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A Systematic Analysis of Post-Protocol Therapy in First Line Checkpoint Inhibitor Trials

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Abstract

Although first-line approvals of checkpoint inhibitors (CPI) are often preceded by approval in the relapsed setting, many control patients in trials evaluating upfront CPI, do not receive a CPI upon disease progression. In this systematic analysis, we reviewed trials evaluating upfront use of CPI in metastatic tumors to evaluate the amount of control arm patients that receive CPI upon disease progression and the timing difference between FDA approval for a CPI in the relapsed setting and enrollment periods for first-line trials. We used the FDA website to review approvals for PD1/PD-L1 inhibitors in metastatic solid tumors through September 2021 and identified instances where a first line trial was preceded by a trial in the relapsed setting. We found 28 FDA approvals for a PD1 or PD-L1 inhibitor in the first line, with 23 instances of a first line trial preceded by a trial of the same or similar drug in the relapsed setting. We reviewed summary data from the correlating randomized trials for these approvals and found that first line trial start of accrual preceded approval of a same/similar drug by a mean of 5.4 months, median 9 months and ended accrual by a mean of 11.3, median of 14 months after approval in the relapsed setting. A mean of 53% of patients in the control arm received subsequent therapy in first-line CPI trials, with a mean of 34% of control arm patients receiving a CPI. This systematic analysis shows that many control arm patients in trials evaluating first line CPI are not exposed to CPI with known efficacy at disease progression, highlighting a need to standardize post-protocol approach to reflect evolving standards of care. This analysis is limited by a lack of individual

patient level data and heterogeneity of trials. No external funding was provided for this analysis.

Introduction

Since 2015, checkpoint inhibitors gained FDA approval as first line treatment in many different solid tumors. There are over twenty FDA approved indications for checkpoint inhibitors (CPI) as first line treatment in different solid tumors(1). The majority of these approvals stem from programmed cell death protein 1 (PD-1) and programmed death-ligand (PD-L1) inhibitors (1). Often, first line investigations are preceded by seminal trials and FDA approval in the refractory or second line setting. In 1st line CPI trials, some patients in the control arm will receive post-protocol or subsequent treatment. However, post-protocol therapy is not standardized for control arm patients, leading to variable treatment exposure that may be suboptimal—particularly in international studies where each nation has different access to treatment and novel therapeutic agents. This introduces a confounding variable in 1st line CPI trials where the clinical scenario that is being tested may be any exposure to a CPI rather than upfront treatment. The purpose of this paper is to systematically analyze post-protocol therapy for the control arm of all randomized controlled trials (RCTs) for checkpoint inhibitors that led to an FDA approval for first line treatment through September 2021, with a focus on scenarios where upfront trials were preceded by a positive study in the relapsed setting and subsequent FDA approval. By performing this analysis, we aim to clarify the need for standardizing treatment of control arm in upfront CPI trials upon progression of disease, to evaluate if timing differences between trials evaluating upfront and relapsed use of same/similar drugs offer an opportunity for protocol amendments

and highlight the need for a formalized process of reporting subsequent care in clinical trials.

Methods

We searched the Drugs@FDA: FDA-Approved Drugs data to review indication listing for Pembrolizumab, Nivolumab, Atezolumab, Durvalumab and Avelumab. Indications were last reviewed on August 31st, 2021. Only indications that had both a first-line and relapsed approval were included. Once the FDA approvals were identified, we used a Google search to identify the approval date for each indication. If different medications had similar approvals (i.e. the use of a CPI and a tyrosine kinase inhibitor for renal cell carcinoma), the drug with the earliest approval was included. Additional exclusion criteria were accelerated approvals that were later withdrawn, 1st line approvals based on single arm studies and approvals without fully published data. We found the clinical trial that supports each indication by reviewing the Drugs@FDA page or the medications package insert. Once identified, the trial, appendix and supplementary table were reviewed to extract enrollment dates and post-protocol therapy (S1 included studies, S2 search strategy). We did not have access to individual patient post-protocol therapy. A prior relapsed approval for either a PD-1 or PD-L1 inhibitor was applied to each specific medication. The difference in months between FDA approval in the relapsed setting and both start and end of randomization was calculated (Table 1). We then calculated the percent of control patients receiving any post-protocol therapy and

the percent that receive a CPI (Table 2). One reviewer, AM, was responsible for the above process.

