Marginal Zone Lymphoma

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Disclosures:

**Self:**
Novartis, consultant
Kite, consultant
Pharmacyclics, consultant
Plexus Communications, consultant

**Immediate family member:**
Juno, IP rights
Seres, consultant
Marginal Zone Lymphoma

- Splenic (SMZL) w/ or w/o villous lymphocytes
- Nodal (NMZL)
- Extanodal (ENMZL) of Mucosa-associated Lymphoid Tumor (MALT)

Pre-malignant – clonal B cell lymphocytosis of MZ origin (CBL-MZ)
Marginal Zone Lymphoma
Epidemiology

- Rare: 5-10% of all NHL in Western world
- ENMZL most frequent (30-35%), SMZL (20%), NMZL (10%)
- Environmental and geographic factors
Incidence of indolent B-cell lymphoma by subtype, race, sex and age

## Immunophenotype of indolent lymphomas

<table>
<thead>
<tr>
<th>Surface Marker</th>
<th>Mantle Cell</th>
<th>Follicular</th>
<th>CLL/SLL</th>
<th>Marginal Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Ig</td>
<td>+</td>
<td>+</td>
<td>Dim +</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>CD10</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>Dim +</td>
<td>+</td>
</tr>
<tr>
<td>CD23</td>
<td>– (+)</td>
<td>– (+)</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>CD43</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>– (+)</td>
</tr>
<tr>
<td>CD103</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(--(+) = <50\% positive.\)
Marginal Zone Lymphoma diagnosis

Small-medium size, centrocyte-like B cells with variable cytoplasm (can be monocytoid or lymphoplasmacytic)

CD20+, CD5-, CD23-, CD10-, CyclinD1-

Differential Diagnosis: LPL (usually MYD88 L265P, but 10-20% of MZL can have MYD88 mutation), atypical CLL/SLL (CD5+-/-, CD23 +/-)
Clonal B-cell lymphocytosis

• Healthy individuals without clinical evidence of lymphoma
• Small monoclonal B-cell clone ***5000/μL
• Can be CLL-like (CD5+, CD23+) or «atypical»
• In a study of 102 patients with MBCL with MZL phenotype:
  • Strong CD19, CD20
  • No CD5 expression
  • BM infiltration always present
  • Frequent cytogenetic abnormalities (Chr7 most frequent)
  • 9/102 had paraprotein
  • 17/102 pts progressed to clinical lymphoma

Extranodal Marginal Zone Lymphoma (ENMZL)/MALT
Extanodal (ENMZL)/Mucosa-associated Lymphoid Tumor (MALT)

- Arises in organs that normally lack lymphoid tissue
- Chronic infection or autoimmune processes (Sjögren, Hashimoto)
- Sustained antigenic or auto-antigenic stimulation not only triggers polyclonal B-cell proliferation, but also recruits inflammatory cells, including T-lymphocytes, macrophages and neutrophils, to the site of inflammation.
- Most common pathogens is H. Pylori (gastric), followed by Chlamydia Psittaci (ocular)
- Patients with Sjogren Syndrome (SS) have a 1000-fold increased risk of developing MALT lymphoma of the parotid gland.
Microenvironmental Factors in HP infection lead to MALT lymphoma

- Hp-specific infiltrating T-cells which act via CD40/CD40 ligand axis
- Chemotaxis of neutrophils, a source of reactive oxygen species (ROS)
- Lymphoma-associated macrophages release a proliferation-inducing ligand (BAFF), which sustains Hp-associated MALT lymphoma progression
- Hp-related gastric MALT up-regulation of CCR7, CXCR3, CXCR7 and CXCL12 as well as loss of CXCR4, in contrast to Hp-associated gastritis

Genetic and epigenetic of MALT lymphoma

- 72 cases from different anatomic sites (lung 32%, ocular adnexa 28%, salivary glands 18%, thyroid 7%, stomach 5%, and other 10%) analyzed for DNA copy number variations (CNV) and for the mutational status of a panel of genes previously reported to be mutated in B-cell lymphomas
  - Average of three mutated genes per patient (range: 0-11)
  - Frequent lesions affecting chromatin remodeling, BCR/NF-κB and NOTCH pathways
  - MZL from different anatomic sites exhibit a different spectrum of genetic lesions
  - TET2 is recurrently inactivated

Cascione et Al. Haematologica, 2019
Heatmap of the genetic landscape of MALT lymphomas

Cascione et Al. Haematologica, 2019
Beyond H. Pylori

Espinoza et Al., Gastric microbiota: An emerging player in Helicobacter pylori-induced gastric malignancies, Cancer Letters 2018
Clinical presentation and staging of gastric MALT

- Clinical symptoms of gastric MALT lymphoma are **non-specific** and include epigastric pain, nausea, weight loss, diarrhea and gastrointestinal bleeding.

