FIRELIGHT: DAY101-102a, a phase 2 subprotocol of DAY101 monotherapy for patients with recurrent, progressive, or refractory solid tumors with an activating *BRAF* gene fusion

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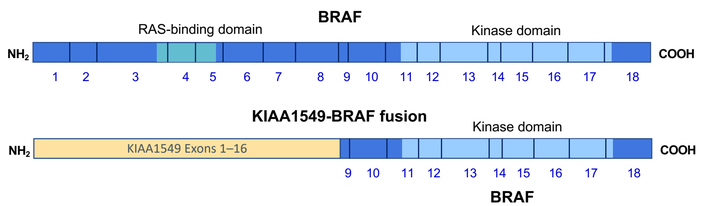
Trial in Progress Poster #128

Background

- *BRAF* fusions that retain a functional BRAF kinase domain (e.g., the *KIAA1549-BRAF* fusion; **Figure 1**) occur in approximately 0.3% of tumors, but the incidence across specific tumor types differs:[1,2]
  - *BRAF* gene fusions were identified in 3% of melanomas, 2% of gliomas, and ≤1% of thyroid, pancreatic, colorectal and non-small cell lung cancers (NSCLCs)[2]
- BRAF fusions are oncogenic and enable BRAF to signal as a constitutively active dimer independent of RAS activation[3,4]
- Currently approved RAFi are type I inhibitors with demonstrated efficacy against RAF monomers and are indicated for use in adult patients with tumors harboring a BRAF V600 mutation:[5–7]
  - Type I RAFi cause paradoxical activation of wild-type RAF, dimerization and kinase transactivation, and may increase the risk of tumor growth in BRAF fusion-driven cancers[8,9]
- DAY101(TAK-580, MLN2480, BIIB-024) is an oral, selective, central nervous system (CNS)-penetrant, type II pan-RAF inhibitor that targets both monomeric and dimeric forms of RAF[10]
- To date, >200 patients have been treated across 3 phase 1 trials (NCT01425008, NCT02327169 and NCT03429803) in adults and children with RAF alteration-driven cancers:
  - In adults with advanced solid tumors or *NRAS/BRAF*-altered melanoma, a 600 mg QW dosing schedule of DAY101 showed an acceptable safety profile and single-agent activity has been observed in patients with *BRAF*- and *NRAS*-mutant melanoma[11]
  - In the ongoing pediatric phase 1 study (PNOC014), DAY101 was well tolerated and induced a complete response (CR) or partial response (PR) with a median time-to-response of 10.5 weeks in 5 of 8 patients with pediatric low-grade glioma (LGG) and the classic *KIAA1549-BRAF* gene fusion[12]
- DAY101 was granted **breakthrough therapy designation** by the U.S. Food and Drug Administration for the treatment of pediatric patients with an advanced LGG with an activating *RAF* alteration and **orphan drug designation** for the treatment of malignant glioma

Figure 1. Example of an activating BRAF fusion



FIRELIGHT and DAY101-102a subprotocol

- DAY101 single-agent activity has been observed in patients with *BRAF*- and *NRAS*-mutant melanoma and LGG[11,12]
- **FIRELIGHT** (DAY101-102, NCT04985604), an open-label, multicenter, international, phase 1b/2a study structured as a master protocol, was designed to evaluate the safety and efficacy of DAY101 as monotherapy or in combination with other targeted therapies in recurrent, progressive, or refractory solid tumors harboring MAPK pathway aberrations
- DAY101-102a is the first phase 2, multicenter, open-label sub-study of FIRELIGHT that will evaluate the efficacy and safety of DAY101 monotherapy in adults and adolescents with tumors harboring an activating *BRAF* fusion, who have exhausted available standard of care treatments
- Patients (aged ≥12 years) will be enrolled into either a melanoma cohort or a "tissue agnostic" cohort (**Figure 2**)
- DAY101 will be administered to adult patients (aged ≥18 years) at 600 mg orally (PO) QW on days 1, 8, 15, and 22 and to patients aged 12 to <18 years, at a dose of 420 mg/m^2 PO QW
- Cycles will repeat every 28 days in the absence of radiographic evidence of disease progression, unacceptable toxicity, patient withdrawal of consent, or death
- Radiographic evaluation will be performed at the end of every 2 cycles for 1 year and every 3 cycles thereafter
- Response assessment will be performed according to the RECIST version 1.1 for solid tumors and response assessment in neuro-oncology (RANO) criteria for CNS tumors

Figure 2. FIRELIGHT subprotocol(a) study design schema

FU, follow-up; QW, once weekly.

Study objectives

Primary objective
- To evaluate the efficacy of DAY101 by RECIST v1.1 or other appropriate tumor response criteria

Secondary objectives
- To assess the safety and tolerability
- To assess additional efficacy parameters
- To characterize the tumor responses
- To characterize the PK profile
- To characterize the PD effects
- To determine the relationship between PK and PD

Exploratory objectives
- To evaluate the genomic profile of archival tumor or fresh tumor biopsies and ctDNA:
  - Pathway modulation and/or genomic alterations in tumor biopsies and/or ctDNA
  - The relationship between genomic biomarkers in archival or fresh tumor tissue and/or ctDNA and clinical efficacy
- The relationship between PK and drug effects

ctDNA, circulating tumor DNA; PD, pharmacodynamic; PK, pharmacokinetic; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1.

