, with over thirty FDA approved indications by the end of 2021. Often, first-line investigations are preceded by FDA approval based on seminal trials in the second line/refractory setting. In 1st line PDI trials, some patients in the control arm will receive subsequent systemic treatment at disease progression. However, subsequent therapy is not standardised for control arm patients, leading to variable treatment exposure that may be suboptimal – particularly when the crossover is not prespecified and in international studies where each nation has different access to therapeutic agents. This introduces a confounding variable in 1st line PDI trials where the clinical scenario that is being tested may be any exposure to a PDI rather than upfront treatment. This issue is particularly relevant when overall survival is a primary endpoint. The purpose of this study is to systematically analyse the management of progressive disease for the control arm of all randomised controlled trials (RCTs) for PDI that led to an FDA approval for first-line treatment through December 2021, with a focus on scenarios where upfront trials were preceded by a study and FDA approval of a checkpoint inhibitor in the second line/refractory setting. We aim to clarify the need for standardising treatment of control arm patients upon disease progression, to evaluate if timing differences between trials evaluating upfront and 2nd line/refractory use of same/similar drugs offer an opportunity for protocol amendments and highlight the need for a formalised process of reporting subsequent care in clinical trials.

2. Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines were adhered to for the reporting of this systematic analysis. We searched the Drugs@FDA: FDA-Approved Drugs data to review indications for PDI, including pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab. Indications were last reviewed on 31st December 2021. Only drugs that had both a first-line and second-line/refractory approval were included. Once the FDA approvals were identified, we used a Google search to identify the approval date for each indication. Exclusion criteria included accelerated approvals that were later withdrawn, 1st line approvals based on single-arm studies and approvals based on trials that did not publish data regarding subsequent care of patients upon disease progression. We found the clinical trial that supported each FDA approval by reviewing the Drugs@FDA page or the medications package insert. Once identified, the trial publication, appendix and supplementary table were reviewed to extract enrolment dates and subsequent therapy (Supplemental Table S1: included studies and Supplemental Table S2: search strategy). We then compared the FDA approval of a PDI in the second-line/refractory setting to the first-line PDI trial for the same disease type. We calculated the difference in months between FDA approval in the refractory setting and both the start and end of enrolment in first-line trials (Table 1). We then calculated the percent of control patients receiving any post-protocol therapy and the percent that receive a PDI in first-line trials (Table 2). We did not have access to individual patient subsequent therapy. One reviewer, AM, was responsible for the above process. No external funding was provided for this analysis.

3. Results

A total of 32 FDA approvals for first-line treatment with a PDI were reviewed. In 30 of the 32 instances, a first-line approval was preceded by approval of a PDI in the second line/refractory setting. These 30 indications stem from 30 trials. We excluded 5 of these indications that were based on a single-arm study or a study where subsequent treatment of control patients was not published. Thus, a total of 25 indications from 25 trials were included in this analysis (Supplement Table 1). For PD-1 inhibitors specifically, we found 17 instances of a first-line trial preceded by a 2nd line or refractory approval and for PD-L1 inhibitors we found 8 instances of a first trial preceded by a 2nd line or refractory approval.

The start date of randomisation/enrolment in a first-line trial preceded FDA approval in the refractory/2nd line by a mean time of 4 months and a median time of 6 months. The end date of randomisation in the first line trial was preceded by an FDA approval in the refractory/2nd line by a mean time of 14 months and a median time of 14 months (Table 1). Fig. 1 shows the amount of patient accrual time in a first-line trial both before and after approval in the 2nd line/refractory setting. The combined mean percentage of patients that received subsequent therapy was 51%, median 51%. The

Table 1
FDA approval dates for drugs used in the second-line/refractory setting and corresponding randomisation dates for the same drug tested in the first-line setting. A negative number indicates first-line trial start/end of randomisation occurred many months before FDA approval of the drug in the 2nd line/refractory setting.

