All that you need to know about follicular lymphoma in 2018

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Why this Webinar?

• In the era of digital medicine, a vast amount of information is available at a click.

• The main role of a teacher is to assimilate this enormous knowledge, concise it and give it in a nutshell to the students.

• Even more difficult is the job to decide optimal investigations and optimal management of a pt who is sitting across the table.
Frequency of NHL Subtypes in Adults

- Diffuse large B-cell (31%)
- Indolent (35%)
- Composite lymphomas (13%)
- Other subtypes with a frequency ≤2% (9%)
- Peripheral T-cell (6%)
- Mantle cell (6%)
India
Normal lymph node

Lymph node with follicular lymphoma
Follicular lymphoma

- FL is the 2nd most common NHL
- 5 new cases per 100,000 persons per year
- Median age: 60 years (India: 52 years)
- Only 10% of pts occur < 40 years of age
- A germinal centre B cell lymphoma
Follicular lymphoma

- Mixture of neoplastic centrocytes & centroblasts
- Non-neoplastic cells include T cells & macrophages
- Low grade (1 & 2) & high grade (3A & 3B)
- This is based on number of centroblasts (hpf)
Follicular lymphoma

- Indolent clinical course
- Largely incurable
- With modern CIT, median survival has increased to almost 18 years
- Clinical course is however, heterogenous
- There are multiple relapses and increasing chemotherapy resistance leading to progression and/or transformation to aggressive subtype which has dismal outcome
FL: Pathogenesis

- FL lymphomagenesis is a multi-step process
- The hallmark is t(14;18) (q32;q21) translocation
- This leads to overexpression anti-Apoptotic bcl2
- This is present in 85–90% of FL
- It begins in the bone marrow
- There are genomic and epigenomic changes
- Microenvironment is equally important
t(14;18) (q32;q21) translocation
FL: Pathological variants

• In situ follicular neoplasia

• t(14;18) negative follicular lymphoma (10–15%)

• Absence of CD10 expression

• Duodenal–type FL (closer to MALT lymphoma)
FL: Pathological variants

• PTFL (Pediatric-type follicular lymphoma): WHO 2016
  • Usually localized
  • Relapses are uncommon after excision
  • High proliferation index
  • Usually t(14;18) negative
FL: Progression

• Progression without transformation
• Transformation to aggressive lymphoma
  • Usually DLBCL or other high-grade B cell NHL
  • Myc translocation is a common event
  • Double-hit lymphoma (Myc & Bcl2)
  • About 16% are ABC phenotype
As stated earlier, median OS has improved from 11 years to 18 years. This applies to both early and advanced stages. This is attributed to:

- Advanced diagnostic measures
- Use of anthracyclin based therapy
- Use of monoclonal antibodies
- Use of targeted therapies and small molecules
- Superior treatment of transformed FL
Follicular Lymphoma: Risk stratification
FL is a heterogenous disease
Risk stratification at diagnosis

• If this is accurate, one can tailor the therapy as per the risk involved
• This is an area of ongoing research
• Classical example is CLL where FISH & IgVH hypermutation help you in deciding the nature of front line therapy i.e. CIT Vs BTK inhibitor
• Clinical
• Time to progression
• Response to therapy
• Biologic marker (grading)
• Tumour microenvironment
• Mutational burden
• Radiographic
• Minimal residual disease
• Circulating Tumour DNA
FLIPI Score

- Follicular lymphoma international prognostic index
- This was developed in pre-Rituximab era
- Five adverse factors were identified
- Three risk groups: Low, intermediate and high
- These predicted OS (Overall survival)
# Follicular Lymphoma International Prognostic Index (FLIPI) Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adverse Factor</th>
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<tr>
<td>No. of nodal sites</td>
<td>&gt;4</td>
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<tr>
<td>LDH level</td>
<td>Elevated</td>
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<tr>
<td>Age</td>
<td>≥60 y</td>
</tr>
<tr>
<td>Stage</td>
<td>III-IV</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>&lt;120 g/dL</td>
</tr>
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</table>
FLIPI Score (risk groups)

- Low risk (0–1) : 36% (10 y OS: 70%)
- Inter risk (2) : 37% (10 y OS: 50%)
- High risk (3 or more) : 27% (10 y OS: 35%)
FLIPI–2 Score

- Age > 60 years
- Elevated $\beta_2$MG
- Lymph node mass > 6 cms
- BM involvement
- Hemoglobin < 12 g/dl
FLIPI–2 Score