<table>
<thead>
<tr>
<th>Lugano staging system</th>
<th>TNM (or Paris) staging system</th>
<th>Disease extension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I₁: confined to mucosa or submucosa</td>
<td>T1 N0 M0</td>
<td>Mucosal or submucosal layer</td>
</tr>
<tr>
<td>I₂: confined to muscularis propria or serosa</td>
<td>T2 N0 M0</td>
<td>Muscularis propria</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td>Serosa</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I₁: extending into abdomen with local nodal involvement</td>
<td>T1-3 N1 M0</td>
<td>Perigastric lymph nodes</td>
</tr>
<tr>
<td>I₂: extending into abdomen with distant nodal involvement</td>
<td>T1-3 N2 M0</td>
<td>More distant regional lymph nodes</td>
</tr>
<tr>
<td><strong>Stage II E</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penetration of serosa to involve adjacent organs or tissues</td>
<td>T4 N0 M0</td>
<td>Adjacent structures</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated extranodal involvement or concomitant supradiaphragmatic involvement</td>
<td>T1-4 N3 M0</td>
<td>Lymph nodes on both sides of the diaphragm</td>
</tr>
<tr>
<td></td>
<td>T1-4 N0-3 M1</td>
<td>Bone marrow invasion, additional extranodal sites</td>
</tr>
</tbody>
</table>
MALT-IP\(\text{I}\)

- >400 pts from the International Extranodal Lymphoma Study Group 19 (IELSG-19) trial, plus >600 pts in the validation cohort
- Greatest prognostic significance for EFS
  - Age ≥70 years (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.26-2.33)
  - Ann Arbor stage III or IV (HR, 1.79; 95% CI, 1.35-2.38)
  - Elevated lactate dehydrogenase level (HR, 1.87; 95% CI, 1.27-2.77).

Thieblemont, Blood 2017
MALT Treatment approach

MALT lymphoma

Ann Arbor IIE / IIE

Gastric MALT lymphoma
- H. pylori-positive eradication
- H. pylori-negative: eradication, radiotherapy
  systemic treatment (chemo/ immuno)

Extragastric MALT lymphoma
- Any localisation: radiotherapy
  systemic treatment (chemo/ immuno)
- Ocular adnexal MALT lymphoma: evaluate for clathromycin

Ann Arbor III E / IV

Systemic treatment (chemo/ immuno)
- Wait and see

Relapse

Rebiopsy

## Microbial eradication

### Antibiotic-induced lymphoma remission in MALT lymphomas

<table>
<thead>
<tr>
<th>Involved organ</th>
<th>Targeted pathogen</th>
<th>Antibiotic regimen</th>
<th>No. of patients</th>
<th>Type of study</th>
<th>Overall lymphoma remission rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td><em>H. pylori</em></td>
<td>Mostly PPI plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10-14 d</td>
<td>1408</td>
<td>32 studies either retrospective or prospective</td>
<td>77.5</td>
</tr>
<tr>
<td>Ocular adnexa</td>
<td><em>C. psittaci</em></td>
<td>Doxycycline 100 mg Twice daily × 21 d</td>
<td>120</td>
<td>2 prospective, 4 retrospective, 1 case report</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin* 500 mg Twice daily × 6 mo</td>
<td>11</td>
<td>Prospective</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin* 2 g/d, days 1-14, every 21 d (4 courses)</td>
<td>23</td>
<td>Prospective</td>
<td>52</td>
</tr>
<tr>
<td>Skin</td>
<td><em>B. burgdorferi</em></td>
<td>Ceftixanone 2 g/d × 14 d (in most cases)</td>
<td>5</td>
<td>Case reports</td>
<td>40</td>
</tr>
</tbody>
</table>

*The clarithromycin activity may also depend on the immunomodulatory and direct antitumor effect of this macrolide antibiotic.*
Frontline antibiotic therapy for early-stage Helicobacter pylori-negative gastric MALT lymphoma

- 26 patients with stage IAE HP-gastric MALT, who received frontline triple antibiotic therapy, consisting of 14 days of amoxicillin or metronidazole, clarithromycin, and a PPI
- 38 HP+ patients, treated with frontline antibiotic therapy, matched by age, sex, race, and stage, was used as control

