RESORT vs. PRIMA

Brad Kahl, MD

University of Wisconsin

Disclosures

- Consulting
  - Genentech/Roche, Millennium, Pharmacyclics, Gilead
- Research Funding
  - Genentech/Roche, Millennium, Abbvie

Simplified approach to Follicular Lymphoma

	Low Tumor Burden	High Tumor Burden
Symptoms absent	**Watch/Wait vs. single agent rituximab**	R-chemo +/- MR vs. Watch/Wait
Symptoms present	Single agent rituximab vs. R-chemo	R-chemo +/- MR

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Results of E4402 (RESORT): A Randomized Phase III Study Comparing Two Different Rituximab Dosing Strategies for Low Tumor Burden Follicular Lymphoma

Brad Kahl, Fangxin Hong, Michael Williams, Randy Gascoyne, Lynne Wagner, John Krauss, Sandra Horning

eastern cooperative oncology group

Background: Low Tumor Burden FL

- Watch and wait (with initiation of chemotherapy upon development of high tumor burden) considered a reasonable standard

- 3 RCTs failed to show an OS advantage for immediate chemotherapy vs. watch and wait
  - Young et al, Sem Hematol, 1988
  - Brice et al, JCO 1997
  - Ardeshna et al, Lancet 2003

Background: Rituximab in Low Tumor Burden FL

- Is W & W, until high tumor burden develops, the best strategy in the rituximab era?
  - Single agent R active and well tolerated in frontline LTB FL
    - Colombat et al, Blood 2001
- Could rituximab provide a low risk treatment strategy which could delay the time to first chemotherapy?
  - ~ 3 years in most studies of W & W

Background: Rituximab in Low Tumor Burden FL

- Recently we were shown:
  - R monotherapy superior to W & W for the endpoint of time to first chemotherapy
    - Ardeshna et al, Lancet Oncology, 2014
  - 15 – 20% of US FL patients receive R monotherapy as their initial treatment
    - Friedberg et al, JCO 2009

Background: How should the rituximab be dosed?

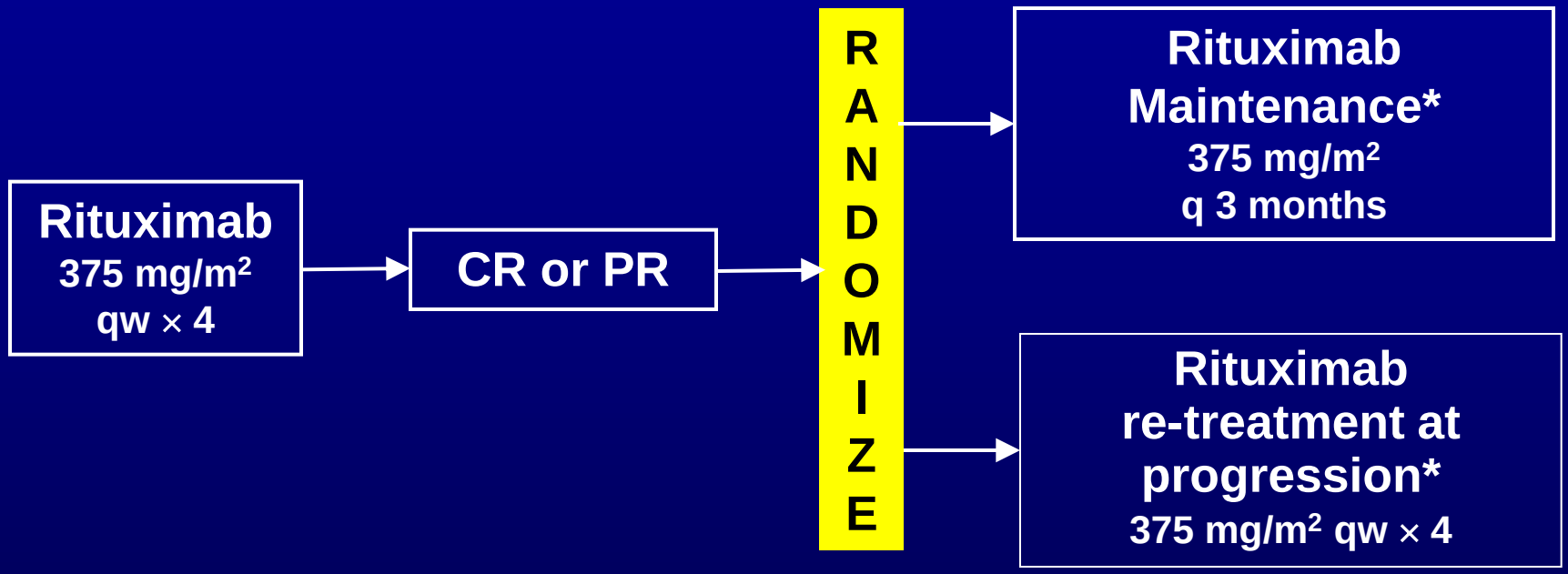
- SAKK 35/98
  - Maintenance superior to observation for RD
    - Ghielmini et al, Blood 2003
  - Unclear if translates into better "disease control" as patients on observation can be re-treated with R at PD
    - Davis et al, JCO 2000
- One trial of R maintenance vs. re-treatment
  - PFS improved by MR
  - No difference in disease control
  - Small study (45 per arm) in R/R population
    - Hainsworth et al, JCO 2005

