

Supplementary Materials

Overcoming resistance to anti-PD-1/PD-L1 therapy in cancer

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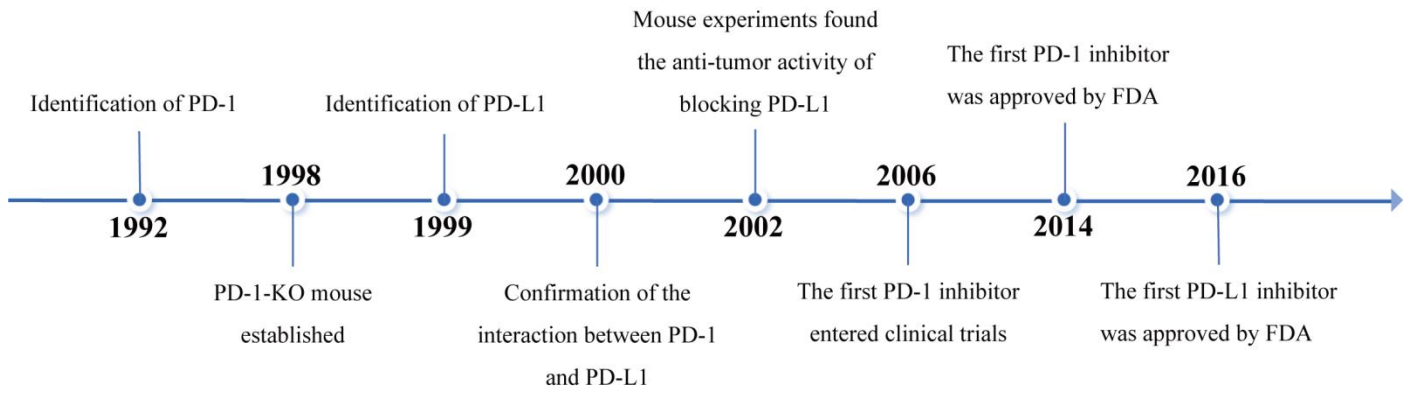
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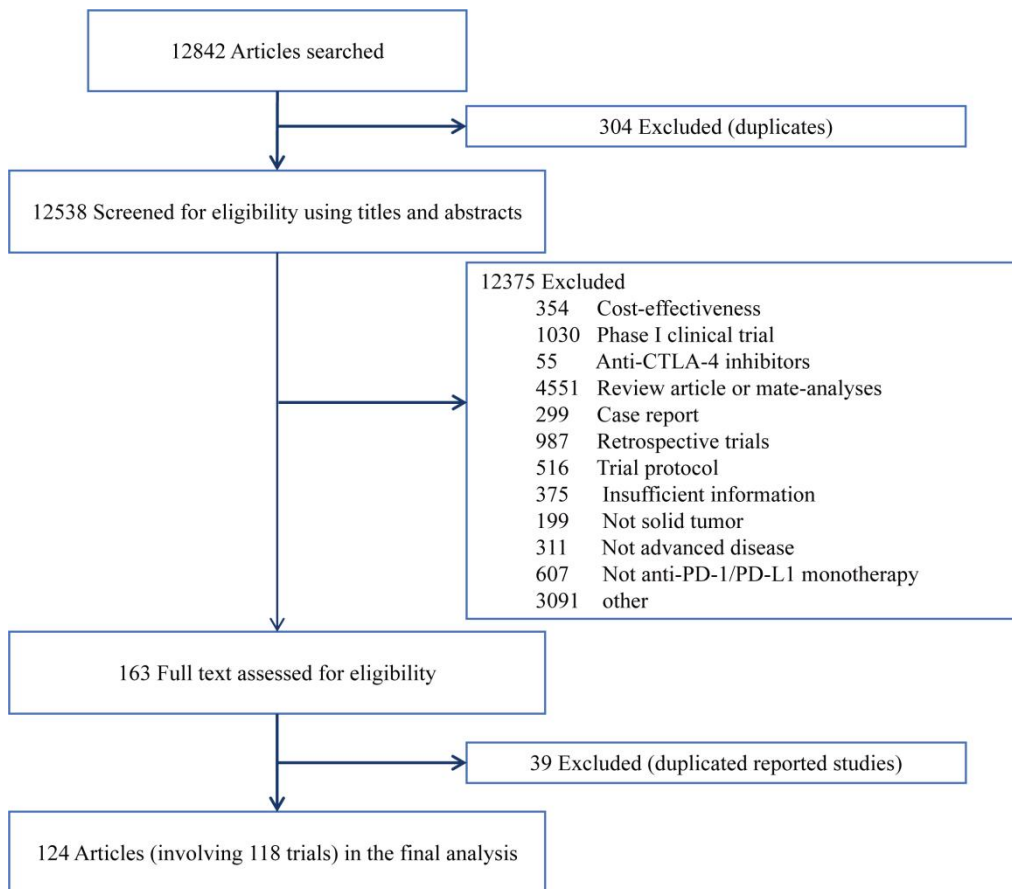
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Supplementary Figure 1. Timeline for major events leading to the development of anti-PD-1/PD-L1 drugs.



Supplementary Figure 2. Flow diagram for the selection of eligible studies to evaluate the objective response rate of anti-PD-1/PD-L1 monotherapy.

Supplementary Table 2. The clinical trials of PD-1/PD-L1 inhibitors as monotherapy in advanced cancers

Study	Trial ID	Phase	Cancer type	Line of therapy	Treatment	Number of patients	ORR (95% CI)	Ref.
CheckMate-143	NCT02017717	III	Glioblastoma	2L	Nivolumab	153	7.8% (4.1%-13.3%)	[1]
KEYNOTE-048	NCT02358031	III	Head and neck cancer	1L	Pembrolizumab	301	17%	[2]
CheckMate-714	NCT02823574	II	Head and neck cancer (platinum-refractory)	1L	Nivolumab	82	19.5% (11.6%-29.7%)	[3]
CheckMate-714	NCT02823574	II	Head and neck cancer (platinum-eligible)	1L	Nivolumab	61	29.5% (18.5%-42.6%)	[3]
EAGLE	NCT02369874	III	Head and neck cancer	2L	Durvalumab	240	17.9% (13.3%-23.4%)	[4]
Checkmate-141	NCT02105636	III	Head and neck cancer	≥2L	Nivolumab	240	13.3% (9.3%-18.3%)	[5]
KEYNOTE-040	NCT02252042	III	Head and neck cancer	≥2L	Pembrolizumab	247	14.6% (10.4%-19.6%)	[6]
CONDOR	NCT02319044	II	Head and neck cancer	2L	Durvalumab	65	9.2% (3.46%-19.02%)	[7]
HAWK	NCT02207530	II	Head and neck cancer	2L	Durvalumab	111	16.2% (9.9%-24.4%)	[8]
KEYNOTE-122	NCT02611960	III	Nasopharyngeal cancer	2L	Pembrolizumab	117	21.4% (14.3%-29.9%)	[9]
CPDR001X2201	NCT03866967	II	Nasopharyngeal cancer	2L	Spartalizumab	82	17.1% (9.7% to 27.0%)	[10]
JS001-Ib-CRP-1.0	NCT02915432	II	Nasopharyngeal cancer	≥3L	Penpulimab	125	28.0% (20.3%-36.7%)	[11]
POLARIS-02	NCT02605967	II	Nasopharyngeal cancer	≥3L	Toripalimab	190	20.5% (15.0%-27.0%)	[12]
