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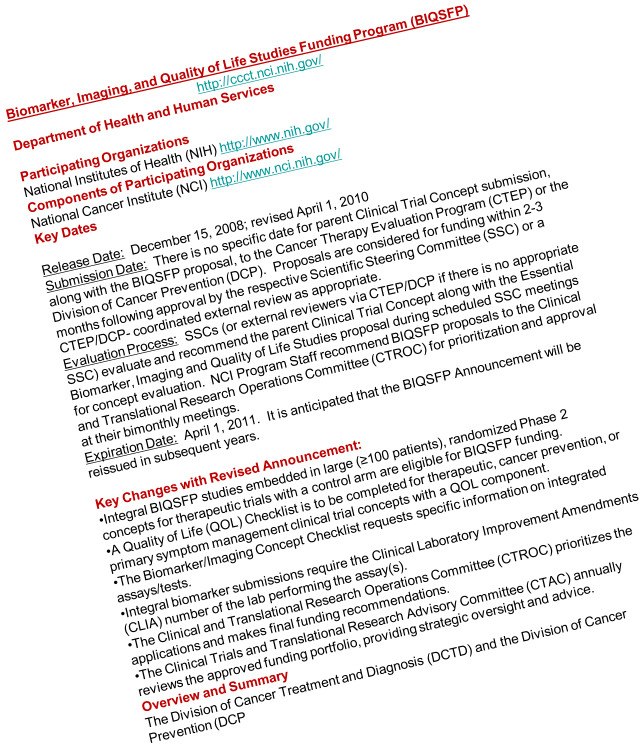
Biomarker, Imaging, & QOL Studies Funding Program (BIQSFP) Annual Update



Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)
http://ccct.nci.nih.gov/

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH) http://www.nih.gov/
Components of Participating Organizations
National Cancer Institute (NCI) http://www.nci.nih.gov/
Key Dates

Release Date: December 15, 2008; revised April 1, 2010
Submission Date: There is no specific date for parent Clinical Trial Concept submission, along with the BIQSFP proposal, to the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP). Proposals are considered for funding within 2-3 months following approval by the respective Scientific Steering Committee (SSC) or a CTEP/DCP- coordinated external review as appropriate.
Evaluation Process: SSCs (or external reviewers via CTEP/DCP if there is no appropriate SSC) evaluate and recommend the parent Clinical Trial Concept along with the Essential Biomarker, Imaging and Quality of Life Studies proposal during scheduled SSC meetings for concept evaluation. NCI Program Staff recommend BIQSFP proposals to the Clinical and Translational Research Operations Committee (CTROC) for prioritization and approval at their bimonthly meetings.
Expiration Date: April 1, 2011. It is anticipated that the BIQSFP Announcement will be reissued in subsequent years.

Key Changes with Revised Announcement:
•Integral BIQSFP studies embedded in large (≥100 patients), randomized Phase 2 concepts for therapeutic trials with a control arm are eligible for BIQSFP funding.
•A Quality of Life (QOL) Checklist is to be completed for therapeutic, cancer prevention, or primary symptom management clinical trial concepts with a QOL component.
•The Biomarker/Imaging Concept Checklist requests specific information on integrated assays/tests.
•Integral biomarker submissions require the Clinical Laboratory Improvement Amendments (CLIA) number of the lab performing the assay(s).
•The Clinical and Translational Research Operations Committee (CTROC) prioritizes the applications and makes final funding recommendations.
•The Clinical Trials and Translational Research Advisory Committee (CTAC) annually reviews the approved funding portfolio, providing strategic oversight and advice.
Overview and Summary
The Division of Cancer Treatment and Diagnosis (DCTD) and the Division of Cancer Prevention (DCP

http://biqsfp.cancer.gov/

CTAC Meeting
December 15, 2010
Raymond Petryshyn, PhD

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BACKGROUND

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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

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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

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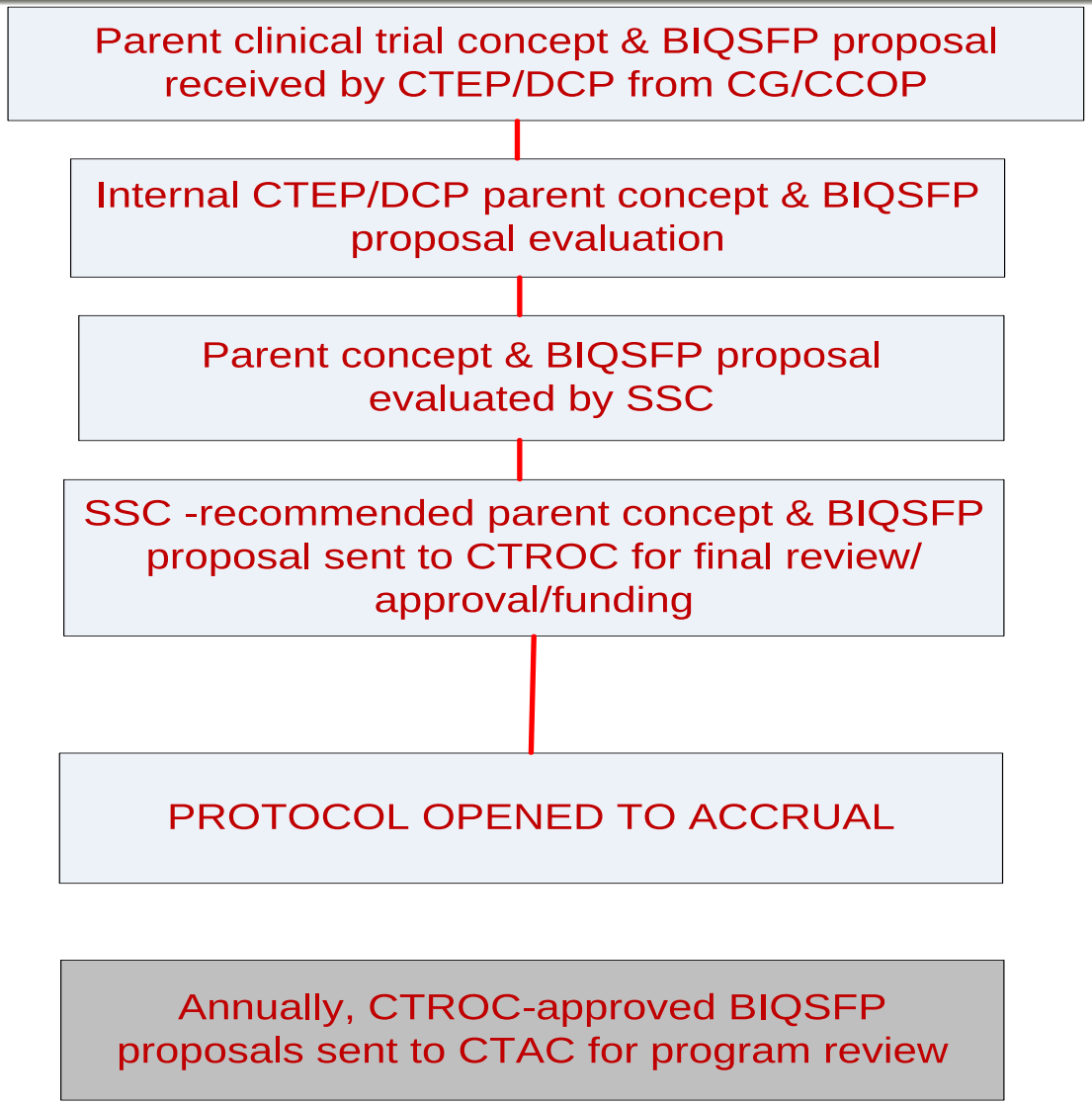
BIQSFP Review and Funding Process



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

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CURRENT STATUS OF PROGRAM

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Summary of BIQSFP Proposals Submitted by Cooperative Groups '08–'10

