MSKCC: Risk-Adapted Sequential Therapy: Biopsy confirmation of an abnormal interim FDG-PET

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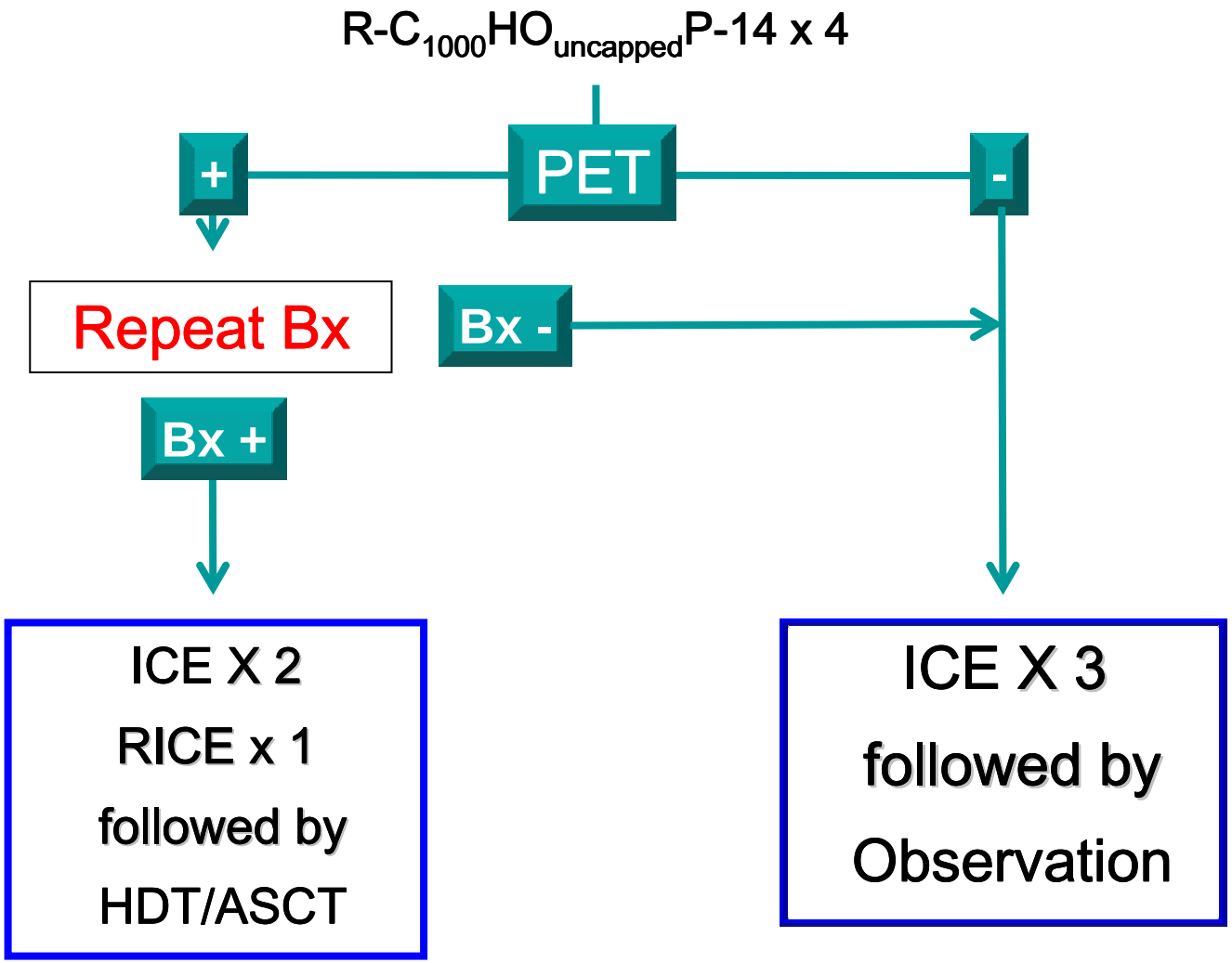
MSKCC 01-142: DLBCL: Risk Adapted for Therapy

CS IIX, III or IV disease, age-adjusted IPI 1, 2, or 3 Risk Factors, Transplant Eligible

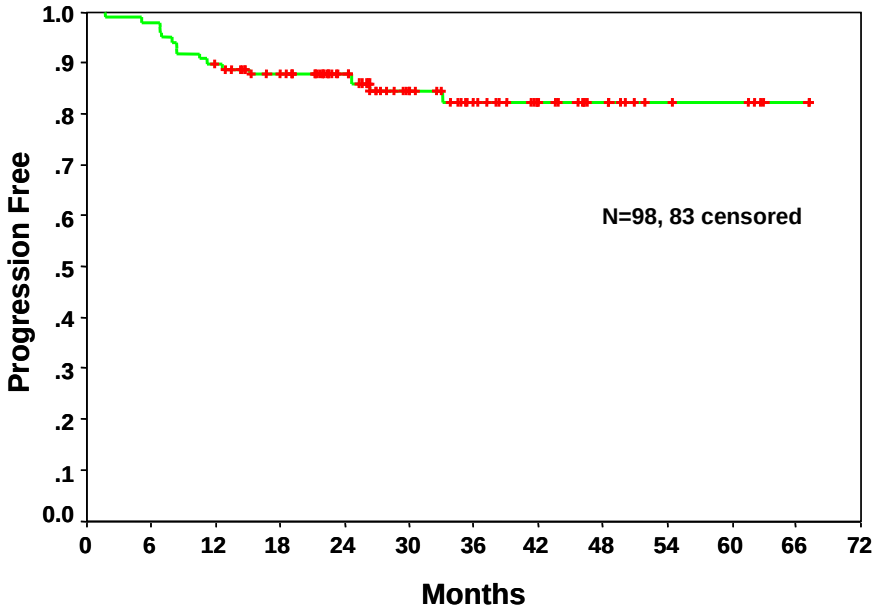


- Prospective, biopsy controlled determination of "positive PET"
- Therapy interval 2 weeks
- PET 10-14 days post cycle 4
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM

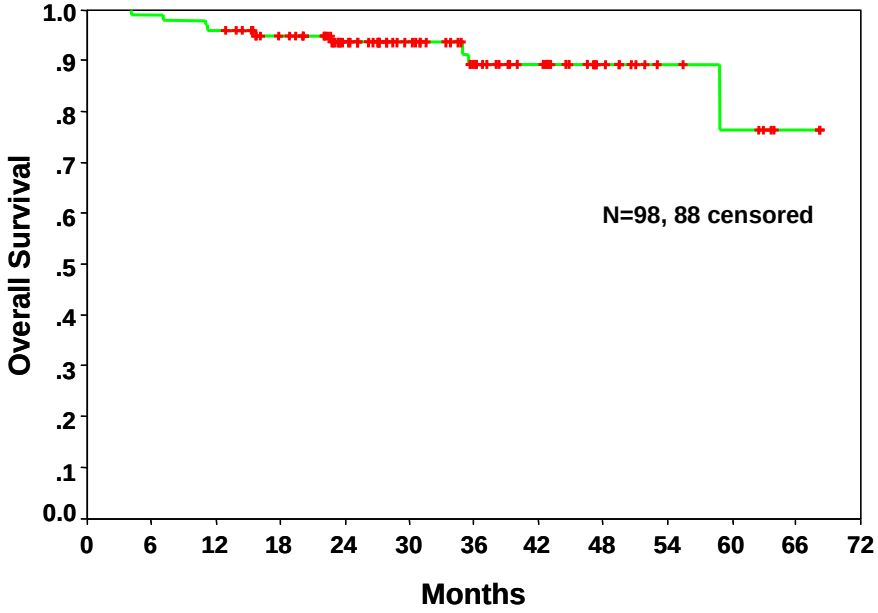
Moskowitz, C. H. et al. J Clin Oncol; 28:1896-1903 2010

