Phase 3 study of ivosidenib vs placebo in locally advanced or metastatic IDH1-mutant conventional chondrosarcoma untreated or previously treated with 1 systemic treatment regimen (CHONQUER)

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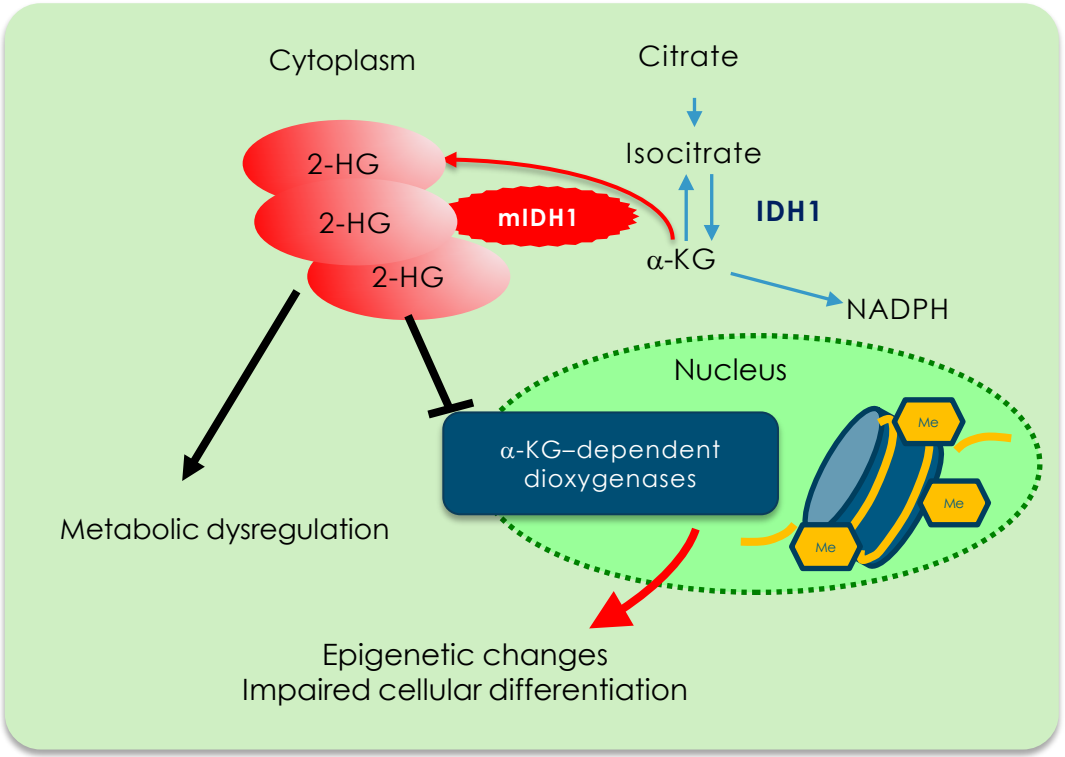
Declaration of conflict of interest for William D. Tap:
Leadership (Atropos; Certis Oncology Solutions; Innovo Therapeutics), Stock and Other Ownership Interests (Atropos; Certis Oncology Solutions), Consulting or Advisory Role (Adcendo; Amgen; AmMax Bio; Ayala Pharmaceuticals; Bayer; BioAtla; Boehringer Ingelheim; Cogent Biosciences; Daiichi Sankyo; Deciphera; Epizyme; Foghorn Therapeutics; inhibrx; Kowa Pharmaceutical; Lilly; Medpacto; Servier), Research Funding (AmMax Bio (Inst); Avacta Life Sciences (Inst); BioAtla (Inst); Blueprint Medicines (Inst); C4 Therapeutics (Inst); Cogent Biosciences (Inst); Daiichi Sankyo (Inst); Deciphera (Inst); Theseus Pharmaceuticals (Inst)), Patents, Royalties, Other Intellectual Property (Companion Diagnostic for CDK4 inhibitors - 14/854,329; Enigma and CDH18 as companion Diagnostics for CDK4 inhibition – SKI2016-021-03)

