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A phase 1 study of AG-120, an IDH1 mutant enzyme inhibitor: results from the chondrosarcoma dose escalation and expansion cohorts

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BACKGROUND

- Mutations in the metabolic enzymes isocitrate dehydrogenase 1 and 2 (IDH1, IDH2) confer a gain of function, leading to elevated levels of the oncometabolite D-2-hydroxyglutarate (2-HG).[1,2]
- 2-HG accumulation results in epigenetic dysregulation and a block in cellular differentiation, leading to oncogenesis.[3,4]
- IDH mutations occur in multiple hematologic and solid tumors, including >50% of chondrosarcomas,[5] which account for approximately one-third of bone malignancies.
- In addition to their occurrence in conventional chondrosarcomas, IDH mutations have been detected in 50% of dedifferentiated chondrosarcomas, but not in clear cell or mesenchymal chondrosarcomas.[6]
- In chondrosarcomas, ~90% of the IDH mutations are in IDH1.[5]
- Primary management of both local and metastatic chondrosarcoma involves surgical resection. Radiotherapy can be used following incomplete resection or for symptom palliation; chemotherapy may have a role in dedifferentiated disease. Clinical trials are recommended for systemic recurrence.[7]
- AG-120 is a first-in-class, potent, oral inhibitor of mutant IDH1 (mIDH1) that is being assessed in an ongoing phase 1 study of solid tumors, including chondrosarcoma.

OBJECTIVE

- A phase 1 study of AG-120 in mIDH1 advanced solid tumors to determine safety, tolerability, maximum tolerated dose and/or recommended phase 2 dose; to characterize pharmacokinetics and pharmacodynamics; and to determine preliminary clinical activity.

METHODS

- A phase 1, multicenter, open-label, dose escalation and expansion study (ClinicalTrials.gov NCT02073994).
  - Subjects with advanced cholangiocarcinoma, chondrosarcoma, glioma and other advanced solid tumors were enrolled in the dose escalation phase and four expansion cohorts.
  - The dose escalation phase is now complete.
- Here we report data from subjects with chondrosarcoma enrolled in the dose escalation and expansion cohorts.

Participants

- Subjects with mIDH1 advanced solid tumors, an Eastern Cooperative Oncology Group (ECOG) score of 0–1, and measurable disease (by Response Evaluation Criteria In Solid Tumors [RECIST] 1.1) that has recurred or progressed following standard therapy are eligible.
- IDH mutation status was determined locally by participating sites.
- For the chondrosarcoma expansion cohort, disease was required to be either locally advanced or metastatic and not amenable to complete surgical excision.

Treatment

- AG-120 was escalated in a standard 3+3 design from 100 mg twice daily (BID) up to 1200 mg once daily (QD), dosed in 28-day cycles (N=164 total subjects).
- Based on safety, tolerability and pharmacokinetic/pharmacodynamic data from the dose escalation phase, the 500 mg QD dose was selected for four expansion cohorts (mIDH1 recurrent or progressive chondrosarcoma, cholangiocarcinoma, nonenhancing glioma and other solid tumors not otherwise eligible for the other tumor-specific cohorts).

Assessments

- Response was assessed every 8 weeks according to RECIST 1.1.
- Plasma, archived tissue and optional tumor biopsies were collected for exploratory analyses.
- Pharmacokinetic assessments were conducted.

RESULTS

Study status and subject characteristics

- As of 23 September 2016, 21 subjects with chondrosarcoma had been enrolled in the dose escalation (n=12) and expansion cohorts (n=9) and seven remain on treatment.
- Reasons for discontinuation were adverse event (AE) (n=1), death (n=2), progression of disease (n=10) and withdrawal by subject (n=1).
- Doses received were 100 mg BID, and 300, 400, 500, 600, 800, 900 and 1200 mg QD.

Table 1. Subject demographic/baseline characteristics

Characteristic	Chondrosarcoma (n=21)
Women/men, n	8/13
Age in years, median (range)	55 (30–88)
ECOG status at baseline, n (%)	
0	9 (43)
1	12 (57)
Subtype, n (%)	
Dedifferentiated	6 (29)
Other	13 (62)
Unknown	2 (9)
Tumor grade 1 / 2 / 3 at screening[a], n	3 / 8 / 4
IDH1 mutation R132C / R132G / R132L[b], n	11 / 3 / 2
Prior systemic therapy, n (%)	11 (52)
Number of lines, median (range)	1 (1–5)
Prior surgery, n (%)	12 (57)
Prior radiotherapy, n (%)	7 (33)
Prior chemotherapy, n (%)	5 (24)

[a]Unknown or missing for 6 subjects
[b]Missing for 4 subjects, 1 subject had an IDH2 mutation

Safety

- No dose-limiting toxicities were reported.
- Grade ≥3 AEs were observed in 11 subjects (52%); one event was considered to be possibly treatment related (hypophosphatemia).
- Median treatment duration was 2.6 months (range, 0.0–24.4).

