Advancing ARGX-110 to clinical proof-of-concept in AML and CTCL

Gail Roboz MD, Weill Cornell Medical College
Hans de Haard PhD, CSO argenx
Nicolas Leupin MD, CMO argenx

ASH workshop, December 11, 2017, Atlanta
Safe Harbor: Certain statements contained in this presentation, other than present and historical facts and conditions independently verifiable at the date hereof, may constitute forward-looking statements. Examples of such forward-looking statements include those regarding our investigational product candidates and preclinical and clinical trials and the status and related results thereto, future results of operations and financial positions, business strategy, plans and our objectives for future operations. When used in this presentation, the words “anticipate,” “believe,” “can,” “could,” “estimate,” “expect,” “intend,” “is designed to,” “may,” “might,” “will,” “plan,” “potential,” “predict,” “objective,” “should,” or the negative of these and similar expressions identify forward-looking statements. Such statements, based as they are on the current analysis and expectations of management, inherently involve numerous risks and uncertainties, known and unknown, many of which are beyond the Company’s control. Such risks include, but are not limited to: the impact of general economic conditions, general conditions in the biopharmaceutical industries, changes in the global and regional regulatory environments in the jurisdictions in which the Company does or plans to do business, market volatility, fluctuations in costs and changes to the competitive environment. Consequently, actual future results may differ materially from the anticipated results expressed in the forward-looking statements. In the case of forward-looking statements regarding investigational product candidates and continuing further development efforts, specific risks which could cause actual results to differ materially from the Company’s current analysis and expectations include:

failure to demonstrate the safety, tolerability and efficacy of our product candidates; final and quality controlled verification of data and the related analyses; the expense and uncertainty of obtaining regulatory approval, including from the U.S. Food and Drug Administration and European Medicines Agency; the possibility of having to conduct additional clinical trials and our reliance on third parties such as our licensors and collaboration partners regarding our suite of technologies and product candidates. Further, even if regulatory approval is obtained, biopharmaceutical products are generally subject to stringent on-going governmental regulation, challenges in gaining market acceptance and competition. These statements are also subject to a number of material risks and uncertainties that are described in the Company’s filings with the U.S. Securities and Exchange Commission (“SEC”), including in the final prospectus related to the Company’s initial U.S. public offering filed with the SEC pursuant to Rule 424(b) of the Securities Act of 1933, as amended, as well as subsequent filings and reports filed by the Company with the SEC. The reader should not place undue reliance on any forward-looking statements included in this presentation. These statements speak only as of the date made and the Company is under no obligation and disavows any obligation to update or revise such statements as a result of any event, circumstances or otherwise, unless required by applicable legislation or regulation.
12:00 Welcome & Introduction

12:05 ARGX-110 in acute myeloid leukemia

- AML: High unmet medical need
  
  Gail Roboz, MD, Weill Cornell Medical College

- CD70: Novel AML target
  
  Hans de Haard, PhD, CSO

- Phase 1/2 trial in newly diagnosed AML: Proof-of-Biology
  
  Nicolas Leupin, MD, CMO

13:00 ARGX-110 in cutaneous T-cell lymphoma

- Phase 1/2 clinical trial: Status update
  
  Nicolas Leupin, MD, CMO

13:10 Q&A
Epidemiology

• Most common acute leukemia in adults
• Lifetime risk: ~0.5% of population
• Estimated incidence in 2017: ~21,400 new cases (1.3% of new cancer cases)
• Estimated mortality in 2017: ~10,600 deaths

Risk Factors & Etiologies

- Genetic disorders
  - Down syndrome
  - Klinefelter syndrome
  - Patau syndrome
  - Ataxia telangiectasia
  - Shwachman syndrome
  - Kostman syndrome
  - Neurofibromatosis
  - Fanconi anemia
  - Li-Fraumeni syndrome
  - Noonan syndrome

- Physical and Chemical Exposures
  - Benzene
  - Organic solvents
  - Pesticides
  - Cigarette smoking
  - Herbicides/Agent Orange
  - WTC/911 exposure

- Nontherapeutic, therapeutic radiation

- Chemotherapy
  - Alkylating agents
  - Topoisomerase-II inhibitors
  - Anthracyclines
  - Taxanes

