Myelodysplastic syndromes 2020

Guillermo Garcia-Manero MD
McCredie Professor of Medicine
Chief Section of MDS
Department of Leukemia
MD Anderson Cancer Center
University of Texas
Houston, TX
Diagnosis of MDS is based on morphology

Courtesy of Dr. Carlos Bueso-Ramos
Slow progress in MDS

- **Chronological order of discoveries in MDS:**
- IPSS classification: 1997
- Approval of azacitidine: 2004
- Approval of lenalidomide: 2005
- Approval of decitabine: 2006
- Improved cytogenetic classification: 2012
- Application of NGS assays in MDS: 2013
Weighting of Cytogenetics in Relation to BM blast counts in IPSS

Figure 1 A-D
Overall survival and cumulative risk of AML-transformation in IPSS cytogenetic and FAB bone marrow blast count subgroups (univariate analysis; pts. treated with supportive care exclusively)

(Schanz et al., JCO, 2011)
Cytogenetic Scoring System in MDS

(Schanz et al., JCO, 2011)
# Revised IPSS

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk score</th>
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<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5-3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3-4.5</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5-6</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>
Genomics of MDS

Papaemmanuil et al Blood 2013;122:3616-27
17 genes sequenced in 1996 patients with OS data

**Overall Survival by Mutation Number**

- **0** (n=377)
- **1** (n=595)
- **2** (n=460)
- **3** (n=210)
- **4** (n=125)
- **5/6/7** (n=22)
- **SF3B1 only** (n=207)

- **ASXL1**
- **CBL**
- **DNMT3A**
- **ETV6**
- **EZH2**
- **IDH1**
- **IDH2**
- **JAK2**
- **KRAS**
- **NPM1**
- **NRAS**
- **RUNX1**
- **SRSF2**
- **TET2**
- **TP53**
- **U2AF1**
- **SF3B1**
Clonal Progression from Myelodysplastic Syndrome (MDS) to Secondary Acute Myeloid Leukemia (sAML).

Proposed treatment algorithm for patients with MDS

MDS

Lower-risk
(IPSS low, INT-1)
(BM blasts < 10%)

Any age

• Iron chelation
• Growth factors
  (Epo + G-CSF)
• MTI (5-AZA/decitabine)
• Lenalidomide (5q-)
• Immunomodulation
• Clinical trial

Higher-risk
(IPSS INT-2, high)
(BM blasts ≥ 10%)

Age < 70

• Intensive chemotherapy
• MTI (5-AZA/decitabine)
• Clinical trial

Age ≥ 70

• MTI (5-AZA/decitabine)
• Clinical trial
• Intensive chemotherapy

Failure/
Progression

Failure

Failure

Allo SCT

Modified from Atallah. Cancer Inv. 2008;26:208-16
MDS 2019: Outline

• Immediate impact:
  – Luspatercept
  – ASTX727 (oral decitabine)

• Coming 2020:
  – ABT-199
  – APR-246
  – IDH2, IDH1
  – Magrolimab

• Other agents: TIM-3, rigosertib, CB393, H3BIO
Assessment of Longer-Term Efficacy and Safety in the Phase 3, Randomized, Double-Blind, Placebo-Controlled MEDALIST Trial of Luspatercept to Treat Anemia in IPSS-R Very Low-, Low-, or Int-Risk RBC Transfusion-Dependent MDS with Ring Sideroblasts (RS)

Pierre Fenaux1,2, Ghulam J. Mufti3, Rena Buckstein4, Valeria Santini5, María Díez-Campelo6, Carlo Finelli7, Mario Cazzola8, Osman Ilhan9, Mikkael A. Sekeres10, Rami S. Komrokji11, Alan F. List11, Amer M. Zeidan12, Amit Verma13, Abderrahmane Laadem14, Rodrigo Ito14, Jennie Zhang14, Anita Rampersad14, Daniel Sinsimer14, Peter G. Linde15, Guillermo Garcia-Manero16, Uwe Platzbecker17

1Service d’Hématologie Séniors, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, Paris, France; 2Université Paris 7, Paris, France; 3Department of Haematology-Oncology, King’s College London, London, UK; 4Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 5MDS Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; 6Hematology Department, Institute of Biomedical Research of Salamanca, University Hospital of Salamanca, Salamanca, Spain; 7Department of Oncology and Hematology, S. Orsola-Malpighi University Hospital, Bologna, Italy; 8Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; 9Department of Hematology, Ankara University School of Medicine, Ankara, Turkey; 10Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; 11Moffitt Cancer Center, Tampa, FL, USA; 12Department of Internal Medicine, Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; 13Department of Oncology, Albert Einstein College of Medicine, Bronx, NY, USA; 14Bristol-Myers Squibb, Summit, NJ, USA; 15Acceleron Pharma, Cambridge, MA, USA; 16Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; 17Medical Clinic and Policlinic 1, Hematology and Cellular Therapy, University Hospital Leipzig, Hematology and Cellular Therapy, Leipzig, Germany

Abstract #841
Luspatercept is a first-in-class erythroid maturation agent that binds several TGF-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis.