Table 2. Most common AEs (≥3 subjects) regardless of attribution

AE	Chondrosarcoma (n=21)	
	Any grade, n (%)	Grade ≥3, n (%)
Diarrhea	6 (29)	0
Nausea	5 (24)	0
Decreased appetite	4 (19)	0
Electrocardiogram QT prolonged	4 (19)	0
Fatigue	4 (19)	0
Anemia	3 (14)	1 (5)
Blood alkaline phosphatase increased	3 (14)	1 (5)
Edema peripheral	3 (14)	1 (5)

AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03

Pharmacokinetics

- Plasma AG-120 exposure was well above the projected efficacious level based on a xenograft mouse model.
- Long mean terminal half-life from 66.8 to 86.5 hr supports QD dose regimen.

Clinical activity

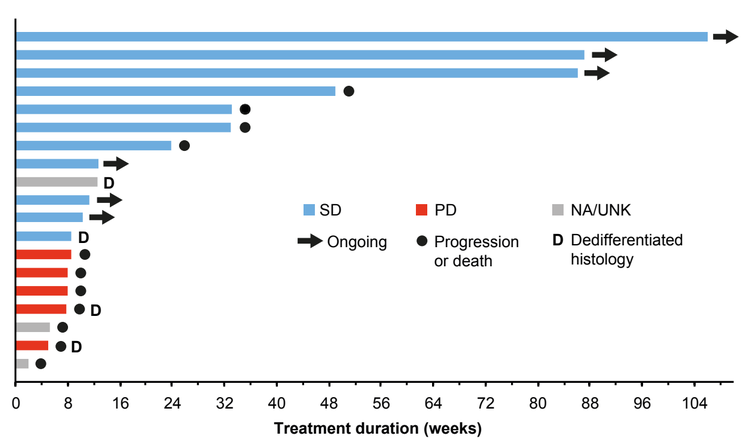
- Of the 20 efficacy evaluable subjects with chondrosarcoma, 55% experienced stable disease (SD) as their best overall response (**Table 3**, **Figure 1**).
- The 3-month progression-free survival rate was 58%.
- The best % change in sum of the longest diameter (SLD) of the target lesion is shown in **Figure 2**.
- Scans showing tumor shrinkage after AG-120 treatment in a subject with chondrosarcoma are shown in **Figure 3**.
  - 59-year-old man with mIDH1R132L, stage IV, grade 2, conventional chondrosarcoma.
  - Prior hemipelvectomy with fixation followed by adriamycin and cisplatin chemotherapy and most recently pazopanib, with a best overall response of progressive disease (PD).
  - Subject received AG-120 for 343 days in total, with stabilization of disease involving the left pelvis and reduced fluorodeoxyglucose (FDG) avidity on positron emission tomography–computed tomography (PET-CT) at Cycle 5 Day 1 (**Figure 3**).

Table 3. Best overall response (efficacy evaluable subjects[a])

Characteristic	Chondrosarcoma (n=20)
Best response, n (%)	
SD	11 (55)
PD	6 (30)[b]
Unknown/not assessed[c]	3 (15)
Progression-free survival rate at 3 months, %	58

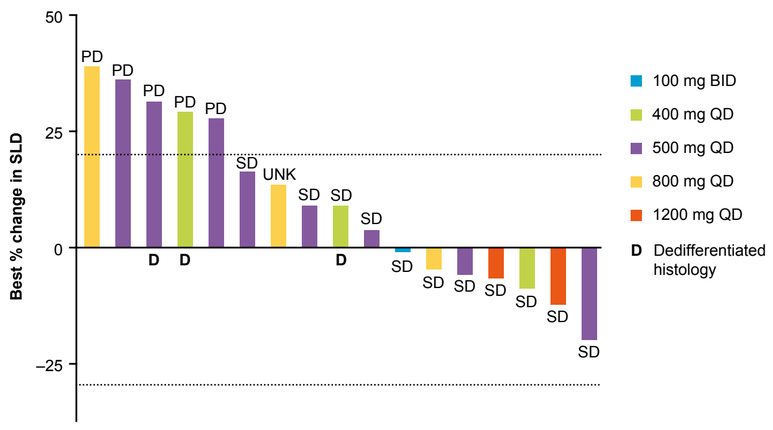
[a]Includes subjects who had baseline and at least one postbaseline tumor assessment or discontinued prematurely
[b]One subject with PD had an IDH2 mutation
[c]Unknown = subjects with SD per RECIST for <6 weeks; not assessed = subjects who discontinued prior to response assessment or were missing RECIST assessment at the time of the data cutoff

