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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Phase 2 Trial of Single-Agent Cobimetinib for Adults with Histiocytic Neoplasms

Eli L. Diamond, MD[1], *Benjamin Durham, MD PhD*[2], *Ahmet Dogan, MD PhD*[3], *Mariko Yabe, MD PhD*[4], *Kseniya Petrova-Drus, MD PhD*[3], *Raajit K. Rampal, MD PhD*[5,5], *Raajit K. Rampal, MD PhD*[5,5], *Gary Ulaner*[6], *Mario Lacouture, MD*[7], *Veronica Rotemberg*[8], *Anne Covey*[2], *Lynn Brody*[9], *Omar Abdel-Wahab, MD*[10]

[1]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Memorial Sloan Kettering Cancer Center, New York, NY
[3]Department of Pathology and Laboratory Medicine, Hematopathology Service, Memorial Sloan Kettering Cancer Center, New York, NY
[4]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[5]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Institute, New York, NY
[6]Hoag Family Cancer Institute, Newport Beach, CA
[7]Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[8]Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York
[9]MSKCC, New York, NY
[10]Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Histiocytic neoplasms (HN) are clonal hematopoietic disorders characterized by diverse mutations in the mitogen-activated protein kinase (MAPK) pathway. BRAF inhibition is highly effective for patients with HN harboring the *BRAF*V600E mutation, and implementation of BRAF inhibitors transformed management of *BRAF*V600E-mutated Erdheim-Chester disease (ECD) and Langerhans cell histiocytosis (LCH). No standard or approved therapies existed, however, for patients with HN lacking the *BRAF*V600E mutation. Efficacy of mitogen-activated protein kinase (MEK) inhibition for HN harboring various MAPK pathway mutations has been observed in case reports and series. We present here results from 26 patients treated in a phase 2 trial of single-agent cobimetinib for adults with HN (NCT02649972). The data were submitted to the Food and Drug Administration (FDA) in a supplemental new drug application for cobimetinib, and FDA approval was granted in October, 2022.
Methods: This is an open-label phase 2 trial of cobimetinib 60mg daily for patients with (1) BRAFV600-wildtype (wt) histiocytosis or (2) BRAFV600-mutant histiocytosis intolerant or without access to BRAF inhibitor therapy. Eligible patients were age 16 or older, had histologic confirmation of HN diagnosis, ECOG 0 to 3, multi-system HN or HN refractory to conventional (i.e. chemotherapeutic or immunosuppressive) therapy or single-system HN deemed unlikely to benefit from conventional therapy, and with disease measurable by positron emission tomography (PET) Response Criteria (PRC). Patients were eligible with any tumor mutation or with no identified tumor mutation. The primary endpoint was overall response rate (complete metabolic response + partial metabolic response; ORR) by PRC. Secondary endpoints included safety (CTCAE 4.0), duration of response (DoR) and progression-free survival (PFS) as determined by modified PERCIST, overall survival (OS), and response rate by RECIST. Data cut-off was March 28, 2019 for efficacy evaluation, and safety follow-up cut-off was September 28, 2019.
Results: Twenty-six patients (13 ECD, with Rosai-Dorfman disease [RDD], 4 with LCH, 2 with juvenile xanthogranuloma [JXG], 3 with mixed histiocytosis) with a median age of 50.5 were analyzed. Six patients had *BRAF*V600E-mutant disease, one of these with additional mutations in KRAS and NRAS. Of the remaining 20, 15 had non-BRAFV600 MAPK pathway mutations (4 KRAS [one of them with ARAF mutation as well], 6 MEK1, 1 MEK2, 1 RAF1, 1 ARAF, 2 non-V600 BRAF mutations, and 5 had no mutation identified). Twenty-six patients were evaluable for safety, 24 for PRC, 19 for RECIST. Response rates are listed in Table 1 and PRC responses are presented in Figure 1. The ORR by PRC was 83.3% (95% CI 62.62-95.26), in the PRC-evaluable population. Responses were observed across MAPK mutations, histiocytosis subtypes and tumor genotypes. By BRAFV600 status, in PRC-evaluable population, the ORR for BRAFV600E-mutant disease was 100% (95% CI 47.82-100), and for BRAFV600-wt disease was 78.9% (95% CI 54.43-93.95). Median DoR was 31.1 months (95% CI 16.8-NE) in the PRC-evaluable population. ORR by RECIST was 63.2% (95% CI 38.36-83.71), in the RECIST-evaluable population.

