

Mantle Cell Lymphoma

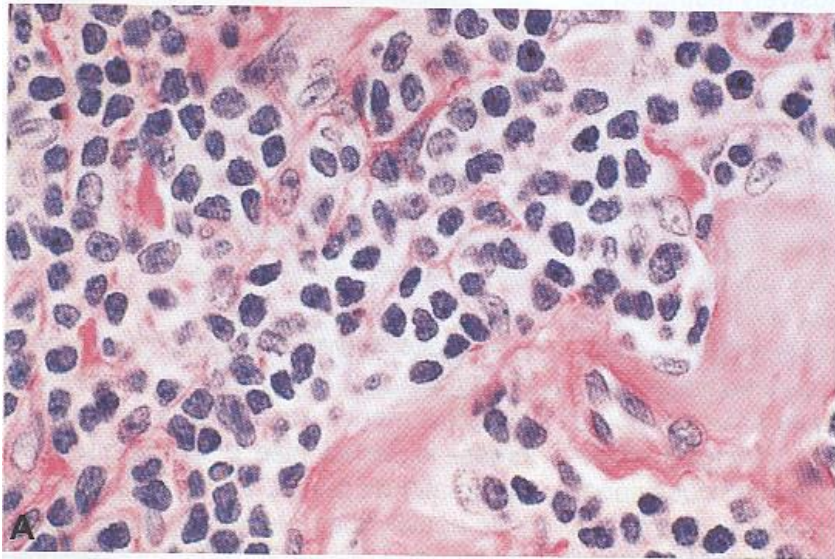
Michele Ghielmini

*Oncology Institute of Southern Switzerland
Ospedale San Giovanni - 6500 Bellinzona, Switzerland*

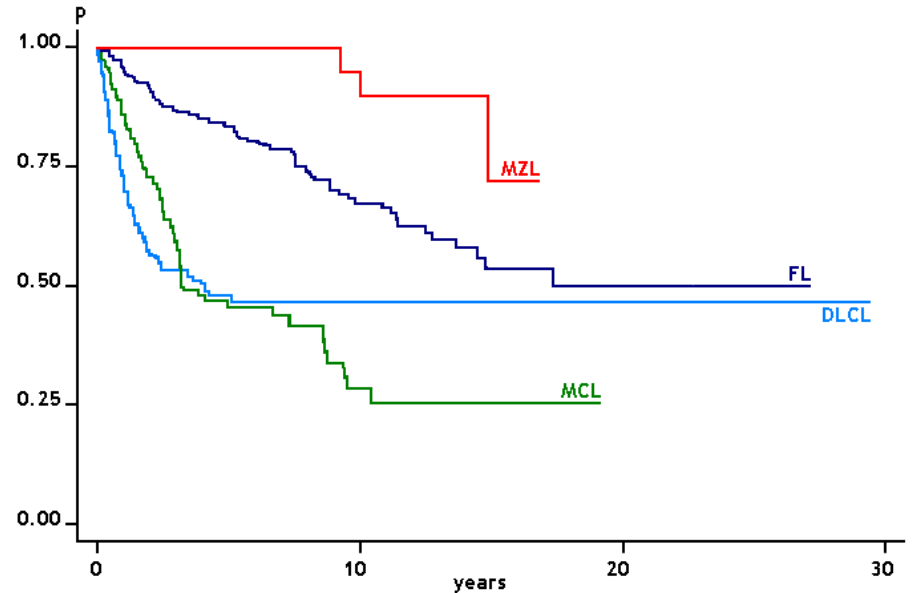
Summary of the talk

- The disease
 - Treatment of the young/fit
 - Treatment of the elderly/unfit
 - Relapse and new drugs
 - Indolent MCL