MSKCC 01-142: Outcomes

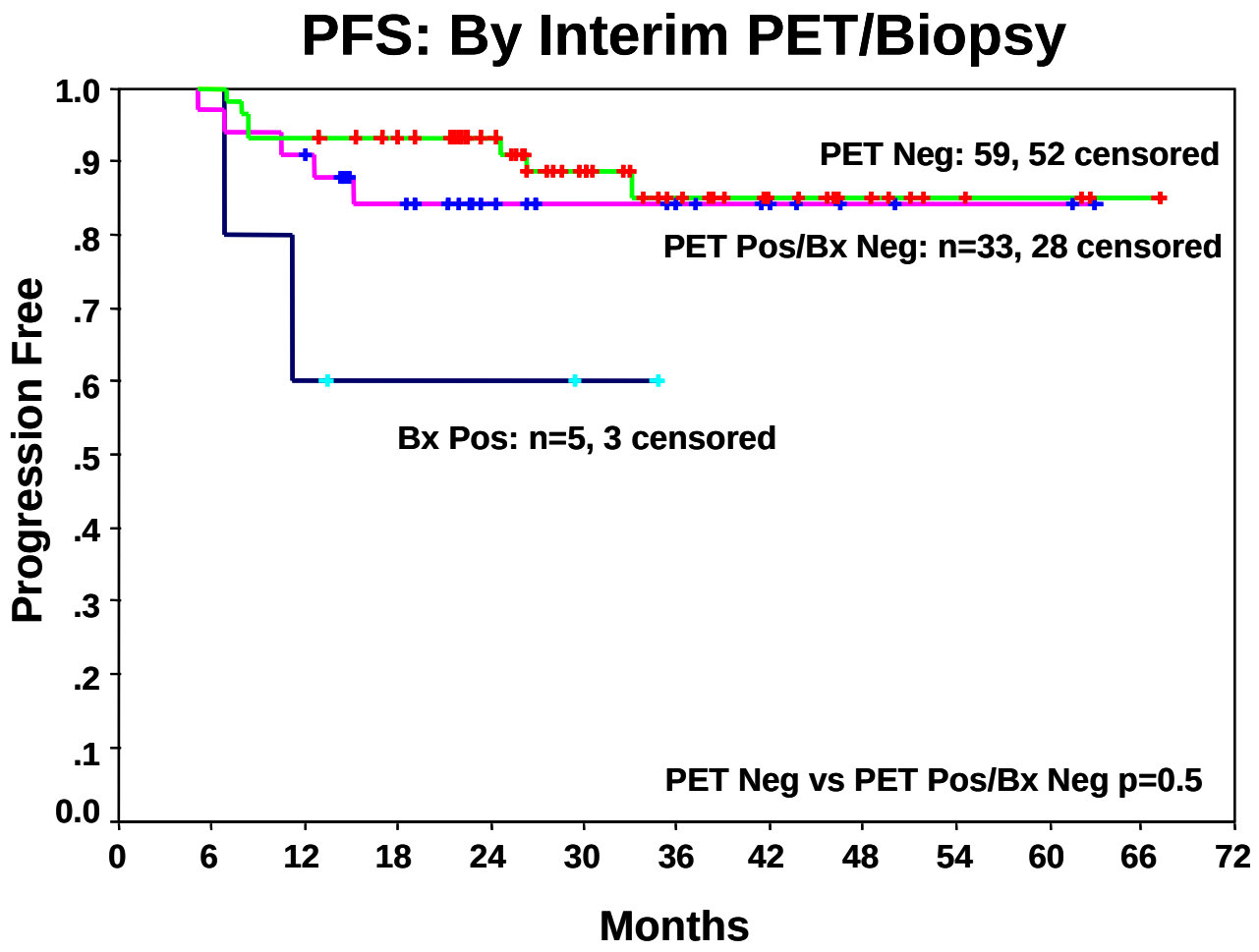
Progression Free Survival



Overall Survival

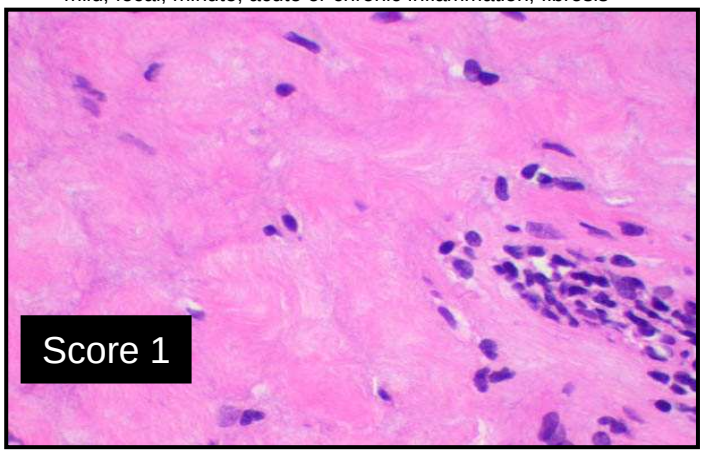


MSKCC 01-142: Outcome By Previously Identified Prognostic Factors

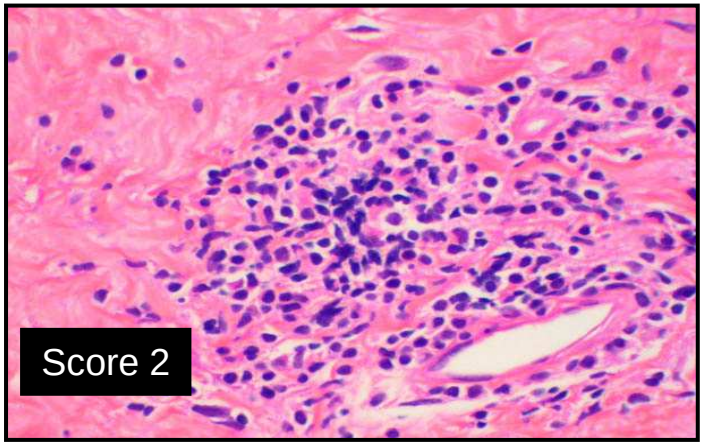


Inflammation Score for Interim Biopsies

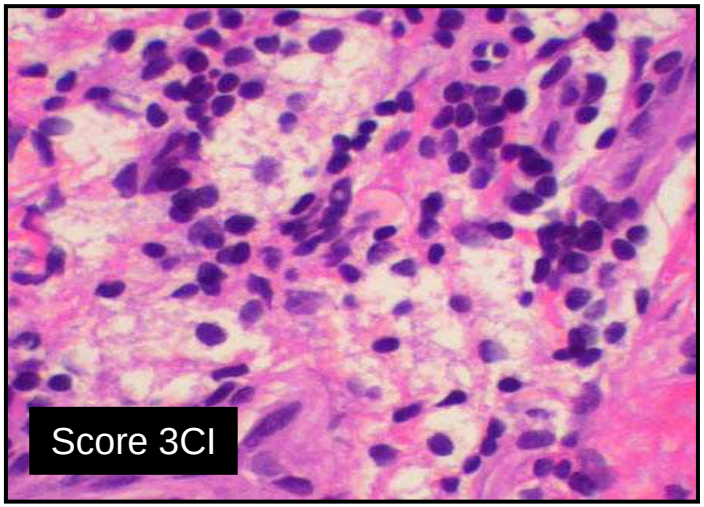
mild, focal, minute, acute or chronic inflammation, fibrosis



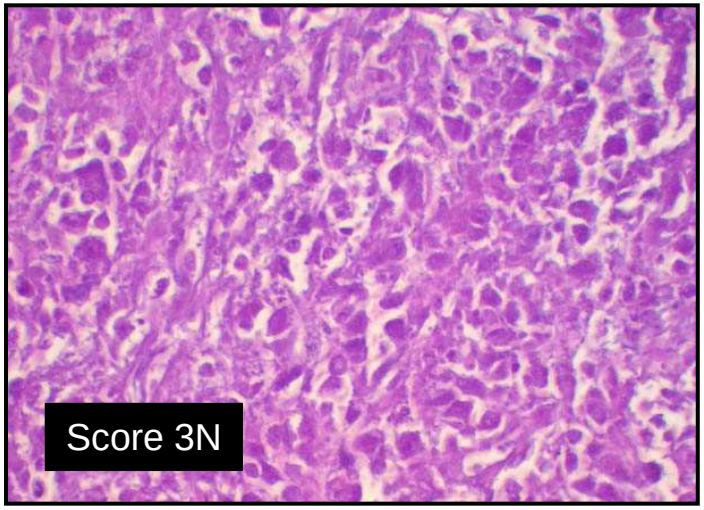
moderate inflammation with macrophages



marked inflammation



marked necrosis



FDG-PET Adapted therapy in DLBCL

What have we learned?