- Bone marrow failure syndromes
  - Dyskeratosis congenita
  - Fanconi anemia

- Myeloid neoplasms with germ line predisposition
  - germ line mutations in CEBPA, DDX41, RUNX1, ANKRD26, ETV6, GATA2, SRP72, 14q32.2 genomic duplication (ATG2B/GSKIP)

Pathogenesis and Biology of AML

<table>
<thead>
<tr>
<th>Gene</th>
<th>Overall Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3 (ITD, TKD)</td>
<td>37 (30, 7)</td>
</tr>
<tr>
<td>NPM1</td>
<td>29</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>23</td>
</tr>
<tr>
<td>NRAS</td>
<td>10</td>
</tr>
<tr>
<td>CEBPA</td>
<td>9</td>
</tr>
<tr>
<td>TET2</td>
<td>8</td>
</tr>
<tr>
<td>WT1</td>
<td>8</td>
</tr>
<tr>
<td>IDH2</td>
<td>8</td>
</tr>
<tr>
<td>IDH1</td>
<td>7</td>
</tr>
<tr>
<td>KIT</td>
<td>6</td>
</tr>
<tr>
<td>RUNX1</td>
<td>5</td>
</tr>
<tr>
<td>MLL-PTD</td>
<td>5</td>
</tr>
<tr>
<td>ASXL1</td>
<td>3</td>
</tr>
<tr>
<td>PHF6</td>
<td>3</td>
</tr>
<tr>
<td>KRAS</td>
<td>2</td>
</tr>
<tr>
<td>PTEN</td>
<td>2</td>
</tr>
<tr>
<td>TP53</td>
<td>2</td>
</tr>
</tbody>
</table>

200 clinically annotated cases
23 genes commonly mutated
237 genes mutated in 2 or more cases

Genetic Mutations in AML
Functional Categories

- Signaling genes
- Tumor-suppressor genes
- DNA-methylation genes
- Chromatin-modification genes
- Cohesin-complex genes
- Spliceosome-complex genes
- Myeloid transcription factor fusions
- Nucleophosmin

# 2017 European LeukemiaNet Stratification by Genetics

<table>
<thead>
<tr>
<th>Genetic Risk Group</th>
<th>Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td>• t(8;21)(q22;q22); RUNX1-RUNX1T1&lt;br&gt;• inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11&lt;br&gt;• Mutated NPM1 without FLT3-ITD (normal karyotype)&lt;br&gt;• Biallelic mutated CEBPA (normal karyotype)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>• Mutated NPM1 and FLT3-ITD\textsuperscript{high} (normal karyotype)&lt;br&gt;• Wild-type NPM1 without FLT3-ITD or FLT3-ITD\textsuperscript{low} (normal karyotype)&lt;br&gt;• t(9;11)(p22;q23); MLLT3-MLL&lt;br&gt;• Any cytogenetics not classified as favorable or adverse</td>
</tr>
<tr>
<td><strong>Adverse</strong></td>
<td>• inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2.MECOM(EVI1)&lt;br&gt;• t(6;9)(p23;q34); DEK-NUP214&lt;br&gt;• t(v;11)(v;q23); KMT2Arearranged&lt;br&gt;• Monosomy 5 or del(5q); monosomy 7; -17p; complex karyotype (≥3 abnormalities)&lt;br&gt;• Mutated RUNX1&lt;br&gt;• Mutated ASXL1&lt;br&gt;• Mutated TP53</td>
</tr>
</tbody>
</table>

Revised Risk Stratification of Patients with AML on the Basis of Integrated Genetic Analysis

Patel et al. NEJM 2012 March 22; 366(12):1079-89.
Treating Newly Diagnosed AML

Current Paradigms

Comorbid Medical Conditions

Age, y

18

65

75

95

Intensive Induction "7+3"

Low-Intensity Strategy

Supportive Care

Newly diagnosed AML*

Age < 60 years

Intensive induction (7+3)

Candidate for intensive induction

De novo, no unfavorable markers, AHD, or tAML

Standard 7+3

Unfavorable markers, AHD, or tAML

Azacitidine Decitabine Standard 7+3

Non-intensive therapy candidate

Lower-intensity therapy such as azacitidine or decitabine, LD cytarabine, or BSC

*Or clinical trial in all scenarios.

