INITIATING COVERAGE
Biotechnology
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AGIOS PHARMACEUTICALS INC (NASDAQ:AGIO)

Initiation: A Precise Approach To Metabolic Medicine

We are initiating coverage of Agios with an Outperform rating. We believe Agios' targeted approach will enable rapid clinical proof of concept for its lead candidates in cancer metabolism and orphan metabolic disease, driving stock appreciation over the next 12-18 months.

Recommendation

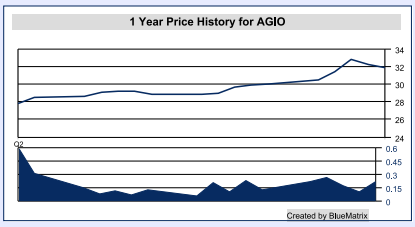
Rating:	Outperform
Price Target (in $):	NA
Dividend:	NA
Enterprise Value (MM):	$730.0

Stock Statistics as of 08/16/2013 (in $)

Price:	$31.91
52W Range:	$33.45-$18.00
Shares Out (MM):	30.1
Market Cap (MM):	$961.0
Net Debt (MM):	$0.0

Fundamentals

Revenue (MM) ('12A)	25.1
Revenue (MM) ('13E)	25.2
Revenue (MM) ('14E)	38.0
Earnings Per Share ('12A)	*$(1.19)*
Earnings Per Share ('13E)	*$(1.22)*
Earnings Per Share ('14E)	*$(0.95)*



Efficient Drug Development In Cellular Metabolism...

Agios' therapeutic focus is on two promising, related disease areas: (1) cancer metabolism and (2) inborn errors of metabolism (IEMs). Its advanced metabolic analysis platform and field-leading scientific advisors have yielded key insights that enable Agios' commitment "precision medicine" - meaning that for all Agios' programs, a targeted drug is matched to selected patient populations, and a biomarker gives an early clinical read of activity. We applaud this approach, as we believe it drives to value inflection points quickly, while minimizing risk and potentially abbreviating time to market.

Potential Proof Of Concept For Cancer In 2014...

Agios' lead candidates in cancer, AGI-221 and AGI-120, target several cancers mutant in the metabolic genes IDH2 and IDH1, respectively. AGI-221 entered the clinic in August, and AGI-120 will follow in early 2014. Each has shown encouraging preclinical efficacy, with preclinical updates expected at ASH 2013. We believe each has the potential to demonstrate clinical proof of concept in 2014, and estimate that they could generate $650MM+ and $450MM+ in global revenue, respectively. A partnership with Celgene provides nondilutive financing and validation of Agios' leadership position in cancer metabolism, while Agios retains meaningful economics.

...With Inborn Error Of Metabolism Just Behind.

Agios' leading IEM candidate is AG-348 for pyruvate kinase deficiency, a rare form of hemolytic anemia. The unmet need is great in this indication, and there may be 1,000 - 3,000 diagnosed patients in the U.S. alone. AG-348 will enter Phase I in 2014, and we would expect proof of concept data by 2015. We believe AG-348 could generate $600MM+ in peak revenue, and is wholly owned by Agios.

Please see addendum of this report for important disclosures.

Investment Summary

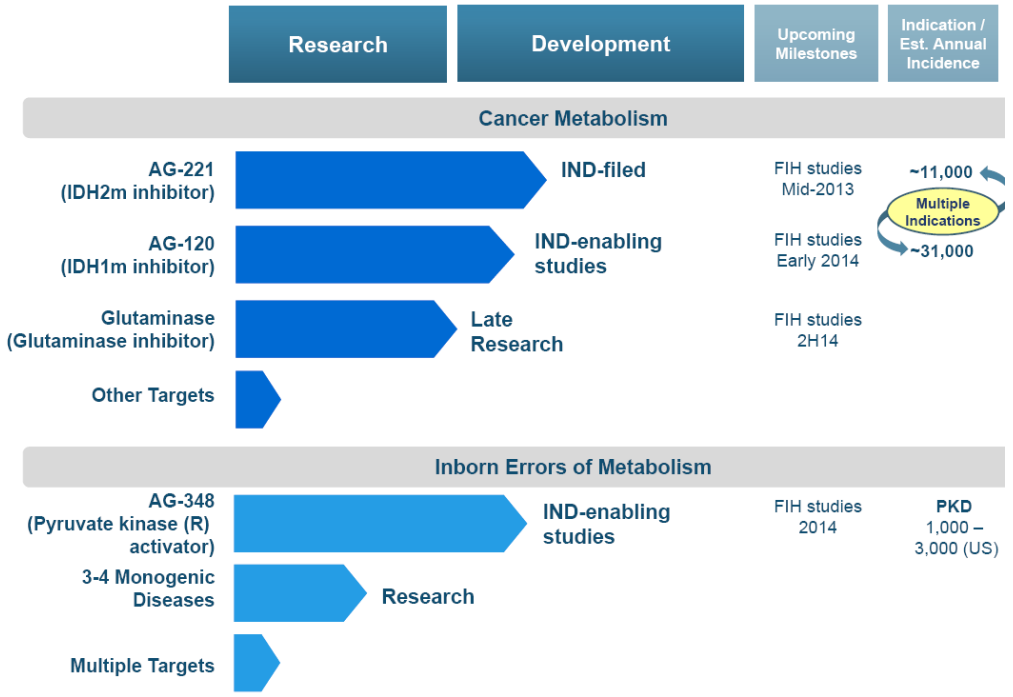
Agios Pharmaceuticals is leveraging its leading expertise in cellular metabolism to develop therapeutics in two related areas: (1) cancers driven by rewired metabolic pathways; and (2) orphan diseases caused by inborn errors of metabolism (IEMs). Insights gleaned from the company's advanced metabolic flux platform and world-class scientific board have engendered four lead drug candidates (three in cancer, one in IEMs) that are entering the clinic between Q3:13 and H2:14, as well as a rich pipeline of additional candidates. All of Agios' programs follow a "precision medicine" strategy, meaning that the targeted patients are well-defined and prospectively identifiable, that the drug candidates are tailored to meet the specific patient segments' needs, and that a biomarker is available to provide early proof of mechanism in humans. Thus, we expect Agios' candidates to generate early proof of concept data as they move into the clinic, perhaps even in first-in-human trials, driving near-term value inflection points. Agios' leadership position in cancer metabolism is validated by a partnership with Celgene through which Agios receives significant nondilutive funding and retains substantial economic interest in the cancer programs. Agios retains full ownership of the IEM programs. Following a $120MM+ IPO completed in July, Agios has over $220MM in cash, and including expected payments under the Celgene collaboration, should be funded at least through 2017. We expect multiple value-creating clinical readouts to drive stock outperformance over the next 12-18 months.

Metabolic Expertise And A Commitment To Precision Medicine

Agios is focused on developing therapeutics for two related areas, cancer metabolism and inborn errors of metabolism. "Cancer metabolism" refers to the growing realization that many cancers depend on "rewiring" cellular metabolic pathways in order to support the tumor's maintenance and growth, and therefore interference with these altered metabolic pathways provides a potential mechanism for specifically targeting the cancers therapeutically. Inborn errors of metabolism (IEMs) are a collection of rare orphan disorders, in which Agios can utilize its metabolic expertise to develop novel therapeutic interventions. Agios' analytic platform has enabled it to identify cases where targeting metabolic pathways is a viable therapeutic approach, which enzyme to target in the pathway, and what metabolites can best act as biomarkers to identify target patients and monitor drug activity.

All of Agios' development programs employ a personalized, or "precision" medicine approach, which can essentially be summarized as giving "the right drug to the right patients." In other words, in all of its development programs, Agios will always be able to identify defined patient subsets who should benefit from its drugs in advance and will have biomarkers that will demonstrate the activity of the drug in early human trials. This approach is expected to drive rapid, low-risk clinical development, with early value-creating data readouts and the potential for accelerated approval. Examples such as Xalkori for ALK+ NSCLC, Zelboraf for B-RAF+ melanoma, and Gleevec for CML, each of which was approved within about 5 years of first entering the clinic, illustrate the power of the precision medicine approach.

Agios' Pipeline And Near-Term Milestones



Source: Agios

Cancer Metabolism Program Led By Two Candidates Targeting Mutant IDH

Agios' first two programs to enter the clinic focus on cancer metabolism, and specifically on cancers with mutations in a metabolic enzyme called isocitrate dehydrogenase (IDH). Cancer genome sequencing efforts have determined that the gene IDH1 is frequently mutated in a subset of several cancer types, including most prominently brain cancer, but also two rare but poor-prognosis cancers called chondrosarcoma and cholangiocarcinoma, fractions of AML, MDS/MPN, and others. Another human IDH gene, IDH2, has been found to be frequently mutated in AML, as well as MDS/MPN, angioimmunoblastic NHL, and others. Altogether, Agios estimates that IDH1 mutations might be present in 31,000 new cancer patients per year in the US/EU/Japan, while IDH2 mutations may occur in 11,000.

Agios' lead candidate AGI-221 targets IDH2 mutant disease. The IND for AGI-221 was filed in June, and the Phase I trial in liquid tumors began enrolment in mid-August. The next candidate, AGI-120, targets IDH1 mutant disease and is expected to start Phase I trials in liquid and solid tumor patients in early 2014. Both have demonstrated encouraging preclinical safety profiles and signals of efficacy. Both target genetically defined patient populations and can use a metabolite called 2-HG as an early pharmacodynamics marker of drug activity in the clinic. Thus we expect rapid clinical validation of mechanisms for these programs. While the development indication(s) and regulatory path for each of these candidates are data-dependent and remain to be determined, we model initial sales in 2018 and peak global revenue of $650MM+ for AGI-221 in IDH2m AML and $450MM+ for AGI-120 in brain cancer.

Under a partnership with Celgene, we expect Agios to receive a 10-15% tiered royalty on sales for AGI-221, and approximately 50/50 profit share economics on AGI-120.

Celgene Partnership Validates Agios' Leadership In Cancer Metabolism

Agios is partnered with Celgene on the cancer metabolism programs in what we view as a very validating deal for Agios' leadership position in cancer metabolism. For two out of every three cancer candidates, Celgene will fund all clinical development and Agios will receive a royalty and milestones, as well as a U.S. co-promote option. For one out of every three cancer programs, Agios and Celgene will share development costs, and Agios will commercialize the drug in the U.S., while Celgene will handle ex-U.S. commercialization. Celgene has said that its partnership with Agios is perhaps its most important external research collaboration because of the promise of cancer metabolism to generate novel therapies. Moreover, Celgene has indicated that, in fact, it had little choice but to partner with Agios to enter the space, finding that Agios was by far the most advanced in the field and furthermore had all the academic scientist talent "locked up" on its advisory board, which represents a real competitive advantage, in our view.

A Focus On Orphan Inborn Errors Of Metabolism Rounds Out Agios' Pipeline

Inborn errors of metabolism comprise a collection of 600+ genetic diseases caused by mutations in metabolic enzymes. These can have very severe disease presentation and often have great unmet need, with few, if any, treatment options. Enzyme replacement therapies such as Genzyme's Cerezyme for Gaucher's disease and Lumizyme for Pompe's disease illustrate the clear commercial opportunity in these niche disorders. Unfortunately, most IEMs are caused by defects in intracellular enzymes that are not amenable to biologic approaches. However, Agios' expertise in cellular metabolism enables the company to identify optimal targets for small molecule approaches to the great unmet needs in certain IEMs.

Agios' lead candidate in the IEM space, AGI-348, targets PK deficiency, a rare IEM cause by mutation in the PK-R gene and characterized by potentially severe hemolytic anemia. Current treatment consists of chronic, lifelong blood transfusion and iron chelation, and patients experience considerable comorbidities. The prevalence of symptomatic PK deficiency is still coming into focus, but Agios estimates that there may be 1,000 – 3,000 patients in the US alone. AGI-348 has demonstrated encouraging preclinical ability to rescue the defects in mutant PK-R, and will enter the clinic in 2014.

Symptomatic similarities between PK deficiency and PNH (for which Alexion's Soliris is approved) suggest that Agios may be able to use Soliris' established regulatory endpoints to support approval from early trials. We assume initial revenue generation in from AGI-348 in 2019, and model peak global sales in PK deficiency of $600MM+. Agios retains full rights to the IEM programs.

Agios R&D Pipeline

Therapeutic Class/Product	Indication	P-C	I	II	III	FILING	MKT	Comments
Cancer Metabolism								
AGI-221	IDH2-mutant cancers		•					Phase I began August 2013
AGI-120	IDH1-mutant cancers	⇒						Phase I to start early 2014
GLS	Glutaminase-dependent cancers	•						Phase I expected to start H2:14
Inborn Errors Of Metabolism								
AGI-348	Pyruvate kinase deficiency	•						Phase I expected to start 2014
Total Drugs In Development		**3**	**1**	**0**	**0**	**0**	**0**	
Cambridge, MA	**Investor Relations Contact: Glenn Goddard (617) 649-8660**							

Source: Company reports

A Framework To Value AGIO Shares

Agios completed a $122MM IPO in July. Including a concurrent $12.75MM private placement to Celgene and prior cash on hand, we estimate pro forma net cash of over $225MM at the end of July. Inclusive of expected milestones from the Celgene collaboration, we believe Agios is well-financed at least through 2017. AGIO shares have performed well in the public markets, and as of mid-August, had an enterprise value of about $700MM.

Despite its early stage, we view Agios as a very high quality company with several characteristics justifying substantial share value. Agios is a clear leader in the promising field of cancer metabolism, driven by a first-mover advantage with its flux biochemistry platform and the top scientific talent in the space on the company's advisory board. Agios' metabolic expertise has also enabled a second attractive therapeutic focus on orphan diseases caused by inborn errors of metabolism. All of Agios' programs target well defined patient populations and have clear biomarkers that should provide proof of concept quickly, possibly even in Phase I first in human trials, driving potential value inflection points in the relatively near term. These types of development programs lend themselves well to potential accelerated marketing approval pathways. Lastly, we view Agios' management as top-tier.

All that said, rigorously valuing such an early-stage enterprise is difficult, as multiple elements of the development paths for Agios' candidates are data dependent and remain to be determined. Because IDH mutations occur in a variety of cancers, we do not yet know which indication(s) will be chosen for development. We also do not know the time to market with any precision, as this depends on the indication, level of activity, whether the drugs are developed as single agents or combinations, and whether the drugs achieve accelerated or regular approval, among other variables. We have chosen to take a risk-adjusted sum of the parts approach to valuation. We sum the NPV of Agios' economic interest in the three most advanced drug programs, based on what we view to be a likely path to market for each, and risk adjust each by a reasonable probability of success. Assigning some value to the pipeline (GLS and Agios' 13+ other early stage candidates, plus the potential for AG-221 and AG-120 to be approved in indications we do not currently model) and including net cash, our analysis suggests that Agios' stock may be 20%+ undervalued. We expect AGIO shares to appreciate over the next 12-18 months as data updates increase investor confidence in the programs. Key

milestones include a preclinical data update expected at ASH 2013, and especially clinical data updates beginning in 2014.

Agios Sum Of The Parts Valuation

	NPV ($MM)	NPV per share	% chance of success	Risk-adjusted NPV per share
AG-221 Royalty In AML	$355	$10	50%	$5
AG-120 50% Share In Brain Cancer	$519	$15	40%	$6
AG-341 In PKD	$451	$13	40%	$5
Other Indications for '221 and '120, GLS, Rest of Pipeline and Platform	$500	$15		$15
Net Cash	$223	$7		$7
Sum-Of-The-Parts Value		$60		$38

Source: Cowen and Company

The chief risks to an investment in AGIO primarily stem from the obviously early nature of the clinical programs. Agios' lead candidates are just entering initial clinical trials, and face a certain amount of clinical risk. It is also likely to be 4-5 years or more before the company derives meaningful revenue from commercial products. Agios' stock has benefited from current market enthusiasm toward biotech IPOs, and shares could trade at the market's whim until Agios' data mature further. Although Agios' clinical programs should provide comparatively rapid proof of mechanism, the next clinical milestone is likely about a year away (namely, Phase I data from AGI-221, likely sometime in 2014). Moreover, given the wide variety of cancer segments in which its candidates have potential, the development path that Agios will ultimately take remains to be determined and depends on the data generated in initial trials. Hence, investors may need to exercise some patience in order to reap the rewards as Agios' clinical programs progress and the pathways to market crystallize.