- Some factors overlap with original FLIPI
- Additional factors
  - Bone marrow involvement
  - Lymph node mass of 6 cms or greater
  - Elevated $\beta_2$MG
- Not so useful as $\beta_2$MG is not commonly measured
- It looked at PFS and not OS
FLIPI–2 Score

- Low risk (0) : 20% (5 y PFS: 79%)
- Inter risk (1–2) : 53% (5 y PFS: 51%)
- High risk (3 or more) : 27% (5 y PFS: 18%)
2. Time to progression
Length of first remission
Time to progression

- Standard CIT (Chemoimmunotherapy) using R–CVP, R–CHOP or BR gives median PFS of 4–5 yrs
- CIT followed by maintenance Rituximab (PRIMA study) showed 50% PFS at 10 years
- However, 20% of pts have early progression of disease (POD) i.e. within first 2–years
- This early POD is predictor of inferior OS (50% OS at 5 yrs as against 90%)
- This remains an unmet need in FL therapy
OS of FL wrt early POD (<24 months)
S1608: Randomized phase II trial in early progressing or refractory FL

FL progressing within 2 years or refractory to bendamustine based therapy

- TGR-1202 + Obinutuzumab (N = 45)
- Lenalidomide + Obinutuzumab (N = 45)
- CHOP + Obinutuzumab (N = 45)

TGR-1202 is PI3K inhibitor
3. Response to therapy
EOT PET–CT scan
EOT PET–CT scan

- EOT PET–CT scan was studied in a pooled analysis of 3 large multicenter clinical trials
- After CIT, 83% of pts have negative EOT PET–CT
- 4-year PFS of those with +ve PET was 23% has against 63% for those with –ve PET
- A +ve EOT PET scan is not such an indolent disease

Prognostic Value of Post-Treatment PET Scan

EOT PET scan as a prognostic tool

![Graph showing progression-free survival probability over time since registration for PET negative and PET positive patients. Log-rank test P < .001.]

- **PET negative**
  - No. of Patients: 90
  - Events: 28 (31%)
  - Censored: 62 (69%)
  - Median Survival: NA (51.75 to NA)

- **PET positive**
  - No. of Patients: 32
  - Events: 21 (66%)
  - Censored: 11 (34%)
  - Median Survival: 20.45 (12.29 to 35.09)
EOT PET scan as a prognostic tool

$P < 0.001$

![Graph showing cumulative probability vs. follow-up months for PET- and PET+ patients. Patients at risk are listed for each group.]
4. Biologic prognostic marker
Histological grade

• Low-grade (grade 1, 2 & 3a)
  • Almost similar outcomes
  • Indolent behavior
  • Perpetual risk of relapse

• High-grade (grade 3b)
  • Aggressive behavior
  • Behaves like DLBCL
  • Curable with Anthracyclin based therapy
5. Tumour microenvironment
5. Tumour microenvironment

- Using whole genome microarray analysis
- Two key “gene signatures” were identified in non-neoplastic microenvironment
- Immune response 1 (IR1): T cells: Favorable
- Immune response 2 (IR2): Macrophages & Dendritic cells: Unfavorable
- This was shown to be independent of tumor related factors – clinical or biologic
6. Mutational burden (by NGS)
7/74 mutated genes that matter

- EP300
- FOX01
- CREBBP
- CARD11
- MEF2B
- ARID1A
- EZH2

Pastore, A. et al. Lancet Onc. 2015
7. Total Metabolic tumor volume (TMTV)

\[
MTV = \sum_{i=1}^{n} S_i \times d
\]

\[
TLG = \sum_{i=1}^{n} MTV_i \times SUV_{\text{mean}_i}
\]
7. TMTV by PET scan

- Pre treatment **Total Metabolic Tumor Volume**
- This is assessed by PET scan
- There were 3 randomized European clinical trials
- Median TMTV was 297 cm$^3$
- The cut off of prognostic value was 510 cm$^3$
- 5–year OS of pts with high TMTV was inferior
- Currently, this is a research tool
8. Minimal Residual Disease

- t(14;18) is present in 85% of FL
- This reflects bcl2 translocation
- This produces a specific clonal sequence that can be found in blood or marrow by PCR
- This was studied as the target for MRD
- MRD –ve at 12 & 24 months has improved PFS
9. Circulating tumor DNA
9. Circulating Tumor DNA (ctDNA)

- Circulating Tumor DNA (ctDNA) is an emerging technical advance
- This detects lymphoma in the absence of circulating tumor cells
- NGS techniques identified clonal VDJ regions of immunoglobulin receptors
- This captures DNA shed from multiple disease sites and hence has added benefit
Integrated prognostic markers
7/74 mutated genes that matter