NCCN website.
Results of Selected Trials of Intensive Induction Therapy For Adult AML

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>CR total (%)</th>
<th>CR cycle 1 (%)</th>
<th>Early death (%)</th>
<th>Resistant disease (%)</th>
<th>OS 3-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALG³</td>
<td>DA</td>
<td>211</td>
<td>56</td>
<td>51</td>
<td>10</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>DAF</td>
<td>219</td>
<td>59</td>
<td>55</td>
<td>9</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>DAC</td>
<td>222</td>
<td>67.5</td>
<td>62</td>
<td>11</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>SWOG⁶</td>
<td>DA</td>
<td>300</td>
<td>69</td>
<td>50</td>
<td>1</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>JALSG⁷</td>
<td>DA</td>
<td>525</td>
<td>77.5</td>
<td>61.1</td>
<td>2</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>IA</td>
<td>532</td>
<td>78.2</td>
<td>64.1</td>
<td>5</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>ECOG⁵</td>
<td>D45A</td>
<td>293</td>
<td>57.3</td>
<td>41.1</td>
<td>4.5</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>D90A</td>
<td>289</td>
<td>70.6</td>
<td>58.8</td>
<td>5.5</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>MRC²</td>
<td>DA</td>
<td>240</td>
<td>83</td>
<td>NA</td>
<td>6</td>
<td>11</td>
<td>41*</td>
</tr>
</tbody>
</table>

*5-year overall survival. Abbreviations: CR, complete remission; D45A, DA 45 mg/m² per day; D90A, DA 90 mg/m² per day; DA, daunorubicin and cytarabine; DAC, daunorubicin, cytarabine and cladribine; DAF, daunorubicin, cytarabine and fludarabine; IA, idarubicin; NA, not applicable; OS, overall survival.

Allogeneic stem cell transplantation for AML patients in first remission

Mutant *NPM1*, No *FLT3*-ITD

No benefit from allo SCT in patients with: mutated *NPM1* and wild-type *FLT3*

Other Genotypes

In cases other than ELN favorable: allo SCT may be superior: DON’T transplant ELN favorable in CR1

## CR, Early Death, and Survival Rates in Older (≥ 55 years) AML

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Induction / Consolidation</th>
<th>CR</th>
<th>ED</th>
<th>OS (3-5 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB</td>
<td>388</td>
<td>DA/A or MA</td>
<td>52%</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>ECOG</td>
<td>348</td>
<td>D or I or M (each) + A/A</td>
<td>42%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>SWOG</td>
<td>328</td>
<td>DA or ME/DA</td>
<td>43%</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>MRC</td>
<td>1,314</td>
<td>DAT or ADE or MAC/DAT Or COAP, DAT, COAP</td>
<td>55%</td>
<td>19%</td>
<td>10%</td>
</tr>
<tr>
<td>Kantarjian H, et al.*</td>
<td>466</td>
<td>Various cytarabine-based intensive chemotherapy regimens</td>
<td>45%</td>
<td>-</td>
<td>4 weeks = 26% 8 weeks = 36% 1 year = 28%</td>
</tr>
</tbody>
</table>

*Age 70 years or older.

UK NCRI AML 14 Trial (Non-Intensive)

<table>
<thead>
<tr>
<th>Response</th>
<th>Ara-C (N=102)</th>
<th>HU (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Death</td>
<td>18%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Favorable/intermediate-risk karyotype

Poor-risk karyotype

AML therapies: Inhibition of DNA methyltransferase

Azacitidine

- FDA-approved for MDS\(^1\)
- EMA-approved for AML with 20–30% blasts and multilineage dysplasia and for AML with >30% marrow blasts\(^2\)
- Incorporates into DNA and RNA\(^2\)

Decitabine

- FDA-approved for MDS\(^3\)
- EMA-approved for *de novo* or secondary AML\(^4\)
- Incorporates into DNA\(^3\)

Both azacitidine and decitabine inhibit DNMT at low doses\(^{1–4}\)

Mechanism of action NOT fully understood

---


MDS, myelodysplastic syndromes.
What we know about decitabine in AML

### Decitabine clinical trials

**1L AML** in patients $>60$ years, unfit for chemotherapy$^{1,3-5}$ or with intermediate/poor risk cytogenetics$^{2,6,7}$