Cooperative Group	Total Submitted	Total in Evaluation	Total Approved
ACOSOG	1		0
ACRIN	0		0
CALGB	2		1
COG	6	3	3
ECOG	10		0
GOG	3		1
NCCTG	3		1
NSABP	2	1	1
RTOG	4		2
SWOG	7		1
CCOP Research Bases *	2		0
TOTAL	40	4	11

* Not affiliated with Cooperative Groups

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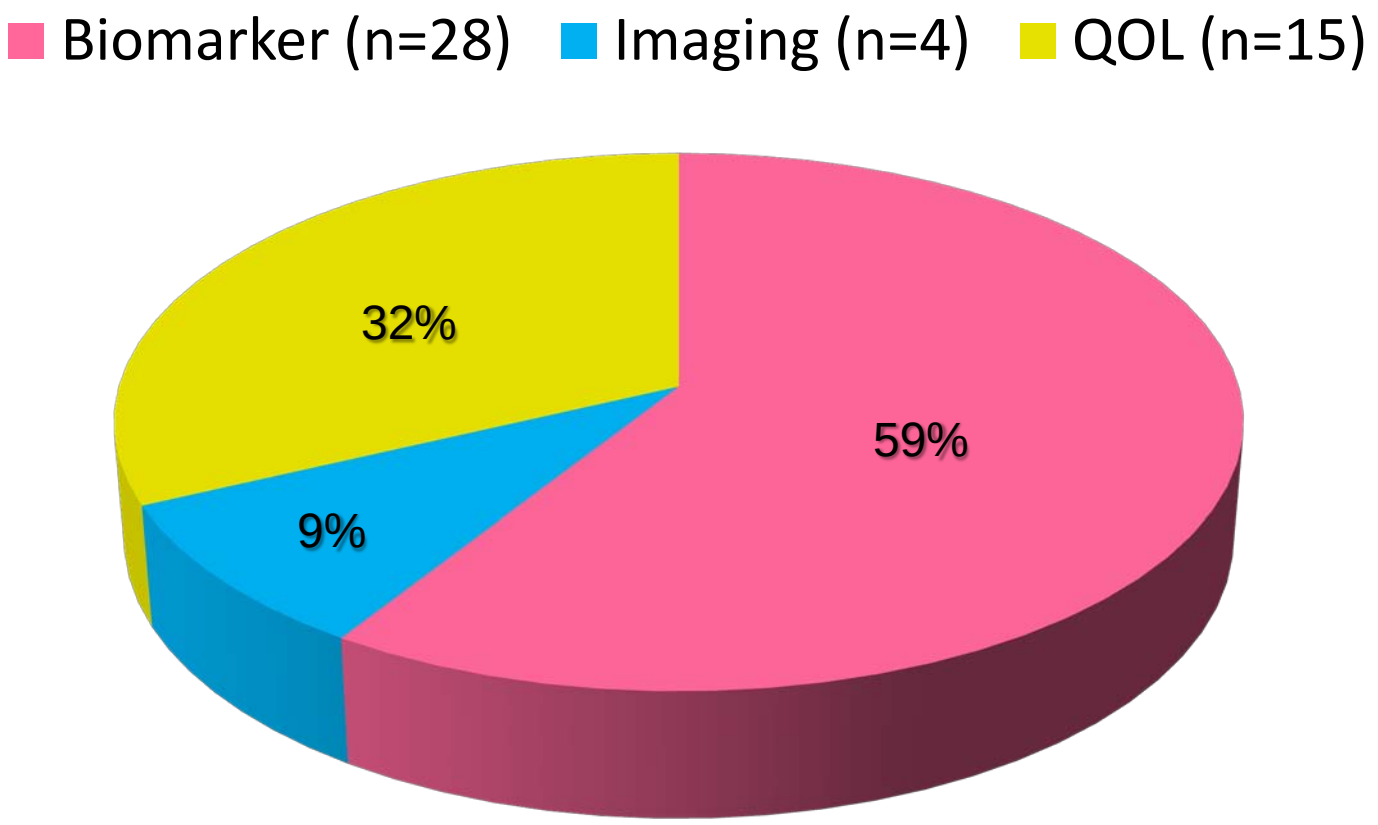
Total ‘08 – ’10 BIQSFP Project Areas **



** Applications may include more than one project area

'08 –'10 BIQSFP Approved Studies

Type of Study / Year Submitted	Year Approved	Integral/ Integrated	Coop Group/ CCOP	Document Number	Concept Title	Cancer Site	Approved Funding ($$$)
Biomarker '10	2010	Integral & Integrated	SWOG	SWOG 0819	A Randomized , Phase 3 Study Comparing Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)	NSCLC	$ 986,753
Biomarker '10	2010	Integral	SWOG	SWOG S1007	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)	Breast	$ 5,000,000
QOL '09	2010	Integrated	COG	AALL 0932	Longitudinal assessment of vincristine-associated peripheral neuropathy	Peds ALL	$ 1,633,012
Biomarker '10	2010	Integral & Integrated	COG	AAML 1031	A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Lestaurtinib for patients with FLT3 ITD	Peds AML	$ 4,851,631
Imaging '09	2010	Integrated	RTOG	RTOG 0825 / ACRIN 6686	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	Glioblastoma	$ 671,556
Biomarker '09	2010	Integral	RTOG	RTOG 1010	A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma	Esophageal	$ 1,726,321
Biomarker '09	2010	Integral	NCCTG	N0577	Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma	Glioma	$ 576,010
Biomarker '09	2009	Integral & Integrated	CALGB	CALGB 30801	A Randomized Phase III Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer	Lung	$ 350,939
Biomarker '08	2008	Integral	COG	AAML 0531	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	Peds AML	$ 1,500,000
QOL '08	2008	Integrated	NSABP	B-45	A Phase III Clinical Trial Comparing Adjuvant Sunitinib Malate to Placebo in Women with Residual Invasive Breast Cancer Following Neoadjuvant Chemotherapy	Breast	$ 1,046,226
QOL '08	2008	Integrated	GOG	UC 0604	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	Uterine	$ 76,000
					GRAND TOTAL APPROVED STUDIES ('08 - '10)		**$ 18,418,448**

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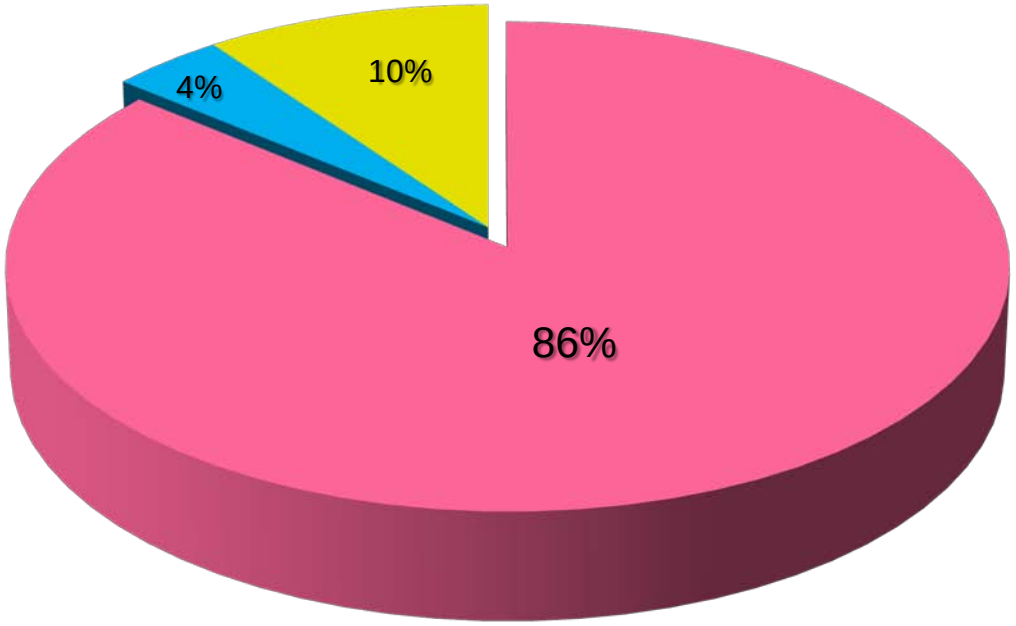
‘08 – ’10 Total BIQSFP-Funded Proposals