MCL, a bad luck disease: the worse of FL and DLBCL

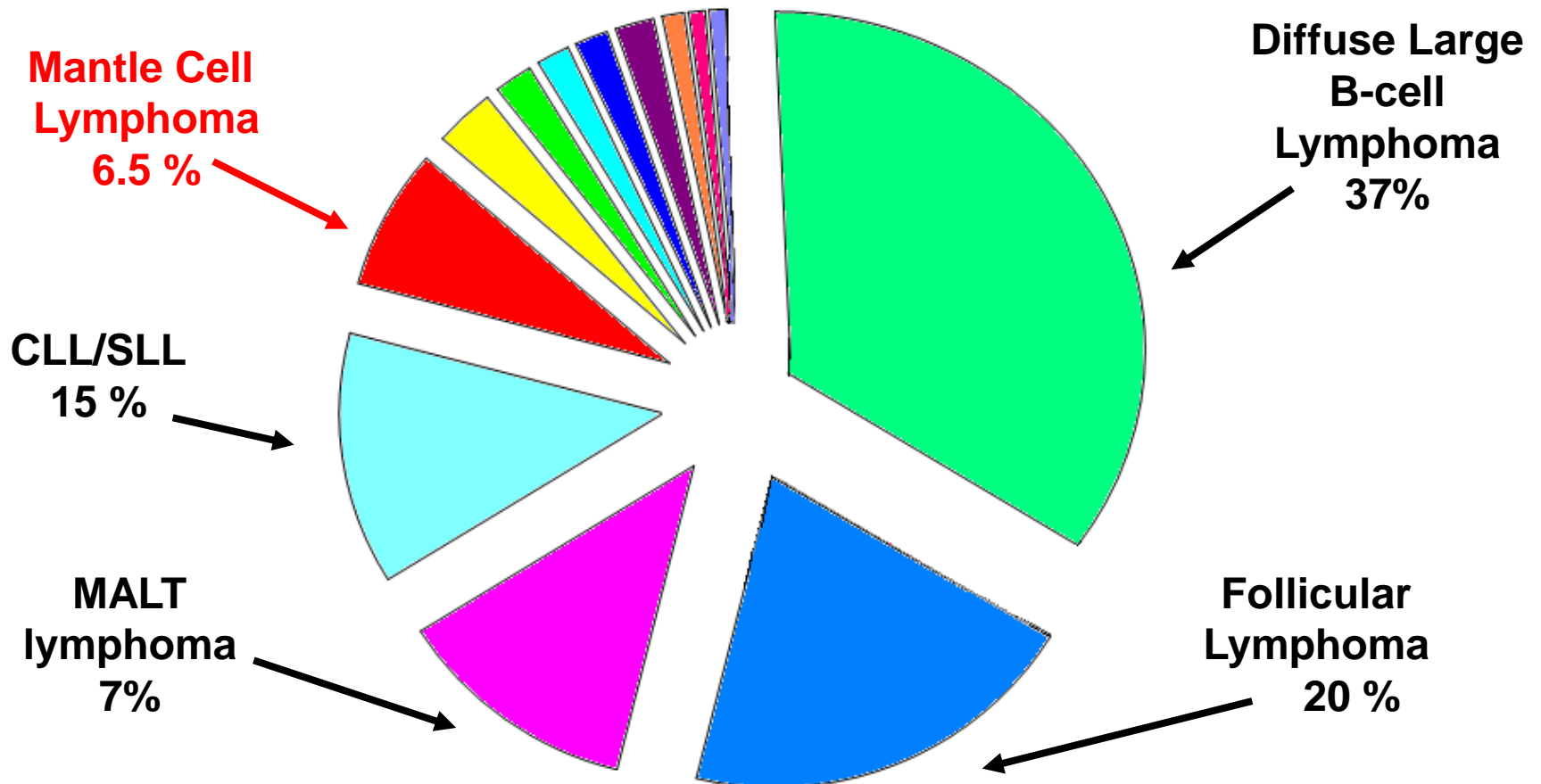


Centrocytic lymphoma



IOSI Database

NHL frequency at the IOSI

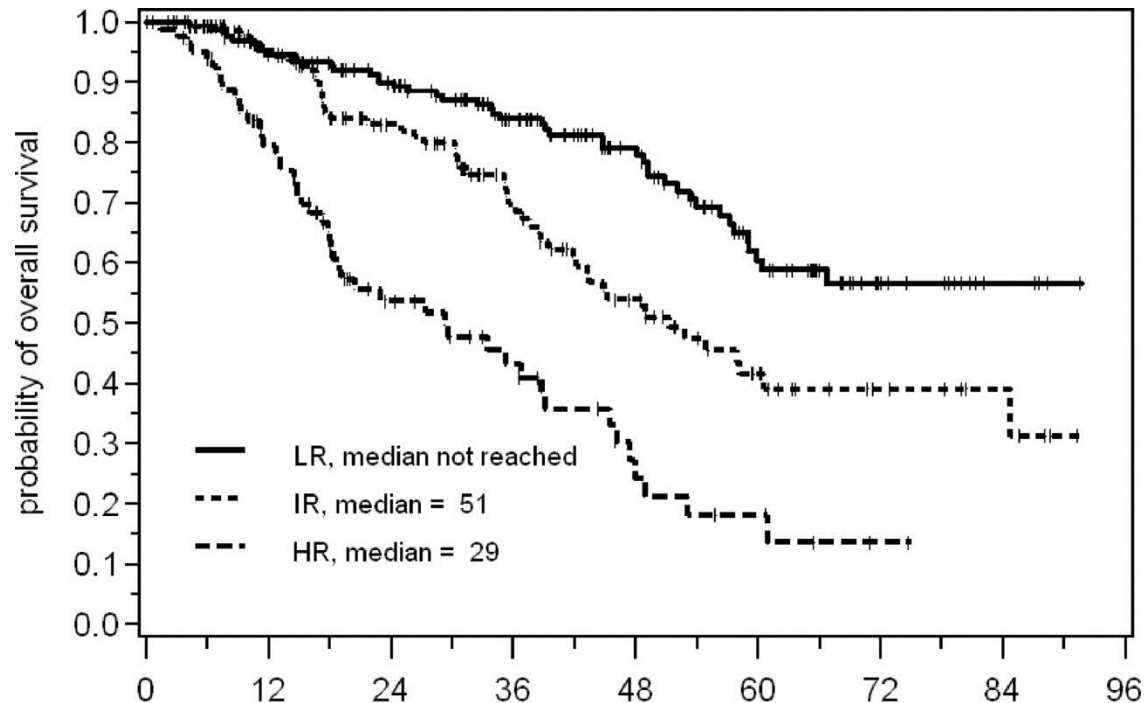


Clinical prognostic factors: MIPI

N = 455

Adverse factors:

- Age
- ECOG PS
- LDH
- WBC



Score calculated with a rather complex formula

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MCL: ESMO guidelines 2013

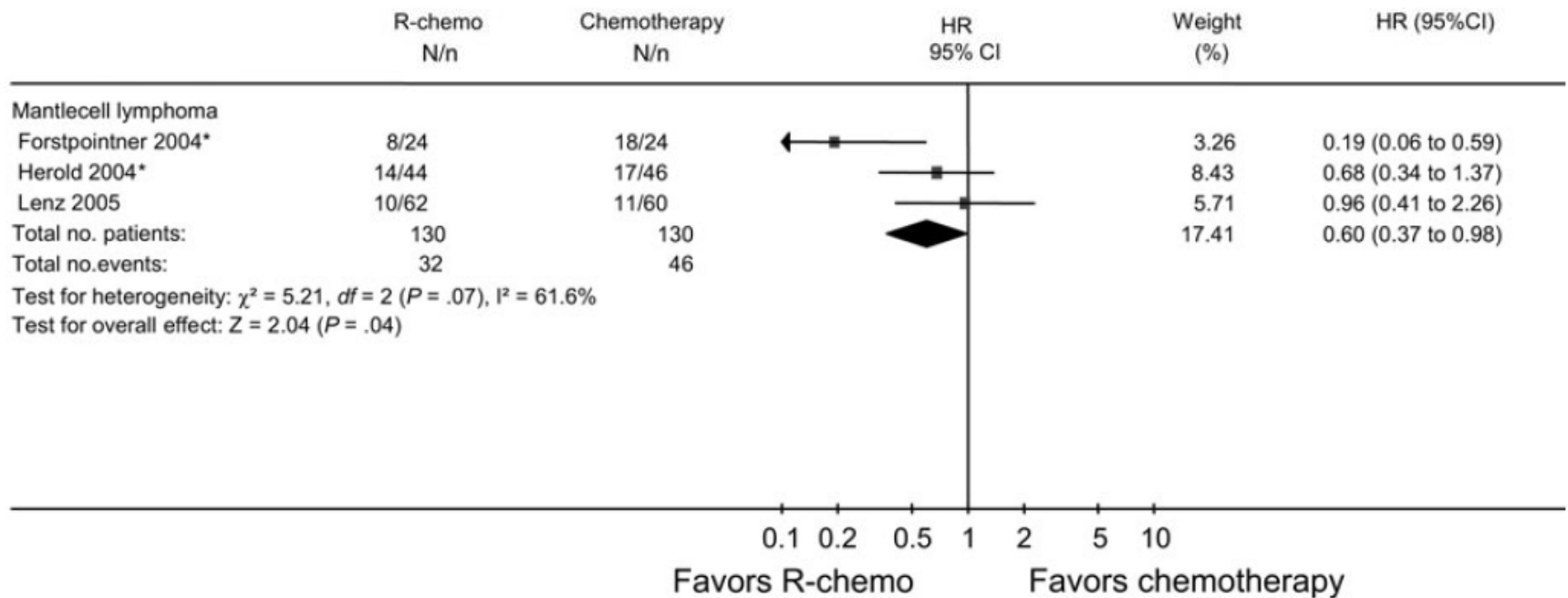
First line

| ≤ 65 y | > 65 y |
|--|---|
| R-chemo Containing HD-Ara C + HDT | R-benda or R-CHOP + R-maintenance (after R-CHOP) |

