Biomarker, Imaging, & QOL Studies Funding Program (BIQSFP) Annual Update

http://biqsfp.cancer.gov/

CTAC Meeting
December 15, 2010
Raymond Petryshyn, PhD
BACKGROUND
Program Summary

- BIQSFP is a unique and first-of-kind pilot project initiated in ‘08 as the result of the CTWG recommendations.
- A funding mechanism and prioritization process to ensure that the most important biomarker, imaging, and quality of life studies can be initiated in a timely manner in association with clinical trials.
- Primary purpose is to fund studies conducted in association with phase 3 trials when the cost of such studies is too large to be covered by the Cooperative Group / CCOP mechanisms in a timely manner.
- In ‘10, BIQSFP was expanded to include large, phase 2 clinical trials with integral assays/tests.
Prioritization

1. **Integral studies**: a test or assessment that must be performed in order for the trial to proceed
   - Test to establish patient eligibility
   - Test for patient stratification
   - Test to assign patient to treatment arm, including early response endpoints for assignment of treatment during a trial
   - CLIA-certified lab required

2. **Integrated studies**: a test or assessment that is intended to identify or validate assays, markers or imaging tests, or SxQOL instruments that might be used in future trials
   - Study plans clearly described in trial protocol
   - Tests performed on all cases although results not used to guide decisions in current trial
BIQSFP Review and Funding Process

Parent clinical trial concept & BIQSFP proposal received by CTEP/DCP from CG/CCOP

Internal CTEP/DCP parent concept & BIQSFP proposal evaluation

Parent concept & BIQSFP proposal evaluated by SSC

SSC-recommended parent concept & BIQSFP proposal sent to CTROC for final review/approval/funding

PROTOCOL OPENED TO ACCRUAL

Annually, CTROC-approved BIQSFP proposals sent to CTAC for program review

CG = Cooperative Group
CCOP = Community Cancer Oncology Program
BIQSFP = Biomarker, Imaging, and Quality of Life Studies Funding Program
SSC = Scientific Steering Committee
CTROC = Clinical Trials and Translational Research Operations Committee
CTAC = Clinical and Translational Research Advisory Committee
CURRENT STATUS OF PROGRAM
<table>
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<tr>
<th>Cooperative Group</th>
<th>Total Submitted</th>
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<td></td>
<td>2</td>
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<tr>
<td>SWOG</td>
<td>7</td>
<td></td>
<td>1</td>
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<tr>
<td>CCOP Research Bases *</td>
<td>2</td>
<td></td>
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<td><strong>TOTAL</strong></td>
<td><strong>40</strong></td>
<td><strong>4</strong></td>
<td><strong>11</strong></td>
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</tbody>
</table>

* Not affiliated with Cooperative Groups
Total ‘08 – ’10 BIQSFP Project Areas **

- Biomarker (n=28)
- Imaging (n=4)
- QOL (n=15)