Luspatercept is approved by the US FDA for the treatment of anemia in adult patients with β-thalassemia who require regular RBC transfusions.

In the primary results of the MEDALIST trial, luspatercept met the following endpoints with statistical significance versus placebo:

- Primary endpoint: RBC-TI ≥ 8 weeks (Weeks 1–24)
- Key secondary endpoint: RBC-TI ≥ 12 weeks (Weeks 1–24, Weeks 1–48)

Presented here is an updated analysis of longer-term clinical benefit and safety data from the MEDALIST trial.

**Inclusion Criteria**

- MDS with RS (WHO): ≥ 15% RS or ≥ 5% with SF3B1 mutation
- < 5% blasts in bone marrow
- Non-del(5q) MDS
- IPSS-R Very low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 U/8 weeks
- No prior treatment with disease-modifying agents (e.g. IMiD agents, HMAs)

**Randomized 2:1**

- **Luspatercept 1.0 mg/kg (s.c.) every 21 days**
  - (n = 153)
  - Dose titrated up to a maximum of 1.75 mg/kg

- **Placebo (s.c.) every 3 weeks**
  - (n = 76)

**Disease and response assessment**

- Week 24 and every 6 months
- Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria

**Patients followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment, and overall survival; crossover between groups was not allowed**

Primary analysis data cutoff date May 8, 2018; current data cutoff date July 1, 2019.

Patients were randomized between March 2016 and June 2017 at 65 sites in Belgium, Canada, France, Germany, Italy, Netherlands, Spain, Sweden, Turkey, UK, and USA.

AML, acute myeloid leukemia; EPO, erythropoietin; HMA, hypomethylating agent; IMiD, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; WHO, World Health Organization.
When assessed during the entire treatment period, a greater proportion of luspatercept-treated patients achieved RBC-TI ≥ 8 weeks compared with placebo than previously reported (37.9% of patients receiving luspatercept achieved RBC-TI ≥ 8 weeks during Weeks 1–24 of treatment vs 13.2% of placebo-treated patients; \( P < 0.0001 \))^1

Abstract #841
### RBC-TI ≥ 8 WEEKS ACHIEVED DURING THE ENTIRE TREATMENT PERIOD
#### RESPONSE BY BASELINE TRANSFUSION BURDEN

<table>
<thead>
<tr>
<th>RBC-TI ≥ 8 Weeks Over the Entire Treatment Period</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
<th>Luspatercept Minus Placebo OR (95%CI)a</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average baseline RBC transfusion requirement, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 6 U/8 weeks</td>
<td>14/66 (21.2)</td>
<td>2/33 (6.1)</td>
<td>4.17 (0.89–19.60)</td>
<td>0.0547</td>
</tr>
<tr>
<td>≥ 4 to &lt; 6 U/8 weeks</td>
<td>20/41 (48.8)</td>
<td>2/23 (8.7)</td>
<td>10.00 (2.07–48.28)</td>
<td>0.0013</td>
</tr>
<tr>
<td>&lt; 4 U/8 weeks</td>
<td>39/46 (84.8)</td>
<td>8/20 (40.0)</td>
<td>8.36 (2.51–27.83)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

a Determined using a Cochran-Mantel-Haenszel test.

- More luspatercept-treated patients achieved RBC-TI ≥ 8 weeks over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden.
COMBINED DURATION OF RBC-TI ≥ 8 WEEKS AND mHI-E ACHIEVED DURING THE ENTIRE TREATMENT PHASE

Duration, median (95% CI), weeks: 69.6 (52.0–111.6) vs 22.7 (14.9–52.0)
Hazard ratio (95% CI): 0.494 (0.256–0.953)

Abstract #841
Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross-Over Phase 3 Study (ASCERTAIN) of an Oral Hypomethylating Agent ASTX727 (cedazuridin/decitabine) Compared to IV Decitabine

Guillermo Garcia-Manero¹, James McCloskey², Elizabeth Griffiths³, Karen Yee⁴, Amer Zeidan⁵, Aref Al-Kali⁶, Kim-Hien Dao⁷, H Joachim Deeg⁸, Prapti Patel⁹, Mitchell Sabloff¹⁰, Mary-Margaret Keating¹¹, Nancy Zhu¹², Nashat Gabrail¹³, Salman Fazal¹⁴, Joseph Maly¹⁵, Olatoyosi Odenike¹⁶, Aditi Shastri¹⁷, Amy E DeZern¹⁸, Casey O’Connell¹⁹, Gail Roboz²⁰, Aram Oganesian²¹, Yong Hao²¹, Harold Keer²¹, Mohammad Azab²¹, Michael Savona²²

