Checkmate Pharmaceuticals Presents Clinical Data at the 2018 American Association for Cancer Research (AACR) Annual Meeting

CMP-001 - pembrolizumab combination reverses resistance to PD-1 inhibition in patients with advanced melanoma who had progressed on prior anti-PD-1 therapy

CMP-001 shows deep and durable clinical responses in both injected and noninjected lesions

CAMBRIDGE, Mass., April 17, 2018 – Checkmate Pharmaceuticals (Checkmate) announced the first presentation of data from an ongoing Phase 1b study evaluating CMP-001, Checkmate's Toll like receptor 9 (TLR9) agonist, in combination with pembrolizumab (KEYTRUDA®), an anti-PD-1 therapy, in patients with advanced melanoma resistant to prior anti-PD-1 checkpoint inhibition. CMP-001 is designed to activate innate immunity to convert "uninflamed" tumors, which generally do not respond to anti-PD-1 therapy, into "inflamed" tumors, which are PD-1 responsive. Data were presented in the clinical trials plenary session on Tuesday, April 17 at the American Association for Cancer Research (AACR) annual meeting in Chicago by principal investigator Mohammed Milhem, MBBS, clinical professor of internal medicine, University of Iowa, Iowa City.

The combination of CMP-001 and pembrolizumab was generally well tolerated and induced deep and durable clinical responses with systemic regression of noninjected cutaneous, nodal, hepatic, and splenic metastases in patients who had progressed on a median of 2 prior therapies. "The abscopal effect observed in these patients is a hallmark of successful intratumoral immunotherapy treatment," said Dr. Milhem. "In this patient population, pembrolizumab alone would be unlikely to provide more than a 7% response rate. If the current results are confirmed, it appears that this combination could offer an effective treatment option for patients with advanced melanoma who are not responsive to pembrolizumab," he noted.

As of March 27, 2018, 85 patients had been treated in the trial; 44 patients were enrolled in the dose escalation phase, while 41 patients have been enrolled in the ongoing expansion phase. CMP-001 was administered intratumorally (IT) into one or more accessible lesion(s), and response assessed in all target lesions, both injected and noninjected, as well as non-target lesions by RECIST v1.1. Study therapy was continued until progression, toxicity, investigator decision or withdrawal of consent. Baseline and on-therapy serum was collected for cytokine analysis at various timepoints. Immunohistochemical and RNA-Seq analysis was performed on available pre- and post-treatment tumor biopsies.

Data were presented on 69 patients in the Intent To Treat (ITT) population, defined as those who received at least one dose of CMP-001 in the Dose Escalation (44 patients) and Dose Expansion (25 patients) phases of the study, and who had at least one follow-up scan or who discontinued treatment for any reason prior to having a follow-up scan as of March 27, 2018.

- The Objective Response Rate (ORR) by RECIST v1.1 in the ITT population was 22.0% (15/69; 95% confidence interval 13-33%), including 2 complete responses and 13 partial responses.
- Among the 15 RECIST responders, 11 remain on study; 1 has withdrawn due to progressive

disease, and 3 have withdrawn consent (1 with progressive disease, and 1 each with a complete response and a partial response).
• Six of the responders continuing on study have maintained their response over 6 months and, of these 2 have maintained their responses over 84 weeks: median response duration has not been reached.
• Three additional patients who continued study therapy beyond their initial progression responded according to iRECIST criteria.
• Of the 18 patients who responded by either RECIST or iRECIST, 17 had previously progressed on anti-PD-1, either as monotherapy, and/or in combination with other agents, including IDO inhibitors (N=4), TLR9 agonist (N=1), or CCR4 agonist (N=1). In addition to their prior treatment with one or more anti-PD-1 regimens, 5 of the 18 responders to CMP-001 + pembrolizumab had received prior therapy with ipilimumab monotherapy.

The combination of CMP-001 and pembrolizumab was generally well tolerated in this study population. No maximum tolerated dose was identified during the dose escalation phase of the study. Two subjects discontinued study therapy due to toxicity.