Results

A total of 29 FDA approvals for first line treatment with a PD-1/PD-L1 inhibitor were reviewed. Both pembrolizumab and avelumab had a 1st line approval in metastatic renal cell carcinoma in combination with a tyrosine kinase inhibitor, as the avelumab approval occurred first, only this trial was included in the analysis, creating a total of 28 unique instances. In 23 of the 28 instances, a first line approval was preceded by approval of a PD-1 or PDL-1 inhibitor in the relapsed setting. These 23 indications stem from 22 trials that were included in this analysis (supplement table 1). For PD-1 inhibitors specifically, we found 16 instances of a first line trial preceded by a 2nd line or relapsed trial and for PD-L1 inhibitors we found 7 instances of a first trial preceded by a 2nd line or relapsed trial. The start date of randomization/enrollment in a first line trial preceded FDA approval in the relapsed/2nd line by a mean time of 5.4 months and a median time of 9.0 months. The end date of randomization in the first line trial was preceded by an FDA approval in the relapsed/2nd line by a mean time of 11.3 months and a median time of 14.0 months (table 1). Figure 1 shows the amount of patient accrual time in a first line trial both before and after approval in the relapsed setting. The combined mean percent of patients that received post-protocol therapy 53%, median 53%. The combined mean percent of all patients that received post-protocol CPI was 34.1%,

median 31.5%. Of those patients that received any subsequent treatment, the mean percent that received a PD-1 or PD-L1 antibody was 58.6%, median 60.8% (table 2). Figure 2 graphically displays the percent of patients on the control arm in each first line trial that were exposed to subsequent treatment. All trials included in this analysis were multi-center, multi-country trials and industry sponsored. Crossover was explicitly prohibited in the following trials: Checkmate 227 (NCT02477864), Checkmate 9LA (NCT03215706), IMPower 110 (NCT02409342), IMPower150 (NCT02366143), CASPIAN (NCT 03043872). Although crossover was not permitted in the Checkmate 9LA trials, patients were still allowed to receive subsequent immunotherapy upon discontinuing initial treatment at the providing physician's discretion.

Discussion

Within a short timeframe, checkpoint inhibitors have made a major impact on many facets of solid tumor 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 truncated time, the majority of first line trials are preceded by a trial in the relapsed/refractory setting. Furthermore, first line trials start accruing patients within a median time of 9 months prior to FDA approval of the same drug in the relapsed/refractory setting and stop accruing at a median time 14 months after the same FDA approval. In the control arm of the included trials, 53% of patients will receive any subsequent therapy and approximately 60% of those patients will receive a PD1/PDL1 inhibitor

with proven efficacy, which equates to only 32% of all patients in the control arm. Overall, the percent 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 tumors will receive multiple lines of treatment with discrepancies influenced by primary tumor type(2-4) Amongst the trials we reviewed there were 5 trials in particular (Keynote 189, Keynote 407, Keynote 426, Checkmate 9LA, IMBrave 150 and Javelin 101 Renal) where an FDA approval existed for relapsed disease of the specific tumor for 100% of the trial enrollment period, and yet the control arm immunotherapy exposure was <50% in each trial.

Together, this data suggests that—although a majority of control arm patients that received any subsequent care received a CPI; 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 relapsed setting. Since nearly 70% of patients in first line CPI trials may never receive a CPI during their disease course, the first line trials may be testing a redundant hypothesis of exposure to a CPI (already studied in the relapsed setting) rather than testing the clinical question of when to give a patient a CPI. Additionally, the variability in subsequent therapy raises a concern about heterogeneity of post-protocol therapy when comparing costly medications in a global setting. This holds particularly true in clinical trials where patients commonly have excellent performance status and are thus more likely to receive subsequent treatment upon progression of disease. Although enrollment in these trials started a median of 5.4 months prior to FDA approval in the relapsed setting,

enrollment ended almost 1 year after FDA approval, 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.

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 relapsed setting. This type of protocol would both test the sequence of drug administration and ensure all patients get equal access to regardless of country of origin. As the overwhelming majority of these trials are industry sponsored (100% in this instance), it is reasonable to expect all patients to have equitable access to a study drug if there is data to support its use in the relapsed setting.

