Clinical Trials in the Management of Hematological Malignancies

Clinical Trials at CHS and in the TRIO-US Network

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Risk in Acute Myelogenous Leukemia - Potential Strategies for Drug Development

- Clinical Variables
  - Antecedent hematologic disturbance
    - Secondary vs. Therapy-related AML - distinct molecular features
  - Advanced age at presentation - distinct cytogenetic and molecular features
  - Leukocytosis at presentation
  - Male gender
  - Elevated LDH at presentation
Risk in Acute Myelogenous Leukemia - Pathways to Drug Approval

• Biologic Variables
  – Adverse Cytogenetics
    • Monosomies
    • Complex (≥ 3) abnormalities
    • \textit{inv}(3), \textit{t}(3;3), \textit{t}(6;9), \textit{t}(6;11), \textit{t}(9;22), 17p
  – Less-certain adverse cytogenetic features
    • 11q23
  – Adverse molecular features
    • Flt3, IDH1, and IDH2 mutations, TP53, MLL
Flt3 Tyrosine Kinase Inhibitor in Induction Treatment

- **Stone, et al. 126: 23 (Abs) 2015:**
  - N= 717 of 3279 previously untreated AML patients, age 18-60, in 225 sites screened
  - Induction consisted of Dauno (60) and Cytarabine (200)
  - Randomized to midostaurin (50 mg po b.i.d, d8-22) vs. placebo, and stratified by allelic fraction (high= >0.7, n=214 vs. low 0.05-0.7, n=341). TKD allowed (n=162)
  - Retreatment permitted after day 21
  - Consolidation consisted of 4 cycles of HiDaC or Transplantation
  - Median follow-up 57 months
  - Similar adverse events, and similar rate of CR (59% vs. 54%)
  - Similar rate of allo SCT at any time (58% vs. 54%)
  - Superior overall survival in favor of midostaurin (50.8% vs. 43.1%) even with censoring
  - Superior EFS in favor of midostaurin (26.7% vs. 19.1%)
Chemotherapeutic Approaches of High-Risk AML

- Improvements in supportive care
- Combination of targeted agents
- Alternative agents with distinct pharmacology
- Alternative agents with distinct and novel targets
- Allogeneic hematopoietic stem-cell transplantation and engineered cell therapy
# IDH2 mutant enzyme Inhibitors

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>Study Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein, et al. (in MDS: Abs 637; 2016)</td>
<td>AG-221 (Enasidenib)</td>
<td>IDH2 mutation-positive heme malignancies</td>
<td>N=198 accrued to parallel bid and qd cohorts, 181 evaluable. Responses in 74 duration about 6 m; in MDS, HI 4/15</td>
</tr>
<tr>
<td>DiNardo, et al. (Abs 1073, 2016)</td>
<td>IDH305</td>
<td>N=21 AML w/ R132 mut.-response in 7</td>
<td>Reduction of tumor burden in other cancers</td>
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<tr>
<td>Matre et al.</td>
<td>Inhibition of glutaminase</td>
<td>Panel of AML cell lines</td>
<td>Induction of apoptosis, decr in metabolites</td>
</tr>
<tr>
<td>Herold, et al.</td>
<td>Analysis of MLL-PTD by whole exome sequencing</td>
<td>Most prevalent mutations in ATM, DNMT3b, TET1</td>
<td></td>
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</tbody>
</table>
Clinical Trials at UCLA for Acute Myeloid Leukemia

• Disease Stage
  – Relapsed/Refractory AML
    • OX1222 (Mateon)
      – Dose-escalation phase 1b and subsequent phase 2 trial of a vascular-disruptive agent.
      – Eligibility: adult subjects with pathologically confirmed R/R AML that has been treated with systemic therapy

• Incyte INCB59872-101
  – A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies
  – Relapsed/Refractory AML or High-Risk MDS age >18

• D8540C00001 - MEDI7247 (MedImmune)
  – A Phase 1 Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Antitumor Activity of MEDI7247 in Patients with Selected Relapsed/Refractory Hematological Malignancies
Clinical Trials at UCLA for Acute Myeloid Leukemia

• Targeted therapy
  – FT-2102 (Forma)
    • A phase 1/1b multicenter, randomized, open-label study of orally administered this IDH1 inhibitor in combination with azacitidine for patients with AML or MDS with an IDH1 mutation
      – FT-2102 has single-agent activity producing remission in nearly 50% of patients with IDH1-mutated AML
      – Patients with disease eligible for therapy with hypomethylating agents are eligible
  – Agios AG120-C-009
    • A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ≥ 18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation
  – Agios AG120-221
    • Phase 1 open-label study of AG-120 or AG-221 in combination with induction therapy and consolidation in patients with AML with an IDH1 and/or IDH2 mutation
Clinical Trials at UCLA for Acute Myeloid Leukemia

