The case against maintenance rituximab in Follicular lymphoma

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Follicular lymphoma: What are goals of treatment?

• Change natural history of disease:
  – Decrease transformation
  – Improve survival

• Remission:
  – Make patients feel better
  – Active disease is often asymptomatic

• Improve quality of life
  – “Avoid chemotherapy” (now many non chemo options)
  – “VALUE” considerations
The past: Observation vs. Chlorambucil in asymptomatic “low grade” NHL

1990’s study

Approximately 2/3rds of patients had FL.

Median follow-up 16 yrs.

19% of patients never required systemic therapy

OS Stanford cohort: Immediate vs. delayed treatment

No evidence that timing of therapy initiation impacts overall survival.

No initial therapy (n=645): Median OS 15.1 yrs

Immediate treatment (n=688): Median OS 12.1 yrs

Improving overall survival in FL: Stanford cohort

Watch and wait vs. rituximab: PFS improvement demonstrated

Watch and wait vs. rituximab: No change in OS

Low tumor burden FL

44% of observation patients have not yet required therapy

Overtreatment in experimental group?

E4402 (RESORT) Schema

Rituximab
375 mg/m² qw × 4

CR or PR

RAN DOMIZE

Rituximab
Maintenance*
375 mg/m² q 3 months

Rituximab
re-treatment at
progression*
375 mg/m² qw × 4

Continue until treatment failure
No response to retreatment or PD within 6 months of R
Initiation of cytotoxic therapy or Inability to complete rx

Kahl et al, JCO 2014
RESORT: Primary Endpoint: Time to Treatment Failure

Two-sided Log-rank p = 0.80
RESORT: Time to First Cytotoxic Therapy

Two-sided Log-rank p=0.03
Conclusions: RESORT

• 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 3.5x more R
  • Enrollment before approval of idelalisib
RESORT: No QoL difference between maintenance and retreatment rituximab

- Illness-related anxiety was comparable between treatment arms at all time points (P > .05).
  
  - Illness-related anxiety and general anxiety significantly decreased over time on both arms.

- HRQoL scores were relatively stable and did not change significantly from baseline for both arms.

Wagner et al, *JCO* 33:740-8 2015
Lack of value of maintenance rituximab in low tumor burden patients with FL

- No survival benefit
- No evidence of changing natural history of disease
- Does not impact duration of rituximab sensitivity
- Does not make patients feel better
- Increases costs and toxicities
“Updated 6 Year Follow-Up Of The PRIMA Study Confirms The Benefit Of 2-Year Rituximab Maintenance In Follicular Lymphoma Patients Responding To Frontline Immunochemotherapy”

Gilles Salles et al.

ASH 2013
PRIMA: study design

**INDUCTION**

Registration

- High tumor burden untreated follicular lymphoma

Immunotherapeutic therapy
- 8 x Rituximab
- 8 x CVP or
- 6 x CHOP or
- 6 x FCM

CR/CRu PR

PD/SD off study

**MAINTENANCE**

Rituximab maintenance
- 375 mg/m² every 8 weeks for 2 years‡

Random 1:1*

Observation‡

* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up
PRIMA: Primary endpoint (PFS): 3 years
Original publication

Event-free rate

Stratified HR = 0.55
95% CI: 0.44–0.68
*p < 0.0001

Salles et al., Lancet 2011
PRIMA 6 years follow-up
Progression free survival from randomization

Median follow-up since randomization: 73 months

HR = 0.57
P < 0.001
6 years = 59.2%
6 years = 42.7%
PRIMA 6 years follow-up
Time to next treatment

Median follow-up since randomization: 73 months

TTNT according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

HR = 0.625
P < .0001

70 months = 63.5%
70 months = 51.0%
PRIMA 6 years follow-up
Overall survival

Median follow-up since randomization: 73 months

OS according to maintenance (ITT patients)
With Number of Subjects at Risk and 95% Confidence Limits

HR = 1.027
P = .885

6 years = 88.7%
6 years = 87.4%

<table>
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<tr>
<th></th>
<th>No. of Subjects</th>
<th>Event</th>
<th>Censored</th>
<th>Median Survival (95%CL)</th>
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<tbody>
<tr>
<td>OBSERVATION</td>
<td>513</td>
<td>11.3%</td>
<td>88.7%</td>
<td>NA (NA; NA)</td>
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<tr>
<td>RITUXIMAB</td>
<td>505</td>
<td>11.7%</td>
<td>88.3%</td>
<td>NA (NA; NA)</td>
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PRIMA = 6 years follow-up
Rate of histological transformation

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<tr>
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<th>OBSERVATION</th>
<th>RITUXIMAB MAINTENANCE</th>
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<tr>
<td>Progression</td>
<td>278</td>
<td>186</td>
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<tr>
<td>With morphology documentation</td>
<td>114</td>
<td>80</td>
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<tr>
<td>Transformed histology</td>
<td>24 (21%)</td>
<td>16 (20%)</td>
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Long term follow-up of PRIMA: Data summary

- A durable and significant benefit of rituximab maintenance for PFS and TNLT persists at 6 years

- **No survival benefit** was observed, with similar numbers of patients dying from lymphoma in both arms
  - Confirms excellent outcomes compared with historical experiences

- **No differences in histological transformation**

- More than half of patients in control group (no maintenance) did not require any additional therapy at 70 months of follow-up.
Is retreatment rituximab an option in advanced stage disease, rather than rituximab maintenance?
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I suspect if RESORT design were employed in PRIMA trial, there would be no difference between a maintenance rituximab and retreatment rituximab strategy.
RCHOP is no longer standard FL induction treatment; no maintenance data with BR

Impact of post-treatment PET on outcome: PRIMA study: No clear rationale for maintenance?

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**Observation**

Rituximab maintenance

Trotman et al JCO 29:3194
No routine role for maintenance rituximab in FL

No survival benefit in a disease where most pts are doing extremely well

Does not impact transformation

In low tumor burden disease, retreatment rituximab is equivalent

No clear quality of life benefit

Costs more; more toxicity than observation

No data of maintenance following bendamustine/rituximab

New treatment options (lenalidomide, ibrutinib) will likely further change treatment paradigm, further questioning role of maintenance rituximab
Thank you!
Questions?