There are several significant limitations of this analysis to note. We did not have access to individual patient data so it is unclear which immunotherapy medication patients received for post-protocol therapy, underscoring the need for publications deidentified data from these trials to promote further research. Every trial did not explicitly define or comment on crossover and post-protocol therapy was not always available. Additionally, we considered a prior approval of a PD1 inhibitor as applicable to a PD-L1 inhibitor trial and there is evidence to suggest that they have dissimilar efficacy and safety profiles (5, 6).

Conclusion

In summary, this analysis highlights an important concern regarding post-protocol treatment of control arm patients in trials evaluating CPI. It also shows that is often feasible to design or amend 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-center, international trials—particularly when industry sponsored. Future work should center on creating adaptive protocols to optimize patient care and further knowledge of when to administer a drug within a specific disease course.

Tables and Figures

Table 1 – timing difference

Medication	FDA approved indication	1st line approval date	2nd line/relapsed approval date	1st line randomization dates	Months between start of randomization initiation and 2nd line approval	Months between end of randomization and 2nd line approval
Pembrolizumab	mMelanoma (regardless of BRAF)	12/18/15	9/4/14	9/18/13-3/3/14	-12.0	-6.0
	mNSCLC monotherapy (PDL1>50%)	10/14/16	10/2/15	9/19/14-10/29/15	-11.0	0.5
	mNSCLC monotherapy (PDL1>1%)	4/11/19	10/2/15	12/19/14-3/6/17	-11.0	17.0
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	5/10/17	10/2/15	11/25/14-1/25/16	-11.0	3.0
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	5/10/17	10/2/15	2/26/16-3/6/17	4.0	17.0
	mNSCLC (squamous, with carbo and paclitax/nab-pac, regardless PDL1)	10/30/18	3/4/15	8/19/16-12/28/17	17.0	26.0
	mHNSCC (with platinum + 5FU or mono if CPS >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

	mCRC (MSI-H)	6/29/20	5/23/17	2/11/16-2/19/18	-15.0	9.0
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 ipi)	9/28/19	3/4/15 (sq) 10/10/15 (non-sq)	8/2015-11/2016	-2.0	13.0
	mNSCLC (with ipi + 2c of 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 ipi if intmd-poor risk)	4/16/8	11/23/15	10/2014-2/2016	-13.0	3.0
	mGastric/mGEJ/ mEsophageal	4/16/21	9/22/17	3/27/17-4/24/19	-6.0	19.0
Atezolizumab	mNSCLC (PDL1>50%, TIL>10%)	5/18/20	10/2/15	7/21/15-2/2/18	-3.0	28.0
	mNSCLC (with bev, paclitaxel and carbo)	12/6/18	10/2/15	3/2015-12/2016	-7.0	14.0
	mNSCLC (with nab-paclitaxel and carbo)	12/3/19	10/2/15	4/4/15-2/3/17	-6.0	14.0
	eSCLC (w/ carbo + 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 cis/carbo + etoposide)	3/27/20	8/17/18 (nivolumab)	3/27/17-5/29/18	-17.0	-3.0
Avelumab	advanced RCC (with axitinib)	5/14/19	11/23/15	3/29/16-12/19/17	4.0	25.0
					Mean = -5.4 mo Median -9.0 mo	Mean = 11.3 mo Median = 14.0 mo

Table 1 summarizes the timing difference between FDA approval of a CPI in the relapsed setting and both initiation and end of enrollment of a trial evaluating first-line CPI use the same metastatic disease. Negative signs in front of a number indicate that a trial started or stopped enrolling patients that many months *before* the FDA approved a CPI in the relapsed setting.

Table 2 - Post protocol therapy summary

Medication	Indication	1st line trial / phase	Number of control that received subsequent/post-protocol therapy N(%)	Number of all control patients that received immunotherapy N (%)	Number of pts receiving subsequent treatment that received immunotherapy N(%)
Pembrolizumab	mMelanoma (regardless of BRAF)	Keynote 006 (NCT01866319) / phase III(7)	133/256 (52.0%)	78/256 (30.4%)	78/133 (58.6%)
	mNSCLC monotherapy (PDL1>50%)	Keynote 024 (NCT02142738) / phase III (8)	Not provided	97/151 (64.2%)	Not provided
	mNSCLC monotherapy (PDL1>1%)	Keynote 042 (NCT0220894)/ phase III (9)	282/637 (44.2%)	126/637 (19.8%)	126/282 (44.7%)
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	Keynote 021 (NCAT02039674) / phase II (10)	36/62 (58.1%)	33/62 (53.2%)	33/36 (89.2%)
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	Keynote 189 (NCT02578680) / phase III (11)	96/206 (46.6%)	85/206 (41.3%)	85/96 (88.5%)