Upcoming Agios Milestones

Event	Timing
Preclinical data presentations on clinical candidates (at ASH)	Q4:13
Begin enrollment in AGI-120's Phase I trials in IDH1m liquid and solid tumors	Early 2014
Begin enrollment in AG-348's Phase I trial in PK deficiency	2014
Possible initial proof of mechanism data for AGI-221 in IDH2m liquid tumors, start of Phase II expansion cohorts	2014
Begin enrollment in Phase I for glutaminase inhibitor program	H2:14
Possible initial proof of mechanism data for AGI-120 in IDH1m tumors, start of Phase II expansion cohorts	H2:14/H1:15
Possible initial proof of mechanism data for AGI-348 in PK deficiency	H2:14/2015

Source: Cowen and Company

Financial Year End	12/31/2012
Valuation Date	8/17/2013
Discount Rate	10.0%
Perpetual Growth Rate	-30.0%

Agios - AG-221 In AML NPV Valuation

Valuation Date: Saturday, August 17, 2013

$MM	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
AG-221 Royalty On Global Sales	0	0	0	0	0	1	4	10	35	52	69	81	90	94	97	99	101	103	105	107	109	92
Growth (%)									*248%*	*49%*	*33%*	*17%*	*10%*	*5%*	*3%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*-10%*
Milestones From Celgene	0	43	20	25	0	25	25	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0
Growth (%)																						
Total Revenue	0	43	20	25	0	26	29	10	55	52	69	81	90	94	97	99	101	103	105	107	109	92
COGS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
COGS as a % of total sales																						
R&D	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R&D as a % of Revenues																						
SG&A	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SG&A as a % of Revenues																						
Operating Income	-8	43	20	25	0	26	29	10	55	52	69	81	90	94	97	99	101	103	105	107	109	92
Operating Margin									*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*
Tax	0	0	0	0	0	0	0	0	0	3	21	24	27	28	29	30	30	31	31	32	33	28
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Approx Free Cash Flow	(8)	43	20	25	0	26	29	10	55	49	49	57	63	66	68	69	70	72	73	75	76	65
Years	0.37	1.37	2.37	3.37	4.37	5.37	6.37	7.37	8.37	9.37	10.37	11.37	12.37	13.37	14.37	15.37	16.37	17.37	18.37	19.37	20.37	21.37
Discount Factor	0.97	0.88	0.80	0.73	0.66	0.60	0.55	0.50	0.45	0.41	0.37	0.34	0.31	0.28	0.25	0.23	0.21	0.19	0.17	0.16	0.14	0.13
NPV of Cash flows	(8)	37	16	18	0	15	16	5	25	20	18	19	19	18	17	16	15	14	13	12	11	8

Terminal Value Calculation

Final year FCF	65
Perpetual Growth Rate	-30.0%
Terminal Value	**113**
Discount Factor	0.23
Present Value of Terminal Value	**26**
Present Value of Cash Flows	**329**
Market Value	**355**
Fully Diluted Shares Outstanding	34.0
Value per Fully Diluted Share	**$10.44**

Source: Cowen and Company

Agios AG-120 In Brain Cancer – NPV Valuation

Financial Year End	12/31/2012
Valuation Date	8/17/2013
Discount Rate	10.0%
Perpetual Growth Rate	-30.0%

Agios - AG-120 In Brain Cancer NPV Valuation

Valuation Date: Saturday, August 17, 2013

$MM	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034
AG-120 Global Sales To Agios (50% Share)	0	0	0	0	0	7	33	60	175	200	188	195	210	235	242	247	252	257	262	267	257	231
Growth (%)									*192%*	*14%*	*-6%*	*4%*	*8%*	*12%*	*3%*	*2%*	*2%*	*2%*	*2%*	*2%*	*2%*	*-10%*
Milestones From Celgene	0	0	0	50	0	25	25	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0
Growth (%)																						
Total Revenue	0	0	0	50	0	32	58	60	195	200	188	195	210	235	242	247	252	257	262	267	257	231
COGS	0	0	0	0	0	0	2	3	9	10	9	10	11	12	12	12	13	13	13	13	13	12
COGS as a % of total sales						*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
R&D	2	10	12	16	19	19	16	12	18	14	9	6	4	2	0	0	0	0	0	0	0	0
R&D as a % of Revenues						*250%*	*50%*	*20%*	*10%*	*7%*	*5%*	*3%*	*2%*	*1%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
SG&A	1	2	2	4	4	22	20	18	35	36	34	35	36	40	41	42	43	44	45	45	44	23
SG&A as a % of Revenues						*300%*	*60%*	*30%*	*20%*	*18%*	*18%*	*18%*	*17%*	*17%*	*17%*	*17%*	*17%*	*17%*	*17%*	*17%*	*17%*	*10%*
Operating Income	-3	-12	-14	31	-23	-9	20	27	134	140	135	144	160	181	189	193	196	200	204	208	200	197
Operating Margin									*69%*	*70%*	*72%*	*74%*	*76%*	*77%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*85%*
Tax	0	0	0	0	0	0	0	0	0	7	41	43	48	54	57	58	59	60	61	63	60	59
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Approx Free Cash Flow	(3)	(12)	(14)	31	(23)	(9)	20	27	134	133	95	101	112	127	132	135	137	140	143	146	140	138
Years	0.37	1.37	2.37	3.37	4.37	5.37	6.37	7.37	8.37	9.37	10.37	11.37	12.37	13.37	14.37	15.37	16.37	17.37	18.37	19.37	20.37	21.37
Discount Factor	0.97	0.88	0.80	0.73	0.66	0.60	0.55	0.50	0.45	0.41	0.37	0.34	0.31	0.28	0.25	0.23	0.21	0.19	0.17	0.16	0.14	0.13
NPV of Cash flows	(3)	(10)	(11)	22	(15)	(5)	11	13	60	54	35	34	34	35	34	31	29	27	25	23	20	18

Terminal Value Calculation

Final year FCF	138
Perpetual Growth Rate	-30.0%
Terminal Value	**241**
Discount Factor	0.23
Present Value of Terminal Value	**56**
Present Value of Cash Flows	**464**
Market Value	**519**
Fully Diluted Shares Outstanding	34.0
Value per Fully Diluted Share	**$15.27**

Source: Cowen and Company

AG-341 In PK Deficiency – NPV Valuation

Financial Year End	12/31/2012
Valuation Date	8/17/2013
Discount Rate	10.0%
Perpetual Growth Rate	-30.0%

Agios - AG-341 In PK Deficiency NPV Valuation

Valuation Date: Saturday, August 17, 2013

$MM	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
AG-120 Global Sales To Agios	0	0	0	0	0	0	40	105	180	280	385	490	540	575	600	540
Growth (%)									*71%*	*56%*	*38%*	*27%*	*10%*	*6%*	*4%*	*-10%*
Total Revenue	0	0	0	0	0	0	40	105	180	280	385	490	540	575	600	540
COGS	0	0	0	0	0	0	2	5	9	14	19	25	27	29	30	27
COGS as a % of total sales							*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
R&D	2	10	15	22	44	60	120	53	36	28	19	15	11	6	0	0
R&D as a % of Revenues							*300%*	*50%*	*20%*	*10%*	*5%*	*3%*	*2%*	*1%*	*0%*	*0%*
SG&A	1	2	3	5	10	30	100	68	63	70	73	88	97	104	108	97
SG&A as a % of Revenues							*250%*	*65%*	*35%*	*25%*	*19%*	*18%*	*18%*	*18%*	*18%*	*18%*
Operating Income	-3	-12	-18	-27	-54	-90	-182	-21	72	168	273	363	405	437	462	416
Operating Margin									*40%*	*60%*	*71%*	*74%*	*75%*	*76%*	*77%*	*77%*
Tax	0	0	0	0	0	0	0	0	0	8	82	109	122	131	139	125
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Approx Free Cash Flow	(3)	(12)	(18)	(27)	(54)	(90)	(182)	(21)	72	160	191	254	284	306	323	291
Years	0.37	1.37	2.37	3.37	4.37	5.37	6.37	7.37	8.37	9.37	10.37	11.37	12.37	13.37	14.37	15.37
Discount Factor	0.97	0.88	0.80	0.73	0.66	0.60	0.55	0.50	0.45	0.41	0.37	0.34	0.31	0.28	0.25	0.23
NPV of Cash flows	(3)	(10)	(14)	(20)	(36)	(54)	(99)	(10)	32	65	71	86	87	86	82	67

Terminal Value Calculation

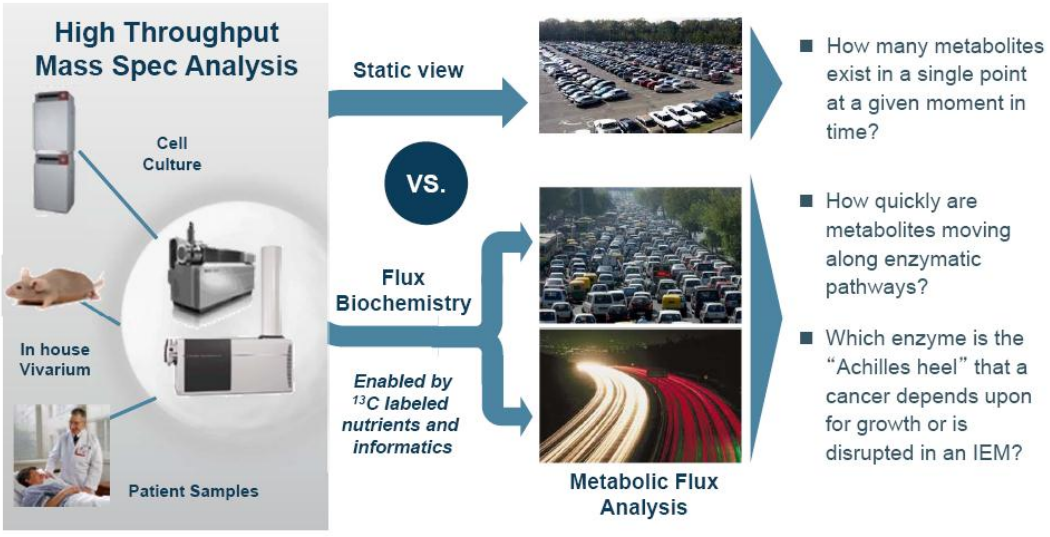
Final year FCF	291
Perpetual Growth Rate	-30.0%
Terminal Value	**509**
Discount Factor	0.23
Present Value of Terminal Value	**118**
Present Value of Cash Flows	**333**
Market Value	**451**
Fully Diluted Shares Outstanding	34.0
Value per Fully Diluted Share	**$13.25**

Source: Cowen and Company

Agios' Metabolic Flux Platform…

Agios' key capability enabling its identification of novel therapeutic targets is its "flux biochemistry" mass spectrometry platform. Mass spectrometry allows the identification and quantification of the molecular constituents of a biological sample. "Static" mass spec is a relatively standard laboratory technique that permits identification of the levels of various metabolites at a single point in time. This is certainly useful information when one seeks to understanding the metabolic state of a sample. However, Agios' approach adds the element of time by measuring changes in the levels of metabolites and their movement through metabolic pathways, or "flux." This is accomplished by radiolabeling a pulse of a given molecular species and tracking the radiolabeled atoms as they move through metabolic pathways and enzymatic processes. Agios is then able to develop mathematical models of biochemical pathways and how metabolites move through them in normal and diseased states. This approach permits Agios to identify the "metabolic fingerprint" of a disease in questions, elucidating both the key choke point that should be optimally targeted with potential therapeutic agents, as well as crucial metabolites that can be tracked to: (1) identify the correct patients for the drug and (2) verify the drug's efficacy in patients as pharmacodynamic biomarkers. Without the element of time and the ability to follow the biosynthetic pathways by which critical biomarkers are made, Agios would be much less able to identify these key targets and pathways. While flux biochemistry was first developed by academic labs and continues to be practiced in academia, Agios has scaled and automated the process into a massively parallel, robot-enabled process that is far beyond the capabilities of any academic lab or, to Agios' knowledge, any other pharmaceutical company. Though other companies are now active in the flux metabolic space, Agios' first-mover status, considerable existing insights, and close relationships with pioneering scientific collaborators represent significant competitive advantages.

Agios' Flux Biochemistry Platform



Source: Agios

The testing and validation of Agios' target enzymes and drug candidates is further enabled by several other core capabilities. Agios has in-house bioinformatics capabilities that have enabled it to identify commonly mutated metabolic enzymes in publicly available genomic data from patient tumor samples. The company also utilizes a multiplexed RNAi library approach to inactivate large swaths of the "metabolome" (the 2,000-3,000 cellular metabolic enzymes) in both cells and xenograft models to identify novel targets. Finally, Agios' in-house rational drug design capability (based on crystal structure, computational chemistry, and high-throughput sequencing) allows the creation of effective drug candidates. The tools are combined to validate target enzymes through inactivation in tissue culture and xenograft models, identify predictive biomarkers, and refine clinical drug candidates to maximize the chance of success in the clinic.

…Enables A Precision Medicine Strategy

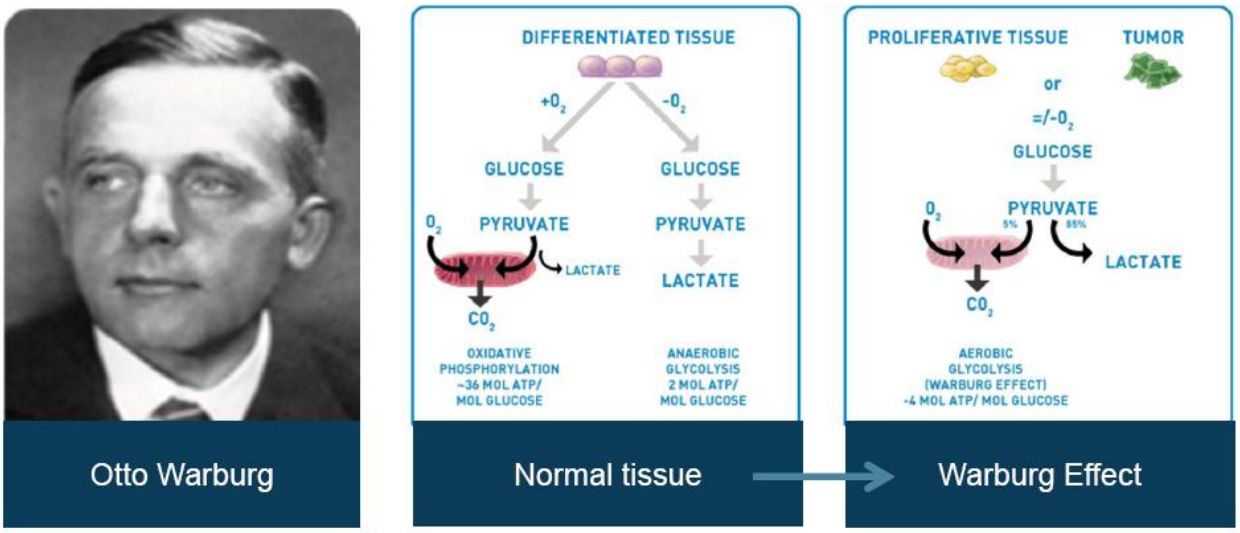
Agios' "flux metabolism" methodology is crucial to enabling its "precision medicine" approach to drug development. Precision medicine is a concept that can essentially be summarized as "the right drug for the right patient." Agios' approach enables the company to identify the crucial target enzyme to focus on with its drug candidates. The approach also enables identification of critical metabolite(s) that can be monitored to verify the drug's efficacy in patients at an early stage of clinical development. Moreover, the correct patients to receive the drug can be identified in advance, by detecting mutations in the critical biochemical pathway and/or dysregulation of the biomarker metabolite. The inability to predict which patients might benefit from a candidate drug treatment is a major reason for technical failure in drug development, and certainly increases the size of trials, the time to proof of concept, and the expense even for ultimately successful drugs. The precision medicine approach, in contrast, allows matching of the proper patients to the proper drug and early clinical proof of concept, and a relatively high likelihood of technical success with limited time and expense. Moreover, this approach enables potential rapid paths to market such as accelerated approval. The power of precision medicine as a drug development strategy is well-illustrated by examples such as Pfizer's Xalkori for ALK+ NSCLC and Novartis' Gleevec for CML, each of which targets genetically identifiable patients and each of which was approved within five years of first entering the clinic. All of Agios' programs will pursue this relatively low-risk, potentially rapid path to the market; notably, all the programs will therefore be developed with a companion diagnostic.