59% 32% 9%

** Applications may include more than one project area
<table>
<thead>
<tr>
<th>Type of Study / Year Submitted</th>
<th>Year Approved</th>
<th>Integral/Integrated</th>
<th>Coop Group/CCOP</th>
<th>Document Number</th>
<th>Concept Title</th>
<th>Cancer Site</th>
<th>Approved Funding ($$)</th>
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<tbody>
<tr>
<td><strong>Biomarker ‘10</strong></td>
<td>2010</td>
<td>Integral &amp; Integrated</td>
<td>SWOG</td>
<td>SWOG 0819</td>
<td>A Randomized , Phase 3 Study Comparing Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)</td>
<td>NSCLC</td>
<td>$ 986,753</td>
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<td><strong>Biomarker ‘10</strong></td>
<td>2010</td>
<td>Integral</td>
<td>SWOG</td>
<td>SWOG S1007</td>
<td>A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer according to Recurrence Score (RS)</td>
<td>Breast</td>
<td>$ 5,000,000</td>
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<td><strong>QOL ’09</strong></td>
<td>2010</td>
<td>Integrated</td>
<td>COG</td>
<td>AALL 0932</td>
<td>Longitudinal assessment of vincristine-associated peripheral neuropathy</td>
<td>Peds ALL</td>
<td>$ 1,633,012</td>
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<tr>
<td><strong>Biomarker ‘10</strong></td>
<td>2010</td>
<td>Integral &amp; Integrated</td>
<td>COG</td>
<td>AAML 1031</td>
<td>A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Lestaurtinib for patients with FLT3 ITD</td>
<td>Peds AML</td>
<td>$ 4,851,631</td>
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<td><strong>Imaging ’09</strong></td>
<td>2010</td>
<td>Integrated</td>
<td>RTOG</td>
<td>RTOG 0825 / ACRIN 6686</td>
<td>Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma</td>
<td>Glioblastoma</td>
<td>$ 671,556</td>
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<tr>
<td><strong>Biomarker ‘09</strong></td>
<td>2010</td>
<td>Integral</td>
<td>RTOG</td>
<td>RTOG 1010</td>
<td>A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma</td>
<td>Esophageal</td>
<td>$ 1,726,321</td>
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<td><strong>Biomarker ‘09</strong></td>
<td>2010</td>
<td>Integral</td>
<td>NCCTG</td>
<td>N0577</td>
<td>Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma</td>
<td>Glioma</td>
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<td><strong>Biomarker ‘09</strong></td>
<td>2009</td>
<td>Integral &amp; Integrated</td>
<td>CALGB</td>
<td>CALGB 30801</td>
<td>A Randomized Phase III Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer</td>
<td>Lung</td>
<td>$ 350,939</td>
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<tr>
<td><strong>Biomarker ’08</strong></td>
<td>2008</td>
<td>Integral</td>
<td>COG</td>
<td>AAML 0531</td>
<td>A Phase III Randomized Trial of Gemtuzumab Ozogamicin Mylotarg® Combined with Conventional Chemotherapy for De Novo Acute Myeloid Leukemia (AML) in Children, Adolescents, and Young Adults</td>
<td>Peds AML</td>
<td>$ 1,500,000</td>
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<td><strong>QOL ’08</strong></td>
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<td>Integrated</td>
<td>NSABP</td>
<td>B-45</td>
<td>A Phase III Clinical Trial Comparing Adjuvant Sunitinib Malate to Placebo in Women with Residual Invasive Breast Cancer Following Neoadjuvant Chemotherapy</td>
<td>Breast</td>
<td>$ 1,046,226</td>
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<td><strong>QOL ’08</strong></td>
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<td>GOG</td>
<td>UC 0604</td>
<td>A Phase III Trial of Pelvic Radiation Therapy vs Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin Chemotherapy in Patients with High Risk Early Stage Endometrial Carcinoma</td>
<td>Uterine</td>
<td>$ 76,000</td>
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</table>

**GRAND TOTAL APPROVED STUDIES (‘08 - ‘10)** $ 18,418,448
‘08 – ’10 Total BIQSFP-Funded Proposals

- Biomarker (n=7) $15,914,145
- Imaging (n=1) $671,556
- QOL (n=3) $1,832,747

Total '08-'10 BIQSFP-Funded Proposals = $18,418,448
Biomarkers:

**NSCLC:** COX-2  urinary PGE-M  KRAS  EGFR

**AML:** FLT3/ITD  KIT  MRD  RT-PCR  WT1  RUNX1  TET2  MLL-PTD  c-CBL  CEBPa  CD74  PSMB5

**Esophageal cancer:** HER2

**Glioma:** translocation of 1p:19q

**Breast cancer:** OncoType DX

**Imaging:**

**Glioblastoma:** Advanced MRI (DSC-MRI & DCE-MRI)

**QOL:**

**ALL:** vincristine-associated neuropathy & neuromotor function

**Endometrial cancer:** PROMIS 7 (HRQOL)

**Breast cancer:** Fatigue  Behavioral & Health Outcomes
Summary of BIQSFP Proposals Approved ‘08 – ‘10

- 11-Approved Studies
- ~$18M
- ~14K patients
- Studies Completed = 1
- Studies Open = 5
- Studies Approved & Pending Opening = 5
**Biomarkers: FLT3/ITD & CEBPα**

**Objectives:** To determine the mutation status of genes with known prognostic significance (FLT3/ITD) for AML to assign therapy, specifically FLT3/ITD with high allelic ratio (high ITD-AR).

