AG-120 (ivosidenib), a first-in-class mutant IDH1 inhibitor, promotes morphologic changes and upregulates liver-specific genes in IDH1 mutant cholangiocarcinoma

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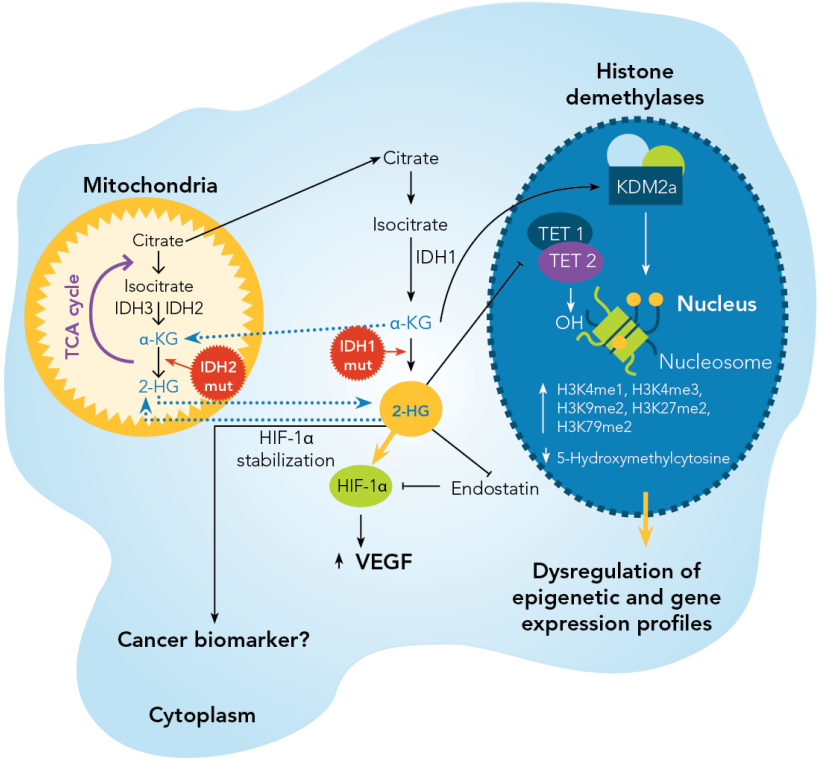
I will discuss the following off label use and/or investigational use in my presentation: ClinicalTrials.gov NCT02073994: Study of Orally Administered AG-120 in Subjects With IDH1 Mutant Advanced Solid Tumors, Including Cholangiocarcinoma

IDH1 mutations in cholangiocarcinoma

- Mutations in the isocitrate dehydrogenase 1 (IDH1) gene are detected in 13–15% of cholangiocarcinoma (CC).[1-3]
  - ~25% of intrahepatic CC
- The mutant IDH1 (mIDH1) enzyme produces the oncometabolite D-2-hydroxyglutarate (2-HG),[4,5] which leads to epigenetic dysregulation and a block in cellular differentiation.[6-9]
- AG-120 (ivosidenib) is a first-in-class, oral, potent, reversible, selective inhibitor of the mIDH1 enzyme.[10-12]

