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Review Article

Improving Outcome of PD-1/PD-L1 Inhibitors

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Abstract

Monoclonal antibodies targeting PD-1/PD-L1 as a monotherapy are useful in varieties of tumors to provide durable response not seen with other therapies. However large majority patients do not respond. Various pre-treatment parameters like PD-L1 expression, presence/absence of tumor infiltrating lymphocytes, their type and density help in identifying patients likely/not likely to benefit from anti PD-1/PD-L1 antibodies. Limitations of currently available anti-PD1/PD-L1 antibodies can be overcome by administration other appropriate therapies like chemotherapy, other checkpoint inhibitors, active immunotherapy with anti-PD1/PD-L1 antibodies.

Keywords: PD-1; PD-L1; Checkpoint Inhibitors; Patient Selection; Co Therapies; CTLA-4; Chemotherapy

Introduction

Cancer progression is associated with immunosuppression which is apparent in tumor microenvironment compared to elsewhere. Of various component of immune response, increased cell mediated immunosuppression is found to be the key for progression of tumor [1]. Increased immunosuppression is achieved by an increase in intratumoral immunosuppressive cells, decrease in intratumoral immunostimulant cells, change in ratio of immunostimulant cells to immunosuppressive cells, expression of immunosuppresive checkpoint proteins etc. Checkpoint inhibitors (CPI) like anti-PD1/PD-L1 antibodies are designed to overcome cell mediated immunosuppression and harness immune system to mount effective immune response against tumor. They have been hailed as a major revolution in management of cancer as they provide durable response and is recognised by Noble prize this year. They are approved for management of varieties of solid tumours like melanoma, renal-cell carcinoma (RCC), non-small-cell lung cancer (NSCLC), bladder carcinoma, merkel cell carcinoma, head and neck squamous cell cancer, hepatocellular carcinoma, cervical cancer etc. The response seen following administration of CPI are durable are associated with prolonged PFS. However, the response rate achieved in for solid tumours when used as a monotherapy for various CPI ranges from 12% to 34% (Table 1).

SI	Tumor Type	Pembrolizumab	Nivolumab	Avelumab	Atezoilzumab	Durvalumab
1	Melanoma	34%	34%			
2	NSCLC Maintenance following chemoradiotherapy					26%
3	NSCLC second line Monotherapy	19%	20%		14%	
4	Head and Neck cancer	16%				
5	Gastric cancer	13.30%				
6	Urothelial carcinoma	21%	19.60%	13.30%	23.50%	17%
7	Cervical cancer	14.30%				
8	Small cell lung cancer		12%			
9	Hepatocellular		14.30%			
10	Metastatic merckle Carcinoma			33%		

Table 1: Response rate of PD-1/PD-L1 therapies.

Improving the response rate and extending duration of response seen with CPI is an active area of research. In this mini review, current scenario to improve outcome of checkpoint inhibitor anti PD-1, PD-L1 antibodies therapy is reviewed.

Immune mechanism underlying response to anti PD-1/ PD-L1 antibodies [CPI]:

For killing of cancer cells by cell mediated immune response, (1) cancer cell needs to be identified as foreign by immune cells and (2) generation of adequate cancer cell specific immune response at the site of cancer.

1. Identification of cancer cell as foreign by immune cells is facilitated by:
   a. Presence of an antigen on cancer cell.
   b. Recognition of antigen by immune cells.
2. Generation of adequate immune response at the site of cancer is facilitated by
   a. Activated immune cells, exposed to the antigen.
   b. Their trafficking and infiltration to tumor.
   c. Overcoming immunosuppressive tumor microenvironment (TME).

CPI reactivates intratumoral immune cells and induces their clonal-proliferation by inhibiting checkpoint proteins present on cells. It leads to tumor shrinkage, if they are antigen-experienced prior to initiation of therapy [2-6]. Since, prior antigen experience is required, efficacy is seen only in those who have pre-existing immune infiltrate (inflamed phenotype) of CD4 and CD8 cells [6,7]. The response is best seen those which have significant no. of pre-existing tumor infiltrating immune cells. The efforts related to improving outcome of CPI are directed to either identifying those (sub group) who are more likely to respond or combining with other therapies which are likely to help overcome primary resistance [8].