- **Interim FDG-PET is effected by treatment strategy**
  - **Treatment interval**
  - **Degree of inflammation induced by therapy**
  - **Timing of scan relative to therapy**
  - **Efficacy of therapy**

- **Several studies demonstrate high incidence of false positives:**
  - **Rituximab may contribute (speculative)**
  - **Dose density likely is a factor**
  - **In the MSKCC data, a high false positive rate was documented by biopsy**

- **Understanding the source of false positives has a critical role in clinical trial design**

More lessons learned

- **Therapy should only be changed if there is histologic confirmation of active disease**
  - **Giving less doxorubicin and transplanting more patients is not a good goal!**
- **If this was not true then patients with interim PET+ biopsy negative patients would have a worse prognosis then patients with interim PET negative disease**
- **Our treatment is clearly more aggressive than R-CHOP, it is dose-dense induction/consolidation and the primary endpoint of studies are to improve PFS, imaging endpoints are secondary**

Interim PET assumptions

- **Is there a “consolidated” literature evidence on its prognostic role in DLBCL?**
  - **PPV is poor, it needs to be in the HL range**
- **Is qualitative or semiquantitative assessment the preferred interpretation**
  - **I suspect most of the lymphoma docs are hoping for a delta SUV win**
- **Is the histological confirmation the “gold standard” reference for interim-PET?**
  - **Absolutely**
- **Is it feasible in multicenter Clinical trial settings ?**
  - **Yes when we get a winner for interim reporting**

Changes made for new study

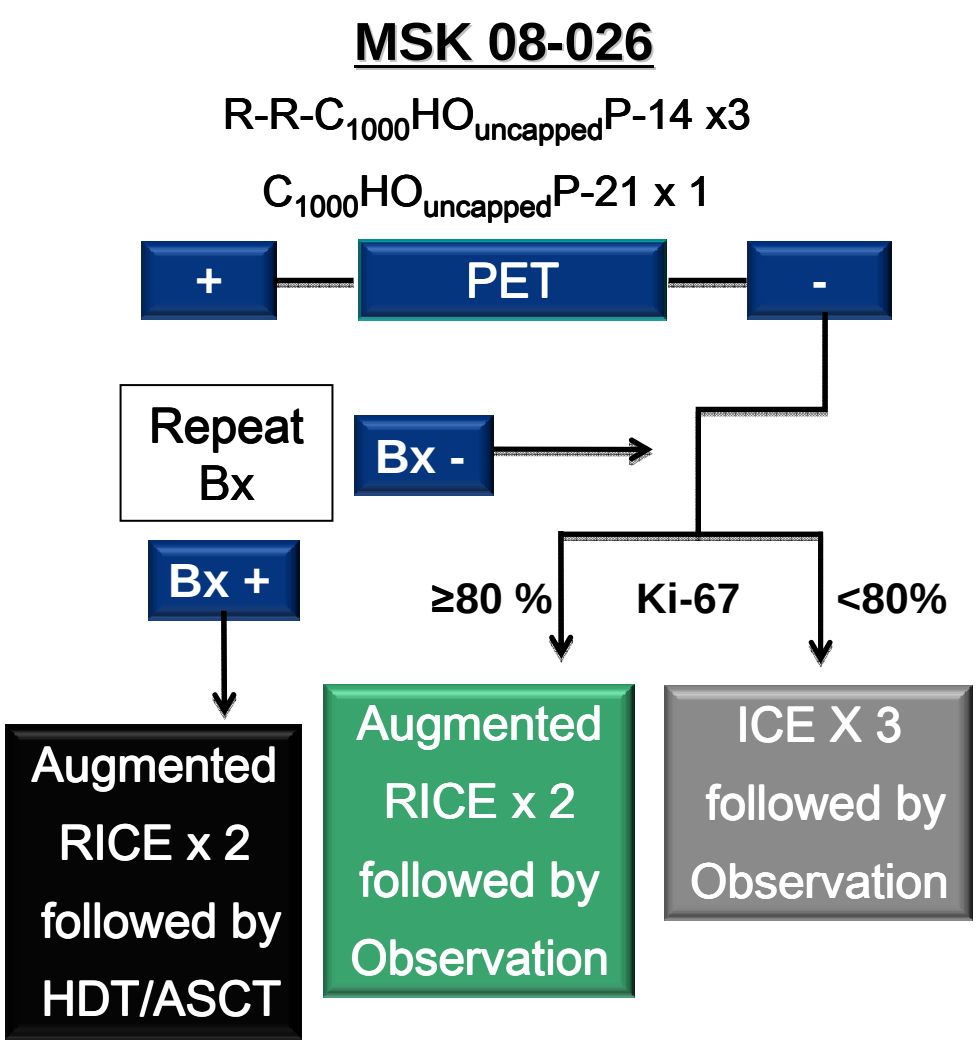
In the hope to decrease false positive interim FDG-PET scans

- **First 3 cycles is R-R-CHOP-14**
  - **uncapped vincristine, and the dose of cyclophosphamide is 1000 mg/m2**
- **Cycle 4 is CHOP-21**
  - **Same doses and above**
- **Interim FDG-PET: 17-20 days post cycle 4**
  - **One week later than previous study**
  - **Uptake >liver is positive scan**
- **Pts who are FDG-PET+/biopsy negative with ki-67 expression ≥ 80, consolidation is with 2 cycles of augmented RICE**

MSKCC 08-026: DLBCL: Risk Adapted for Therapy
CS IIX, III or IV disease, age-adjusted IPI 1, 2, or 3 Risk Factors, Transplant Eligible

Subject Inclusion Criteria:
- ages 18-70
- Advanced DLBCL or PMBL stage II with tumor bulk (>10cm)

Pre-treatment Evaluation
- FDG-PET avid (min SUV 2.5) measurable disease
- Normal cardiac function
- FLT-PET scan
- Ki-67 evaluation of tumor tissue
- Hepatitis B , C and HIV neg
- No history of prior malignancy



- Prospective, biopsy controlled determination of "positive PET"
- PET 17-20 days post cycle 4
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM

3 cohorts

- Cohort 1:
  - Pretreatment: CT/FDG-PET and FLT
  - Post cycle 1: FLT, post cycle 4:CT/FDG-PET
  - One month post ICE: CT/FDG-PET
- Cohort 2:
  - Pretreatment: CT/FDG-PET and FLT
  - Post cycle 2: FLT, post cycle 4: CT/FDG-PET
  - One month post ICE: CT/FDG-PET
- Cohort 3
  - Pretreatment: CT/FDG-PET
  - Post cycle 2: CT/FDG-PET, post cycle 4: CT/FDG-PET
  - One month post ICE: CT/FDG-PET

Nuclear Medicine Definitions

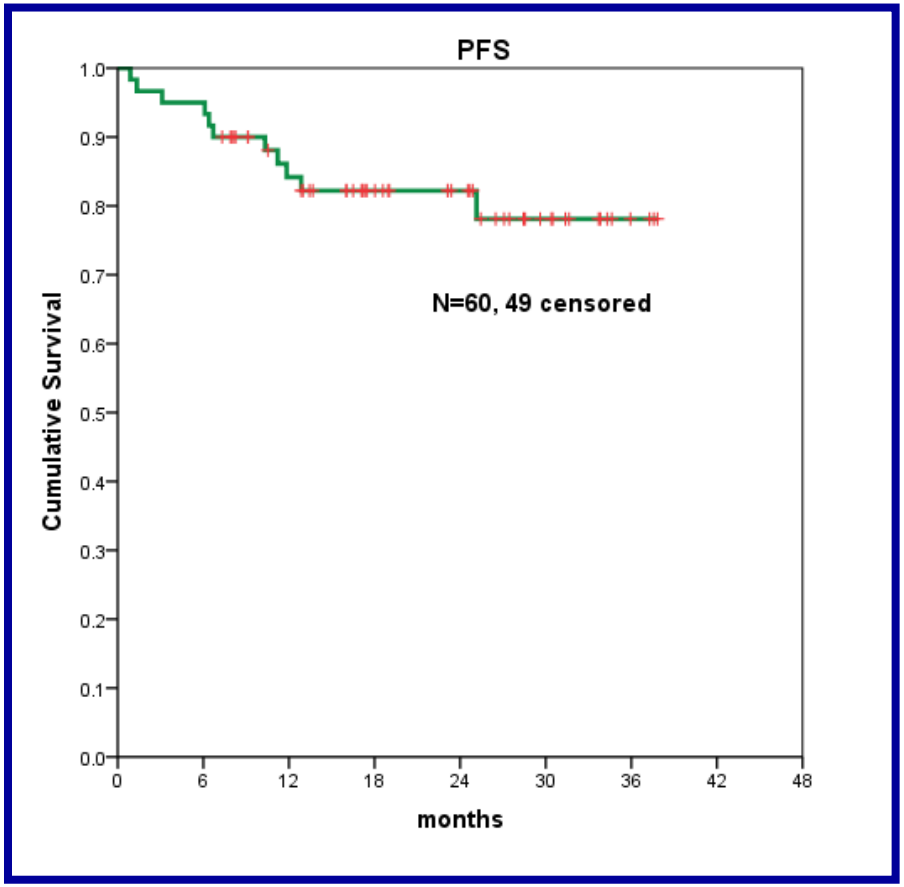
- **Positive FDG-PET: > than liver uptake**
- **FLT**
  - **Complete metabolic response (CMR)**
  - **Partial metabolic response (PMR): at least a 33% improvement in the area of highest pre-treatment uptake (delta SUV)**
  - **Minimal Residual Uptake (MRU): > 66% improvement in delta SUV:**

