



Follicular Lymphoma

“Maintenance therapy: To be or not to be”

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- Clinical trial grant support (PI) to the University of Virginia:
 - Celgene, Gilead, Janssen, Novartis, Pharmacyclics, Takeda
- Data Safety Monitoring Committee:
 - Celgene, Takeda
- Consultant:
 - TG Therapeutics, Gilead

Observation vs Rituximab therapy for low tumor burden FL: Considerations.....

- High Rituximab response in setting of low disease burden
- Opportunity for durable responses in many patients
- Delay time to cytotoxic therapy
- Bridge patient to novel, non-cytotoxic agents
- Avoid “Watch and Worry”

GELF Criteria: Low FL disease burden

- No systemic or B symptoms
- Non-bulky nodal disease
 - No single mass > 7 cm
 - 3 or fewer nodal areas > 3 cm
- No splenomegaly > 16 cm by CT
- No cytopenias or leukemic phase
- No effusions or risk of organ compression

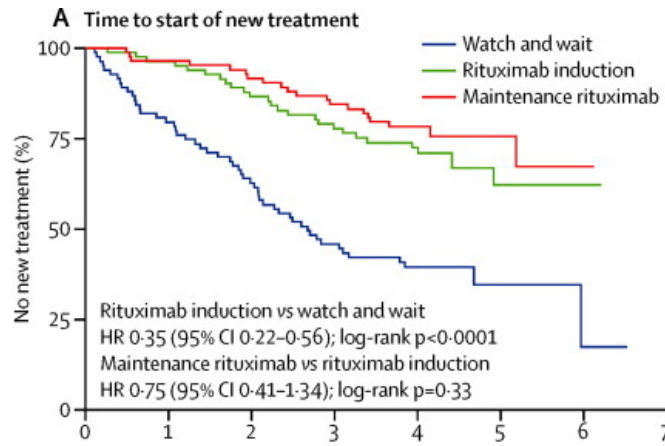
Background: Rituximab in Low Tumor Burden FL

- 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)
- Rituximab provides a low-risk treatment strategy that delays time to first chemotherapy
 - ◆ **Versus ~3 years in most studies of W & W**

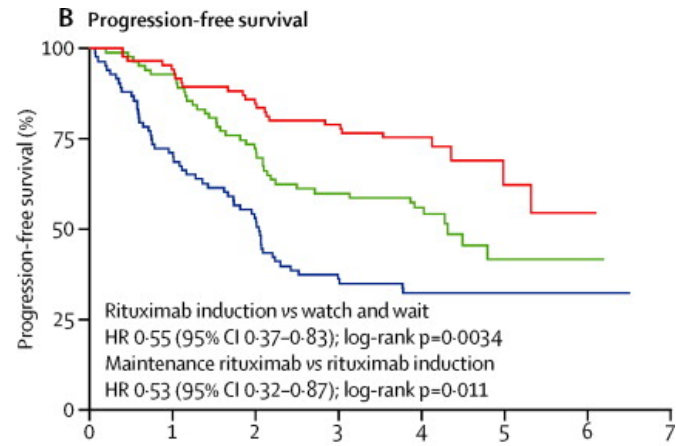
Rituximab +/- Maintenance R versus Watch & Wait in Non-bulky FL

- UK Intergroup trial
- Stage II-IV, asymptomatic, **no prior therapy**
- **3 arms:**
 - Watch/Wait
 - R weekly x 4 (closed early)
 - R x 4 → R q 2 months x 2 years
- **Primary endpoints:** Time to next Rx & QOL
- Indications for initiating a new line of therapy:
 - Symptomatic increase in nodes or spleen
 - B symptoms or pruritis
 - Mass > 7 cm if > 25% increase
 - > 3 nodal masses > 5 cm

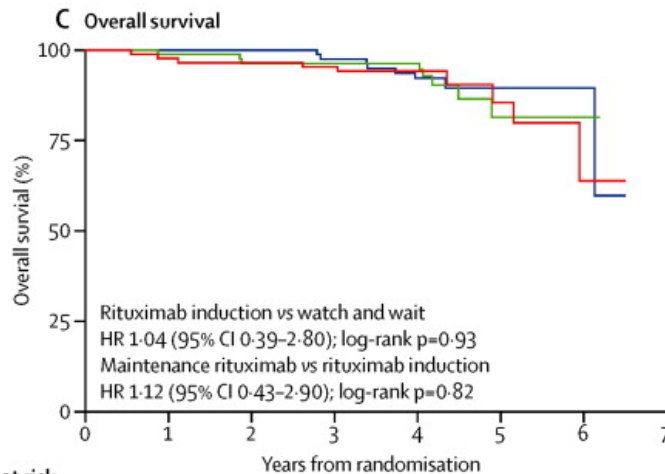
Rituximab +/- Maintenance R versus Watch & Wait: Results