Improving outcome

Selection of potential beneficiaries (enrichment):

Currently there is no guideline/diagnostic with high specificity and sensitivity to identify patients for treatment with CPI. However, studies done suggest that it is possible to increase response rate and duration of response (enrichment) by selecting potential beneficiaries. They can be broadly grouped as under:

Quantification of neoantigen load

PD-L1 expression.

Preexisting immune response

Neoantigen load

Neo-antigen present within tumor is key to response to anti-PD1/PD-L1 therapy. Presence of Mutation burden and microsatellite instability or mismatch repair deficiency indicated neo-antigen load.

Mutation burden: Mutational load governs availability of neoantigen particularly in inflamed cancer phenotype [5]. Higher non-synonymous mutation load is correlated with increased expression of genes and increases availability of neoantigen [4].

Microsatellite high cancer OR mismatch repair deficiency: Mismatch repair deficiency is associated with increased availability of neoantigens. Patients with colorectal cancer in spite of having presence of immune cells do not respond well to anti-PD1 therapies as immune cells are believed to lack antigen exposure. However colorectal cancer with presence of higher microsatellite instability respond well to anti PD-1 therapy (Table 2) as tumors with high microsatellite instability are associated with antigen experienced immune cells [9]. Pembrolizumab is approved for any type of tumor with high microsatellite instability.

		Objective Response Rate	Durable response at 6 months	Reference
Colorectal Cancer				
1	Checkmate 142 Nivo + Ipili	49%	83% > six months	[10]
2	Checkmate 142 Nivolumab	32%	63% > six months	
3	KEYNOTE-006 Pembrolizumab	36%		

Table 2: Response to CPI in patients with Microsatellite high cancer OR mismatch repair deficiency.

PD-L1 expression

CPI are designed to neutralize PD-L1. PD-L1 expression on tumors is one of the biomarker identified for efficacy of CPI. Ap-

proval of CPI is also accompanied by approval of diagnostic tests specific to qualitative and quantitative evaluation of PD-L1 expression using immunohistochemistry.

PD-L1 expression on tumor: The approval of Pembrolizumab as a monotherapy is accompanied by detection of PD-L1 on tumor. In general, higher PD-L1 expression provides better response to anti PD-1 therapy. This is seen across various tumor types. The effect is most marked for Pembrolizumab (Table 3).

PD-L1 expression on tumor cells				
		Cut off value	**ORR**	**Reference**
Non-small cell lung cancer				
1.1	KEYNOTE-024	≥ 50%	45%	[11]
1.2	KEYNOTE-010	≥ 01%	18%	
1.3	KEYNOTE-010	≥ 50%	30%	
Urothelial cancer				
2.1	KEYNOTE-052	≥ 10%	47%	[10]
2.2	KEYNOTE-052	< 10%	21%	
2.3	CHECKMATE-275	≥ 01%	25%	[10]
2.4	CHECKMATE-275	<01%	15.10%	
Gastric cancer				
3	KEYNOTE-059	≥ 1%	13.30%	[10]
Cervical cancer				
4	KEYNOTE-158	≥ 1%	14.30%	[10]
PD-L1 expression on immune cells				
Urothelial cancer				
5	IMvigor210	≥5%.	26%	[10]
	(cohort 2)	<5%	9.50%	
6	NCT01693562	High	26%	[10]
		Low	4%	

Table 3: Objective Response Rate (ORR) with Pembrolizumab and PD-L1 expression.