Strati et al. Am J Hem, 2019
Radiation for Gastric MALT Lymphoma

<table>
<thead>
<tr>
<th>N</th>
<th>CS</th>
<th>Perf¹</th>
<th>Hem²</th>
<th>Dose (Gy) Med (range)</th>
<th>CR (%)</th>
<th>EFS (%)</th>
<th>FU³ Med (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I_E</td>
<td>II_E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>51³</td>
<td>0</td>
<td>0</td>
<td>30 (22.5-43.5)</td>
<td>100</td>
<td>94</td>
<td>63 (19-117)</td>
</tr>
<tr>
<td>13</td>
<td>13³</td>
<td>0</td>
<td>0</td>
<td>25 (20-35)</td>
<td>100</td>
<td>100</td>
<td>55 (26-126)</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>30.6 (30-39)</td>
<td>100</td>
<td>100</td>
<td>12 (5-65)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>39 (36-49)</td>
<td>100</td>
<td>100</td>
<td>42 (24-72)</td>
</tr>
</tbody>
</table>

¹Perforation
²Hemmorhage
³Follow up in months
⁴Distribution of CS I_E and II_E not stated
Involved-site radiotherapy for Helicobacter pylori–independent gastric MALT lymphoma: 26 years of experience with 178 patients

- 86% St I, 7% St II, 7% St IV
- Median RT dose 3000 cGy
- 95% complete pathologic response
- With mFU of 6.2 years, 9.6% had local failures and 11.8% distant
- 10 yr OS was 79%
The HELYX trial

- A prospective, multicenter study
- Eradication tx in *H. pylori*-positive MALT lymphoma stages IE and II1E (HELYX I)
- Refractory lymphoma or *H. pylori*-negative patients were randomized to either 25.2 Gy or 36 Gy radiotherapy (HELYX II)
- 102 patients were included in HELYX I: 75/99 (75.8%) achieved CR after a median of 2.8 months. 18 (18.2%) had PR and 6 (6.0%) no change
- 29 patients were included in HELYX II (7 primarily *H. pylori*-negative, 15 patients from HELYX I with refractory disease after eradication). The CR rate in both radiation groups was 100% with less AEs in the lower dose group
- Short f/u

Schmelz, J of Gastroenterology, 2019  
Gastric ENMZL: Slow Response to HP Eradication

1 Month Post Treatment  22 Months Post Treatment

BCL10 nuclear expression and t(11;18)(q21;q21) correlates with nonresponsiveness to *Helicobacter pylori* eradication primary gastric MALT lymphoma

- Nuclear BCL10 expression is seen in about 50% of MALT lymphomas
- T(11;18)(q21;q21) is also observed and results in a chimeric transcript between the API2 and the MALT1 genes
- T(11;18)(q21;q21) closely correlated with BCL10 nuclear expression
- T(11;18)(q21;q21) was found in 4 (57.1%) of 7 patients who showed NR following *H. pylori* eradication, but only in 1 in 11 CR patients (P < 0.05)
Optimal approach to persistent minimal residual gastric MALT?

• Patient in whom H. pylori is eradicated but there is persistent minimal residual disease have a good outcome
  • N=108 pts enrolled on European GI Lymphoma Study group studies
  • At a medium follow up of 42 months:
    • 94% of patients are alive and clinically well
    • 32% entered CR with prolonged follow up

• NCCN consensus guideline for gastric MALT that is:
  • H. pylori negative
  • Refractory to antibiotic therapy
    • Involved field RT
    • In selected circumstances: Rituximab or Chemoimmunotherapy

Radiation volumes in the treatment of ocular adnexa MALT lymphomas

Orbital MALT lymphomas
Clinical target volume (CTV) includes:
• the entire bony orbit;
• any definite or suspected extraorbital extensions.

Lyphoma of the conjunctiva
Clinical target volume (CTV) includes:
• the entire conjunctival sac;
• any local extensions to the eyelid.

