Long-Term Treatment for Patients with AML with IDH Mutations

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## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td>Advisory Committee</td>
<td>Agios Pharmaceuticals Inc, Amgen Inc, Astellas, Daiichi Sankyo Inc, FUJIFILM Pharmaceuticals USA Inc, Menarini Group, Novartis</td>
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<td>Contracted Research</td>
<td>Astellas, FUJIFILM Pharmaceuticals USA Inc, Novartis</td>
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<td>Data and Safety Monitoring Board/Committee</td>
<td>Astex Pharmaceuticals</td>
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What initial treatment would you recommend for a 77-year-old woman with AML with an IDH1 mutation?

- Azacitidine + venetoclax: 17
- Decitabine + venetoclax: 2
- Azacitidine + venetoclax + ivosidenib: 2
- Azacitidine: 2
- Azacitidine + ivosidenib: 1
- Azacitidine + venetoclax or ivosidenib: 1
A 58-year-old patient with post-polycythemia vera myelofibrosis presents for management of AML and is found to have acquired an IDH1 mutation at the time of transformation. What would you recommend?

- Azacitidine + venetoclax: 10
- 7 + 3 induction: 4
- Azacitidine + ivosidenib: 3
- 7 + 3 induction + ivosidenib: 2
- Azacitidine + venetoclax + ivosidenib: 1
- Decitabine + venetoclax: 1
- Venetoclax: 1

N = 22
A 48-year-old patient with relapsed AML and an IDH1 mutation attains a complete remission with ivosidenib and proceeds to transplant. Upon engraftment, which of the following would you recommend to maintain remission?

- Ivosidenib: 16 votes
- Azacitidine/decitabine maintenance: 2 votes
- None: 7 votes

N = 25
A 64-year-old patient presents with new-onset shortness of breath, hypoxemia and fever 3 weeks into therapy with ivosidenib for relapsed AML. Chest CT reveals diffuse ground glass infiltrates. The patient has an ANC of 600, 27% blasts in the blood and has been receiving prophylaxis with levofloxacin and acyclovir only. What would you recommend?

- Continue ivosidenib and begin antibiotics and corticosteroids
- Discontinue ivosidenib and begin antibiotics and corticosteroids
- Continue ivosidenib and begin antibiotics
A 65-year-old man with relapsed/refractory AML and an IDH2 R140 mutation presents with a WBC of 25K and 80% blasts and is started on enasidenib. After 3 weeks, his WBC has risen to 50K and the patient still has 80% blasts. He is clinically stable otherwise. What would you recommend?

- Continue enasidenib and begin hydroxyurea: 17
- Continue enasidenib and begin hydroxyurea and corticosteroids for differentiation syndrome: 6
- Discontinue enasidenib and begin hydroxyurea and corticosteroids for differentiation syndrome: 2
- Stop enasidenib due to disease progression: 1

N = 26
Older patient, limited therapy options: 85 yo woman

• August 2015:
  • Several weeks of fatigue
• Past medical history- distant appendectomy, partial oophorectomy
• WBC 0.8, Hgb 8.7, plt 80K
• Bone marrow: 15% blasts
• Cytogenetics: 5q-
• Started therapy with azacitidine (with a community oncologist)

• December 2015:
  • Now transfusion dependent, both platelets and red cells
  • Follow up bone marrow- 95% blasts
• Lenalidomide added to 4th cycle of aza:
  • Transfusion dependence worsens
  • Pulmonary edema from recurrent transfusions
  • Fungal pneumonia, voriconazole started
Older patient, limited therapy options: 85 yo woman

- Referral to tertiary care (Hopkins)
- Admitted for management of fungal pneumonia, volume overload

- Leukemia mutation panel on bone marrow:
  - IDH1 R132L 45% VAF
  - SF3B1 K700E 45% VAF

- March 2016:
  - Pneumonia stabilized on voriconazole
  - Euvolemic on furosemide
  - Enrolls on ivosidenib protocol- 500 mg per day Day 1 3/9/16
  - Admitted on day 13 with leukocytosis, discharged on day 20 (see graph)
  - Proliferative phase of response managed with hydroxyurea.
  - Bone marrow biopsy on Day 28- 10% blasts

- Cycles 2 and 3 uneventful- transfusion independent
Older patient, limited therapy options: 85 yo woman