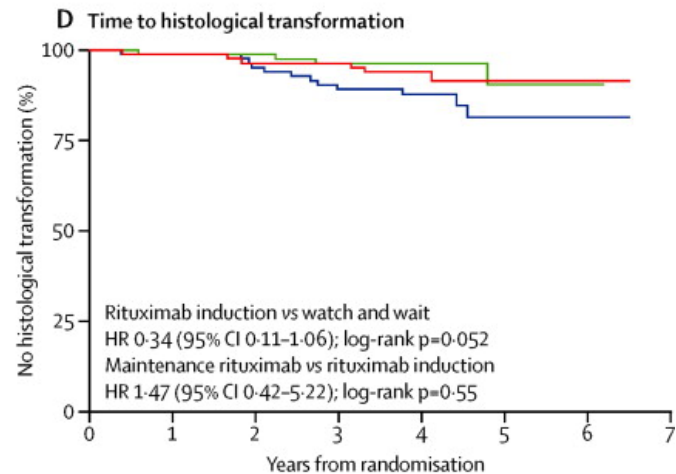
Number at risk	0	1	2	3	4	5	6	7
Watch and wait	83	66	52	36	29	6	1	0
Rituximab induction	84	80	69	61	44	13	5	0
Maintenance rituximab	85	81	76	70	49	10	1	0




83	59	44	29	25	6	1	0
84	77	59	48	35	11	4	0
85	80	72	67	48	9	1	0



Number at risk	0	1	2	3	4	5	6	7
Watch and wait	83	83	83	79	62	18	4	0
Rituximab induction	84	82	78	77	61	16	5	0
Maintenance rituximab	85	83	82	81	61	16	3	0