FLAT	NCT05783882	III	Melanoma	1L	Prolgolimab (250mg)	114	33.3% (24.8%-42.8%)	[13]
FLAT	NCT05783882	III	Melanoma	1L	Prolgolimab (1mg/kg)	61	32.8% (21.3%-46.0%)	[13]
/	JapicCTI-142533	II	Melanoma	1L	Nivolumab	23	34.8% (20.8%-51.9%)	[14]
CARSKIN	NCT02883556	II	Cutaneous squamous cell carcinoma	1L	Pembrolizumab	57	42% (29%-56%)	[15]
NIVOSQUACS	NCT04204837	II	Cutaneous squamous cell carcinoma	1L	Nivolumab	31	61.3% (42.2%-78.2%)	[16]
R2810-ONC-1620	NCT03132636	II	Basal cell carcinoma	2L	Cemiplimab	84	31% (21%-42%)	[17]
KEYNOTE-913	NCT03783078	III	Merkel cell carcinoma	1L	Pembrolizumab	55	49% (35%-63%)	[18]
KEYNOTE-017	NCT02267603	II	Merkel cell carcinoma	1L	Pembrolizumab	50	58% (43.2%-71.8%)	[19]
JAVELIN Merkel-200	NCT02155647	II	Merkel cell carcinoma	≥2L	Avelumab	88	33.0% (23.3%-43.8%)	[20]
KEYNOTE-062	NCT02494583	III	Gastric cancer	1L	Pembrolizumab	256	14.8%	[21]
ONO-4538-12	NCT02267343	III	Gastric	or ≥3L	Nivolumab	330	11.2%	[22]

			gastro-oesophageal junction cancer					(7.7%–15.6%)	
JAVELIN Gastric-300	NCT02625623	III	Gastric	or	3L	Avelumab	185	2.2%	[23]
			gastro-oesophageal junction cancer					(0.6%–5.4%)	
KEYNOTE-061	NCT02370498	III	Gastric	or	≥2L	Pembrolizumab	196	16%	[24]
			gastro-oesophageal junction cancer					(11%–22%)	
GS-US-296-2013	NCT02864381	II	Gastric cancer		≥2L	Nivolumab	72	6.9%	[25]
								(2.3%–15.5%)	
MCC-18684	NCT02829918	II	Biliary tract cancer		≥2L	Nivolumab	46	22%	[26]
CheckMate-459	NCT02576509	III	Hepatocellular carcinoma		1L	Nivolumab	371	15%	[27]
								(12%–19%)	
RATIONALE-301	NCT03412773	III	Hepatocellular carcinoma		1L	Tislelizumab	342	14.3%	[28]
								(10.8%–18.5%)	
KEYNOTE-224 (cohort 2)	NCT02702414	II	Hepatocellular carcinoma		1L	Pembrolizumab	51	16%	[29]
								(7%–29%)	
KEYNOTE-240	NCT02702401	III	Hepatocellular carcinoma		2L	Pembrolizumab	278	18.3%	[30]
								(14.0%–23.4%)	
KEYNOTE-394	NCT03062358	III	Hepatocellular carcinoma		2L	Pembrolizumab	300	12.7%	[31]
								(9.1%–17.0%)	
SHR-1210-II/III-HCC	NCT02989922	II	Hepatocellular carcinoma		≥2L	Camrelizumab	217	14.7%	[32]