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

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Scope of BIQSFP Assays/Tests

Biomarkers:

NSCLC: COX-2 urinary PGE-M KRAS EGFR
AML: FLT3/ITD KIT MRD RT-PCR WT1 RUNX1 TET2 MLL-PTD c-CBL CEBPα 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

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Summary of BIQSFP Proposals Approved '08 – '10

- 11-Approved Studies
- ~$18M
- ~14K patients
- Studies Completed = 1
- Studies Open = 5
- Studies Approved & Pending Opening = 5

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Closed to Accrual

Coop Group / Document Number	Study Title	Opened	Accrual Goal	Total Accrual
COG AAML0531	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	**8/14/06**	**1012**	**1070**

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)

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Open BIQSFP Studies

Coop Group / Document Number	Study Title	Opened	Accrual Goal
SWOG 0819	A Randomized , Phase 3 Study Comparing Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)	7/15/09	1546
CALGB 30801	A Randomized Phase III Double Blind Trial Evaluating Selective COX-2 Inhibition in COX-2 Expressing Advanced Non-Small Cell Lung Cancer	2/15/10	792
NCCTG N0577	Phase III Intergroup Study of Radiotherapy versus Temozolomide Alone versus Radiotherapy with Concomitant and Adjuvant Temozolomide for Patients with 1p/19q Codeleted Anaplastic Glioma	9/22/09	488
RTOG 0825 / ACRIN 6686	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	7/20/09	264
GOG UC0604 / 0249	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	3/23/09	562

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Approved – Not Open

Coop Group / Document Number	Study Title	Anticipated Opening	Accrual Goal
NSABP / NCIC CTC MA.32.F (previously NSABP B-45)	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)	2011	454
COG AAML1031	A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Lestaurtinib for patients with FLT3 ITD	**2011**	**1140**
SWOG S1007	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)	**2011**	**9400**
RTOG 1010	A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma	**2011**	**480**
COG AALL 0932	Longitudinal Assessment of Vincristine-Associated Peripheral Neuropathy	**2011**	**520**

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PROPOSED CHANGES & FUTURE CONSIDERATIONS

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OEWG / CTAC Recommendation Implemented (FY'10)

- Expanded the Program to include large, randomized phase 2 clinical trials with integral assays/tests
  - Phase 2 submissions to date: NONE

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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

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Proposed Changes for ’11 (cont)

2. Release New Funding Announcement April ‘11

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

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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

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AAML0531 and AAML1031 BIQSFP Projects

Malcolm A. Smith, MD, PhD

CTEP, NCI

December 2010

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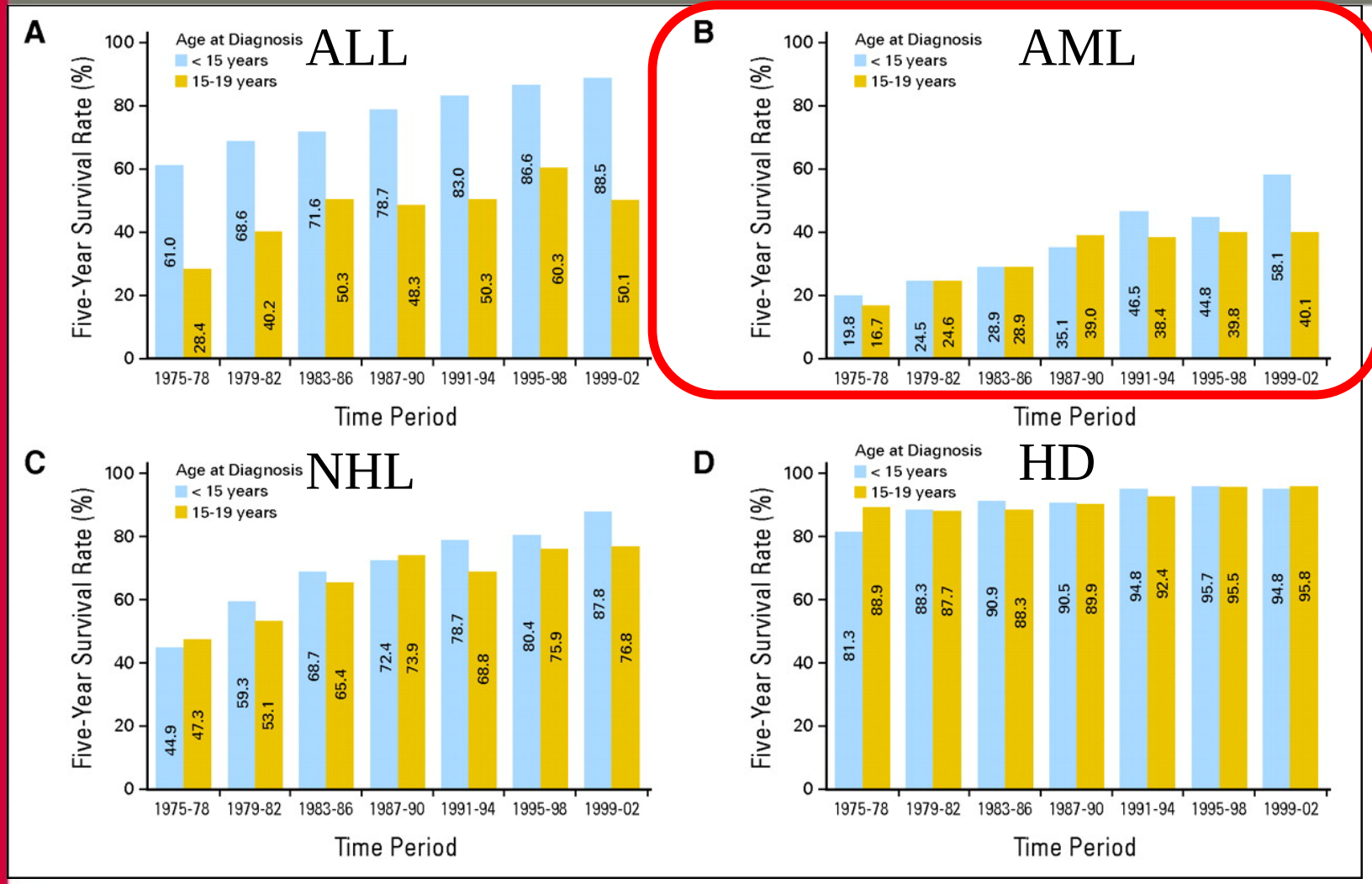
5-Year Survival Rates for ALL, AML, NHL and Hodgkin Lymphoma by Age Group