In a second line therapy of metastatic non squamous NSCLC treated with nivolumab, higher PD-L1 expression was associated with better overall survival (OS) compared to lower OS. However, the trend was not seen in squamous NSCLC. OS was better in PD-L1 negative compared to PD-L1 positive tumors (HR 0.58 vs 0.69) [10]. In squamous cell carcinoma of head and neck OS was better in PD-L1 positive tumors compared to negative (8.7 vs 5.7 months) [10]. In urothelial carcinoma (CHECKMATE-275), response rate was 15.1% for PD-L1 expression < 1% and 25.0% for PD-L1 expression > 1.0% [10]. This is also seen in combination of Iplimumab with Nivolumab in melanoma. Better efficacy of combination compared to Nivolumab alone is seen in patients with PD-L1 < 1% [10]. Efficacy of Atezolizumab (anti PD-L1 antibody) does not seem to be associated with PD-L1 expression on tumor.

PD-L1 expression by immune infiltrate

Anti PD-L1 antibody, atezolizumab provided better efficacy in locally advanced or metastatic urothelial carcinoma if higher no. of tumor infiltrating immune cells express PD-L1. ORR was 9.5% for PD-L1 expression of < 5% and 26% for PD-L1 expression of ≥ 5% [10].

Combination of PD-L1 expression by immune infiltrate and tumor cells

Durvalumab used a composite of PD-L1 expression by immune infiltrate as well as tumor cells and classified urothelial tumors as PD-L1 high and low. ORR was 26% in tumors with high score and 4% for tumors with low score [10].

Immune profile of tumor

Response to CPI is dependent on preexisting adaptive immune response. This pre-existing immune response (immune profile) of tumor can be evaluated by various methods. It includes:

Hematoxylin and eosin stain: Presence of lymphocytes in TME can be detected by staining paraffin section with hematoxylin and eosin. As per response to therapy to CPI, tumors are classified as inflamed or non-inflamed based on presence / absence of tumor infiltrating lymphocytes. Response to CPI are seen only in inflamed tumors. Amongst inflamed tumor, response is dependent on ratio of immune cells to tumor cells. Though critical ratio for CPI therapy is not determined, tumor with high ratio are more likely to respond and while those with low ratio fail to respond.

Immunohistochemistry

Immunohistochemistry (IHC) provides better information related to immune profile of tumor compared to simple histological techniques. Using IHC it is possible to better characterize immune cells. Generally, CD8+ T cells are associated with better outcome. Low PD-1 to CD8 ratio in NSCLC was associated with increased response which were durable [12].

Gene expression

It is possible to have gene expression profile of tumor using pre-treatment biopsy/paraffin section. Gene expression profile with IFN gamma signature is indicative of better chance of response irrespective of tumor type [13]. Negative IFN-γ signature predicts failure to respond with high accuracy (90%) [13]. Similarly, gene expression profile for CD8 suggest better outcome. Similarly, expression of PBRM1, ARID2, and BRD7 indicated better outcome and expression of B2M, MDM2/MDM4 gene indicates poor prognosis [14].

Identifying/Avoiding those not likely to benefit potential beneficiaries (enrichment)

Co-expression of other co-inhibitory receptors

Presence of other inhibitory molecules like lymphocyte-activation gene 3 protein (LAG-3), T-cell immunoglobulin domain, mucin domain-3 (TIM-3), T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) [15] predict poor response to anti PD-1/PDL1 therapy and may be avoided while treating with same.

Significant presence of immunosuppressive cells

- M2-like macrophages, which produce IL-10 [16].
- Myeloid derived suppressor cells [17].
- T_{regs}: An increase in frequency of T_{reg} or higher ratio of T_{reg} to effector Tcells are indicative of progression with anti-PD1 therapy [18].

Increased tumor derived soluble factors

- Vascular endothelial growth factor (VEGF).
- Transforming growth factor β (TGF-β).
- Prostaglandin E2.
- Interleukin (IL) 10.
- Macrophage colony-stimulating factor.
- Adenosine [19].
- Indoleamine 2,3-dioxygenase (IDO) [20].

Tumors with lower TIL or absent TIL. This category represents non inflamed tumor and they do not respond to CPI.

