Final report of a phase I study of 2-hydroxyoleic acid (2OHOA), a novel sphingomyelin synthase activator in patients (pt) with advanced solid tumors (AST) including recurrent high grade gliomas (rHGG)

2017 ASCO ANNUAL MEETING JUNE 2-6, 2017 McCormick Place | Chicago, Illinois | ASCO.ORG
Poster #2554

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Introduction

2-Hydroxyoleic acid (2-OHOA) is an orally administered synthetic analogue of oleic acid that crosses the Blood Brain Barrier and activates sphingomyelin synthase 1 (SMS1), a key enzyme for the synthesis of different lipid classes in the cell membrane.
SMS activation results in a significant rise in the levels of sphingomyelin (SM), and reduced levels of phosphatidylethanolamine (PE) and phosphatidylcholine (PC), achieving a normalization of PE:SM ratio to the levels found in non-cancer cell membranes.
Modification of membrane lipids in cancer cells translocates Ras from the membrane to cytosol leading to inactivating the MAPK pathway, PI3K/Akt and Cyclin/CDK/E2F-1 downregulation (Fig1)

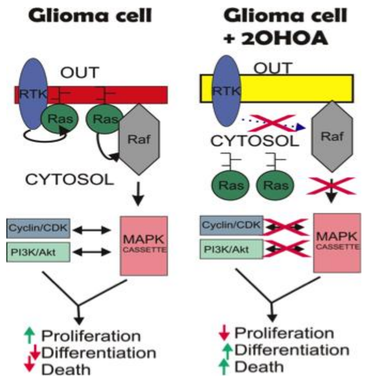
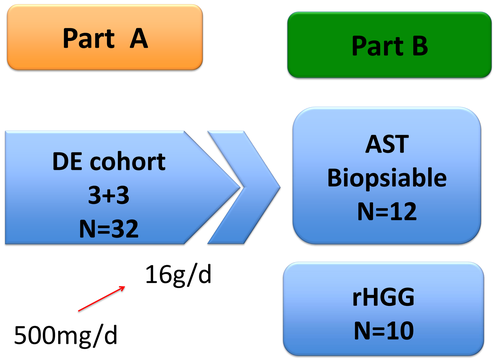


Fig 1: Left: MAPK signaling in glioma cells. **Right**: modification of cell membrane by 2-OHOA leads to downregulation of MAPK as a result of membrane-to-cytosol translocation of Ras in glioma cells

Study Background

MIN 001-1203 (NCT01792310), Ph I open label study which originally included a dose escalation (DE) and expansion cohorts (EC) conducted in AST and rHGG
In the completed EC part of the study, the 2-OHOA RP2D was established

Method



Objectives

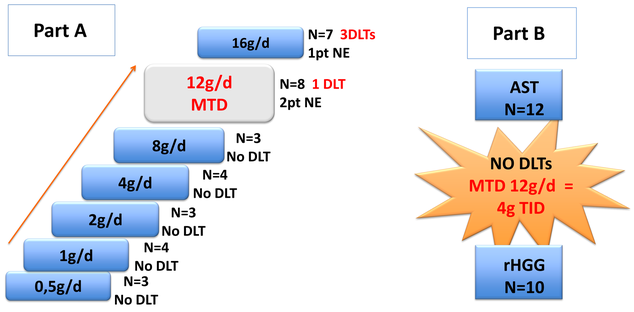
Primary objectives
To determine safety, tolerability and recommended phase 2 dose of 2-OHOA
Secondary objectives
To determine pharmacokinetic (PK) and pharmacodynamic (PD) profile and preliminary anti-tumoral activity.

Exploratory objectives
To evaluate the effect of 2-OHOA on dihydrofolate reductase (DHFR) in AST and glial fibrillary acidic protein(GFAP) in rHGG.
To study miRNA as a potential response biomarker.

