AML COMMITTEE

AML in Older Population

- Poor prognosis due to inherently worse disease (CG) and inability to tolerate intensive chemotherapy
- Hypomethylating agents (azacytidine, decitabine) have become the standard of care
- In randomized trials:
  - CR rates: 17-27%
  - Median OS: 7.7-10.4 months

Lots of room for improvement!

Kantarjian et al J Clin Oncol 2012; 30(21):2670-2677

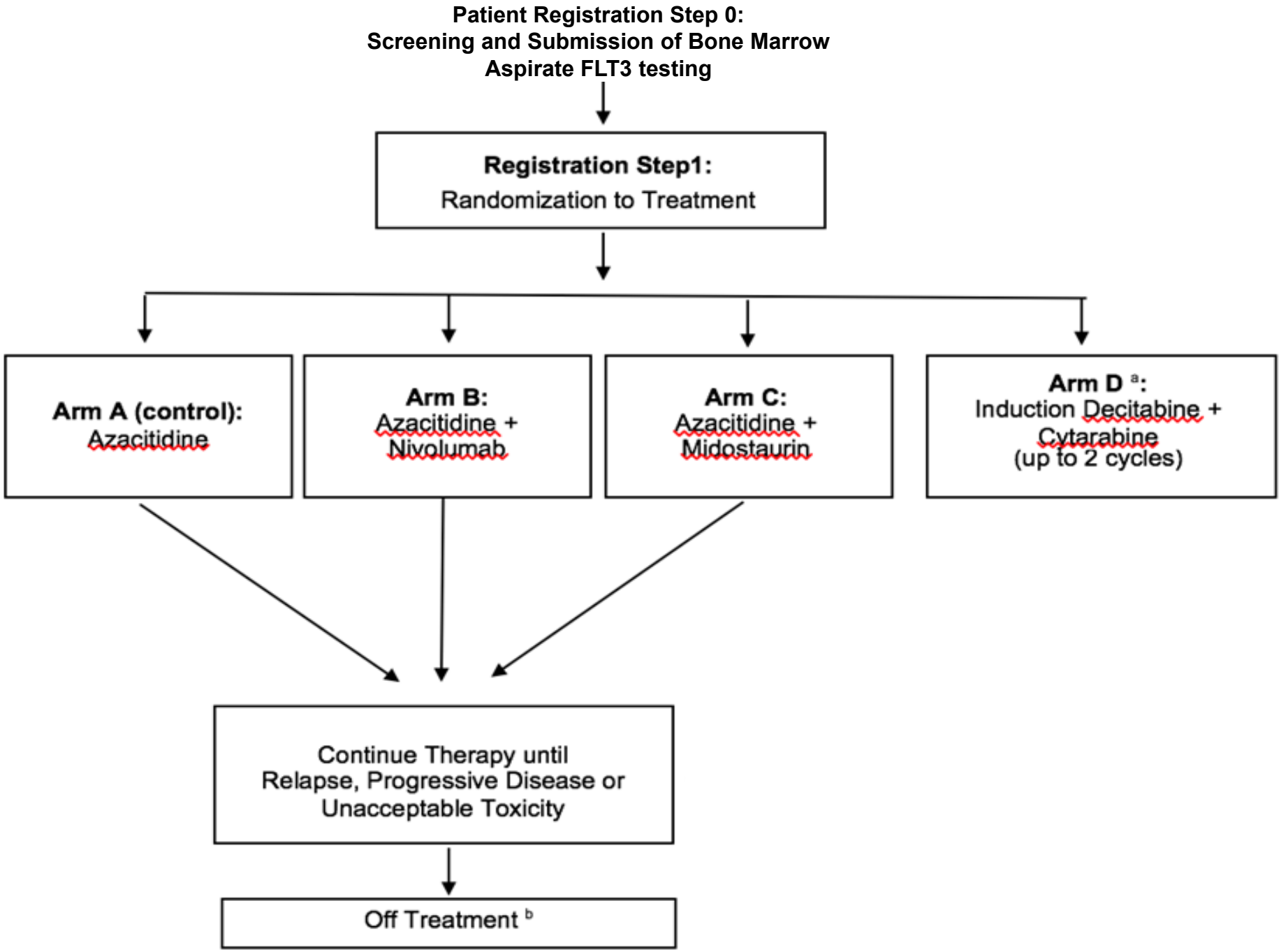
Dombret et al Blood 2015; 126(3):291-299

LEAP Trial

S1612, "A Randomized Phase II/III Trials of "Novel Therapeutic Regimens" versus Azacitidine in Newly Diagnosed Patients with Acute Myeloid Leukemia Age 60 or Older"

L. Michaelis and R. Walter
Statistician: M. Othus

Intergroup Trial and Canada


Patient Registration Step 0:
Screening and Submission of Bone Marrow
Aspirate FLT3 testing
Registration Step1:
Randomization to Treatment
Arm A (control):
Azacitidine
Arm B:
Azacitidine +
Nivolumab
Arm C:
Azacitidine +
Midostaurin
Arm D [a]:
Induction Decitabine +
Cytarabine
(up to 2 cycles)
Continue Therapy until
Relapse, Progressive Disease or
Unacceptable Toxicity
Off Treatment [b]

Objectives

Primary

Phase II:

To select, based on overall survival, any or all of the "Novel Therapeutic" regimens for further testing against azacitidine in patients age 60 and older with newly diagnosed acute myeloid leukemia