On behalf of ASCERTAIN Investigators Team

¹The University of Texas MD Anderson Cancer Center, Houston, TX; ²John Theurer Cancer Center, Hackensack Medical Center, NJ; ³Roswell Park Comprehensive Cancer Center, Buffalo, NY; ⁴Princess Margaret Cancer Centre, Toronto, Ontario, Canada; ⁵Yale University and Yale Cancer Center, New Haven, CT; ⁶Mayo Clinic, Rochester, MN; ⁷Oregon Health & Science University, Portland, OR; ⁸Fred Hutchinson Cancer Research Center, Seattle, WA; ⁹University of Texas Southwestern Medical Center, Dallas, TX; ¹⁰Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada; ¹¹Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; ¹²University of Alberta, Edmonton, Alberta, Canada; ¹³Gabrail Cancer Center, Canton, OH; ¹⁴West Penn Hospital, Allegheny Health Network, Pittsburgh, PA; ¹⁵Norton Cancer Institute, Louisville, KY; ¹⁶University of Chicago, Chicago, IL; ¹⁷Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY; ¹⁸Johns Hopkins University Hospital, Baltimore, MD; ¹⁹USC Keck School of Medicine, University of Southern California, Los Angeles, CA; ²⁰Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

Clinicaltrials.gov NCT03306264
Current HMA treatment poses significant patient burden due to 5–7 days per month of parenteral administration in a clinic setting.

Oral bioavailability of HMAs decitabine and azacitidine is limited due to rapid degradation by CDA in the gut and liver.

Cedazuridine is a novel, potent, and safe CDA inhibitor. Large safety margin, with no adverse events at up to 200 mg/kg in monkeys (~2400 mg/m² human equivalent).

CDA, cytidine deaminase.
Oral ASTX727 (cedazuridine 100 mg / decitabine 30 to 40 mg) achieved decitabine AUC 5-day exposures oral/IV ratio between 81% and 128%.

Oral ASTX727 (cedazuridine 100 mg / decitabine 35 mg) selected for Phase 2.


AUC, area under concentration-time curve; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.
**ASTX727 Phase 2: Durable Clinical Responses in MDS/CMML Patients**

<table>
<thead>
<tr>
<th>Best Response</th>
<th>N=80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>21.3%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>0</td>
</tr>
<tr>
<td>Marrow CR (mCR)</td>
<td>22.5%</td>
</tr>
<tr>
<td>mCR with hematologic improvement</td>
<td>7.5%</td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>16.3%</td>
</tr>
<tr>
<td>HI-erythroid</td>
<td>10%</td>
</tr>
<tr>
<td>HI-neutrophils</td>
<td>2.5%</td>
</tr>
<tr>
<td>HI-platelet</td>
<td>13.8%</td>
</tr>
<tr>
<td>Overall response (CR + PR + mCR + HI)</td>
<td>60%</td>
</tr>
</tbody>
</table>

RBCs transfusion independence (n=38)* 50%
Platelets transfusion independence (n=12)* 50%

* No transfusion for at least 8 consecutive weeks in patients who were transfusion dependent at baseline.


Median FU: 24 months; median number of cycles: 7
CR median duration of response: 13.3 months
Median overall survival: 18.3 months
ASTX727 Phase 3 Study (ASCERTAIN) in MDS/CMML

Trial Design: Randomized Cross-Over

**Major entry criteria**
- Candidates for IV decitabine
- ECOG PS 0–1
- Life expectancy of ≥3 months
- Adequate Organ Function
- One prior cycle of HMA is allowed

**Primary endpoint**
- Total 5-d decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

**Secondary endpoints**
- Efficacy: Response rate; Transfusion independence; duration of response; Leukemia-free and overall survival
- Safety of ASTX727
- Max LINE-1 demethylation

(int/high risk MDS; CMML; AML 20–30% blasts)

**Trial Design**

<table>
<thead>
<tr>
<th>Sequence A</th>
<th>Sequence B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Cycle 2</td>
</tr>
<tr>
<td>Oral ASTX727 1 tablet x 5 d</td>
<td>IV Decitabine 1 h IV infusion x5 d</td>
</tr>
<tr>
<td>IV Decitabine 1 h IV infusion x 5 d</td>
<td>Oral ASTX727 1 tablet x 5 d</td>
</tr>
</tbody>
</table>

≥3 Cycles

Oral ASTX727 1 tablet x 5 d

At least 118 evaluable patients with adequate PK in Cycles 1 and 2
ASTX727: Primary Endpoint (5-day Decitabine AUC Equivalence)

- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~99% with 90% CI of ~93-106%
- All Sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

Abstract #846
Pharmacodynamics
(LINE-1 DNA Demethylation in Cycles 1 and 2)

- No significant difference in % LINE-1 DNA demethylation between ASTX727 and IV decitabine (<1% difference in each cycle)

Abstract #846
A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine in Treatment-Naïve Patients with Higher-Risk Myelodysplastic Syndrome