- EP300
- FOX01
- CREBBP
- CARD11
- MEF2B
- ARID1A
- EZH2

Pastore, A. et al. Lancet Onc. 2015
m7–FLIPI: A clinicogenetic risk model

• The GLSG & BCCA created m7–FLIPI
• This model incorporates FLIPI score, performance status & frequently occurring 7 mutated genes
• By this, 50% of high risk standard FLIPI subjects were reclassified as low risk m7–FLIPI
• These low risk m7–FLIPI subjects had survival which was similar to low–risk FLIPI
Summary of risk stratification

• FLIPI remains the standard tool
• POD–24 months is a robust marker
• EOT PET is extremely useful
• m7–FLIPI is a research tool
Management
<table>
<thead>
<tr>
<th>High tumor burden</th>
<th>Low tumor burden</th>
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<td>Asymptomatic</td>
<td>Asymptomatic</td>
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<tr>
<td></td>
<td>Symptomatic</td>
</tr>
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</table>

High tumor burden: 
- Asymptomatic
- Symptomatic

Low tumor burden: 
- Asymptomatic
- Symptomatic
GELF criteria for high tumor burden

- Any nodal or extra-nodal mass >7 cms
- More than 3 nods >3 cms
- Systemic symptoms
- Substantial splenomegaly
- Serious effusions
- Local risk of compression (epidural, ureteral)
- Leukaemia or blood cytopenia
1. Asymptomatic, low tumor burden
1. Asymptomatic, low tumor burden

- Surgical excision
- Radiotherapy
- Watchful Wait (WW)
- Rituximab: Weekly x 4
- Rituximab: Weekly x 4 followed by RM Vs RR
  - RM: Rituximab maintenance
  - RR: Rituximab re-treatment at progression
Figure 3. Event-free survival after prolonged rituximab versus observation

Median follow-up: 9.4 years

Prolonged rituximab
Observation

p = 0.0007

25% still in remission at 8 years

Early Rituximab followed by RR at progression

- Early Rituximab induction therapy followed by RR at progression has an advantage of
  - Psychological benefit
  - Postpones (toxic) chemotherapy
  - Cost effective
  - Targeted agents may get approved upfront saving pt from (toxic) chemotherapy even further
2. Asymptomatic, high tumor burden

- A clinical dilemma
- Fortunately, this is rare
- Many pts complaint of fatigue
- Unfortunately, fatigue a subjective phenomenon
- WW can still be a sound policy
- FLIPI/FLIPI–2 can be helpful in making decision
3. Symptomatic, low tumor burden

- This is more often due to compression & rarely due to constitutional symptoms
- This is also rare and hence there are no studies
- Clinical judgment will decide between R–monotherapy Vs CIT
symptomatic

HIGH

tumor

BURDEN
THE STORY OF
WHAT & HOW
• R–chemotherapy replaces chemotherapy
• What is the best chemotherapy remains unanswered
• In past, it was R–CVP, R–CHOP or R–FM
• Recently, Bendamustine has taken the spotlight
• European STiL study showed doubling of PFS with BR vs R–CHOP (69.5 mths Vs 31.2 mths, P<0.0001, hazard ratio 0.58, 95% CI 0.44 – 0.74)
• However, there was no difference in OS
How to treat? / What to use?

- R–CVP
- R–CHOP
- BR
- Any other
  - R–FM
R–CVP: median 35 months

CVP: median 14 months

Log-rank P-values
Without stratification by center: $P < .0001$
With stratification by center: $P < .0001$

Patients at risk:

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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
No difference by arms
Toxicities

- Anemia:
  - R-CVP: 0.6%
  - R-CHOP: 3.1%
  - R-FM: 4.2%

- Neutropenia:
  - R-CVP: 28.0%
  - R-CHOP: 49.7%
  - R-FM: 63.7%

- Thrombocytopenia:
  - R-CVP: 0.0%
  - R-CHOP: 3.1%
  - R-FM: 7.7%

- Infections:
  - R-CVP: 2.5%
  - R-CHOP: 3.1%
  - R-FM: 4.8%

Federico, M et al. Abst # 135 ICML Lugano 2011
StiL NHL 1-2003 Phase III Study

Eligibility
- Untreated indolent NHL or MCL (N = 549)

R

Bendamustine + Rituximab (BR)

R-CHOP

BR vs. R-CHOP: The StiL Study

Bendamustine-Rituximab (BR)
- Bendamustine 90 mg/m² Days 1-2
- Rituximab 375 mg/m² Day 1