Smith M A et al. JCO **2010;28:2625-2634**

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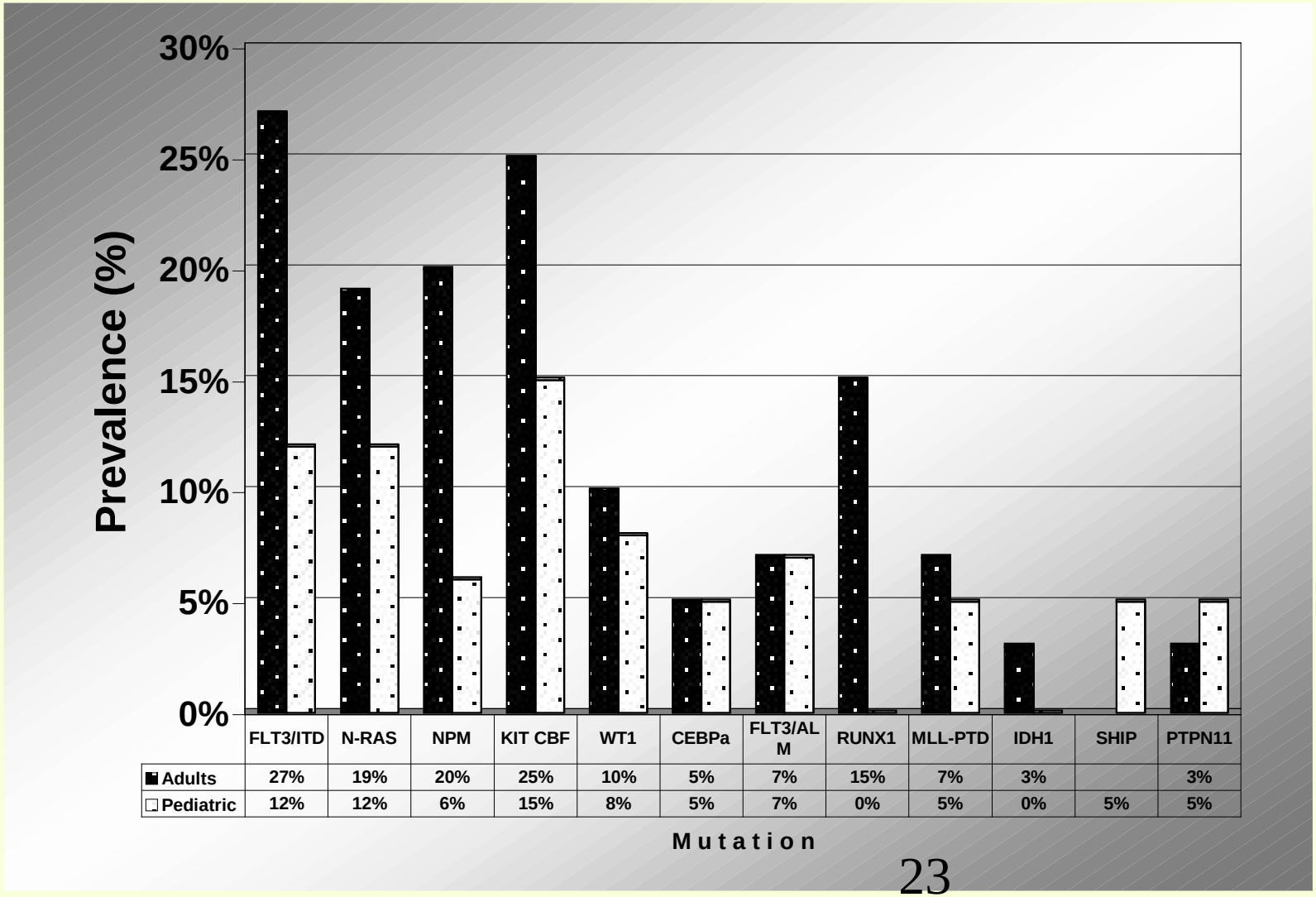
Genomic alterations in AML



	FLT3/ITD	N-RAS	NPM	KIT CBF	WT1	CEBPa	FLT3/ALM	RUNX1	MLL-PTD	IDH1	SHIP	PTPN11
Adults	27%	19%	20%	25%	10%	5%	7%	15%	7%	3%		3%
Pediatric	12%	12%	6%	15%	8%	5%	7%	0%	5%	0%	5%	5%

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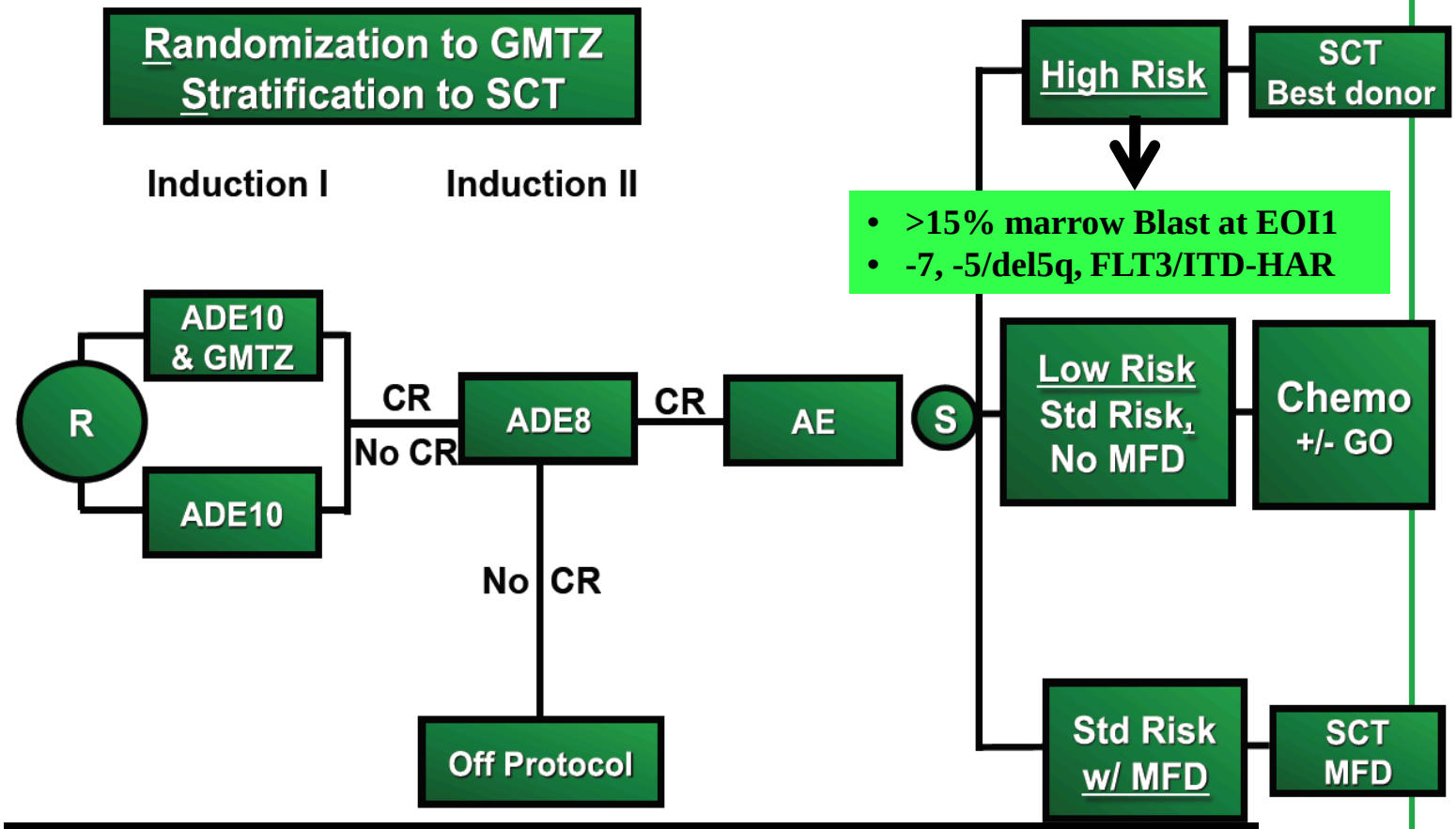
AAML0531 Study Design



Study Enrollment: Aug 2006 – Jun 2010

1026 eligible patients

Too early for analysis of DFS/survival data

Remission rates (blinded by arm) are available

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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)

