Tuesday, April 17, 2018

Suzanne L. Topalian, MD, director of the Melanoma Program at Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins and associate director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy, will moderate a press conference highlighting the following research:

- TLR9 Agonist CMP-001-Pembrolizumab Combination Shows Early Efficacy in Patients With Metastatic Melanoma Resistant to Anti-PD1
- Dual Inhibition of IDO1 and PD-L1 Safe in Patients With Advanced Solid Tumors
- Short-acting Calcium Channel Blockers Were Associated With Increased Risk of Pancreatic Cancer in Postmenopausal Women

TLR9 Agonist CMP-001-Pembrolizumab Combination Shows Early Efficacy in Patients With Metastatic Melanoma Resistant to Anti-PD-1

CHICAGO—A combination of CMP-001, an intratumoral Toll-like receptor 9 (TLR9) agonist, and pembrolizumab (Keytruda), tested in patients withmetastatic melanoma resistant to PD-1 checkpoint inhibition, was well tolerated and had clinical activity according to preliminary data presented from the ongoing phase Ib clinical trial at the AACR Annual Meeting 2018, April 14-18, in Chicago.

“Checkpoint inhibition is quickly becoming a key tool for oncologists to treat cancer,”said Mohammed Milhem, MBBS, clinical professor of internal medicineat the University of Iowa, Iowa City. “However, there are many patients that either initially respond to checkpoint inhibition and then progress, or never respond to this therapy to begin with. Finding safe and effective therapies for these patients is critical.

”While pembrolizumab is the standard of care for patients with metastatic melanoma, over 50 percent of these patients develop resistance, explained Milhem. In an attempt to address this, Milhem and colleagues

combined the TLR9 agonist CMP-001 with checkpoint inhibition.

Previous work has shown that tumors with an increase in interferon (IFN) gene expression are more responsive to PD-1 inhibition, explained Milhem. “The strongest known inducer of IFN production is the TLR9 pathway, so we thought that adding a TLR9 activator to anti-PD-1therapy would elicit a response in patients who stopped or never responded to PD-1 inhibition,” he noted.

In this phase Ib clinical trial, Milhem and colleagues enrolled patients with advanced melanoma who had either not responded to or had progressed during prior anti-PD-1 therapy. As of March 27, 2018, 85 patients have been treated in the trial; 44 patients were enrolled in the dose escalation phase, while 41 patients have been enrolled in the ongoing dose expansion phase.

Throughout the completed dose escalation phase, patients received CMP-001 via direct intratumoral injection at doses ranging from 1to 10mg in combination with pembrolizumab. There were two treatment schedules for the administration of CMP-001: one injection per week for seven weeks followed by every three weeks until discontinuation (weekly treatment); or one injection per week for two weeks followed by every three weeks until discontinuation (q3w treatment). During the dose escalation phase, one dose-limiting toxicity occurred; no maximum tolerated dose (MTD) was identified.

Target lesions (both injected and not injected with CMP-001) were assessed via RECIST v1.1. “To date, across both the dose escalation and expansion cohorts,15 patients have responded,”Milhem said. The objective response rate(ORR) is 22 percent. The ORR is 23 percent and 15 percent for patients on weekly and q3w treatment, respectively.

Among the 15 patients who had responded, 11 remain on study; three of these patients have maintained their response beyond one year. Three additional patients that continued study therapy beyond their initial progression had responded according to iRECIST criteria, Milhem said. The median duration of response has not been reached.

Notably, Milhem and colleagues saw a reduction in non-injected tumors in cutaneous, nodal, hepatic, and splenic metastases.“The abscopal effect observed in these patients is a hallmark of successful intratumoral immunotherapy treatment,” noted Milhem.

“Based on these preliminary findings, the combination of CMP-001 and pembrolizumab appears to have a manageable safety profile and meaningful clinical activity,” said Milhem. “Additional larger studies in this patient population will need to be conducted to further evaluate the clinical benefit, but if the current results are confirmed, it appears that this combination could offer a new treatment option for patients with advanced melanoma who are not responsive to pembrolizumab.

”This study is sponsored and managed by Checkmate Pharmaceuticals. Milhem declares no conflict of interest.