Medication	FDA approved indication	1st line approval date	2nd line/ refractory approval date	1st line randomisation dates	Months between the start of randomisation initiation and 2nd line approval	Months between the end of randomisation and 2nd line approval
Pembrolizumab	mNSCLC monotherapy (PD-L1>50%)	10/14/16	10/2/15	9/19/14-10/29/15	−11.0	0.5
	mNSCLC monotherapy (PD-L1>1%)	4/11/19	10/2/15	12/19/14-3/6/17	−11.0	17.0
	mNSCLC (non-sq, regardless of PD-L1, combined with carboplatin/ pembrolizumab, non-EGFR/ALK mutation	5/10/17	10/2/15	11/25/14-1/25/16	−11.0	3.0
	mNSCLC (non-sq, regardless of PD-L1, combined with carboplatin/ pembrolizumab, non-EGFR/ALK mutation (Keynote 189 trial)	5/10/17	10/2/15	2/26/16-3/6/17	4.0	17.0
	mNSCLC (sq, with carboplatin and paclitaxel/ nab-paclitaxel, regardless PD-L1) (Keynote 021 trial)	10/30/18	3/4/15	8/19/16-12/28/17	17.0	26.0
	mHNSCC (with platinum + 5FU or monotherapy if combined positive score>1)	11/6/19	8/5/16	4/20/15-1/17/17	−16.0	14.0
	mRCC (with axitinib)	4/19/19	11/23/15	10/24/16-1/24/18	11.0	26.0
	mRCC (with lenvatinib)	8/10/21	11/23/15	10/13/16-7/24/19	11.0	33.0
	mCRC (MSI-H)	6/29/20	5/23/17	2/11/16-2/19/18	−15.0	9.0
	mOesophageal	3/22/21	7/30/19	7/25/17-6/03/19	−24.0	−1.0
Nivolumab	mMelanoma	10/1/15	12/22/14	07/2013-03/2014	17.0	−9.0
	mMelanoma	10/1/15	12/22/14	09/2013-02/2014	15.0	−10.0
	mNSCLC (with ipilimumab)	9/28/19	3/4/15 (sq) 10/10/15 (non-sq)	8/2015-11/2016	−2.0	13.0
	mNSCLC (with ipilimumab + platinum)	9/16/20	3/4/15 (sq) 10/10/15 (non-sq)	8/24/17-1/30/19	29.0	46.0
	mRCC (with ipilimumab if intermediate-poor risk)	4/16/18	11/23/15	10/2014-2/2016	−13.0	3.0
	mRCC (with cabozantinib)	1/22/21	11/23/15	9/2017-5/2019	22.0	42.0
	mGastric/mGEJ/ mEsophageal	4/16/21	9/22/17	3/27/17-4/24/19	−6.0	19.0
Atezolizumab	mUrothelial carcinoma (platinum ineligible)	4/17/17	5/18/16	7/15/16/-7/20/18	2.0	26.0
	mNSCLC (PD-L1>50%, TIL>10%)	5/18/20	10/2/15	7/21/15-2/2/18	−3.0	28.0
	mNSCLC (with bevacizumab, paclitaxel and carboplatin)	12/6/18	10/2/15	3/2015-12/2016	−7.0	14.0
	mNSCLC (with nab-paclitaxel and carboplatin)	12/3/19	10/2/15	4/4/15-2/3/17	−6.0	14.0
	eSCLC (with carboplatin + etoposide)	3/18/19	8/17/18	6/6/16-5/31/17	−26.0	−15.0
	HCC (with bevacizumab)	5/29/20	9/22/17	3/15/18-5/29/18	6.0	16.0
Durvalumab	eSCLC (with cisplatin/ carboplatin + etoposide)	3/27/20	8/17/18 (nivolumab)	3/27/17-5/29/18	−17.0	−3.0

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Table 1 (*continued*)

Medication	FDA approved indication	1st line approval date	2nd line/ refractory approval date	1st line randomisation dates	Months between the start of randomisation initiation and 2nd line approval	Months between the end of randomisation and 2nd line approval
Avelumab	advanced RCC (with axitinib)	5/14/19	11/23/15	3/29/16-12/19/17	4.0 Mean = −5.4 months Median −9.0 months	25.0 Mean = 11.3 months Median = 14.0 months

m = metastatic; NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell carcinoma; RCC = renal cell carcinoma; CRC = colorectal cancer; MSI = microsatellite instability; GEJ = gastroesophageal; TIL = tumour infiltrating lymphocytes; HCC = hepatocellular carcinoma; SCLC = small cell lung cancer; sq = squamous.