83	82	79	71	58	15	4	0
84	82	79	75	59	15	5	0
85	83	80	79	59	16	3	0



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

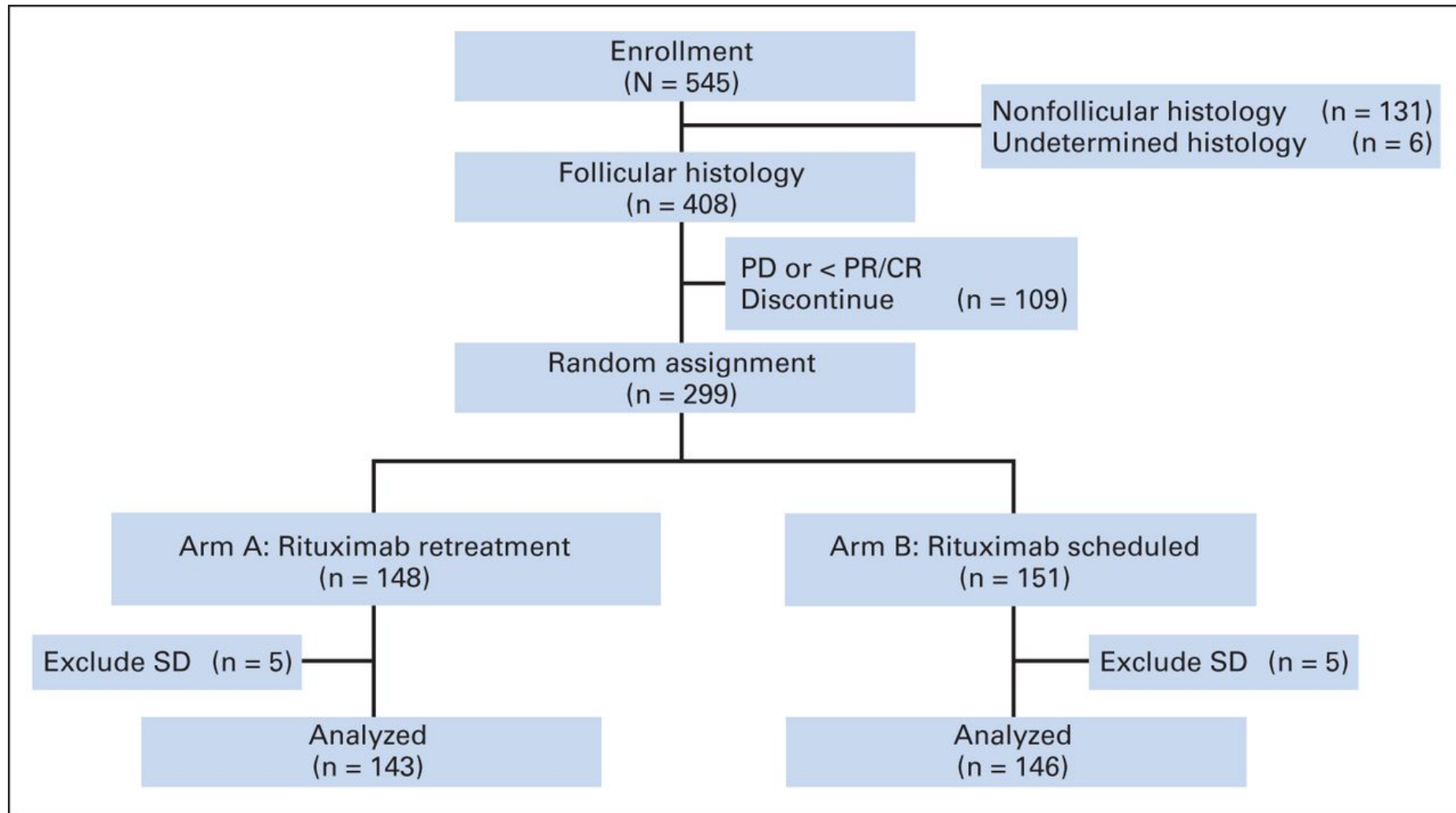
Brad Kahl, Fangxin Hong, Michael
Williams, Randy Gascoyne, Lynne
Wagner, John Krauss, Sandra Horning