Epithelial mesenchymal transition: Expression of genes like AXL, TWIST2, WNT5A, LOXL2, ROR2, TAGLN, FAP are involved in the epithelial-to-mesenchymal transition [15] and tumors expressing them carry poor prognosis when treated with anti PD-1 monotherapy.

Tumors with increased lactate and LDH levels [21].

Patients with melanoma with increased lactate and LDH levels do not respond well to CPI.

Improving outcome by combination therapy

Combination of two therapeutic agents with additive/synergistic activity is needed to improve outcome of CPI monotherapy. This can be achieved by having compounds with different and / or overlapping mechanism of action.

Current scenario

Some of the combination are also associated with increased toxicity. Combinations evaluated include.

Other checkpoint inhibitors

Anti PD-1 therapy fails to respond or provides inadequate response when other immune checkpoints are co-expressed. Co-expression of more than one immune checkpoint is known [22].

Nivolumab + Ipilimumab: Anti CTLA4 antibody iplimumab is an approved product. Its administration is associated with expansion of tumor-infiltrating exhausted-like CD4 T cells. Administration of anti PD-1 therapy is associated with expansion of tumor-infiltrating exhausted-like CD8 T cells [23]. Combination is synergistic and increase plasm concentration of sIL-2Ra IL-1a levels, and CXCL10. Alteration in gene profile of T cell following administration of anti CTLA-4 are seen predominantly in a subset of transitional memory T cells, whereas with anti PD-1 therapy are seen in genes responsible for cytolysis and NK cell function. Combination of two results in greater increase in genes compared to increase seen with an individual agent. There is also expression of distinct genes not expressed by individual agents and includes potent chemokines (such as IL-8) responsible for immune infiltration [24].

NSCLC: Nivolumab+ Ipilimumab increased response rate by 18.4% (45.3% vs. 26.9%) as well as improved PFS (HR 0.58; 95% CI: 0.41–0.81; $p < 0.001$) compared to chemotherapy, regardless of tumor PD-L1 expression [10].

Melanoma: Combination improved survival in advanced melanoma with OS at three years of 58% vs 34% and HR of 0.55 [25]. The benefit of combination is also seen in patients with brain metastasis with complete response in 26% and partial response 30% [26].

Advanced renal cancer: Combination of Nivolumab + iplimumab was associated with higher response rate [42% vs 27%] and improved 18 month OS [75% vs 60%] compared to sunitinib [27].

Durvalumab + Tremelimumab: Tremelimumab is also an anti-iCTLA4 antibody. Combination of Tremelimumab with Durvalumab was associated with ORR of 26% [28] in advanced NSCLC and is undergoing phase III study.

Chemotherapy

Response to anti PD-1 therapy depends on infiltrating Tcell / tumor burden ratio [29] following anti PD-1 therapy. Anti PD-1 therapy improves this by clonal expansion of intratumoral antigen exposed Tcells. Efficacy of chemotherapy, though considered cytotoxic, depends on pretreatment immune profile of tumor and is associated with increased infiltration of immune cells and decrease in immunosuppressive TME [30]. This has been exploited successfully by combining appropriate chemotherapy with CPI in NSCLC.

Squamous NSCLC: Pembrolizumab [KEYNOTE-407] as well as atezolizumab [IMpower 131] in combination with paclitaxel containing platinum doublet improved outcome. Pembrolizumab in combination with paclitaxel containing platinum doublet increased in response rate by 23.4% [ORR 58.4% vs. 35%, $p < 0.01$], PFS [HR=0.56, $p < 0.01$] improved OS (HR = 0.64, 95% CI: 0.49–0.85, $p = 0.0008$) compared to patients treated with chemotherapy alone [31]. Addition of atezolizumab improved response rate by 8% (49% vs 41%). Improvement in PFS was 0.7 months (6.3 months vs 5.6 months, HR = 0.71 [95% CI: 0.60–0.85], $p < 0.0001$) [32].