								(10.3%–20.2%)	
KEYNOTE-224(c cohort 1)	NCT02702414	II	Hepatocellular carcinoma		2L	Pembrolizumab	104	18.3%	[33]
								(11.4%–27.1%)	
RATIONALE-208	NCT03419897	II	Hepatocellular carcinoma		≥2L	Tislelizumab	249	13%	[34]
								(9%–18%)	
KEYNOTE-177	NCT02563002	III	MSI-H/dMMR colorectal cancer		1L	Pembrolizumab	153	45.8%	[35]
								(37.7%–54.0%)	
CheckMate-142	NCT02060188	II	MSI-H/dMMR colorectal cancer		≥2L	Nivolumab	74	32.4%	[36]
								(22.0%–44.3%)	
/	NCT03435107	II	MSI-H/dMMR or POLE-mutated colorectal cancer	or	≥2L	Durvalumab	33	42.4%	[37]
								(25.5%–60.8%)	
KEYNOTE-164 (cohort A)	NCT02460198	II	MSI-H/dMMR colorectal cancer		≥3L	Pembrolizumab	61	32.8%	[38]
								(21.3%–46.0%)	
KEYNOTE-164 (cohort B)	NCT02460198	II	MSI-H/dMMR colorectal cancer		≥2L	Pembrolizumab	63	34.9%	[38]
								(23.3%–48.0%)	
KEYNOTE-158	NCT02628067	II	Anal squamous cell carcinoma		≥2L	Pembrolizumab	112	11%	[39]
								(6%–18%)	
PODIUM-202	NCT03597295	II	Anal squamous cell carcinoma		≥2L	Retifanlimab	94	13.8%	[40]
								(7.6%–22.5%)	
NCI9673	NCT02314169	II	Anal cancer, except adenocarcinoma		≥2L	Nivolumab	37	24%	[41]
								(15%–33%)	
KEYNOTE-181	NCT02564263	III	Esophageal cancer		2L	Pembrolizumab	314	13.1%	[42]
								(9.5%–17.3%)	
RATIONALE-302	NCT03430843	III	Esophageal squamous cell carcinoma		2L	Tislelizumab	256	20.3%	[43]
								(15.6%–25.8%)	
ESCORT	NCT03099382	III	Esophageal squamous		2L	Camrelizumab	228	20.2%	[44]

			cell carcinoma					(15.2%–26.0%)	
ATTRACTION-3	NCT02569242	III	Esophageal squamous cell carcinoma	2L	Nivolumab	210	19%	[45]	
CheckMate-032	NCT01928394	III	Esophageal cancer	≥2L	Nivolumab	59	12%	[46]	
							(5%–23%)		
KEYNOTE-180	NCT02559687	II	Esophageal cancer	≥3L	Pembrolizumab	121	9.9%	[47]	
							(5.2%–16.7%)		
ORIENT-2	NCT03116152	II	Esophageal squamous cell carcinoma	2L	Sintilimab	95	12.6%	[48]	
/	NCT02971956	II	Esophageal cancer	≥2L	Pembrolizumab	49	8%	[49]	
/	JapicCTI-No. 142422	II	Esophageal squamous cell carcinoma	≥2L	Nivolumab	64	17%	[50]	