eastern cooperative

oncology group



CONSORT diagram for E4402: RESORT (Rituximab Extended Schedule or Re-Treatment Trial)



Kahl B, Hong F, Williams ME, et al. JCO 2014;32:3096-3102

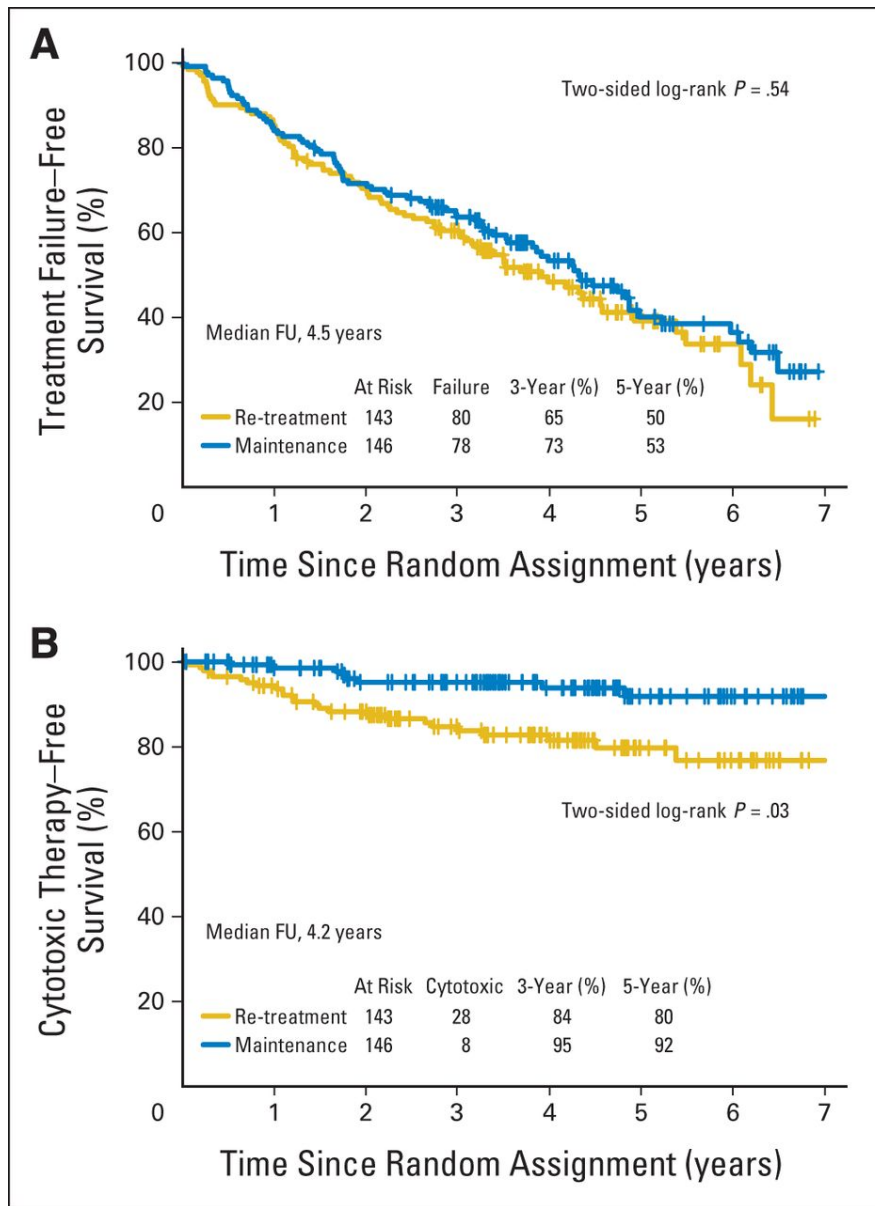
E4402 (RESORT)