Relapse

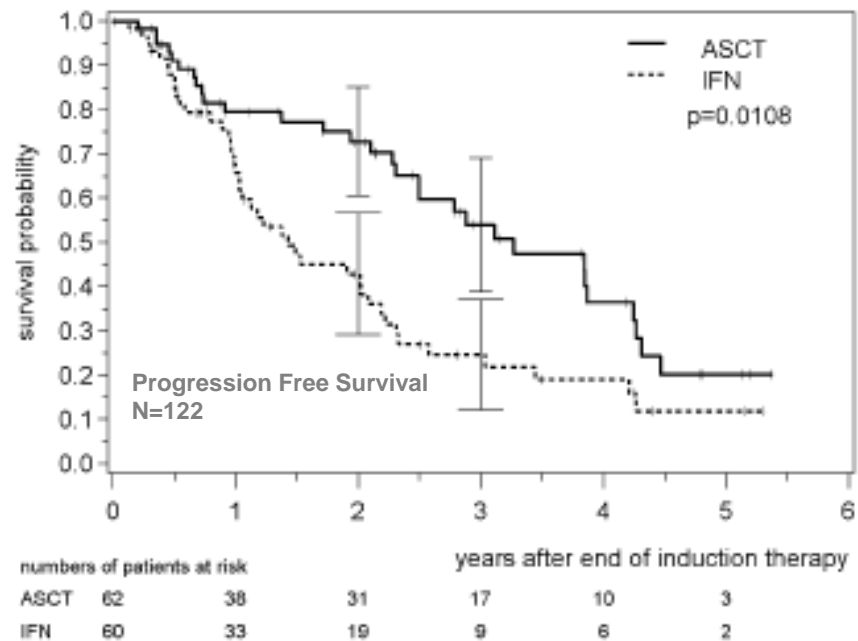
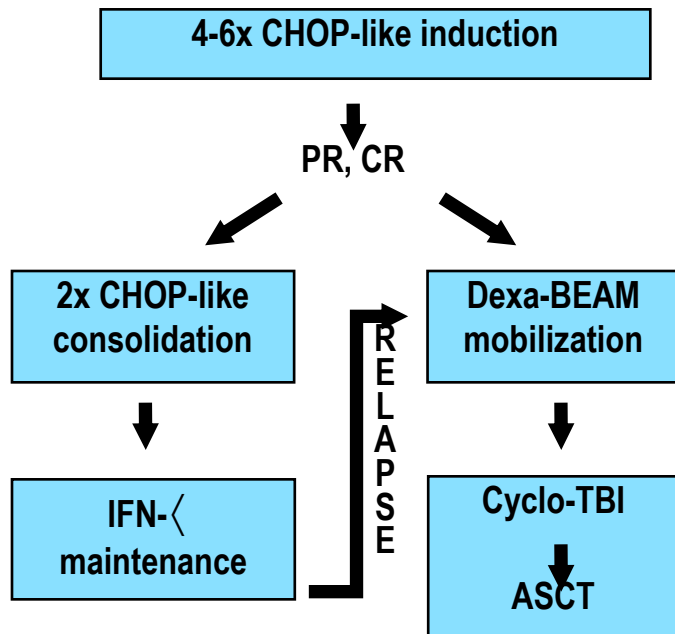
| | | |
|-------------|--|----------------------------|
| 1st relapse | (R) – chemo | (consider Allo transplant) |
| 2nd relapse | Temsirolimus Bortezomib Lenalidomide | |