combined mean percentage of all patients that received subsequent PDI was 33%, median 31%. Of those patients that received any subsequent treatment, the mean percentage that received a PD-1 or PD-L1 inhibitor was 57%, median 61% (Table 2). Fig. 2 graphically displays the percentage of patients in the control arm in each first-line trial that was exposed to subsequent treatment. All trials included in this review were multi-centre, multi-country trials and industrysponsored. The crossover was explicitly prohibited in the following trials: Keynote 042 (NCT0220894), Keynote 590 (NCT03189719), Checkmate 227 (NCT02477864), Checkmate 9LA (NCT03215706), IMPower 110 (NCT02409342), IMPower150 (NCT02366143), CASPIAN (NCT 03043872). Table 2 summarises if the crossover was explicitly permitted, not permitted or not prespecified within the included trials. In Checkmate 9LA, patients in the control arm were not permitted to crossover over to the chemotherapy with Ipilimumab and Nivolumab arm, however, patients were permitted to receive subsequent immunotherapy off trial upon discontinuation of study treatment.

4. Discussion

Within a short timeframe, checkpoint inhibitors have made a major impact on many facets of solid tumour oncology. The impressive pace of that impact came with a multitude of trials investigating a medication at different time points within the same disease. Our analysis shows that, despite the brief time, most first-line trials that met their primary endpoint are preceded by a trial and FDA approval in the 2nd line/refractory setting. Furthermore, first-line trials start accruing patients within a mean time of 4 months prior to FDA approval of the same drug in the 2nd line/refractory setting and stop accruing at a mean time 14 months after the same FDA approval. In the control arm of the included trials, 51% of patients received any subsequent therapy and approximately 57% of those patients received a PDI with proven efficacy, which equates to only 33% of all patients in the control arm. Overall, the percentage of control arm patients that we calculated as receiving subsequent therapy was similar to other observational studies that suggest 30–80% of patients with metastatic solid tumours receive multiple lines of treatment, with discrepancies influenced by primary tumour type [1–3]. Amongst the trials we reviewed, there were 8 trials (Keynote 189, Keynote 407, Keynote 426, CLEAR, Checkmate 9LA, Checkmate 9 ER, IMBrave 150 and Javelin 101 Renal) where an FDA approval for a PDI in the 2nd line/refractory setting of the specific disease existed for 100% of the trial enrolment period, and yet, the control arm immunotherapy exposure was <50% in each trial.

Together, these data suggest that although a majority of control arm patients that received any subsequent care received a PDI, adjustments are needed to ensure that all patients receive the highest existing standard of care regardless of treatment arm and that trials test the sequence of drug administration when the drug has proven efficacy in the 2nd line/refractory setting. Since nearly 70% of patients in the first line PDI trials may never receive a PDI during their disease course, the first line trials may be testing a redundant hypothesis of exposure to a PDI (already studied in the 2nd line/refractory setting) rather than testing the clinical question of when to give a patient a PDI. Additionally, the variability in subsequent therapy raises a concern about the heterogeneity of subsequent therapy when comparing costly medications in a global setting, which can affect overall survival outcomes. This holds particularly true in clinical trials where patients commonly have excellent performance status and are thus more likely to receive subsequent treatment upon the progression of the disease. Although enrolment in these trials started a mean of 4 months prior to FDA approval in the 2nd line/refractory setting, average enrolment ended 14 months after FDA approval for the 2nd line/refractory setting, suggesting that there is an opportunity to amend trial protocols during the accrual phase to ensure all patients receive the most updated standard of care.

Table 2
Summary of management of disease progression for control arm patients in each trial, identification of trials that permitted, prohibited or did not prespecify crossover and corresponding 2nd-line/refractory trial.