E4402: RESORT Rationale

- **Hypothesis:**
  - **After initial rituximab therapy, extended scheduled dosing (maintenance rituximab - MR) will prolong disease control compared to retreatment dosing administered upon disease progression (rituximab retreatment - RR)**

- **Previously untreated, low tumor burden, FL an ideal patient population to test this hypothesis**
  - **Reasonably homogenous population**

E4402 (RESORT) Schema



***Continue until treatment failure**

- No response to retreatment or PD within 6 months of R
- Initiation of cytotoxic therapy or Inability to complete rx

E4402 Major Eligibility

- Indolent NHL
  - Follicular grade 1 or 2
  - Small Lymphocytic
  - MALT
  - Marginal Zone nodal
  - Marginal Zone splenic
- No prior lymphoma therapy
- Stage III or IV disease
- Measurable disease
- Low tumor burden as defined by GELF
  - No tumor mass ≥ 7cm
  - Fewer than 3 nodal masses > 3 cm
  - No system symptoms or B symptoms
  - No splenomegaly greater than 16 cm by CT scan
  - No risk of organ compression
  - No leukemic phase
  - No cytopenias

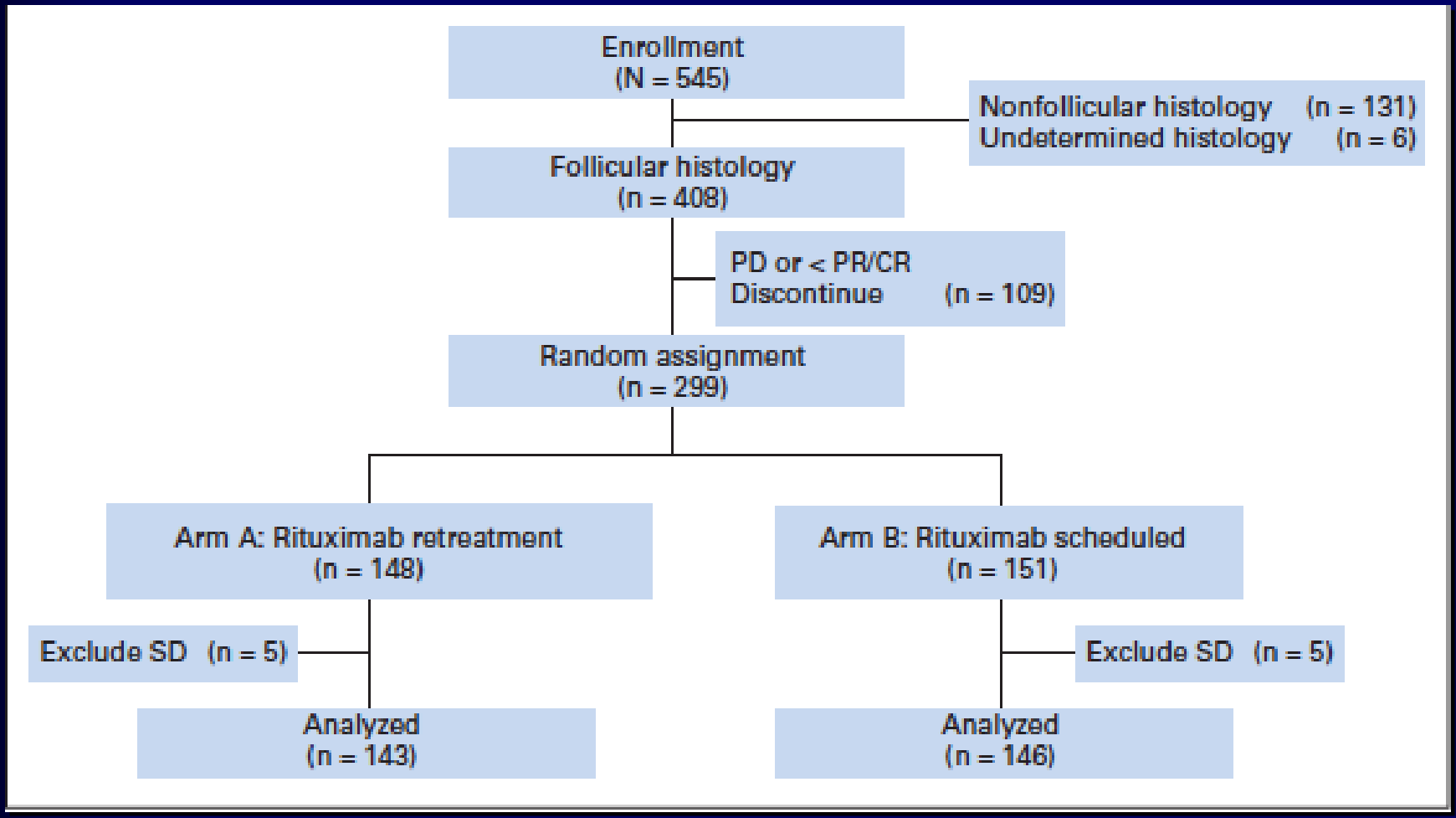
E4402 (RESORT) Objectives

- Primary
  - To compare the TTTF between the MR and the RR arms
- Secondary
  - To compare time to first cytotoxic therapy between the MR and the RR arms
  - To compare QOL between the arms
  - To compare toxicities between arms

E4402 (RESORT) Statistical Considerations

- 81% power to detect 36% reduction in the TTTF hazard rate in FL patients
  - Type I error 5% (two sided)
- Requires 270 randomized FL patients
- Stratification factors
  - Age (< 60 vs ≥ 60)
  - Time from diagnosis (< 1 year vs ≥ 1 year)
- Interim analysis by DMC q 6 months.
  - DMC recommended release of study results at a planned interim analysis