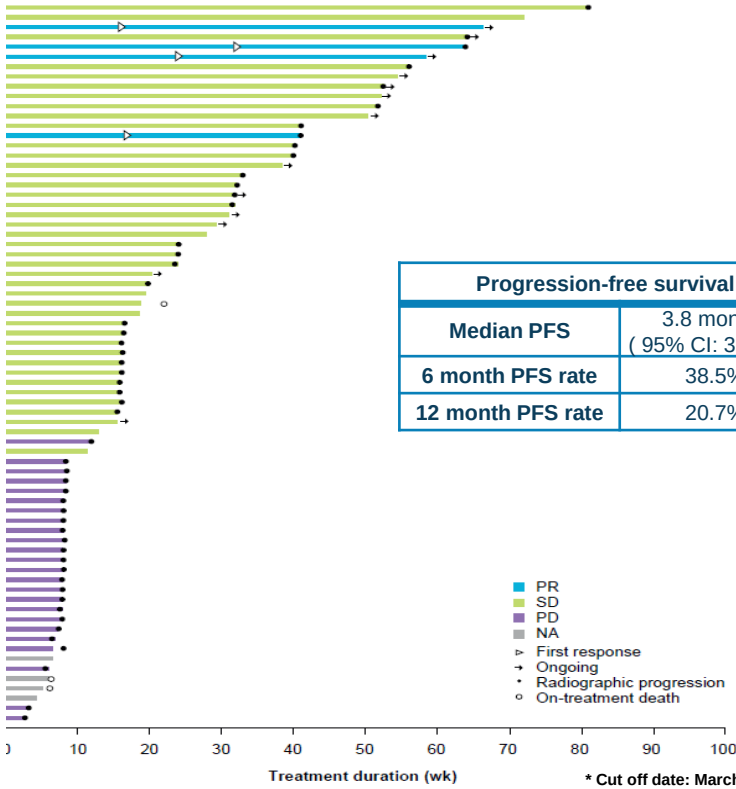


1. Goyal L et al. *Oncologist* 2015;20:1019-27. 2. Borger DR et al. *Oncologist* 2012;17:72-9. 3. Kipp BR et al. *Hum Pathol* 2012;43:1552-8. 4. Ward PS et al. *Cancer Cell* 2010;17:225-34. 5. Dang L et al. *Nature* 2009;462:739-44. 6. Saha SK et al. *Cell Cycle* 2014;13:3176-82. 7. Saha SK et al. *Nature* 2014;513:110-4. 8. Lu C et al. *Nature* 2012;483:474- 8. 9. Xu W et al. *Cancer Cell* 2011;19:17-30. 10. de Botton S et al. *Haematologica* 2015;100(s1):214;P563. 11. Fan B et al. *Haematologica* 2015;100(s1):218;P572. 12. Fan B et al. *Blood* 2015;126(23):A1310.

AG-120 in mIDH1 cholangiocarcinoma

- AG120-C-002 (ClinicalTrials.gov NCT02073994), a first-in-human phase 1 study, assessed AG-120 in patients with mIDH1 advanced solid tumors.
  - 73 patients with mIDH1 CC (median 2 prior lines of therapy).
- AG-120 was well tolerated and associated with a favorable safety profile.
  - no dose-limiting toxicities or treatment-related deaths[13,14]
- AG-120 demonstrated encouraging clinical activity in this heavily pre-treated mIDH1 CC population.[13,14]
- The exploratory objectives included the assessment of morphological and molecular changes in serial tumor biopsy samples.

Duration of treatment until progression*



Progression-free survival	
Median PFS	3.8 months (95% CI: 3.6, 7.3)
6 month PFS rate	38.5%
12 month PFS rate	20.7%

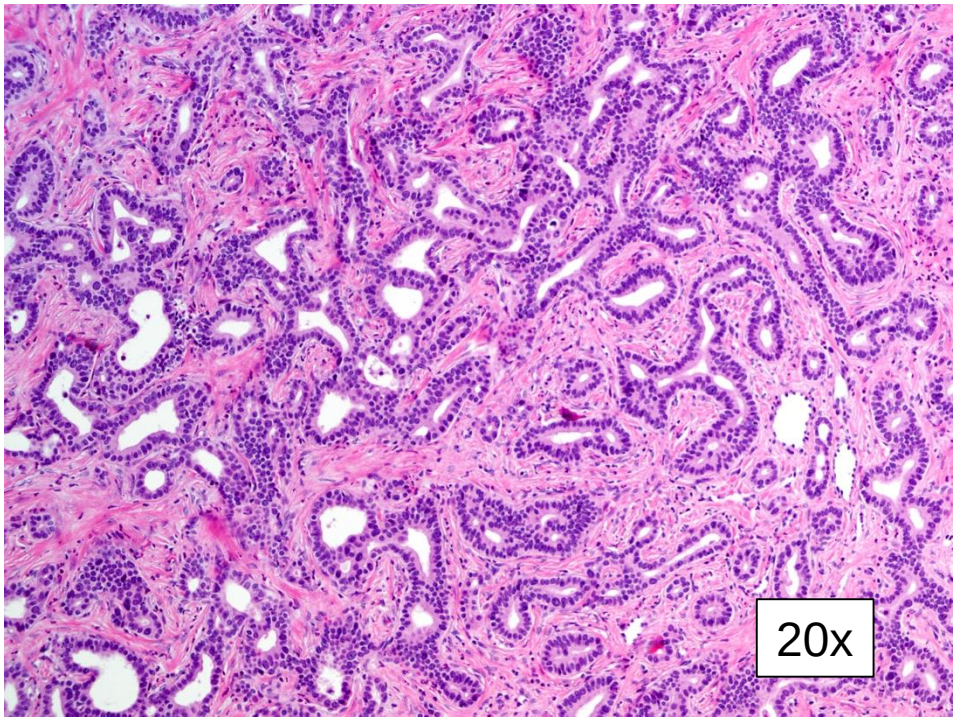
*** Cut off date: March 10, 2017**

13Lowery MA et al. *J Clin Oncol* 2017;35(Suppl):Abstr 4015. 14. Lowery MA et al. *ASCO Annual Meeting* 2017: Poster 4015.