Recommended dose: 24 Gy or 4 Gy (2 Gy + 2 Gy)
Rituximab in Extranodal Marginal Zone B-Cell MALT Lymphoma (IELSG)

- Primary end point: ORR
- Secondary end point: toxicity

Untreated or relapsed MALT lymphoma
- Stomach (n=15)
- Extragastic (n=20)
  (N=35)

Rituximab 375 mg/m² qw × 4

## Rituximab in Extranodal Marginal Zone B-Cell MALT Lymphoma: Results

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (n=34)</th>
<th>No Prior Chemo (n=23)</th>
<th>Prior Chemo (n=11)</th>
<th>Primary Gastric Site (n=14)*</th>
<th>Primary Nongastric Site (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>73</td>
<td>87†</td>
<td>45†</td>
<td>64</td>
<td>80</td>
</tr>
<tr>
<td>CR</td>
<td>44</td>
<td>48</td>
<td>36</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>PR</td>
<td>29</td>
<td>39</td>
<td>9</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>

* One patient with primary gastric disease was not evaluable and did not complete treatment.
† ORR significantly different between chemotherapy-naive and pretreated groups (P=0.03).

E4402 (RESORT) Trial: Design

Randomized phase III trial in patients with previously untreated low tumor burden nonfollicular lymphoma: rituximab induction with or without maintenance

SLL=57
MZL=71

Rituximab
375 mg/m²
q week × 4

CR or PD

Rituximab maintenance*
375 mg/m²
q 3 months

Rituximab retreatment at progression*
375 mg/m²
q week × 4

*Continue until treatment failure (failure defined as no response to retreatment or PD within 6 months of rituximab, initiation of cytotoxic therapy, or inability to complete treatment)

CR, complete response; PD, progressive disease; RESORT, rituximab extended schedule or retreatment trial
Higher response rates to R x 4 induction in FL vs non-FL
CR/PR = 70% vs 39% (p < .001)
ORR for MZL = 52%
with 17/28 nodal, 15/38 extranodal and 5/5 splenic MZL patients responding to induction rituximab.
Responses improved following randomization, with one-third of MZL patients with PR converting to CR/CRu on both the MR (16/24) and the RR arms (6/18).

PFS, progression-free survival

RESORT Trial: maintenance has no effect on OS in Non-FL NHL

OS, overall survival

Time Since Randomization, Years

Overall Survival, %

Median FU: 5.6 years

At Risk Death 3-year 5-year
Retreatment 23 3 91% 91%
Maintenance 29 4 93% 90%

Two-sided Log-rank $P = .72$

RESORT: Different Outcomes Observed for Follicular versus non-Follicular Subtypes

- Higher response rates to R x 4 induction in FL vs non-FL
  - CR/PR = 70% vs 39% (p < .001)
    - ORR for non-FL: MZL = 51% vs SLL = 22%

- A time to cytotoxic chemotherapy benefit was observed for MR in both FL and non-FL subtypes, with a greater difference for the non-FL

- Difficult to separate effects on SLL and MZL in terms of contribution to the PFS differences
Splenic Marginal Zone Lymphoma (SMZL)
Splenic Marginal Zone (with or without villous lymphocytes)

• Symptoms at presentation from splenomegaly and/or cytopenias often related to hypersplenism or autoimmune phenomenon
  • Splenectomy: Clinical responses in up to 90% with over half not requiring treatment at 5 years.
  • Those without bulky spleens but with cytopenias, rapidly rising WBC and/or adenopathy do NOT benefit

• One third are asymptomatic at presentation
  • Watchful waiting

• High frequency of association with Hepatitis C infection
SMZL prognosis: the HPLL/ABC score

- Retrospective study of 593 Splenic Marginal Zone Lymphoma (SMZL) patients
- Hemoglobin < 9.5 g/dL, Platelet count < 80 × 10^3/μL, high LDH or extrahilar Lymphadenopathy were independently associated with lymphoma specific survival (LSS)
- Three risk groups with significantly different five-year LSS of 95%, 87% and 68%

Montalban et al. Leukemia & Lymphoma, 2014
Antiviral Therapy in HCV-Associated Indolent Lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (median)</th>
<th>NHL</th>
<th>Therapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IFN</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IFN/Rib</td>
<td>PR</td>
</tr>
<tr>
<td>Hermine et al. 2002</td>
<td>9</td>
<td>55</td>
<td>SMZLVL(9)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Kelaidi et al. 2004</td>
<td>8</td>
<td>50</td>
<td>SMZL(2) SMZLVL(3) EMZL(2) Others (2)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Saadoun et al. 2005</td>
<td>18</td>
<td>58</td>
<td>SMZLVL (18)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Vallisa et al. 2005</td>
<td>13</td>
<td>58</td>
<td>Nodal MZL(2) SMZL (4) EMZL (2) FL (1) Plasmacytoid (4)</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