Three patients died on study, none related to cobimetinib. Grade 3 or 4 toxicities in >10% of patients included decreased lymphocyte count (19%), increased blood creatine phosphokinase (12%), decreased ejection fraction (12%), hypokalemia (12%), hyponatremia (12%), acute kidney injury (12%) and dyspnea (12%).
Conclusions: Cobimetinib demonstrates robust efficacy in HN irrespective of underlying MAPK pathway mutation, including BRAF-wt and BRAFV600-mutant HN. Safety of cobimetinib in this patient population was consistent with the known safety profile.

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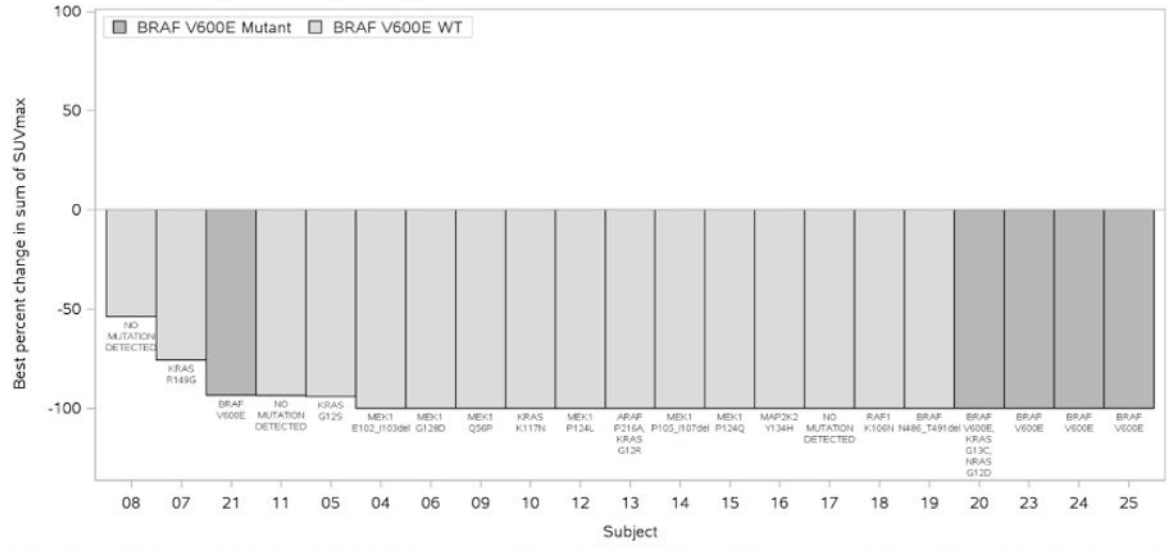
Table 1. Overall response rates of cobimetinib in histiocytic neoplasms

Response	PET Response, PET Evaluable Population (N=24)*	RECIST Response, RECIST Evaluable Population (N=19)**
Overall response rate, n (%) (95% Clopper-Pearson CI)	20 (83.3%) (62.62-95.26)	12 (63.2%) (38.36-83.71)
Best Response, N (%)		
Complete Response	16 (66.7)	3 (15.8)
Partial Response	4 (16.7)	9 (47.4)
Stable Disease	1 (4.2)	5 (26.3)
Progressive Disease	0 (0)	0 (0)
Missing	3 (12.5)	2 (10.5)

clinical cut-off date (CCOD): March 28, 2019
*24 PET-evaluable patients. 1 patient had missing baseline scan. 1 patient had short follow-up duration (not enrolled at least 16 weeks prior to CCOD)
**19 RECIST-evaluable patients. 6 patients had missing baseline scans. 1 patient had short follow-up duration (not enrolled at least 16 weeks prior to CCOD)

Figure 1. Waterfall plot of the maximum change in tumor metabolism according to standardized uptake values (SUVmax), measured by modified PET response criteria in solid tumors (PRC), PET Evaluable Population (N=24)



Each bar in the waterfall plot represents, for a given patient, either (a) the largest percentage "decrease" in tumor size from baseline (if there was any tumor shrinkage) or (b) the smallest percentage "increase" in tumour size from baseline (if there was no tumor shrinkage), at any time point.Â Tumor size is defined as the sum of normalized SUVmax for all lesions, evaluated per PRC (PET Response Criteria).

Three patients do not have post-baseline measurements per PRC (PET Response Criteria), and hence are not included in this plot.
Clinical Cut-off Date: Mar 28, 2019; Snapshot Date: Oct 10,2022

Figure 1

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