Histological characteristics of mIDH1 CC

- A cholangiolar pattern was defined as being composed of glands with an antler-horn configuration and angulated shapes, and lined with low cuboidal epithelium.[15-17]
- Cholangiolar histology is associated with better clinical outcomes and survival rates in patients with ICC.[15,19]
- Untreated mIDH1 ICCs often show heterogeneous histoarchitecture.
  - 61% of tumors lack a dominant pattern[18]
  - Cholangiolar histology is commonly present in mIDH1 CC, but often to a limited extent (median 10% cholangiolar histology).[15,18]
- Tumor phenotype and morphologic differentiation in CC patients treated with AG-120 have not previously been examined.

Cholangiolar pattern[19]



15. Liau JY et al. *Mod Pathol* 2014;27:1163-73, 16. Komuta M et al. *Hepatology* 2012;55:1876-88. 17. Komuta M et al. *Hepatology* 2008;47:1544-56, 18. C. Sigel, unpublished data, 2017. 19. V. Deshpande, unpublished data, 2017.

Sample and data summary

Sample Collection
(n = number of patients with samples at baseline and ≥ 1 on-treatment time point)

Procedure
(n = number of patients with data available at baseline and ≥ 1 on-treatment time point)

Morphology

Hematoxylin and eosin (H&E) stained slides from FFPE tissue (n = 27)

Blinded evaluation of architectural, cytologic, and stromal patterns by two gastrointestinal pathologists (n = 17[a])

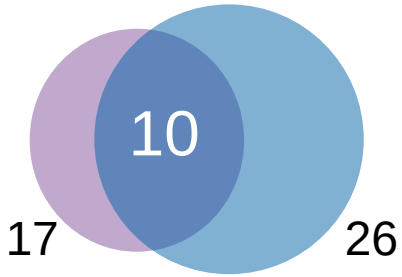
Gene Expression

Fresh frozen biopsies (n = 38)

Tumor content and assay quality control

Personalis® ACE Transcriptome™ RNAseq platform (n = 26[b])

10 patients have both morphology and gene expression data available.



[a]Includes 16 patients dosed at 500 mg QD and one patient dosed at 100 mg BID

[b]Includes 22 patients dosed at 500 mg QD, two patients dosed at 1200 mg QD, and two patients dosed at 300 mg QD

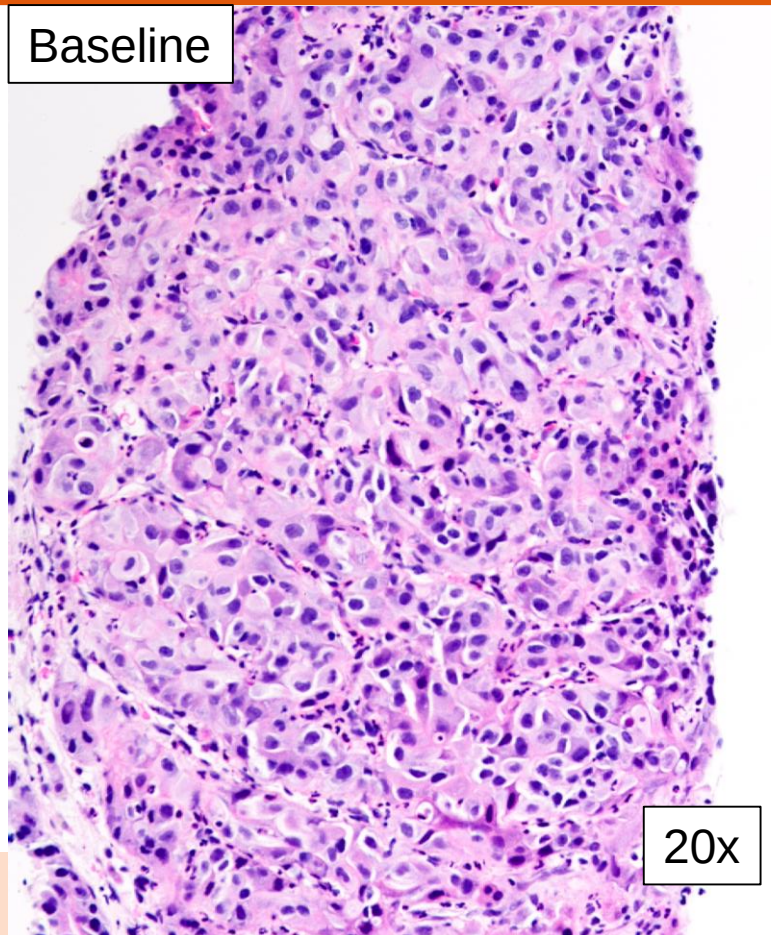
Baseline to post-dose morphologic changes in AG-120-treated mIDH1 CCs