Non squamous NSCLC: Addition of pembrolizumab to chemotherapy resulted in improved ORR by 28.8% [more than double (47.6% vs. 18.9%, $p < 0.01$)]. There was an improvement in PFS [HR=0.52, $p < 0.01$] and OS (HR=0.49; 95% CI: 0.38–0.64; $p < 0.001$) at median follow up 10.5 months [33].

Addition of atezolizumab was associated with improvement in ORR by 15.5%, improved PFS of 1.5 months (HR=0.61) and OS [HR=0.78] [21]. The efficacy was best seen in patients with high Teffector gene signature and was negligible in patients with low Teffector signature [PFS 4.5 months vs 0.3 months] [34].

Radiotherapy

Radiotherapy creates a permissive tumor microenvironment through increasing PD-L1 expression on tumor cells [35] and stimulating the accumulation and activation of CD8+ T cells [35] Preclinical evidence clearly indicates that combining radiotherapy with anti-PD-1 treatment increases the anti-tumoral activity of both treatments and even produces long-term survival [36]. Durvalumab has utilized the advantage offered by change in microenvironment following chemoradiotherapy in NSCLC. Durvalumab as consolidation/maintenance therapy following chemoradiotherapy improves ORR by 12% [26% vs 14%; $p < 0.001$] and median PFS by 11.2 months (16.8 vs. 5.6 months; HR 0.52; 95% CI: 0.42–0.65; $p < 0.001$) [37].

Active immunotherapy

Active immunotherapy generates immune response directed to tumor and has potential to increase TIL and converting tumors from non-inflamed to inflamed type. It also increases PD-L1 expression. Thus, there is a potential synergy between active immune therapy and anti PD-1/PD-L1 therapy.

Oncolytic virus: Active immunotherapy in form of oncolytic virus [38] is associated with presence of non-exhausted antigen-specific T-cells within the tumor. It is associated with us up-regulation of IFN-regulated gene expression, as well as the PD-1/PD-L1 axis in tumors, via an IFN-mediated mechanism. In animal studies it is found synergistic to anti PD-1 therapy leading to complete responses.

In human clinical study of melanoma, combination of oncolytic virus Talimogene Laherparepvec and Pembrolizumab resulted in OR of 61.9% with 33.3% achieving complete response [39]. Responders had increased CD8+ T cells, elevated PD-L1 expression and IFN-γ gene expression following talimogene laherparepvec treatment. Pretreatment CD8+ T cell infiltration or and IFN- γ signature were not associated with response to therapy. Pembrolizumab was started on week six after initiation of oncolytic virus therapy.

Anti VEGF: VEGF- is produced by tumor microenvironment is a key player in inducing tumor associated immunosuppression by;

a. Inhibiting dendritic cell maturation.

b. Accumulation of Myeloid – derived suppressor cells (MD -SCs).

c. Induction of Treg proliferation.

VEGF also increases expression of PD-1, Tim-3, CTLA-4 (immune checkpoints) in a dose dependent manner [39]. Inhibition of VEGF reduces expression of immune checkpoints [39]. In animal models producing high level of VEGF-A, combination of anti PD-1, antibodies and VEGF-A blockade provides strong synergetic effect [40].

In a phase – III study, atezolizumab with bevacizumab improved PFS compared to sunitinib in tumors expressing PD-L1 (HR = 0.74; ORR = 43% vs 35%) [41].

In human clinical trials, atezolizumab with bevacizumab enhances migration of antigen specific Tcells within tumor and improved PFS in PD-L1 expressing renal cancer [42] Efficacy was related to angiogenesis and IFN-γ response but not with the mutation load or neo antigen burden [43].

IDO inhibitors

IDO is frequently expressed with PD-L1 is known [44]. Increased IDO activity as well as its expression is associated with resistance to anti-PD-1 therapy [44]. In pre-clinical studies, combination of IDO with anti PD-1 therapy provided synergistic effect which was associated with increased infiltration of proliferating CD8 cells secreting IFN gamma and IL-2. [48] There was also an increase in antigen specific circulating Tcells [45]. In a single arm study administration of combination led to ORR of 56% in melanoma [46] PFS at 6, 12 and 18 months were 70%, 54%, and 50%, respectively. Combination also achieved OR in NSCLC [5 of 8] and renal cancer [47]. However, it failed to provide any significant advantage over Pembrolizumab in phase III trial [48] combination is being evaluated with other cancers. Epacadostat is also being evaluated with Nivolumab.