- **Disease Stage**
  - Newly Diagnosed
    - **Trovagene TROV-052**
      - A Phase 1b/2 Study of PCM-075 in Combination with either Low-Dose Cytarabine or Decitabine in Subjects with Acute Myeloid Leukemia (AML)
    - **ASP2215**
      - 2215-CL-0201: Randomized study of ASP2215 alone or in combination with low-dose cytarabine in older patients with newly diagnosed, flt3-mutated AML
      - 2215-CL-0103: A Phase 1 Study of ASP2215 in Combination with Induction and Consolidation Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia
  - **Ulocuplumab (BMS-936564)** in combination with low-dose cytarabine in patients with newly diagnosed AML.
  - **GS-US-339-1559 (Gilead)** - A Phase 1b/2 Study of Entospletinib (GS-9973) Monotherapy and in Combination with Chemotherapy in Subjects with AML
    - **Further targeted therapy**
      - **Astellas-2215-CL-9100**: A Multicenter, Open-label Treatment Protocol of Gilteritinib (ASP2215) in Patients with FMS-like Tyrosine Kinase 3 (FLT3) Mutated Relapsed or Refractory Acute Myeloid Leukemia (AML) or FLT3 Mutated AML in Complete Remission (CR) with Minimal Residual Disease (MRD)
Antileukemic Activity of Gilteritinib

Response in FLT3mut+ and FLT3WT Patients (N=249)

- PR
- CRi
- CRp
- CR

Proportion of Patients Achieving Response (%)

- FLT3WT (N=58)
- FLT3mut+ (N=191)

ORR=49%
CRc=37%

ORR=12%
CRc=9%

Response in FLT3mut+ Patients by Gilteritinib Dose (N=191)

<table>
<thead>
<tr>
<th>Dose</th>
<th>PR</th>
<th>CR</th>
<th>CRi</th>
<th>CRp</th>
<th>CRc</th>
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<tr>
<td>20 mg</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>40 mg</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>80 mg</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>1</td>
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<tr>
<td>120 mg</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>200 mg</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>300 mg</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>450 mg</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>1</td>
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</table>

ORR=67%
CRc=42%

ORR=55%
CRc=46%

ORR=47%
CRc=39%

ORR=60%
CRc=30%

ORR=50%
CRc=0

Gilteritinib ≥80 mg/day ORR=52%

ORR=52%
CRc=42%

CR, complete remission; CRc, composite remission (CRc=CR+CRi+CRp); CRi, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; ORR, overall response rate (ORR=CRc+PR); PR, partial remission.

CRc included patients who achieved complete remission, complete remission with incomplete hematologic recovery, and complete remission with incomplete platelet recovery.

ORR included patients in CRc plus patients who achieved PR.
BIOMARKER-BASED TREATMENT OF AML (THE BEAT AML PROGRAM)

Protocol Overviews, including BAML-16-001-M1, S2, S3, S4, S5, S6 and S9
• **Primary Objectives, to determine:**
  – The feasibility of completing molecular, immunophenotypic and/or biochemical studies for older AML subjects in < 7 calendar days
  – The feasibility of assigning these subjects to a novel therapeutic treatment group in one of several sub-studies based on this result
  – The clinical efficacy (defined in each sub-protocol) of each novel treatment strategy
Inclusion Criteria Highlights

- ≥ 60 years old at the time of diagnosis (unless there is an open sub-protocol with a different age requirement)

- **Group A:** previously untreated AML (Hydrea and prior therapy for MDS, MPD and aplastic anemia allowed except for hypmethylating agents)

- **Group B:** relapsed/refractory AML
  - Currently no sub-protocols open

Exclusion Criteria Highlights

- Isolated myeloid sarcoma (patients must have blood or marrow involvement)

- Acute promyelocytic leukemia

- Signs of leukostasis requiring urgent therapy

- Symptomatic central nervous system (CNS) involvement

- DIC with active bleeding or signs of thrombosis

- Psychological, familial, social, or geographic factors that would prevent compliance

- Other significant medical condition confound the interpretation of results
BAML-16-001-M1 – Master Protocol – Schedule