• Day 84 of therapy (May 2016)
  • Bone marrow biopsy morphologically normal, no evidence of AML
  • WBC 3.53, ANC 2.3, Hgb 9.6, platelets 142

• June 2016 - travels to Europe to visit sister

• March 2017 - progressive disease, IDH2 R140Q is now present in addition to IDH1 R132L

• No response to Aza/ven

• Dies of progressive AML October 2017
Differentiation syndrome causing acute kidney injury: 63 yo man

- August 2017:
  - Referred to community oncologist for abnormal counts

- Past medical history:
  - Diabetes, hypertension, gout, obesity
  - Mild thrombocytopenia (platelet count ~100K) for prior two years

- WBC 4.8, Hgb 9.1, plt 67K- 10% blasts

- Bone marrow: 15% blasts, high-grade MDS

- Cytogenetics: Normal

- Leukemia mutation panel:
  - IDH2 R140Q, 45% VAF
  - SRSF2 P95L, 49% VAF
  - DNMT3a R882P, 45% VAF

- Azacitidine for 3 cycles
Differentiation syndrome causing acute kidney injury: 63 yo man

- December 2017 bone marrow: 20% blasts
  - No change in mutation panel
- January 2018:
  - Enasidenib 100 mg per day
- Day 29 of therapy:
  - Patient complains of “feeling strange”
  - WBC increased to 13K, mostly neutrophils
  - Creatinine increased from 1.2 to 1.7
- Days 29-40 of treatment:
  - Steroids initiated
  - WBC peaks at 20K, creatinine peaks at 2.5 (see graph)
- Day 56 of treatment
  - Bone marrow biopsy- 2% blasts
  - Still requires platelet transfusions weekly
Differentiation syndrome causing acute kidney injury: 63 yo man

- March 2018
  - Non-myeloablative allogeneic transplant
- Grade 1 chronic GVHD
- Currently well (as of Dec 2019), no evidence of leukemia or GVHD
Isocitrate Dehydrogenase and Cancer

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

D. Williams Parsons,1,2*, Sián Jones,3* Xiaosong Zhang,1,1* Jimmy Cheng-Ho Lin,1,2* Rebecca J. Leary,1,2* Philipp Angenendt,1* Parminder Mankoo,1 Hannah Carter,1 J-Mei Siu,4 Gary L. Gallia,4 Alessandro Olivi,4 Roger McLendon,2 B. Ahmed Rasheed,2 Stephen Keir,5 Tatiana Nikolskaya,6 Yuri Nikolsky,7 Dana A. Busam,8 Hanna Tekleab,Luis A. Diaz Jr.,1 James Hartigan,9 Doug R. Smith, Robert L. Strausberg,10 Sueli Kazue Nagahashi Marie,10 Sueli Mieko Oba Shinjo,10 Hai Yan,2 Gregory J. Riggins,4 Darel D. Bigner,5 Rachel Karchin, Nick Papadopoulos,1 Giovanni Parmigiani,1 Bert Vogelstein,1† Victor E. Velculescu,1† Kenneth W. Kinzler†

Glioblastoma multiforme (GBM) is the most common and lethal type of brain cancer. To identify the genetic alterations in GBMs, we sequenced 20,661 protein coding genes, determined the presence of amplifications and deletions using high-density oligonucleotide arrays, and performed gene expression analyses using next-generation sequencing technologies in 22 human tumor samples. This comprehensive analysis led to the discovery of a variety of genes that were not known to be altered in GBMs. Most notably, we found recurrent mutations in the active site of isocitrate dehydrogenase 1 (IDH1) in 12% of GBM patients. Mutations in IDH1 occurred in a large fraction of young patients and in most patients with secondary GBMs and were associated with an increase in overall survival. These studies demonstrate the value of unbiased genomic analyses in the characterization of human brain cancer and identify a potentially useful genetic alteration for the classification and targeted therapy of GBMs.