Andrew H Wei1, Jacqueline S Garcia2, Uma Borate3, Chun Yew Fong4, Maria R Baer5, Florian Nolte6, Pierre Peterlin7, Joseph Jurcic8, Guillermo Garcia-Manero9, Wan-Jen Hong10, Uwe Platzbecker11, Olatoyosi Odenike12, Ilona Cunningham13, Martin Dunbar14, Ying Zhou14, Jason Harb14, Poonam Tanwani14, Sathej Gopalakrishnan15, Johannes Wolff14, Meagan Jacoby16

1Department of Haematology, Alfred Hospital and Monash University, Melbourne, Australia, 2Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 3Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
4Olivia Newton John Cancer Research Institute, Austin Health, Melbourne, VIC, Australia, 5Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, University of Maryland, Baltimore, MD, USA, 6Department of Hematology and Oncology, Charité University Hospital, Campus Benjamin Franklin, Berlin, Germany, 7Hematology Department, Nantes University Hospital, Nantes, France, 8Myelodysplastic Syndromes Center, Columbia University Medical Center, Columbia University, New York, NY, USA, 9Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, 10Genentech, South San Francisco, CA, 11Medical Clinic and Policlinic 1, Hematology and Cellular therapy, University Hospital Leipzig, Germany, 12University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, 13Concord Clinical School, University of Sydney, Sydney, Australia
14AbbVie Inc, North Chicago, IL, USA, 15AbbVie Deutschland GmbH & Co KG, Germany, 16Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO, USA

American Society of Hematology (ASH) – 61st Annual Meeting
Orlando, FL, USA ● December 9, 2018
Venetoclax front line MDS

Phase 1B, Open label, Multicenter Study (*Design developed over time*)
Venetoclax + Azacitidine combination for treatment naïve HR-MDS

**NCT01682616**

**Venetoclax Dosing**

<table>
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<tr>
<th>Cohorts</th>
<th>mg/day</th>
<th>days</th>
<th>g/ cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>400</td>
<td>28</td>
<td>11.2</td>
</tr>
<tr>
<td>B</td>
<td>800</td>
<td>28</td>
<td>22.4</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>14</td>
<td>2.8</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>14</td>
<td>5.6</td>
</tr>
<tr>
<td>SE1</td>
<td>400</td>
<td>14</td>
<td>5.6</td>
</tr>
<tr>
<td>SE 2</td>
<td>400</td>
<td>14</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**2017**

Randomized

- A: 400 mg + Aza (N=5)
- B: 800 mg + Aza (N=5)
- C: Aza only 75 mg/m² (N=2)

**2018**

Protocol Amendments

1. 100 mg (N=8)
2. max 200 mg (N=9)
3. max 400 mg (N=8)

Venetoclax dose-level cohorts*  
Dosing duration 14/28 days

Venetoclax + azacitidine (75 mg/m²)

**2019**

Option of a 2nd Safety expansion cohort (N=20)

R2PD: Recommended Phase 2 dose

Abstract #568
Venetoclax: Response Rates (IWG 2006)

Proportion of patients with complete remission is 37% and marrow complete remission is 40% excluding patients of arm C (Aza only).

Excludes patients of arm C (Aza only)
Venetoclax: Overall Survival

Survival estimates (95% CI)
Month 18 62% (28%, 83%)

Includes all patient that received Ven+Aza (excluding arm C) N=57
A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax as Monotherapy or in Combination with Azacitidine for the Treatment of Relapsed/Refractory Myelodysplastic Syndrome

Amer M. Zeidan¹, Daniel A Pollyea², Jacqueline S Garcia³, Andrew M Brunner⁴, Fernando Roncolato⁵, Uma Borate⁶, Olatoyosi Odenike⁷, Ashish Bajel⁸, Anne Marie Watson⁹, Katharina Götze¹⁰, Florian Nolte¹¹, Peter Tan¹², Haifa K Al-Ali¹³, Wan-Jen Hong¹⁴, Ying Zhou¹⁵, Lori Gressick¹⁵, William Ainsworth¹⁵, Jason Harb¹⁵, Ahmed H Salem¹⁵, John Hayslip¹⁵, Ronan Swords¹⁵

¹Section of Hematology, Department of Internal Medicine, Yale University and Yale Cancer Center, New Haven, CT, USA, ²Department of Hematology, University of Colorado, Aurora, CO, USA, ³Department of Medicine, Dana Farber Cancer Institute, Boston, Massachusetts, US, ⁴Center for Leukemia, Massachusetts General Hospital, United States, ⁵Department of Hematology, University of New South Wales, Sydney, Australia, ⁶Division of Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA, ⁷University of Chicago Medicine and Comprehensive Cancer Center, Chicago, IL, ⁸Department of Clinical Hematology and BMT, The Royal Melbourne Hospital, Parkville, Australia, ⁹Department of Haematology, Liverpool Hospital, Liverpool, Australia, ¹⁰MLL Munich Leukemia Laboratory, Munich, Germany, ¹¹Department of Hematology and Oncology, Medical Faculty Mannheim of the Heidelberg University, Mannheim, Germany, ¹²Department of Haematology Cell and Tissue Therapies, Royal Perth Hospital, Perth, Western Australia, Australia, ¹³Department of Hematology and Medical Oncology, University Hospital of Halle, Germany, ¹⁴Genentech, South San Francisco, CA, USA; ¹⁵AbbVie Inc, North Chicago, IL, USA