Phase III:

To compare overall survival of the "Novel Therapeutic" regimens selected in the Phase II portion of the trial to azacitidine in this patient population

Secondary

- **To estimate the frequency and severity of toxicities of the regimens in this patient population**
- **To estimate remissions rates, event-free survival, and relapse-free survival for these regimens in this patient population**
- **To investigate associations between cytogenetic abnormalities and outcomes for each of the regimens in this patient population**
- **To develop models to predict treatment-mortality in this patient population**

Eligibility

Inclusion Criteria:

- Age ≥60 years; newly diagnosed AML or high-risk MDS
- No prior therapy for AML (except hydrea). No prior demethylating agents.
- ECOG performance status 0-3
- Patients are eligible regardless of cardiac, kidney, and liver function abnormalities (drug-specific exclusions are possible)

Exclusion Criteria:

- Active infection, unless under treatment with antimicrobials and controlled/stable.
- Known active CNS disease
- Patients deemed, in the judgment of their treating physician, to be candidates for induction with intensive therapy

Statistics

- Stratification
  - Age and PS (age ≥70 and older AND PS 2-3 vs. age < 70 OR PS 0-1)
  - FLT3 (wild-type FLT3 versus mutated)
- Power
  - Based on French data – Med OS of AZA alone approximately 10.4 mo
  - Improvement defined as Med OS of 15.6 mo
- Phase II:
  - Up to 100/arm; HRs < 0.87 favoring the experimental arm →Phase III testing
- Phase III:
  - Up to 300/arm; HR of ≦ 0.67 will determine improvement over control

Statistics

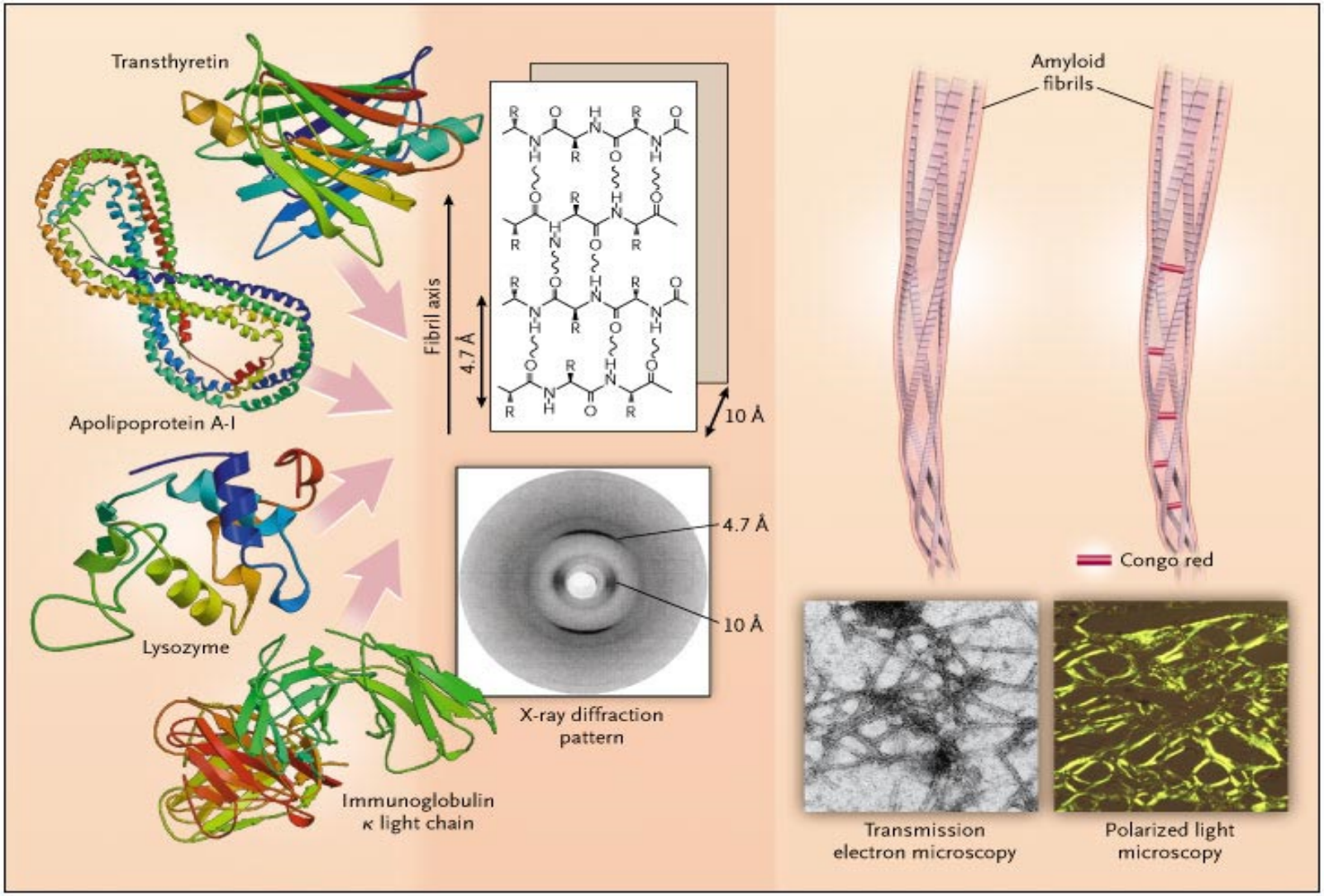
- Time to accrual
  - Phase II: ~1 year
  - Phase III: 3 years
- Estimate of accrual rate: 38pts/month
- No competing cooperative groups studies
- QOL companion study
- Collecting biological samples for future correlative studies
- All data housed in SWOG operations but academic credit shared