	mNSCLC (squamous, with carbo and paclitax/nab-pac, regardless PDL1)	Keynote 407 (NCT02578680)/ phase III (12)	Not provided	89/280 (31.8%)	Not provided
	mHNSCC (with platinum + 5FU)	Keynote 048 (NCT02358031)/ phase III (13)	159/300 (53%)	75/300 (25%)	75/159 (47.2%)
	mHNSCC (mono if CPS>1)	Keynote 048 (NCT02358031)/ phase III (13)	159/300 (53%)	75/300 (25%)	75/159 (47.2%)
	mRCC (with axitinib)	Keynote 426 (NCT02853331)/ phase III (14)	147/242 (60.7%)	91/242 (37.6%)	91/147 (61.9%)
	mCRC (MSI-H)	Keynote 177 (NCT02563002)/ phase III (15)	Not provided	91/154 (59%)	Not provided
Nivolumab	mMelanoma (monotherapy Nivo or Nivolumab/Ipilimumab)	Checkmate 067 (NCT01844505)/ phase III (16)	237/315 (75.2%) (pts in the ipilimumab arm)	144/315 (45.7%) (pts in the ipilimumab arm that received PD1/PDL1 based tx)	144/237 (60.8%) (pts in the ipilimumab arm that received PD1/PDL1 based tx)
	mMelanoma (Nivolumab/Ipilimumab)	Checkmate 069 (NCT01927419)/ phase II (17)	33/47 (70.2%)	29/47 (61.7%)	29/33 (87.9%)
	mNSCLC (with ipi)	Checkmate 227 (NCT02477826)/ phase III (18)	313/583 (53.7%)	238/583 (40.8%)	238/313 (76.0%)
	mNSCLC (with ipi + 2c of platinum)	Checkmate 9LA (NCT03215706) / phase III (19)	144/358 (40.2%)	108/358 (30.2%)	108/144 (75.0%)
	mRCC (with ipi if intmd-poor risk)	Checkmate 214 (NCT02231749) / phase III (20)	295/546 (54.0%)	197/546 (36.1%)	197/295 (66.8%)
	mGastric/mGEJ/ mEsophageal	Checkmate 649 (NCT02872116)/ phase III (21)	311/792 (39.3%)	64/792 (8.1%)	64/311 (20.6%)
Atezolizumab	mNSCLC (PDL1>50%, TIL>10%)	IMPower 110 (NCT02409342)/ phase III (22)	130/263 (49.4%)	76/263 (28.9%)	76/130 (58.5%)
	mNSCLC (with bev, paclitaxel and carbo)	IMPower 150 (NCT02366143)/ phase III (23)	Not available	126/400 (31.5%)	Not available

	mNSCLC (with nab-paclitaxel and carbo)	IMPower 130 (NCT02367781)/ phase III (24)	151/228 (66.2%)	135/228 (59%)	135/151 (89.4%)
	eSCLC (w/ carbo + etoposide)	IMPower 133 (NCT02763579)/ phase III	116/202 (57.4%)	15/202 (7.4%)	15/116 (12.9%)
	HCC (with bevacizumab)	IMBrave 150 (NCT03434379)/ phase III (25)	73/165 (44.2%)	31/165 (18.8%)	31/73 (42.5%)
Durvalumab	eSCLC (with cis/carbo + etoposide)	CASPIAN (NCT03043872)/ phase III (26)	119/269 (44.2%)	14/269 (5.2%)	14/119 (11.8%)
Avelumab	advanced RCC (with axitinib)	JAVELIN Renal 101 (NCT02684006)/ phase III (27)	174/444 (39.1%)	107/444 (24.1%)	107/174 (74.3%)

Table 2 summarizes the percent of control arm patients in each included first-line CPI based trial that received 2nd line treatment following disease progression. The 5th column shows the total percent of control arm patients that received a CPI at disease progression and the 6th column shows the percent of control patients that received subsequent treatment that specifically received a CPI.