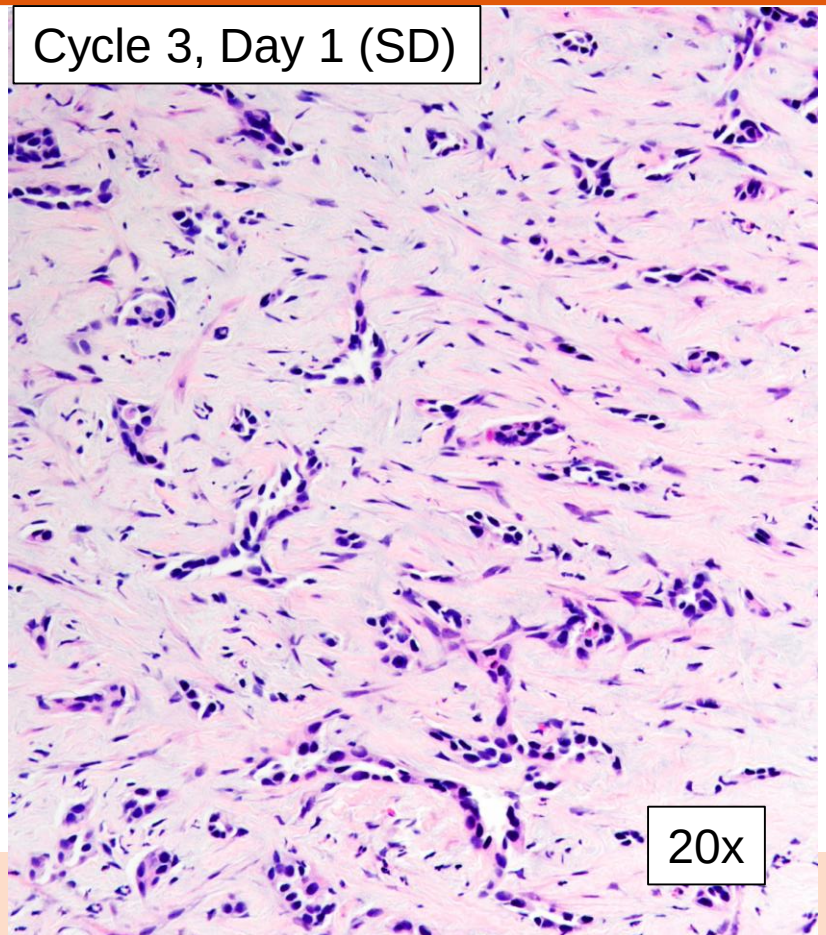
- The percentage of tumor with a cholangiolar pattern was recorded. A baseline to postdose increase was defined as a ≥20% increase in cholangiolar histology.
- The volume of cytoplasm in tumor cells was semi-quantitatively assessed.
- These morphologic changes were not associated with AG-120 dose level. All patients had plasma 2-HG reduction upon AG-120 treatment, regardless of post-dose morphology.[20]

	Morphology data available	Increase in cholangiolar histology	Cytoplasmic reduction	Cholangiolar and cytoplasmic changes
Number of patients	**17**	**5**	**9**	**4**
By treatment response[a]				
PR	3	1	3	1
SD	12	4	6	3
PD	2	–	–	–