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ABSRACT CT144:

M. Milhem, et al. **Intratumoral toll-like receptor 9 (TLR9) agonist, CMP-001, in combination with pembrolizumab can reverse resistance to PD-1 inhibition in a phase Ibtrial in subjects with advanced melanoma**

Background: CMP-001 comprises a CpG-A oligodeoxynucleotide packaged within a virus-like particle. It is designed to activate tumor-associated plasmacytoid dendritic cells via TLR9 inducing an interferon-rich tumor microenvironment and anti-tumor CD8+T cell responses.

Materials and Methods: CMP-001-001 is an ongoing phase Ib trial evaluating intratumoral (IT) CMP-001 in combination with pembrolizumab (administered per label) in subjects with advanced melanoma resistant (either did not respond or progressed) on prior anti-PD-1 monotherapy or in combination. During dose escalation, subjects were enrolled to cohorts of ≥ 3 subjects 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). CMP-001 was administered IT into an accessible lesion(s), and response assessed in all target lesions (injected and non-injected) by RECIST v1.1. Study therapy was continued until progression, toxicity, investigator decision or withdrawal of consent. Baseline and on-therapy serum was collectedfor cytokine analysis. Immunohistochemical and RNA-Seq analysis was performed on available pre-and post-treatment tumor biopsies.

Results: As of December 31, 2017, 68 subjects have been treated (44 in Escalation and 24 in Expansion). Safety data from 63 subjects demonstrated a manageable acute toxicity profile consisting predominately of fever, N/V, headache, hypotension and rigors. Grade 3/4 related AEs reported in ≥1 subject; hypotension (n=7), anemia (n=2), chills (n=2), hypertension (n=2) and fever (n=2). The Objective Response Rates (ORR) across all dose cohorts on weekly (n=40) and q3week schedules (n=13) were 22.5% (9/40; 95 % CI 11-39%) and 7.7%% (1/13; 95% CI 0-36%) respectively. For subjects dosed weekly at 3 and 5 mg, the ORR was 33.3% (6/18 95% CI 13-59%). Of the 10 responders, 1 progressed (w36), 2 withdrew consent (w13, w25), 7 remain on study with 2 subjects maintaining their response though w72. Regression of non-injected tumors occurred in cutaneous, nodal, hepatic, and splenic metastases. CMP-001 induced TLR9 activation with a median 5.9 fold increase in serum CXCL10 (range of 0.9 -276.3; mean fold increase of 21.8 with SD=48.8; n=39). Immunohistochemical and RNA-Seq analysis of tumor biopsies revealed increases in tumor-infiltrating CD8 T cells (>5 fold), PD-L1 expression (>3 fold increase in H score), and transcriptional signature of inflammation in 2/4 subjects with analyzable pre-and post-treatment samples.

Conclusions: CMP-001 in combination with pembrolizumab resulted in objective, durable tumor responses with tolerable toxicities in subjects with advanced melanoma resistant to prior anti-PD-1 therapy. CMP-001 dosing at 5 mg/weekly has been selected for further evaluation in the ongoing dose expansion phase of this study.

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Dual Inhibition of IDO1and PD-L1 Safe in Patients With Advanced Solid Tumors

CHICAGO—An immunotherapy treatment combining the IDO1 inhibitor epacadostat and the PD-L1 inhibitor durvalumab was found to be safe in patients with advanced solid tumors, with safety data similar to treatment with durvalumab alone, according to data presented from the ongoing ECHO-203 clinical trial at the AACR Annual Meeting 2018, April 14-18, in Chicago.

“Immune checkpoint inhibitors, including PD-1 and PD-L1 inhibitors, have provided meaningful clinical benefits for patients with cancer; however, novel immunotherapy combination treatments are needed to improve efficacy with limited additive toxicity,” said Aung Naing, MD, FACP, associate professor, Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston. “This is the first report of IDO1 inhibition in combination with PD-L1 antagonism, and we found that epacadostat plus durvalumab was generally well-tolerated in patients with advanced cancers, with a safety profile consistent with previous reports of durvalumab monotherapy.

”Prior preclinical work suggested that dual inhibition of both IDO1 and the PD-1/PD-L1 axis was more efficacious than targeting either component alone, noted Naing. “These studies laid the foundation for the human trials of agents that target the PD-1/PD-L1 pathway and IDO1,” he explained.