Translational studies supported the expected CMP-001 mechanism of action of activating TLR9 in tumor-associated plasmacytoid dendritic cells (pDC), showing:

• Median 5.9 fold increase in serum CXCL10 (IP-10), a chemokine induced by interferons.
• Increased CD8+ T cells and PD-L1 expression in injected and noninjected post-treatment biopsies by immunohistochemistry.
• Induction of a "T cell-inflamed," PD-1 response associated, transcriptional signature in posttreatment biopsies by RNA-Seq.
• A low frequency of tumor-associated pDC in baseline tumor biopsies from patients who subsequently progressed (N=9; mean %pDC = 0.1, SD=0.1, range 0.02-0.4), and an approximately ten times higher baseline frequency of tumor-associated pDC in patients who subsequently responded to therapy or had stable disease (N=7; mean %pDC = 1.2, SD=1.3, range 0.02-3.6).

"CMP-001 stimulation of the TLR9 pathway in pDC activates the immune system, providing a synergistic anti-tumor effect when combined with checkpoint inhibitors that block tumor-mediated immune suppression," observed Dr. Art Krieg, Checkmate's founder and CEO. "We are pleased with the data from this ongoing study showing that CMP-001 in combination with pembrolizumab can reverse resistance to PD-1 inhibition. The duration of response, which is ongoing in most of the responders, is particularly encouraging and supports further clinical development of CMP-001. The mechanism of action of CMP-001 is not specific to melanoma, and should apply across most or perhaps all tumor types, including those that have not been PD-1 responsive in the past," he said.

CMP-001 is being evaluated in multiple tumor types to assess its safety, activity, alternative routes of administration and combination with other immunotherapies and modalities. For information on CMP-001 trials that are currently recruiting patients, please visit www.clinicaltrials.gov.

About Checkmate's Phase 1b Study (CMP-001-001)

CMP-001-001(NCT02680184) is an ongoing, multicenter two-part, open label Phase 1b clinical study phase with advanced melanoma. The study is being conducted at 13 sites in the USA.
The primary objective of the study is to determine the recommended phase 2 dose (RP2D) of CMP001 when given in combination with pembrolizumab in PD-1 resistant patients. Secondary objectives

are to assess the safety profile of CMP-001 when given in combination with pembrolizumab, and to assess the pharmacodynamic effects of the addition of CMP-001 to pembrolizumab on serum concentrations of CXCL10 (IP-10).

Part 1 of the study utilized a dose escalation scheme to identify the RP2D and schedule. During dose escalation, patients were enrolled to cohorts of ≥ 3 patients at CMP-001 doses of 1, 3, 5, 7.5, and 10 mg in two dosing schedules (weekly for 7w, followed by q3w; or weekly for 2w, followed by q3w). The 5 mg dose and weekly dosing schedule for 7w, followed by q3w were selected as the RP2D and dosing schedule, and are being evaluated in the ongoing dose expansion phase of the study.

Part 2 of the study is also enrolling and is evaluating the safety and efficacy of CMP-001 administered as monotherapy at the same RP2D and schedule selected in Part 1 of the study.

About CMP-001

CMP-001 is a first in class CpG-A TLR9 agonist that is encapsulated in a virus-like particle (VLP). It is the only CpG-A TLR9 agonist in clinical trials and differs from other CpG classes by having a native DNA backbone that induces the highest levels of type I interferon (IFN).

The highly immunogenic VLP of CMP-001 provides multiple advantages beyond protecting the native DNA CpG-A from degradation, which include facilitating lymphatic distribution, and promoting broader immune activation via anti-VLP IgG immune complexes that also drive productive uptake into the target plasmacytoid dendritic cells (pDC). The type 1 IFN production resulting from TLR9 mediated activation of pDC upon CMP-001 uptake, leads to recruitment of conventional dendritic cells and other antigen presenting cells, and T cell activation toward tumor associated antigens. Together, these CMP-001 activities can convert the tumor microenvironment from “uninflamed”, to “inflamed”, and promote a systemic anti-tumor cytotoxic T cell response.

Based on analyses of gene expression in human tumors showing that increased IFN gene expression is associated with better response to PD-1 inhibition, it is believed that this mechanism of action may restore, enable or improve responses to anti-PD-1/PD-L1 therapeutics.

About Checkmate

Checkmate Pharmaceuticals is a clinical stage company that is leveraging its expertise in the field of CpG oligonucleotides to discover and develop immunotherapies designed to increase the efficacy of existing immunotherapies and to provide new treatment options for patients and their healthcare providers. Checkmate’s lead product candidate, CMP-001, is an investigational cancer immunotherapeutic that has been shown to reverse resistance to PD-1 therapy in some patients.

Checkmate is a privately held company headquartered in Cambridge, MA.

Information regarding Checkmate is available at www.checkmatepharma.com.

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