Operationalizing

- Charter being written with input from Cooperative Group Leukemia Committee chairs, operations and biostatistics from each group, CTEP, NCI, IDB, and FDA
- Smaller working group will establish clear authorship expectations and deal with the protocol for integrating new arms into the trial: cassettes

MYELOMA COMMITTEE

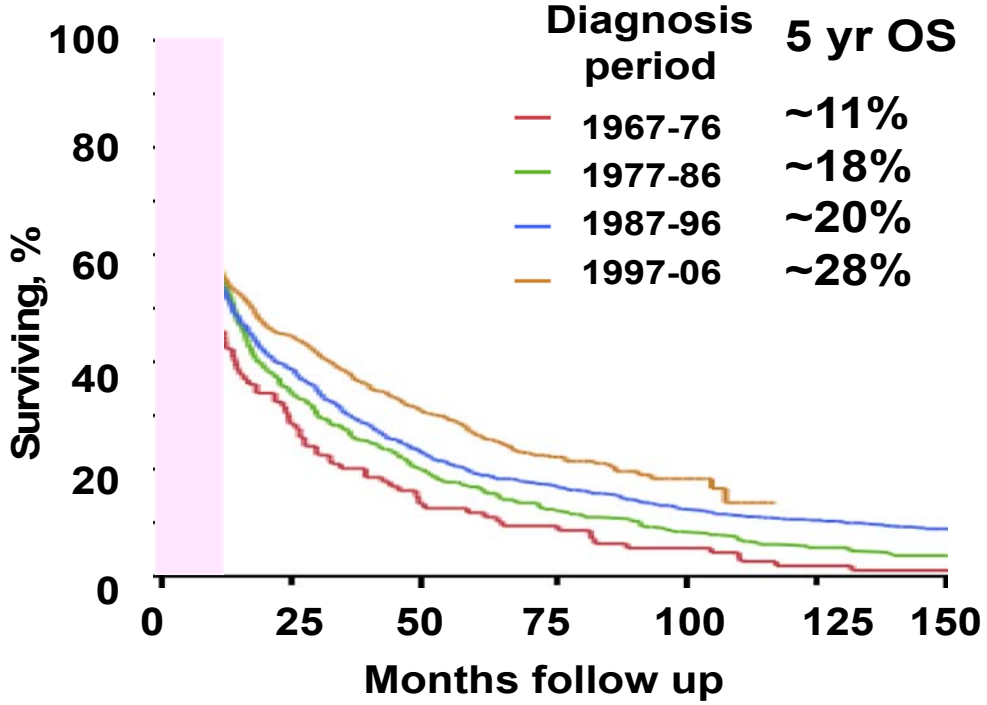
Amyloidosis is a protein misfolding disease



>28 different proteins can form fibrillar deposits

Merlini & Bellotti N Engl J Med 2003;349:583-96

Amyloidosis Mortality Remains High



5-year OS improved, but 6-12 month mortality unchanged

Kumar et al, Mayo Clinic Proc, 2011 86(1):12-8.