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose</th>
<th>Response</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>German multicenter, phase 2$^1$</td>
<td>227</td>
<td>135 mg/m$^2$ over 72 hours, every 6 weeks</td>
<td>CR + PR 26%</td>
<td>5.5</td>
</tr>
<tr>
<td>US multicenter, phase 2$^2$</td>
<td>55</td>
<td>20 mg/m$^2$ daily for 5 days, every 4 weeks</td>
<td>CR 24%</td>
<td>7.7</td>
</tr>
<tr>
<td>3 single-center US$^{3-5}$</td>
<td>53$^3$</td>
<td>20 mg/m$^2$ daily for 10 days, every 4 weeks</td>
<td>CR 47%$^3$</td>
<td>$\sim 13^3$</td>
</tr>
<tr>
<td></td>
<td>52$^4$</td>
<td></td>
<td>CR 40%$^4$</td>
<td>$\sim 11^4$</td>
</tr>
<tr>
<td></td>
<td>45$^5$</td>
<td></td>
<td>CR 31%$^5$</td>
<td>9$^5$</td>
</tr>
<tr>
<td>Multinational, phase 3$^{6,7}$</td>
<td>242</td>
<td>20 mg/m$^2$ daily for 5 days, every 4 weeks</td>
<td>CR + CRp 17.8%</td>
<td>7.7</td>
</tr>
</tbody>
</table>

LDAC, low-dose cytarabine; 
CRp, CR with incomplete platelet recovery.

What we know about azacitidine in AML

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dose</th>
<th>Response</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austrian multicenter, 1L and R/R AML¹</td>
<td>302</td>
<td>75 mg/m² SC for 7 days (reached in 33% of applied cycles)</td>
<td>ORR 48%</td>
<td>9.6</td>
</tr>
<tr>
<td>French multicenter, 1L AML in patients ineligible for intensive chemotherapy²</td>
<td>149</td>
<td>75 mg/m² SC for 7 days, every 4 weeks</td>
<td>ORR 33%</td>
<td>9.4</td>
</tr>
<tr>
<td>International, phase 3, 1L AML with &gt;30% blasts³</td>
<td>241</td>
<td>75 mg/m² SC for 7 days, every 4 weeks</td>
<td>CR/CRi 27.8%</td>
<td>12.1</td>
</tr>
</tbody>
</table>


SC, subcutaneous.
What we know about decitabine and azacitidine in AML

• Older patients$^{1-10}$
• Responses despite unfavorable karyotype/poor prognostic features$^{1-10}$
• Proliferative patients included$^{3,4,8,9}$
• Low 30-day$^{2-7}$ and 60-day mortality$^{4,6,7,9}$
  – Most common toxicities with both decitabine and azacitidine are hematological$^{1,2,4,5}$
  – Extramedullary toxicity generally mild$^{1,2,4,7,8,10}$
• Can take several cycles for response$^{1-10}$
• ARE THEY BETTER THAN LDAC?

Open questions with DNA methyltransferase inhibitors

- Dose?
- Schedule?
- Ongoing therapy beyond response? Forever?
- Priming post-remission therapy?
- Biomarkers?
- Molecular prognostic factors?
- Combination partners?
TARGET

PRAC TICE

FLT3  CD33  BRD4  CD33  CD47  BCL2

ID 1  1  IDH 1  IDH 2  HDAC

CD123  CD70  MLL
Novel/Newly Approved Therapies

- Cytotoxic chemotherapy (eg. CPX-351, Vosaroxin)
- BCL-2 inhibitors (venetoclax)
- Hypomethylating agents (guadecitabine, oral azacitidine)
- Immunotherapies (bispecific and other antibodies, CAR-T)
- Immunoconjugates (eg. Gemtuzumab ozogamicin)
- FLT3 inhibitors
- IDH1 and IDH2 inhibitors
- And many others at ASH 2017
ELN 2017 New Response Category in AML: CR without minimal residual disease

**Standard morphologic CR:** Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC \( \geq 1.0 \times 10^9/L \); platelet count \( \geq 100 \times 10^9/L \)

Standard morphologic CR is not good enough in AML. THE HOLY GRAIL in AML Therapy: Eradication of MRD

CD70: Novel AML target
CD70/CD27 axis involved in lymphoma and leukemia pathogenesis

- Signaling via CD27, NF-κB/ JNK: proliferation, survival
- Shedding of soluble CD27 (sCD27): biomarker of CD70 activity