• **Schedule**
  1. Master Protocol Informed Consent
  2. BM / PB Sample Collection
  3. Shipment of Samples to Central Labs
  4. Assignment of Sub-Protocol based on Genomic Screening (≤ 7 calendar days)
     • 7 days starts from time/day of sample receipt at Foundation Medicine
     • Recommend scheduling subject’s return visit 8 days after sample receipt at Foundation Medicine

• Subject then decides whether to enroll in the sub-protocol.
## BAML-16-001-M1 – Master Protocol – Central Labs

<table>
<thead>
<tr>
<th>Central Lab</th>
<th>FUNCTION</th>
<th>SHIPMENT</th>
<th>INITIAL KIT SUPPLY</th>
<th>KIT RESUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation</td>
<td>Genotyping</td>
<td>Same day Mon-Fri</td>
<td>Automatic from Syneos Health</td>
<td>Upon email request to Syneos Health</td>
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<tr>
<td>Nationwide</td>
<td>Bio-Banking</td>
<td>Same day Mon-Fri</td>
<td>Site orders from vendor website</td>
<td>Site orders from vendor website</td>
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<tr>
<td>Medicine</td>
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Objective

BAML-16-001-S2: PHASE 1B/2 STUDY OF BI 836858 WITH AZACITIDINE IN PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA (AML) PATIENTS >60 YEARS WITH UNIQUE MOLECULAR FEATURES

• Primary Objectives
  – Phase 1b:
    • Demonstrate the feasibility of enrolling patients with TET2/IDH1/IDH2/WT1 mutations and marker negative patients into monoclonal antibody + azacitidine therapy.
    • Determine the recommended Phase 2 dose of BI 836858 with azacitidine.
  – Phase 2: Determine the CR + CRi rate in the mutation and marker negative groups.
Schedule

• **Cycle 1**
  – Days 1-7 – Azacitidine
  – Days 9, 16, 23 – BI 836858 with premedication

• **Cycles 2+**
  – Days 1-7 – Azacitidine
  – Days 1, 8, 15, 22 – BI 836858 with premedication

**Assessment Highlights**
- PRO Assessment
- Drug-Induced Liver Injury (DILI)
Schedule

- **AG-221 Monotherapy**
  - AG-221 daily dosing

- **AG-221 + Azacitidine**
  - AG-221 daily dosing
  - Days 1-7 of the 28-day cycle for up to 12 cycles.

**Assessment Highlights**
- PRO Assessment
- Phototoxicity Precautions
- Differentiation-Like Syndrome
BAML-16-001-S4 – Gilead (MLL, Marker Negative) – Objective

**BAML-16-001-S4:**
A PHASE 1B/2 STUDY OF ENTOSPLETINIB (ENTO) IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML) ≥ 60 WITH MLL GENE REARRANGEMENT AND/OR MLL-PARTIAL TANDEM DUPLICATIONS (MLL-PTD)

- **Primary Objectives**
  - Determine the tolerated phase 2 dose of Entospletinib (ENTO) with azacitidine in this subject population
  - Evaluate the rate of composite complete remission and tolerability in this subject population at 6 months of treatment
    - Composite complete remission includes CR and CRi responses
BAML-16-001-S5 – Gilead (Mt TP53, Complex Kary.) – Objective

BAML-16-001-S5:
A PHASE 2 STUDY OF ENTOSPLETINIB AND DECITABINE TARGETING MUTANT TP53 AND OR COMPLEX KARYOTYPE IN PATIENTS WITH UNTREATED ACUTE MYELOID LEUKEMIA ≥ AGE 60 YEARS

• **Primary Objective**
  – Evaluate the rate of composite complete remission among newly diagnosed AML patients in this subject population

  • Composite complete remission includes CR and CRi responses at end of induction therapy (up to cycle 3).
BAML-16-001-S6 – Gilead (MT NPM1, WT FLT3 ITD) - Objective

BAML-16-001-S6:
A PHASE 2 STUDY OF ENTOSPLETINIB IN NPM1 MUTANT/FLT3 ITD WILD TYPE AML PATIENTS AGE > 60 YEARS

- Primary Objectives
  - Determine overall survival rate at 3 years of NPM1+/FLT3–ITD elderly AML patients who are treated with ENTO in combination with induction and consolidation therapy (Cohort A).
  - Determine overall survival rate at 1 year in NPM1+/FLT3–ITD elderly AML patients of ENTO monotherapy or ENTO + azacitidine (Aza) regimen (Cohort B)
BAML-16-001-S9: PHASE 2 STUDY WITH PEVONEDISTAT IN COMBINATION WITH AZACITIDINE TARGETING NEDD8-ACTIVATING ENZYME (NAE) IN TP53 MUTANT UNTREATED ACUTE MYELOID LEUKEMIA PATIENTS ≥ 60 YEARS OF AGE