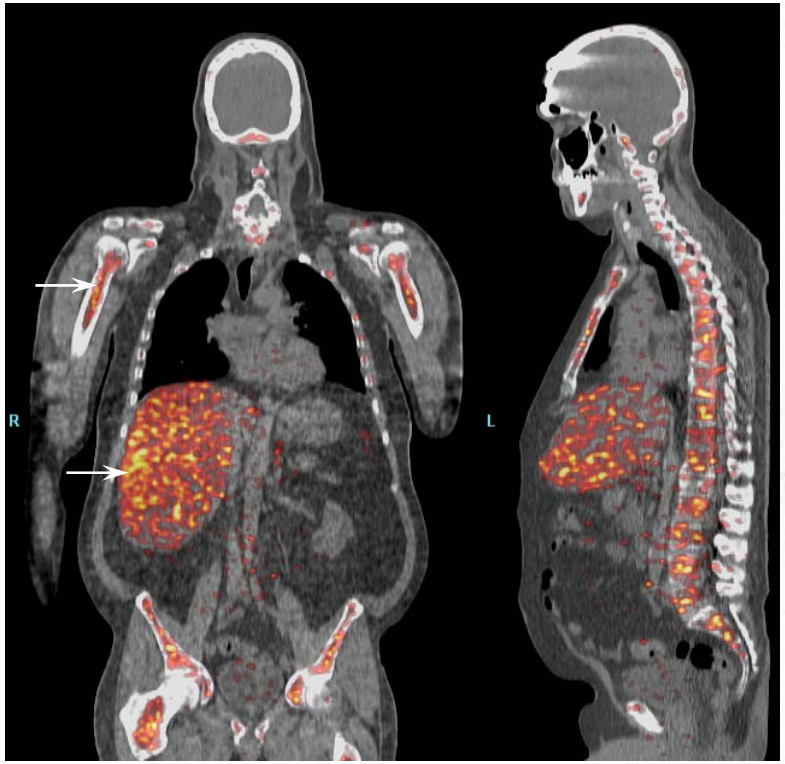
Background

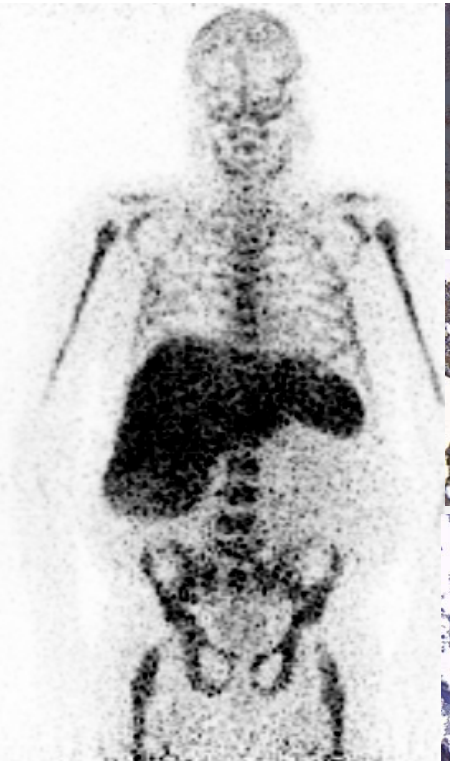
- Utilizing amyloid-specific mAb to promote amyloid resolution is a novel approach to reverse organ damage/improve organ function.
- Phase 1a/b study performed at Columbia University, NY was funded by the FDA (R01 FD005110-01) and the GMP-grade amyloid-reactive chimeric 11-1F4 mAb was produced by the NCI's Biological Resource Branch (NExT grant)
- Presentation of Phase 1a data at ASH 2015 raised considerable interest and voiced NCI support for a multi-center Phase II trial with the idea of producing more 11-1F4 mAb by the Biological Resource Branch, Developmental Therapeutics Program, DCTD, NCI

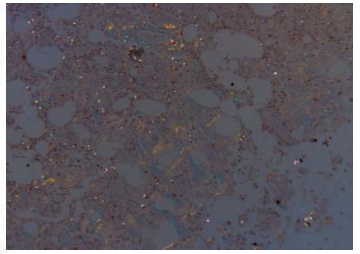
Specificity of Antibody Binding

Co-localization of ^{124}I-m11-1F4 with Hepatosplenic and Bone AL Amyloid

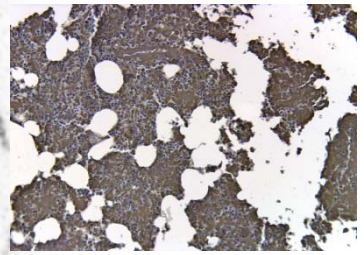
AL11 λ



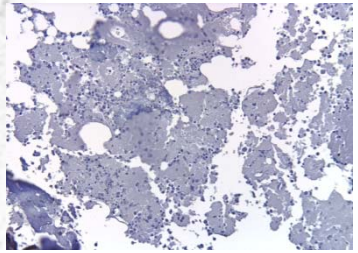




CR



m11-1F4



m11-1F4
+ peptide

coronal sagittal MIP biopsy IHC

Wall, JS et al. Blood. 2010 Sep 30;116(13):2241-4.

Results – Phase I

- 21 patients accrued and were evaluable for toxicity
- 18 patients evaluable for response (N=1 had no measurable disease, N=2 did not complete treatment)
- 12 of 18 patients (67%) showed organ response
- **Phase 1a: 63% of patients (5 of 8) with measurable disease burden demonstrated organ response**
  - ❖ 2 renal, 2 cardiac and 1 GI
- **Phase 1b: 70% of patients (7 of 10) with measurable disease burden showed organ response**
  - ❖3 patients with cardiac response
  - ❖4 patients with renal response
  - ❖1 patient with GI response
  - ❖1 patient with soft tissue response with improvement of arthritis °3 → °1

SWOG Phase 2 Trial in Amyloidosis

A Phase II, Non Randomized Study of 11-1F4 mAb Chimeric Monoclonal Ab added to standard treatment in Untreated Subjects with Light Chain (AL) Amyloidosis

- **PI: Suzanne Lentzsch, MD, PhD**
- **SWOG LOI approved**

Objectives

Primary study objective:

- To determine the efficacy and safety of 11-1F4 mAb in untreated patients with AL amyloidosis who have measurable organ involvement

Sample size:

- 60 enrolled to achieve 55 eligible (treated with 11-1F4 mAb)

Funding:

- NCI approved a NExT grant application to leverage NCI resources for this study.
- Ongoing conversations with Fortress to manufacture 11-1F4 antibody for the phase 2 trial and further commercialization

LYMPHOMA COMMITTEE: FOLLICULAR TRIAL

Background

- Outcome of patients with follicular lymphoma can be highly variable
  - Median survival 18 years[1]
- Investigating novel therapies in the patients with the worst outcomes holds the most promise for further improving FL outcomes
- High-risk FL has an inferior survival (Median of 5 yrs)
  - Patients not achieving a CR to initial chemoimmunotherapy[2]
  - Patients relapsing within 2 yrs of chemoimmunotherapy[3]