CHOP-Rituximab (R-CHOP)
- Cyclophosphamide 750 mg/m² Day 1
- Doxorubicin 50 mg/m² Day 1
- Vincristine 1.4 mg/m² Day 1
- Prednisone 100 mg/m² Days 1-5
- Rituximab 375 mg/m² Day 1

(N=549)

BR vs. R-CHOP: PFS

Median (months)
- B-R: 69.5
- CHOP-R: 31.2

OS at 5 years was 80% for BR and 78% for R-CHOP

HR, 0.58 (95% CI 0.44 to 0.74)
P=0.0000148 (stratified log rank)

Figure 1. Time to next treatment

HR = 0.53 (95% CI: 0.40–0.68)

p <0.0001

BR = bendamustine, rituximab; CI = confidence interval; HR = hazard ratio; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
OS: BR Vs R–CHOP

10 yrs  deaths

- B-R  70.3%  62
- CHOP-R  66.3%  71

Probability vs Time (months)
“Bright” Study

(N=447)

- RANDOMIZE

(N=224)

- Bendamustine 90 mg/m² Days 1-2
  Rituximab 375 mg/m² Day 1

(N=223)

- CHOP-Rituximab (R-CHOP)
  (Standard Dosing)

  or

- CVP-Rituximab (R-CVP)
  (Standard Dosing)

Flinn, I. et al ASH 2012
## BRIGHT Study: ORR, CR, PR

<table>
<thead>
<tr>
<th>Overall Response</th>
<th>BR</th>
<th>R–CHOP/R–CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>97%</td>
<td>91%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>65%</td>
<td>66%</td>
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</table>
Toxicity of BR vs R–CHOP / R–CVP

• Toxicity rate appears similar
• However, toxicity profile is different
• R–CHOP / R–CVP has more hematological toxicity
• Still BR had more infection
• BR had less alopecia, but more skin reactions and nausea / vomiting
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>BR</th>
<th>R–CHOP</th>
<th>R–CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>25–29%</td>
<td>13%</td>
<td>13%</td>
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<tr>
<td>Infections (Gr3+)</td>
<td>7–12%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Rash</td>
<td>12–18%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>4%</td>
<td>20%</td>
<td>26%</td>
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<tr>
<td>Alopecia</td>
<td>4%</td>
<td>51%</td>
<td>21%</td>
</tr>
<tr>
<td>Neutropenia (Gr3+)</td>
<td>39–49%</td>
<td>86%</td>
<td>56%</td>
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<tr>
<td>Lymphopenia (Gr3+)</td>
<td>61–63%</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>Platelets (Gr3+)</td>
<td>5–10%</td>
<td>12%</td>
<td>2%</td>
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</table>
Conclusion (BR vs R–CHOP / R–CVP)

- BR offers higher overall responses and longer time to next treatment but without increasing overall survival
- It causes different toxicity profile with less hematological toxicity, less alopecia but more vomiting & more infections
- Bendamustine is more immunosuppressive & if followed by Rituximab maintenance, there is some increase in mortality
MAINTENANCE
Figure 4. PRIMA study design

**INDUCTION**

Registration

- High tumour burden untreated follicular lymphoma

Immunotherapy

- 8 x rituximab
- 8 x CVP (n = 272)
- 6 x CHOP (n = 769)
- 6 x FCM (n = 28)

CR/CRu
PR

PD/SD off study

**MAINTENANCE**

Rituximab maintenance†

- 375 mg/m² every 8 weeks for 2 years (n = 505)

Random 1:1*

Observation†

(n = 513)

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*Stratified by response after induction, regimen of chemotherapy, and geographic region
†Frequency of clinical, biological, and CT-scan assessments identical in both arms

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CR = complete response; CRu = unconfirmed complete response; CVP = cyclophosphamide, vincristine, prednisone; FCM = fludarabine, cyclophosphamide, mitoxantrone; PD = progressive disease; PR = partial response; SD = stable disease

Adapted from Salles, et al. Blood 2010;116:1788
Figure 1. Progression-free survival in the rituximab maintenance group versus the observation group

Rituximab maintenance median: 44 months

Overall log-rank test: $p < 0.0001$

Hazard ratio: 0.55

Observation median: 16 months

Number of patients at risk

<table>
<thead>
<tr>
<th>Years</th>
<th>Observation</th>
<th>Rituximab</th>
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<tbody>
<tr>
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<td>1</td>
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<tr>
<td>8</td>
<td>1</td>
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</table>