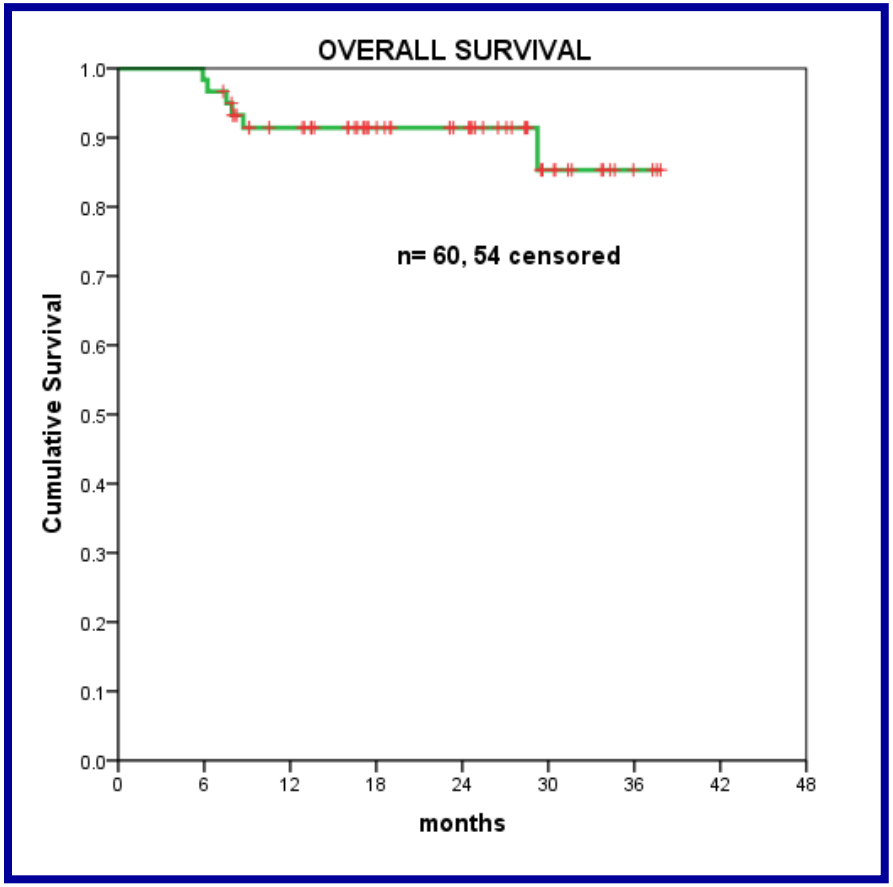
Objectives and Pre-treatment Characteristics (N=60)

- Determine 2-year PFS and OS for patients with advanced stage DLBCL based upon interim evaluation with FDG-PET or biopsy
- Determine 2-year PFS and OS based upon risk-stratified consolidation therapy
- Determine if 2-year PFS and OS can be improved for patients with Ki-67 expression ≥80% by augmenting consolidation
- Obtain preliminary data on biodistribution, dosimetry, and potential clinical usefulness of the proliferation marker FLT (^{18}F-fluorothymidine) in patients with DLBCL, using combined PET/CT.

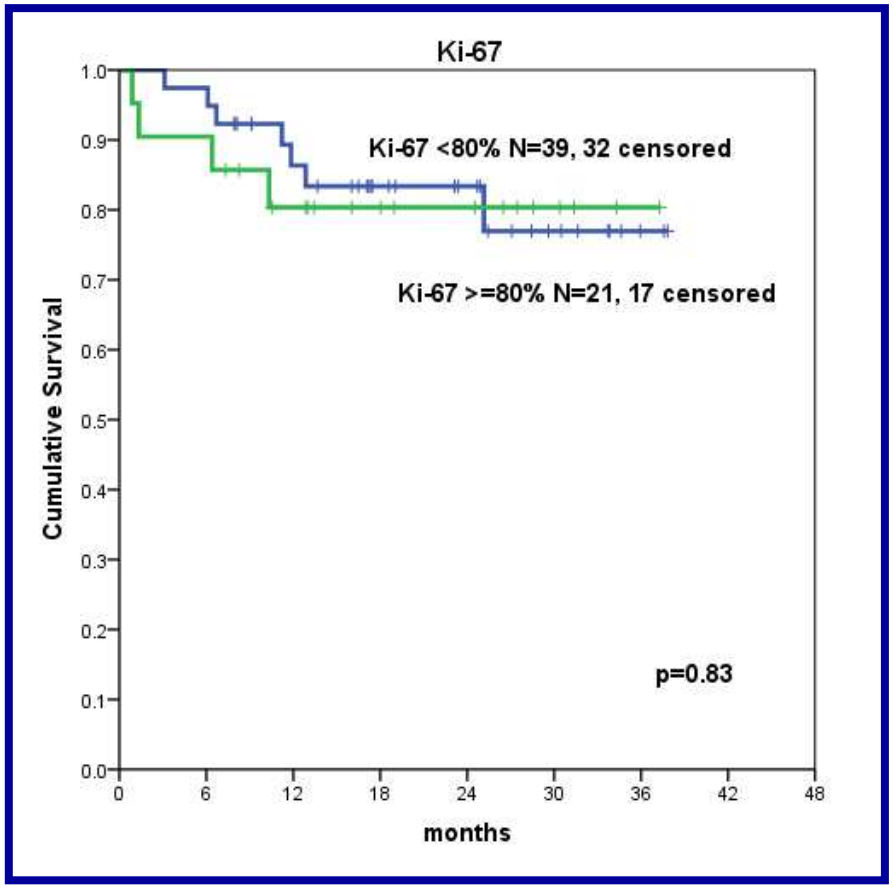
Female	55%
Median age Range >60	54 21-71 42%
PMBL	20%
Tumor Bulk >10cm	37%
KPS <80	25%
LDH >normal	81%
Stage IV	75%
aaIPI HIR/HR	75%
Ki-67 ≥ 80%	35%
ENS ≥2	62%
Cell of Origin GC Non-GC PMBL Indeterminate	 43% 30% 20% 7%