Science 2008; 321:1807-12

Recurring Mutations Found by Sequencing an Acute Myeloid Leukemia Genome

We identified 12 acquired (somatic) mutations within the coding sequences of genes and 52 somatic point mutations in conserved or regulatory portions of the genome. All mutations appeared to be heterozygous and present in nearly all cells in the tumor sample. Four of the 64 mutations occurred in at least 1 additional AML sample in 188 samples that were tested. Mutations in NRAS and NPM1 had been identified previously in patients with AML, but two other mutations had not been identified. One of these mutations, in the IDH1 gene, was present in 15 of 187 additional AML genomes tested and was strongly associated with normal cytogenetic status; it was present in 13 of 80 cytogenetically normal samples (16%). The other was a nonsenic mutation in a genomic region with regulatory potential and conservation in higher mammals; we detected it in one additional AML tumor. The AML genome that we sequenced contains approximately 750 point mutations, of which only a small fraction are likely to be relevant to pathogenesis.

Isocitrate Dehydrogenase: Role in normal and malignant metabolism

**IDH1**
- Cytoplasmic enzyme
- Dimer
- NADP-dependent
- Mutated in cancer

**IDH2**
- Mitochondrial enzyme
- Dimer
- NADP-dependent
- Mutated in cancer

**IDH3**
- Krebs cycle enzyme
- Tetramer
- NAD-dependent
- Not mutated in cancer

\[ \text{IDH1} \rightarrow \text{IDH2} \rightarrow \text{IDH3} \]

\[ \text{NAD}^+ \rightarrow \text{NADH} \]

\[ \text{NADP}^+ \rightarrow \text{NADPH} \]

\[ \text{Isocitrate} \rightarrow \alpha\text{-ketoglutarate} \]

\[ \text{2-hydroxylglutarate (2HG)} \]

\[ \text{Co-substrate for epigenetic regulatory enzymes} \]

\[ \text{Functional antagonist of} \ \alpha\text{-ketoglutarate} \]

Nature 2009;462:739-744
Cancer Cell 2011;19:17-30
Science 2013;339:1621-1625
IDH mutations

- Identified in clinical specimens using NGS “hotspot” panel or targeted sequencing assay
- Occur only at specific sites
  - Destabilize a regulatory segment in the enzyme
  - IDH1: R132
  - IDH2: R140 and R172
- Confer a “neomorphic” enzyme function
  - Generates the “oncometabolite” 2-HG
- Open an allosteric pocket in the enzyme…
  - …making them susceptible to an inhibitor.

Structure 2017; 25:506-513
Clonal evolution of AML patient treated with the FLT3 inhibitor, gilteritinib

The impact of IDH mutations on myeloid stem cells

Relatively early mutation in leukemogenesis

Blood 2010; 115:2749

Biomarker to follow in plasma of AML patients

Blood, 2012;120:4649

Transforming effects on neighboring cells, microenvironment

Sci Rep 2016; 6:32428

Generates genetic heterogeneity


2HG

2HG

2HG

2HG

IDH-mutated AML cell

IDH2/SF3B1 clone

NRAS clone

Day 0 28 112 204

Baseline On-Treatment On-Treatment Relapse

= FLT3 / SF3B1 / IDH2

= FLT3 / SF3B1 / IDH2 / NRAS

= SF3B1 / IDH2

Cancer Discovery 2019; 9:1050-66
<table>
<thead>
<tr>
<th>IDH 1</th>
<th>IDH 2</th>
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<td>~7%</td>
<td>~10%</td>
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Blood. 2010;116:2122-2126  
J Clin Oncol 2010; 28:3636-3643  
Blood. 2010;116:5486-5496  
Prognostic impact of IDH mutations in AML

**IDH 1**

- IDH1 mutations: Slightly unfavorable

**IDH 2**

- IDH2 mutations: Neutral to favorable
Enasidenib

- Study AG221-C-001 (NCT01915498)
- 199 patients with relapsed/refractory IDH2-mutated AML
  - Median age 68
  - 78% R140
  - 22% R172
- 100 mg daily dose

Approved for treatment of relapsed or refractory AML with an IDH2 mutation

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>199 patients treated with 100 mg/day enasidenib</th>
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<tr>
<td>CR</td>
<td>19%</td>
</tr>
<tr>
<td>CRh</td>
<td>4%</td>
</tr>
<tr>
<td>CR/CRh</td>
<td>23%</td>
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Median duration of response 8.2 months
What the heck is a “CRh”? 

“Complete remission with partial hematological recovery if platelets > 50,000/microliter and absolute neutrophil counts > 500/microliter.”