“ECHO-203 is part of the broader ECHO clinical development program investigating efficacy and safety of epacadostat as a core component of combination therapy in a broad range of solid tumor types as well as hematological malignancies,”said Naing. “Ongoing clinical studies are evaluating epacadostat in combination with PD-1 and PD-L1 inhibitors including pembrolizumab, nivolumab, and durvalumab.

”Naing and colleagues tested the combinatorial treatment in 34 patients with advanced pancreatic cancer, melanoma, non-small cell lung cancer (NSCLC), or squamous cell carcinoma of the head and neck (SCCHN). Exclusion criteria included prior checkpoint inhibition therapy for any unapproved indications.

Patients received doses of epacadostat ranging from 25 to 300mg twice daily in combination with 3 or 10mg/kg of durvalumab every two weeks. Safety data were compiled from patients who received at least one treatment dose. One dose-limiting toxicity (DLT) was observed.

Common adverse events (AEs) included fatigue (32 percent), pruritus (severe itching; 15 percent), diarrhea, nausea, and rash (12 percent each); five patients discontinued treatment due to AEs.

As of Oct. 29, 2017, efficacy data for 15 patients with advanced pancreatic cancer treated at various dose levels revealed no responses. Four patients had stable disease, resulting in a disease control rate of 27 percent; one patient discontinued treatment following clinical progression.

“Because pancreatic cancer has an immunosuppressive tumor microenvironment that generally excludes T cells, combinatorial therapies that enhance the immune response will be needed for an effective immunotherapeutic regimen,” explained Naing.

“However, as pancreatic cancer is not generally responsive to immunotherapy, these results were not a complete surprise,” he noted. “We found that epacadostat drug levels were slightly lower in pancreatic cancer patients who had prior pancreatic and duodenal surgeries, which are commonly performed in this patient population.”

Phase II expansions, with epacadostat doses of 100 and 300mg in combination with 10mg/kg of durvalumab, are currently being evaluated in patients with NSCLC, SCCHN, and urothelial carcinoma. “Since these tumor types have demonstrated efficacy with checkpoint inhibition monotherapy, they were considered more likely to potentially benefit from combination immunotherapy,” noted Naing.

This trial is sponsored by Incyte Corporation; Incyte and AstraZeneca provided funding for this study.

Naing has received grants and/or research support from the National Cancer Institute, EMD Serono, MedImmune, Healios Oncology Nutrition, Attercor, Amplimmune, ARMO Biosciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, and Bristol-Myers Squibb. He is an advisory board member for CytomXand Novartis, and he has received travel and accommodation expenses from ARMO Biosciences.

ABSTRACT CT177:

A. Naing, et al. **Epacadostat plus durvalumabin patients with advanced solid tumors: preliminary results of the ongoing, open-label, phase I/II ECHO-203 study**

Introduction: Epacadostat, a potent and highly selective oral inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme, plus durvalumab, an anti-PD-L1 antibody, is being studied in patients with advanced solid tumors (NCT02318277). Phase 1 preliminary safety data for the overall population and efficacy data for patients with advanced pancreatic cancer (PC) are reported as of 29 Oct 2017 data cutoff.

Methods: Adult patients with PC, melanoma, NSCLC, or SCCHN were enrolled in the 3+3 dose-escalation phase 1. Prior treatment with immune checkpoint inhibitors (in unapproved indications) or IDO inhibitors was not allowed. Patients received epacadostat (25, 50, 75, 100, or 300 mg twice daily [BID]) plus durvalumab (3 or 10 mg/kg every 2 weeks [Q2W]). Safety was assessed in patients receiving ≥1 treatment dose. Response was measured in evaluable patients (≥1 postbaseline scan or discontinued/died before the first scan) per modified RECIST v1.1.