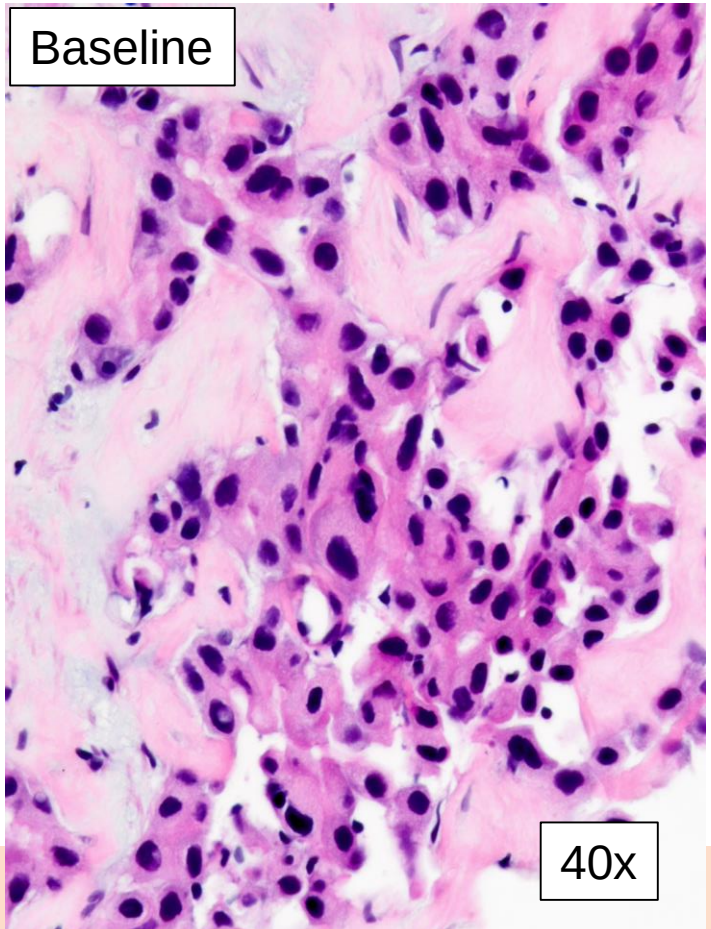
15. Liau JY et al. *Mod Pathol* 2014;27:1163-73. 20. Fan B et al. *J Clin Oncol* 2017;35(Suppl):Abstr 4082.
[a]Treatment response measured according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (PR = partial response; SD = stable disease; PD = progressive disease). The clinical data were based on a cutoff date of May 12, 2017.

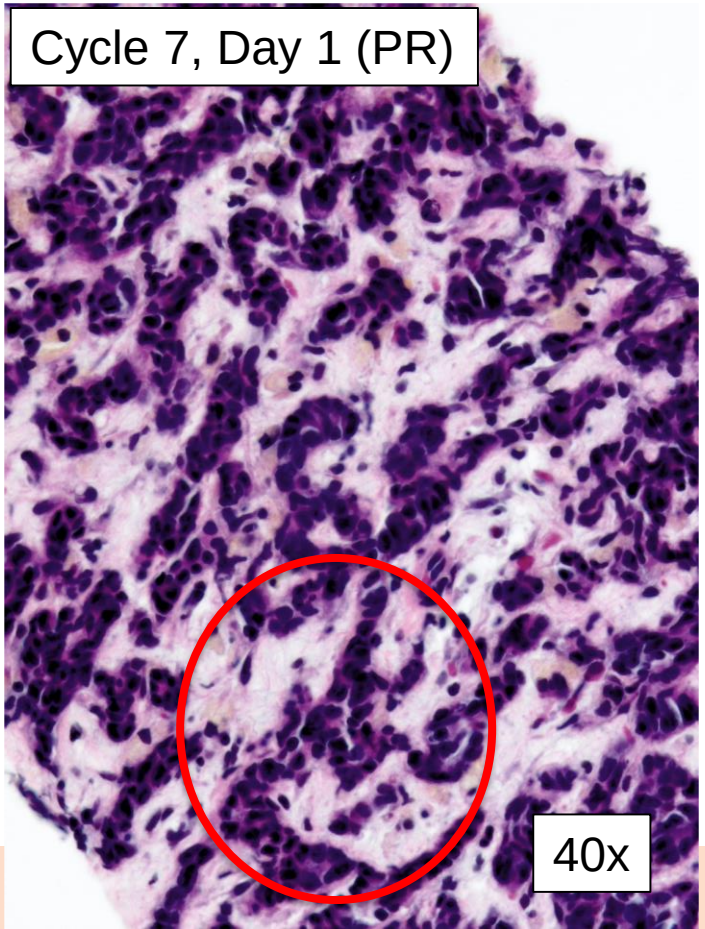
Example 1: Increased cholangiolar histology and decreased cytoplasm upon AG-120 treatment