Background On Cancer Metabolism

Agios' oncology efforts are focused on cancer metabolism. The basic concept underlying this approach is that some cancers "rewire" certain metabolic pathways to behave differently than they do in normal cells. This may be because the cancers' rapid growth requires extremely high levels of particular metabolites, or because the metabolic changes promote development and maintenance of the tumorigenic state, or potentially for other reasons. The notion underlying the field of cancer metabolism is that the exquisite dependence of cancers on altered metabolic states, relative to normal cells, provides a potential means of differentially attacking the cancers therapeutically while leaving normal tissues unaffected.

The earliest validation of an altered metabolic state in tumor cells comes from the Warburg Effect, described in the 1920's by Otto Warburg. In the presence of oxygen, normal tissues will generally utilize oxidative phosphorylation, a mitochondria-dependent process that efficiently converts glucose into ATP, the energy source for the cell. Only in the absence of adequate oxygen will normal tissue undergo substantial glycolytic fermentation, an alternate, much less efficient method of generating ATP that does not require oxygen or mitochondria. Warburg's discovery was that cancer cells tend to undergo the energetically inefficient glycolytic fermentation even in the presence of adequate oxygen. This phenomenon is generally true of many cancer types, and in fact forms the basis of PET imaging, in which cancers' tendency to take up (labeled) glucose much more rapidly than normal tissue is exploited to image the tumors. This example of metabolic rewiring was a puzzle, since cancer cells are rapidly growing and one would intuitively expect that they would seek to generate energy efficiently. Warburg's strange observation was not really adequately explained until about the last decade, when researchers determined that this metabolic rewiring comes about because the rapidly proliferating cancer cells depend on intermediates generating during glycolysis to synthesize adequate biomolecules (notably glutamine, among others) to support their growth, and that it is this anabolic need that is limiting for the cancer cells, not the need for energy in the form of ATP.

Warburg Effect An Early Example Of Metabolic Rewiring In Cancer



Source: Agios

Following the greater understanding of the Warburg effect, there has been a growing realization that mutation and alteration of metabolic pathways is a general set of mechanisms that promote and maintain a tumorigenic state and that many cancer cells depend upon to support their rapid growth. Agios and its scientific founders have been at the forefront of this growing understanding of the crucial nature of cancer metabolism and its therapeutic potential;

in fact, we believe that Agios' "locking up" of the key academic talent among its founders and scientific advisory board represents an important competitive advantage in the space.

Agios' Lead Cancer Programs Target IDH-Mutant Disease

Agios believes there are three general mechanisms by which cancers may rewire their metabolic state: (1) the cancer may exhibit a unique mutation in a metabolic enzyme leading to a wholly cancer-specific metabolic state; (2) the cancer may (mis)express certain isoforms of metabolic enzymes, leading to an altered metabolic state; or (3) the cancer may differentially regulate entire metabolic pathways to supply crucial metabolites or nutrients needed for growth. The company's lead cancer metabolisms, focused on IDH1 and IDH2, are an example of the first mechanistic class: neomorphic, cancer-specific mutations in metabolic enzymes.

Isocitrate dehydrogenase enzymes normally function as part of the Krebs cycle, converting isocitrate to alpha-ketoglutarate. Humans have a cytosolic isoform (IDH1) and two mitochondrial isoforms (IDH2 and IDH3). The interest in IDH enzymes in cancer first arose from genomic sequencing of tumor samples, and the discovery that IDH enzymes are frequently mutated in several cancer types. The earliest hint of potential importance of IDH1 in cancer came from a genomic analysis of 105 glioblastoma multiforme (GBM) samples published in *Science* in 2008.Twelve of the 105 GBM samples (12%) were found to carry IDH1 mutations, a gene that had not previously been linked to GBM. GBM occurs in "primary" and "secondary" forms, and intriguingly, nearly all (5 of 6) of the secondary GBM samples analyzed carried IDH1 mutations. This work was expanded in a 2009 *NEJM* publication, which reported that of 192 samples analyzed from patients with WHO Grade II-III astrocytomas and oligodendrogliomas, and secondary glioblastomas that evolved from these lesions, more than 70% exhibited IDH1 mutations. Many of such patients without IDH1 mutations had IDH2 mutations, so that more than 80% of patients tested had a mutation in one of these two IDH genes. Importantly, all of the IDH1 mutations and all of the IDH2 mutations affected the same residue in the active site, allowing drugs to potentially affect all patients with typical mutations. IDH mutations were uncommonly found in primary glioblastomas (6 of 123 samples), and were not found in other CNS tumor types tested (Grade I pilocytic astrocytomas, ependymomas, medulloblastomas, or 494 tested non-CNS tumors). Subsequently, several genomic screening efforts reported that IDH mutations were commonly found in subsets of blood cancers such as AML and myeloproliferative neoplasms (MPNs). IDH mutations have also been identified in a number of rarer tumor types, including chondrosarcoma, intrahepatic cholangiocarcinoma, angio-immunoblastic NHL, and others. In all, Agios estimates that the annual incidence of IDH1-mutant cancer in the US, EU, and Japan may exceed 30,000 patients, and the annual incidence of IDH2-mutant cancer may exceed 10,000 patients.

Potential Addressable Patient Incidence In IDH-Mutant Cancer

Product	Indication	% IDHm	# pts / year***
IDH1m (~31,000*)	Low grade glioma & 2ary GBM**	70%	11,000
	Chondrosarcoma	>50%	4,600
	Acute Myeloid Leukemia (AML)	7.5%	3,600
	MDS/MPN	5%	2,000
	Intrahepatic Cholangiocarcinoma	20%	1,600
	Others* (colon, melanoma, lung)	1-2%	~8,000+
IDH2m (~11,000*)	Acute Myeloid Leukemia (AML)	15%	7,200
	MDS/MPN	5%	2,000
	Angio-immunoblastic NHL	25%	400
	Others* (melanoma, glioma, chondro)	3-5%	1,500
	Type II D-2HG Aciduria (Inborn Error of Metabolism)	100%	50 reported

* Includes "basket" of emerging unconfirmed indications; all patient populations being further refined with new sequencing
** Includes 8.5% of Primary GBM
*** Estimated, US + EU27 + JP incidence

Source: Agios – estimates based on published reports

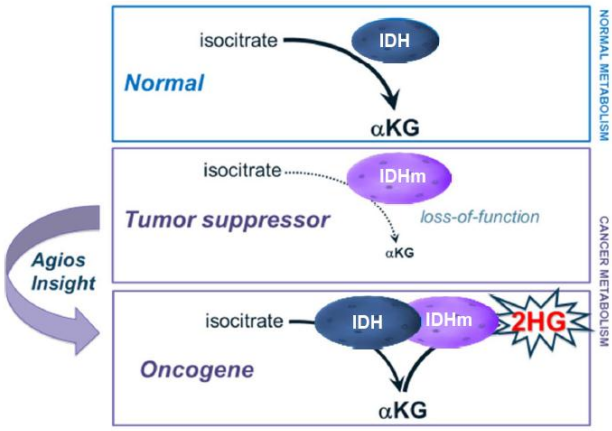
These seminal reports provided a clear indication that IDH mutations were likely to play some role in certain subtypes of cancer. Importantly, the evidence seems to suggest that IDH mutations tend to occur early in the progression of cancerous lesions and promote the development and maintenance of more aggressive tumor states. For example, initially low-grade CNS tumors tend to progressively acquire mutations in a characteristic set of genes as they progress, with TP53 being a common early mutation and PTEN and EGFR being common late mutations. In the 2009 *NEJM* article, the IDH mutations in low grade tumors tended to be found in combination with TP53 mutations, but not PTEN or EGFR mutations, suggesting that IDH mutation is an early event that promotes tumorigenesis. Similarly, a small study published in *Leukemia* in 2010 reported that IDH mutations were found in blast-phase myeloproliferative neoplasms (MPNs) and post-myelofibrosis AML, though not in AML without antecedent myelofibrosis or in chronic-phase MPNs; these findings suggests to us that, like with brain cancer, IDH mutations may tend to occur relatively early in the progression of low-grade neoplasms and drive them toward a higher-grade, more invasive state. Consistently, a 2012 *Cancer Leukemia* report analyzed the genomes of 24 AML patient samples and concluded that IDH1 mutation is also likely an early initiating event in that context as well. Preclinical evidence (detailed below) suggests that correcting the defect caused by IDH mutations should have a beneficial effect on patients' cancers. That said, we believe a general risk of the IDH development programs is that more advanced cancers bearing IDH mutations may no longer

depend on the IDH mutations to maintain the tumor state, at least not in every indication or context.

Agios Discovered The Mechanism Of IDH Mutations In Cancer

The genomic analyses described above established a high index of suspicion that IDH mutations played some role in promoting tumorigenesis in certain subsets of cancer, but the underlying mechanism remained a mystery until Agios scientists and their academic collaborators discovered the solution. What Agios discovered (and published in *Nature* in 2009) was that the IDH mutations found in cancer do not merely disrupt the normal activity of IDH enzymes (converting isocitrate into alpha-ketoglutarate), but also confer an entirely new activity not normally possessed by the enzyme: converting isocitrate into an entirely different metabolite, 2-hydroxyglutarate (2-HG), which is not normally found in appreciable quantities in normal cells.

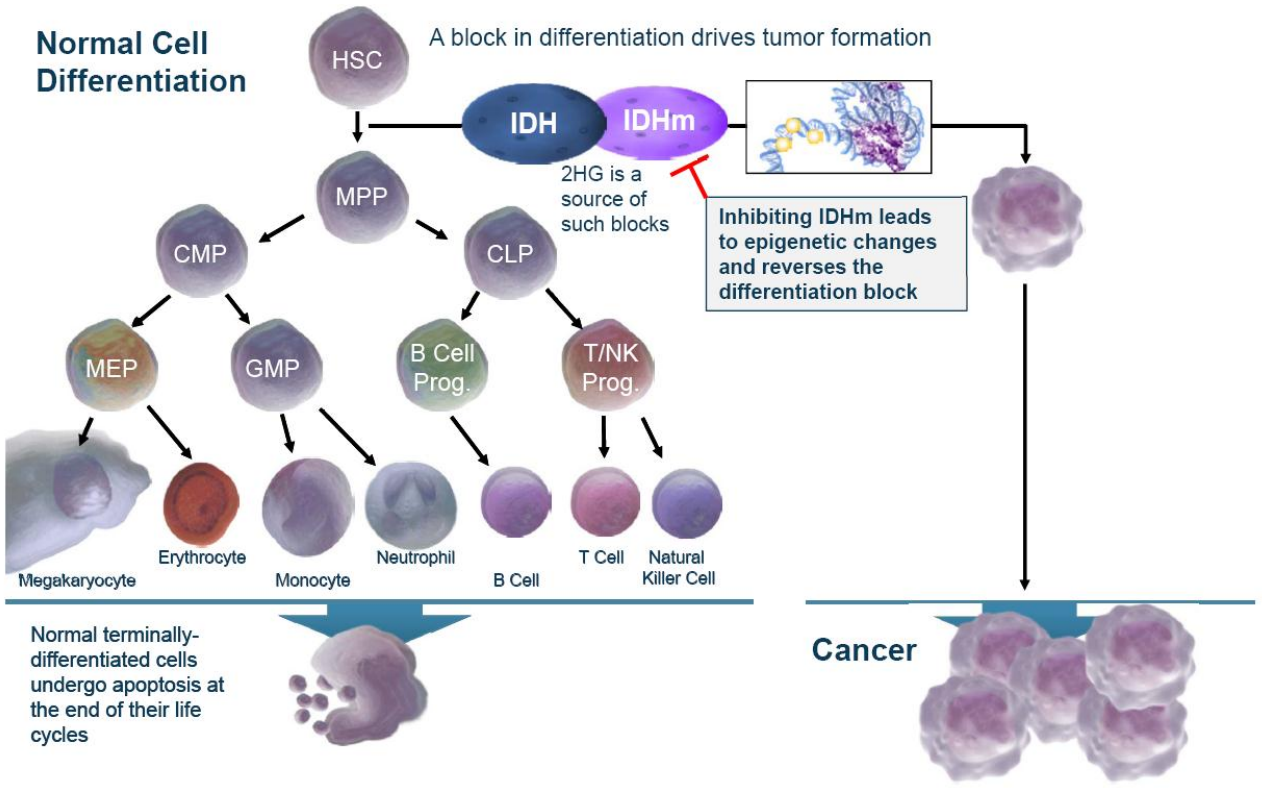
Mechanism of IDH Mutation



Source: Agios

In a series of additional high-profile publications, Agios and collaborators went on to elucidate a great deal about the mechanism by which 2-HG seems to promote tumorigenesis. In short, high 2-HG levels appear to bring about epigenetic changes that introduce a block in differentiation. This appears to prevent cells from progressing normally from a proliferative progenitor stage toward a terminally differentiated, nonproliferative stage; instead, the cells continue dividing in an unregulated manner, driving tumor growth and enabling continued accumulation of mutations driving increasingly aggressive tumor states.

IDH Mutation Thought To Cause A Block In Differentiation



Source: Agios

Specific published evidence supporting this model includes the following:

(1) In a 2012 *Nature* publication, the authors reported that IDH1-mutant glioma samples from patients exhibited a hypermethylated histone signature associated with enhanced expression of genes also enriched in neural progenitors. Transfection of mutant IDH1 genes or introduction of cell-permeable 2-HG itself was also sufficient to induce hypermethylation and block differentiation *in vitro*.

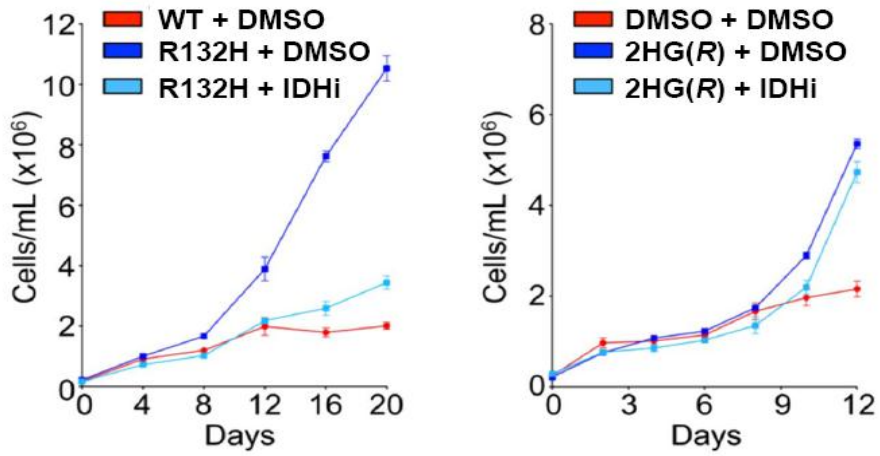
(2) A second 2012 *Nature* publication reported that introduction of a mutant IDH1 transgene into astrocytes *in vitro* is sufficient to induce a hypermethylated epigenomic signature reminiscent of lower-grade gliomas, supporting the idea that IDH mutation is an early, tumor-driving event in the evolution of cancers.