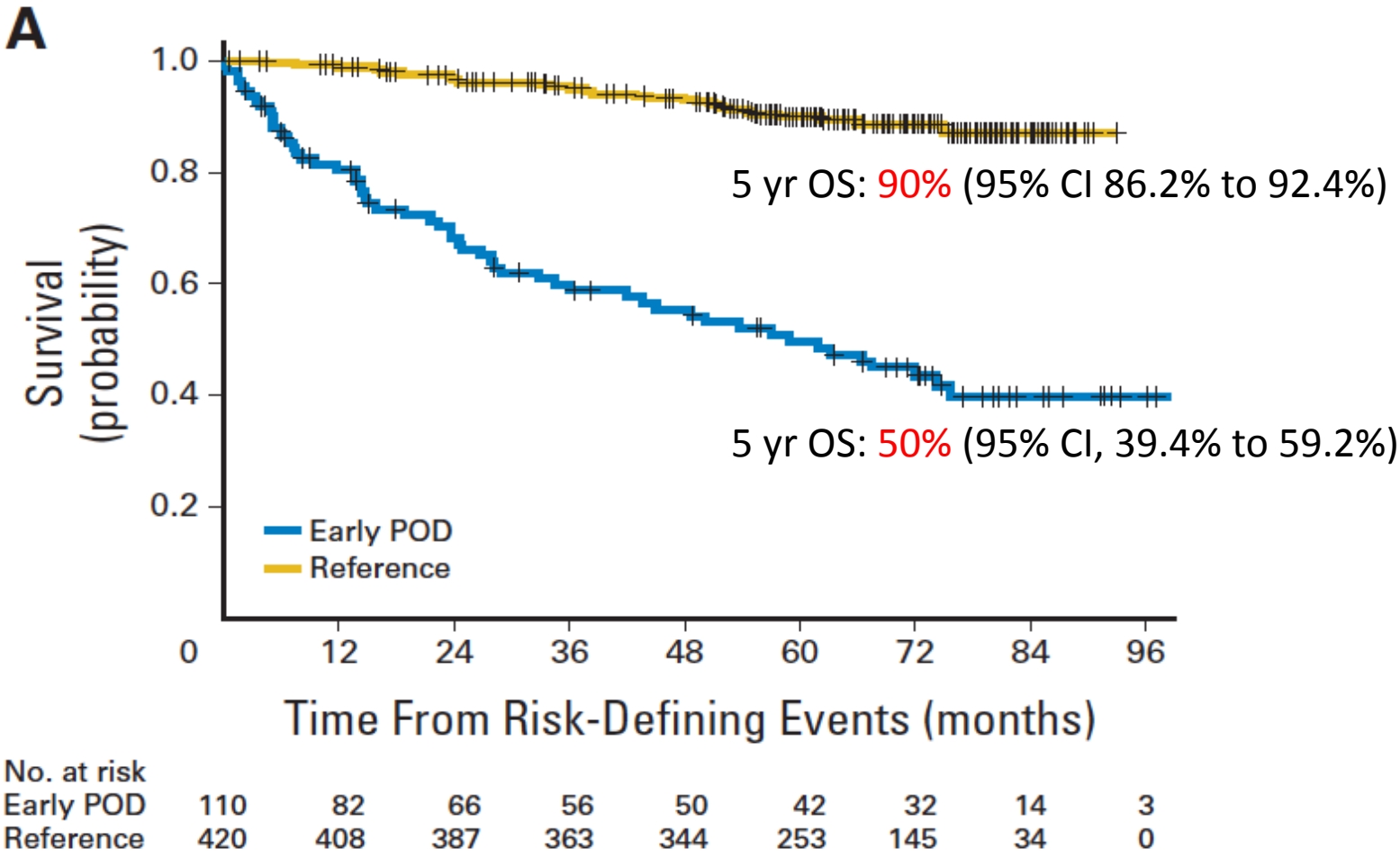
[1]Tan et al Blood 2013

[2]Trotman et al Lancet Haem 2014

[3]Casulo et al. J Clin Oncol 2015

Survival after RCHOP: Early (<2 yrs) Worse than Late Progression.