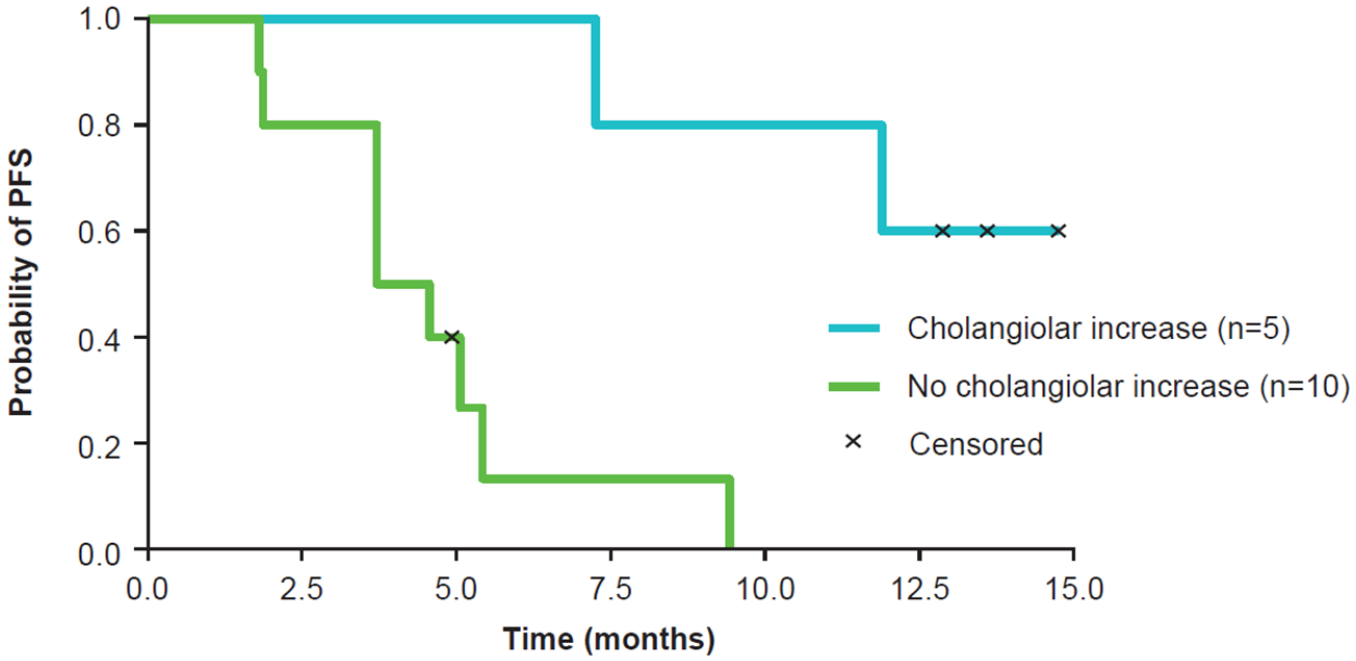


Example 2: Increased cholangiolar histology and decreased cytoplasm upon AG-120 treatment