To validate the prognostic significance of CEPBα as a favorable marker and to optimize the utility of multidimensional flow cytometry to identify patients in morphologic remission with minimal residual disease (MRD) who are at high risk of relapse.

(Dr. Malcolm Smith, MD, PhD – will present AAML1031 and AAML0531 BIQSFP Projects)
# Open BIQSFP Studies

<table>
<thead>
<tr>
<th>Coop Group / Document Number</th>
<th>Study Title</th>
<th>Opened</th>
<th>Accrual Goal</th>
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<tbody>
<tr>
<td>SWOG 0819</td>
<td>A Randomized, Phase 3 Study Comparing Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)</td>
<td>7/15/09</td>
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<td>CALGB 30801</td>
<td>A Randomized Phase III Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer</td>
<td>2/15/10</td>
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<tr>
<td>NCCTG N0577</td>
<td>Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma</td>
<td>9/22/09</td>
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<td>RTOG 0825 / ACRIN 6686</td>
<td>Exploration of Imaging Response Criteria, A Companion Study to RTOG 0825 - Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma</td>
<td>7/20/09</td>
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<td>GOG UC0604 / 0249</td>
<td>A Phase III Trial of Pelvic Radiation Therapy vs. Vaginal Cuff Brachytherapy Followed by Paclitaxel/Carboplatin Chemotherapy in Patients with High Risk Early Stage Endometrial Carcinoma</td>
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<td>NSABP / NCIC CTC MA.32.F</td>
<td>Biobehavioral Mechanisms of Fatigue in Patients Treated on NCIC CTG MA.32: A Phase III Randomized Trial of Metformin Versus Placebo on Recurrence and Survival in Early Stage Breast Cancer (NCIC CTG MA.32 Ancillary Study led by the National Surgical Adjuvant Breast and Bowel Project)</td>
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<td>COG AAML1031</td>
<td>A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Lestaurninib for patients with FLT3 ITD</td>
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<td>SWOG S1007</td>
<td>A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer according to Recurrence Score (RS)</td>
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<td>RTOG 1010</td>
<td>A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma</td>
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<td>COG AALL 0932</td>
<td>Longitudinal Assessment of Vincristine-Associated Peripheral Neuropathy</td>
<td>2011</td>
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PROPOSED CHANGES & FUTURE CONSIDERATIONS
• Expanded the Program to include large, randomized phase 2 clinical trials with integral assays/tests

➢ Phase 2 submissions to date: NONE
Proposed Changes for ‘11

1. *Cost-Effectiveness Analysis (CEA)*

Provide a scientific economic analysis of the study endpoints, where information from an economic analysis may have the greatest influence on both clinical decision-making and health policy.

In November ‘10, CTAC accepted the CEA WG report and recommendations on a one-year pilot basis for:

- The evaluation and prioritization of Cost-Effectiveness Analyses (CEA) paired with NCI-sponsored treatment trials
- Funding CEA studies through the existing BIQSFP
2. Release New Funding Announcement April ‘11

3. Limit BIQSFP funding to $5M for any one clinical trial.
Future Considerations for CTAC

- Develop a Program Evaluation Plan: Value-added
  - Potential metrics
    - Improve medical decision-making
    - Facilitate change in design of clinical trials
    - Acceptance of assays/tests as standard of care
    - Commercialization of validated assays/tests (FDA approvals)
    - Reimbursement of assays/tests by payer system