Key inclusion criteria

- Patients ≥12 years of age
- Histologically confirmed diagnosis of non-hematologic tumor with an activating *BRAF* fusion
- Radiographically-recurrent or radiographically-progressive disease measurable by the appropriate tumor response criteria. Imaging must be performed within 28 days prior to the initiation of treatment
- Patients must have progressed after, be intolerant of, or refused standard-of-care treatment prior to documented radiographic progression
- If brain metastases are present, they must have been previously treated and be stable as assessed by radiographic imaging (must have at least 2 images taken ≥4 weeks apart) OR, if receiving corticosteroids, they must be neurologically stable by clinical examination and be on a stable or a decreasing dose within 7 days prior to the start of the study
- Availability of archival tumor tissue or fresh tumor tissue for correlative studies
- Previous chemotherapy and hormone therapy (excluding physiologic replacement) must be completed at least 4 weeks or 5 half-lives, whichever occurs first, prior to initiation of therapy
- Previous immunotherapy/monoclonal antibody use must be completed at least 4 weeks or 5 half-lives (whichever is shorter) prior to initiation of therapy. In addition, radiation therapy to the target lesion must be completed at least 6 months prior to initiation of therapy
- All associated toxicity from previous therapies must be resolved to grade ≤1 or considered baseline prior to initiation of therapy
- ECOG performance status of 0 or 1
- Acceptable end-organ function

Key exclusion criteria

- Prior therapy with MEK and/or RAF inhibitors
- Current enrollment in any other investigational treatment study
- Known presence of concurrent activating mutations, including but not limited to *EGFR*, *ALK*, *MET*, *ROS*, and *FGFR* mutations in NSCLC; *RET* and *NTRK* in thyroid cancer; *EGFR* and *PIK3A* in colorectal cancer; *IDH1/2* and *EGFR* in glioma; and *KIT* in melanoma (genetic profile of tumor under study, if available, will be reviewed by the sponsor to confirm eligibility)
- History of central serous retinopathy, retinal vein occlusion, or ophthalmopathy present at baseline
- Unstable neurological condition, despite adequate treatment (e.g., uncontrolled seizures)
- Evidence of current uncontrolled cardiovascular conditions within the past 6 months
- Concomitant treatment with strong cytochrome P4502C8 (CYP2C8) inhibitor and/or inducers within 14 days before initiation of therapy
- Concomitant treatment with medications that are sensitive substrates of CYP2C8 and CYP2C9 or predominantly transported by breast cancer resistance protein
- Active, uncontrolled systemic bacterial, viral, or fungal infection
- History of any major disease that might interfere with safe protocol participation
- History of drug reaction with eosinophilia and systemic symptoms syndrome, Stevens Johnsons syndrome, or hypersensitivity to the investigational medicinal product
- History of second malignancy within 3 years prior to study treatment, except for curatively treated cervical cancer *in situ*, non-melanoma skin cancer, or superficial bladder cancer

Statistical methods

- Up to 43 patients will be enrolled: up to 18 patients in the melanoma cohort and up to 25 patients in the "tissue agnostic" cohort
- Simon's 2-stage design[13] will be used to determine whether DAY101 has sufficient anticancer activity to warrant further development for each cohort
- In the melanoma cohort, up to 7 patients will be enrolled in stage 1. If no patients achieve a CR or PR (confirmed or unconfirmed), then enrollment within the cohort will terminate. If at least 1 patient achieves a CR or PR, 11 additional patients will be enrolled within the cohort in stage 2:
  - The null hypothesis assumes a true overall response rate (ORR) of <10%, and an alternative hypothesis of an ORR of ≥10%. It is assumed that the true ORR is 30%. At a 1-sided alpha of <0.10, there is 80% power for this cohort
- In the "tissue agnostic" cohort, up to 10 patients will be enrolled in stage 1. If at least 2 patients achieve a CR or PR, an additional 15 patients will be enrolled within the cohort in the second stage:
  - The null hypothesis assumes a true ORR of <10% and an alternative hypothesis of an ORR of ≥10%. It is assumed that the true ORR is 30%. At a 1-sided alpha of <0.1, there is 81% power for this cohort
- For the primary analysis of the primary endpoint, for both cohorts, a 90% exact confidence interval will be calculated. Success will be achieved if the lower bound of the confidence interval is >10%

Outcome measures

Primary endpoint: ORR as the proportion of patients with the best overall confirmed response of CR or PR according to the appropriate response assessment criteria for the disease setting (RECIST v1.1 or RANO criteria)

Secondary endpoints: incidence and severity of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events version 5), change from baseline in targeted vital signs and targeted clinical laboratory test results, duration of response (DOR), duration of progression-free survival, duration of overall survival, time to response, comparison of DOR in patients with CR or PR, plasma concentration of DAY101, MAPK pathway signaling, and the relationship between pharmacokinetic (PK) and pharmacodynamic biomarkers

Exploratory endpoints: pathway modulations and/or genomic alterations from tissue biopsies or ctDNA, the relationship between genomic biomarkers and/or ctDNA and efficacy, and the relationship between PK and efficacy or safety endpoints

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