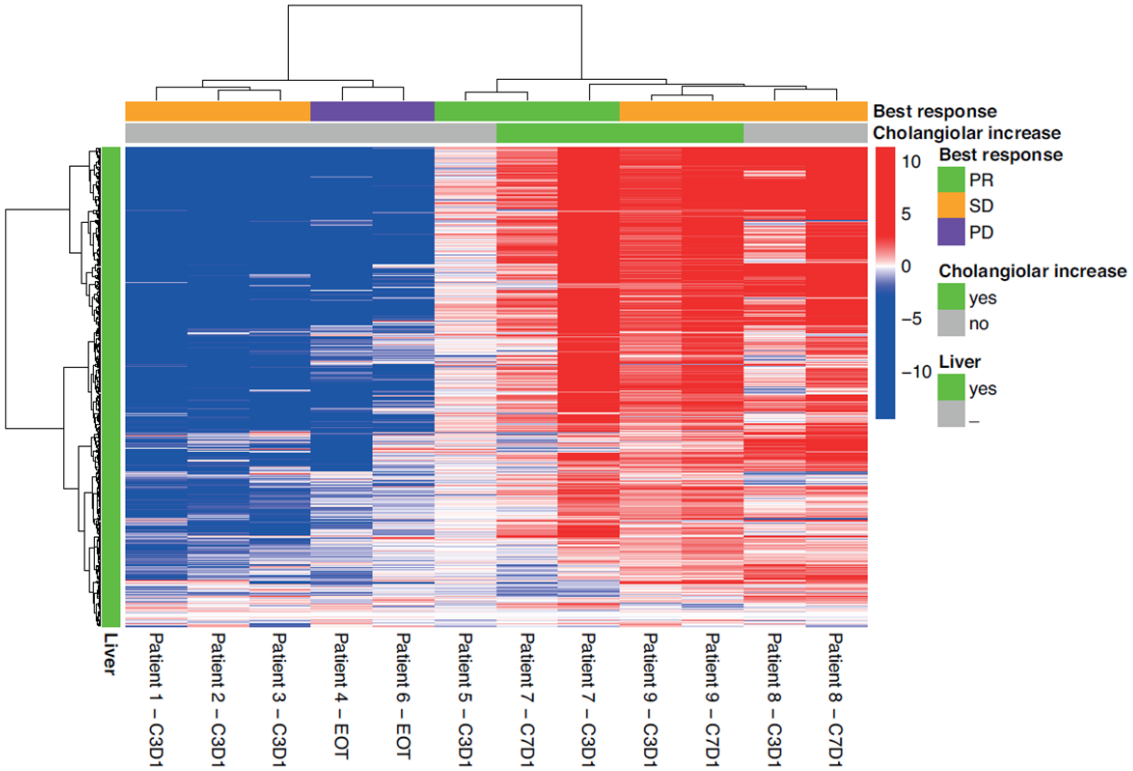


Increased cholangiolar pattern seems to be associated with increased PFS



Two patients with a 100% cholangiolar pattern at screening and post dose were excluded from this analysis, as they are expected to have better clinical outcomes and survival (Liau JY et al. *Mod Pathol* 2014;27:1163-73; V. Despande, unpublished data, 2017). [a]Defined as a ≥20% increase from screening to C3D1.

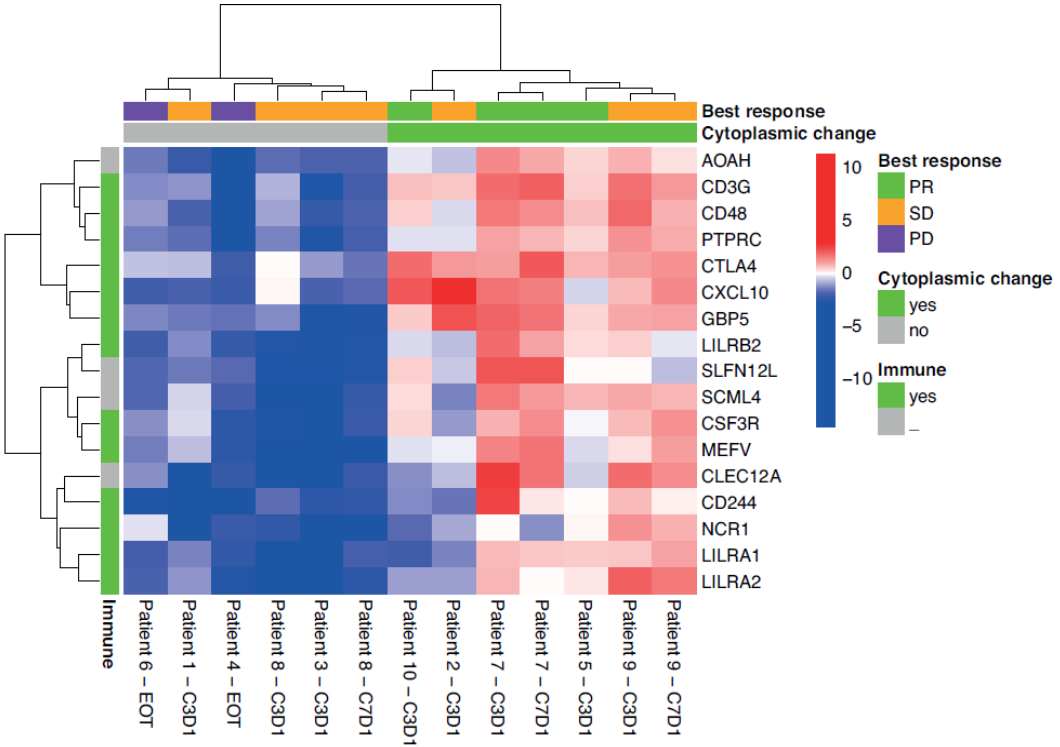
mIDH1 CCs with cholangiolar increase show upregulation of a broad set of adult liver-specific genes