Medication	Indication	1st line trial/phase	Number of control that received subsequent/therapy N (%)	Number of all control patients that received immunotherapy N (%)	Number of pts receiving subsequent treatment that received immunotherapy N (%)	Crossover permitted in 1st line trial	Corresponding 2nd-line/refractory trial
Pembrolizumab	mNSCLC monotherapy (PD-L1>50%)	Keynote 024 (NCT02142738)/phase III [7]	Not provided	97/151 (64%)	Not provided	Yes	Keynote 010 (NCT01905657) [31]
	mNSCLC monotherapy (PD-L1>1%)	Keynote 042 (NCT0220894)/phase III [8]	282/637 (44.2%)	126/637 (20%)	126/282 (45%)	No	Keynote 010 (NCT01905657) [31]
	mNSCLC (non-sq, regardless of PD-L1, combined with carboplatin/pembrolizumab, no EGFR/ALK mutation	Keynote 021 (NCAT02039674)/phase II [9]	36/62 (58%)	33/62 (53%)	33/36 (89%)	Yes	Keynote 010 (NCT01905657) [31]
	mNSCLC (non-sq, regardless of PD-L1, combined with carboplatin/pembrolizumab, no EGFR/ALK mutation	Keynote 189 (NCT02578680)/phase III [10]	96/206 (47%)	85/206 (41%)	85/96 (89%)	Yes	Keynote 010 (NCT01905657) [31]
	mNSCLC (sq, with carboplatin and paclitaxel/nab-paclitaxel, regardless PD-L1)	Keynote 407 (NCT02578680)/phase III [11]	Not provided	89/280 (32%)	Not provided	Yes	Keynote 010 (NCT01905657) [31]
	mHNSCC (with platinum + 5FU OR monotherapy if combined positive score>1)	Keynote 048 (NCT02358031)/phase III [12]	159/300 (53%)	75/300 (25%)	75/159 (47%)	Not prespecified	Keynote 012 (NCT01848834) [32]
	mRCC (with axitinib)	Keynote 426 (NCT02853331)/phase III [13]	147/242 (61%)	91/242 (38%)	91/147 (62%)	Not prespecified	Checkmate 025 (NCT01668784) [33]
	mRCC (with lenvatinib)	CLEAR (NCT02811861)/phase III [14]	206/357 (58%)	154/357 (43%)	154/206 (75%)	Not prespecified	Checkmate 025 (NCT01668784) [33]
	mCRC (MSI-H)	Keynote 177 (NCT02563002)/phase III [15]	Not provided	91/154 (59%)	Not provided	Yes	Keynote 164 (NCT02460198) [34]
	mOesophgeal	Keynote 590	177/370 (48%)	35/370 (10%)	35/177 (20%)	No	Keynote 180

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Table 2 (*continued*)

Medication	Indication	1st line trial/ phase	Number of control that received subsequent/ therapy N (%)	Number of all control patients that received immunotherapy N (%)	Number of pts receiving subsequent treatment that received immunotherapy N (%)	Crossover permitted in 1st line trial	Corresponding 2nd-line/ refractory trial
	cancer	(NCT03189719)/ phase III [16]					(NCT02559687) [42]
Nivolumab	mMelanoma	Checkmate 067 (NCT01844505)/ phase III [17]	237/315 (75%) (pts in the ipilimumab arm)	144/315 (46%) (pts in the ipilimumab arm that received PD1/PDL1 based tx)	144/237 (61%) (pts in the ipilimumab arm that received PD1/PDL1 based tx)	Not prespecified	Checkmate 037 (NCT01721746) [35]
	mMelanoma	Checkmate 069 (NCT01927419)/ phase II [18]	33/47 (70%)	29/47 (62%)	29/33 (88%)	Yes	Checkmate 037 (NCT01721746) [35]
	mNSCLC (with ipilimumab)	Checkmate 227 (NCT02477826)/ phase III [19]	313/583 (54%)	238/583 (41%)	238/313 (76%)	No	Checkmate 057 (NCT01673867) [36]
	mNSCLC (with ipilimumab + platinum)	Checkmate 9LA (NCT03215706)/ phase III [20]	144/358 (40%)	108/358 (30%)	108/144 (75%)	No	Checkmate 057 (NCT01673867) [36]
	mRCC (with ipilimumab if intermediate-poor risk)	Checkmate 214 (NCT02231749)/ phase III [21]	295/546 (54%)	197/546 (36%)	197/295 (67%)	Yes	Checkmate 025 (NCT01668784) [33]
	mRCC (with cabozantinib)	Checkmate 9 ER (NCT03141177)/ phase III [22]	108/328 (33%)	67/328 (20%)	67/108 (62%)	Not prespecified	Checkmate 025 (NCT01668784) [33]
	mGastric/mGEJ/ mOesophageal	Checkmate 649 (NCT02872116)/ phase III [37]	295/546 (54.0%)	197/546 (36%)	197/295 (67%)	Yes	Keynote 059 (NCT02335411) [38]
Atezolizumab	mUC (platinum ineligible)	IMVigor 130 (NCT02807636)/ phases III [23]	164/400 (41%)	79/400 (20%)	79/164 (48%)	Not prespecified	IMVIgor 210 (NCT02108652) [39]
	mNSCLC (with PDL1>50% or TIL >10%)	IMPower 110 (NCT02409342)/ phase III [24]	130/263 (49%)	76/263 (29%)	76/130 (59%)	no	Keynote 010 (NCT01905657) [31]
	mNSCLC (with bevacizumab, paclitaxel and carboplatin) nab-paclitaxel and carboplatin)	IMPower 150 (NCT02366143)/ phase III [25]	Not available	126/400 (32%)	Not available	No	Keynote 010 (NCT01905657) [31]