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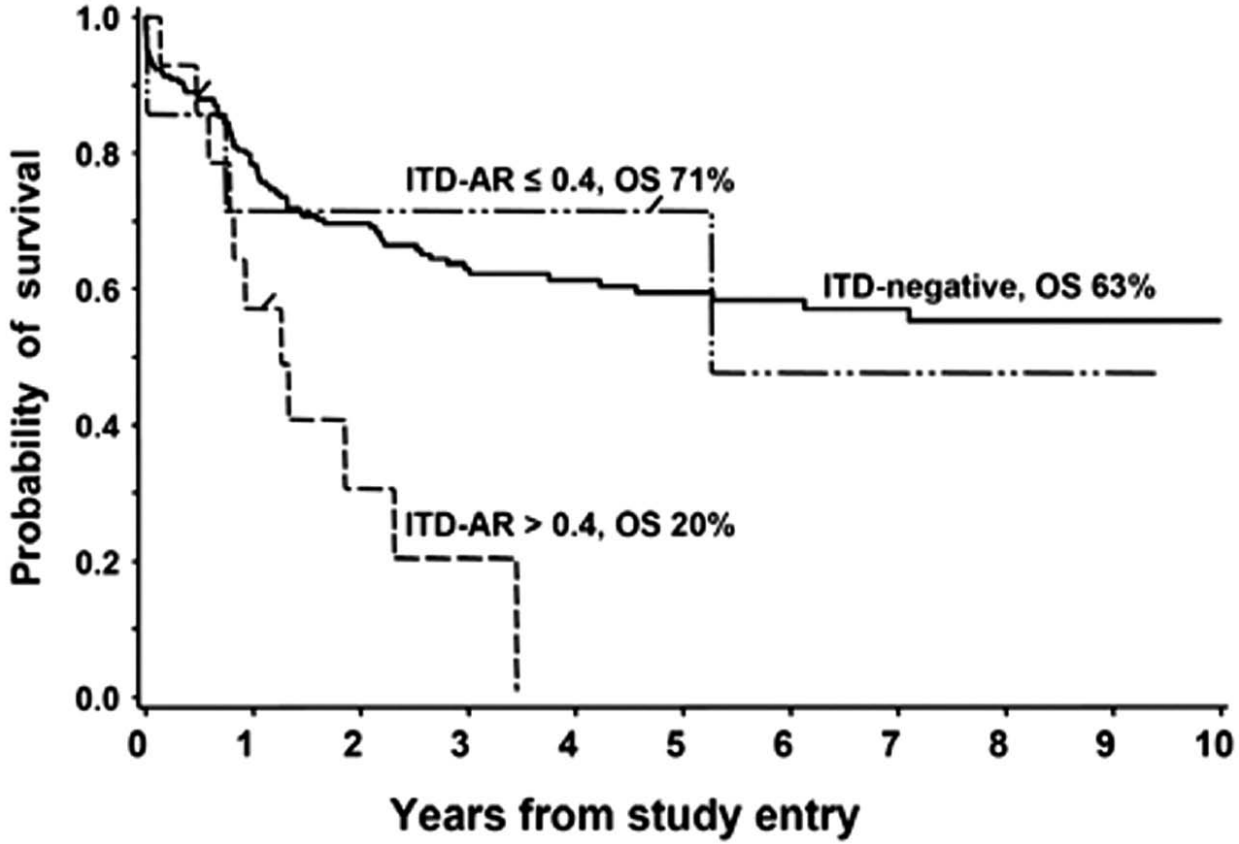
Evaluation of Prognostic Significance of ITD-AR Threshold of 0.4 in BFM SG & Dutch DCOG Cohort



Meshinchi, S. et al. Blood 2006;108:3654-3661

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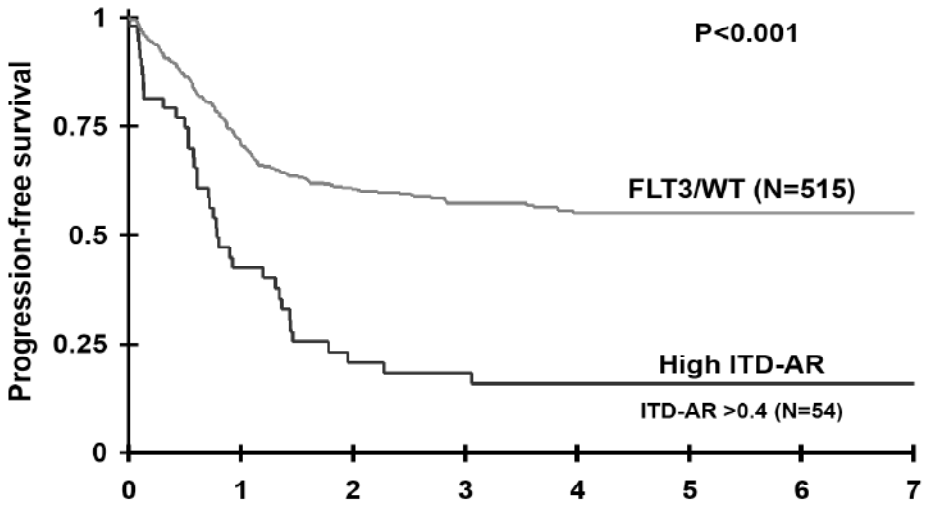
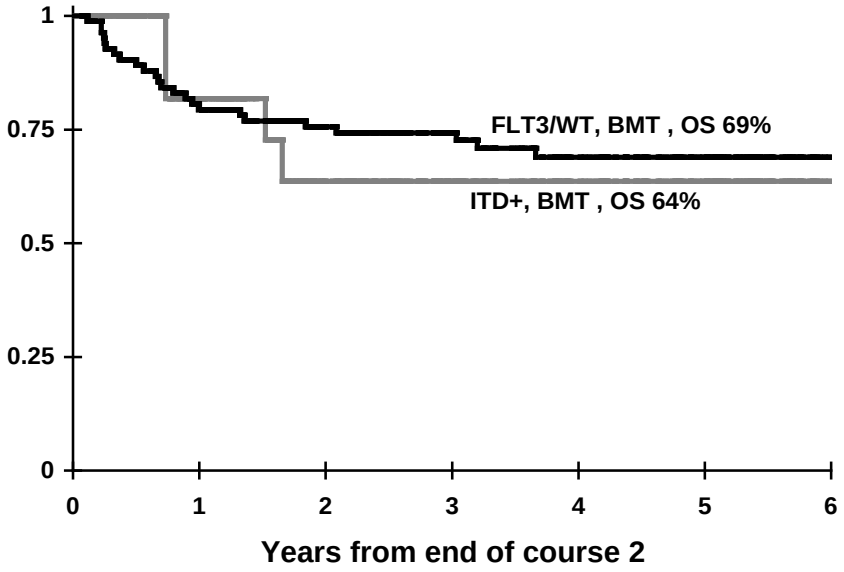
Clinical outcome - FLT3/ITD