- Preclinical studies have shown IDH1 mutations to block hepatocyte differentiation and promote biliary cancers.[6,7]
- Gene expression data were available for two patients with observed cholangiolar pattern increase (≥20%).
- Both showed increased expression of liver specific genes (N = 485), derived from two sources:
  - Farshidfar et al. (2017)[21]
  - Hsiao et al. (2001)[22]

Heatmap depicts log2 fold change relative to baseline.
Among those with available RNA sequencing data, one patient with a 100% cholangiolar pattern at baseline and post dose was excluded from this analysis.
Patient 8 showed a 10% increase in cholangiolar pattern. This patient had also received another mIDH1 inhibitor prior to AG-120 treatment.
21. Farshidfar et al. (2017) Cell Rep 19(13):2878-2880, 22. Hsiao et al. (2001) Physiol Genomics 7(2):97-104.

Patients with cytoplasmic decrease show increased expression of immune-response related genes



- Gene expression data were available for five patients with observed cytoplasm decrease.
- These five patients showed upregulation of multiple immune response-related genes, including CXCL10, CD3G, and CTLA4.
- In preclinical studies, IDH1m glioma showed lower expression of the chemokine CXCL10, and combined IDH1m inhibitor / vaccine treatment resulted in increased CXCL10 expression and CD8 T cell infiltration.[23]

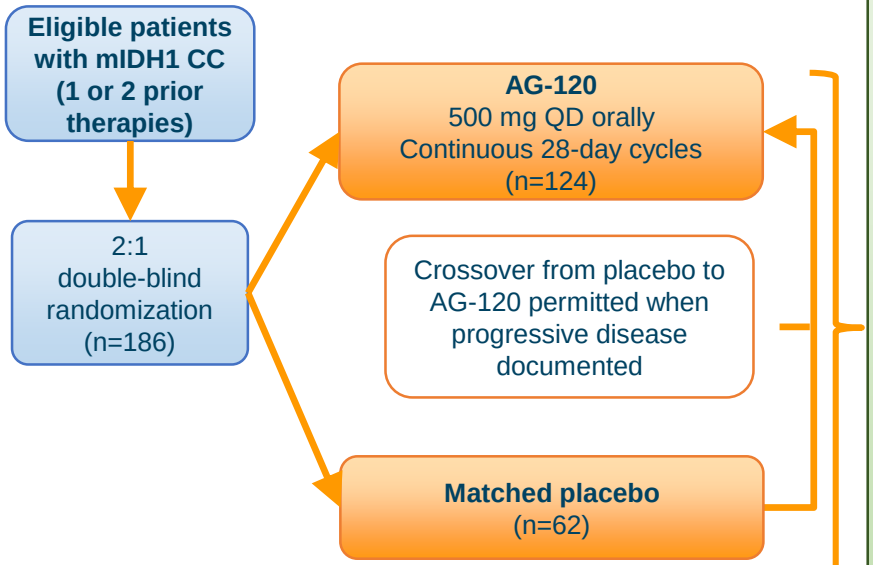
Heatmap depicts log2 fold change relative to baseline.

23. Kohanbash et al. 2017, J Clin Invest. 127(4):1425-1437.

Conclusions

- This is the first demonstration that AG-120 treatment may induce morphologic and molecular changes in a subset of mIDH1 CCs.
- Increased cholangiolar histology seems to be associated with increased PFS.
- Tumors with increased cholangiolar histology showed upregulation of genes associated with mature liver cells.
- The increased expression of immune response related genes in some tumors suggests a potential rationale for AG-120 in combination with immunotherapies.
- Given the limited sample size of this dataset, additional studies are warranted to explore the biological and clinical significance of these observations.
- AG-120 is under further evaluation in an ongoing, global, phase 3, randomized, placebo-controlled study in previously treated mIDH1 CC (ClarIDHy; ClinicalTrials.gov NCT02989857).

Phase 3 ClarIDHy Trial Design



Assessments

Primary

- Progression free survival (PFS), assessed by independent radiology center review

Secondary

- Safety and tolerability
- Overall response rate (ORR)
- Overall survival (OS)
- Duration of response (DOR)
- Time to response (TTR)
- Pharmacokinetic and pharmacodynamic analyses on plasma
- Quality of life as assessed by:
  - EORTC QLQ-C30
  - EORTC QLQ-BIL21
  - EQ-5D-5L

Exploratory:

- TBC

ClinicalTrials.gov NCT02989857
ClarIDHy.com

Acknowledgments

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