DIADEM	NCT04115111	II	Malignant pleural mesothelioma	2L	Durvalumab	58	10.3%	[51]	
							(3.9%–21.2%)		
MERIT	JapicCTI163247	II	Malignant pleural mesothelioma	2–3L	Nivolumab	34	29.4%	[52]	
/	NCT02364076	II	Thymic carcinoma	≥2L	Pembrolizumab	40	22.5%	[53]	
/	NCT02607631	II	Thymic carcinoma	≥2L	Pembrolizumab	26	19.2%	[54]	
							(8.5%–37.9%)		
ML41253	NCT04321330	II	Thymic carcinoma	≥2L	Atezolizumab	34	14.7%	[55]	
							(5.0%–31.1%)		
PRIMER	UMIN000022007	II	Thymic carcinoma	≥2L	Nivolumab	15	0%	[56]	
							(0%–21.8%)		
IFCT-1603	NCT03059667	II	Small cell lung cancer	2L	Atezolizumab	43	2.3%	[57]	
							(0–6.8%)		
CheckMate-026	NCT02041533	III	Non-small cell lung cancer	1L	Nivolumab	211	26%	[58]	
							(20%–33%)		
KEYNOTE-024	NCT02142738	III	Non-small cell lung cancer	1L	Pembrolizumab	154	44.8%	[59]	
							(36.8%–53.0%)		
EMPOWER-Lung 1	NCT03088540	III	Non-small cell lung cancer	1L	Cemiplimab	283	39%	[60]	
							(34%–45%)		
KEYNOTE-042	NCT02220894	III	Non-small cell lung cancer	1L	Pembrolizumab	637	27.3%	[61]	
							(23.9%–31.0%)		
IPSOS	NCT03191786	III	Non-small cell lung cancer	1L	Atezolizumab	302	17%	[62]	
							(12.8%–21.6%)		
JAVELIN Lung 100	NCT02576574	III	Non-small cell lung cancer	1L	Avelumab (Q2W)	366	25.4%	[63]	
							(21.0%–30.2%)		
JAVELIN Lung 100	NCT02576574	III	Non-small cell lung cancer	1L	Avelumab (QW)	322	23.3%	[63]	
/	NCT02879617	II	Non-small cell lung cancer	1L	Durvalumab	38	26%	[64]	
							(13%–43%)		
KEYNOTE-654/E CHO-305	NCT03322540	II	Non-small cell lung cancer	1L	Pembrolizumab	77	39.0%	[65]	
							(28.0%–50.8%)		
POD1UM-203 (NSCLC cohort)	NCT03679767	II	Non-small cell lung cancer	1L	Retifanlimab	23	34.8%	[66]	
							(16.4%–57.3%)		
CTONG1901 (arm A)	NCT04252365	II	Non-small cell lung cancer	1L	Sintilimab	13	46.2%	[67]	
							(19.2%–74.9%)		

CTONG1901 (arm B)	NCT04252365	II	Non-small cancer	cell	lung	1L	Pembrolizumab	14	42.9% (17.7%-71.1%)	[67]
SAKK 19/17	NCT03620669	II	Non-small cancer	cell	lung	1L	Durvalumab	48	17% (8%-30%)	[68]