• Primary Objectives
  – Evaluate overall response rate (CR + CRi) and tolerability in this subject population with pevonedistat and azacitidine
Clinical Trials at UCLA for Acute Lymphoblastic Leukemia

- **Disease Stage**
  - Relapsed/ Refractory
  - KTE-C19-103
    - To assess remission, rate of relapse, and overall survival among subjects with relapsed ALL with expression of CD19; if history of Ph+, then intolerant to or relapse/refractory after TKI. Eligibility: ≥ 18 years old with newly diagnosed ALL
Chimeric Antigen Receptor T cells

- A phase 1/2 multicenter, open-label study evaluating the safety and efficacy of KTE-C19-103 in adults with relapsed/refractory acute lymphoblastic leukemia.
  - Initial phase will consist of subjects with high tumor burden
  - In phase 2, 50 subjects with disease, regardless of blast percentage in bone marrow or blood, will be evaluated for response, duration of remission, rate of MRD-negative remission, rate of allogeneic transplant, and survival
  - Subjects will be allowed “bridging chemotherapy” between leukapheresis and the start of conditioning fludarabine and cyclophosphamide
  - KTE-C19 consists of a single infusion of CAR-transduced autologous T cell administered intravenously at a target dose of 2 million anti-CD19 CAR+T cells/kg
Research Studies at UCLA for HSCT

• Disease Stage: Presence of Hematological Malignancy
  – Cord Blood expansion trial from Gamida
    • A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies
  – Kiadis enriched haplo trial
    • A Phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical HSCT and adjunctive treatment with ATIR101, a T-lymphocyte enriched leukocyte preparation depleted ex vivo of host alloreactive T-cells, versus a haploidentical HSCT with post-transplant cyclophosphamide in patients with a hematologic malignancy (HATCY study)
Research Studies at UCLA for HSCT

- Gene Therapy trials in non-malignant hematology Sickle Cell Disease and Thalassemia
  - A Phase 1/2, Open-label, Single-arm Study to Assess the Safety, Tolerability, and Efficacy of ST-400 Autologous Hematopoietic Stem Cell Transplant for Treatment of Transfusion-dependent β-thalassemia (TDT)
  - Clinical Research Study of Autologous Bone Marrow Transplantation for Sickle Cell Disease (SCD) using Bone Marrow CD34+ Cells Modified with the Lenti/βAS3-FB Lentiviral Vector

- GvHD Studies
  - Incyte JAK1 inhibitor Itacitinib or placebo with steroids in aGvHD
Clinical Trials in Myeloproliferative Disease

- Previously Untreated
  - Open-label Phase 2 study of the safety and efficacy of INCB050465 in combination with Ruxolitinib in myelofibrosis
  - A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 2 - Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myelofibrosis

- Relapsed/Refractory
  - A Randomized, Single-Blind, Multicenter Phase 2 Study of SL-401 in Patients with Advanced, High Risk Myeloproliferative Neoplasms
  - An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib
Clinical Trials in Myelodysplasia

• **Incyte INCB59872-101**
  - A Phase 1/2, Open-Label, Dose-Escalation/Dose-Expansion, Safety and Tolerability Study of INCB059872 in Subjects With Advanced Malignancies

• **Imetelstat**
  - Telomerase inhibitor for patients with low or intermediate-1 risk myelodysplastic syndrome, transfusion dependent, and relapsed/refractory to therapy with ESA
Clinical Trials in Myelodysplasia

• Onconova 04-30 Rigosertib
  – A Phase III, International, Randomized, Controlled Study of Rigosertib versus Physician’s Choice of Treatment in Patients with Myelodysplastic Syndrome after Failure of a Hypomethylating Agent

• MedImmune MEDI4736
  – A Phase 1 Study to Evaluate the Safety and Tolerability of MEDI4736 in Subjects with Myelodysplastic Syndrome after Treatment with Hypomethylating Agents

• UC Davis UCDCC#256
  – Phase 1b Trial of the Combination of Ibrutinib and Azacitidine for the Treatment of Higher Risk Myelodysplastic Syndromes in Previously Treated Patients or in Untreated Patients Unfit for or Who Refuse Intense Therapy