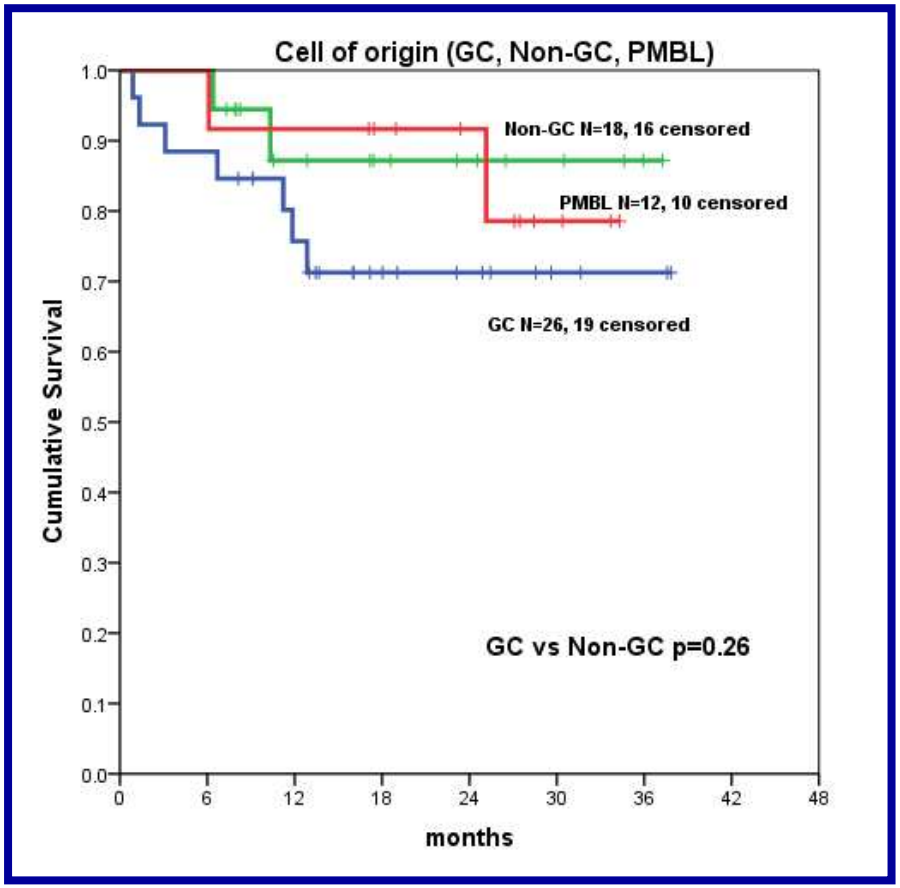
Survival Endpoints



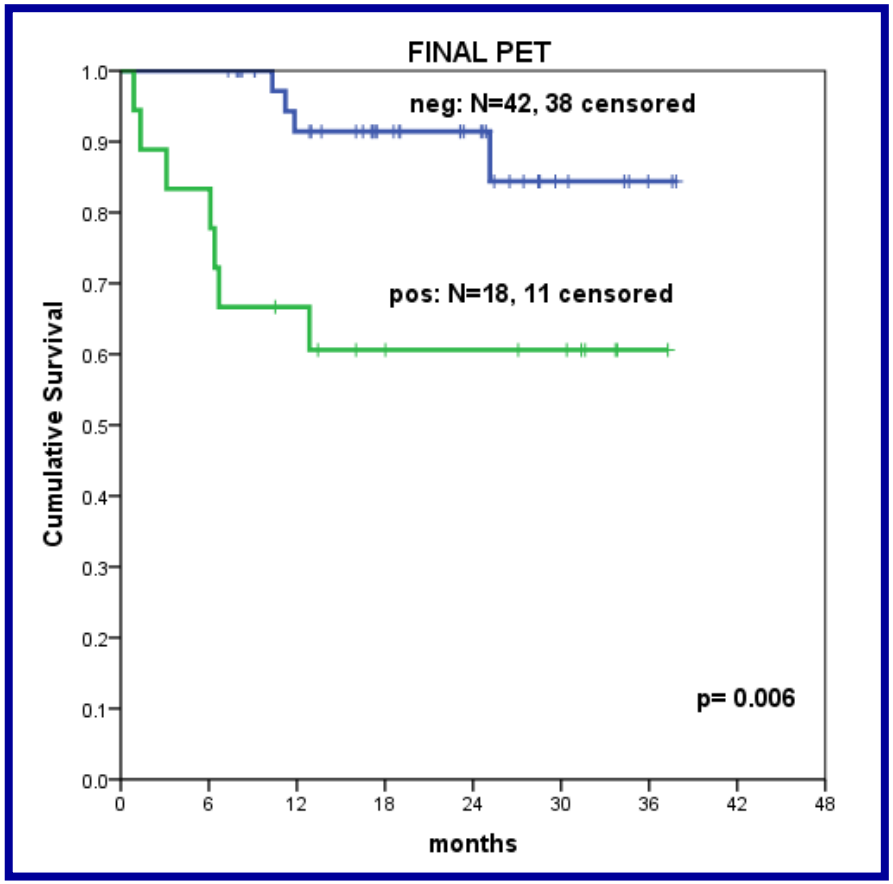


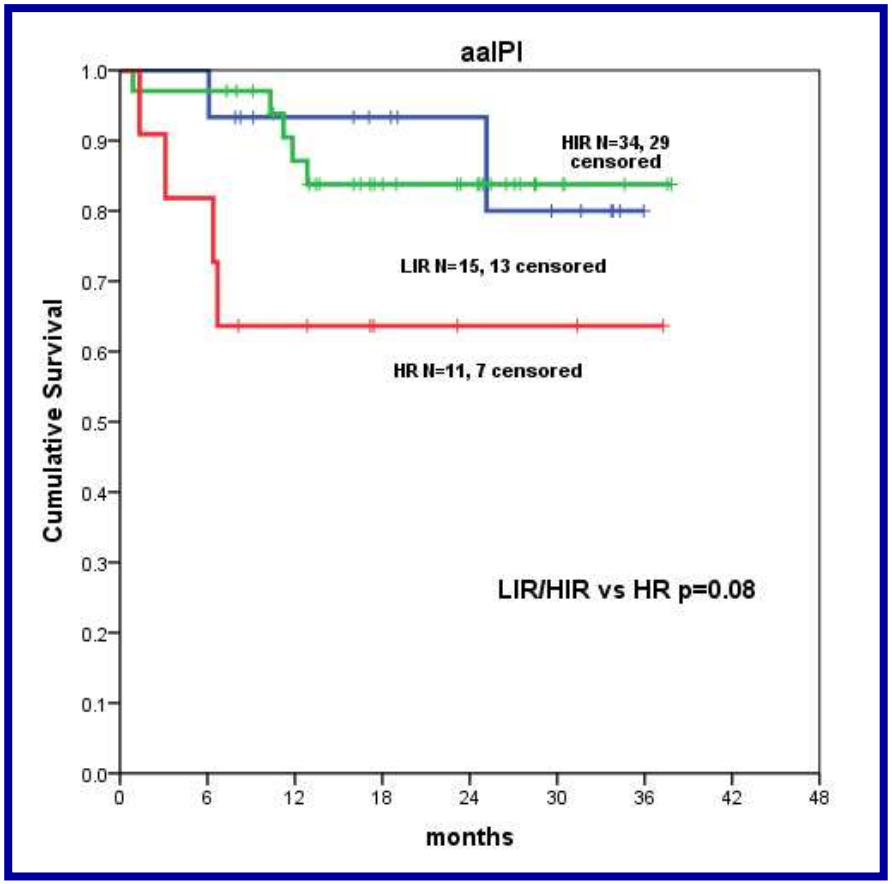
Pre-TX Pathology



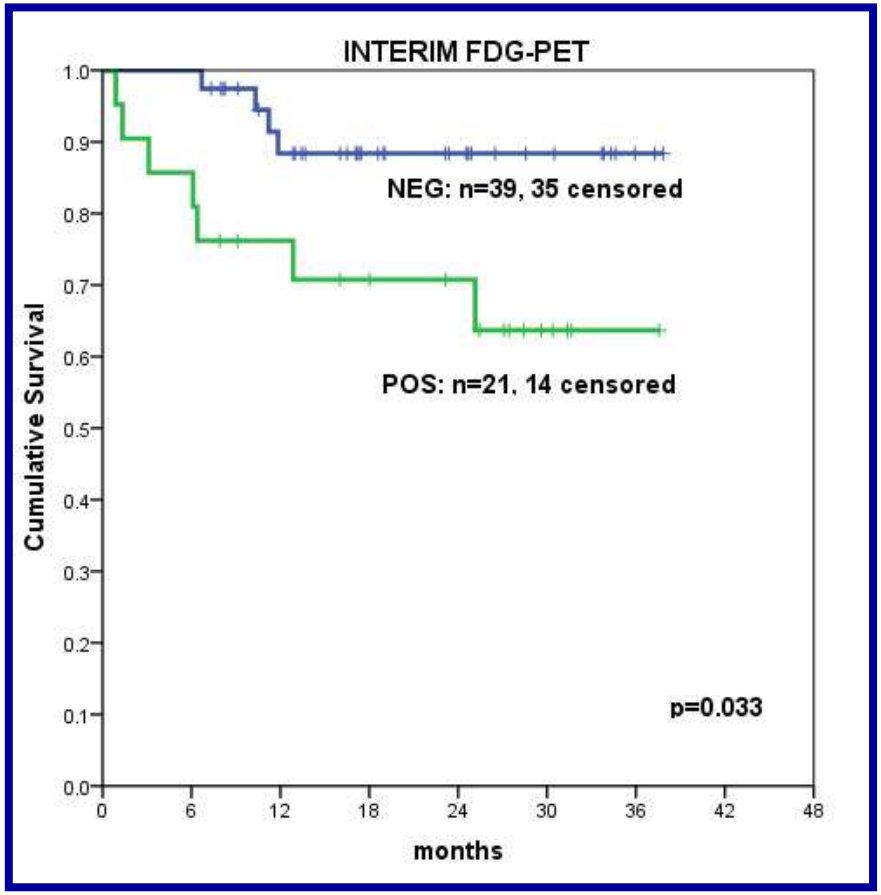


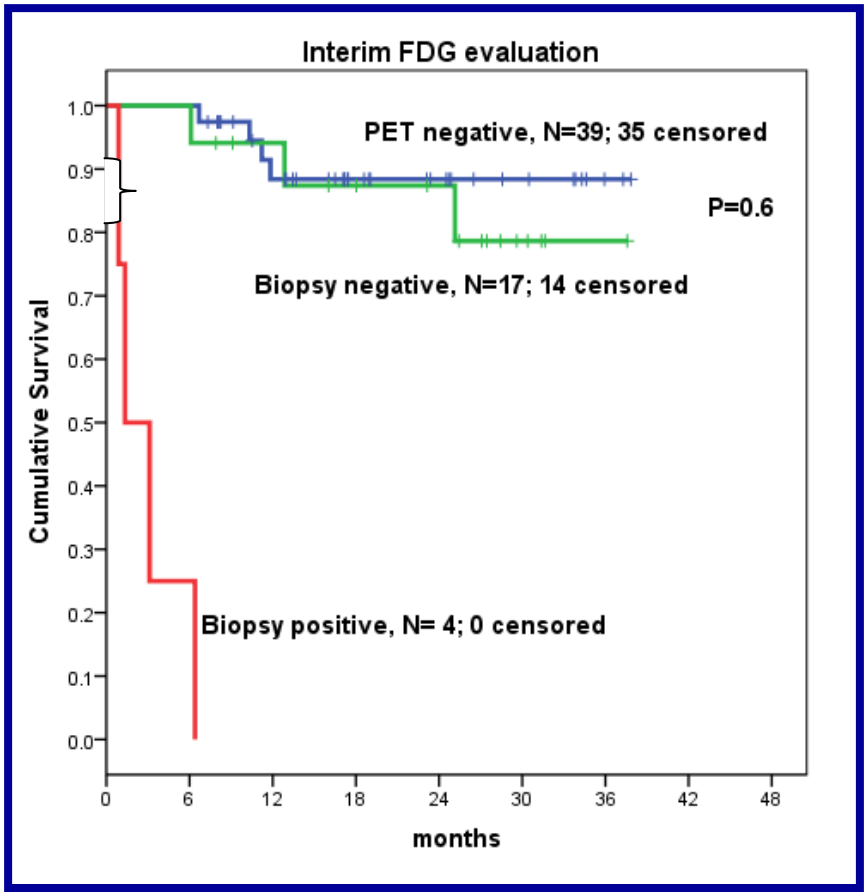
Statistically significant, but meaningful?