This is likely to improve with more effective therapy for HCV
SMZL: Splenectomy versus Rituximab

Overall Survival

Progression-Free Survival

Christina Kalpadakis et al. The Oncologist 2013;18:190-197
SMZL: Rituximab +/- Maintenance
Strategy For SMZL

- Check hepatitis serologies
  - Antiviral therapy for Hepatitis C+
- Watch and wait for asymptomatic patients
- Rituximab monotherapy
  - Consider low dose cladribine with R
  - Alkylators relatively ineffective
- Splenectomy – once the gold standard – may be best as second line therapy or for treatment failure (PR or less) after rituximab
Novel agents for R/R MZL
# MZL Novel Agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Setting</th>
<th>Pts</th>
<th>ORR%</th>
<th>CR%</th>
<th>Median PFS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanazzi, 2014</td>
<td>$^{90}$Y-ibritumomab tiuxetan</td>
<td>MALT relapsed</td>
<td>30</td>
<td>90</td>
<td>77</td>
<td>Not reached</td>
</tr>
<tr>
<td>Samaniego, 2014</td>
<td>$^{90}$Y-ibritumomab tiuxetan</td>
<td>MALT de novo</td>
<td>11</td>
<td>100</td>
<td>—</td>
<td>Not reached</td>
</tr>
<tr>
<td>Lossos, 2015</td>
<td>$^{90}$Y-ibritumomab tiuxetan</td>
<td>MZL de novo</td>
<td>16</td>
<td>88</td>
<td>56</td>
<td>47.6</td>
</tr>
<tr>
<td>Lolli, 2020</td>
<td>$^{90}$Y-ibritumomab tiuxetan</td>
<td>MZL de novo + relapsed</td>
<td>16</td>
<td>94</td>
<td>63</td>
<td>37.3</td>
</tr>
<tr>
<td>Zinzani, 2008</td>
<td>Chemotherapy + $^{90}$Y-ibritumomab tiuxetan</td>
<td>MZL de novo</td>
<td>10</td>
<td>90</td>
<td>90</td>
<td>—</td>
</tr>
<tr>
<td>Kiesewetter, 2013</td>
<td>Lenalidomide</td>
<td>MALT de novo + relapsed</td>
<td>18</td>
<td>61</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>Kiesewetter, 2017</td>
<td>Lenalidomide + rituximab</td>
<td>MALT de novo + relapsed</td>
<td>46</td>
<td>80</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>Becnel, 2019</td>
<td>Lenalidomide + rituximab</td>
<td>MZL de novo</td>
<td>30</td>
<td>93</td>
<td>70</td>
<td>59.8</td>
</tr>
<tr>
<td>Noy, 2017</td>
<td>Ibrutinib</td>
<td>MZL relapsed</td>
<td>63</td>
<td>48</td>
<td>3</td>
<td>14.2</td>
</tr>
<tr>
<td>Gopal, 2014</td>
<td>Idelalisib</td>
<td>MZL relapsed</td>
<td>15</td>
<td>47</td>
<td>7</td>
<td>7.0</td>
</tr>
<tr>
<td>Flinn, 2019</td>
<td>Duvelisib</td>
<td>MZL relapsed</td>
<td>18</td>
<td>39</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dreyling, 2017</td>
<td>Copanlisib</td>
<td>MZL relapsed</td>
<td>23</td>
<td>70</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Forero-Torres, 2019</td>
<td>Parsaclisib</td>
<td>MZL relapsed</td>
<td>9</td>
<td>78</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>Zinzani, 2019</td>
<td>Umbraulisib</td>
<td>MZL relapsed</td>
<td>69</td>
<td>55</td>
<td>10</td>
<td>71% (@12 mos)</td>
</tr>
</tbody>
</table>
AUGMENT: study design

**Primary endpoint:** PFS by IRC (2007 IWG criteria w/o PET)

- **R-**lenalidomide (R²)
  - Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
  - Lenalidomide: 20 mg/d*, d1-21/28 (12 cycles)
  - *10 mg if CrCl between 30 to 59 mL/min.