(3) A 2013 *Science* paper reported that an Agios tool compound that selectively inhibits IDH1, called AGI-5198, was able to impair the growth of patient-derived, IDH1-mutant gliomas *in* vitro and in a xenograft model. In contrast, the tool compound had no effect on the growth of IDH1 wild-type glioma cells in this assay. Moreover, AGI-5198 induced a gene expression pattern reminiscent of differentiation in these tumor cells. This provided important preclinical evidence that pharmacological inhibition of IDH1-mutant glioma cells could impair their growth.

(4) A 2012 *Nature* paper from Agios founders reported that knock-in of mutant human IDH1 in a mouse model such that the mutant enzyme was expressed in hematopoetic cells led to dramatic increases the number of hematopoetic progenitors and epigenetic changes reminiscent of those seen in human IDH-mutated AML. This provides further evidence of the potential for IDH mutation prevent terminal differentiation and to act as an early initiating event in tumorigenesis.

(5) A 2013 *Science* paper from Agios collaborators transfected the TF-1 leukemic cell line with mutant or wild-type IDH1. (TF-1 is a unique line in that it is cytokine dependent and retains the ability to differentiate in response to erythropoietin.) Results showed that the mutant enzyme dramatically enhanced the speed and frequency with which TF-1 cells became cytokine-independent. Moroever, the mutant-transfected cells lost the ability to differentiate in response to EPO. The emergence of these two hallmarks of leukemic transformation (growth factor independence and differentiation block) again suggest that mutant IDH1 can promote tumor development. Importantly, these authors also showed that the growth factor independence and differentiation block in these cells could be relieved by treatment with the tool compound AGI-5198.

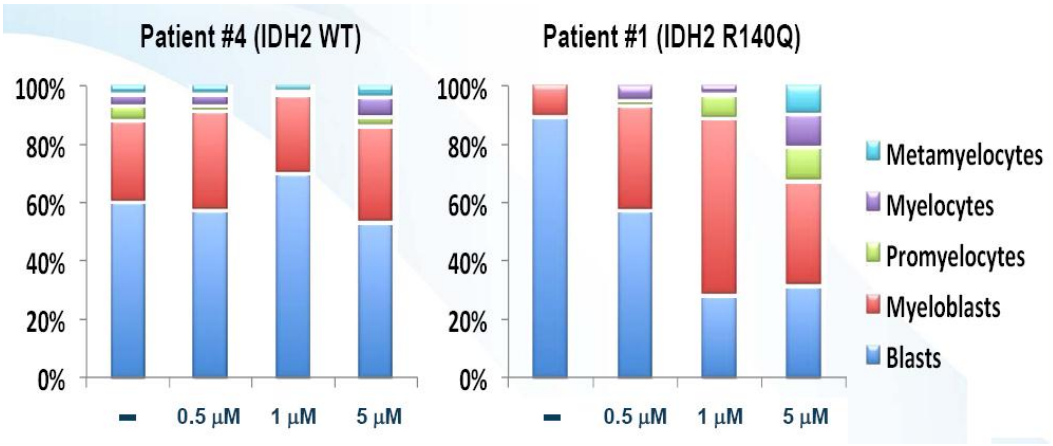
Mutant IDH1 Leads To Reversible Growth Factor Independence In A Leukemia Line



Source: Agios

(6) A second 2013 Science paper employed a short-term *in vitro* differentiation assay to show that an IDH2-specific tool compound, AGI-6780, could restore differentiation in IDH2-mutant AML patient samples. In this assay, primary human AML cells were placed in a differentiation-promoting cell culture. In IDH2-mutant primary cells, AGI-6780 treatment caused disappearance of undifferentiated myeloblast cells, and appearance of differentiated descendent cells, in a dose dependent manner. AGI-6780 had no effect on differentiation in IDH wild-type AML, as would be expected.

Pharmacological Inhibition Of Mutant IDH2 Restores Differentiation In Primary Cells *In Vitro*



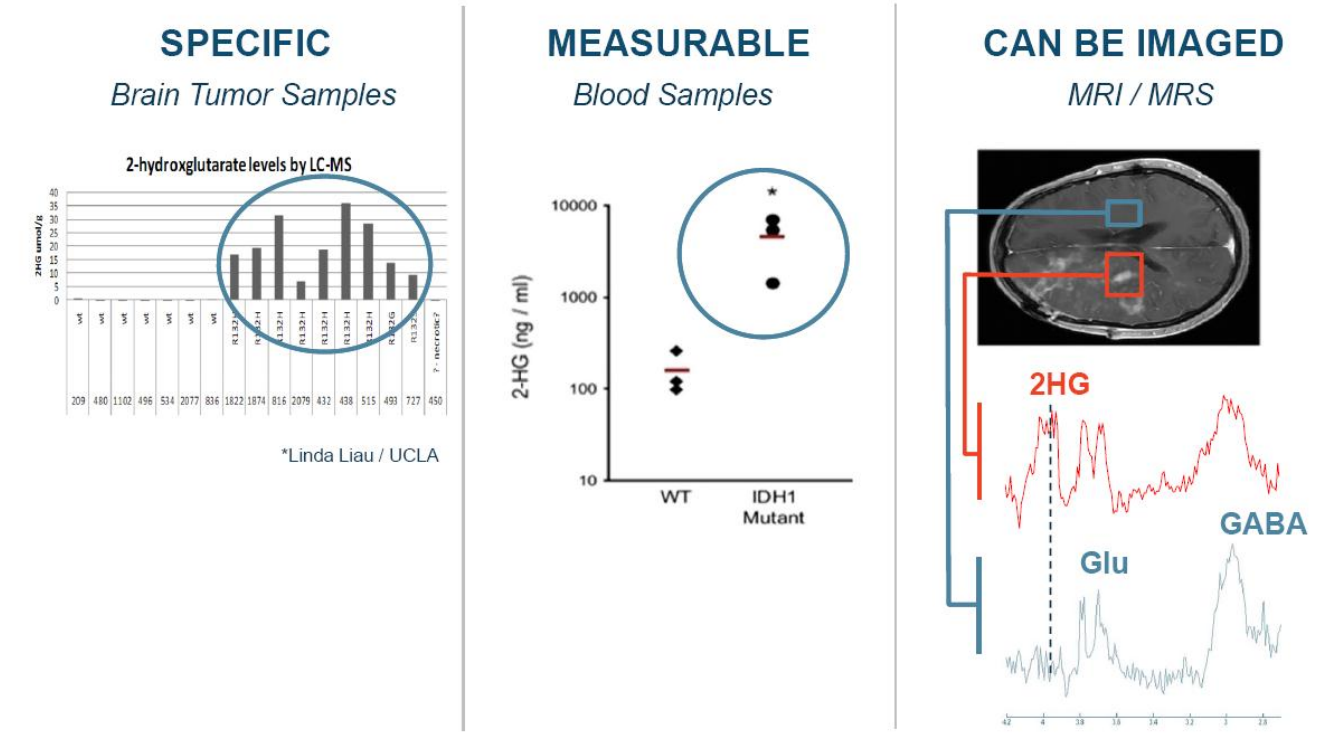
Source: Agios

Taken together, these data provide strong evidence that mutation of IDH enzymes promotes tumorigenesis by producing 2-HG, leading to a block in differentiation, and that this differentiation block can be relieved by pharmacological inhibition of the mutant IDH enzyme. We believe the mechanistic understanding of the role of IDH mutation in tumorigenesis elucidated by Agios and its collaborators provide a strong rationale for pursuing development of drugs targeting these mutations in affected patients. Consultants concur, noting that the evidence is strong that IDH mutations are early initiator events in tumorigenesis, with particularly strong evidence for this in brain cancer, AML, and chondrosarcoma.

2-HG Is A Great Biomarker, Too

As with all of Agios' drug development programs, the mutant IDH programs feature a robust biomarker useful for appropriate patient identification and for monitoring of drug activity. 2-HG has been shown to be markedly elevated in tumor samples from IDH1-mutant brain cancer patients, and can also be monitored noninvasively via an MRI-based assay. For liquid tumors, 2-HG is produced in such large quantities that it can simply be measured directly in blood or even urine samples. Thus, 2-HG is a useful biomarker for identifying appropriate patients. Moreover, a 2012 publication in *Blood* showed that in AML patients, blood 2-HG levels correlate closely with response and relapse to (conventional) therapy. Therefore, 2-HG is also a useful, early pharmacodynamic biomarker of drug activity in humans.

2-HG Is An Excellent Biomarker



Source: Agios

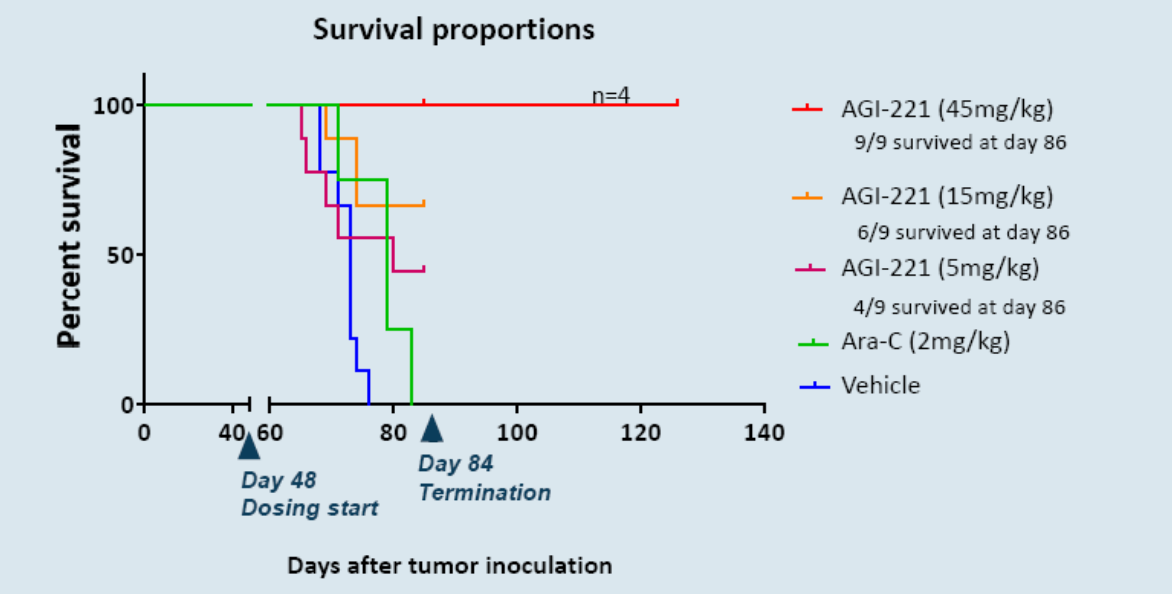
AG-221 Targets Mutant IDH2

Agios' most advanced program is AGI-221, an oral, selective inhibitor of mutant IDH2. AGI-221 began its Phase I trial in August 2013. Preclinical evidence suggests that AGI-221 has the potential to show striking single agent efficacy and a clean safety profile. Of course, the 2-HG biomarker should provide early evidence of the drug's activity, as well. Based on the preclinical data, we view IDH2 as Agios' most de-risked asset. We expect that Agios will retain a royalty interest under a licensing deal with Celgene.

Preclinically, Agios has shown that AG-221 achieves potent (IC50 = 12 nM), selective inhibition of mutant IDH2, sparing the wild-type protein (100-fold selectivity) and IDH1. *In vitro,* Agios has shown that AG-221 can reduce 2-HG levels to those found in normal cells, and that the drug can reverse the differentiation block in primary IDH2-mutant AML cells derived from patients. Most strikingly, Agios has shown dramatic single agent survival benefits in a mouse xenograft model of IDH2-mutant AML. In this model, irradiated mice are transplanted with human IDH2-mutant AML cells. The human cells colonize the bone marrow compartment and the mice invariably develop aggressive leukemia by day 40 post-injection, with death by day 76 without treatment. Treatment with a standard chemotherapeutic agent used in AML (cytarabine, a.k.a. AraC) provides modest survival benefit in this model, though all mice are still dead by about day 82. However, treatment with AGI-221 conferred dose dependent survival benefit that far

exceeded that seen with AraC: at lower doses, roughly 50% of mice survived and were doing well (stable weight) at day 84, when the experiment was terminated and mice sacrificed; at the highest dose tested (45 mg/kg), 100% (9 of 9) of mice remained alive and healthy at day 84, and though 5 were sacrificed at this point, the 4 that remained on treatment continued to survive past day 120 (the longest timepoint Agios has disclosed). The mice also showed lower 2-HG levels and signs of differentiation. These mouse data are quite striking, and suggest that AGI-221 has the potential to produce rapid, durable responses as a single agent in IDH2-mutant AML.

AG-221 Produces A Dose-Dependent Survival Benefit In A Xenograft AML Model



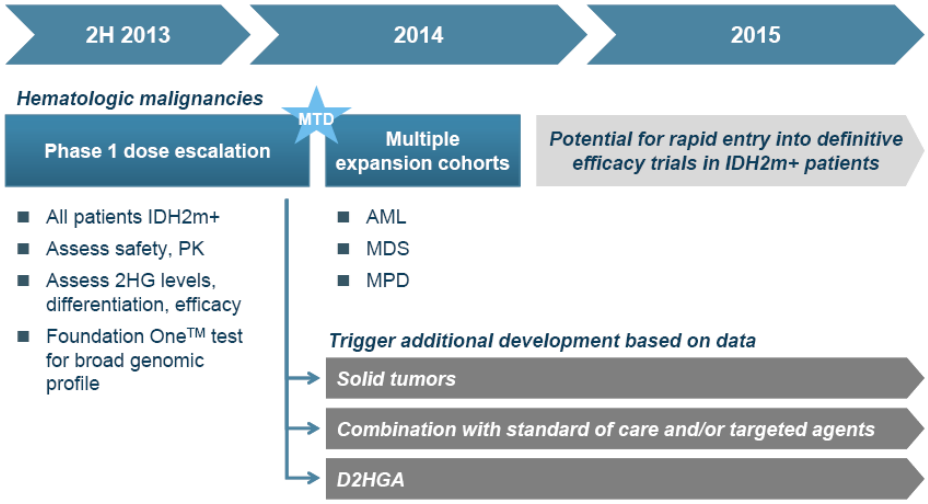
Source: Agios

Given AGI-221's selectivity only for the mutant, cancer-specific enzyme, one would expect a good safety profile with a tide therapeutic window. Indeed, Agios' preclinical toxicology work has supported this expectation. No particular safety signals were seen in the preclinical work at doses near the expected human dose (up to 5-8x the AUC97 dose). One monkey developed ulcerative colitis when inadvertently overdosed at 13x the AUC97 level. The rat no-effect dose level was higher still.

Agios' initial Phase I/II trial will enroll IDH2-mutant patients with advanced hematological malignancies, including relapsed/refractory or elderly AML and recurrent/refractory MDS. The multicenter Phase I, dose escalation portion will dose patients twice daily, and will primarily assess safety and PK, and determine the MTD and appropriate Phase II dose. The required proof of mechanism in Phase I will consist of demonstrated reduction in 2-HG levels, though efficacy (response rate at day 28 and every 56 days thereafter) will also be monitored. Exploratory endpoints will include the blast differentiation status in serial blood and bone marrow samples from patients, changes in metabolomics flux, and changes in DNA and histone methylation patterns in patient samples. Following Phase I, 10-20 patient Phase II

monotherapy expansion cohorts will be enrolled, each with a specific condition (e.g. AML, MDS, MPD). Additionally, cohorts testing AG-221 in IDH2-mutant solid tumors (e.g. IHCC, chondrosarcoma) and/or cohorts combining AG-221 with other therapeutic agents may begin enrollment. Any of these expansion cohorts could lead rapidly to proof of concept and registrational trials, under either an accelerated or standard approval framework. Notably, Agios is collaborating with Foundation Medicine to genotype patients entering the trial, in case genetic modifiers other than IDH2 status are needed to prospectively predict response to therapy via a companion diagnostic.