Role of IDH mutations in chondrosarcoma

mIDH in Chondrosarcoma

- Isocitrate dehydrogenase 1 mutation (m*IDH*1) occurs in ~40% of patients with chondrosarcoma and prevalence increases with tumor grade[1]
- IDH mutation is a key initiator of disease[2] and causes
  - Overproduction of the oncometabolite D-2-hydroxyglutarate (2-HG)
  - Aberrant DNA methylation patterns and alterations in gene expression
  - mIDH represents and early genetic event implicating its potential as a therapeutic vulnerability[3]

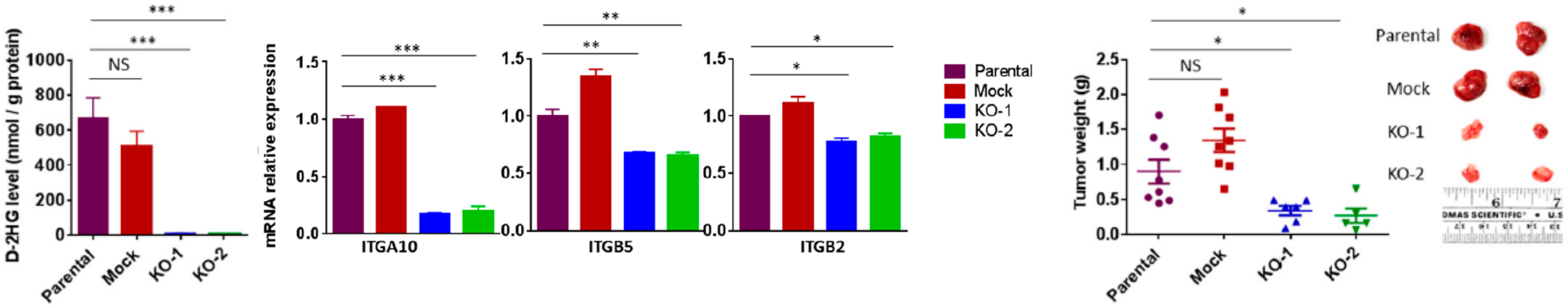


References
1. Vuong HG et al. *Cancer Med*. 2021;10(13):4415-4423. 2. Cross W et al. *Genome Med*. 2022;14(1):99. 3. Tinoco G et al. Am Soc Clin Oncol Educ Book 35, e648-e655(2015).

Targeting IDH mutations in chondrosarcoma

Targeting mIDH1

- Ivosidenib is a selective, oral, potent inhibitor of mIDH1 enzyme
- Approved in heme and solid tumor indications (e.g. AML, MDS, CCA)
- Inhibition or elimination of mIDH results in loss of 2-HG[1,2], downregulation of integrins[2], and *in vitro* antitumor activity[2]