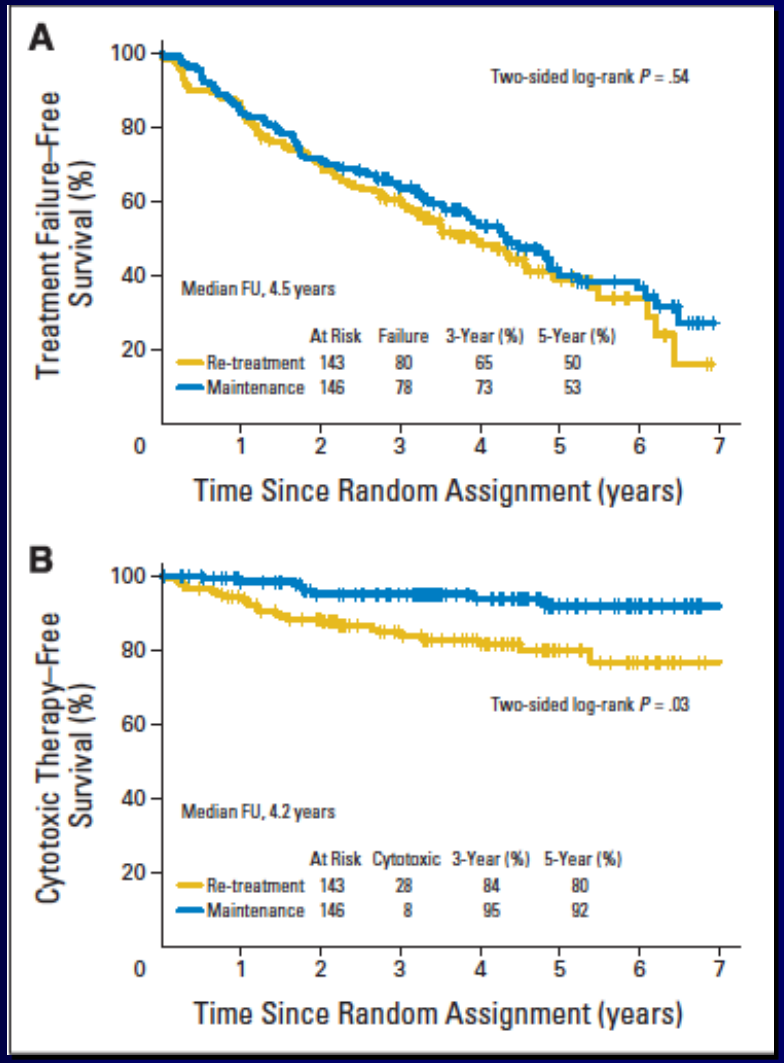
RESORT: Consort Diagram

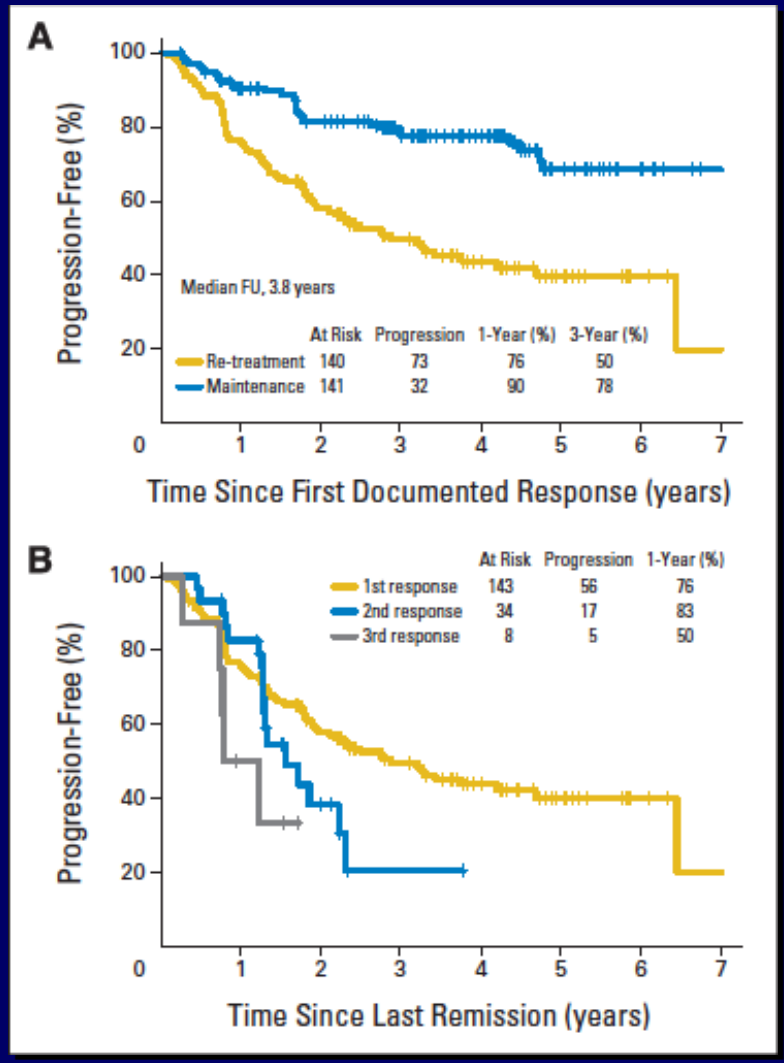


Baseline Characteristics at Randomization

	RR (N=134)	MR (N=140)
Age	59.7 (26-86)	59.0 (25-86)
Gender (M/F)	46/54%	46/54%
PS (0/1)	84/15%	87/10%
Stage		
• **III**	56%	48%
• **IV**	43%	51%
FLIPI		
• **0-1**	15%	16%
• **2**	46%	43%
• **3-5**	39%	41%
B2M elevated	46%	39%

Time to Event Data





Quality of Life Analysis

- Is there a psychological benefit to being maintained in remission?
- Tools administered at randomization, 13, 26, 52, 104, 156, 208 weeks post randomization, and at treatment failure.
  - FACT-G total score
  - FACT-G emotional well being
  - Impact of event scale
  - HADS Anxiety
- At all time points, no difference in QOL change score is observed. (Wagner et al, JCO 2015)

Toxicity

- Second malignancies
  - 9 RR arm
  - 7 MR arm
- One progressive multifocal leukoencephalopathy
  - MR arm
- Deaths
  - 10 RR arm
  - 12 MR arm

Treatment Information

- **Analysis of # doses rituximab received, including 4 induction doses**

	Min	Max	Median	Mean
RR	4	16	4	4.5
MR	5	35	18	16.8

Conclusions

- In this study of previously untreated low tumor burden FL:
  - Rituximab retreatment was as effective as maintenance rituximab for time to treatment failure
  - MR was superior to RR for time to cytotoxic therapy
    - At a cost of 4x more R
  - No benefit in QOL or anxiety with MR

RESORT Conclusions

- So who won?
  - Given the excellent outcomes with RR
    - 84% chemotherapy free at 3 years