- **R-placebo**
  - Rituximab: 375 mg/m² d1, 8, 15, 22 of cycle 1; d1 of cycles 2-5
  - Placebo: matched capsules (12 cycles)

**Stratification**
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

**Key eligibility criteria**
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

Leonard et al. ASH 2018
Primary endpoint: progression-free survival (ITT, IRC)

Leonard et al. ASH 2018
The MAGNIFY Phase IIIb Trial of Induction R² Followed By Maintenance

• 393 patients with FL grades 1-3a and MZL enrolled; 76 (19%) had MZL
• median age of MZL patients was 68 years (range, 46-90), 68 (89%) had stage III/IV disease, and 72 (95%) had prior rituximab-containing therapy

| Table. MAGNIFY Efficacy in Overall Population (FL Grades 1-3a + MZL) and MZL Only Patients |
|---------------------------------|----------|----------|----------|-----------|
|                                | Overall (FL + MZL) (n = 393) | All MZL (n = 74) | Nodal (n = 43) | Splenic (n = 16) | MALT (n = 15) |
| Median PFS, mo (95% CI)*        | 40.1 (37.6-NR)               | 41.2 (38.4-NR)   | 41.6 (26.5-NR) | 38.4 (5.4-41.2)  | NR (16.6-NR)   |
| ORR, n (%)                      | 270 (69)                      | 50 (68)          | 29 (67)        | 8 (50)           | 13 (87)        |
| CR + CRu, n (%)                 | 158 (40)                      | 29 (39)          | 18 (42)        | 4 (25)           | 7 (47)         |
| Median DOR, mo (95% CI)         | 39.0 (36.8-NR)                | 38.6 (29.4-NR)   | 39.0 (22.4-NR) | 35.8 (40.5-NR)   | NR (NR-NR)     |

CR, complete response; CRu, CR unconfirmed; DOR, duration of response; FL, follicular lymphoma; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

*If patients were in maintenance at cutoff, response assessment also contributed to PFS.

Coleman et al. ASH 2020
PI3K is Involved in Multiple Critical Signaling Pathways of B cell survival

O’Brien et al. ASCO 2013, EHA 2012
Idelalisib for “double refractory” iNHL Phase II: the DELTA study

Gopal et al. ASH 2013, Abstract 85; NEJM (2014) 370:1008-18

| ORR     | 57% (47.6-65.6) |
| CR      | 6%              |
| PR      | 50%             |
| Median time to response | 1.9 months (1.6-8.3) |
| Median time to CR        | 3.7 months (1.9-12) |
| Subtype              |
| FL                  | 54%             |
| SLL                 | 61%             |
| MZL                 | 47%             |
| WM                  | 80%             |
| Bendamustine refractory | 59%          |
| Prior therapy <4/≥4 | 50%/62%         |
| Bulk <7/7           | 57%/57%         |
| DOR                 | 12.5 months    |
| PFS                 | 11 months       |
| OS                  | 20.4 months     |

Median follow up 9.4 months

15 pts with MZL

Median PFS = 11 months

(N=125) ORR 57%

% Change in SPD

Time from Start of idelalisib, Months
(N, Patients at Risk)
Phase 2 CHRONOS-1 study: Copanlisib (BAY 80-6946) – MZL cohort

Drug Specs and Efficacy
- **MOA:** α/δ PI3K inhibitor (FDA approved)
- **Route:** IV
- **Dose:** 60 mg
- **Frequency:** Days 1,8,15 of 28 day cycle

Nine patients (39.1%) had TEAEs leading to dose reduction, with the most frequent (≥13%) being hypertension (17.4%, 4/23) and hyperglycemia (13.0%, 3/23).

Panayotidis et al., Blood Advances, 2021
Umbralisib: open-label, multi-center, multi-cohort UTX-TGR-205 UNITY-NHL trial

- 69 previously treated patients with MZL who had at least 1 prior systemic therapy
- MOA: $\delta$ PI3K + CK1-ε inhibitor
- Route: PO
- Dose: 800 mg
- Frequency: Daily

<table>
<thead>
<tr>
<th>FL</th>
<th>MZL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>117</td>
</tr>
<tr>
<td>ORR</td>
<td>43%</td>
</tr>
<tr>
<td>ENMZL</td>
<td>NA</td>
</tr>
<tr>
<td>NMZL</td>
<td>NA</td>
</tr>
<tr>
<td>SMZL</td>
<td>NA</td>
</tr>
<tr>
<td>CR</td>
<td>3%</td>
</tr>
<tr>
<td>DOR (mo)</td>
<td>11.1 m (0.3,16.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
<th>Grade %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>58%</td>
<td>10%</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>33%</td>
<td>8%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;1%</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>Anemia</td>
<td>27%</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41%</td>
<td>3%</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>79%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Fowler at al. JCO, 2021
PCYC-1121 Ibrutinib for R/R MZL: Study Design