AG-221 Clinical Development Plan



Source: Agios

Consultants believe AG-221's clinical program is soundly designed. In the initial results, they will primarily focus on safety, particularly any signs of non-hematological toxicities since liquid tumor patients tend to exhibit hematologic problems secondary to their disease. Though they remain cautious on the potential for early efficacy, they believe that in advanced AML patients, a 20-25% response rate in Phase I would be very suggestive of meaningful activity.

Agios also plans to explore AG-221 as a treatment for a rare inborn error of metabolism (IEM), 2-HG aciduria, which is caused by germline mutation of IDH2 (discussed in more detail in the IEM section later in this report).

ATRA Experience In APML As Models For The IDH Liquid Program

In considering what outcome might be expected from the initial clinical trials of IDH2-mutant AML, it is interesting to consider the case of acute promyelocytic leukemia (APML). This rare form of AML is caused by a reciprocal translocation between chromosomes 15 and 17, resulting in the oncogenic fusion of the PML and retinoic acid receptor (RAR) genes. APML is extremely malignant, with a fatal course typically measured in weeks without treatment and a poor prognosis even with standard chemotherapy: despite 70-80% CR rates on a

chemotherapy cocktail, duration of remission was about 1-2 years and the cure rate about 40%. However, the introduction of all-trans retinoic acid (ATRA) in 1985, in one of the earliest examples of a targeted cancer therapy, dramatically improved the prognosis of the disease, increasing the CR rate to 90-95% and the cure rate to 74%.

The interesting parallel between APML and IDH2-mutant AML is that both appear to be driven by a block in differentiation. In APML, abnormal, immature promyelocytes dominate the bone marrow and accumulate in the blood. Conveniently, the diseased cells are visibly marked by a "rod" resulting from the translocation. When ATRA was given, it is clear that a differentiation block had been relieved, because the immature cells disappear and are replaced by differentiated cells, still bearing the "rod" and therefore descended from the previously blocked cells. An abundance of differentiated white blood cells appears within about 8-10 days, which are then cleared through chemotherapy and normal cellular attrition. Chemotherapy may also be needed to actually kill the malignant clones, rather than merely normalizing their differentiation as chronic ATRA treatment can do for a time. Patients generally achieve remission with ATRA+chemo in about 30-40 days. If the IDH2 program parallels ATRA, then, we may just possibly see comparable signs of disease modification in the IDH2 AML trials as soon as the first week or two of treatment at an effective dose, and perhaps even responses within a month or so.

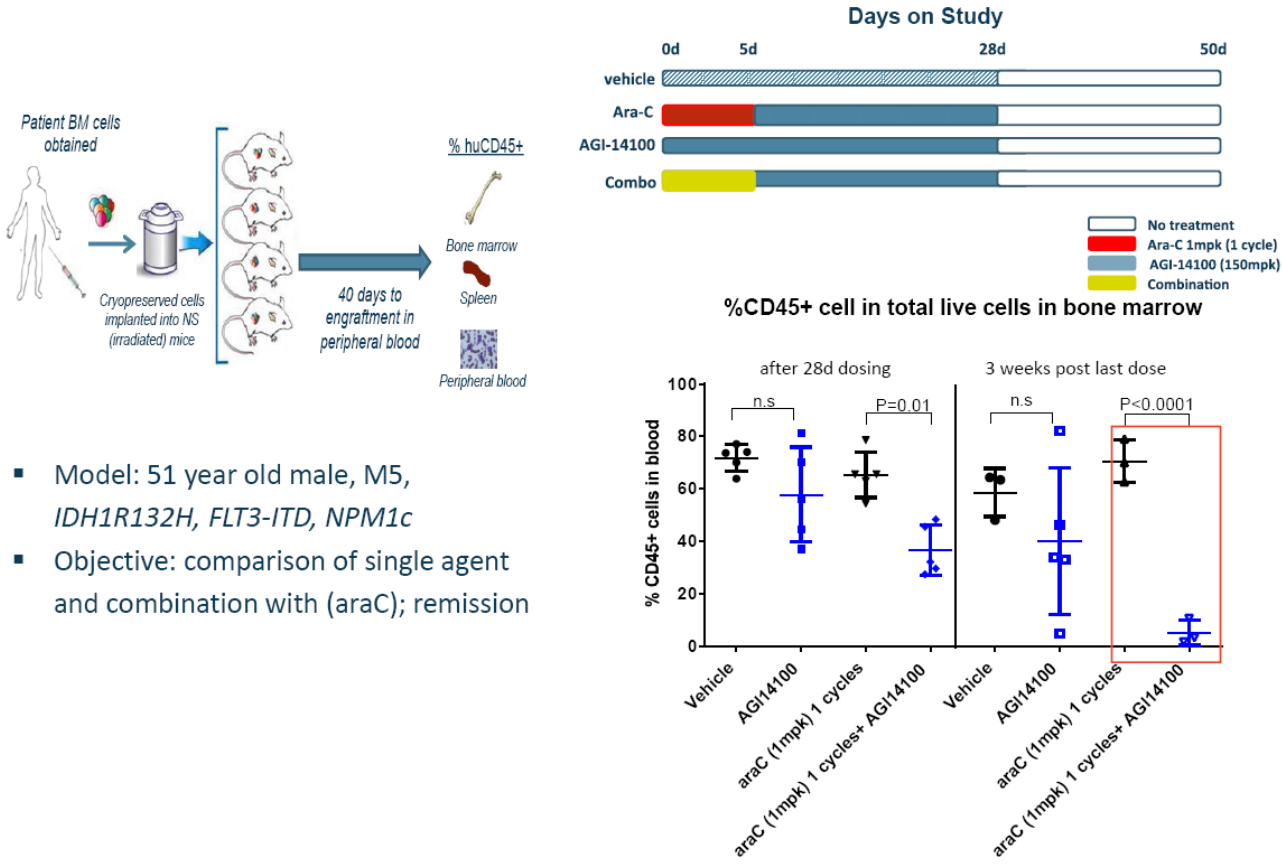
Consultants find the idea that IDH mutations block differentiation intriguing. They concur that AML is a disease of undifferentiated cells, and note that Ambit's FLT3 inhibitor quizartinib may function by relieving a differentiation block in FLT3-ITD mutant AML.

AG-120 Targets Mutant IDH1

Agios' next program in cancer metabolism is AG-120, targeting mutant IDH1. Agios expects to file the IND and enter Phase I in 2014. Preclinical evidence suggests that this candidate has good safety and single agent activity. Presently disclosed data suggest that it may be most effective in combination with other treatments, though we expect updated preclinical data at ASH in December 2013 to clarify AG-120's profile further.

Agios' preclinical work has shown that AGI-120 is a potent (IC50 = 8 nM), selective inhibitor of mutant IDH1 with oral bioavailability. The safety profile appears clean, with no MTD identified in rats and a 20x AUC97 margin of safety in monkeys. Agios is continuing efforts to identify a lethal dose in rats. In a preclinical model, in which IDH1 mutant AML cells from a patient are transplanted into irradiated mice, a related IDH1 inhibitor tool compound showed modest reduction of human cancer cell presence when given as a single agent after 28 days of dosing, and more robust reduction of human tumor cells after 28 days in combination with AraC. With longer followup (3 further weeks past the end of dosing), the response deepened dramatically in the combination-treated animals, and some individual single-agent animals appeared to develop deep responses as well. Agios has suggested that the apparent synergy between the two agents may be a result of the fact that IDH1 inhibition would only be expected to differentiate the cancer cells, not necessarily kill them, and the addition of a second, cytotoxic therapeutic agent might be necessary to actually clear the cells rapidly.

IDH1 Inhibitor Preclinical Efficacy



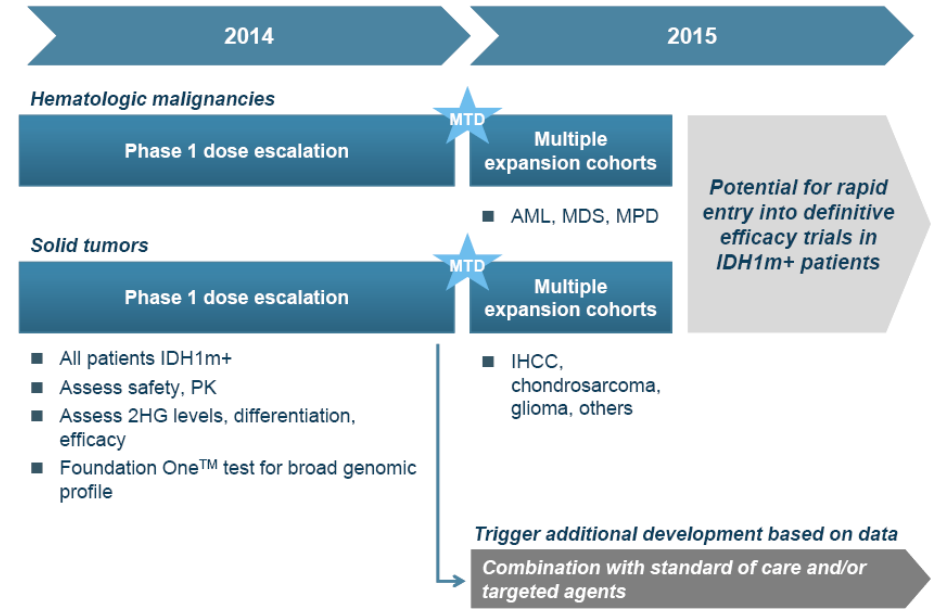
Source: Agios

Overall, we consider these preclinical data encouraging for AGI-120's potential in combination with other agents, and perhaps also as a single agent. The data are not quite as compelling as with AG-221, which showed robust single-agent survival data in the mouse model, but this is likely because: (1) the IDH1 data use a less potent tool compound, rather than the AG-120 clinical candidate, and/or (2) the IDH1 experiment had limited followup time due to CRO policy restrictions. Agios expects to present preclinical data generated in-house with the actual AG-120 clinical compound and less restrictive follow-up at ASH 2013, which should help clarify the drug's potential. It is also worth noting that IDH1 mutations tend to occur in solid tumors more than in liquid, and we would welcome additional preclinical data in solid tumor models, as we are unsure how applicable preclinical liquid tumor data is to the solid tumor settings.

Agios' clinical development plan for AG-120 is generally similar to the plan for AGI-221. The main difference is that AG-120 will simultaneously begin two Phase I dose escalation trials, one in hematological tumors and one in solid tumors. Following determination of the MTD, each will begin enrolling Phase II expansion cohorts of about 15 patients, with the liquid cohorts enrolling AML, MPD, and MDS patients, and the solid tumor cohorts enrolling IHCC,

chondrosarcoma, and glioma patients. Phase II combination cohorts may also enroll following Phase I.

AG-120 Clinical Development Plan



Source: Agios

Glutaminase Inhibitor Leads The Rest Of The Cancer Pipeline

Agios' third disclosed target in cancer is glutaminase (GLS). Glutaminase converts the amino acid glutamine into glutamate. Agios indicates that many cancers appear to rely on glutamine as a nutrient source, and believes that inhibition of glutaminase could be beneficial in these cancers. Agios has developed a proprietary data to allow identification of patients with tumors dependent on glutamine. The drug candidate is currently in the late lead optimization stage. Current candidates have < 20 nM IC50's and have shown inhibition of tumor growth in xenograft models. Few other specifics have been disclosed. We note that a glutaminase isoform that is particularly critical to cancer metabolism is glutaminase C, which is needed to keep the TCA cycle functioning (by catabolizing glutamine) in the context of a Warburg shift away from oxidative phosphorylation. Agios expects to enter the clinic with the glutaminase inhibitor in H2:14. The only competitor of which Agios is aware is Calithera, which has its own preclinical glutaminase inhibitor.

Behind glutaminase, Agios has one other validated program in drug discovery (target undisclosed) and 10 other potential cancer programs in early stages of validation.

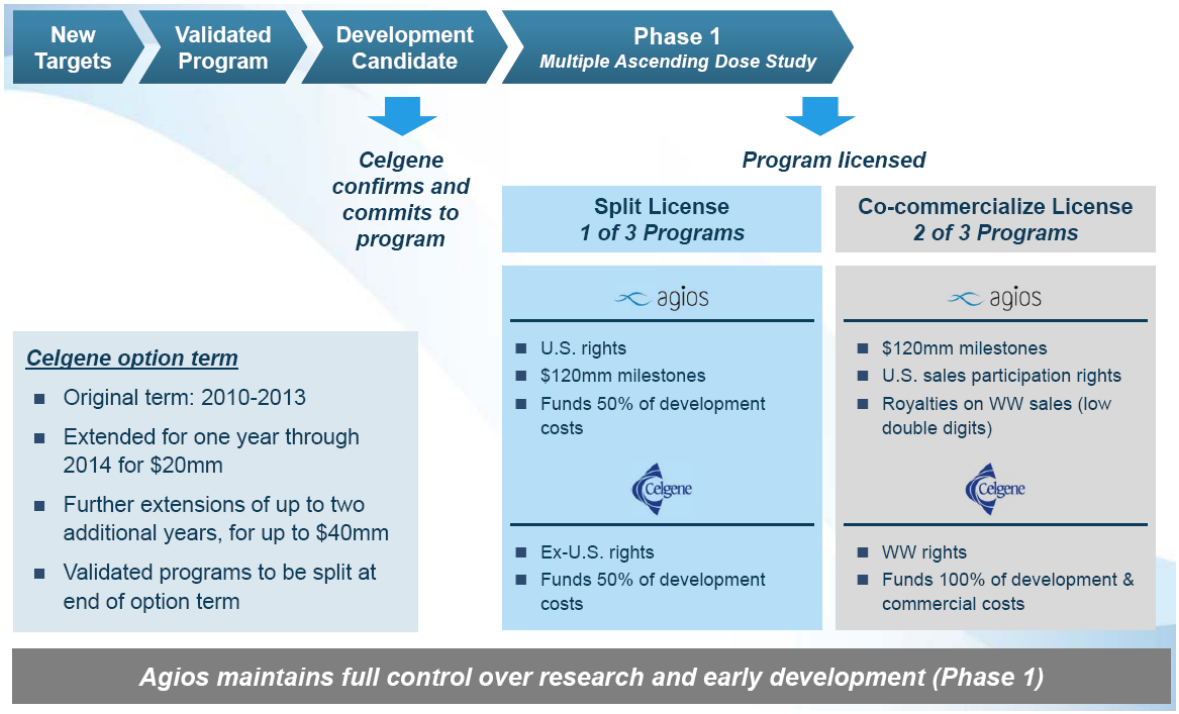
Partnered With Celgene On Cancer

All candidates Agios develops in cancer are currently covered by an exclusive research collaboration with Celgene. The initial term of the collaboration was from April 2010 – April 2013, for which Celgene paid $121MM cash and $9MM equity up front; subsequently, Celgene exercised the first of three one-year extension options, paying another $20MM fee. Should Celgene exercise its remaining two one-year options ($20MM apiece), the collaboration would extend to April 2016. Separately, Celgene invested $29MM in Agios' Series C private fundraising round and $12.75MM in its IPO.

Under the terms of the collaboration, Agios controls research and development of the covered compounds through IND filing. Celgene has the option to license the programs at IND filing, or it may choose to defer the decision on whether to license until after Phase I is complete (though in the latter case Celgene must pay milestones of at least $5MM to fund the conduct of the Phase I trial).

Of every group of three candidates that Agios nominates for development and that the Joint Research Committee confirms, up to two will be licensed to Celgene under a "co-commercialization" license (at Celgene's option), and one will be licensed under a "split license." Under the co-commercialization license, Celgene receives worldwide commercialization rights and funds all development after Phase I. Agios remains entitled to tiered 10-15% royalties on sales, up to $120MM in milestones per program, and a U.S. co-promote option (enabling Agios to build a commercialization organization at Celgene's expense). Under the split license, Agios retains full U.S. commercial rights and funds 50% of global development costs, as well as all of U.S.-specific development costs. Agios is also entitled to up to $120MM in milestones under each split licensed program. A crossing royalty between the partners on sales in their respective geographies is expected to lead to approximately equal global economic participation.