  - Given the toxicity profile with RR (fewer AE failures)
  - Given the lack of QOL difference
  - Given the fewer R doses required with RR
    - $70,000/patient in drug costs
- Rituximab retreatment is our recommended strategy if opting for rituximab monotherapy in LTB FL

Kahl et al, JCO 2014;32(28) 3096-102

RESORT vs. PRIMA

- Suppose one did a RESORT type design in the PRIMA population?
  - R-chemo x 6 plus MR vs. R-chemo x 6 plus RR
  - PFS can not be the primary endpoint
  - Needs to be some other measure of disease control
    - "current PFS"
    - time to treatment failure
- The endpoint matters
  - How do you define clinical benefit?

RESORT vs. PRIMA

- Endpoint issues
  - MR clearly improves PFS
  - MR improves time to next treatment
  - MR does not improve OS
  - MR does not improve QOL
- If PFS is sufficient then a reasonable trial would be:
  - R-chemo x 6 cycles plus by MR followed by idelalisib for until PD vs. R-chemo plus MR.
  - For “fun”, do the math on idelalisib drug cost for a 1000 patient trial.

RESORT vs. PRIMA

- PRIMA demonstrates of substantial PFS benefit for MR
  - No QOL benefit
  - No OS benefit
- RESORT demonstrates there is a viable alternative strategy to maintenance therapy
  - Resource utilization benefit
- Given the costs of new oncology agents
  - Can no longer tack additional treatment at end of planned FL therapy and declare victory when remissions last longer

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Questions?