National LymphoCare Study



Casulo et al. J Clin Oncol 2015

Background II

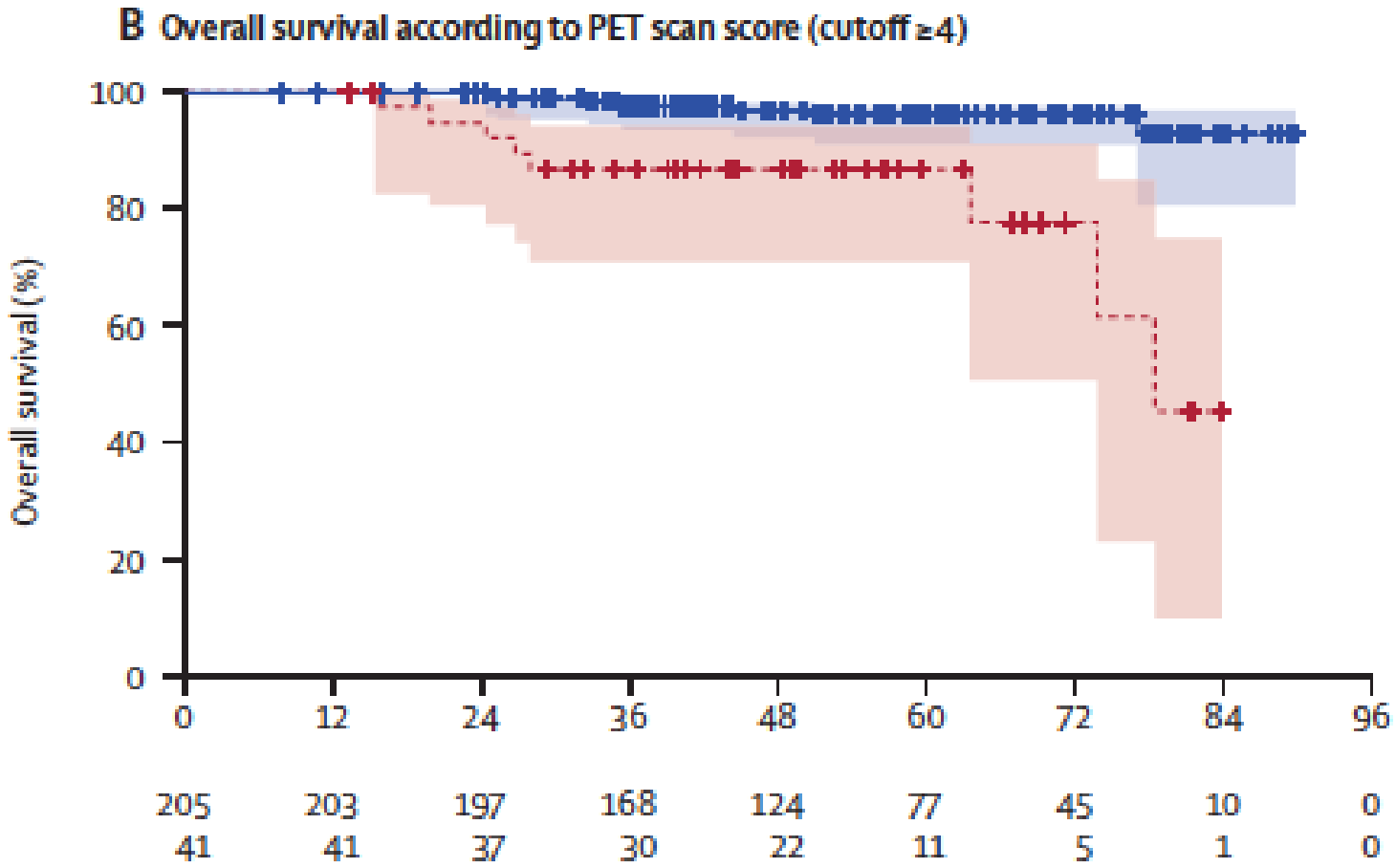
Therapy for follicular lymphoma is currently not tailored to the underlying disease biology

1. **There is a need for better predictive biomarkers**
   - **Response by PET/CT following therapy is the most accurate predictor of outcomes[1]**
2. **Need to identify patients at diagnosis likely to respond poorly to chemotherapy**
   - **Future studies can investigate novel regimens before these patients receive initial chemoimmunotherapy**
   - **The m7-FLIPI at diagnosis more accurately stratifies patients in risk categories compared to other prognostic systems**
     - **Combines FLIPI, ECOG PS, mutations status of 7 genes[2]**