Table 1: Patient characteristics

Characteristics		All patients N=54
Age (median) years Range		60 19-78
Sex, n (%)	Male Female	30 (56) 24 (44)
ECOG n (%)	0 1 2	8 (15) 43 (80) 3 (5)
Histology, n (%) Gliomas Colorectal Others		 27 (50) 14 (26) 13 (24)

Results



Pharmacokinetics

Pharmacokinetic data were available for seven dose cohorts (500mg, 1g, 2g, 4g, 8g, 12g and 16g of 2-OHOA daily; 32 eligible participants in total. PK sessions presenting known vomiting episodes were excluded from analyses. Plasma (pl) 2-OHOA levels were measured using a validated assay by using a LC-MS/MS method.
For all treatments, 2-OHOA was quantifiable and C_{max} was reached at 1 hour after administration in the fasted state. When administered under fed conditions, 2-OHOA had bioavailability comparable to that found in the fasted state, but food caused a delay in T_{max} from 1 hour to 2-4 hours. However, these are not expected to be clinically significant; therefore, 2-OHOA could be taken without regard to food.
The half-life (t1/2) derived from the 8 hours post dose concentrations [C] was between more than 1 hour to 5 hours up to 8kg/day increasing for the 2 higher doses (7 hours to 10 hours). Terminal half-life was longer than 12hours when 48h points were included in terminal elimination rate calculation (fasted state).
Following single and multiple BID dose administration of 2-OHOA under fed conditions, systemic exposure of 2-OHOA increased in proportion to dose following single and repeat BID administration in the fed state, based on the results of the power analysis (Figure 3).
After repeat BID dosing, systemic exposure (C_{max} and AUC_{last}) of 2-OHOA, increased between 1- and 1.7-fold from first dose on Day 1 to last dose on Day 21.

Safety

The most frequent AEs regardless of study drug relationship of 2-OHOA are presented in table 3. Study drug related Aes (≥10%) at any grade were diarrhea (53 [26%]), vomiting (29[14%]), nausea (26 [13%]). No G3/G4 whether regardless of study drug relationship or suspected as being study drug related occurred over 10% of patients (pt)

Table 3: Adverse events occurring related to 2-OHOA (All grades occurring ≥ 10%)

Preferred term	Dose escalation									Expansion cohorts	
	Total n (%) N= 32	G3/4 * n	0,5g/d (n=3) n (%)	1g/d (n=4) n (%)	2g/d n=3 n (%)	4g/d n=4 n (%)	8g/d n=3 n (%)	12g/d n=8 n(%)	16g/d n=7 n (%)	All grades N=22 n (%)	G3/4 grade n (%)
Diarrhea	40 (29)	2	0 (0)	3 (18)	1 (50%)	3(25)	7 (35)	11 (36)	15 (26)	13 (21)	0 (0)
Vomiting	25 (18)	1	0 (0)	3 (18)	0 (0)	2 (17)	2 (10)	5 (16)	13(23	4 (6)	0 (0)
Nausea	18 (13)	1	0 (0)	2(12)	0 (0)	3(25)	3 (15)	3 (10)	7 (12)	8 (13)	0 (0)
ALT increased	3 (2)	0	0 (0)	1 (6)	0 (0)	1(8)	0 (0)	1 (3)	0 (0)	6 (10)	0 (0)

* 1 intolerance due to multiple toxicities at 16g/d - Data cut off 15-MAY-2017

Pharmacodynamics

GFAP was assayed using a Millipore ELISA kit on plasma (pl) samples taken at baseline (B), C1D8 (4h post dose [D8 4H]) and C2D1 pre-dose. Results show a decrease in circulating GFAP between B and D8 4H sample. In more than 80% of the 15 rHGG pt a decrease was observed. The average decrease for the whole set was around 20% (n=15). This clear effect was not reproduced using C2D1 samples. Possible explanations would be: 1) GFAP modulation needs high 2-OHOA and trough is not high enough; 2) at C2D1, some of the pt (they were progressing at inclusion) had an increase in tumor volume, counter balancing GFAP decrease due to 2-OHOA.
In a subset of 22 pt, pl miRNA expression profiles in response to 2-OHOA (B / C2D1) were performed with the Affymetric GeneChip miRNA 4.0 Array. Different miRNAs differentially expressed in response to 2-OHOA in treated pt have been identified. Of those, hsa-miR-26a-5p, hsa-miR342-5p and hsa-miR-542-3p are the miRNAs with higher modulation patterns. Target genes analysis of these miRNAs is ongoing.