Cytokine: IL-15 is known to promote CD8-positive T-cell and natural killer (NK)-cell activation and proliferation. Combination of IL-15 with its soluble receptor (IL-15Rα) improves efficacy of IL-15. In a pre-clinical study IL-15/IL-15Rα complex fused to an IgG1 Fc is found to be synergistic with anti PD-1 therapy [49]. In a phase I study, its combination with Nivolumab provided objective response in previously treated metastatic NSCLC relapsed or refractory to prior anti PD-1 therapy [50].

Future scenario: Large number of clinical trials are ongoing wherein CPI is being evaluated in combination with other agents. They can be grouped in two broad categories.

Novel indications

Novel indications being investigated includes

a. Glioblastoma

b. Triple negative breast cancer

c. Mesothelioma

d. Pancreatic Cancer etc.

Improving outcome of existing indications: To improve outcome of disease, wherein CPI have shown some efficacy or are approved, various combinations are being evaluated and include.

a. Using approved compounds for same indication or different indication.

b. Novel compounds with proven mechanism of action identified to improve outcome of CPI.

c. Compounds with novel mechanism of action on the basis of preclinical studies.

Table 4 provides a list of ongoing clinical trials with compounds (based on pre-clinical studies) having novel mechanism of action which has a potential to improve outcome in various clinical conditions.

	Study Title	Conditions	Interventions	NCT Number
1.	**FLX475: CCR-4 antagonist**			
	Dose Escalation and Expansion Study of FLX475 Monotherapy and in Combination with Pembrolizumab	Advanced Cancer	Pembrolizumab	NCT03365661

2.	**ALT-803 IL-15 agonist**			
	QUILT-3.055: A Study of ALT-803 in Combination with Pembrolizumab or Nivolumab in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer	Non-Small Cell Lung Cancer	**ALT-803** + Pembrolizumab **ALT-803** + Nivolumab	NCT03228667
	ALT-803 Plus Nivolumab in Patients with Pre-treated, Advanced or Metastatic Non-Small Cell Lung Cancer	Non-small Cell Lung Cancer	Nivolumumab	NCT02523469
	QUILT-2.023: A Study of ALT-803, a Fusion Protein Activator of Natural Killer and T-Cells, in Combination with Pembrolizumab vs Pembrolizumab Alone as First-Line Treatment for Patients with Metastatic NSCLC.	Non-Small Cell Lung Cancer	**ALT-803** + Pembrolizumab Pembrolizumab	NCT03520686
3.	**Itacitinib: JAK-1 inhibitor**			
	Pembrolizumab and Itacitinib (INCB039110) for NSCLC	Non-Small Cell Lung Cancer	Pembrolizumab	NCT03425006
	Pembrolizumab Combined with Itacitinib (INCB039110) and/or Pembrolizumab Combined with INCB050465 in Advanced Solid Tumors	Colorectal Cancer (CRC) Endometrial Cancer	Pembrolizumab	NCT02646748
4.	**LYC-55716: ROR γ agonist**			
	Study of LYC-55716 With Pembrolizumab in Adult Subjects with Non-Small Cell Lung Cancer	Non-small Cell Lung Cancer	Pembrolizumab	NCT03396497
5.	**AM0010: Pegilodecalin**			
	Study of AM0010 With Nivolumab Compared to Nivolumab Alone Second-line Tx in Patients with Metastatic Non-Small Cell Lung Cancer	Non-Small Cell Lung Cancer	Nivolumab	NCT03382912
	Study of AM0010 With Pembrolizumab Compared to Pembrolizumab Alone First-line Tx in Patients with Metastatic Non-Small Cell Lung Cancer	Non-Small Cell Lung Cancer	Pembrolizumab	NCT03382899
6.	**Tremetinib: MEK inhibitor**			
	A Study of the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Trametinib and Dabrafenib in Participants With Advanced Melanoma (MK-3475-022/KEYNOTE-022)	Melanoma	Biological: Pembrolizumab	NCT02130466
	Study Comparing Pembrolizumab With Dual MAPK Pathway Inhibition Plus Pembrolizumab in Melanoma Patients	Metastatic Melanoma	Pembrolizumab	NCT02625337
	Study of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer	Colorectal Cancer Colon Cancer	Durvalumab	NCT03428126
	Pembrolizumab and Trametinib in Treating Patients with Stage IV Non-Small Cell Lung Cancer and KRAS Gene Mutations	Metastatic Non-Squamous Non-Small Cell Lung Carcinoma Recurrent Non-Squamous Non-Small Cell Lung Carcinoma Stage IV Non-Small Cell Lung Cancer AJCC v7	Pembrolizumab	NCT03299088
	BGB324 in Combination with Pembrolizumab or Dabrafenib/Trametinib in Metastatic Melanoma	Melanoma	BGB324 + pembrolizumab BGB324+dabrafenib and trametinib pembrolizumab dabrafenib and trametinib	NCT02872259