	mNSCLC (with nab-paclitaxel and carboplatin)	IMPower 130 (NCT02367781)/ phase III [26]	151/228 (66%)	135/228 (59%)	135/151 (89%)	Yes	Keynote 010 (NCT01905657) [31]
	Extensive SCLC (with carboplatin and etoposide)	IMPower 133 (NCT02763579)/ phase III [27]	116/202 (57%)	15/202 (7%)	15/116 (13%)	Not prespecified	Checkmate 032 (NCT01928394) [40]
	HCC (with bevacizumab)	IMBrave 150 (NCT03434379)/ phase III [28]	73/165 (44%)	31/165 (19%)	31/73 (42%)	Not prespecified	Checkmate 040 (NCT01658878) [41]
Durvalumab	Extensive SCLC (with cisplatin or carboplatin and etoposide)	CASPIAN (NCT03043872)/ phase III [29]	119/269 (44%)	14/269 (5%)	14/119 (12%)	No	Checkmate 032 (NCT01928394) [40]
Avelumab	mRCC (with axitinib)	JAVELIN Renal 101 (NCT02684006)/ phase III [30]	174/444 (39%)	107/444 (24%)	107/174 (74%)	Not prespecified	Checkmate 025 (NCT01668784) [33]

m = metastatic; NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell carcinoma; RCC = renal cell carcinoma; CRC = colorectal cancer; MSI = microsatellite instability; GEJ = gastroesophageal; TIL = tumour infiltrating lymphocytes; HCC = hepatocellular carcinoma; SCLC = small cell lung cancer; sq = squamous.

Potential remedies to these issues include streamlining trial amendment processes to allow trials to reflect evolving standard of care data, as well as mandating crossover protocols if a medication is already approved/known to be efficacious in the 2nd line/refractory setting. This type of protocol would both test the sequence of drug administration and ensure all patients get equal access regardless of country of origin. As the overwhelming majority of these trials are industry-sponsored (100% in this review), it is reasonable to expect all patients to have equitable access to a study drug if there are data to support its use in the second-line setting. As established and novel checkpoint inhibitors continue to be evaluated in a multitude of solid tumour settings, we advocate for the adoption of these recommendations for future trials. Amongst those involved in performing clinical trials, Data Safety Monitoring Committees may serve as the most appropriate group for identifying practice-changing updates in care and suggesting protocol amendments for clinical trials to reflect these updates. Although protocol amendments are ubiquitous within clinical trials, there is a significant cost associated with major protocol amendments that likely dissuade investigators and associated stakeholders from performing these types of amendments [4]. As the type of protocol amendment, we are suggesting within this article involves potentially offering an experimental drug to all patients within a trial, we expect this amendment would significantly increase the cost of conducting an involved trial. However, as this amendment would only be implemented when a drug is shown to be effective in the 2nd line/refractory setting, this is a necessary cost to ensure equitable care to all patients, particularly in international trials.

There are several limitations of this review to note. This analysis focuses only on first-line PDI trials that met their primary endpoint and subsequently led to an FDA approval for a PDI in the first-line setting. By excluding trials that did not meet their primary endpoint and lead to an FDA approval, it is possible that this analysis selects trials where control arm patients were less likely to receive a PDI upon disease progression. As the aim of this analysis was to analyse only those PDI with FDA approval for upfront use, this type of exclusion was necessary. We did not have access to individual patient data, so it is unclear which specific checkpoint inhibitor medication patients received for subsequent therapy, underscoring the need for publication's de-identified data from these trials to promote further research. Every trial did not explicitly define or comment on crossover and subsequent therapy data were not always available. Additionally, we considered a prior approval of a PD-1 inhibitor as applicable to a PD-L1 inhibitor trial, and there is evidence to suggest that they may have dissimilar efficacy and safety profiles [5,6].