Perception by Stakeholders
  - Potential metrics
    - Quality of applications submitted
    - Enhanced clinical and translational collaborations
    - Accelerated development of new integral assay/test
AAML0531 and AAML1031 BIQSFP Projects

Malcolm A. Smith, MD, PhD
CTEP, NCI
December 2010
5-Year Survival Rates for ALL, AML, NHL and Hodgkin Lymphoma by Age Group

**A. ALL**

<table>
<thead>
<tr>
<th>Time Period</th>
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**B. AML**

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**C. NHL**

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**D. HD**

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<tr>
<td>1999-02</td>
<td>96.8</td>
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</tbody>
</table>
Genomic alterations in AML

![Bar chart showing prevalence of mutations in AML](image)

- **FLT3/ITD**: 27% (Adults), 12% (Pediatric)
- **N-RAS**: 19% (Adults), 12% (Pediatric)
- **NPM**: 20% (Adults), 6% (Pediatric)
- **KIT CBF**: 25% (Adults), 15% (Pediatric)
- **WT1**: 10% (Adults), 8% (Pediatric)
- **CEBPa**: 5% (Adults), 5% (Pediatric)
- **FLT3/AL**: 7% (Adults), 7% (Pediatric)
- **RUNX1**: 7% (Adults), 5% (Pediatric)
- **MLL-PTD**: 15% (Adults), 0% (Pediatric)
- **IDH1**: 7% (Adults), 5% (Pediatric)
- **SHIP**: 3% (Adults), 0% (Pediatric)
- **PTPN11**: 3% (Adults), 5% (Pediatric)
AAML0531 Study Design

Randomization to GMTZ
Stratification to SCT

Induction I
ADE10 & GMTZ
ADE10

Induction II
ADE8
CR
No CR

CR

AE

High Risk

Low Risk
Std Risk, No MFD

S

SCT
Best donor

• >15% marrow Blast at EOI1
• -7, -5/del5q, FLT3/ITD-HAR

Chemo +/- GO

SCT MFD

Std Risk w/ MFD

Off Protocol

Study Enrollment: Aug 2006 – Jun 2010
1026 eligible patients
Too early for analysis of DFS/survival data
Remission rates (blinded by arm) are available
COG AML0531 BIQSFP Project

- One integral study: **FLT3 ITD with high allelic ratio (AR)**
  - Performed at Seattle Cancer Care Alliance Molecular Diagnostics Laboratory (CLIA certified)
  - Patients positive for this finding are assigned to allogeneic SCT with the most suitable donor

- **Integrated studies:**
  - **CEBPA mutation** and other mutations with potential prognostic significance (Meshinchi laboratory)
  - **Minimal Residual Disease (MRD)** using Second Generation Four-Color Multidimensional Flow (MDF) cytometry (Hematologics, Inc.; CLIA certified although results not used for clinical decision-making)
Evaluation of Prognostic Significance of ITD-AR Threshold of 0.4 in BFM SG & Dutch DCOG Cohort

Clinical outcome - FLT3/ITD

Conventional chemotherapy

Stem cell transplantation
Selected Patient Characteristics
AAML0531

- **Age:**
  - Median 10 yrs (0-29 yrs)
  - 0-15 yrs: 84% & 0-1 yrs: 10%

- **WBC:**
  - Median 24,000 (0.2-827,000)
  - >100,000: 19% & >300,000: 3%

- **Path/Cyto:**
  - Centrally Reviewed
  - LR – Inv16 & t(8;21): 25%
  - HR – -7 & -5/del5q: 3%

- **FLT3-ITD**
  - Incl Risk groups in 4/08 (n=615)
  - HAR: 7%, LAR: 10%, WT: 82%
Overall Cumulative Response Rates after Induction 1 & 2

