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# Abstract CT017: A phase I study evaluating safety, pharmacokinetics, and clinical activity of the novel, paradox breaker BRAF inhibitor RG6344 in patients with BRAF V600-mutant solid tumors FREE

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## Abstract

### Background:

Clinical benefit of first generation BRAF inhibitors (BRAFi) as monotherapy is limited due to paradoxical feedback activation of downstream MAPK or EGFR; combinations with MEK inhibitors (in melanoma) or EGFR antibodies (in colorectal cancer [CRC]) have become a standard of care in BRAF V600-mutant tumors. RG6344 (RO7276389) is a novel brain penetrant paradox breaker BRAFi designed to address the limitations of approved BRAFi.

### Methods:

Dose escalation of RG6344, as a single agent and in combination with standard dose of cobimetinib, is being conducted in participants with solid tumors harboring a BRAF V600E mutation up to the protocol specified maximum daily dose. The objectives were to define the maximum tolerated dose (MTD), the recommended Phase 2 dose and additionally to characterize safety, PK/PD, and clinical outcomes (ISRCTN13713551).

### Results:

As of December 5, 2024, 66 patients (56% with prior BRAFi treatment), including 7 patients with non-measurable brain lesions, have been treated with RG6344 in the monotherapy dose escalation part of the study and 12 patients in the combination part with cobimetinib including 5 patients with measurable and one with non-measurable brain lesions. Eleven melanoma, 51

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CRC, 4 patients with other cancers received at least one dose of study drug as a single agent (dose escalation in combination still ongoing and not reported). One dose limiting toxicity event of grade 3 rash maculo-papular was reported. MTD has not been reached up to the highest daily dose of 3600 mg. Grade 3 treatment-related AEs (TRAEs) occurred in 11 patients (16.6 %), grade 4 TRAEs in 2 patients (3%; both laboratory findings) and no grade 5 TRAEs were reported. 2 patients (3%) discontinued study treatment due to TRAEs. None of the known BRAFi class toxicities, such as cutaneous squamous cell carcinomas, including Palmar-Plantar Erythrodysesthesia (PPE) and keratoacanthoma, have been observed to date. Linear and time-independent PK was demonstrated across the tested dose range, reaching Ctrough levels exceeding PK-derived pERK inhibition >90%. Exposure -response (metabolic responses measured with FDG-PET) relationship was observed. Objective response rate (ORR) was 25% in a total of 64 evaluable patients across tumor types and doses including patients with brain metastases and/or refractory to or relapsing on prior BRAFi treatment.

## Conclusions:

RG6344 is well tolerated allowing unprecedented exposure for pERK inhibition and shows promising preliminary activity.

## Citation Format:

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