References:
Wajant et al. 2016, Exp Opin Therap Targets; Silence et al. 2014, mAbs; Reviews: Croft 2009 & 2014; Nolte, 2009; Talabian, 2009
ARGX-110: Highly differentiated antibody targeting CD70

- SIMPLE Antibody™ with multiple modes of action addressing leukemic stem cells (LSCs) in AML
  - Blocking of CD70/CD27 axis
  - Killing of CD70+ cells through enhanced ADCC and ADCP (POTELLIGENT®) and CDC

ADCC: antibody-dependent cellular cytotoxicity, ADCP: antibody-dependent cellular phagocytosis, CDC: complement-dependent cytotoxicity
CD70 provides unifying rationale across risk & age classes in AML
Potential to selectively target leukemic stem cells in AML patients

Elevated sCD27 serum levels correlate with poor prognosis

- Elevated sCD27 serum levels in all newly diagnosed AML patients, regardless of risk or age categories
- sCD27 levels are an independent negative prognostic marker in all newly diagnosed AML patients
- CD70 expressed on ~86-100% of AML blasts, majority of malignant cells are CD70/CD27 double-positive
- CD70/CD27 selectively overexpressed on leukemic stem cells (LSCs), not on hematopoietic stem cells (HSCs)


Legend: adv., adverse; CI, confidence interval; fav., favorable; int., intermediate; OS, overall survival. Statistics: left: one-way ANOVA; middle: log-rank test. *, P < 0.05; **, P < 0.01; ***, P < 0.001.
CD70 is a highly selective marker of primary AML cells

Selective CD70 expression on AML cells vs. healthy hematopoietic cells

- Extensive transcriptome and proteome analysis independently revealed CD70 as 1 of only 4 targets of interest for selective targeting of AML blasts and LSCs

Perna et al. 2017, Cancer cell
Leukemic stem cells responsible for disease relapse in AML

- Accumulation of blasts in bone marrow and blood results in reduction in red blood cells, platelets and normal white blood cells
- Symmetric division increases disease aggressiveness
Blocking CD70 drives AML cells into myeloid differentiation

Proteome level

- Increased asymmetric division results in decreased stemness and disease aggressiveness
- Increased myeloid differentiation demonstrated on proteome levels
Blocking CD70 induces myeloid differentiation factors

Transcriptome level

- Increased myeloid differentiation demonstrated at transcriptional and translational levels
- Expression differentiation-inducing genes RUNX1, SPI1 (PU.1), CEBPα, CEBPβ, and ID1 significantly increased in AML leukemic stem cells cultured overnight in the presence of blocking ARGX-110 compared with control mAb

Legend: adv., adverse; ctrl, control; fav., favorable; int., intermediate. Statistics: Student’s t test; *, P < 0.05; **, P < 0.01; ***, P < 0.001; ****, P < 0.0001.

ARGX-110 inhibits leukemic stem cell proliferation
Long-term effects *ex vivo*

- Reduces LSC colony formation across patient risk categories (favorable/intermediate/adverse risk)
- Reduces LSC numbers as determined in serial re-plating experiments
- Blocking CD70 results in: (1) lasting down-regulation of stem cell genes (2) increasing myeloid differentiation

ARGX-110 variant = ARGX-110 without Fc effector functions
Statistics: Student’s t test; *, P < 0.05; **, P < 0.01
Curative potential of ARGX-110 monotherapy in mouse model
Shown to reduce leukemic stem cells, increasing survival in AML model

- Increased survival after secondary transplantation of AML bone marrow cells from primary recipients transiently treated with ARGX-110 variant
- Increased survival observed for AML blasts taken from all 3 AML risk categories (fav/int/adv)

Initial in vivo treatment
+ARGX-110 variant

Grafting Whole Bone Marrow cells from treated into new mice (14d after start of treatment)

Transplant, evaluation
-ARGX-110 variant

Statistics: log-rank test; *, P < 0.05; **, P < 0.01.