Figure 1. Duration on treatment



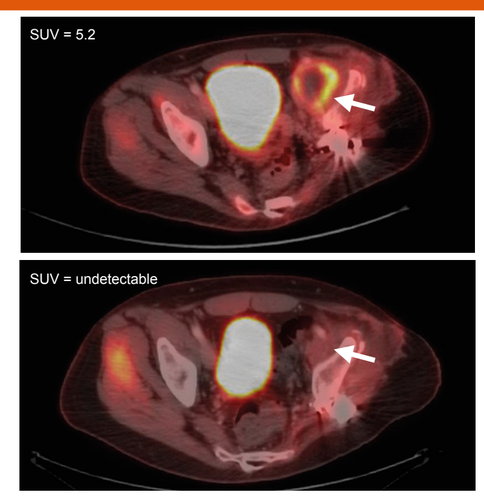
Excludes subject with IDH2 mutation
NA = not assessed
UNK = unknown

Figure 2. Best % change in SLD of the target lesions



Dotted lines show RECIST thresholds for PD (20% growth) and partial response (30% shrinkage)
Data not available for 2 subjects, excludes subject with IDH2 mutation

Figure 3. Improvement in FDG-avid disease after 4 cycles of AG-120 in a subject with metastatic chondrosarcoma



PET-CT at screening (**A**) and at Cycle 5 Day 1 (**B**). Subject achieved SD as best response and remained on AG-120 for 343 days (49 weeks)
SUV = standardized uptake value
Courtesy of William Tap

Exploratory analyses

- Plasma 2-HG inhibition was observed in all subjects with chondrosarcoma, with consistent and substantial 2-HG inhibition in plasma after multiple doses.
- Plasma 2-HG levels were reduced to those seen in healthy volunteers (up to 94.6% inhibition; **Figure 4**).
- In three subjects who underwent on-study tumor biopsies, substantial reduction of 2-HG was observed in tumor compared with baseline (up to 99.7% inhibition).
- Archived screening formalin-fixed paraffin-embedded samples from six subjects with chondrosarcoma were genotyped by Foundation Medicine (FoundationOne assay).
  - Genes with known/likely oncogenic mutations detected are shown in **Figure 5**.
  - Of the six samples that were centrally tested, mIDH1 was confirmed in five subjects.

Figure 4. Mean (standard deviation) plasma 2-HG inhibition

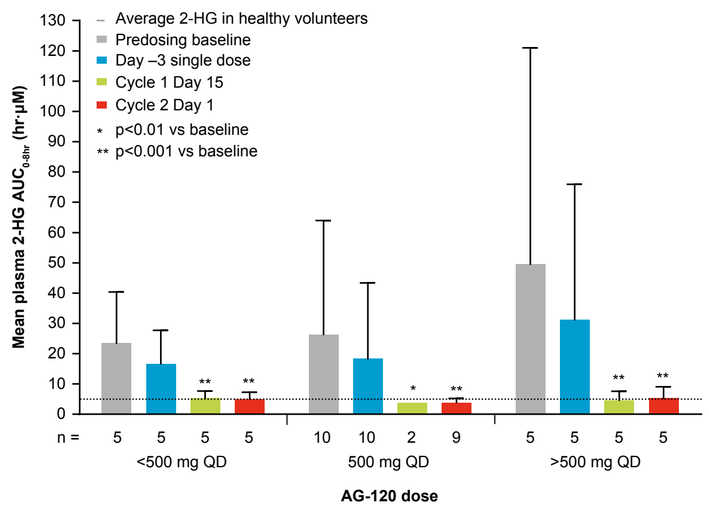
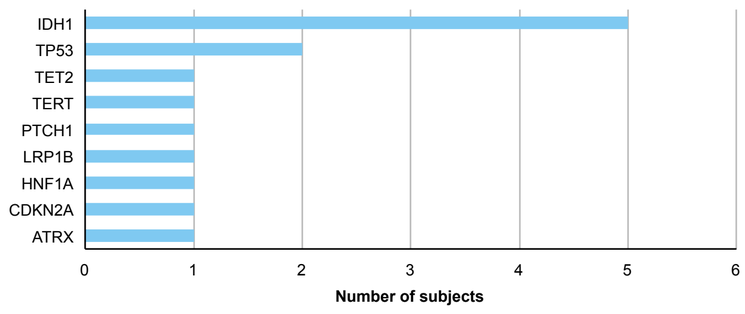


Figure 5. Co-occurring mutations in chondrosarcoma (n=6)



Subject	mIDH	Known/likely mutations
1	IDH1-R132C	TP53 V274F, ATRX S2116fs*7
2	IDH1-R132C	PTCH1 N97fs*43, LRP1B trunc, HNF1A R272H, CDKN2A loss
3	IDH1-R132C	TP53 E258D, TET2 Q916*, TERT promoter
4	IDH1-R132C	–
5	IDH1-R132C	–
6	None	–

COL2A1 is not included in the panel

CONCLUSIONS

- AG-120 was well tolerated in this pretreated chondrosarcoma population.
- AG-120 showed encouraging evidence of clinical activity, with an SD rate of 55% and a 3-month progression-free survival rate of 58%.
- AG-120 resulted in significant reduction of plasma and tumor 2-HG, indicating an on-target pharmacodynamic effect.
- Further investigation of AG-120 is warranted in mIDH1 chondrosarcoma.

References

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Disclosures

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