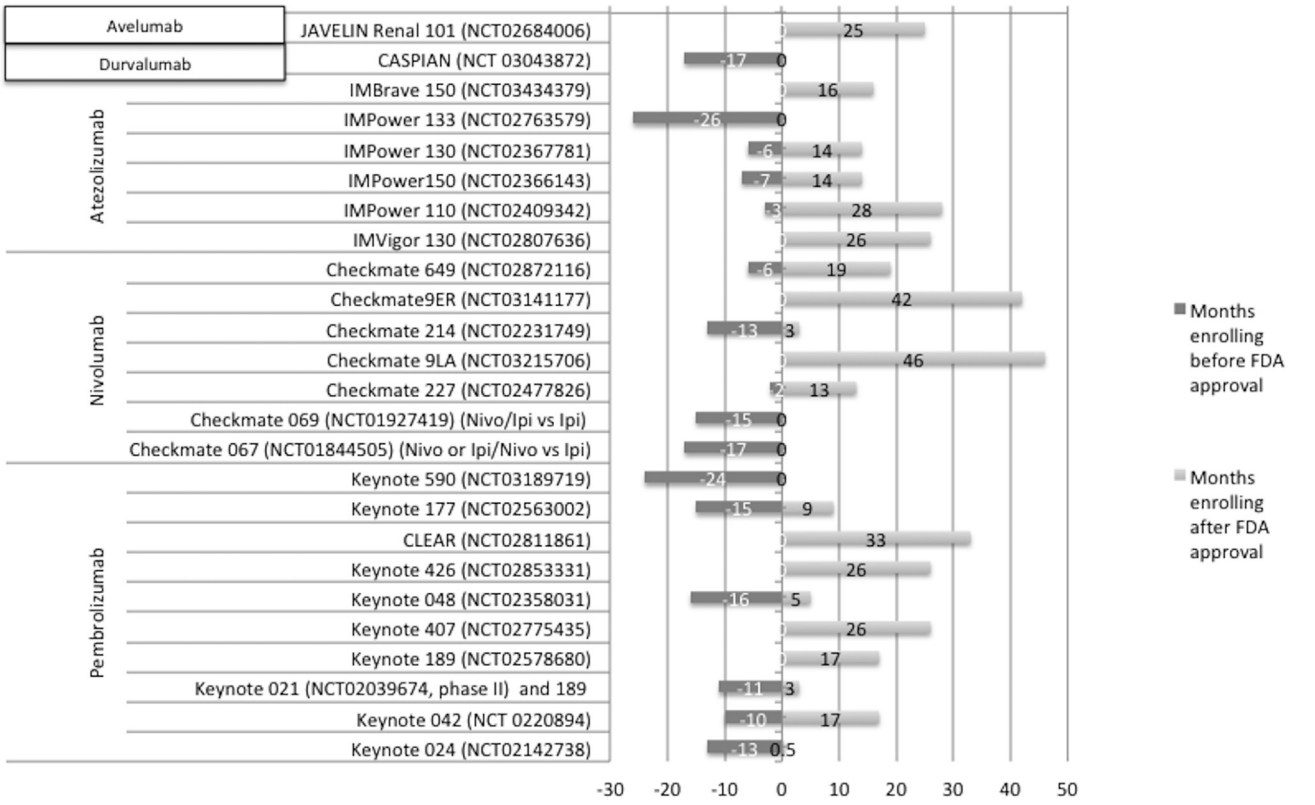

Fig. 1. Time Overlap Between FDA approval for drugs approved in the 2nd line/refractory disease and start/end of 1st line trial enrolment for the same drug. This figure graphically shows the amount of patient accrual time in the first-line setting that occurred before and after an FDA approval of a PD-1 or PD-L1 inhibitor in the 2nd line/refractory setting. The 0-time point is the time of FDA approval. Horizontal bars that do not cross the 0 points indicate that patient accrual occurred entirely before or after FDA approval in the 2nd line/refractory setting.