Celgene Collaboration Schematic



Source: Agios

The AGI-221 program targeting IDH2 has already been designated as a co-commercialization license. When the AGI-120 IND is filed, Agios will have the option to designate either AGI-120 or the GLS candidate as a split license program, though we expect the company will designate AGI-120 as the split license from this first group of three candidates.

In addition to the $120MM in potential milestones per program described above, Agios will receive two "bonus milestones:" $25MM when the last patient is dosed in Phase II for the first split program; and $22.5MM for the IND filing for the third program under the collaboration.

Celgene appears to be taking this partnership very seriously, with company representatives calling it "probably the most important of our collaborations at Celgene." Moreover, Celgene expressed a high level of confidence in AGI-221 and AGI-120, saying that the joint committee put them through a rigorous review process, sending Agios back to do additional experiments before ratifying them, all of which came back positive. Celgene expects an early signal of efficacy and short path to market. The company also believes these agents could have broad potential over time, perhaps as combinations with Celgene's other drug franchises.

The IDH Programs' Market Potential

Estimating the IDH1 and IDH2 programs' market potential is somewhat difficult, in that there is such a wide variety of indications in which each may play a key role and the development path is data-dependent and yet to be determined. In order to get some sense of the value of these

programs, we have chosen to model a scenario in which AGI-221 is successfully developed for AML, and AGI-140 for high-grade glioma. While these two are perhaps the best-studied potential indications, obviously the market opportunities as modeled do not include potential upside from great unmet needs such as cholangiocarcinoma, chondrosarcoma, and others. Indeed, management indicates that cholangiocarcinoma and chondrosarcoma could represent the fastest paths to market for the IDH1 program in particular. We will therefore be watching these indications with interest, but with no efficacy data to go on, we are not including these indications in our model for the moment.

Disease Background On AML

AML is one of the more common leukemias, with an annual incidence of about 14,500 in the U.S., and about 10,000 deaths annually attributed to the disease. However, no targeted agents are approved for AML. Treatment is typically based on chemotherapy, having changed little since the 1970's. The standard of care for AML is AraC (cytarabine), a DNA damaging agent that is widely used in both initial and relapsed disease. A number of other cytotoxic drugs including doxorubicin, idamycin, novantrone, and daunorubicin are also prescribed for AML. The goal of treatment with AML is to put patients into remission and then perform a hematopoetic stem cell transplant, the only potentially curative approach. However, the prognosis for AML remains poor, with a 5-year survival rate of less than 25%. Particular areas of unmet need include the relapsed/refractory setting and elderly AML, neither of which have any approved agents in the U.S.

Consultants indicated that there is a growing appreciation in the field that AML is not necessarily a homogenous disease, but is better defined as a collection of genotypically distinct entities that may be best treated with agents tailored to the specific mutations present. They are intrigued by the finding that a segment of the AML population carries IDH mutations and believe the rationale is strong to target these mutations therapeutically.

Market Opportunity In IDH2-Mutant AML

The American Cancer Society statistics indicate that there are about 14,500 newly diagnosed AML cases in the U.S. annually, and 10,000 deaths. We take these to represent the overall incidence of newly diagnosed and refractory AML, respectively, and assume that 15% of each group is IDH2 mutant. We assume that AGI-221 is developed under some rapid path to market for refractory patients, and that an indication for first-line patients follows about two years later. We assume a U.S. price of $10,000/month, rising by 5% per year and median duration of therapy of 6 months in the refractory setting and 12 months in the first-line setting. In the front line, we would expect an induction/consolidation/maintenance paradigm; ATRA maintenance can last for two years in APML, so our 12 month duration of therapy estimate could be low. (Some consultants have suggested that because IDH mutation may be an initiating event in cancer, drugs inhibiting IDH mutants could exert a Gleevec-like chronic control of the disease, implying a nearly indefinite duration of therapy; however, we await data supporting this paradigm before assuming it in our model.) We assume 70% peak penetration into the IDH2-mutant front line and $300MM+ in peak U.S. revenue. We assume ex-US revenue peaks at

about 120% of US revenue, a reasonable assumption in our view based on other cancer drugs. Altogether, our model projects over $650MM in peak global revenue. We model a 10-15% royalty to Agios, peaking at over $90MM. Approval in indications outside AML (MDS/MPN, angio-immunnoblastic NHL, etc) would represent upside to our estimates.

Market Opportunity For AGI-221 In IDH2-Mutant AML

U.S.	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**
Newly diagnosed AML incidence	14,500	14,500	14,500	14,500	14,500	14,500	14,500	14,500	14,500
% IDH2m	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
# IDH2m	2,175	2,175	2,175	2,175	2,175	2,175	2,175	2,175	2,175
% treated with AGI-221	*0%*	*0%*	*5%*	*35%*	*45%*	*55%*	*65%*	*69%*	*70%*
# treated with AG-221	0	0	116	761	979	1,204	1,408	1,507	1,525
duration of therapy (months)	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*
Relapsed/Refractory AML incidence	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
% IDH2m	*15%*	*15%*	*15%*	*15%*	*13%*	*11%*	*8%*	*7%*	*7%*
# IDH2m	1,500	1,500	1,500	1,450	1,300	1,100	800	700	650
% treated with AGI-221	*6%*	*35%*	*45%*	*54%*	*60%*	*60%*	*60%*	*60%*	*60%*
# treated with AG-221	83	525	675	784	780	660	480	420	390
duration of therapy (months)	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*
Price per patient per month ($000)	$10,000	$10,500	$11,025	$11,576	$12,155	$12,763	$13,401	$14,071	$14,775
U.S. AGI-221 Revenue In AML ($MM)	**$5**	**$33**	**$60**	**$160**	**$200**	**$235**	**$265**	**$290**	**$305**
Ex-U.S.									
Ex-U.S. AGI-221 Revenue In AML ($MM)	**$0**	**$7**	**$40**	**$130**	**$200**	**$260**	**$315**	**$350**	**$365**
% of U.S. revenue	*0%*	*20%*	*67%*	*81%*	*100%*	*111%*	*119%*	*121%*	*120%*
Total Global									
Total Global AGI-221 Revenue In AML ($MM)	**$5**	**$40**	**$100**	**$290**	**$400**	**$495**	**$580**	**$640**	**$670**
% royalty to Agios	*10%*	*10%*	*10%*	*12%*	*13%*	*14%*	*14%*	*14%*	*14%*
Global AGI-221 Royalty To Agios In AML ($MM)	**$0.5**	**$4.0**	**$10.0**	**$34.8**	**$52.0**	**$69.3**	**$81.2**	**$89.6**	**$93.8**

Source: Cowen and Company

Disease Background On Glioma

Gliomas are a group of brain cancers arising from glial cells. Gliomas are graded by severity from Grade 1 – 4, with Grade 1 being relatively noninvasive and potentially curable by resection, while Grade 3 – 4 are more aggressive, invasive, and generally fatal. Depending on the cell lineage from which they arise, Grade 2 brain cancers may be classified as oligoastrocytomas, oligodendrogliomas, or diffuse astrocytomas. Broadly speaking, the Grade 2 tumors can be classified into high- and low-risk groups, with median survivals of 4 and 11 years, respectively. Grade 2 tumors are generally progressive, and will transform into higher grade tumors within 5 years in about 50% of patients. Grade 3 tumors are more invasive versions of the Grade 2 tumors, and include anaplastic oligoastrocytoma, oligodendroglioma, and astrocytoma. Anaplastic astrocytoma is the most serious of these, with a median survival of about three years and a 5-year survival of about 25%. The most invasive and aggressive of gliomas are the Grade 4 lesions, called glioblastomas, or glioblastoma multiforme (GBM).

These cancers can also evolve from lower-grade tumors, in which case they are termed "secondary GBM," or they can arise without an apparent precursor lesion, in which case they are termed "primary GBM" (far the most common type of GBM, about 90%). GBM is almost uniformly fatal, with a 5 year survival rate of less than 5% and a median survival from diagnosis of under one year.

Treatment options for glioma are limited. For high grade lesions, surgical excision is the usual first line treatment, followed by adjuvant radiation (sometimes combined with systemic temzolomide chemotherapy, an FDA-approved option for first line GBM). Unfortunately, nearly all GBMs recur. Upon recurrence, treatments can include more surgery, more radiation, and/or more chemotherapy. The only other FDA-approved drug treatments for high grade gliomas are Roche's Avastin (for recurrent GBM only) and the Gliadel chemotherapeutic wafer, which is indicated for surgical implantation in first-line high grade gliomas and second-line GBMs.

Sequencing efforts have identified mutated IDH1, and less frequently, mutated IDH2, in a variety of glioma subtypes. IDH1 is mutated in the vast majority (80%) of secondary GBM, as well as about 8.5% of primary GBM (possibly representing misdiagnosed secondary GBM where the primary lesion was not identified). IDH1 and/or IDH2 are also mutated in the majority of Grade 2 – 3 gliomas, as shown in the following table.

Agios Estimates Of US/EU/Japan Incidence Of Various Types Of Glioma

	Tumor	Annual Incidence[1]	IDH1m (%)	IDH1m (n)	IDH2m (%)	IDH2m (n)
Higher-grade 3-4	Primary GBM	14,962	8.5%	1272	2%	299
	Secondary GBM	1,662	80.5%	1338	0	0
	Anaplastic Astrocytoma	2911	64%	1863	2.5%	73
	Anaplastic Oligodendrogliomas	1956	62%	1213	6.5%	127
	Anaplastic Oligoastrocytomas	978	83%	812	6%	59
Low-grade 1-2	Diffuse Astrocytoma	1956	78%	1526	4%	78
	Oligodendrogliomas	1956	76.5%	1496	5%	98
	Oligoastrocytomas	1956	89%	1741	1%	20

1. US, EU27, Japan www.globocan.iarc.fr

Source: Agios

Market Opportunity In IDH1-Mutant Glioma

Our revenue model for AGI-120 assumes that it is developed for recurrent GBM initially. We assume a 2-year delay to approval in first-line GBM, given that median survival in IDH1-mutant GBM is about 2.5 years and trials are therefore likely to take time. We also assume approval 2 years later in anaplastic astrocytoma, though this could require cooperative groups trials, as the survival time for IDH1-mutant anaplastic astrocytoma is reportedly quite long (median 5.4 years). While the drug may also have promise in less aggressive forms of glioma, these are

relatively slowly progressive (likely more so when IDH mutated), so we assume the development times would be very long in these conditions and do not include them in our model.

Data from the Central Brain Tumor Registry of the United States (CBTRUS) and the National Brain Tumor Society suggest that the incidence of GBM is about 2-3 per 100,000 in the U.S. We estimate that there are about 7,000 newly diagnosed GBM cases in the U.S. annually. Based on data from the Globocan project, Agios estimates that the US/EU/Japan incidence is about 16,000/year, which seems consistent with our U.S. estimate. In line with Agios' data, we model 15% of all GBM as IDH1 mutant (comprised of 80.5% of secondary GBM and 8.5% of primary GBM), or about 1,000 new IDH1-mutant GBM patients per year. Because the 2009 *NEJM* paper indicated that IDH-mutant GBM had a relatively good median survival prognosis of about 2.5 years, we assume a prevalence pool of around 2,600 GBM patients at the time AGI-120 launches. We model a 12-month treatment duration in the incident patients (once AGI-120 is approved in that setting), a 6-month treatment duration in the more advanced prevalent patients, and an initial price of $10,000/month in U.S., rising by 5% annually. Since Avastin yielded a PFS of about 6 months in its recurrent GBM trial, we think these duration of therapy estimates are reasonable. Because we model the prevalence pool being rapidly depleted after AGI-120 is introduced, by the peak years we model AGI-120 as treating a largely incident disease, with annual U.S. revenue in GBM of nearly $150MM.

The next most serious form of glioma after GBM is anaplastic astrocytoma. Since the CBTRUS data indicate that the incidence of anaplastic astrocytoma is only 11% that of GBM, we model only about 750 incident patients in the U.S. annually. (This may be a little low, as Agios' own estimate based on Globocan data for the US/EU/Japan is about 2,900.) We model 64% of these patients as being IDH1-mutant, or nearly 500 per year. The 2009 NEJM paper indicated that IDH1-mutant patients could live a median of nearly 5.5 years, we assume a prevalence pool at AGI-120's launch of about 2,500 IDH1-mutant anaplastic astrocytoma patients. We assume 12 months of therapy in all IDH1 mutant anaplastic astrocytoma patients, given their good prognosis. We model peak penetration of 70% into the IDH1 anaplastic astrocytoma patient population, with peak sustainable revenues of about $90MM in the U.S. in this indication (lower than a short term peak of $115MM as the prevalent patient bolus is worked through).

We do not model revenues in less aggressive forms of glioma, for the time being, as we would expect IDH1-mutant forms of these cancers would be very slowly progressive and the regulatory path presently unclear. Nevertheless, these indications could represent meaningful upside to our models. We also do not currently include AGI-120 revenues from non-brain cancer indications such as IHCC or chondrosarcoma, indications that management believe could be faster paths to market.

We assume ex-U.S. sales peak at about 120% of the U.S., a reasonable assumption in cancer, in our view. We assume a 50/50 revenue split between Agios and Celgene.

Market Opportunity For AGI-140 In IDH1-Mutant Glioblastoma And Anaplastic Astrocytoma

U.S.	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9
GBM Incidence (Primary & Secondary)	6,670	6,670	6,670	6,670	6,670	6,670	6,670	6,670	6,670
% IDH1m	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*	*16%*
# Incident GBM patients that are IDH1m	1,047	1,047	1,047	1,047	1,047	1,047	1,047	1,047	1,047
% treated with AGI-120	*0%*	*0%*	*5%*	*40%*	*45%*	*50%*	*58%*	*61%*	*71%*
# Incident GBM patients treated with AGI-120	0	0	52	419	471	518	607	638	744
duration of therapy (months)	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*
# Prevalent, IDH1m, AGI-120 Naïve GBM Patients	2,618	2,369	1,523	628	576	529	440	409	304
% treated with AGI-120	*10%*	*34%*	*48%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
# Prevalent GBM patients treated with AGI-341	249	794	731	314	288	264	220	205	152
duration of therapy (months)	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*	*6*
Price per patient per month ($)	$10,000	$10,500	$11,025	$11,576	$12,155	$12,763	$13,401	$14,071	$14,775
U.S. GBM Revenue ($MM)	**$15**	**$50**	**$55**	**$80**	**$90**	**$100**	**$115**	**$125**	**$145**
Anaplastic Astrocytoma Incidence	741	741	741	741	741	741	741	741	741
% IDH1m	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*	*64%*
# Incident AA patients that are IDH1m	474	474	474	474	474	474	474	474	474
% treated with AGI-120	*0%*	*0%*	*5%*	*32%*	*45%*	*48%*	*57%*	*62%*	*66%*
# Incident AA patients treated with AGI-120	0	0	24	152	213	228	272	296	315
duration of therapy (months)	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*
# Prevalent, IDH1m, AGI-120 Naïve GBM Patients	2,561	2,561	2,538	2,259	1,368	600	202	179	159
% treated with AGI-120	*0%*	*0%*	*5%*	*30%*	*40%*	*50%*	*50%*	*50%*	*50%*
# Prevalent AA patients treated with AGI-120	0	0	127	678	540	300	101	89	79
duration of therapy (months)	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*	*12*
Price per patient per month ($)	$10,000	$10,500	$11,025	$11,576	$12,155	$12,763	$13,401	$14,071	$14,775
U.S. Anaplastic Astrocytoma Revenue ($MM)	**$0**	**$0**	**$20**	**$115**	**$110**	**$81**	**$60**	**$65**	**$70**
Total U.S. Brain Cancer Revenue ($MM)	**$15**	**$50**	**$75**	**$195**	**$200**	**$180**	**$175**	**$190**	**$215**
Ex-U.S.									
Ex-U.S. AGI-120 Revenue In Brain Cancer ($MM)	**$0**	**$15**	**$45**	**$155**	**$200**	**$195**	**$215**	**$230**	**$255**
% of U.S. revenue	*0%*	*30%*	*60%*	*79%*	*100%*	*108%*	*122%*	*121%*	*118%*
Total Global									
Total Global AGI-120 Revenue In Brain Cancer ($MM)	**$15**	**$65**	**$120**	**$350**	**$400**	**$375**	**$390**	**$420**	**$470**
% revenue share to Agios	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Global AGI-120 Revenue To Agios In Brain Cancer ($MM)	**$7**	**$33**	**$60**	**$175**	**$200**	**$188**	**$195**	**$210**	**$235**

Source: Cowen and Company

IDH1-Mutant Chondrosarcoma And Cholangiocarcinoma Represent Additional Opportunities

Our models do not reflect any revenues from two other rare cancers in which IDH1 is frequently mutated, chondrosarcoma and intrahepatic cholangiocarcinoma (IHCC), pending evidence that inhibiting IDH1m is beneficial in these conditions. However, management is excited about these indications and believes they could represent rapid paths to market given the high unmet need, so they certainly bear watching.