American Society of Hematology (ASH) – 61st Annual Meeting
Orlando, FL, USA ● December 9, 2019
Venetoclax HMA failure: Study Design

Venetoclax Monotherapy

Venetoclax 400 mg (n=15) → Safety review → Venetoclax 800 mg (n=11)

Venetoclax + Azacitidine Combination Therapy

Venetoclax dose-level cohorts

Aza 75 mg/m² D1-7 + Ven 400 mg (N=7) D1-14
Aza 75 mg/m² D1-7 + Ven 200 mg (N=7) D1-28
Aza 75 mg/m² D1-7 + Ven 100 mg D1-28 (N=9)

Preliminary RP2D determined

Safety expansion cohort
To evaluate RPTD (N=15)*

MTD determination

Abstract #565

*Enrolled until data cut-off 30AUG2019; Aza: Azacitidine; RP2D: Recommended Phase 2 Dose; Ven: Venetoclax

Note: Prophylactic antibiotics mandated
Venetoclax HMA failure: Overall Response Rates

**Abstract #565**

**Venetoclax Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg + Aza 75 mg/m²**

Data cutoff: 30 AUG 2019

**Note:** Observed PR in patients was 0
Venetoclax HMA failure: Overall Survival

Overall survival

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ven Monotherapy</td>
<td>5.5 (3.3 – 11.1)</td>
</tr>
<tr>
<td>Ven+Aza Combination*</td>
<td>65.0 (37.3 – 82.8)</td>
</tr>
</tbody>
</table>

*median OS not reached for Ven+Aza combination therapy

Ven Monotherapy: Ven 400 mg or 800 mg; Ven+Aza Combination: Ven doses 100, 200, or 400 mg+Aza 75 mg/m²

Abstract #565
Genomics of MDS

Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with TP53 Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

David A. Sallman¹, Amy E. Dezern², Guillermo Garcia-Manero³, David P. Steensma⁴, Gail J. Roboz⁵, Mikkael A. Sekeres⁶, Thomas Cluzeau⁷, Kendra Sweet¹, Amy McLemore¹, Kathy McGraw¹, John Puskas¹, Ling Zhang¹, Jiqiang Yao⁸, Qianxing Mo⁸, Lisa Nardelli¹, Najla H Al Ali¹, Eric Padron¹, Greg Korbel⁹, Eyal C. Attar⁹, Hagop M. Kantarjian³, Jeffrey E. Lancet¹, Pierre Fenaux¹⁰, Alan F. List¹, and Rami S. Komrokji¹

¹Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; ²Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; ³Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; ⁴Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; ⁵Weill Cornell Medical College, New York, NY, USA; ⁶Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; ⁷Hematology Department, Cote D'azur University, Nice Sophia Antipolis University, Nice, France; ⁸Department of Biostatistics & Bioinformatics, H. Lee Moffitt Cancer Center, Tampa, FL, USA; ⁹Aprea Therapeutics, Boston, MA, USA, ¹⁰Hospital St Louis, Paris 7 University, Paris, France

Abstract #676
APR-426: Frontline Combination Therapy with APR-246 + Azacitidine: Study Design and Objectives

- IIT evaluating frontline APR-246 + azacitidine in TP53 MT HMA-naïve MDS, oligoblastic AML (≤ 30% blasts) and MDS-MPN
- Phase 1b Results (Sallman D et al., ASH 2018)
  - RP2D of 4500mg/day days 1-4 (~100mg/kg LBM) + azacitidine (75mg/m²)
  - Manageable G1/G2 nausea and transient neurological AEs (dizziness/altered sensation) to APR-246; No DLTs
  - Activation of p53-dependent pathways following monotherapy treatment (1 mCR+partial cytogenetic remission in lead-in phase)
- Phase 2
  - Primary: CR rate
  - Secondary: Safety, ORR, DoR, OS, p53 IHC, and Serial NGS (0.1% VAF sensitivity)

**Phase 1b**
Dose escalation (n=12)
Enrollment complete

**Phase 2**
Dose expansion (n=43)
Enrollment complete

**TP53 mutant myeloid neoplasms**

**APR-246 i.v. infusion days 1-4**
+ **AZA (s.c. or i.v.) days 4-10 or 4-5 and 8-12**

28-day cycles
Doses: 50, 75, 100 mg/kg/d lean body mass

**TP53 mutant myeloid neoplasms**

**APR-246 i.v. infusion days 1-4**
+ **AZA (s.c. or i.v.) days 4-10 or 4-5 and 8-12**

28-day cycles
Dose: 4500 mg/d fixed dose (=100 mg/kg)