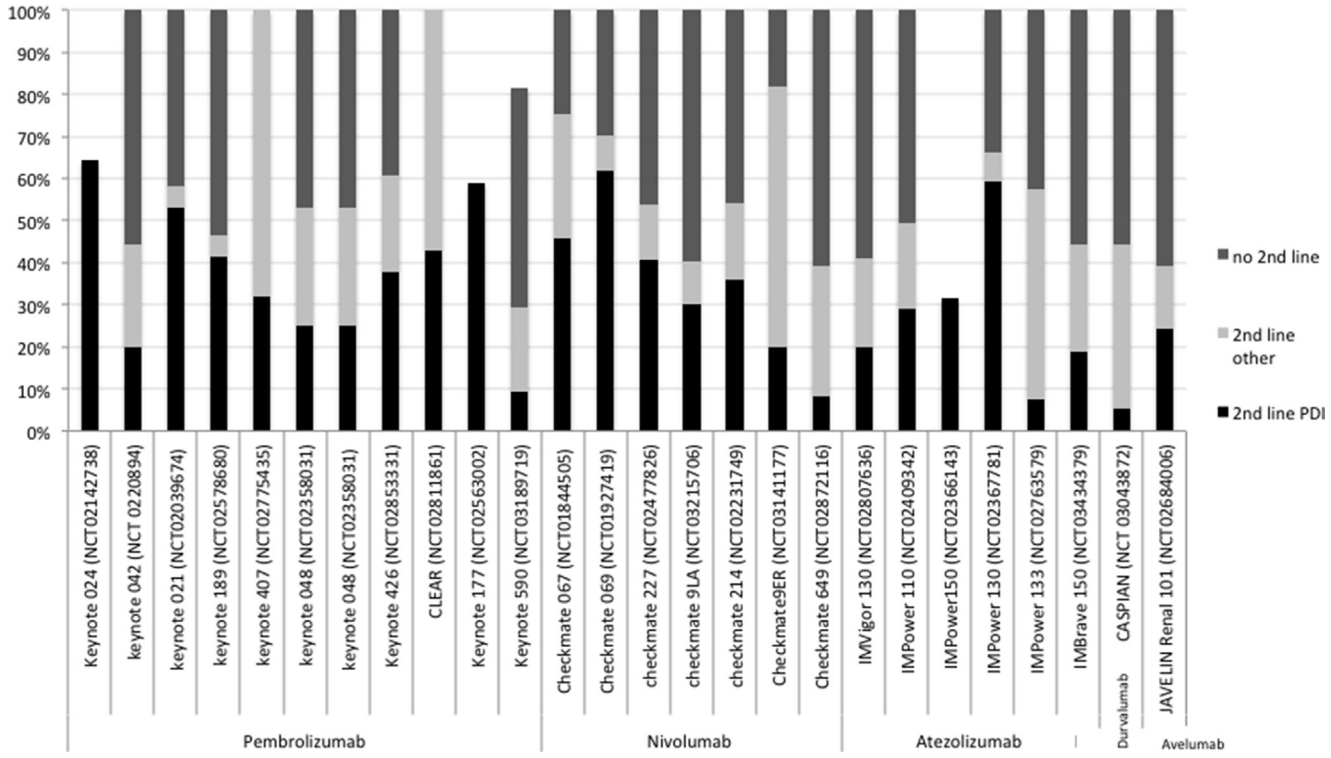

Fig. 2. Subsequent treatment exposure for the control arm patients in first-line PD-1 and PD-L1 drug trials, where the same drug had been FDA approved in the 2nd line/refractory setting. This Figure is a visual representation of subsequent treatment exposure for the control arm patients in each respective trial. Missing data are left blank.

5. Conclusion

In summary, this analysis highlights an important concern regarding the management of disease for control arm patients in trials evaluating PDI. It also suggests the importance of designing or amending first-line trials to ensure control arm patients receive the latest standard of care by embedding either crossover protocols or subsequent therapy protocols. Additionally, steps should be taken to limit heterogeneity in access to care in multi-centre, international trials – particularly when industry-sponsored. Future work should centre on creating adaptive protocols to optimise patient care and further knowledge of when to administer a drug within a specific disease course.

Author contributions

Ashray Maniar: conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft, visualization.

Alyson Haslam: validation, visualization, writing – review & editing.

Vinay Prasad: conceptualization, methodology, writing – review & editing, supervision.

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Conflict of interest statement

The authors Ashray Maniar and Alyson Haslam do not have any conflicts of interest or financial disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.006.

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