BIRCH (cohort 1)	NCT02031458	II	Non-small cancer	cell	lung	1L	Atezolizumab	139	22% (15%-29%)	[69]
OAK	NCT02008227	III	Non-small cancer	cell	lung	≥2L	Atezolizumab	613	13.7% (11.1%–16.7%)	[70]
TAIL	NCT03285763	III/IV	Non-small cancer	cell	lung	≥2L	Atezolizumab	615	11.1% (8.7%-13.8%)	[71]
CheckMate-057	NCT01673867	III	Non-small cancer	cell	lung	≥2L	Nivolumab	292	19% (15%-24%)	[72]
CheckMate-017	NCT01642004	III	Non-small cancer	cell	lung	≥2L	Nivolumab	135	20% (14%-28%)	[73]
CheckMate-870	NCT03195491	III	Non-small cancer	cell	lung	2L	Nivolumab	400	15% (11.65%-18.88 %)	[74]
CheckMate-078	NCT02613507	III	Non-small cancer	cell	lung	2L	Nivolumab	338	18% (13.6%-21.9%)	[75]
ORIENT-3	NCT03150875	III	Non-small cancer	cell	lung	2L	Sintilimab	145	25.50% (18.60%-33.40 %)	[76]
RATIONALE-303	NCT03358875	III	Non-small cancer	cell	lung	2-3L	Tislelizumab	535	22.6% (19.1%-26.4%)	[77]
KEYNOTE-033	NCT02864394	III	Non-small cancer	cell	lung	≥2L	Pembrolizumab	213	20.7% (15.4%-26.7%)	[78]
JAVELIN Lung 200	NCT02395172	III	Non-small cancer	cell	lung	2L	Avelumab	396	15.2% (11.8%–19.1%)	[79]
BIRCH (cohort 2)	NCT02031458	II	Non-small cancer	cell	lung	2L	Atezolizumab	268	19% (15%-25%)	[69]
BIRCH (cohort 3)	NCT02031458	II	Non-small cancer	cell	lung	≥3L	Atezolizumab	252	18% (13%-23%)	[69]
ONO-4538-09	NCT02175017	II	Non-small cancer	cell	lung	2-3L	Nivolumab	100	21.0% (14.2%-30.0%)	[80]
SWOG S1400A	NCT02154490	II/III	Non-small cancer	cell	lung	≥2L	Durvalumab	68	16% (7%-25%)	[81]
CheckMate-171	NCT02409368	II	Non-small cancer	cell	lung	≥2L	Nivolumab	472	11.0% (8.3%-14.2%)	[82]
ONO-4538-25	NCT02582125	II	Non-small cancer	cell	lung	≥2L	Nivolumab	53	9.4% (4.10%-20.25%)	[83]
SHR-1210-II-201- NSCLC	NCT03085069	II	Non-small cancer	cell	lung	≥2L	Camrelizumab	146	17.8% (12.0%-25.0%)	[84]
NIDO-101	NCT04023617	II	Non-small cancer	cell	lung	2L	Nivolumab	10	10% (0-28.6%)	[85]
/	JapicCTI132072	II	Non-small cancer	cell	lung	≥2L	Nivolumab	35	25.7% (14.2%-42.1%)	[86]
/	JapicCTI132073	II	Non-small cancer	cell	lung	≥2L	Nivolumab	76	22.4% (14.5%-32.9%).	[87]