7.	**Defactinib: Focal adhesion Kinase inhibitor**			
	Defactinib Combined with Pembrolizumab and Gemcitabine in Patients with Advanced Cancer	Advanced Solid Tumors	Pembrolizumab	NCT02546531
	Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)	Carcinoma, Non-small-cell Lung	Pembrolizumab	NCT02758587
		Mesothelioma		
		Pancreatic Neoplasms		
	Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Preliminary Clinical Activity of Defactinib in Combination with Avelumab in Epithelial Ovarian Cancer	Epithelial Ovarian Cancer	Part A - VS-6063	NCT02943317
			Part A - Avelumab	
8.	**Vorinastat: HDAC inhibitor**			
	Phase I/Ib Study of Pembrolizumab With Vorinostat for Patients with Advanced Renal or Urothelial Cell Carcinoma	Renal Cell Carcinoma	Pembrolizumab	NCT02619253
		Urinary Bladder Neoplasms		
	Pembro and Vorinostat for Patients with Stage IV Non-small Cell Lung Cancer (NSCLC)	Non-small Cell Lung Cancer	Pembrolizumab	NCT02638090
	Pembrolizumab and Vorinostat Combined with Temozolomide for Newly Diagnosed Glioblastoma	Glioblastoma	Pembrolizumab	NCT0342689
			Temozolomide	
			Radiation: Radiotherapy	
	Reversing Therapy Resistance with Epigenetic-Immune Modification	Breast Neoplasms	Tamoxifen Pembrolizumab	NCT02395627
9.	**Entinostat: HDAC inhibitor**			
	A Study of Multiple Immunotherapy-Based Treatment Combinations in Hormone Receptor (HR)-Positive Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Breast Cancer	Breast Neoplasms	Atezolizumab (MPDL3280A), an engineered anti-programmed death-ligand 1 (PD-L1) antibody	NCT03280563
			Bevacizumab	
	Phase II Anti-PD1 Epigenetic Therapy Study in NSCLC.	Non-Small Lung Cancer, Epigenetic Therapy	Azacitidine Nivolumab	NCT01928576
	Efficacy Study of Pembrolizumab With Entinostat to Treat Metastatic Melanoma of the Eye	Metastatic Uveal Melanoma	Pembrolizumab	NCT02697630
	Atezolizumab in Combination with Entinostat and Bevacizumab in Patients With Advanced Renal Cell Carcinoma	Metastatic Cancer	Atezolizumab	NCT03024437
		Renal Cancer	Bevacizumab	
	Ph1b/2 Dose-Escalation Study of Entinostat With Pembrolizumab in NSCLC With Expansion Cohorts in NSCLC, Melanoma, and Colorectal Cancer	Non-Small Cell Lung Cancer	Entinostat	NCT02437136
		Melanoma	Pembrolizumab	
		Mismatch Repair-Proficient Colorectal Cancer		
	Study of Entinostat With Nivolumab Plus Ipilimumab in Previously Treated Renal Cell Carcinoma	Renal Cell Carcinoma	Nivolumab Ipilimumab	NCT03552380
	Combination Therapy with Entinostat and Pembrolizumab in Relapsed and Refractory Lymphomas	Lymphoma	Pembrolizumab	NCT03179930
		Relapsed		
		Refractory		
	Randomized Phase 2 Study of Atezolizumab and Entinostat in Patients With aTN Breast Cancer with Phase 1b Lead In	Breast Cancer	Atezolizumab Placebo	NCT02708680