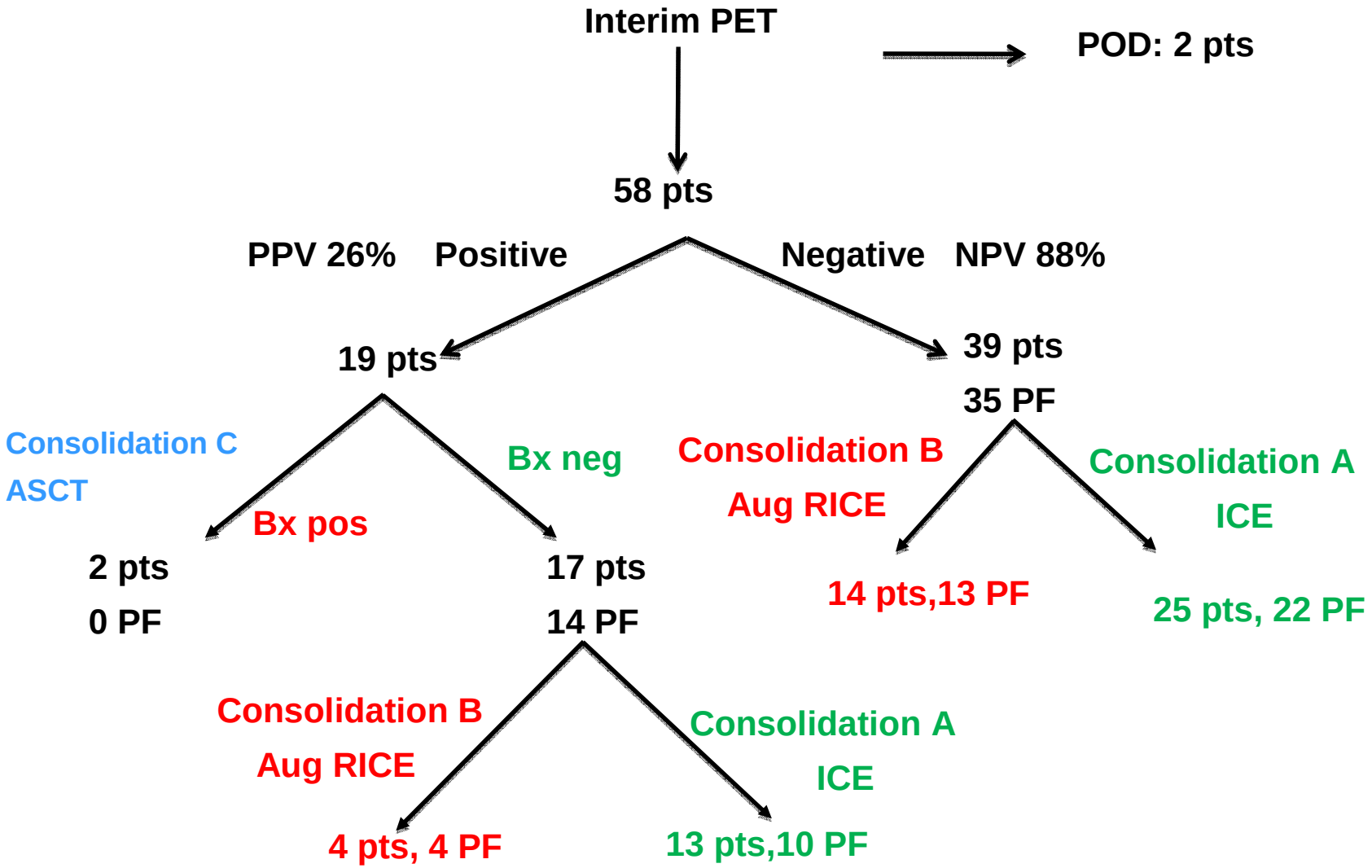


Interim Evaluation

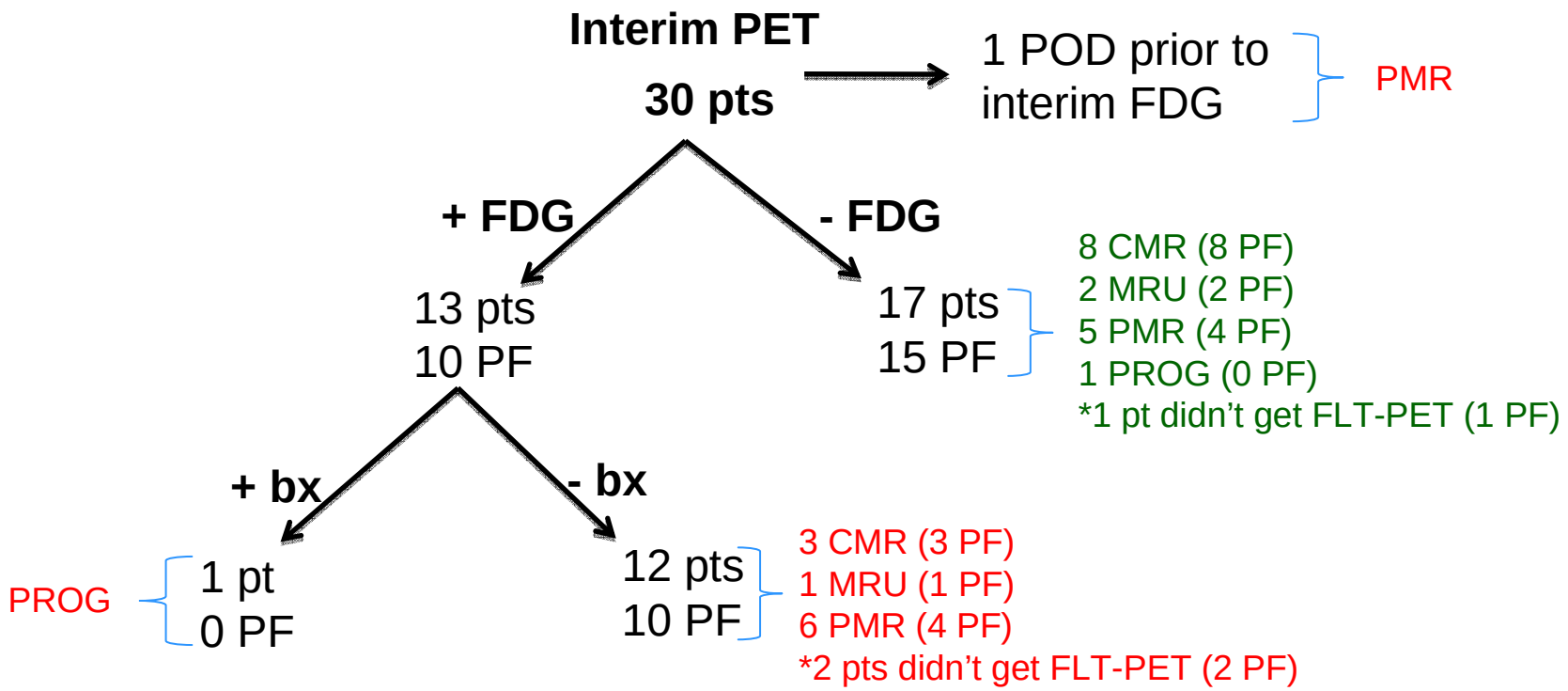




Results of protocol 08-026



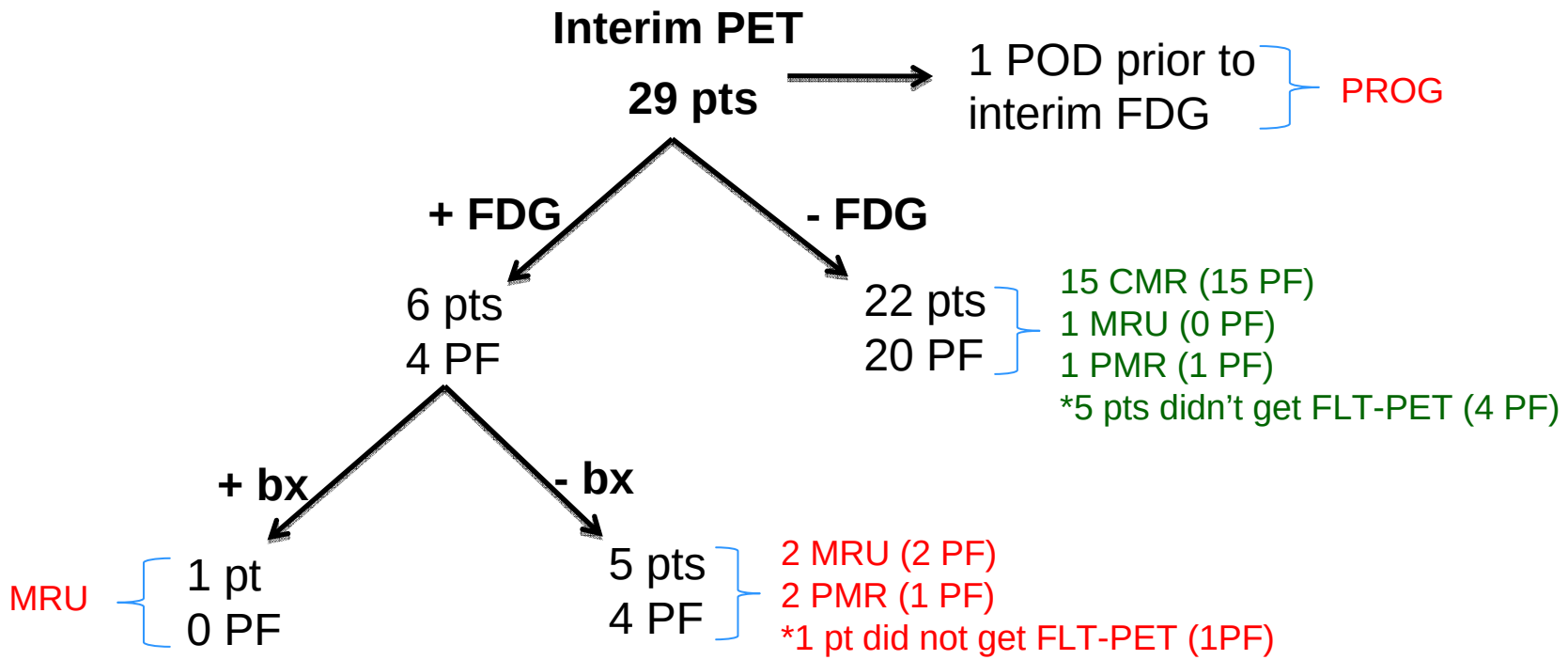
COHORT 1: FLT-PET: Pre-treatment and after cycle 1
FDG-PET: Pre-treatment and after cycle 4



*Why patients did not get FLT-PET:

-miscommunication between research staff and patient, technical difficulty manufacturing FLT tracer, pt injected with FDG tracer instead of FLT tracer

COHORT 2: FLT-PET: Pre-treatment and after cycle 2