Key eligibility criteria

- Histologically confirmed MZL of all subtypes
- Refractory or progressive MZL
- At least 1 measurable lesion (>1.5 cm in longest dimension) outside of the spleen
- ECOG PS ≤ 2
- ≥ 1 prior therapy including at least 1 anti-CD20-directed regimen (CIT or rituximab monotherapy)

Primary Endpoint

- ORR by independent review committee (IRC) by 2007 IWG criteria

Secondary Endpoints

- DOR
- PFS
- OS
- Safety

Ibrutinib 560 mg oral daily
Continuous until POD or unacceptable toxicity

R/R MZL N = 63
Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis
Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis

- Mutations in A20 (A) and MYD88 (B) correlate to favorable prognosis.
- Mutations in KMT2D (C) and CARD11 (D) correlate to poor prognosis.
Magnolia Trial: Zanubrutinib in Patients with Relapsed/Refractory MZL

- Next-generation BTK inhibitor
- Early-phase study of 20 pts with R/R MZL, at a median follow-up of 27.1 months, ORR was 80%, with a CR rate of 15%, and PR rate of 65%
- Zanubrutinib 160 mg twice daily until PD or unacceptable toxicity
- Median follow-up of 6.8 months

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R/R MZL (N = 68)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>36 (52.9)</td>
</tr>
<tr>
<td>ECOG PS 0-1, n (%)</td>
<td>63 (92.6)</td>
</tr>
<tr>
<td>Bone marrow involvement, n (%)</td>
<td>29 (42.6)</td>
</tr>
</tbody>
</table>

### Efficacy (investigator assessment)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R/R MZL (N = 67)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</td>
<td>40 (60.0) [47.00, 71.51]</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>10 (15.0)</td>
</tr>
<tr>
<td>PR</td>
<td>30 (45.0)</td>
</tr>
<tr>
<td>SD^1</td>
<td>18 (27.0)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Not evaluable^2</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Discontinued study before first assessment</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

### Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R/R MZL (N = 68)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>61 (89.7)</td>
</tr>
<tr>
<td>Grade ≥3 AE, n (%)</td>
<td>20 (29.4)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>18 (26.5)</td>
</tr>
</tbody>
</table>

AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease.
CAR T-cell therapy for R/R MZL
ZUMA-5 Study Design

Phase 2 (N = 151 enrolled)

R/R iNHL N = 146 Treated (124 FL, 22 MZL)

Key Eligibility Criteria
- R/R FL (Grades 1 – 3a) or MZL (nodal or extranodal)\(^a\)
- \(\geq 2\) Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent\(^b\)

Conditioning Regimen
- Fludarabine 30 mg/m\(^2\) IV and cyclophosphamide 500 mg/m\(^2\) IV on Days -5, -4, -3
- Axi-Cel: \(2 \times 10^6\) CAR+ cells/kg

Primary Endpoint
- ORR (IRRC-assessed per the Lugano classification\(^1\))

Key Secondary Endpoints
- CR rate (IRRC-assessed)
- Investigator-assessed ORR\(^1\)
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

\(^a\) Patients with stable disease (without relapse) > 1 year from completion of last therapy were not eligible. \(^b\) Single agent anti-CD20 antibody did not count as line of therapy for eligibility.

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.
ORR by IRRC Assessment Was 92% (95% CI, 85 – 97); CR Rate Was 76% (95% CI, 67 – 84)

- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

The investigator-assessed ORR (N = 104) was 95%, with a CR rate of 77%. Concordance between investigator-assessed and IRRC-assessed ORR was 91%. * For the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and postbaseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.

CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, overall response rate; PR, partial response; SD, stable disease.
Progression-Free Survival and Overall Survival

With a median follow-up of 17.5 months, median PFS and median OS were not reached

- The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
- The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients
Neurologic Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FL (n = 124)</th>
<th>MZL (n = 22)</th>
<th>All Patients (N = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic events, n (%)^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>70 (56)</td>
<td>17 (77)</td>
<td>87 (60)</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>19 (15)</td>
<td>9 (41)</td>
<td>28 (19)</td>
</tr>
<tr>
<td>Most common events of any grade, n/n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>36/70 (51)</td>
<td>9/17 (53)</td>
<td>45/87 (52)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>28/70 (40)</td>
<td>7/17 (41)</td>
<td>35/87 (40)</td>
</tr>
<tr>
<td>AE management, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>38 (31)</td>
<td>14 (64)</td>
<td>52 (36)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>7 (6)</td>
<td>2 (9)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Median time to onset (range), days</td>
<td>7 (1 – 177)</td>
<td>7 (3 – 19)</td>
<td>7 (1 – 177)</td>
</tr>
<tr>
<td>Median duration of events (range), days</td>
<td>14 (1 – 452)</td>
<td>10 (2 – 81)</td>
<td>14 (1 – 452)</td>
</tr>
<tr>
<td>Patients with resolved events, n/n (%)</td>
<td>67/70 (96)</td>
<td>14/17 (82)</td>
<td>81/87 (93)</td>
</tr>
</tbody>
</table>