10.	**Plinabulin: Dendritic cell maturation inducer**			
	A Phase I/II Study of Nivolumab, Ipilimumab and Plinabulin in Patients with Recurrent Small Cell Lung Cancer	Lung Cancer SCLC	Nivolumab Ipilimumab	NCT03575793
	Nivolumab in Combination with Plinabulin in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC)	Non-small Cell Lung Cancer Metastatic	Nivolumab + Plinabulin	NCT02812667
	Nivolumab and Plinabulin in Treating Patients with Stage IIIB-IV, Recurrent, or Metastatic Non-small Cell Lung Cancer	ALK Gene Translocation EGFR Activating Mutation Recurrent Non-Small Cell Lung Carcinoma	Biological: Nivolumab	NCT02846792
11.	**Sitravatinib: Multikinase inhibitor**			
	Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination with Nivolumab in Non-Small Cell Lung Cancer	Carcinoma, Non-Small-Cell Lung	Nivolumab	NCT02954991
	MGCD516 Combined with Nivolumab in Renal Cell Cancer (RCC)	Malignant Neoplasms of Urinary Tract Other Disorders of Kidney and Ureter Renal Cell Carcinoma	Nivolumab	NCT03015740
	Sitravatinib (MGCD516) and Nivolumab in Oral Cavity Cancer Window Opportunity Study	Squamous Cell Carcinoma, Head and Neck Squamous Cell Carcinoma Mouth Squamous Cell Carcinoma of the Oral Cavity	Biological: Nivolumab	NCT03575598
	Sitravatinib and Nivolumab in Urothelial Carcinoma Study	Urothelial Carcinoma Bladder Urothelial Carcinoma Ureter	Nivolumab	NCT03606174
	Neoadjuvant Sitravatinib in Combination with Nivolumab in Patients with Clear Cell Renal Cell Carcinoma	Clear Cell Renal Cell Carcinoma	Nivolumab	NCT03680521
12.	**Regorafenib: Multi kinase inhibitor**			
	Regorafenib and Nivolumab Simultaneous Combination Therapy	Advanced and Metastatic Solid Tumor	Nivolumab	NCT03406871
	Regorafenib and Nivolumab in Mismatch Repair (MMR) Refractory Colorectal Cancer	Metastatic Colorectal Cancer Colon Cancer	Nivolumab	NCT03712943

Table 4: List of ongoing clinical trials combining CPL with compounds having novel mechanism of action.

Conclusion

Anti-PD1/PD-L1 therapies have changed outlook of cancer management. It is possible to achieve durable responses using anti-PD1/PD-L1 therapies. The objective response rate with these therapies are low and needs to be improved. This can be achieved by identifying patients based on pre-treatment parameters (e.g. PD-L1 expression, CD8+ T cells) who are likely to respond as well as those who are not likely to respond (e.g. expression of multiple checkpoint proteins; higher intratumoral immunosuppressive cells). Combining anti-PD1/PD-L1 therapies with other therapies like chemotherapies, other checkpoint inhibitors and active immunotherapies has potential not only to improve the outcome but also to increase the pool of patients who may benefit by these therapies. Ongoing efforts are hold promise of achieving five-year survival in patients with difficult to treat advanced cancers like non-small cell lung cancer.

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