- Activated Nov 2003 - Closed Sept 2008
- Enrolled 545 patients
 - ◆ 161 non-FL patients reported separately
(Williams ME, et al. Brit J Haematol 2016)
- 384 with FL histology
- **274 (71%) responded to R weekly x 4**
 - CR/CRu = 12% (low due to missing BM bx restaging in some pts, classified as PR)
 - ◆ 134 assigned to retreatment rituximab (RR)
 - ◆ 140 assigned to maintenance rituximab (MR)

Baseline Characteristics at Randomization

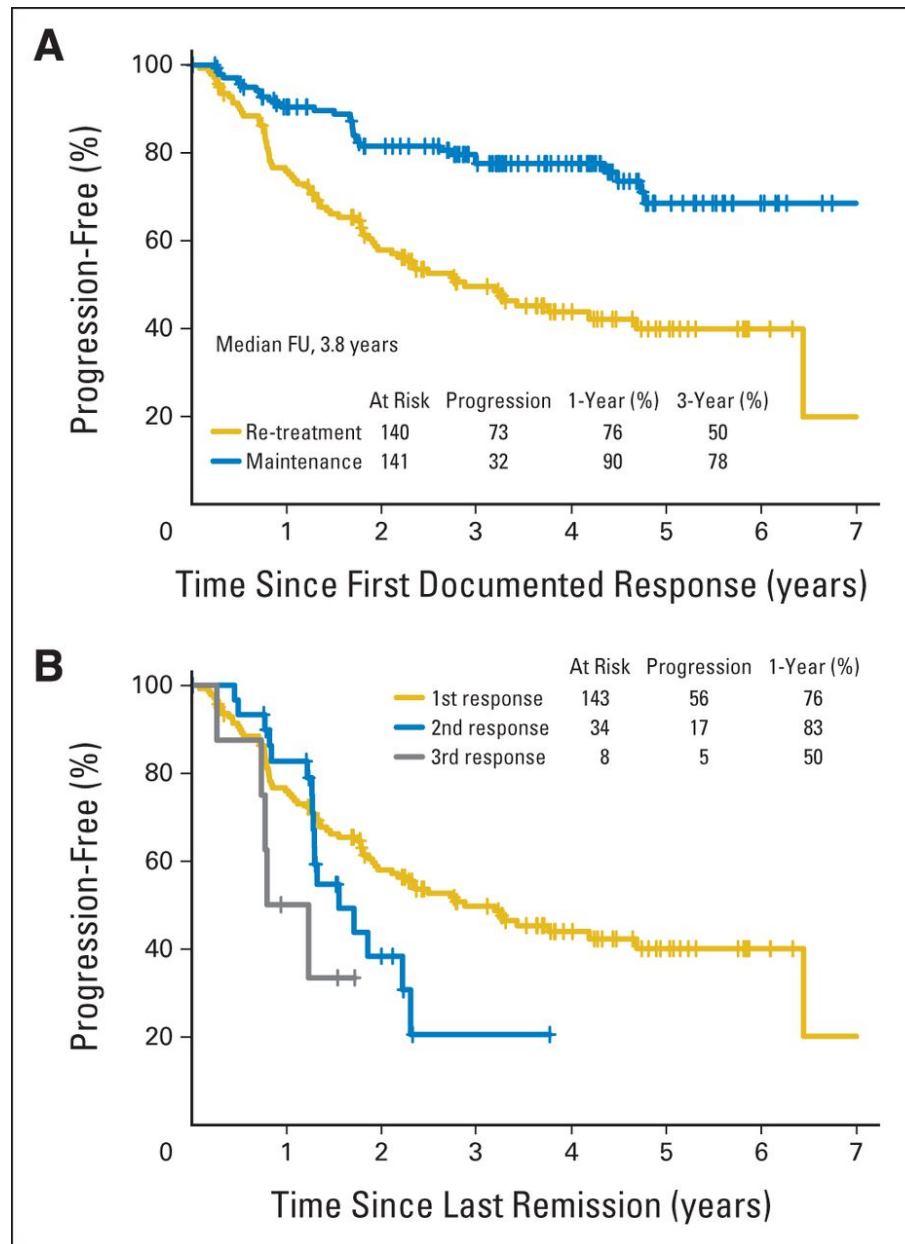
	RR (N=134)	MR (N=140)
Age	59.5 (26-86)	58.9 (25-86)
Gender (M/F)	46/54%	46/54%
PS (0/1)	84/15%	87/10%
Stage		
• III	56%	48%
• IV	43%	51%
FLIPI		
• 0-1	15%	16%
• 2	46%	43%
• 3-5	39%	41%
B2M elevated	46%	39%