Blocking CD70/CD27 signaling in combination with hypomethylating agents eradicates human CD34+ AML stem and progenitor cells in vitro and in vivo

Poster 2652 (Sun Dec 10, 6-8pm)

Leukemia stem cells (LSCs) are the origin of acute myeloid leukemia (AML) and are resistant to standard therapeutic regimens resulting in relapse of the disease and poor prognosis. Consequently, LSCs represent a major obstacle for AML therapy. We recently identified the interaction of the TNF ligand CD70 and its receptor CD27 on LSCs as a promising therapeutic strategy to target LSCs. In this study, we demonstrate for the first time that treatment with hypomethylating agents (HMA) up-regulates CD70 expression on human AML cell lines and on primary CD34+ AML stem/progenitor cells from newly diagnosed AML patients in vitro and in vivo. Co-treatment of CD34+ AML stem/progenitor cells with the HMA and a blocking αCD70 monoclonal antibody reduced colony-forming and re-plating capacity in vitro compared to single agent treatment. Furthermore, combining HMA treatment with CD70 blockade effectively eliminated human CD34+CD38−CD45RA− LSCs in limiting dilution patient-derived xenograft experiments. Consequently, combining HMAs with blocking CD70/CD27 signaling may represent a novel strategy to eradicate human LSCs.

Author(s): Hinterbrandner M1, Kallen NM1, Lüthi U1, Pabst T3, Van Rompaey L2, Leupin N2, De Haard H2, Ochsenbein A1,3 and Riether C1,3*

1Tumorimmunology, Department of Clinical Research, University of Bern, Bern, Switzerland
2argenx BVBA, Zwijnaarde, Belgium
3Department of Medical Oncology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland
* Presenting and corresponding author
Phase 1/2 trial in newly diagnosed AML: Proof-of-Biology
High unmet need in newly diagnosed, elderly AML patients
Standard of care provides limited survival benefit

- 60% of newly diagnosed AML patients are more than 60 years old
- Hypomethylating agents are standard of care in newly diagnosed AML patients unfit for intensive chemotherapy
- Hypomethylating agents have limited effect on leukemic stem cells responsible for relapse

Phase 3 study of azacitidine vs. conventional care regimens in older patients with newly diagnosed AML with >30% blasts (1)

(1) Dombret et al. 2015, Blood
High unmet need in newly diagnosed, elderly AML patients
Azacitidine provides limited response rate and comes with some side effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N=)</th>
<th>Adverse events (G3-G4)</th>
<th>%</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falantes et al. 2017</td>
<td>710</td>
<td>Pancytopenia, Febrile neutropenia, Infections</td>
<td>8 – 75, 11 – 50, 6 – 30</td>
<td>35.5</td>
</tr>
<tr>
<td>Dombret et al. 2015</td>
<td>231</td>
<td>Febrile neutropenia, Neutropenia, Thrombocytopenia, Pneumonia, Anemia, Leukopenia, Hypokalemia, Infections</td>
<td>28, 26, 24, 24, 19, 16, 7, 5</td>
<td>31.1</td>
</tr>
</tbody>
</table>

Dombret et al. 2015, Blood; Falantes et al. 2017, Leukemia & Lymphoma
Open label, non-controlled, non-randomized Phase I study
In newly diagnosed AML patients unfit for intensive chemotherapy

Study design

Phase 1 – Dose escalation

- 10 mg/kg (n = 3+3)
- 3 mg/kg (n = 3+3)
- 1 mg/kg (n = 3+3)

Endpoints

- Safety, tolerability
- Clinical outcome
- Translational data

Phase 2 - Exploratory efficacy

- Selected dose

Treatment schedule

ARGX-110
1, 3, 10 mg/kg q2wk IV

ARGX-110
D-14
C1D3
C1D17
C2D3
C2D17

Azacitidine
75 mg/m² 7d/month sc

Monotherapy

Cycle 1 (28 days)
Cycle 2 (28 days)

Allows unique insight into CD70 pathology via translational program
Patient characteristics and preliminary data
Non-transplantable patients with intermediate & adverse risk and high blast count in bone marrow

