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## PHASE 2 SAFETY AND EFFICACY OF ORAL CCR4 ANTAGONIST FLX475 (TIVUMECIRNON) PLUS PEMBROLIZUMAB IN SUBJECTS WITH NON-SMALL CELL LUNG CANCER NOT PREVIOUSLY TREATED WITH CHECKPOINT INHIBITOR

<sup>1</sup>Tae Min Kim, <sup>2</sup>Nuttapong Ngamphaiboon, <sup>3</sup>Ki Hyeong Lee, <sup>4</sup>Pratibha Desai, <sup>5</sup>Chia-Chi Lin, <sup>6</sup>Jameel Muzaffar, <sup>7</sup>Yin-Hsun Feng, <sup>8</sup>Shang-Yin Wu, <sup>9</sup>Julie Brahmer\*, <sup>10</sup>Michael Chisamore, <sup>11</sup>Paul D Kassner, <sup>11</sup>Dirk G Brockstedt, <sup>12</sup>Rakesh Kumar Goyal, <sup>11</sup>Nicole Nasrah, <sup>11</sup>William Ho. <sup>1</sup>Seoul National University Hospital, Seoul, Republic of Korea; <sup>2</sup>Ramathibodi Hospital, Mahidol Univ., Bangkok, Thailand; <sup>3</sup>Chungbuk National University Hospital, Cheongju, Republic of Korea; <sup>4</sup>Comprehensive Hematology Oncology, St. Petersburg, FL, USA; <sup>5</sup>National Taiwan University Hospital, Taipei, Taiwan; <sup>6</sup>Moffitt Cancer Center, Tampa, FL, USA; <sup>7</sup>Chi Mei Medical Center, Tainan, Taiwan; <sup>8</sup>National Cheng Kung University Hospital, Tainan, Taiwan; <sup>9</sup>Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; <sup>10</sup>Merck and Co., Inc., Rahway, NJ, USA; <sup>11</sup>RAPT Therapeutics, Inc., South San Francisco, CA, USA; <sup>12</sup>RAPT Therapeutics, Redwood City, CA, USA

**Background** FLX475 (tivumecirnon) is a selective CCR4 antagonist designed to block the recruitment of immunosuppressive regulatory T cells (T<sub>reg</sub>) into the tumor microenvironment. The FLX475-02 trial (NCT03674567) is a phase 1/2 study of FLX475 as monotherapy and in combination with pembrolizumab in subjects with advanced cancer. Early encouraging data on the biologic effects, safety and antitumor activity of FLX475 have previously been presented.<sup>1-4</sup> We now present the results from the completed Phase 2 cohort of combination therapy in subjects with non-small cell lung cancer (NSCLC) not previously treated with checkpoint inhibitor (CPI-naïve).

**Methods** Subjects with CPI-naïve, locally advanced or metastatic NSCLC received FLX475 100 mg orally once daily with pembrolizumab (200 mg IV Q3 weeks). The primary study objectives were safety and tolerability, and antitumor activity. The primary efficacy endpoint was objective response rate (ORR), based on RECIST 1.1 criteria. Additional efficacy endpoints included progression-free survival (PFS). Data cutoff was 31Aug2023.

**Results** Of the 35 subjects with relevant NSCLC histologies evaluable for response, median follow-up was 192 days (9 – 660 days) and median lines of prior therapy was 1 (0–5). As previously described,<sup>3</sup> the only adverse event determined to be specifically related to FLX475 treatment was asymptomatic and reversible QT prolongation (managed by dose reduction). Across all the subjects evaluable for response regardless of PD-L1 status (n=35), confirmed partial response (cPR) was observed in 9 (ORR: 26%). Amongst the subgroup of subjects whose tumors expressed PD-L1 (tumor proportion score [TPS] ≥1%) (n=20), cPR was observed in 7 (ORR: 35%), with an ORR of 31% (5/16) and 50% (2/4) in subjects with tumors expressing low and high levels of PD-L1 (TPS 1-49% or ≥50%), respectively. As of the data cutoff, the PD-L1 TPS ≥ 1% subgroup had a median PFS of 6.3 months with 8 subjects still on treatment.

**Conclusions** FLX475, an oral CCR4 antagonist, has previously demonstrated clear monotherapy and encouraging combination activity with pembrolizumab.<sup>2, 3</sup> In this completed Phase 2 cohort of subjects with CPI-naïve NSCLC, FLX475 in combination with pembrolizumab was shown to be well tolerated and has demonstrated encouraging clinical activity compared to pembrolizumab monotherapy in PD-L1+ NSCLC (based on historical results) – in both subjects with low (TPS 1-49%) and those with high (TPS ≥50%) PD-L1 expression – supporting the continued development of this combination therapy for NSCLC.

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**Trial Registration** ClinicalTrials.gov Identifier: NCT03674567

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**Ethics Approval** All patients provided informed consent prior to inclusion in the study, and the protocol was approved by local institutional review boards for each clinical site. IRB Name/Approval no. or ID: Advarra/20132; BSD/IRB18-1199, Columbia Research HRPO/IRB-AAAS7290; JHM/IRB00188614/CIR00077638; Mary Crowley IRB/19-06; Medical School IRB/HUM00160818; Office of Human Subject Protection/2019-0139; Office for Human Research Studies/19-282; Univ. of Louisville IRB/19.0698; UCKA HRPP/IRB#18-001513; WCG®/20181802; Asan Medical Center IRB/S2019-0624-0001; Austin Health HREC/52407/Austin-2019; Belberry HREC/2018-08-671; CREC/CPA-CREC 044/2019; CMMC IRB/10806-002; CBNUH IRB/2019-03-010-001; Chulalongkorn Univ. IRB/1148/2019; Inje Univ. BPIRB/2021-05-020; IRB of the Univ. of Hong Kong/Hosp. Authority HK West Cluster/UW 19-394, UW 21-299; Joint Chinese Univ. of Hong Kong CREC/2019.342-T; NCKUH IRB/AB-CR-108-021; NTUH EC/201905048MSB; SMC IRB/2021-04-156-001; SNU Bundang Hosp. IRB/B-2108/703-401; SNUH IRB/H-1903-158-1023; Ulsan Univ. Hosp. IRB/UUH 2019-05-012, Yonsei Univ./4-2019-0520 and Severance Hosp. IRB/4-2019-0520.

**Consent** Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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