RESORT: Time to (A) treatment failure and (B) first cytotoxic therapy in 289 patients with FL randomly assigned to RR or MR

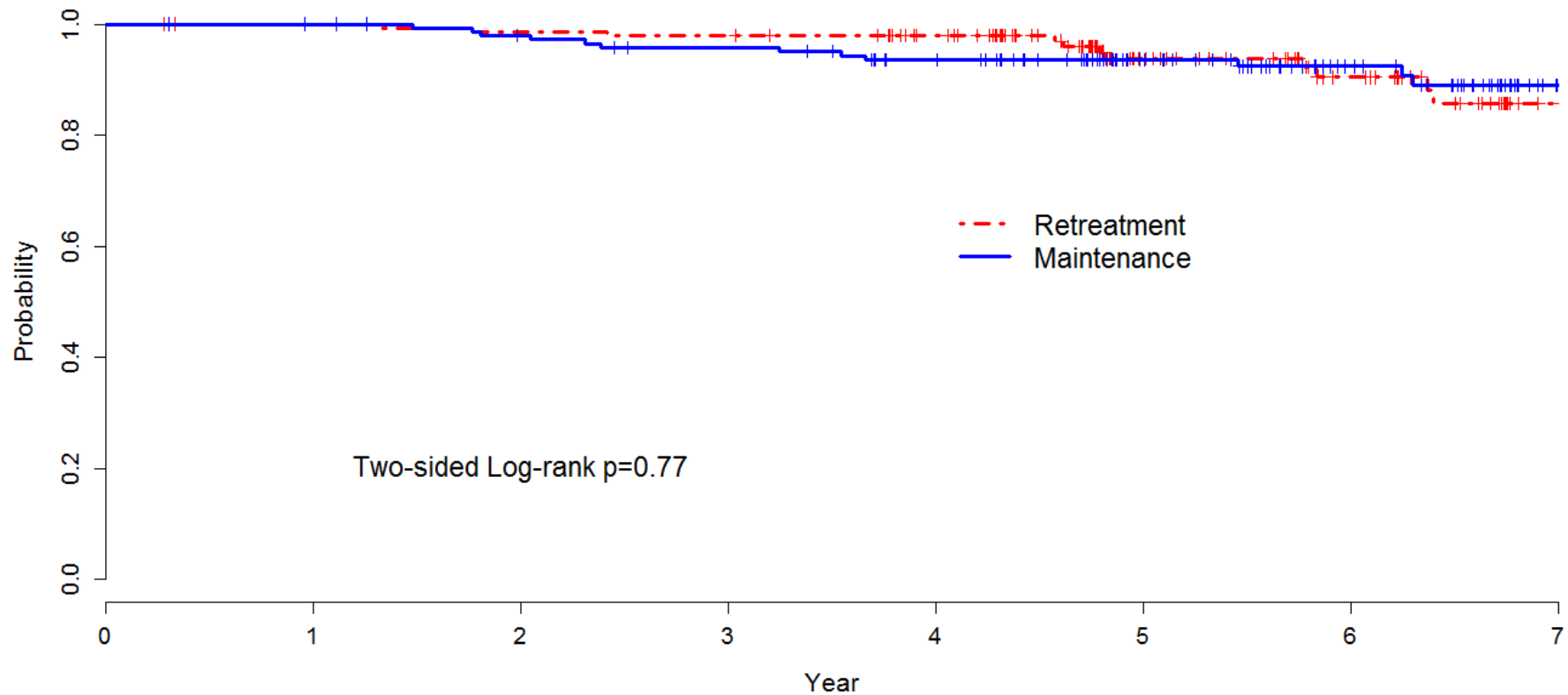


Kahl, Hong, Williams et al. JCO 2014;32:3096-3102

RESORT: response duration of patients with FL (A) assigned to RR (n = 143) or MR (n = 146) and (B) assigned to RR according to first rituximab treatment and re-treatments



RESORT: Overall Survival



Kahl, Hong, Williams et al. JCO 2014;32:3096-3102

RESORT: Quality of Life Analysis

- Is there a psychological benefit to being maintained in remission?
- Tools administered at randomization, at 3, 6, 12, 24, 36 and 48 months post randomization, and at Ritux failure
 - ◆ FACT-G total score
 - ◆ FACT-G emotional well being
 - ◆ Impact of event scale
 - ◆ HADS Anxiety
- **Result:** Surveillance until retreatment at progression was not associated with increased anxiety compared with maintenance R administration
 - no difference regardless of coping style

RESORT: Summary of findings

Kahl B, Hong F, Williams ME, et al. JCO 2014;32:3096-3102

- **Rituximab retreatment was as effective as maintenance for time to treatment failure**
- MR was superior to RR for time to cytotoxic therapy
 - At a cost of 3.5x more R (median 15.5 vs 4 doses)
 - No benefit in QOL or anxiety at 12 months with MR
 - No difference in transformed lymphoma (RR=8, MR=6)

→ Excellent outcomes with RR

→ 86% chemotherapy free at 3 years

- Given no QOL difference and fewer AE failures, and
- Given fewer R doses required with RR.....
- **R retreatment is the recommended strategy if opting for R monotherapy in LTB FL**

→ “End of rituximab maintenance for LTB FL”

(Friedberg J. JCO 2014:3093-5)