9 newly diagnosed AML patients

<table>
<thead>
<tr>
<th>Baseline characteristics (N=9)</th>
<th>ARGX-110 + Azacitidine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>71</td>
</tr>
<tr>
<td>71-80</td>
<td>71-84</td>
</tr>
<tr>
<td>Gender: Male/Female</td>
<td>2/1</td>
</tr>
<tr>
<td>Risk (ELN 2017)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1</td>
</tr>
<tr>
<td>Adverse</td>
<td>2</td>
</tr>
<tr>
<td>Blasts in the bone marrow</td>
<td></td>
</tr>
<tr>
<td>Median %</td>
<td>51.3</td>
</tr>
<tr>
<td>24-90</td>
<td>20-60</td>
</tr>
<tr>
<td>AML classification (WHO 2016)</td>
<td></td>
</tr>
<tr>
<td>Not other specified</td>
<td></td>
</tr>
<tr>
<td>With Myelodysplasia- related changes</td>
<td>2</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>French-American-British subtypes</td>
<td>M4,M1,M2</td>
</tr>
</tbody>
</table>

Source: argenx data – patient anecdotes – uncleaned data

ELN: European Leukemia Net, Dohner et al. 2017, Blood
Limited number of grade 3-4 toxicities

6/9 newly diagnosed AML patients

<table>
<thead>
<tr>
<th>Grade 3-4 Adverse Events in 6 patients</th>
<th>1 mg/kg Events (Patients)</th>
<th>3 mg/kg Events (Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2 (1)</td>
<td>7* (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9* (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Pleuropericarditis</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Lung infection</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Proctitis</td>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Intermittent toxicities for the same patient

- G3-G4 hematological toxicity reflecting the azacitidine safety profile is observed for 1 and 3 mg/kg
- Evaluation for 10 mg/kg is ongoing; so far safety data in line with 1 and 3 mg/kg doses

Cut-off date: 15 November 2017

Source: argenx data – patient anecdotes – uncleaned data
Favorable safety and tolerability profile in 94 patients
Monotherapy ARGX-110 in heavily pre-treated CD70+ patients

Adverse events ≥ 2 patients

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Grade 3 Events (Patients)</th>
<th>Grade 4 Events (Patients)</th>
<th>Grade 5 Events (Patients)</th>
<th>Total % of Patients**</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health deterioration due to progressive disease</td>
<td>4 (4)</td>
<td></td>
<td>6 (6)</td>
<td>10.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (9)</td>
<td></td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (8)</td>
<td></td>
<td></td>
<td>8.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (4)</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>3 (3)</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (2)</td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Haemolytic anemia</td>
<td>3 (2)</td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (2)</td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (2)</td>
<td>1 (1*)</td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>2 (2)</td>
<td></td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Adverse events ≥ 2 patients

- Anemia and fatigue are the most frequent G3-G4 toxicities in this heavily pre-treated population

94 patients= ARGX-110-1201 clinicaltrials.gov NCT 01813539
cut off: 15 Nov 2017

Source: argenx data – patient anecdotes – uncleaned data
Response in 6/6 evaluable newly diagnosed AML patients
ARGX-110/Aza treatment

- So far, all patients responded (3 CR, 1 CRi, 2 PR), MRD negativity reached in 2 patients so far (exploratory)
- 1 patient reached CR and bridged to allogeneic stem cell transplant after 5 cycles
- 6/9 patients are currently still on treatment

Source: argenx data – patient anecdotes – uncleaned data
Case studies
Case 1: Patient cohort 1 – 1 mg/kg – 8 cycles on study

- 80 year old female
- Therapy-related AML, M4; BM ~65% blasts
- Molecular genetics: FLT3-ITD; DNMT3Amut; RUNX1mut; WT1mut; cytogenetics: normal

<table>
<thead>
<tr>
<th>Risk</th>
<th>Best response</th>
<th>Cycle 8 Day 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (1 mg/kg)</td>
<td>Adv CRi</td>
<td></td>
</tr>
<tr>
<td>Int</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Cohort 2 (3 mg/kg)</td>
<td>Int CR</td>
<td></td>
</tr>
<tr>
<td>Int</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>Int PR</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Adv PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 3 (10 mg/kg)</td>
<td>Int</td>
<td></td>
</tr>
<tr>
<td>Int</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment duration (months) cut off: 15 Nov 2017

Source: argenx data – patient anecdotes – uncleaned data
Case 1: Complete remission with incomplete hematological recovery

Bone marrow: % Blasts, flow cytometry

Blood analysis: Absolute counts (G/L)

ARGX-110/Aza reduces experimental LSC gene signature

Source: argenx data – patient anecdotes – uncleaned data
Case 2: Patient cohort 1 – 1 mg/kg – 5 cycles on study