Chondrosarcoma is a rare cancer of cartilage and bone. Standard of care is surgery and adjuvant chemo, which has a low response rate. Relapsed and unresectable tumors are incurable. The rate of IDH1 mutation in these cancers is very high (50-70%), which Agios believes represents an estimated 4,600 incident patients in the US/EU/Japan. We are not convinced that the incidence of chondrosarcoma is quite so high, however. The American cancer society indicates that there are about 3,000 cancers of the bones and joints diagnosed in the U.S. annually. Approximately one-third are chondrosarcomas, according to various published estimates, implying 500-700 IDH1m chondrosarcoma pateints in the U.S. annually. Grade 1 and 2 patients have a good prognosis without the need for systemic therapy, so the real U.S. opportunity is likely somewhat smaller than that. Overall, we estimate that chondrosarcoma might represent a $200MM US/EU/JP end-user revenue opportunity, which is not reflected in our estimates.

The second tumor type is cholangiosarcoma, a cancer of the bile ducts. The intrahepatic subset of these tumors is IDH1 mutant about 20% of the time, representing about 1,600 patients in the US/EU/Japan according to Agios' estimates. These tumors are usually incurable and rapidly fatal, with a 5-year survival rate of less than 5%.

Chondrosarcoma, IHCC, or any of the other indications in which IDH1 and/or IDH2 are mutant could represent additional revenue opportunities not reflected in our model.

Agios' Second Area Of Focus: Inborn Errors Of Metabolism

Outside of cancer metabolism, Agios' second major therapeutic focus is on a group of orphan genetic diseases called Inborn Errors of Metabolism (IEMs). This group comprises more than 600 recognized diseases caused by genetic defects in metabolic enzymes, which typically result in disease phenotypes as a consequence of accumulation of toxic intermediates in a metabolic pathway upstream of the defective enzyme and/or insufficient quantities of important metabolites downstream of the defective enzyme. Despite the rarity of these diseases, there have been notable commercial successes with therapeutics developed to address them, such as the enzyme replacement therapies for lysosomal storage disorders (examples include Sanofi/Genzyme's Cerezyme for Gaucher disease, Lumizyme for Pompe disease, and Fabrazyme for Fabry's disease, as well as BioMarin's Naglazyme for MPS VI, all multi-hundred million dollar products today). However, the vast majority of IEMs are not amenable to enzyme replacement strategies such as these because the defects are intracellular, and apart from the lysosomal disorders listed, intracellular delivery of functional enzymes is not feasible. Agios' metabolic insights should enable the company to develop small-molecule approaches to modulate enzymatic activity in the biochemical pathways in order to alleviate disease symptoms.

Agios' general approach to identifying IEMs amenable to therapeutic intervention and commercial attractiveness involves mining the available literature and genomic databases to identify disorders that are (1) monogenic (caused by a mutation in a single enzyme); (2) have a severe clinical presentation and high unmet need; (3) affect patients in sufficient numbers to conduct a clinical trial; (4) are potentially amenable to defect correction and disease

improvement via a small molecule approach; and (5) have a clear regulatory path to approval. As with all Agios' programs, the target indications also must have a clear means of identifying patients and a biochemical marker allowing monitoring of pharmacodynamic drug effect and rapid proof of concept.

Agios' lead candidate in IEMs, AGI-348, is intended to treat pyruvate kinase (PK) deficiency. AGI-348 is currently undergoing IND-enabling studies and is expected to enter the clinic in 2014. Agios is also interested in exploring the very rare IEM, 2-HG aciduria, which is caused by germline mutations in IDH2 and may be addressable with the cancer candidate AGI-221 or related compounds. Behind those two, Agios is validating 4 candidates for additional potential indications, with more expected to follow.

The IEM programs (with the possible exception of the 2-HG aciduria program) are not covered by the Celgene collaboration in cancer and are wholly owned by Agios.

PK Deficiency Is Agios' First IEM Target

Pyruvate kinase (PK) is the final enzyme in the glycolytic pathway, and is critical for energy (ATP) production in cells. PK exists in several isoforms in humans, with the pyruvate kinase R isoform being expressed specifically in red blood cells. Glycolysis is the only mechanism available to red blood cells to generate ATP, so absence of PKR activity is not compatible with life. However, patients can survive despite carrying mutations causing severely reduced (though not completely absent) PKR activity (typically <50% or normal, and as little as 3-10% of normal in severe cases). The resulting PK deficiency causes hemolytic anemia due to shortened lifespan of the red blood cells. The precise mechanism of destruction of the red blood cells is not fully understood, but is thought to be related to membrane instability downstream of the ATP production defect cause by PKR deficiency.

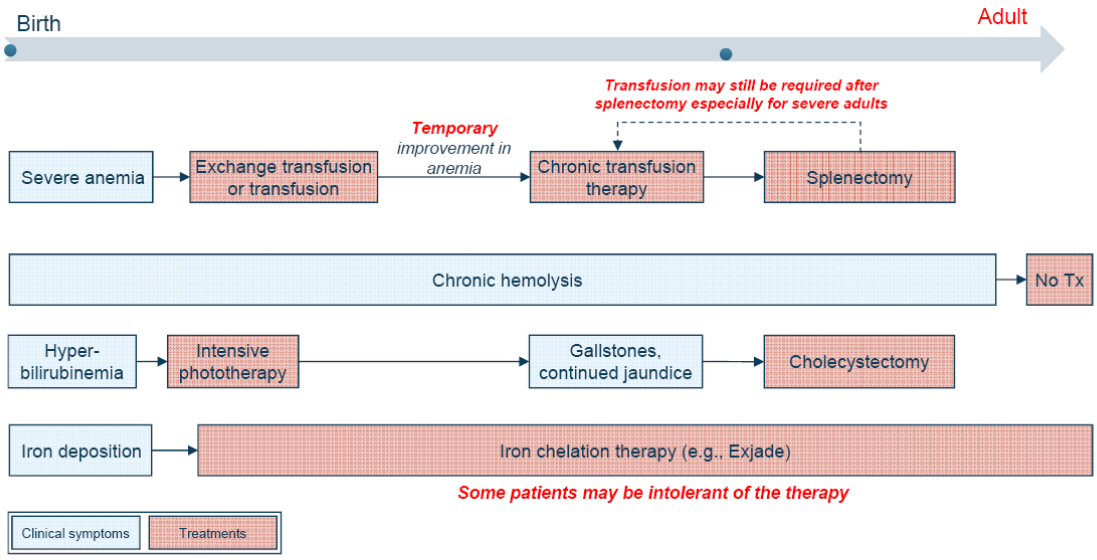
Understanding of the prevalence of PK deficiency is still evolving, but Agios estimates that there are 1,000 – 3,000 diagnosed patients living in the U.S. today, based primarily on several prevalence/natural history studies from the literature and on insurance claims data. Most diagnosed patients are classified as having severe or moderate disease. Consultants say there are pockets of increased incidence among the Amish and in the Middle East, but that symptomatic PKR is very rare.

Severe PK deficiency typically presents in infancy with hemolysis, anemia, jaundice and splenomegaly. In children, severe disease may be defined as an untreated Hb level of less than 8 g/dL and a lifelong need for transfusions, while moderate cases might have untreated Hb between 8-10 g/dL and intermittent transfusion support. Severe adult patients typically require chronic transfusions (perhaps monthly), while moderate adult cases could require intermittent transfusions. All patients can also suffer "hemolytic crises" when faced with infections or other stressors.

Current treatment for PK deficiency consists of chronic blood transfusions to maintain hematocrit, which leads to a requirement for iron chelation to manage the risk of iron overload.

Some patients may also undergo splenectomy, which alleviates the splenomegaly and can reduce the destruction of red blood cells in some cases, raising the Hb level by 1-3 mg/dL.

Current Supportive Treatment Paradigm For Severe PK Deficiency

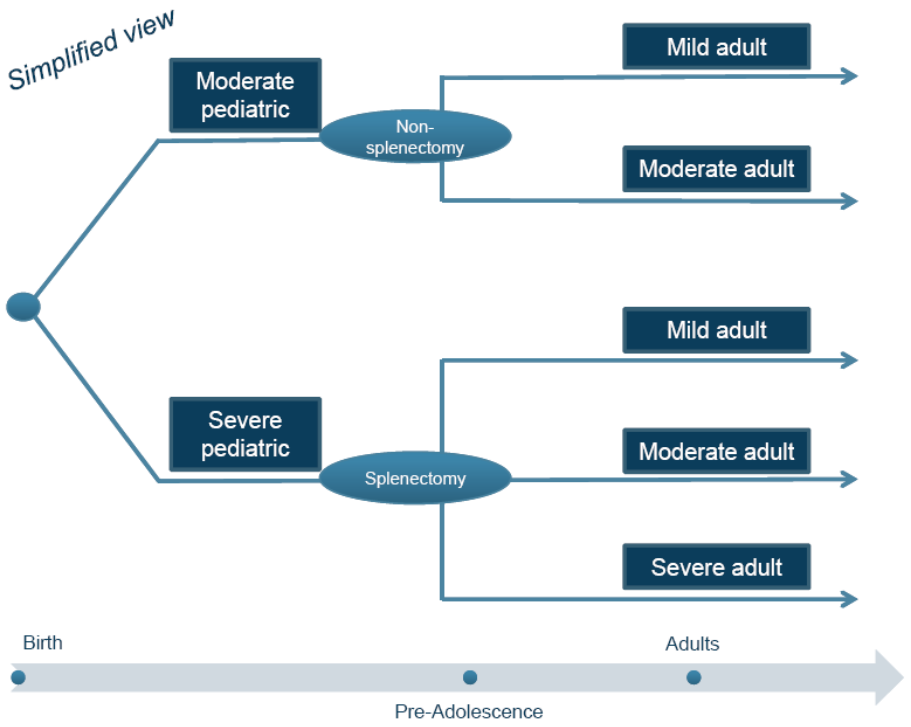


- Splenectomy is a medical intervention that has potential benefit for PKD
- Transfusion provides temporary relief but significantly increases risk of iron overload
- Current interventions do not halt chronic hemolysis which can have long-term consequences

Source: Agios

Moderately affected children can eventually become either moderately or mildly affected adults, while severely affected children may become severe, moderate, or mild adults. To further understanding of the natural history of PK deficiency, Agios is conducting a retrospective chart review of about 50 patients, and will prospectively follow a select group.

Evolution of Disease Course In PK Deficiency

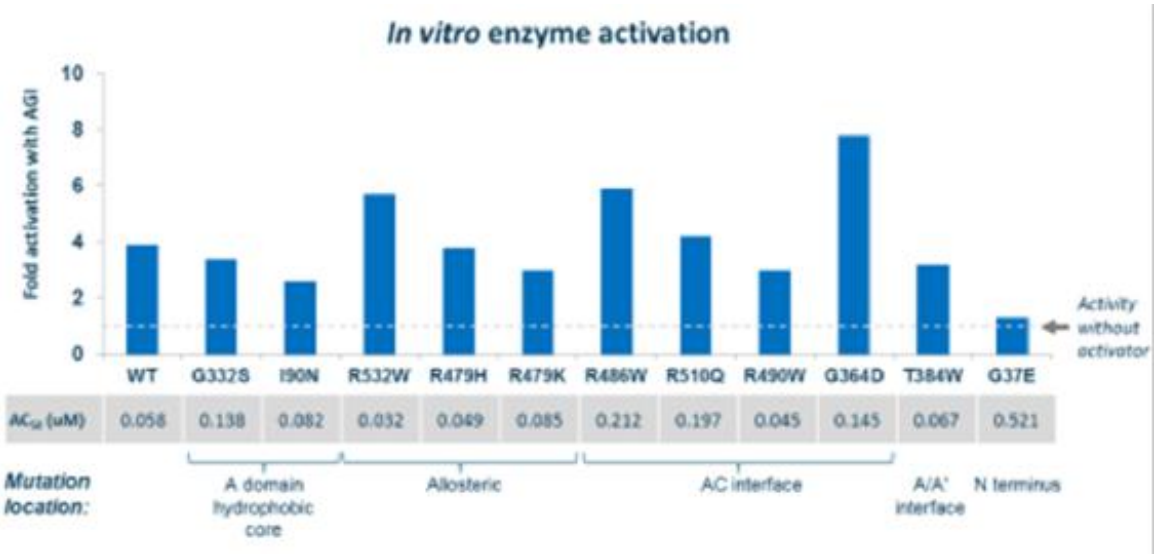


Source: Agios

AGI-348 Is Agios' Candidate For PK Deficiency

Agios is developing AGI-348, a potent, orally bioavailable activator of mutant PKR. More than 120 different human mutations in PKR have been reported, and PK deficiency patients are generally compound heterozygotes of two different hypomorphic alleles. Since their heterozygous parents are normal, we can surmise that ~50% enzyme activity is sufficient to achieve normalcy. AGI-348 binds to an allosteric site to modulate the activity of PK enzymes. Allosterically increasing the activity of an enzyme is a relatively novel notion. In designing AGI-348, Agios leveraged the structural understanding of the PK enzyme and associated metabolic pathways that arose from earlier work on these enzymes in cancer metabolism. *In vitro*¸ AGI-348 is able to substantially increase the activity of 11 of the 12 most common hypomorphic mutations by about 4- to 7-fold (vs. basal activity of perhaps 3-10% of normal). Therefore it is likely that one or both alleles carried by virtually all patients will be amenable to activation by AGI-348 to a degree that will improve disease symptoms.

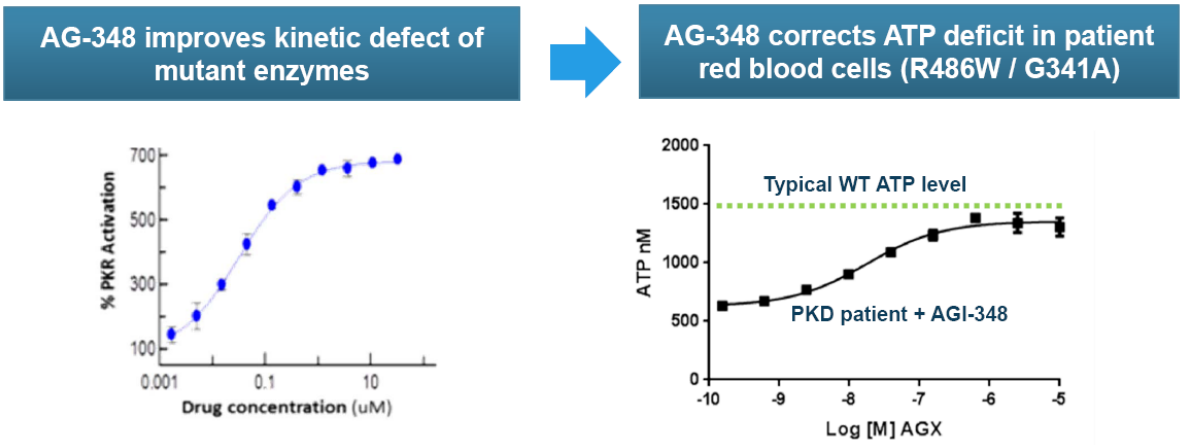
Mutant PK Activation by AGI-348 *In Vitro*



Source: Agios

Indeed, AG-348 is able to correct the metabolic defect *ex vivo* in red blood cells from a PK deficiency patient, resotring ATP levels to near normal. Agios is also generating knock-in mice with the three most common human PK deficiency mutations as a potential model of the disease.