Figure 1 - Time Overlap

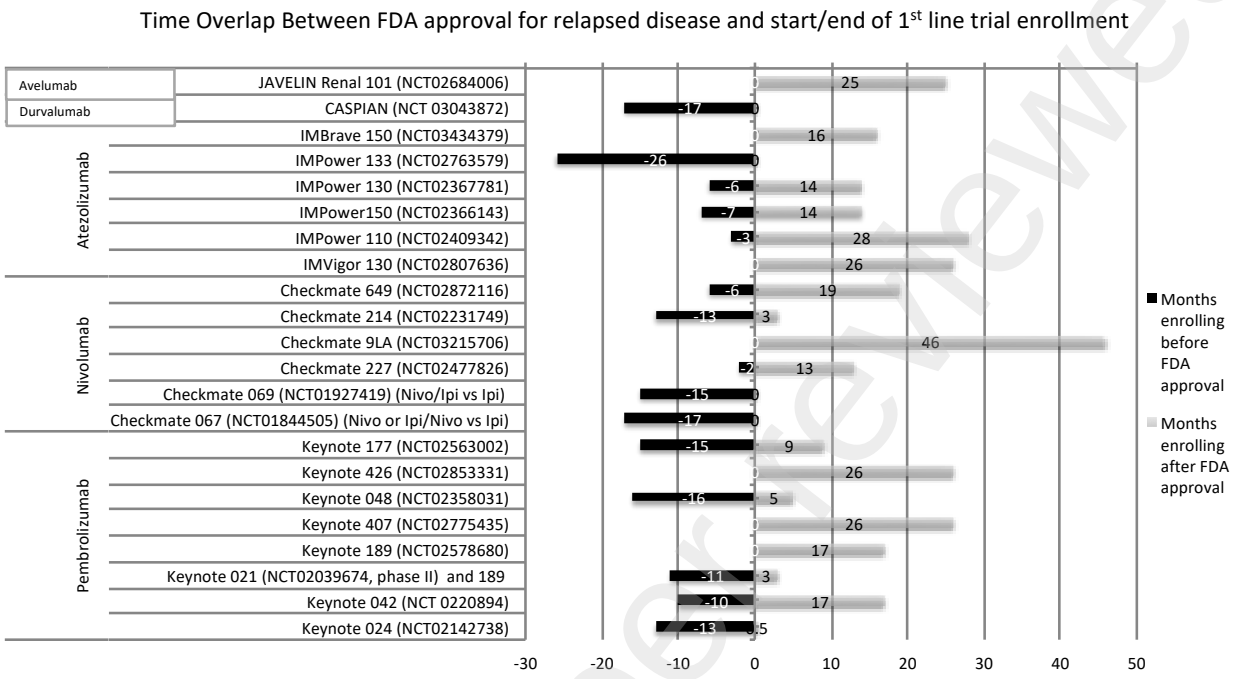


Figure 1 graphically shows the amount of patient accrual time that occurred before and after an FDA approval of a PD1 or PD-L1 inhibitor in the relapsed setting. The 0 time point is the time of FDA approval. Horizontal bars that do not cross the 0 point indicate that patient accrual occurred entirely before or after FDA approval in the relapsed setting.