Results: Thirty-four patients were enrolled in phase 1. Median age (range) was 68 (46-84) years; most patients were male (62%) and had an ECOG PS of 1 (82%). There was 1 dose-limiting toxicity (grade 3 rash requiring systemic steroids; epacadostat 300 mg BID plus durvalumab 10 mg/kg Q2W) during the

42-day observation period. The most common (≥10%) treatment-related adverse events (TRAEs) were fatigue (32%), pruritus (15%), diarrhea, nausea, and rash (12% each). Grade ≥3 TRAEs occurring in >1 patient included fatigue and rash (n=3 [9%] each). Five patients (15%) discontinued because of TRAEs (grade 1 pneumonitis, grade 2 diarrhea, grade 2 subarachnoid hemorrhage, grade 2 peripheral edema, and grade 3 dyspnea). Therewere no TRAEs leading to death.

Fifteen patients with PC were enrolled across multiple dose levels. Median age (range) was 66 (46-72) years, 67% had liver metastases, and 87% had an ECOG PS of 1. Fourteen patients had received ≥1 prior therapy. PD-L1 expression test results were available in 7/15 patients: 2 had detectable (≥1%) staining of tumor cells; 5 did not. No responses were observed among patients with PC; the disease control rate was 27% (4 SD) per RECIST v1.1 (1 of 4 patients with SD discontinued treatment because of clinical progression). The median duration of disease control was 156 days (95% CI, 91-219). Epacadostat exposure was consistent with previous reports, except in patients with PC where somewhat lower peak exposures (Cmax) were observed.

Conclusions: Epacadostat plus durvalumab was generally well tolerated in patients with advanced cancers; the safety profile was consistent with previous reports of durvalumab and epacadostat as monotherapies. In unselected patients with PC, no objective responses were observed; a phase 2 expansion for PC was not conducted. Epacadostat 100 and 300 mg BID are being evaluated in the ongoing phase 2 expansions, including patients with NSCLC, SCCHN, and urothelial carcinoma.

Short-acting Calcium Channel Blockers Were Associated With Increased Risk of Pancreatic Cancer in Postmenopausal Women

CHICAGO—Calcium channel blockers (CCBs), specifically the short-acting form of CCBs, which are prescribed to treat high blood pressure, were associated with an increased risk of pancreatic cancer in postmenopausal women, according to a study presented at the AACR Annual Meeting 2018, April 14-18.

“Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States, with an estimated 44,330 deaths in 2018,” said the study’s lead author, Zhensheng Wang, PhD, a postdoctoral associate at the NCI-designated Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine in Houston.

“Pancreatic cancer typically occurs in elderly individuals who also have chronic comorbid medical conditions, such as hypertension,” Wang said. “Antihypertensive medication use has increased significantly; therefore, it is of great public health significance to address the potential association between antihypertensive medication use and risk of pancreatic cancer in the general population.”

This study sought to evaluate how antihypertensive drugs and a receptor called soluble receptor for advanced glycation end-product (sRAGE) might influence pancreatic cancer risk. Previous research has suggested that sRAGE has an anti-inflammatory effect on the body, and it has been associated with lower risk of pancreatic cancer. Because antihypertensive medications have been shown to increase the concentration of sRAGE levels, the researchers hypothesized that there would be an inverse association between the use of antihypertensive medications and pancreatic cancer risk.

“We were, however, surprised by the unexpected increased risk of pancreatic cancer observed among users of short-acting CCBs,” Wang said.

The authors conducted a prospective cohort study of 145,551 postmenopausal women ages 50 to 79 who were enrolled in the Women’s Health Initiative, a long-termnational health study, between 1993 and 1998. They collected data on any medications the women were taking, including product and generic name, duration of use, and dosage form. They analyzed four types of antihypertensive drugs: beta blockers, diuretics, angiotensin converting enzyme inhibitors (ACEi), and CCBs, and used Cox proportional hazard regression models to obtain hazard ratios for the association of the four types of medication with risk of pancreatic cancer.

By Aug. 29, 2014, the researchers had ascertained 841 pancreatic cancer cases among the women. In these women, the researchers measured serum levels of sRAGE using immunoassay among a subset of 489 pancreatic cancer patients and 977 non-cancer controls.

They found that a 66 percent higher risk of incident pancreatic cancer was found among the women who had ever used short-acting CCBs. Women who had used short-acting CCBs for three or more years were found to have a 107 percent higher risk of pancreatic cancer than those who had used other non-CCB antihypertensive drugs.