FDG-PET: Pre-treatment and after cycle 4

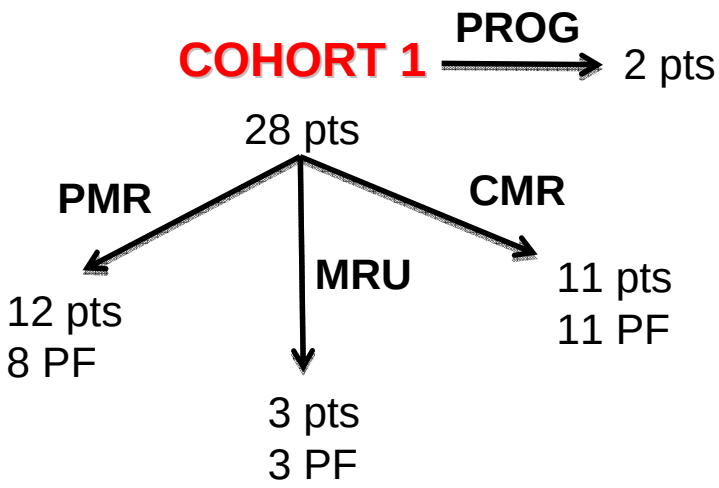


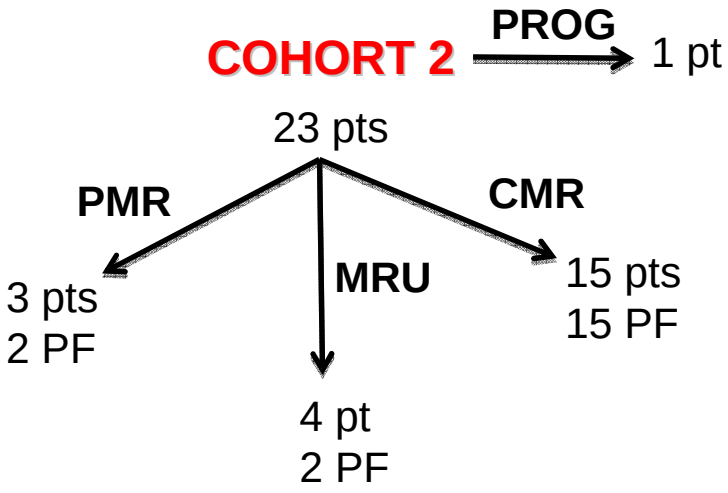
*Why patients did not get FLT-PET:

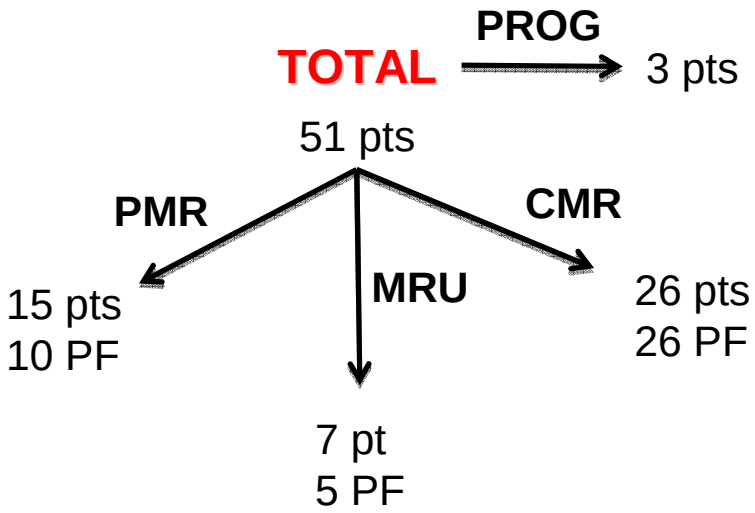
-FLT tracer was unavailable, problem manufacturing FLT tracer, started treatment immediately and couldn't schedule FLT PET in time, immediately admitted for cycle 1 of treatment

FLT-PET results

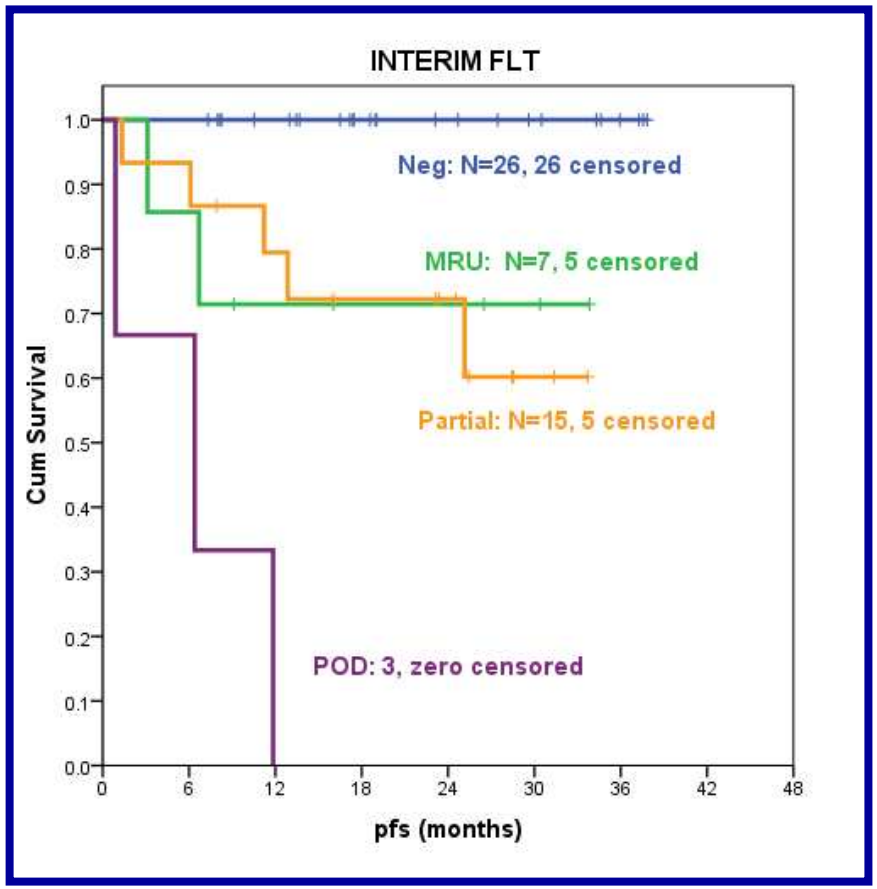
Cohort 1: Pre-treatment and after cycle 1
Cohort 2: Pre-treatment and after cycle 2