[1]Trotman et al Lancet Haem 2014

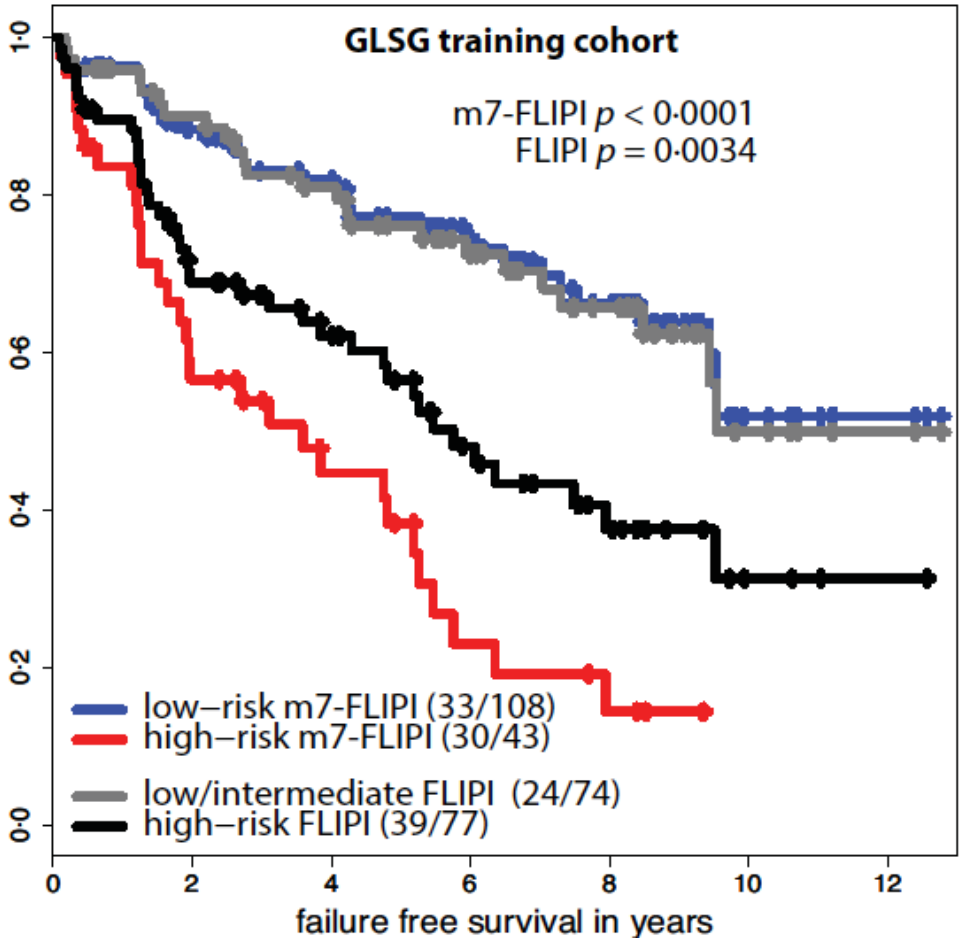
[2]Pastore et al. Lancet Oncology 2015

Positive PET after chemoimmunotherapy induction is associated with inferior OS



Trotman et al Lancet Haem 2014

m7-FLIPI improves prognostication of FL patients receiving chemoimmunotherapy

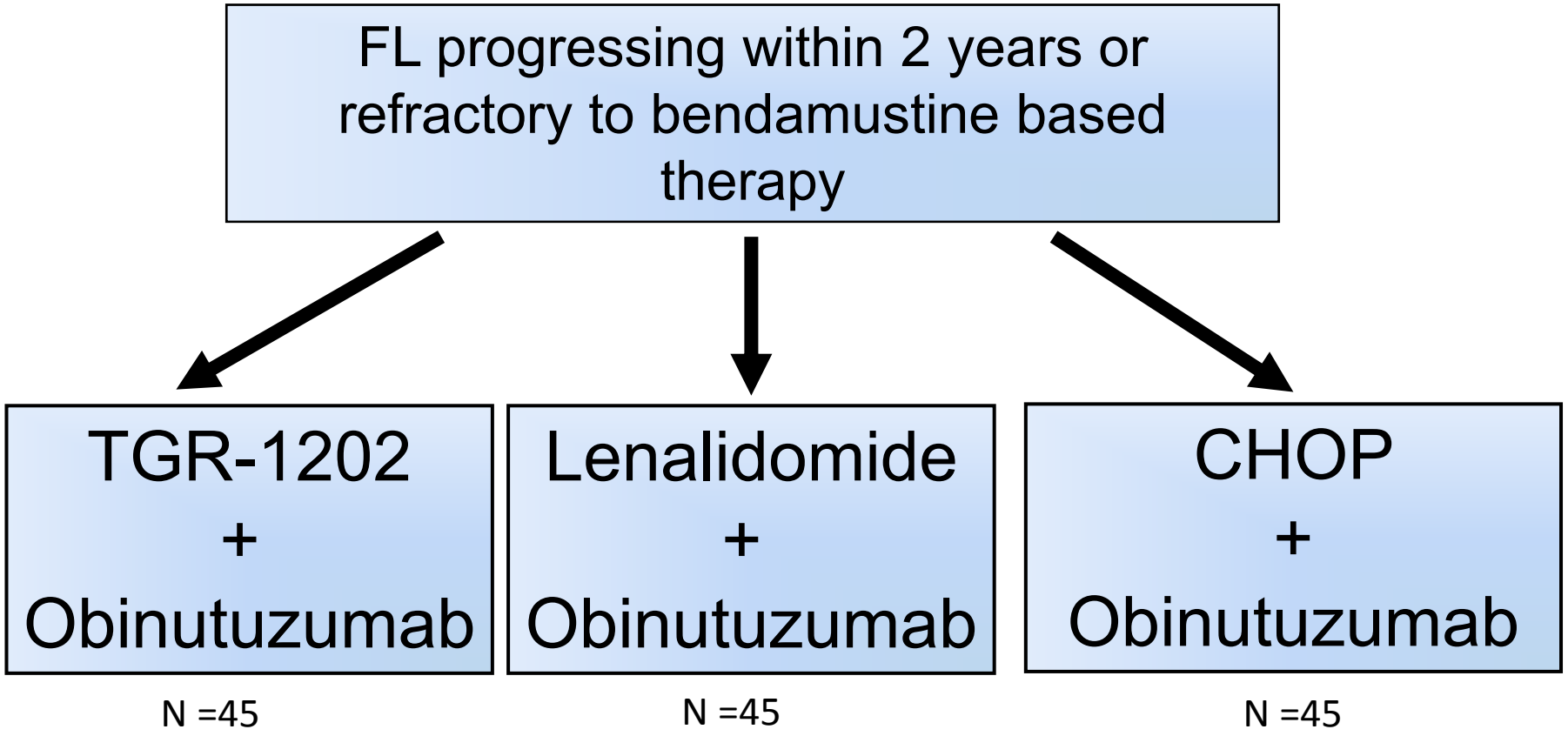


- FLIPI
- ECOG PS
- *EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11*

	5 year FFS (%)	5 year OS (%)
FLIPI low/interm ed	76	91
FLIPI high	57	75
M7-FLIPI low	77	90
M7-FLIPI high	38	65