Sincerely,
The FDA

(Sometimes referred to as “CR-Bahamas”)
• Responses take time…
  • Median time to CR = 3.7 months
  • VAF doesn’t seem to matter
• IDH2 inhibition leads to differentiation
• Clearance of IDH2 clone associated with CR
Ivosidenib

- Study AG120-C-001 (NCT02074839)
- Two cohorts
  - Relapsed/Refractory
    - 174 patients, median age 67
  - Older/unfit, untreated
    - 28 patients, median age 77
    - 13/28 (46%) prior HMA
- 500 mg daily dose


FDA label

Approved for treatment of relapsed or refractory AML with an IDH1 mutation, or for newly diagnosed IDH1 AML in patients who are ≥ 75 or unfit

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relapsed/refractory 174 patients</th>
<th>500 mg/day ivosidenib</th>
<th>Untreated/older 28 patients</th>
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<tr>
<td>CR</td>
<td>25%</td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>CRh</td>
<td>8%</td>
<td></td>
<td>CRh</td>
</tr>
<tr>
<td>CR/CRh</td>
<td>33%</td>
<td></td>
<td>CR/CRh</td>
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Median duration of response 8.2 months
Ivosidenib

• Study AG120-C-001 (NCT02074839)
• Median time to CR: 2.8 months
• Clearance of mutation associated with longer survival

IDH inhibitors

- Response not predicted by mutant allelic burden/VAF
- Kinetics of response may be SLOW
- Proliferative phase initially, followed by differentiation
- MTD not reached for either ivosidenib or enasidenib

**IDH 1**
- QTc prolongation
- Guillain-Barré Syndrome

**IDH 2**
- Indirect hyperbilirubinemia

Adverse Effects

...and differentiation syndrome.

Blood 2017;130:722-731
FDA label
**IDH Inhibitor-induced Differentiation Syndrome**

**Features**
- Develops anywhere from 2 weeks to 3 months after start of therapy.
- ~20% of patients treated.
- Signs, Symptoms
  - Fever, dyspnea, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, bone pain, and hepatic, renal, or multi-organ dysfunction.
- Can be fatal…
- Not associated with response.

**Management**
- Be looking for it!
- Initiate corticosteroids.
  - APL/ATRA syndrome is a useful guide
- Hospitalization often indicated.
- Empiric therapy for other possible conditions
  - i.e., infections
- Hydroxyurea for leukocytosis.
- Consider holding temporarily IDH inhibitor

Resistance to IDH inhibition

**Primary Resistance**
(Patient doesn’t respond at all)

- Remember - a low VAF doesn’t predict for resistance.
- RAS-pathway mutations
  - RAS, FLT3, CBL, PTPN11
- For IDH2 mutations, having 6 or more co-occurring mutations predicted for lower response.

**Secondary Resistance**
(Patient relapses after initial response)

- Isoform switching
  - i.e., going from an IDH1 to an IDH2 mutation, or the reverse.
- Trans or cis dimer interface mutations.
  - Prevents inhibitor from binding

References:
Cancer Discovery 2018; 8; 1540-7.
Blood 2019;133:676-687.
Other IDH inhibitors

• Vorasidenib (AG-881)
  • Oral, brain-penetrant
  • Dual IDH1/2 inhibitor
  • Phase 1 study in gliomas (ongoing)
    • 9.1% ORR
      ASCO 2019

• Olutasidenib (FT-2102)
  • Oral, brain-penetrant
  • IDH1 inhibitor
  • Phase 1 study in gliomas (ongoing)
    SNO 2019

Biochem Biophys Res Commun. 2018;503:2912-2917.
Combination strategies

• Combinations with HMAs
  - Enasidenib + Aza
    - DiNardo (ASH 2019 abstract #643)
    - Randomized
    - CR rate 50% v 12%
  - Ivosidenib + Aza
    - Daigle (ASH 2019 abstract #2706)
      - CR.CRh rate 70%
    - AGILE trial (randomized P3 trial underway)

• Combinations with targeted agents
  - Venetoclax
  - FLT3 inhibitors

• Maintenance therapy after consolidation chemotherapy or transplant.
  - Phase 1/2 trials underway

• Combinations with chemotherapy
  - Stein et al (ASH 2018 abstract #560)
  - Safe, effective
  - High rate of mutation clearance
HOVON/AML-SG Phase 3 Intergroup Frontline AML Trial

Primary Endpoint: EFS
Lots of work still to do…but we are making progress!

Newton- William Blake 1805