ClinicalTrials.gov NCT03072043; i.v., intravenous; s.c., subcutaneous; RP2D, recommended Phase 2 dose; CR, complete remission; DoR, duration of response; LBM, lean body mass
### APR-426: Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=55)</th>
<th>Evaluable Patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%) [95% CI]</strong></td>
<td>39 (71) [57 – 82]</td>
<td>39 (87) [73 – 95]</td>
</tr>
<tr>
<td>Time to first response in months, median (range)</td>
<td>2.1 (0.1 – 5.4)</td>
<td></td>
</tr>
<tr>
<td>Duration of response in months, median [95% CI]</td>
<td>8.0 [6.5 – 11.2]</td>
<td></td>
</tr>
</tbody>
</table>

### Best response by IWG, n (%)

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N=55)</th>
<th>Evaluable Patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>24 (44)</td>
<td>24 (53)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>mCR + HI</td>
<td>8 (15)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>mCR / MLFS</td>
<td>4 (7)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>HI</td>
<td>3 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (7)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>NR</td>
<td>11 (20)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

### CR, n (%) [95% CI]

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N=55)</th>
<th>Evaluable Patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>24 (44) [30 – 58]</td>
<td>24 (53) [38 – 68]</td>
</tr>
<tr>
<td>Time to CR in months, median (range)</td>
<td>3.1 (2.5 – 6.1)</td>
<td></td>
</tr>
<tr>
<td>Duration of CR in months, median [95% CI]</td>
<td>7.3 [5.8 – N.E.]</td>
<td></td>
</tr>
</tbody>
</table>

### Cytogenetic response, n (%) [95% CI]

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N=55)</th>
<th>Evaluable Patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial</td>
<td>8/44 (18) [8 – 33]</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>18/44 (41) [26 – 57]</td>
<td></td>
</tr>
</tbody>
</table>

### TP53

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N=55)</th>
<th>Evaluable Patients (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGS negative, n (%)</td>
<td>20 (44)</td>
<td></td>
</tr>
<tr>
<td>Serial IHC ≤ 5%</td>
<td>22 (49)</td>
<td></td>
</tr>
</tbody>
</table>
APR-426: Overall Survival (ITT)

**ITT Cohort**
- Median OS: 10.8 Months (95% CI: 8.1-13.4)

**Response**
- Median OS: 13.7 months (95% CI: 10.8-16.5)
- No Response: 3.9 months (95% CI: 1.9-6.0)

**P Value:** < 0.0001

**BMT**
- BMT: 14.7 Months (95% CI: 8.6-20.9)
- No BMT: 10.1 Months (95% CI: 6.2-14.0)

**P Value:** 0.1
FRENCH EXPERIENCE APR-426

<table>
<thead>
<tr>
<th>Intention to treat</th>
<th>n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of evaluation</strong></td>
<td>Best Response</td>
</tr>
<tr>
<td>ORR</td>
<td>55%</td>
</tr>
<tr>
<td>CR</td>
<td>39%</td>
</tr>
<tr>
<td>mCR/MLFS</td>
<td>7%</td>
</tr>
<tr>
<td>PR</td>
<td>0%</td>
</tr>
<tr>
<td>SD with HI</td>
<td>9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluable patients*</th>
<th>n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of evaluation</strong></td>
<td>Best response</td>
</tr>
<tr>
<td>ORR</td>
<td>66%</td>
</tr>
<tr>
<td>CR</td>
<td>49%</td>
</tr>
<tr>
<td>mCR/MLFS</td>
<td>9%</td>
</tr>
<tr>
<td>PR</td>
<td>0%</td>
</tr>
<tr>
<td>SD with HI</td>
<td>9%</td>
</tr>
</tbody>
</table>

* ie patients who received at least 3 cycles and had a marrow evaluation after 3 cycles

3 patients underwent Allogeneic SCT, one of them had started maintenance treatment post transplant

Abstract #677
FRENCH EXPERIENCE APR-426

Median FU: 6.4 months
Median OS: NR

Response
No Response
p<0.0001

Median FU: 6.4 months
Median OS in responders: NR
Median OS in non responders: 3 months

Abstract #677
**Pivotal Phase 3 MDS Trial in TP53 Mutant MDS**

- Randomized study of frontline azacitidine ± APR-246 in TP53 mutant MDS

  **Phase 3**
  Target Enrollment, n=154
  Enrollment ongoing: 4500 mg/d fixed dose

  - APR-246 + AZA
  - Intermediate/High/Very High Risk TP53 mutant MDS
  - Primary endpoint: CR rate
  - Secondary endpoints: ORR, DoR, PFS, LFS, OS, transplant rate

- **Status**
  - Enrollment commenced in January 2019
  - Currently targeting full enrollment in first quarter 2020
  - Fast Track Designation for MDS: granted by FDA in April 2019
  - Orphan Drug Designations for MDS: granted by FDA in April 2019 and EMA in July 2019