Pastore et al. Lancet Oncology 2015

S1608: Randomized phase II trial in early progressing or refractory FL



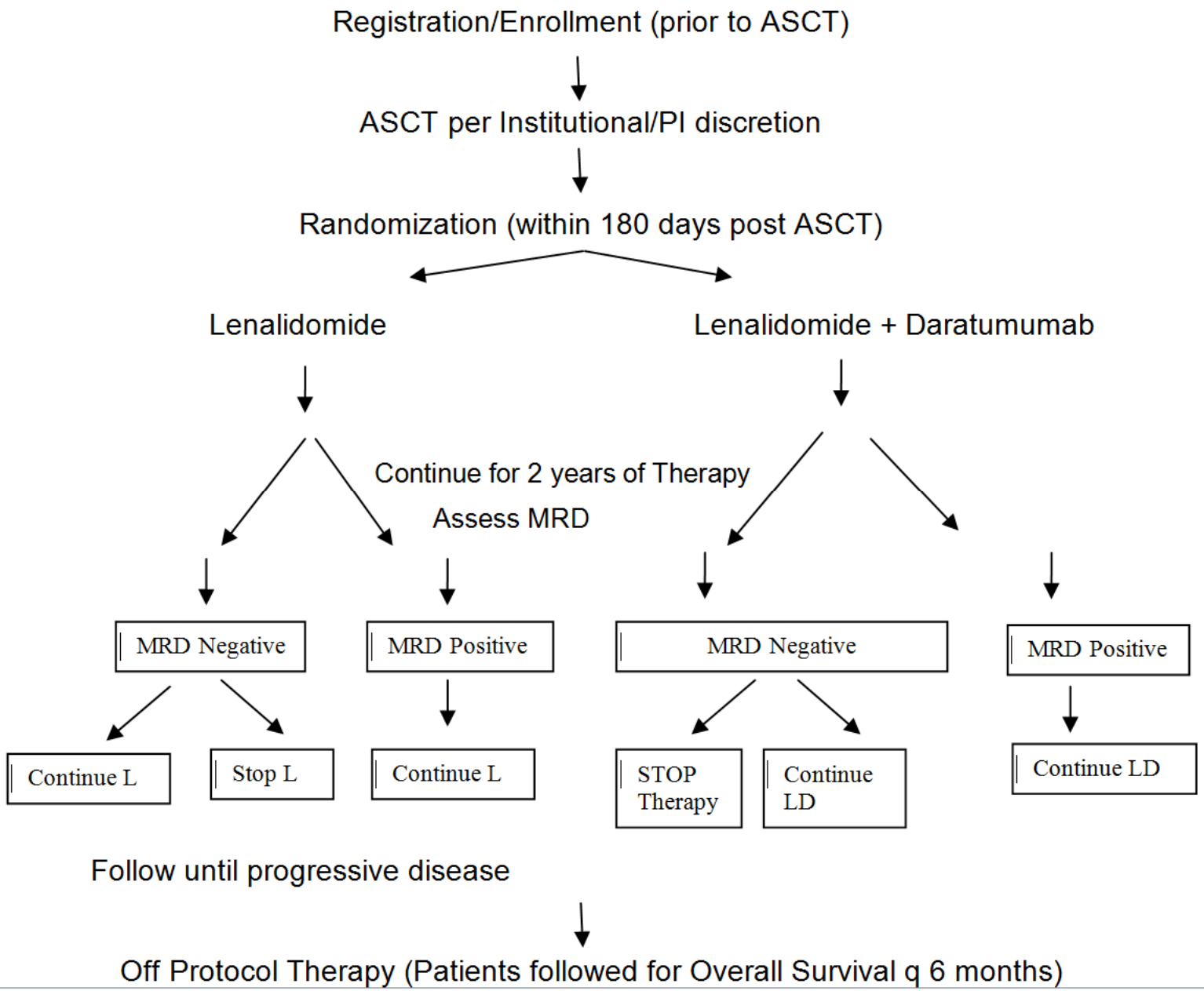
Primary clinical objective: CR by PET/CT

Primary translational objective: Validation of m7-FLIPI in this high-risk population

Statistics and Support

- Primary endpoint is to compare CR rates of 2 experimental regimens to RCHOP
- Randomized phase 2 design
  - Comparing each experimental regimen to O-CHOP (assumed complete response rate of 20%)
  - Interest if CR rate is >45%
- 150 patients (45 in each arm)
  - Estimated 10% ineligibility
- Funding
  - BIQSFP application to support central review of PET/CT
  - Full support from 3 pharmaceutical companies and 3 cooperative groups

BMT/MM Committee Trial Maintenance Post Autologous SCT in Multiple Myeloma


Registration/Enrollment (prior to ASCT)
ASCT per Institutional/PI discretion
Randomization (within 180 days post ASCT)
Lenalidomide
Lenalidomide + Daratumumab
Continue for 2 years of Therapy
Assess MRD
MRD Negative
MRD Positive
MRD Negative
MRD Positive
Continue L
Stop L
Continue L
STOP Therapy
Continue LD
Continue LD
Follow until progressive disease
Off Protocol Therapy (Patients followed for Overall Survival q 6 months)

Maintenance Post Autologus SCT

- N = 950, accrual in 6 years
- 6 yrs of accrual + 4 years of f/u results in a study with 86% power to detect a hazard ratio of 0.6 or an increase in survival from 10 to 16.7 years
- To be submitted back to CTEP for approval
- Working group including BMT-CTN, NCTN and CTEP had input into this trial design
- This will be the only myeloma autologous SCT trial in the US