Conventional chemotherapy



Stem cell transplantation



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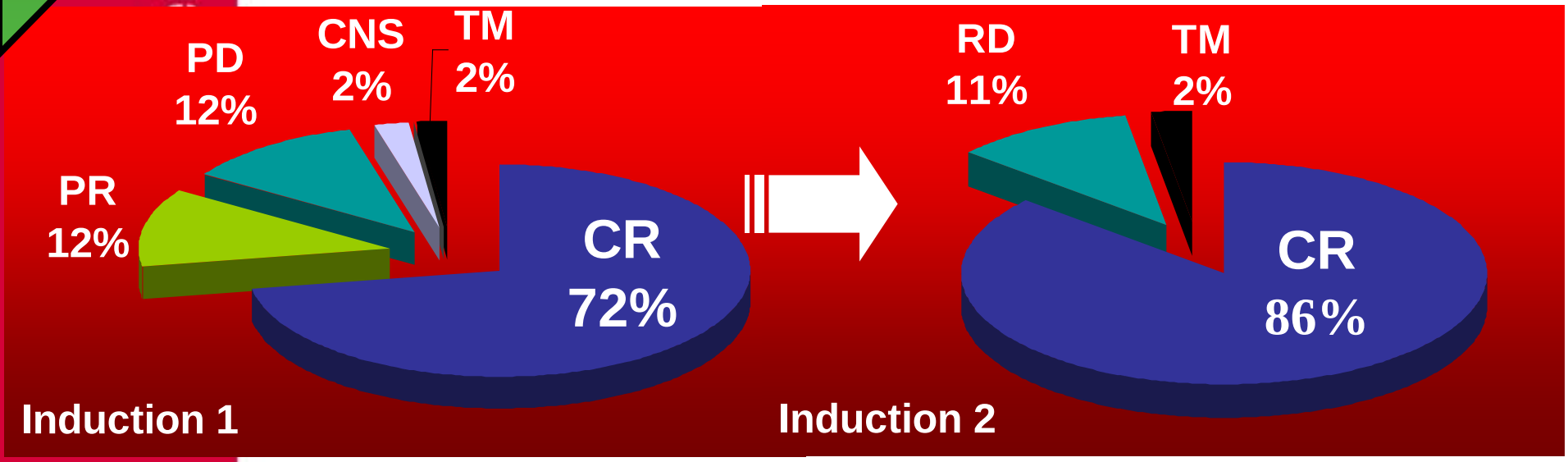
Selected Patient Characteristics AAML0531

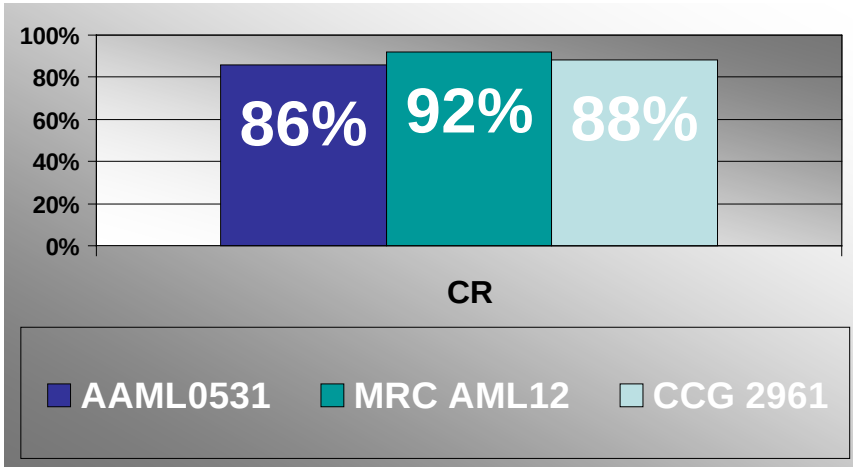
- Age:
  - Median 10 yrs (0-29 yrs)
  - 0-15 yrs: 84% & 0-1 yrs: 10%
- WBC:
  - Median 24,000 (0.2-827,000)
  - >100,000: 19% & >300,000: 3%
- Path/Cyto:
  - Centrally Reviewed
  - LR – Inv16 & t(8;21): 25%
  - HR – -7 & -5/del5q: 3%
- FLT3-ITD
  - Incl Risk groups in 4/08 (n=615)
  - HAR: 7%, LAR: 10%, WT: 82%

• Response

Overall *Cumulative* Response Rates after Induction 1 & 2



Complete Remission Rates
AAML0531, MRC AML12
Peds, CCG2961



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

Diagnostic Induction 2 CR Risk Factors

CR rate comparisons - *Univariate*

Age	▪ **No significant differences except** ▪ **<1 vs >1 y/o: 71% vs 88%, p<.001**
WBC	▪ **>100k vs <100k: 76% vs 89%, p=.001** ▪ **TM: 5% v 2%; RD/CNS Rel: 20% v 9%**
Cytogen	▪ **LR 96% v IR 84% v HR 79%, p<.001** ▪ **RD/CNS Rel: 3% v 13% v 21%**
FLT3 ITD	▪ **HAR 71% v LAR 90% v WT 90%, p<.001** ▪ **RD/CNS Rel: 29% v 10% v 9%**

Adverse Risk Factor Analysis
End of Induction 2 CR rate

- ***Univariate***
- ***Multivariate***

OR	p value	Risk Factor	OR	p value
2.6	<.001	WBC>100k	2.4	.003
2.4	.001	FLT3-ITD HAR	2.0	.030
3.1	<.001	Age <1yr	2.0	.076
0.2	<.001	LR Cyto	0.3	.014

- ***Baseline comparison groups negative for risk factors***

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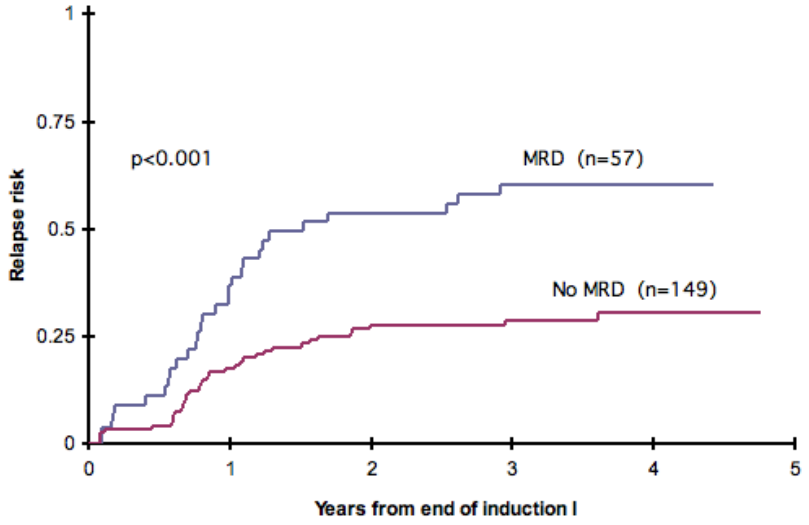
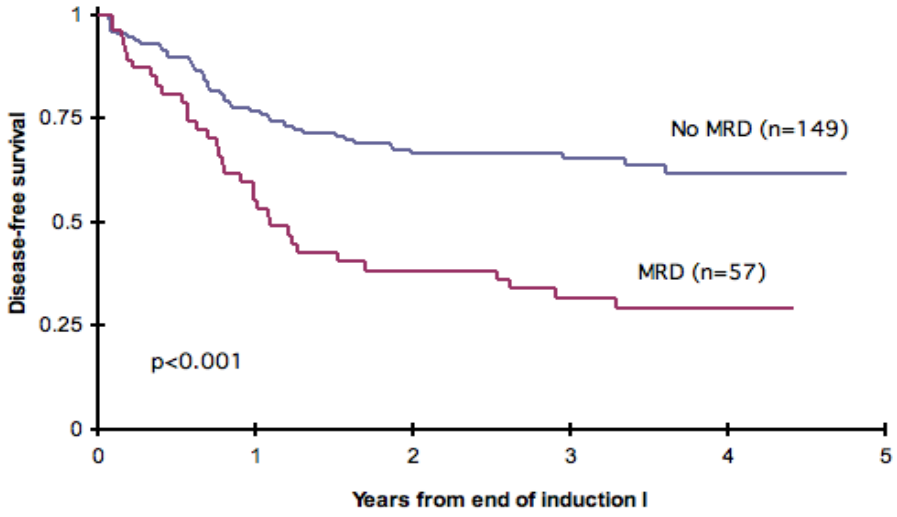
Multi dimensional flow (MDF) cytometry: Pilot data for relapse rate and DFS from AAML03P1