AGI-348 Can Correct The Metabolic Defect In Patient Red Blood Cells



Source: Agios

AGI-348 has completed exploratory rat and primate safety studies with a good safety profile. The company is now initiating manufacturing campaigns to allow IND-enabling studies. An initial Phase I trial is expected to begin in 2014, and will likely enroll severe adult PKD patients, exploring dosing and safety, as well as biomarker response and potentially efficacy. The

company will seek to begin a parallel trial in severe pediatric patients as soon as sufficient experience is gained in the adult patient population.

Agios notes that the disease symptoms of PK deficiency parallel in many ways those of paroxysomal nocturnal hematouria (PNH), for which Alexion's Soliris is approved. This suggests that AGI-348 may be able to use the regulatory endpoints established by Soliris in its pivotal trial in PNH. The coprimary endpoints in Soliris' pivotal TRIUMPH trial in severe PNH were hemoglobin stabilization rate and median transfusion frequency vs. baseline, so these may be ultimately used to register AGI-348. Key secondary endpoints for AGI-348 could include improvements in hemolysis, transfusion independence, reduced risk of comorbidities, and improved quality of life, again comparable to the secondary endpoints in Soliris' pivotal trial.

We would note that the definition of "hemoglobin stabilization" was quite strict in TRIUMPH, requiring both continuous maintenance of hemoglobin above a basal "set-point," and no transfusions at all over a 6-month period. This may present a challenge in AGI-348's development, as achieving this bar will likely require either that AGI-348 be extremely effective in patients, or that patients of moderate severity be carefully selected in the trials. Ultimately, we think reduced transfusion frequency and some measure of improved well-being should be an approvable co-primary endpoint for AG-348.

Consultants note that the high unmet need, lack of treatment options, and small patient numbers lend many IEMs to potential accelerated approval on small trials. One consultant suggested that an approximately 9-patient dose-escalation Phase I trial could be sufficient to give a biochemical proof of principle for AGI-348, and could be followed immediately with a potential registrational trial, in his opinion.

Market Opportunity In PK Deficiency

Consultants emphasize that the size and severity of the PK deficiency population is indeed quite uncertain, and thus the commercial potential of AGI-348 is unclear pending greater clarity from natural history studies. A few literature reports represent perhaps the best source of prevalence estimates. A PK deficiency registry covering a population of 3.1 million in Northern England logged a prevalence of about 1:300,000 in a 2000 *Blood* report. A 2007 report noted that 7 patients had been identified in Northern Ireland; this is a country of 1.8 million, implying a diagnosed prevalence of about 1:250,000. In 1992, researchers reported a diagnosed prevalence of about 1:100,000 in Quebec. These reports, coupled with generally consistent estimates from insurance claims data, have led Agios to estimate that there may be 1,000 – 3,000 diagnosed PK deficiency patients in the U.S. Consultants estimate that about 50% of diagnosed U.S. patients are moderately affected, and 20% severely affected; therefore about 70% of diagnosed patients likely represent potential targets for AGI-348 therapy. The 30% of patients classified as mild do not have a need for additional treatment, in their view. They think about 500 U.S. patients may be pediatric.

We model a diagnosed prevalence of severe and moderate patients of 1,400 in the U.S. and 2,100 in the E.U. In line with ultra orphan pricing, we estimate a starting price of $300K/year in the U.S., growing by 5% annually, and $300K/year, without annual increases, in the E.U. We estimate just over 50% peak penetration in the U.S. and just over 40% in the E.U., driving $600MM+ in peak revenue. A potentially significant source of upside to our model is rest-of-world sales, which we have not included, to be conservative. However, we note that other orphan drugs (Alexion's Soliris, BioMarin's Naglazyme, etc) enjoy a significant contribution from R.O.W. sales, comprising 30% or more of the total. We assume that Agios commercializes AGI-348 itself in the US and EU, a strategy that other orphan disease-focused biotechs have shown to be both feasible and highly value-creating.

PK Deficiency Revenue Model

U.S.	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**
Prevalence of PK Deficiency Patients	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
% Severe or Moderate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# Severe or Moderate	1,400	1,400	1,400	1,400	1,400	1,400	1,400	1,400	1,400
% On Treatment	*8%*	*17%*	*25%*	*35%*	*45%*	*50%*	*52%*	*52%*	*53%*
# Treated	112	238	348	490	631	705	721	734	745
Price per patient per year ($000)	$300	$315	$331	$347	$365	$383	$402	$422	$443
U.S. AGI-348 Revenue ($MM)	**$34**	**$75**	**$115**	**$170**	**$230**	**$270**	**$290**	**$310**	**$330**
E.U.									
E.U. Prevalence of PK Deficiency Patients	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000	3,000
% Severe or Moderate	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
# Severe or Moderate	2,100	2,100	2,100	2,100	2,100	2,100	2,100	2,100	2,100
% On Treatment	*1%*	*5%*	*10%*	*17%*	*25%*	*35%*	*40%*	*42%*	*43%*
# Treated	21	101	217	367	517	733	833	883	900
Price per patient per year ($000)	$300	$300	$300	$300	$300	$300	$300	$300	$300
E.U. AGI-348 Revenue ($MM)	**$6**	**$30**	**$65**	**$110**	**$155**	**$220**	**$250**	**$265**	**$270**
US/EU AGI-348 Revenue In AML ($MM)	**$40**	**$105**	**$180**	**$280**	**$385**	**$490**	**$540**	**$575**	**$600**

Source: Cowen and Company

2-HG Aciduria Could Be An IEM Application Of IDH2-Targeting Agents

Agios' demonstration that IDH2 mutations cause elevated levels of 2-HG led another group of researchers to wonder if IDH2 mutation could play a role in a rare IEM called 2-HG aciduria (2-HGA). 2-HGA is characterized by high levels of 2-HG in patients' urine, plasma, and CSF. This disease manifests a variety of neurometabolic symptoms, including developmental delay, seizures, epilepsy, deformity, and cardiomyopathy. The condition is invariably fatal, usually by the teenage years, usually due to cardiac or nervous system disease. Indeed, when the researchers sequenced patients' IDH2 genes, they found that 2-HGA patients carry germline

mutations in IDH2, similar to the somatic, cancer-causing mutations described in a preceding section of this report.

Agios is potentially interested in evaluating AG-221 as a treatment for 2-HGA. The disease is extremely rare, with only about 50 cases reported globally, so the commercial opportunity may not be large. Still, underdiagnosis is possible, and Agios has initiated collaborations with global metabolic centers to more carefully explore the incidence and prevalence of the disease. Agios has also generated a genetic mouse model that appears to replicate features of 2-HGA (2-HG production, facial dysmorphism, death), which may be useful for evaluating AG-221 and other IDH2 selective compounds. Initial experiments indicate that AG-221 can knock 2-HG down to normal baseline in these animals. However, because AG-221 is not very CNS-penetrant, Agios may also consider developing a follow-on IDH2 inhibitor for 2-HGA.

Consultants View Agios As Still Growing Into The IEM Space

Consultants agree that the IEM space is a large market opportunity with many high unmet needs. Even in the best-studied IEM, phenylketonuria (PKU), they view available treatment options such as diet and BioMarin's Kuvan as woefully inadequate. Moreover, they expect that increasing newborn screening may drive expanded diagnosis of IEM patients, a positive for Agios. They believe the commerical opportunities are defined by the number of affected patients and the severity of disease, but also caution that the length of the therapeutic window must be considered, as some conditions result in irreversible damage by the time of birth. Generally speaking, they view Agios' cancer expertise and medicinal chemistry abilities as top notch, but feel the company needs to interface more with the IEM physician community more to identify top disease candidates, rather than its current strategy, focused largely on sifting through databases. That said, the consultants do believe Agios is properly bringing the right IEM expertise onto the staff and expect success in the IEM field.

Barriers To Competition Include Scientific Board And IP

Agios enjoys a number of competitive advantages and protections in its work. In addition to a clear first-mover advantage in flux metabolism and the associated accumulation of insights, data, knowhow and trade secrets, we believe Agios' scientific founders and board represent a substantial competitive barrier. Founding scientists Thompson, Cantley, and Mak were some of the key pioneers and leaders in the cancer metabolism space, and Agios has since added a number of other academic luminaries in the field to its board. The power of this competitive advantage is really illustrated by commentary from Celgene regarding its decision to partner with Agios. Celgene representatives tell us that the company recognized that cancer metabolism was one of several key areas likely to yield the next generation of important cancer medicines, and so Celgene was keen to partner in the space. Celgene found that there was really little choice but to partner with Agios, given that it had locked up all the scientific talent in the field, and so Celgene aggressively pursued the deal.

Agios also has more traditional competitive protection for its candidates in the form of pending IP. Agios has approximately 30 pending U.S. and 120 pending foreign patent applications.

Most of these are related to Agios' discovery programs, all of which were developed in-house, not inlicensed. The IP estate on AG-221, AG-120, the GLS program, and AG-348 includes pending patent applications covering composition, manufacturing, and methods of use. These patents, if issued, would expire between 2027 and 2034.

Agios Quarterly P&L Model ($MM)

	2012A	Q1:13A	Q2:13E	Q3:13E	Q4:13E	2013E
Product Revenue						
Collaboration Revenue	25.1	6.3	6.3	6.3	6.3	25.2
Total Revenue	**25.1**	**6.3**	**6.3**	**6.3**	**6.3**	**25.2**
COGS	0.0	0.0	0.0	0.0	0.0	0.0
R&D	41.0	11.5	12.0	12.5	13.0	49.0
SG&A	7.1	1.9	2.2	2.5	2.8	9.4
Total Expenses	**48.1**	**13.3**	**14.2**	**15.0**	**15.8**	**58.3**
Operating Income/ Loss	**(23.0)**	**(7.0)**	**(7.9)**	**(8.7)**	**(9.5)**	**(33.1)**
Non-Operating Income	0.1	0.0	0.0	0.0	0.0	0.0
Pre-tax Income/ Loss	**(22.9)**	**(7.0)**	**(7.9)**	**(8.7)**	**(9.5)**	**(33.1)**
Tax rate (%)	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Provision for income taxes	(2.8)	0.2	0.0	0.0	0.0	0.2
Net Income (Loss) From Operations	**(20.1)**	**(7.2)**	**(7.9)**	**(8.7)**	**(9.5)**	**(33.3)**
Cumulative Preferred Stock Dividends	(7.2)	(1.8)	(1.8)			
GAAP EPS	**($1.19)**	**($0.37)**	**($0.32)**	**($0.30)**	**($0.30)**	**($1.22)**
Diluted Shares	23.0	24.1	25.0	29.0	31.5	27.4

Source: Cowen and Company

Agios Annual P&L Model ($MM)

	2012A	2013E	2014E	2015E	2016E	2017E
Product Revenue	0.0	0.0	0.0	0.0	0.0	0.0
Collaboration Revenue	25.1	25.2	38.0	55.0	67.0	25.0
Total Revenue	**25.1**	**25.2**	**38.0**	**55.0**	**67.0**	**25.0**
COGS	0.0	0.0	0.0	0.0	0.0	0.0
R&D	41.0	49.0	58.0	64.0	74.0	76.0
SG&A	7.1	9.4	12.0	14.0	16.0	18.0
Total Expenses	**48.1**	**58.3**	**70.0**	**78.0**	**90.0**	**94.0**
Operating Income/ Loss	**(23.0)**	**(33.1)**	**(32.0)**	**(23.0)**	**(23.0)**	**(69.0)**
Non-Operating Income	0.1	0.0	0.0	0.0	0.0	0.0
Pre-tax Income/ Loss	**(22.9)**	**(33.1)**	**(32.0)**	**(23.0)**	**(23.0)**	**(69.0)**
Tax rate (%)	*NM*	*NM*	*NM*	*NM*	*NM*	*NM*
Provision for income taxes	(2.8)	0.2	0.0	0.0	0.0	0.0
Net Income (Loss) From Operations	**(20.1)**	**(33.3)**	**(32.0)**	**(23.0)**	**(23.0)**	**(69.0)**
GAAP EPS	**($1.19)**	**($1.22)**	**($0.95)**	**($0.65)**	**($0.60)**	**($1.75)**
Diluted Shares	23.0	27.4	33.7	35.5	38.2	39.5

Source: Cowen and Company

Valuation Methodology & Investment Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Company Specific Risks

Agios Pharmaceuticals is developing several, currently preclinical, drug candidates in the areas of cancer metabolism and inborn errors of metabolism. All of Agios' drug candidates face clinical and regualtory risk. With the future development path depending on the evolution of clinical data, future revenue forecasts are uncertain. The commercial outlook for Agios' candidates could additionally be altered by safety/efficacy findings, emerging competition, alterations in the medical treatment paradigm, or changes in the pricing environment. Some of Agios' projected market exclusivity depends on patents, which are subject to challenge by generic drugmakers.

Addendum

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Ticker	Company Name
AGIO	Agios Pharmaceuticals Inc

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

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Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

Neutral (2): Stock expected to perform in line with the S&P 500

Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	380	58.37%	48	12.63%
Hold (b)	247	37.94%	2	0.81%
Sell (c)	24	3.68%	1	4.17%

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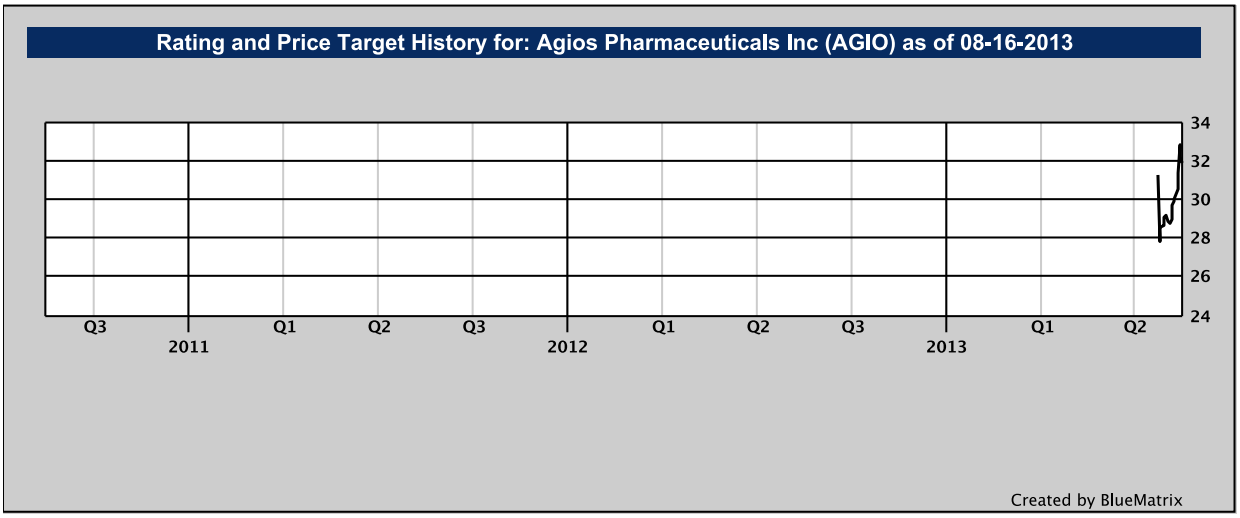

Legend for Price Chart:

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | T = Terminated Coverage | $xx = Price Target | NA = Not Available