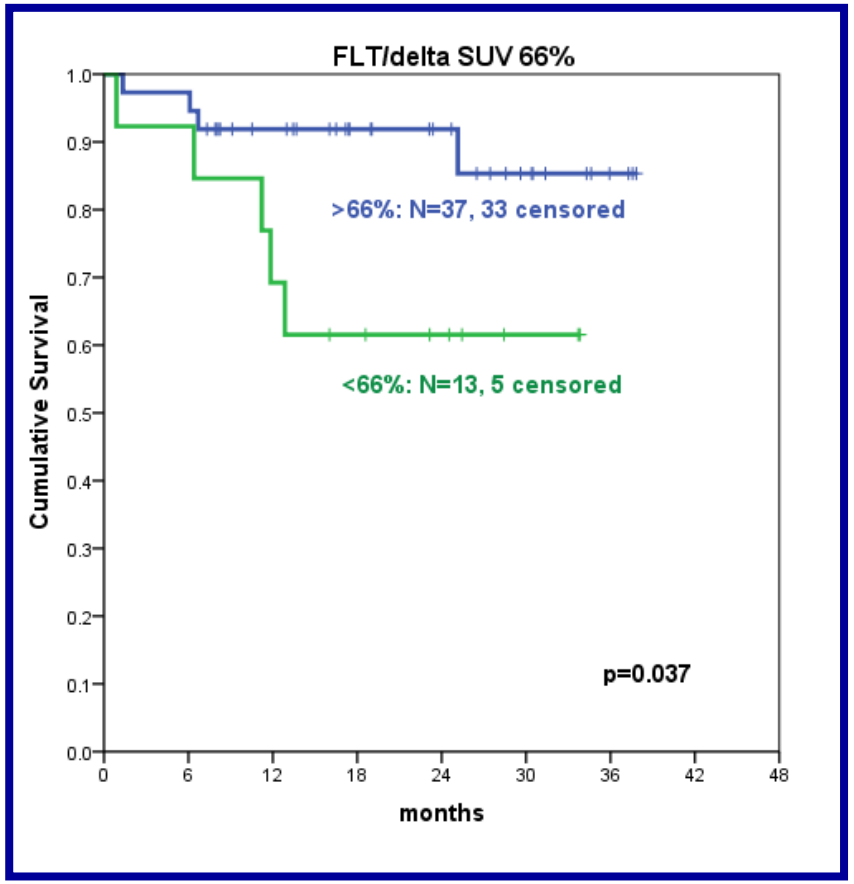






Preliminary PFS according to FLT result

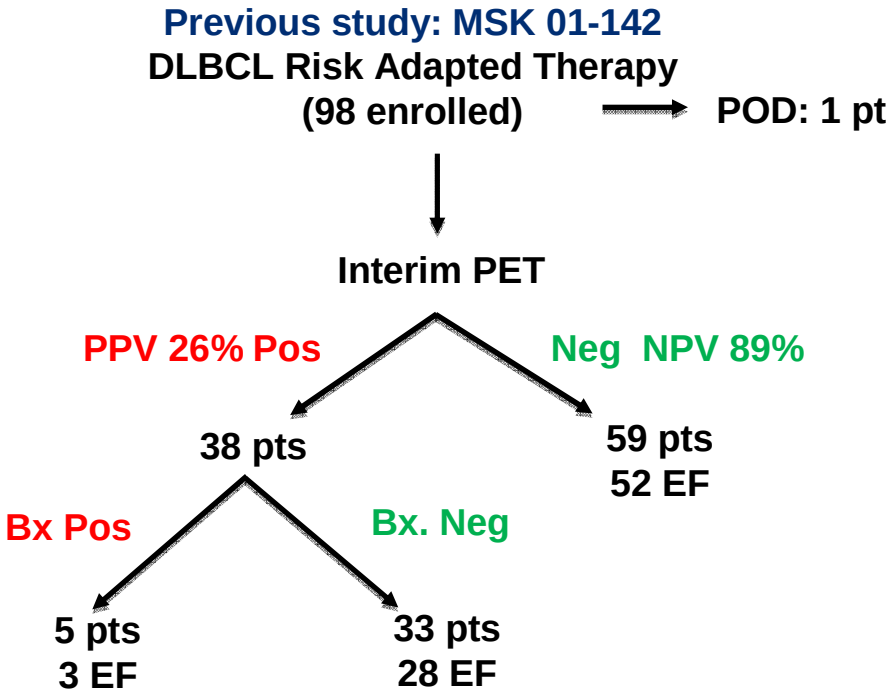




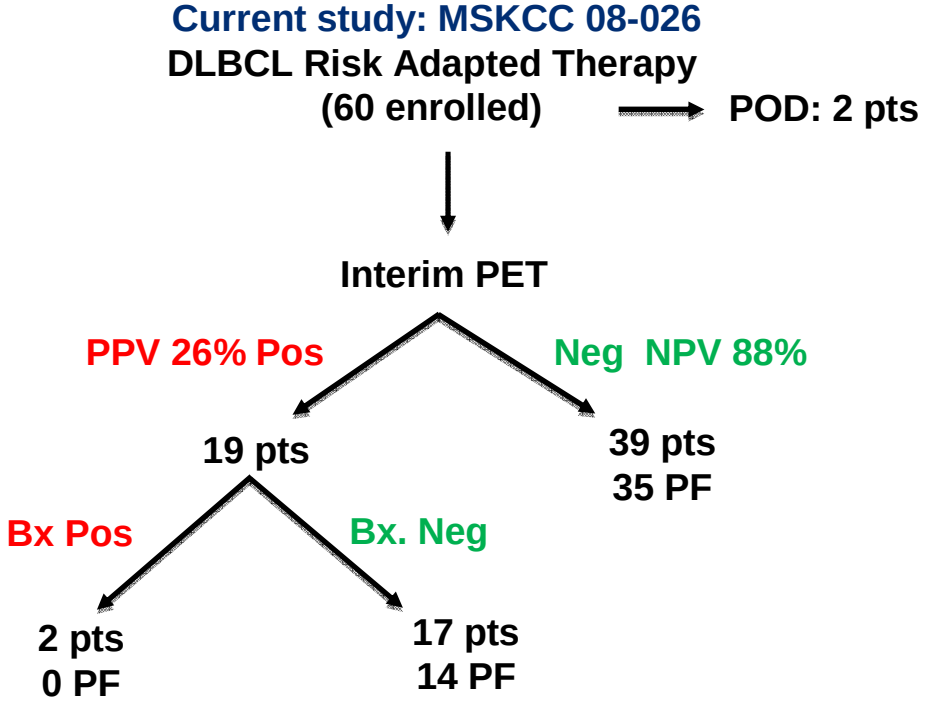
FLT in this study

- It is very expensive
- Pre-TX imaging is not as sensitive as FDG
- The SUV max is not necessarily the same site as FDG and the peak value is lower
- A CMR thus far has a 100% NPV
- There are more CMR after cycle 2 vs 1

Results



Total of 10 patients dead of disease



Total of 6 patients dead of disease

Once again there is no difference in outcome between patients that have a negative interim FDG-PET and those with a negative biopsy after a positive interim FDG-PET

We cannot biopsy 40% of pts!

We need nuclear medicine docs to reliably tell us that the FDG-PET is clearly abnormal and a biopsy is required

Lymphoma Service-MSKCC

- John Gerecitano
- Paul Hamlin
- Steve Horwitz
- Matt Matasar
- Alison Moskowitz
- Craig Moskowitz
- Ariela Noy
- Lia Palomba
- Carol Portlock
- David Straus
- Joachim Yahalom
- Andrew Zelenetz