Relapse Risk



Disease-free Survival



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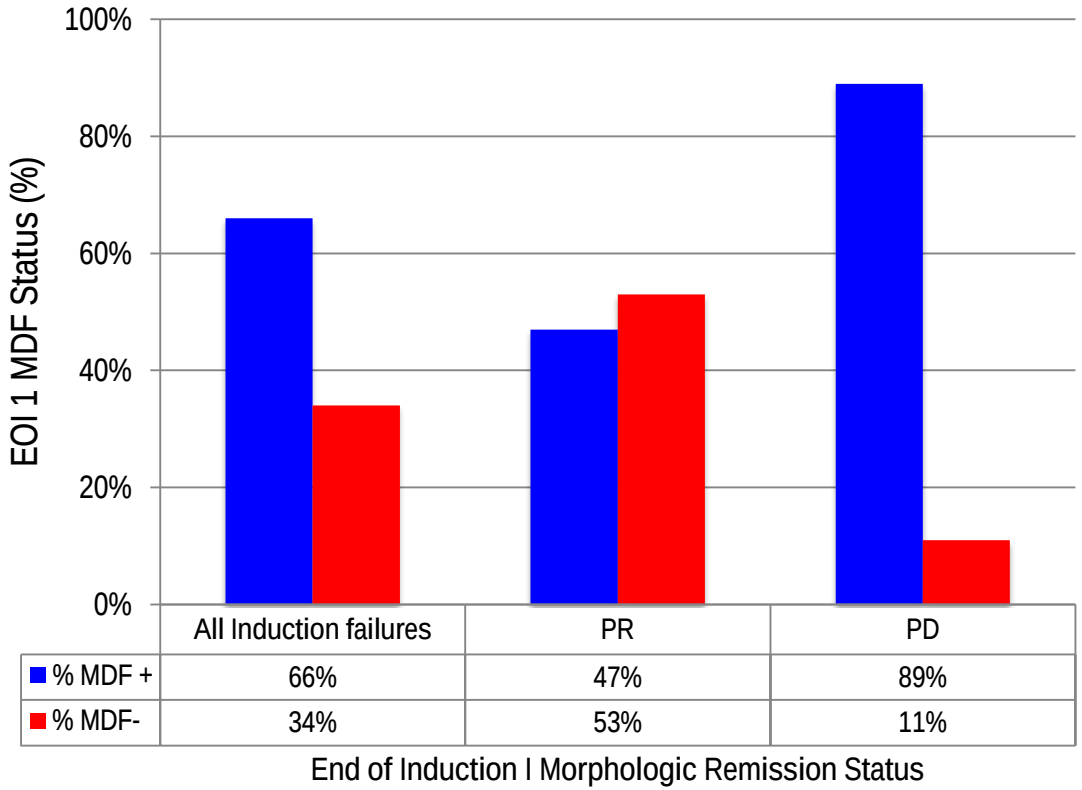
Discrepancy Between Morphology and MDF Assessment



	All Induction failures	PR	PD
% MDF +	66%	47%	89%
% MDF-	34%	53%	11%

- Among patients with PR (5% - 15% blasts at EOI-1) or PD (>15% blasts at EOI-1), a substantial percentage were MDF-negative

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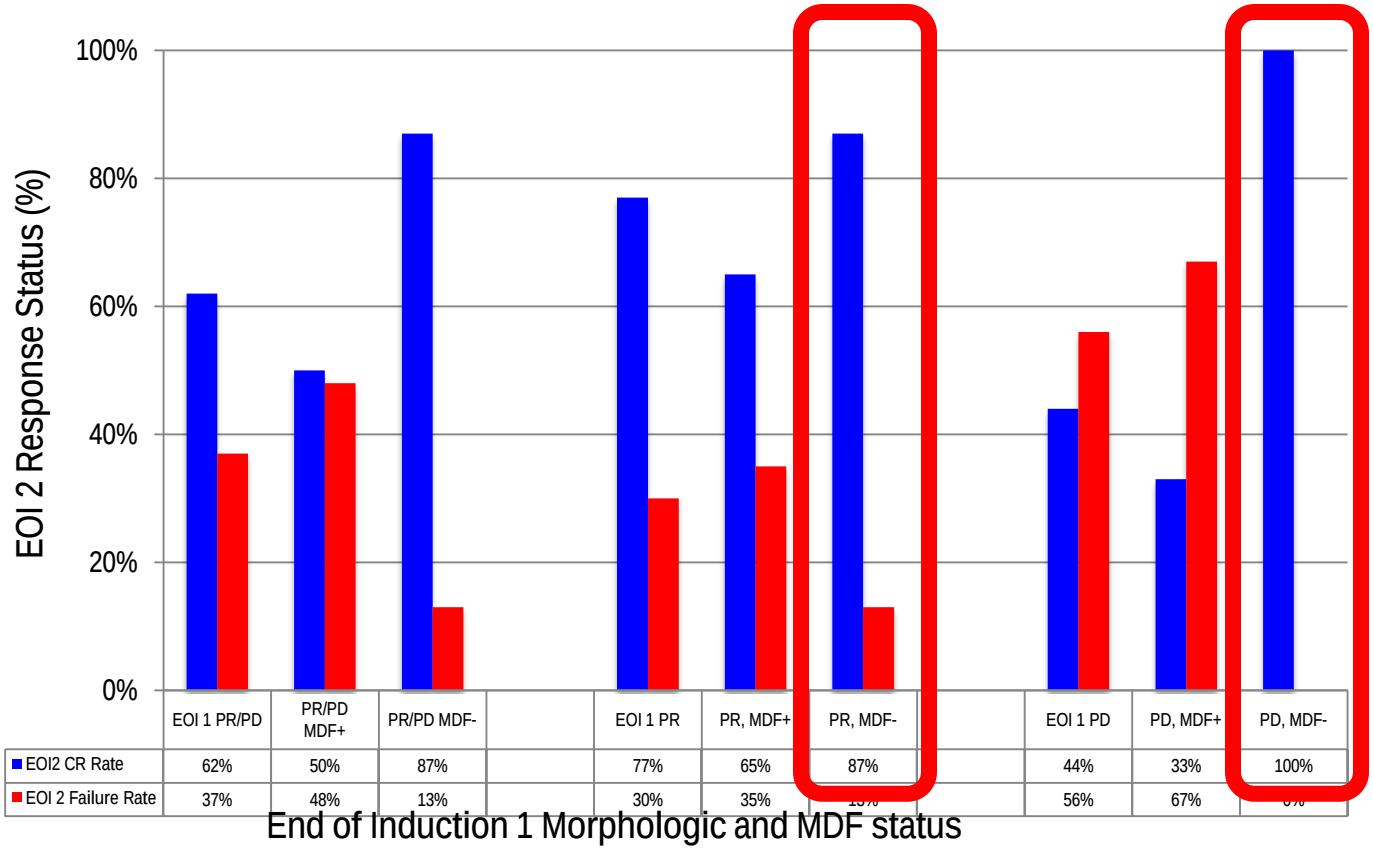
EOI-1 MDF Status Accurately Predicts EOI-2 morphologic CR status



	EOI 1 PR/PD	PR/PD MDF+	PR/PD MDF-		EOI 1 PR	PR, MDF+	PR, MDF-		EOI 1 PD	PD, MDF+	PD, MDF-
EOI2 CR Rate	62%	50%	87%		77%	65%	87%		44%	33%	100%
EOI 2 Failure Rate	37%	48%	13%		30%	35%	13%		56%	67%	0%

- 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.