Figure 2 – Treatment Exposure Summary

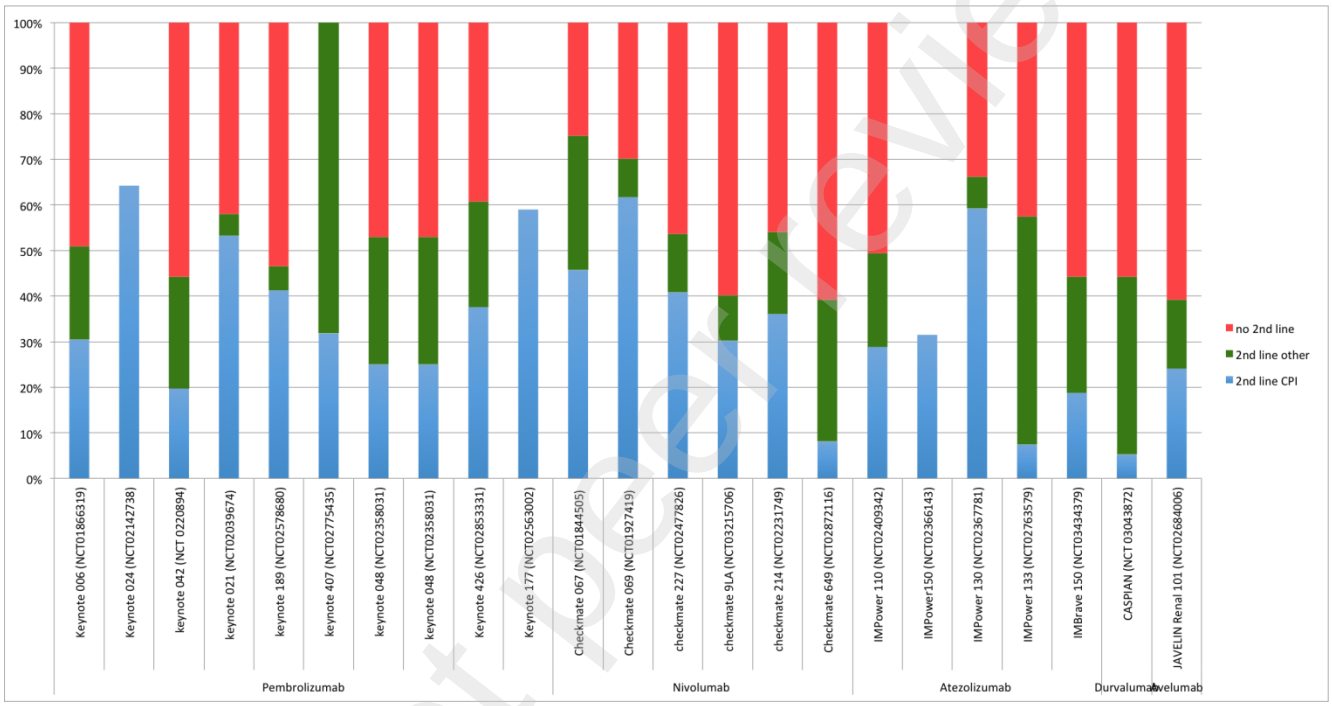


Figure 2 is a visual representation of subsequent treatment exposure for the control arm patients in each respective trial. Missing data is left blank.

Supplemental Material

Systematic Analysis Characteristics

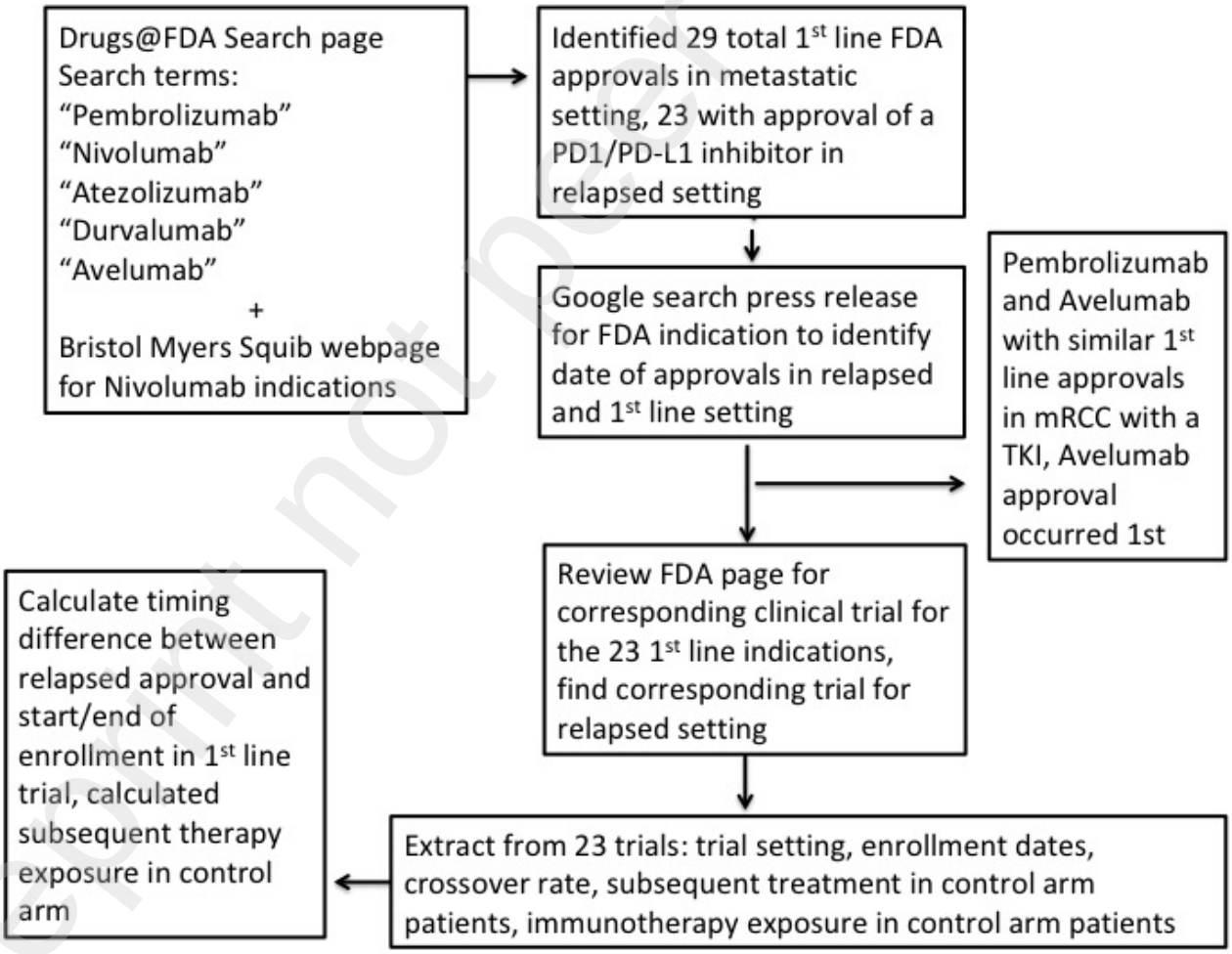
This analysis was not registered with PROSPERO. No external financial support provided. This analysis was not funded by any sponsor. The authors do not have any conflicts of interest to report.