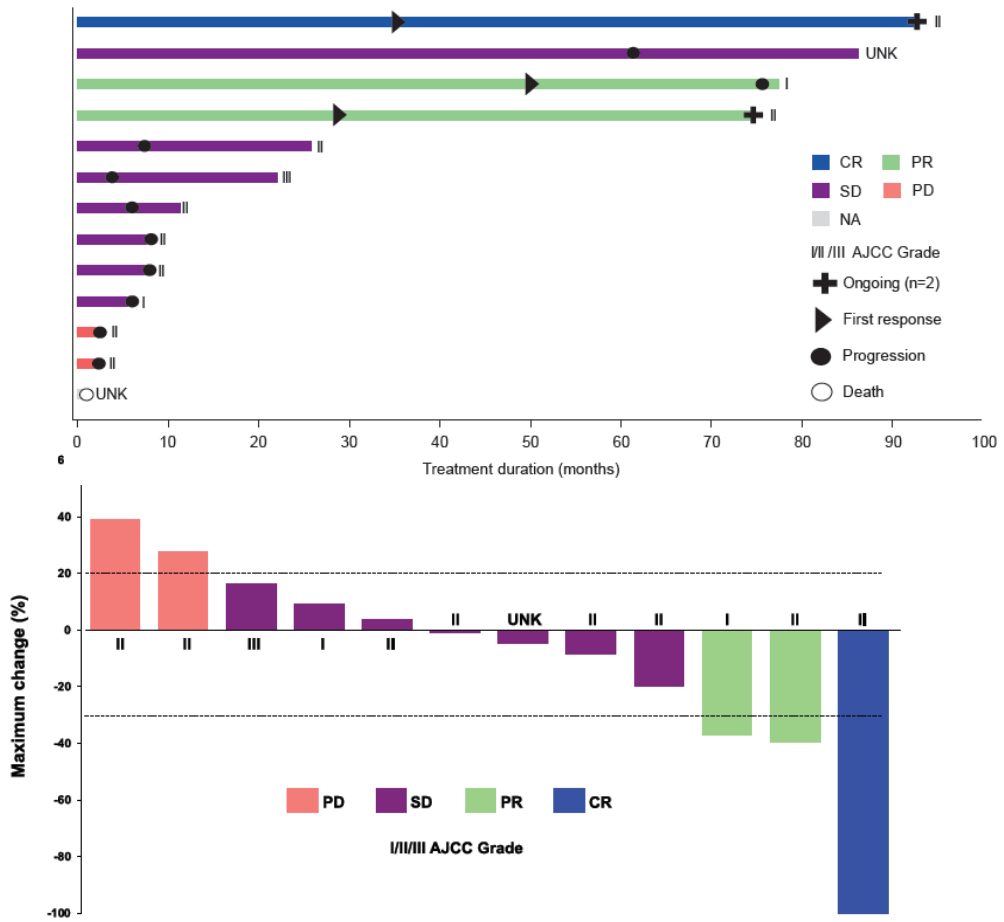


References
1. Li L et al. *PLoS One*. 2015;10(9):e0133813. 2. Li L et al. Cancers (Basel). 2020 Jan 6;12(1):141.

Phase 1 study in patients with conventional chondrosarcoma
(data cut-off of 15 September 2022)

- Long-term safety and efficacy analysis of the subgroup of patients with advanced conventional chondrosarcoma (n=13) ivosidenib demonstrated[1]
  - **Manageable toxicity** with mostly grade 1 or 2 treatment emergent adverse events
  - **Overall response rate:** 23.1% (2 PR and 1 CR occurring after 2 years of treatment)
  - **Median treatment duration:** 11.3 months (range: 0.5-92.6)
  - **Median duration of response:** 42.5 months (range: 25.8–51.8 months)
  - **Median progression-free survival:** 7.4 months (95% CI: 2.0-61.3)

Long-term analysis showing treatment duration (A) and best percentage change from baseline in target lesion measurement (B)



As per RECIST v1.1, SD occurring with <42 days of the first dose is assigned as UNK. AJCC Grade at screening

References
1. Tap WD et al. Presentation at ASCO 2023. Manuscript under development.

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NA, not assessed; UNK, unknown. As per RECIST v1.1, SD occurring with <42 days of the first dose is assigned as UNK. AJCC Grade at screening

Phase 3 CHONQUER Trial Rationale

- Unmet medical need for this population, absence of a standard of care
- IDH1 mutations in conventional chondrosarcoma supports a targeted therapeutic approach
- Positive clinical activity signal for ivosidenib monotherapy in conventional chondrosarcoma patients in the phase 1 trial
- Well tolerated safety profile in the phase 1 trial aligned with the broader knowledge of ivosidenib's safety across indications (heme and solid tumors)

Phase 3 CHONQUER Trial Design

Key eligibility criteria

- Conventional chondrosarcoma grades 1, 2, or 3
- Locally advanced or metastatic disease
- Not eligible for curative resection
- Centrally confirmed IDH1 mutation
- Radiographic RECIST v1.1 disease progression or recurrence
- 0 or 1 prior systemic treatment regimen for advanced / metastatic setting
- ECOG PS 0-1

1:1

Double-blind randomization **(N=136)**

Ivosidenib
500 mg orally
Continuous 28-day cycles
(n=68)

Crossover from placebo to ivosidenib is possible when radiographic progressive disease is confirmed by the BICR

Matched placebo
(n=68)

Primary Endpoint

- Imaging-based PFS per BICR (grade 1 & 2 patients)

Key Secondary Endpoints

- PFS (BICR) in all randomized patients
- OS in grades 1 & 2 patients
- OS in all randomized patients

Other Secondary Endpoints

- PFS – based on Investigator assessment
- OR
- DoR
- Time to Response
- DC
- DoDC
- Safety
- HRQoL
- PK/PD