$O =$ observation; $R =$ rituximab maintenance
FL: 10–Y follow–up of PRIMA study

• Abstract 486

• Salles GA, et al. Long term follow–up of the PRIMA Study: 50% of pts receiving rituximab maintenance remain progression free at 10 years

• Presented at the 2017 Meeting of the American Society of Hematology; December 9–12, 2017; Atlanta, GA
PRIMA Study: PFS at 10 years

R-maintenance
Median: 10.5 yr
51%

Observation
Median: 4.1 yr
35%

P<0.0001
HR=0.61 (95% CI) 0.52–0.73

Special populations

• High-risk subset
• Grade 3 Follicular lymphoma
• Medical co-morbidities
• Renal dysfunction / Hemodialysis
• Congestive heart failure
Role of stem cell transplantation

• HDT with ASCT: after first line therapy (X)
  • High risk subjects
• HDT with ASCT as 2\textsuperscript{nd} or bridge to allo
• Allogenic transplant (R/R setting)
Relapsed follicular lymphoma
Novel agents for R/R FL

- Newer anti CD20 monoclonal antibodies
- Lenalidomide
- PI3k inhibitors
- BTK inhibitors
- Bcl2 inhibitors
- Check point inhibitors
- CAR–T therapy
Obinutuzumab
(Gallium Study)
Hidemann, W. et al. ICML 2017

Untreated Follicular NHL
Marginal Zone NHL
N=1200

1:1 Randomization

Obinutuzumab
+ R-Chemo (Bendamustine, CVP, CHOP)

Obinutuzumab
Every 2 months for 2 years

Responding Patients

Rituximab
+ R-Chemo (Bendamustine, CVP, CHOP)

Rituximab
Every 2 months for 2 years
PFS: G > R
OS: Same
Phase II Study of R2 in FL

Fowler N, et al ASH 2012
PET scan before & after $R^2$
Overall Survival

Probability

Time (months)

Follicular lymphoma
Marginal zone lymphoma
Small lymphocytic lymphoma

P=0.6098
R²: Progression free survival

B

Progression-free Survival in Patients with Follicular Lymphoma

Probability

0.0 0.2 0.4 0.6 0.8 1.0

0 6 12 18 24 30 36 42 48 54 60

Time (months)

95% CI
PFS
Progression-free Survival in Patients with Marginal Zone Lymphoma
Progression-free Survival in Patients with Small Lymphocytic Lymphoma
RELEVANCE Study

(Rituximab & Lenalidomide Vs Any Chemotherapy)

1st line FL N=1000

R

R²

R² Maintenance

R + Chemo

Rituximab Maint.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Len</th>
<th>LR</th>
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<tr>
<td>ORR</td>
<td>53%</td>
<td>76%</td>
</tr>
<tr>
<td>CR</td>
<td>20%</td>
<td>39%</td>
</tr>
<tr>
<td>Med TTP</td>
<td>1.1y</td>
<td>2.0y</td>
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<tr>
<td>2-year TTP</td>
<td>27%</td>
<td>52%</td>
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FL: First line Ibrutinib + Rituximab

Untreated Follicular Lymphoma N=60

Ibrutinib 560 mg PO Daily

Rituximab 375mg IV x 4

Fowler NH et al. (ASH 2015). Abstract 470
ORRs (N = 60)

- CR: 18%
- PR: 55%
- SD: 27%

ORR: 82% (27% CR + 55% PR)

Effect of Ibrutinib/Rituximab on Tumor Size

- Median target lesion SPD at baseline was 24 cm² (range, 2.2-135.5)
<table>
<thead>
<tr>
<th>TGR-1202</th>
<th>Idelalisib (GS-1101)</th>
<th>Duvelisib (IPI-145)</th>
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<tbody>
<tr>
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<tr>
<td><img src="image4" alt="Chemical structure" /></td>
<td><img src="image5" alt="Chemical structure" /></td>
</tr>
</tbody>
</table>

Pi3K inhibitors
Idelalisib: Tumor Response

Graph showing progression-free survival with the median of 11 months (N=125).
Transformation

• Why does transformation happen?
• Can transformation be prevented?
• How is transformation treated?
Future perspective

• Efforts to identify biomarkers capable of detecting high-risk pts at diagnosis
• Continue to develop targeted agents used in association with predictive biomarkers
• To develop interventions that can reduce the risk of histologic transformation
• Achievements of these 3 goals would facilitate a more personalized approach to the management of pts with follicular lymphoma
Thank You!