Figure 2: Hierarchical cluster analysis comparing small RNA expression profiles between baseline and C2D1

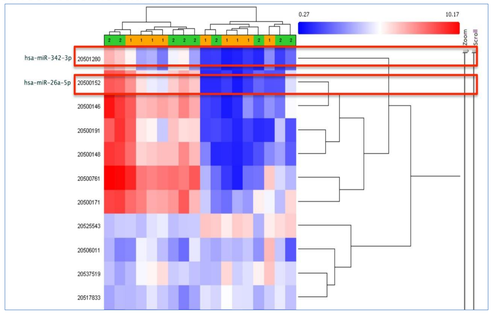
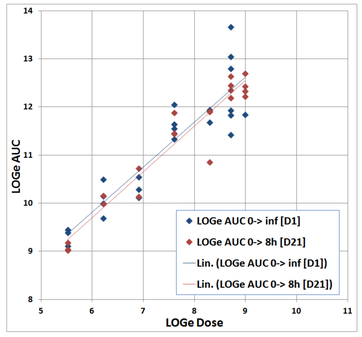


Figure 3: Relationship between the extent of systemic exposure (AUC) and dose following single and repeat BID administration of 2-OHOA



Anti tumor activity

54 pt were evaluable. One glioblastoma (GBM) pt had sustained partial response (>2.5 years) and 4rHGG pt (3 GBM) achieved stable disease for at least 6 months. They had previously received 2 lines of treatment without bevacizumab. Three AST patients had SD (1 pt mesothelioma, SD for 45 weeks; 1pt CRC, SD for 3 months ; and 1 pt biliary duct carcinoma SD for 5 months)

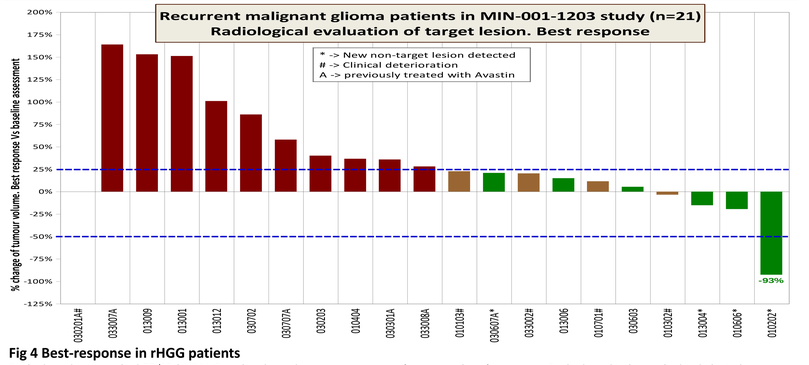


Fig 4 Best-response in rHGG patients
Pt shadowed in green had PR/SD by RANO at the planned reassessment scan after two cycles of treatment. Pt shadowed in brown had radiological outcome within SD range by RANO followed by clinical deterioration or new lesions. Pt 030607 had SD at C2 scan but PD was reported in C3. It was not considered as clinical benefit in the study conclusions

Conclusion

2-OHOA demonstrated a good safety profile at the doses tested in monotherapy in patients with AST and rHGG.

The most common AEs were diarrhea, nauseas and vomiting.

Administration of 2-OHOA with food resulted in a non-clinically significant delay in the T_{max} compared with the fasted state. Therefore, 2-OHOA could be taken without regard to food.

P2RD of 4000mg TID PO daily was confirmed.

Clinical benefit was observed in 3 patients with AST and 5 rHGG patients, including 1 GBM with PR lasting for more 2.5 years.

The preliminary antitumor activity including a sustained PR in heavy pretreated rHGG pt warrants further investigation in a Ph2 study.

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