Sample Search

Pembrolizumab example: Reviewer AM went to Drugs@FDA webpage and searched "Pembrolizumab", medication page opened and FDA indications reviewed, indications sorted into 1st line and relapsed. For this example, AM reviewed 1st line indication of pembrolizumab monotherapy in non-small cell lung cancer (NSCLC) with TPS>1% and relapsed indication for pembrolizumab in NSCLC with TPS>1%. Google search conducted for these indications with search terms: "(pembrolizumab + FDA approval + NSCLC + TPS >1%) + (first line OR relapsed/2nd line/subsequent/refractory). Dates identified for 1st line approval and relapsed approval. FDA page then referenced to find clinical trial corresponding to 1st line approval. Published trial for 1st line indication then reviewed to identify enrollment dates, setting, cross-over, subsequent treatment in control arm. From this data, calculated timing difference between relapsed approval and start/end of enrollment

for a 1st line trial and calculated subsequent treatment and checkpoint inhibitor treatment in control arm patients.

Diagram of Search Methodology



Supplement Table 1- Included Trials

Medication	Indication	1st line trial / phase	Comparison	2nd line/relapsed trial
Pembrolizumab	mMelanoma (regardless of BRAF)	Keynote 006 (NCT01866319) / phase III(7)	Pembrolizumab vs Ipilimumab[1]	Keynote 001 (NCT01295827) (28)
	mNSCLC monotherapy (PDL1>50%)	Keynote 024 (NCT02142738) / phase III (8)	Pembrolizumab vs platinum based chemotherapy	Keynote 010 (NCT01905657) (29)
	mNSCLC monotherapy (PDL1>1%)	Keynote 042 (NCT0220894)/ phase III (9)	Pembrolizumab vs platinum based chemotherapy	Keynote 010 (NCT01905657) (29)
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	Keynote 021 (NCAT02039674) / phase II (10)	Pembrolizumab/carboplatin/pemetrexed vs carboplatin/pemetrexed	Keynote 010 (NCT01905657) (29)
	mNSCLC (non-sq, regardless of PDL1, combined with carbo/pem, no EGFR/ALK mutation	Keynote 189 (NCT02578680) / phase III (11)	Pembrolizumab/platinum/pemetrexed vs platinum/pemetrexed	Keynote 010 (NCT01905657) (29)