- 75 year old male
- AML with myelodysplasia-related changes, M1/M2; BM ~40% blasts
- Molecular genetics: U2AF1mut; DNMT3Amut; cytogenetics: normal

<table>
<thead>
<tr>
<th>Risk</th>
<th>Best response</th>
<th>Treatment duration (months)</th>
<th>cut off: 15 Nov 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (1 mg/kg)</td>
<td>Adv CR</td>
<td>Cycle 5 Day 17</td>
<td>Allogeneic stem cell transplant</td>
</tr>
<tr>
<td>Int CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2 (3 mg/kg)</td>
<td>Int CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 3 (10 mg/kg)</td>
<td>Int</td>
<td>Not yet evaluable</td>
<td></td>
</tr>
<tr>
<td>Int</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adv</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: argenx data – patient anecdotes – uncleaned data
Case 2: ARGX-110/Aza induces complete remission & bridges to transplant

Screening

Leukemic blast persistence – (C1D1)

Leukemic clearance – (EOT)

Bone marrow: % Blasts, flow cytometry

Blood analysis: Absolute counts (G/L)

Source: argenx data – patient anecdotes – uncleaned data
Case 2: ARGX-110/Aza combo reduces AML stemness

- Significantly reduced leukemic stem cell colony formation
- Increased myeloid differentiation (asymmetric division) of leukemic stem cells
- Reduction of LSC gene signature

Ng. et al. 2016, Nature

Source: argenx data – patient anecdotes – uncleaned data
Phase 1 / 2 CTCL clinical trial: Data update
Disease control in 59% (13/22) of RR-CTCL patients

Duration on study

- Encouraging signs of clinical activity
- 5 patients still on study at 5 mg/kg

Source: argenx data – patient anecdotes – uncleaned data

Phase 1 patients

- Subcutaneous panniculitis like PR
- Sézary Syndrome PD
- Mycosis Fungoides PR
- Mycosis Fungoides SD
- Sézary Syndrome PD
- Mycosis Fungoides PD
- Tfh like PD
- Sézary Syndrome PD
- Mycosis Fungoides PD
- Sézary Syndrome PD

Phase 2 patients

- Mycosis Fungoides SD
- Sézary Syndrome SD
- Mycosis Fungoides SD
- ALC SD
- Mycosis Fungoides SD
- Sézary Syndrome SD
- Sézary Syndrome SD
- Mycosis Fungoides SD
- Sézary Syndrome SD

Duration on Study (cut off: 7 Nov 2017)
Favorable safety and tolerability profile in CTCL patients
Monotherapy ARGX-110 (1 and 5mg/kg)

All grade adverse events: >2 events in 22 CTCL patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Astenia</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Diffuse rash</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Flush</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Chill</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Cystitis</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Infusion related Reaction</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hyperaemia of the larynx</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sepsis Staphylococcus</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

cut off: 7 Nov 2017

- Pruritus is the most frequent adverse event - 9 events on 6/22 patients (27%)
- Astenia and fever occurred in 5/22 patients (22.7%)
- No hematological toxicity of any grade detected
- Favorable safety profile observed for 1 and 5 mg/kg

Source: argenx data – patient anecdotes – uncleaned data
ARGX-110 induces complete response
Update on panniculitis patient

- 84 year old female, diagnosed June 2015
- Tumor: Skin T3, nodal NO, visceral MO, blood BO
- Doses: 10 (1 mg/kg q3w) + 8 (5 mg/kg q6w)

Partial response after 6 doses (dose 1 mg/kg) in maintenance (5 mg/kg /6 weeks) since January 2017
Complete response after 17 doses (dose 5mg/kg)
The patient is still on a maintenance dose of 5 mg/kg q6wk

Source: argenx data – patient anecdotes – uncleaned data
ARGX-110 in newly diagnosed AML patients – summary
Preliminary data from first 6 patients – additional data needed

Preliminary clinical data confirm preclinical observations

Promising preliminary activity obtained in first set of patients
  • 6/6 responders
  • 1 patient bridged to transplantation

Encouraging safety and tolerability profile
  • No exacerbation of azacitidine toxicity

Highly differentiated drug profile
  • CD70 uniformly & selectively expressed
  • Driving LSCs into myeloid differentiation

Source: argenx data – patient anecdotes – uncleaned data
Acknowledgement

Thank you to the study teams, the patients and their families