Induction 1
- PR: 12%
- PD: 12%
- CNS: 2%
- TM: 2%
- CR: 72%

Induction 2
- RD: 11%
- TM: 2%
- CR: 87%

Complete Remission Rates
AAML0531, MRC AML12 Peds, CCG2961

Lange et al, Blood 2008
Gibson et al, ASH 2002

Gibson et al, ASH 2002
Lange et al, Blood 2008
## Diagnostic Induction 2 CR Risk Factors

**CR rate comparisons - Univariate**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No significant differences except</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;1 vs &gt;1 y/o: 71% vs 88%, p&lt;.001</td>
</tr>
<tr>
<td>WBC</td>
<td>&gt;100k vs &lt;100k: 76% vs 89%, p=.001</td>
</tr>
<tr>
<td></td>
<td>TM: 5% v 2%; RD/CNS Rel: 20% v 9%</td>
</tr>
<tr>
<td>Cytogen</td>
<td>LR 96% v IR 84% v HR 79%, p&lt;.001</td>
</tr>
<tr>
<td></td>
<td>RD/CNS Rel: 3% v 13% v 21%</td>
</tr>
<tr>
<td>FLT3 ITD</td>
<td>HAR 71% v LAR 90% v WT 90%, p&lt;.001</td>
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<td>RD/CNS Rel: 29% v 10% v 9%</td>
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### Adverse Risk Factor Analysis

#### End of Induction 2 CR rate

**Univariate**

<table>
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<th>OR</th>
<th>p value</th>
<th>Risk Factor</th>
<th>OR</th>
<th>p value</th>
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<td>2.6</td>
<td>&lt;.001</td>
<td>WBC&gt;100k</td>
<td>2.4</td>
<td>.003</td>
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<tr>
<td>2.4</td>
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<td>FLT3-ITD</td>
<td>2.0</td>
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<td>LR Cyto</td>
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**Multivariate**

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**Baseline comparison groups negative for risk factors**
Multi dimensional flow (MDF) cytometry: Pilot data for relapse rate and DFS from AAML03P1

Relapse Risk

Disease-free Survival
• Among patients with PR (5% - 15% blasts at EOI-1) or PD (>15% blasts at EOI-1), a substantial percentage were MDF-negative
EOI-1 MDF Status Accurately Predicts EOI-2 morphologic CR status

- A high proportion of PR/PD pts who were MDF negative at EOI-1 achieved morphologic CR at EOI-2.
- Analyses for MDF effect on DFS and survival are pending.
AAML1031 BIQSFP: Integral Components

- Risk identification & treatment assignment based on the following:
- Response to therapy: Minimal residual disease (MRD) by multi-dimensional flow cytometry (MDF)
  - End of induction I
  - Following 3 chemotherapy courses and pre-SCT
- Molecular prognostic markers
  - FLT3/ITD allelic ratio determination
  - NPM1 mutations
  - CEBPA mutations
Two Tier Risk Class Using Cytogenetic/Molecular/MRD Results

**Low risk**: CBF, CEBPA, NPM, MRD-neg Stnd Risk

**High risk**: cytogenetic HR, high AR FLT3/ITD, MRD-pos Stnd Risk
AAML1031 Phase 3 study design

De Novo AML

- Risk Classification
  - Bortezomib\(^1\)
    - ADE 10 + 3
      - High allelic ratio FLT3 ITD +
        - ADE 10 + 3 Sorafenib\(^3\)
  - Bortezomib\(^1\)
    - ADE 8 + 3
  - Remission Assessment\(^2\)
    - ADE 8 + 3
    - AE
  - Remission Assessment\(^2\)
    - Bortezomib\(^2\)
      - AE
    - ADE 8 + 3
  - Consolidation Assignment
    - Low Risk
      - AraC/Mito +/− Bortezomib\(^1\)
    - High Risk
      - Best Allo SCT

- Any Donor
  - Best Allo SCT
- No Donor
  - AraC/Mito + Sorafenib
http://biqsfp.cancer.gov/

Discussion

Thank you