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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

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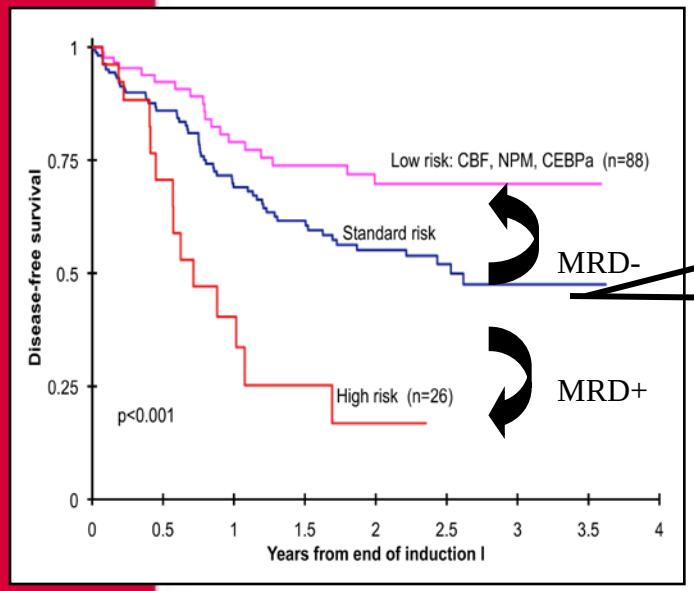
Two Tier Risk Class Using Cytogenetic/Molecular/MRD Results

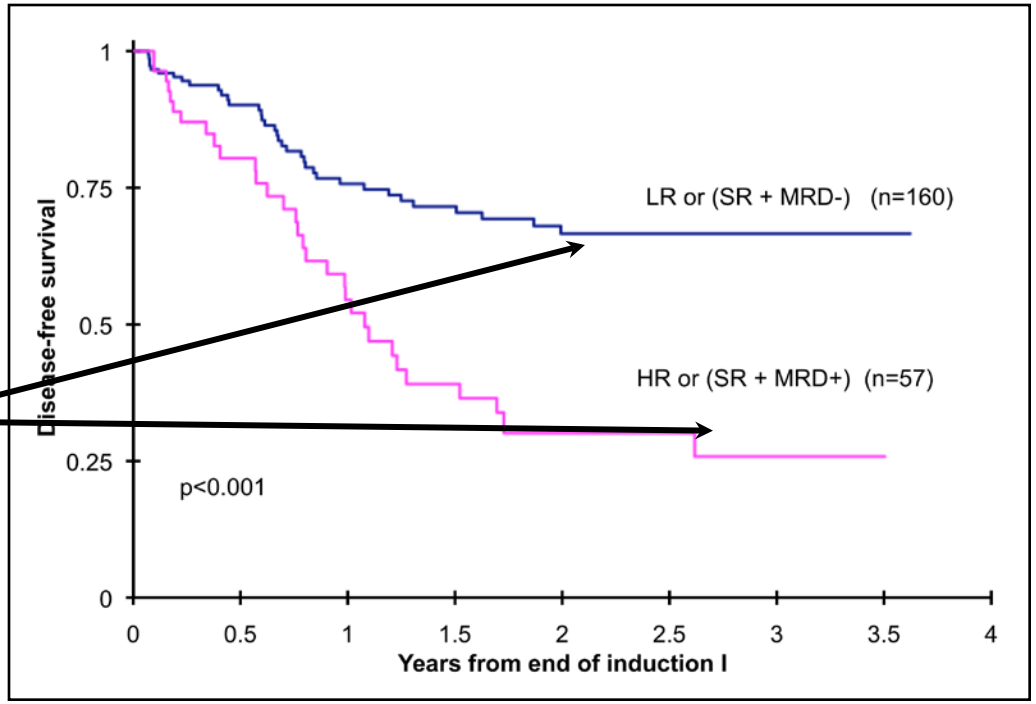
Low risk: CBF, CEBPA, NPM, MRD-neg Stnd Risk

High risk: cytogenetic HR, high AR FLT3/ITD, MRD-pos Stnd Risk



MRD-

MRD+



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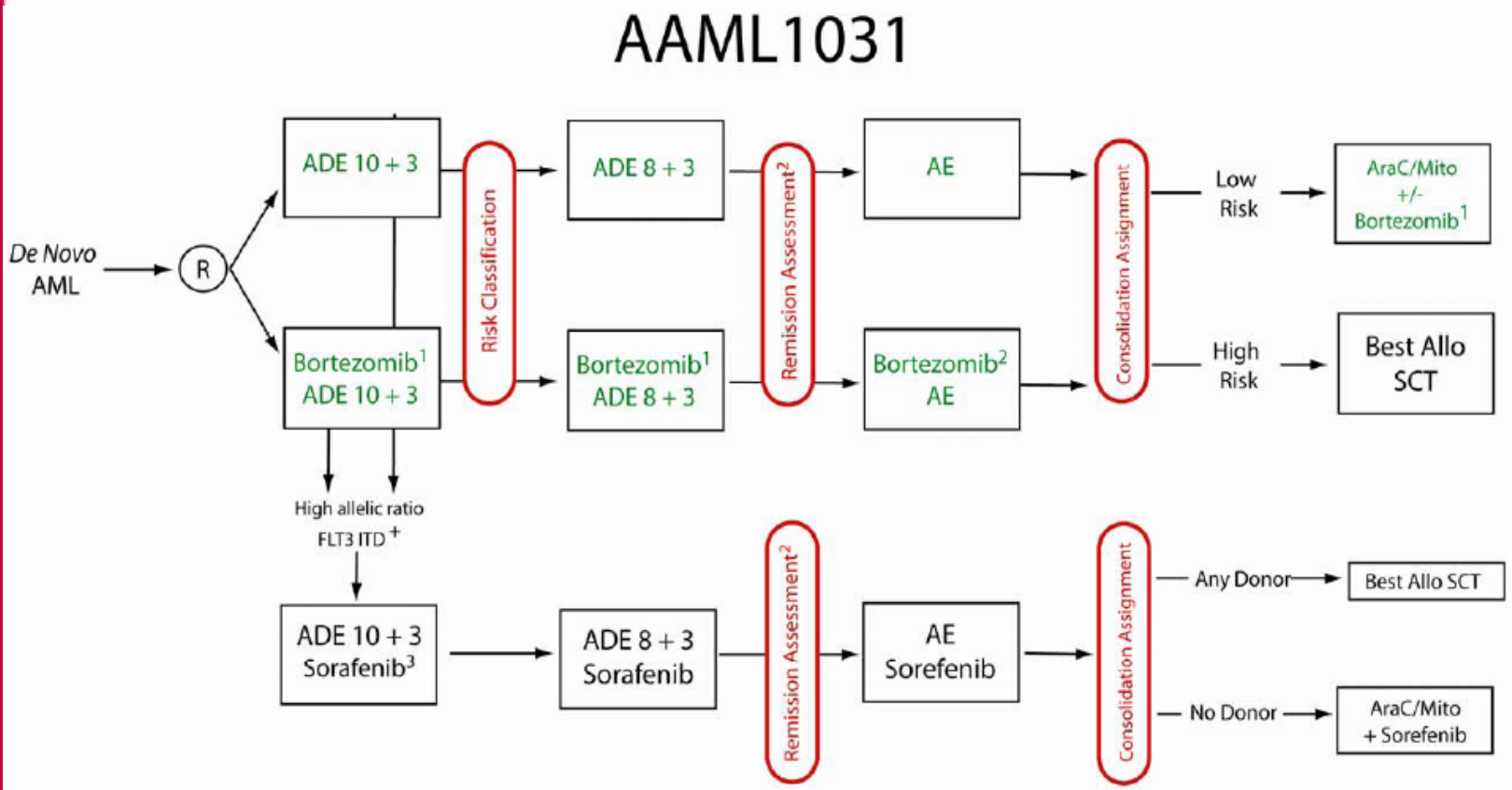
AAML1031 Phase 3 study design



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http://biqsfp.cancer.gov/

Discussion

Thank you

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