CCBs, in particular short-acting CCBs,were the only antihypertensive medication that was associated with an increase in pancreatic cancer risk. Ever-use of ACEi, beta blockers, diuretics, and long-acting CCBs was not associated with increased risk of pancreatic cancer.

The study also found that women who had ever used short-acting CCBs had significantly lower sRAGE levels than women who used any other anti-hypertensive medications.

“sRAGE is thought to mitigate the inflammatory response by blocking pro-inflammatory RAGE signaling,” explained senior author Li Jiao, MD, PhD, associate professor at the Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey VA Medical Center at Baylor College of Medicine.

The authors noted that while further research will be necessary to confirm these findings and understand the mechanisms, “the blockage of the calcium channel caused by use of CCBs may potentially reduce sRAGE release and thus further decrease the levels of anti-inflammatory sRAGE. This is important as

chronic inflammation is a well-recognized risk factor for pancreatic as well as many other cancers."

"Our findings on short-acting CCB use and pancreatic cancer risk are novel and of potential broad medical and public health significance if confirmed. Short-acting CCBs are still prescribed to manage hypertension, which is one of the components of metabolic syndrome, and metabolic syndrome is a possible risk factor for pancreatic cancer," Wang said.

Jiao noted that since this observational study was conducted among postmenopausal women in the United States, the results may not be generalizable to men, to premenopausal women, or to populations outside the United States. Unadjusted confounding factors or residual confounding factors may also contribute to the findings.

This study was funded by NIH-National Cancer Institute (5R01CA172880-03) and by the Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (CIN13-413). Wang is supported by a Research Training Grant from the Cancer Prevention and Research Institute of Texas and the WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health.The authors declare no conflicts of interest.

ABSTRACT 4946:

Zhensheng Wang, et al. **The association between antihypertensive medication, sRAGE, and risk of pancreatic cancer: Results from the Women's Health Initiative Study**

Background: Pancreatic cancer is the 4th leading cause of cancer-related death in the United States. With its anti-inflammatory property, soluble receptor for advanced glycation end-product (sRAGE) has been associated with lower risk of pancreatic cancer. Antihypertensive medications were shown to modulate sRAGE levels and AGE/RAGE signaling pathway. However, few large-scale population-based studies have evaluated the associations between antihypertensive medications and risk of pancreatic cancer.

Methods: A total of 145,553 postmenopausal women aged 50 to 79 years with no prevalent cancer from Women's Health Initiative (WHI) were included in our prospective cohort study with a mean follow-up of 13.8 years. Medication data including product and generic name, duration of use, and dosage form were collected at baseline recruitment (1993-98). We interrogated four antihypertensive drugs including β-blockers, diuretics, angiotensin converting enzyme inhibitors (ACEi) and calcium channel blockers (CCBs). Serum levels of sRAGE were measured in a subset of 842 study participants using immunoassay. Cox proportional hazard regression model was performed to obtain hazard ratio (HR) and its 95%

confidence interval (CI) for each antihypertensive medication use and its duration of use in association with risk of pancreatic cancer. We additionally used Fine and Grey method to account for competing risk of nonpancreatic cancer deaths.

Results: By August 29, 2014, a total of 841 incident pancreatic cancer cases were ascertained through annual self-administered questionnaires and confirmed by central adjudication. A 33% increased risk of pancreatic cancer was found among ever users of CCBs compared with never users (HR=1.33, 95% CI: 1.06-1.67) after adjusting for age, ethnicity, BMI, smoking status, diabetes history, use of β-blockers, ACEi or diuretics. The association remained after accounting for competing risks (HR=1.36, 95% CI: 1.30-1.42). Compared with never users of CCBs, long-term users (>3 years) had a 48% higher risk of pancreatic cancer (HR=1.48, 95% CI: 1.13-1.95,Ptrend = 0.005) and the association slightly attenuated but remained significant in the competing risk model (HR=1.35, 95% CI: 1.28-1.42,Ptrend

Conclusions: We found a positive association between CCB use and risk of incident pancreatic cancer in postmenopausal women. The inverse association between sRAGE level and CCBs use may help explain this association. Future studies are warranted to confirm these findings and further elucidate potential mechanisms by which CCBs may influence development of pancreatic cancer.