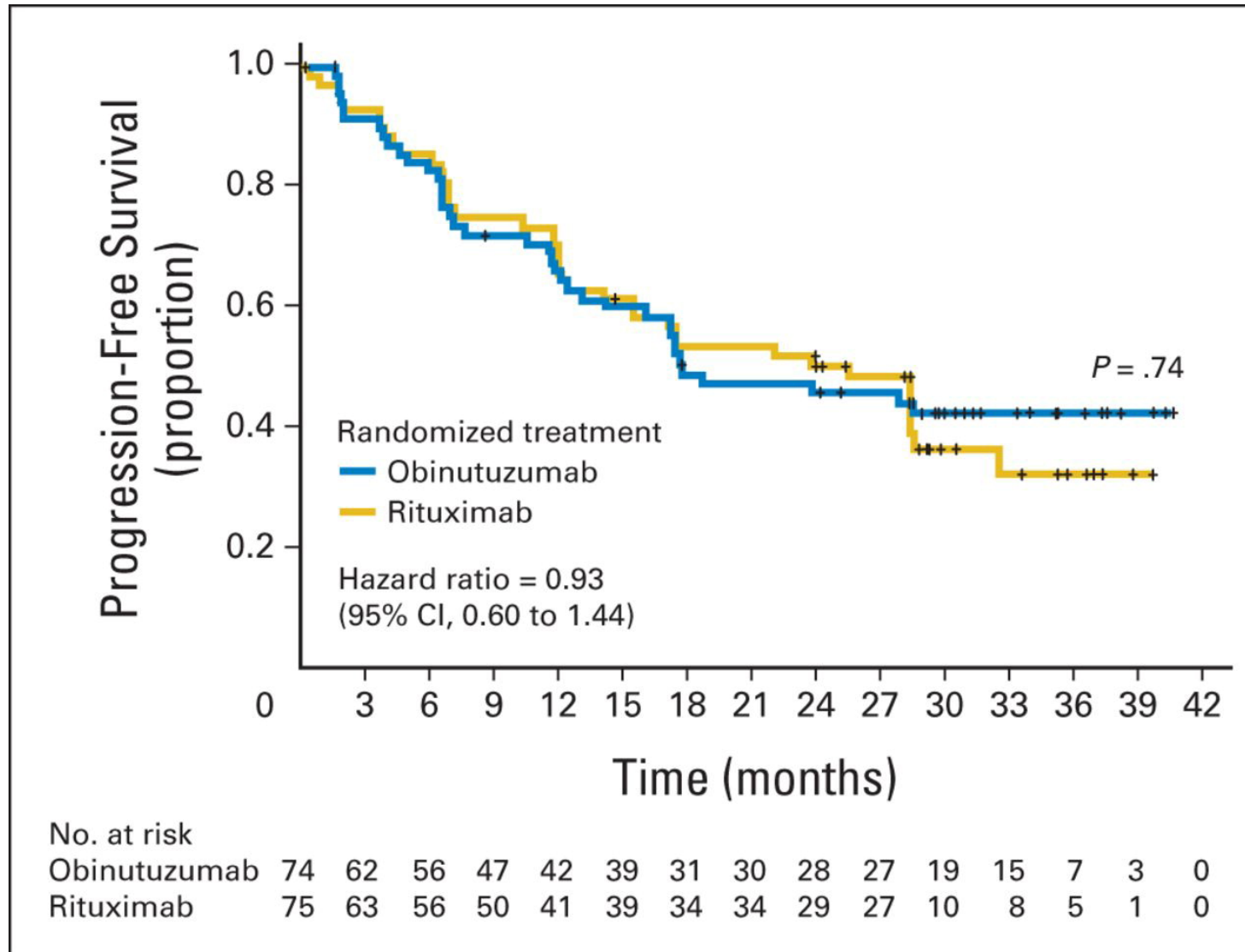
R weekly x 4 as a standard of care for low tumor burden FL

- “Watch and wait is watch and worry.”
 - *S. Ansell, Lancet Oncol 2014, 15:368-9*
- R x 4 provides durable response in many patients, and delays time to chemotherapy in most
- **Approach:** W/W with assessment of pace of disease over 6-12 months, versus R x 4 up front
 - Necessitates a careful discussion regarding patient’s goals and comfort level with either option, including risks/benefits of R therapy

Obinutuzumab vs Rituximab: Single agent data in FL

- GAUSS Study (Sehn et al, *J Clin Oncol* 2015; 33: 3467-74)
- Standard dosing, maintenance x 2 y in those with stable disease or better
- **Relapsed** after prior response to R-containing therapy, need therapy (n=149)
- **ORR 44.6% vs 26.7% (p= .01) by blinded independent review, but no diff in PFS**
- Expected safety profiles, more infusion reactions and cough with obinutuzumab

GAUSS Study: PFS for all patients (FL= 149; other iNHL =26)



Can we improve durable remissions in low tumor burden FL?

- PrECOG trial of Obinutuzumab vs Rituximab: closed due to poor accrual
- R2: Rituximab plus lenalidomide
- Targeted agent +/- anti-CD20
 - Venetoclax?
 - BCR pathway inhibitor?
- MRD-driven maintenance or re-treatment

Thomas Jefferson, Palladio and Virginia

- Jefferson toured northern Italy in April 1787, while ambassador to France
- Great admirer of Palladio





Villa Badoer

Fratta Polesine, Veneto

Andrea Palladio, 1556

Virginia State Capitol

Richmond, Virginia

**T. Jefferson, C-L
Clerisseau, 1785**

(wings added, 20th Century)





Monticello, 1772
T. Jefferson, age 26
Albemarle County
Piedmont Region, Virginia