WJOG9616L	UMIN000028561	II	Non-small	cell	lung	≥2L	Nivolumab	59	8.5%	[88]

			cancer				(2.8%-18.7%)	
KEYNOTE-427 (cohort A)	NCT02853344	II	Clear cell renal cell carcinoma	1L	Pembrolizumab	110	36.4% (27.4%-46.1%)	[89]
KEYNOTE-427 (cohort B)	NCT02853344	II	Non-clear cell renal cell carcinoma	1L	Pembrolizumab	165	26.7% (20.1%-34.1%)	[90]
HCRN GU16-260 (cohort A)	NCT03117309	II	Clear cell renal cell carcinoma	1L	Nivolumab	123	34.1% (25.8%-43.2%)	[91]
HCRN GU16-260 (cohort B)	NCT03117309	II	Non-clear cell renal cell carcinoma	1L	Nivolumab	35	14.3% (4.8%-30.3%)	[92]
POD1UM-203 (RCC cohort)	NCT03679767	II	Clear cell renal cell carcinoma	1L	Retifanlimab	34	23.5% (10.7%-41.2%)	[66]
CheckMate-025	NCT01668784	III	Renal cell carcinoma	2-3L	Nivolumab	410	22.9% (18.9%-27.3%)	[93]
CA209-010	NCT01354431	II	Renal cell carcinoma	≥2L	Nivolumab (0.3mg/kg)	60	20% (13.4%-28.2%)	[94]
CA209-010	NCT01354431	II	Renal cell carcinoma	≥2L	Nivolumab (2mg/kg)	54	22% (15.0%-31.1%)	[94]
CA209-010	NCT01354431	II	Renal cell carcinoma	≥2L	Nivolumab (10mg/kg)	54	20% (13.4%-29.1%)	[94]
/	NCT02118337	II	Clear cell renal cell carcinoma	≥2L	Nivolumab	21	23.8% (8.2%-47.2%)	[95]
/	NCT02673333	II	Adrenocortical carcinoma	/	Pembrolizumab	39	23% (11%-39%)	[96]
NU 15E01	NCT02720484	II	Adrenocortical carcinoma	≥1L	Nivolumab	10	10%	[97]
IMvigor130	NCT02807636	III	Urothelial carcinoma	1L	Atezolizumab	359	23% (19%-28%)	[98]
KEYNOTE-361	NCT02853305	III	Urothelial carcinoma	1L	Pembrolizumab	307	30.3% (25.2%-35.8%)	[99]
KEYNOTE-052	NCT02335424	II	Urothelial carcinoma	1L	Pembrolizumab	370	28.6% (24.1%-33.5%)	[100]
IMvigor210 (cohort 1)	NCT02951767	II	Urothelial carcinoma	1L	Atezolizumab	119	23.5% (16.2%-32.2%)	[101]
IMvigor210 (cohort 2)	NCT02108652	II	Urothelial carcinoma	≥2L	Atezolizumab	310	16.5% (12.5%-21.1%)	[101]
KEYNOTE-045	NCT02256436	III	Urothelial carcinoma	2L	Pembrolizumab	270	21.1% (16.4%-26.5%)	[102]
IMvigor211	NCT02302807	III	Urothelial carcinoma	≥2L	Atezolizumab	462	13.4% (10.5%-16.9%)	[103]