ClinicalTrials.gov
NCT03745716
Preliminary Results from the Phase II Study of the IDH2-Inhibitor Enasidenib (AG-221) in Patients with High-Risk IDH2-Mutated Myelodysplastic Syndromes (MDS)

Guillaume Richard-Carpentier, Amy DeZern, Koichi Takahashi, Marina Konopleva, Sanam Loghavi, Lucia Masarova, Yesid Alvarado, Farhad Ravandi, Christopher Benton, Guillermo Montalban-Bravo, Kiran Naqvi, Koji Sasaki, Ricardo Delumpa, Mikkael A. Sekeres, Gail Roboz, Hagop M. Kantarjian, Guillermo Garcia-Manero and Courtney D. DiNardo

Abstract number 678
American Society of Hematology Annual Meeting
Orlanda, December 9th 2019
Phase II Study of Enasidenib in Patients With High-Risk IDH2-Mutated Myelodysplastic Syndromes

Study Design

- Phase II, multicenter, 2-arm, open-label clinical trial

**Arm A (Untreated)**
1) HMA naïve
   - AND
2) IPSS-R High or Very High
3) High-risk mutation (*TP53*, *ASXL1*, *EZH2* and/or *RUNX1*)

**Arm B (HMA-failure)**
1) Relapsed/Refractory after HMA
2) No response after ≥ 6 cycles
3) Relapse/Progression

- Azacitidine (AZA) 75 mg/m²/day IV or SC on days 1-7 in each 28-day cycle
- Enasidenib (ENA) 100 mg PO daily continuously 28-day cycle

Abstract #678
## Response rates

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 31)</th>
<th>Arm A (Untreated) AZA + ENA (N = 13)</th>
<th>Arm B (HMA-failure) ENA (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate (ORR), n (%)</strong></td>
<td>21 (68)</td>
<td>11 (85)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>8 (26)</td>
<td>3 (23)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Marrow CR (mCR)</td>
<td>9 (29)</td>
<td>7 (54)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Hematological improvement (HI) only</td>
<td>3 (10)</td>
<td>1 (8)</td>
<td>2 (11)</td>
</tr>
<tr>
<td><strong>No response (NR), n (%)</strong></td>
<td>10 (32)</td>
<td>2 (15)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>9 (29)</td>
<td>2 (15)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>
Olutasidenib (FT-2102) Induces Rapid Remissions in Patients with IDH1-Mutant Myelodysplastic Syndrome: Results of Phase 1/2 Single-Agent Treatment and Combination with Azacitidine

Jorge E. Cortes¹, Eunice S. Wang², Justin M. Watts³, Sangmin Lee⁴, Maria R. Baer⁵, Kim-Hein Dao⁶, Shira N. Dinner⁷, Jay Yang⁸, William B. Donnellan⁹, Anthony Schwarer¹⁰, Christian Recher¹¹, Patrick Kelly¹², Jennifer Sweeney¹², Julie Brevard¹², Patrick Henrick¹², Sanjeev Forsyth¹², Sylvie Guichard¹², Hesham Mohamed¹², Andrew H. Wei¹³

¹Georgia Cancer Center, Augusta, GA; ²Roswell Park Comprehensive Cancer Institute, Buffalo, NY; ³Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; ⁴Weill Cornell Medicine, New York, NY; ⁵University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD; ⁶Oregon Health Sciences University, Portland, OR; ⁷Northwestern University, Chicago, IL; ⁸Karmanos Cancer Center, Detroit, MI; ⁹Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; ¹⁰Box Hill Hospital, Box Hill, VIC, Australia; ¹¹Institut Universitaire du Cancer de Toulouse OncoPole, CHU de Toulouse and Université de Toulouse III, Toulouse, France; ¹²FORMA Therapeutics, Inc., Watertown, MA; ¹³The Alfred Hospital and Monash University, Melbourne, VIC, Australia

Abstract #674
## Investigator-Assessed Response, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Olutasidenib (N = 6)</th>
<th>Olutasidenib + AZA (N = 16)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR(^b)</strong> [95% CI]</td>
<td>3 (50) [11.8-88.2]</td>
<td>9 (56) [29.9-80.2]</td>
</tr>
<tr>
<td>CR</td>
<td>2 (33)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>1 (17)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Clinical benefit (CB = SD ≥8 weeks)</td>
<td>1 (17)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>NE</td>
<td>1 (17)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Time to first response, median (range), months</strong></td>
<td>8.3 (&lt;1-9.7)</td>
<td>2.8 (&lt;1-5.1)</td>
</tr>
<tr>
<td><strong>Duration of overall response, median (range), months</strong></td>
<td>NR (6.7-NR)</td>
<td>12.9 (&lt;1-NR)</td>
</tr>
</tbody>
</table>

\(^a\) Efficacy evaluable population. One patient was excluded from efficacy analysis due to lack of R132X mutation.