BICR, blinded independent central review; **DC,** disease control; **DoDC,** duration of disease control; **DoR,** duration of response; **HRQoL,** health-related quality of life; **IDH,** isocitrate dehydrogenase; **OR,** objective response; **OS,** overall survival; **PFS**, progression-free survival; **RECIST,** Response Evaluation Criteria in Solid Tumours;

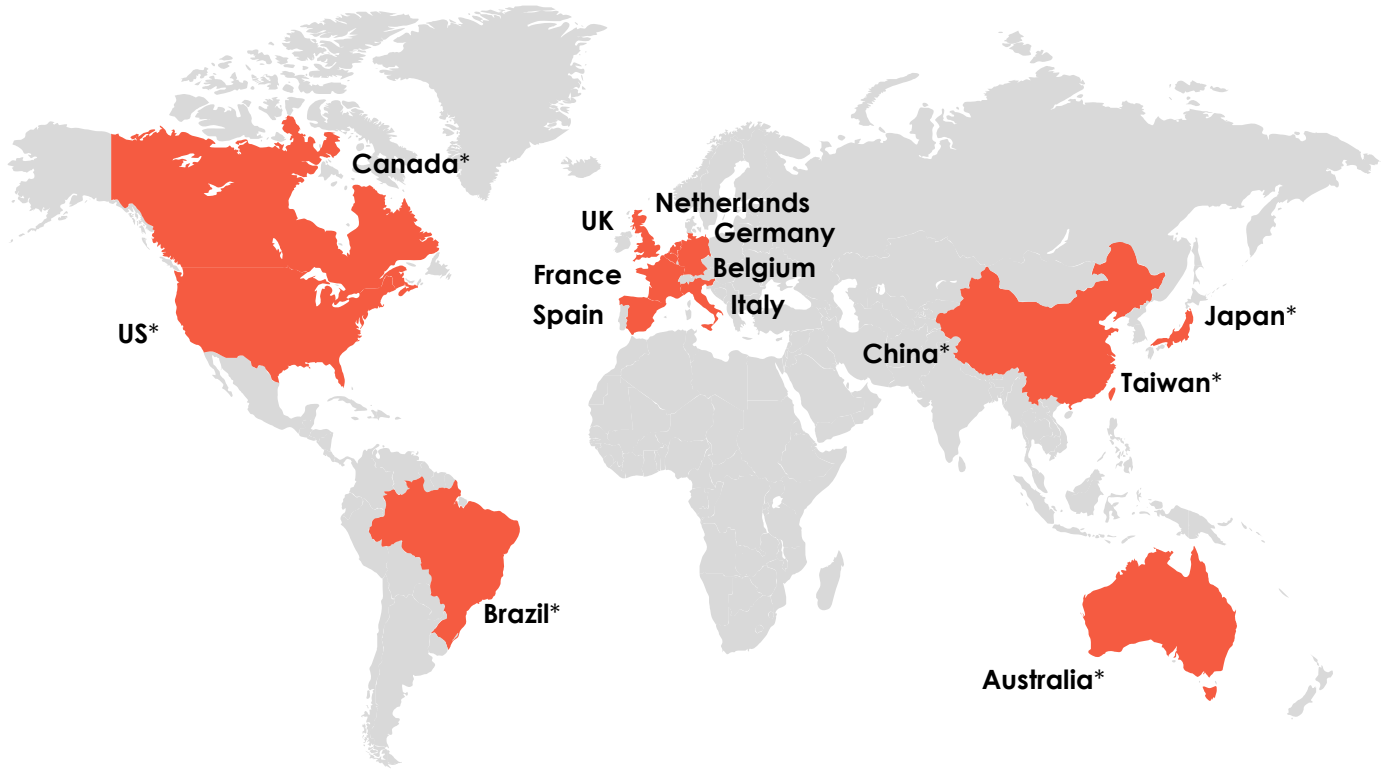
1. NCT06127407. US National Library of Medicine. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT06127407. Accessed February 20, 2024.

CHONQUER: Overview of Study Sites and Timelines

Study Start Date
July 9, 2024

Estimated Primary Completion
February 2028

Estimated Study Completion
November 2030



Estimated enrollment: **136**

*Sites currently open.

1. NCT06127407. US National Library of Medicine. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT06127407. Accessed August 20, 2024.

Acknowledgments

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