	mNSCLC (squamous, with carbo and paclitax/nab-pac, regardless PDL1)	Keynote 407 (NCT02578680)/ phase III (12)	Pembrolizumab/carboplatin/taxane vs caroboplatin/taxane	Keynote 010 (NCT01905657) (29)
	mHNSCC (with platinum + 5FU)	Keynote 048 (NCT02358031)/ phase III (13)	Pembrolizumab/5FU/platinum vs Pembrolizmab vs cetuximab/5FU/platinum	Keynote 012 (NCT01848834) (30)
	mHNSCC (mono if CPS>1)	Keynote 048 (NCT02358031)/ phase III (13)	Pembrolizumab/5FU/platinum vs Pembrolizmab vs cetuximab/5FU/platinum	Keynote 012 (NCT01848834) (30)
	mRCC (with axitinib)	Keynote 426 (NCT02853331)/ phase III (14)	Pembrolizumab/axitinib vs sunitinib	Checkmate 025 (NCT01668784)(31)
	mCRC (MSI-H)	Keynote 177 (NCT02563002)/ phase III (15)	Pembrolizumab vs 5FU +/- bevacizumab or cetuximab	Keynote 164 (NCT02460198) (32)
Nivolumab	mMelanoma (monotherapy Nivo or Nivolumab/Ipilimumab)	Checkmate 067 (NCT01844505)/ phase III (16)	Nivolumab or Nivolumab/Ipilimumab vs Ipilumumab (NCT01844505) (16)	Checkmate 037 (NCT01721746) (33)
	mMelanoma (Nivolumab/Ipilimumab)	Checkmate 069 (NCT01927419)/ phase II (17)	Nivolumab/Ipilimumab vs ipilimumab	Checkmate 037 (NCT01721746) (33)
	mNSCLC (with ipi)	Checkmate 227 (NCT02477826)/ phase III (18)	Nivolumab/Ipilimumab or nivolumab/chemotherapy vs chemotherapy alone (primary endpoint nivo/ipi vs chemo)	Checkmate 057 (NCT01673867) (34)
	mNSCLC (with ipi + 2c of platinum)	Checkmate 9LA (NCT03215706) / phase III (19)	Nivolumab/Ipilimumab/platinum doublet vs chemotherapy	Checkmate 057 (NCT01673867) (34)
	mRCC (with ipi if intmd-poor risk)	Checkmate 214 (NCT02231749) / phase III (20)	Nivolumab/ipilimumab vs sunitinib	Checkmate 025 (NCT01668784) (31)
	mGastric/mGEJ/ mEsophageal	Checkmate 649 (NCT02872116)/ phase III (21)	Nivolumab/Ipilimumab vs Nivolumab/Chemotherapy vs chemotherapy	Keynote 059 (NCT02335411) (35)
Atezolizumab	mNSCLC (PDL1>50%, TIL>10%)	IMPower 110 (NCT02409342)/ phase III (22)	Atezolumab vs chemotherapy	Keynote 010 (NCT01905657) (29)
	mNSCLC (with bev, paclitaxel and carbo)	IMPower 150 (NCT02366143)/ phase III (23)	Atezolizumab/carboplatin/paclitaxel OR atezolizumab/bevacizumab/carboplatin/ paclitaxel VS bevacizumab/carboplatin/paclitaxel	Keynote 010 (NCT01905657) (29)

	mNSCLC (with nab-paclitaxel and carbo)	IMPower 130 (NCT02367781)/ phase III (24)	Atezolizumab/carboplatin/nab-paclitaxel vs chemotherapy	Keynote 010 (NCT01905657) (29)
	eSCLC (w/ carbo + etoposide)	IMPower 133 (NCT02763579)/ phase III	Atezolizumab/carboplatin/etoposide vs carboplatin/etoposide	Checkmate 032 (NCT01928394) (36)
	HCC (with bevacizumab)	IMBrave 150 (NCT03434379)/ phase III (25)	Atezolizumab/bevacizumab vs sorafenib	Checkmate 040 (NCT01658878) (37)
Durvalumab	eSCLC (with cis/carbo + etoposide)	CASPIAN (NCT03043872)/ phase III (26)	Durvalumab/tremelimumab/EP OR durvalumab/EP VS EP[2]	Checkmate 032 (NCT01928394) (36)
Avelumab	advanced RCC (with axitinib)	JAVELIN Renal 101 (NCT02684006)/ phase III (27)	Avelumab/axitinib vs sunitinib	Checkmate 025 (NCT01668784) (31)

1. ~50% of patients were second line immunotherapy and 50% were first line

2. EP = etoposide and carboplatin/cisplatin

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