- Grade 4 neurologic events were reported for 3 patients; no Grade 5 events were reported.
- Events were ongoing at the cutoff date in 6 patients: Grade 1 memory impairment (n = 2) and attention disturbance, intermittent paresthesia, and tremor (n = 1 each) and Grade 2 facial paresthesia (n = 1).
# Cytokine Release Syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FL (n = 124)</th>
<th>MZL (n = 22)</th>
<th>All Patients (N = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>**CRS, n (%)**a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>97 (78)</td>
<td>22 (100)</td>
<td>119 (82)</td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>8 (6)</td>
<td>2 (9)</td>
<td>10 (7)</td>
</tr>
<tr>
<td><strong>Most common symptoms of any grade, n/n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>94/97 (97)</td>
<td>20/22 (91)</td>
<td>114/119 (96)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>39/97 (40)</td>
<td>10/22 (45)</td>
<td>49/119 (41)</td>
</tr>
<tr>
<td><strong>AE management, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>56 (45)</td>
<td>15 (68)</td>
<td>71 (49)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>19 (15)</td>
<td>6 (27)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>Median time to onset (range), days</td>
<td>4 (1 – 15)</td>
<td>4 (1 – 9)</td>
<td>4 (1 – 15)</td>
</tr>
<tr>
<td>Median duration of events (range), days</td>
<td>6 (1 – 27)</td>
<td>6 (2 – 14)</td>
<td>6 (1 – 27)</td>
</tr>
<tr>
<td>Patients with resolved events, n/n (%)b</td>
<td>96/97 (99)b</td>
<td>22/22 (100)</td>
<td>118/119 (99)b</td>
</tr>
</tbody>
</table>

- Grade 4 and Grade 5 CRS occurred in 1 patient each
- No patients had ongoing CRS as of the cutoff dateb
MZL: Summary

• The three subtypes of MZL are distinctive in clinical presentation and therapeutic response
  • Localized ENMZL is treated with local therapy (including excision in selected cases)
  • SMZL and ENMZL of the stomach are associated with infection and may respond to appropriate therapy if the infection is identified and appropriately treated
  • SMZL and ENMZL are highly responsive to rituximab
  • NMZL is managed as FL

• BTKi is active in the setting of R/R MZL

• PI3Ki are active in R/R disease and umbralisib was recently approved

• The role of lenalidomide is controversial in MZL

• CAR T-cell therapy was NOT approved for MZL because of inferior responses in small numbers of patients
WHO Indolent B Cell Lymphoid Neoplasms

- Chronic lymphocytic leukaemia/ small lymphocytic lymphoma
- [Monoclonal B-cell lymphocytosis*](#)
- B-cell prolymphocytic leukaemia
- [Splenic marginal zone lymphoma](#)
- Hairy cell leukaemia
- [Splenic lymphoma/leukaemia, unclassifiable*](#)
  - Splenic diffuse red pulp small B-cell lymphoma
  - Hairy cell leukaemia-variant
- Lymphoplasmacytic lymphoma
- Waldenström’s macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extrasosseous plasmacytoma
- [Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)](#)
- Nodal marginal zone lymphoma
  - [Paediatric nodal marginal zone lymphoma](#)
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type nodal follicular lymphoma
- Large B-cell lymphoma with IRF4 rearrangement*
- Primary cutaneous follicle center lymphoma

• Follicular lymphoma in-situ > In situ follicular neoplasia
  - CD10-positive, BCL2-positive B cells in reactive lymph node without architectural distortion
  - Low risk of progression to overt FL

Swerdlow et al. Blood 2016 127:2375-2390

*Changes from the 2008 classification; Provisional entities listed in *italics*
Magnolia trial
Copanlisib
Magnify trial Phase IIIB R2 followed by maintenance (ASH 2020)
Leonard R2 first line vs R monotx (augment trial)

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