\(^b\) ORR = CR + marrow CR + PR. NR, not reached
The First-in-Class Anti-CD47 Antibody Magrolimab in Combination with Azacitididine is Effective in MDS and AML Patients: Updated Ongoing 1b Results

David A Sallman¹, Adam Asch², Monzr Al-Malki³, Daniel Lee⁴, Guillermo Garcia-Manero⁵, William Donnellan⁶, Daniel Pollyea⁷, Suman Kambhampati⁸, Guido Marcucci³, Rami Komrokji¹, Joanna Van Elk⁹, Ming Lin⁹, Jens-Peter Volkmer⁹, Roy Maute⁹, Chris Takimoto⁹, Mark Chao⁹, Paresh Vyas¹⁰, Naval Daver⁵

¹Moffitt Cancer Center, Tampa, FL; ²University of Oklahoma, Oklahoma City, OK; ³City of Hope, Duarte, CA; ⁴Columbia University, New York, NY; ⁵MD Anderson Cancer Center, Houston, TX; ⁶Sarah Cannon Research Institute, Nashville, TN; ⁷University of Colorado, Denver, CO; ⁸Healthcare Midwest, Kansas City, MO; ⁹Forty Seven, Inc., Menlo Park, CA; ¹⁰University of Oxford, Oxford, UK

Abstract #569
CD47 is a Major Macrophage Immune Checkpoint and “Do Not Eat Me” Signal in Myeloid Malignancies including MDS and AML

- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients

Abstract #569
**5F9005 Study Design: Magrolimab in Combination with Azacitidine in MDS and AML**

- **Primary objectives**
  1. Safety of magrolimab alone or with AZA
  2. Efficacy of magrolimab + AZA in untreated AML/MDS

- **Secondary objectives**
  1. PK, PD and immunogenicity of 5F9
  2. Additional measures of efficacy (DOR, PFS, OS)

- **Exploratory objectives**
  1. To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

- **Magrolimab + AZA Combo Safety Evaluation (N=6)**
  - Magro: 1, 30 mg/kg* weekly
  - AZA: 75 mg/m^2 D1-7
  - *Dose ramp up from 1 to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing

- **Expansion**
  - Magro: 1, 30 mg/kg* weekly
  - AZA: 75 mg/m^2 D1-7

- Untreated AML ineligible for induction chemotherapy or untreated MDS intermediate to very high risk by IPSS-R

- A magrolimab priming dose (1 mg/kg) and dose ramp up was utilized to mitigate on target anemia

- Data from the Expansion Cohort is presented

**Abstract #569**
On Target Anemia is a Pharmacodynamic Effect and is Mitigated with a Magrolimab Priming and Maintenance Dosing Regimen

- An initial priming dose mitigates on target anemia by CD47 blockade, resulting in a transient mild hemoglobin drop on the first dose (mean of 0.4 g/dL), which returns to baseline.
- The majority of patients have had significant hemoglobin improvement and decrease in transfusion frequency with therapy.

Abstract #569
Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal) "-" not applicable

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>1L MDS N=24</th>
<th>1L AML N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>22 (92%)</td>
<td>14 (64%)</td>
</tr>
<tr>
<td>CR</td>
<td>12 (50%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>CRi</td>
<td>-</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>MLFS/marrow CR</td>
<td>8 (33%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>4 with marrow CR + HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>2 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>2 (8%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML

Median time to response is 1.9 months, more rapid than AZA alone

Magrolimab + AZA efficacy compares favorably to AZA monotherapy
Conclusion #1

• Immediate impact:
  – Luspatercept: approved by FDA. Need to define role/position
  – ASTX727 (oral decitabine). Met all endpoints. Role?

• Coming:
  – APR-246: study to complete in 2020
  – Magrolimab: the same
  – ABT-199: starting large randomized trials
  – IDH2, IDH1: expanding single arm experience

• Others: TIM-3, rigosertib, CB393, H3BIO
Conclusion #2

• Multiple areas of opportunity (challenge)
• Increased role of genomic annotation in MDS
• Multiple new targets: Bcl-2, TGF-b, TLR, SF3B1, IDH, Flt-3, NPM1, CD33, CD123
• New ways to deliver HMA: attenuated schedules, CC-486, ASTX727, SGI-110
• Potential for multiple oral combinations
• 3 ongoing Phase III trials: Rigosertib, ACE-536, SGI-110 for failures
Presumption of MDS → MDS Diagnosis → Genetic screening

CHIP detected → Refer to the CHIP Clinic

IDH1 mutation → IDH2 mutation → FLT-3 mutation → NPM1 mutation → TP53 mutation → Splicing mutations

Untreated HMA failure → Untreated Lower-Risk MDS → Untreated Higher-Risk MDS

Ara-C based treatment → APR-246, antiCD47

Attenuated HMA CC-486 (oral AZA) E7727 (oral DAC)

ABT-199 antiCD47 ICPIs, rigosertib

ABT-199 Immune checkpoint inhibitors SGI-110 AZA + ABF199 Rigosertib
Guillermo Garcia-Manero
ggarciam@mdanderson.org