SAUL (IMvigor211-like)	NCT02928406	III	Urothelial carcinoma	≥2L	Atezolizumab	643	14% (11%-17%)	[104]
CheckMate-275	NCT02387996	II	Urothelial carcinoma	≥2L	Nivolumab	265	19.6% (15.0%-24.9%)	[105]
KEYNOTE-143	NCT02351739	II	Urothelial carcinoma	≥2L	Pembrolizumab	35	25.7% (12.5%-43.3%)	[106]
BGB-A317-204	NCT04004221	II	Urothelial carcinoma	≥2L	Tislelizumab	104	24% (16%-33%)	[107]
POLARIS-03	NCT03113266	II	Urothelial carcinoma	≥2L	Toripalimab	151	26%	[108]

KEYNOTE-158	NCT02628067	II	MSI-H/dMMR cancer	$\geq 1L$	Pembrolizumab	233	(19%-34%) 34.3%	[109]
DRUP	NCT02925234	II	MSI-H/dMMR cancer	$\geq 1L$	Nivolumab	130	(28.3%-40.8%) 45%	[110]
PERICLES	NCT03686332	II	Penile squamous cell carcinoma	$\geq 1L$	Atezolizumab	30	(35.9%-53.6%) 16.7%	[111]
ORPHEUS	NCT04231981	II	Penile squamous cell carcinoma	$\geq 1L$	Retifanlimab	18	(6%-35%) 16.7%	[112]
KEYNOTE-199	NCT02787005	II	Prostate cancer	$\geq 2L$	Pembrolizumab	199	(5.8%-39.2%) 5%	[113]
PICK-NEPC	NCT03179410	II	Prostate cancer	$\geq 2L$	Avelumab	15	(2%-8%) 6.7%	[114]
KEYNOTE-086	NCT02447003	II	Breast cancer	$\geq 2L$	Pembrolizumab	170	(2.7-9.9%) 5.3%	[115]
KEYNOTE-158	NCT02628067	II	MSI-H/dMMR endometrial cancer	$\geq 2L$	Pembrolizumab	79	(2.7-9.9%) 48%	[116]
KEYNOTE-158	NCT02628067	II	Cervical cancer	$\geq 2L$	Pembrolizumab	77	(37%-60%) 14.3%	[117]
/	NCT03104699	II	Cervical cancer	$\geq 2L$	Balstilimab	140	(7.4%-24.1%) 15.0%	[118]
EMPOWER-Cervical 1	NCT03257267	III	Cervical cancer	$\geq 2L$	Cemiplimab	304	(10.0%-21.8%) 16.4%	[119]
YH-S001-05	NCT03972722	II	Cervical cancer	$\geq 2L$	Zimberelimab	105	(12.5%-21.1%) 27.6	[120]
SKYSCRAPER-04	NCT04300647	II	Cervical cancer	$\geq 2L$	Atezolizumab	45	(19.34%-37.20%) 15.6%	[121]
JAVELIN Ovarian 200	NCT02580058	III	Ovarian cancer	$\geq 2L$	Avelumab	188	(6.5%-29.5%) 4%	[122]
NINJA	JapicCTI153004	III	Ovarian cancer	$\geq 2L$	Nivolumab	119	(2%-8%) 7.6%	[123]
KEYNOTE-100	NCT02674061	II	Ovarian cancer	$\geq 2L$	Pembrolizumab	376	(3.5%-13.9%) 8.0%	[124]
							(5.4%-11.2%)	

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