Rituximab + Chemo meta-analysis (Overall Survival)



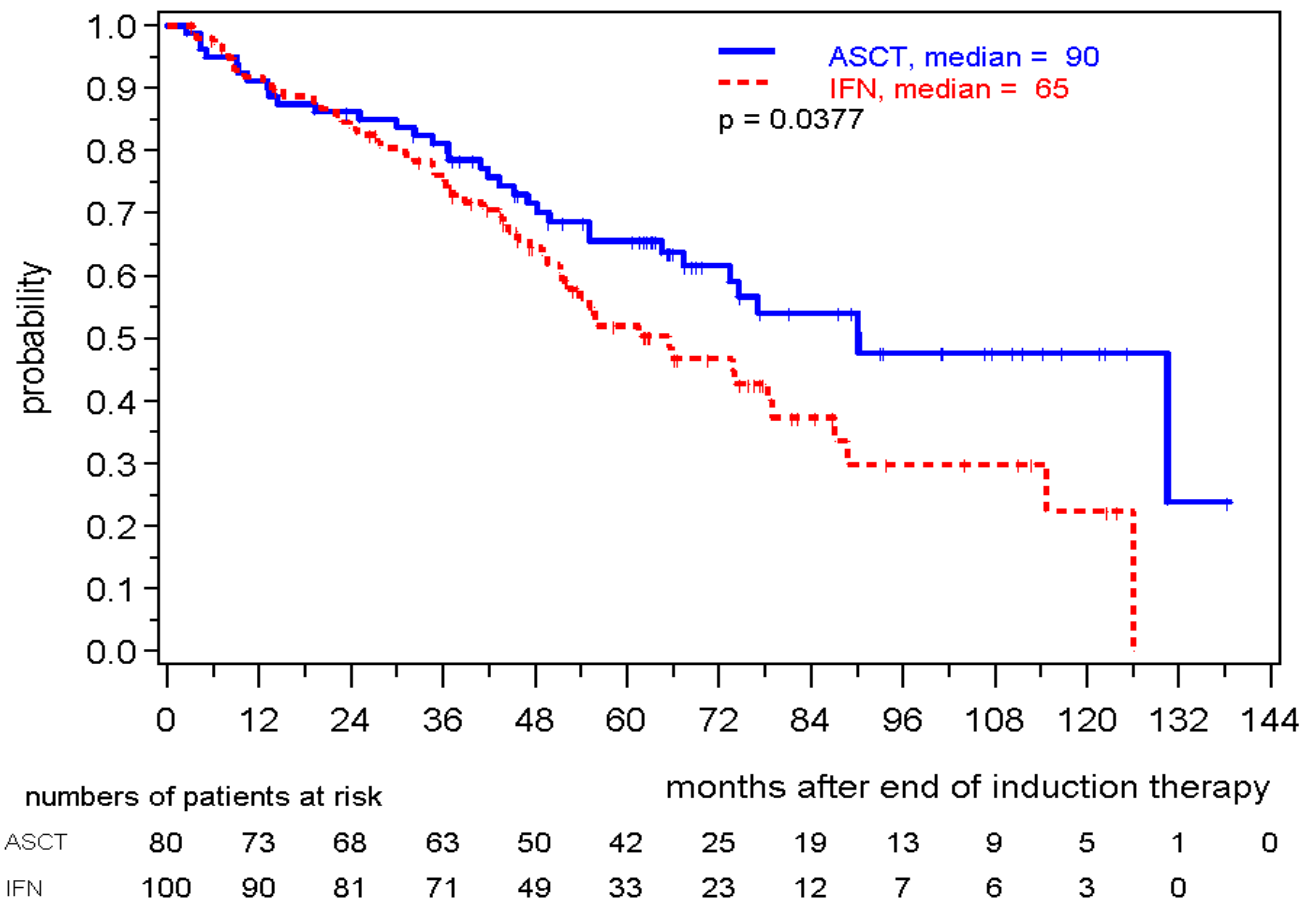
Schulz et al., JNCI 2007

European MCL Network



Median PFS, 39 mos. (ASCT) vs. 17 mos (IFN)

Analysis of 3 pooled trials: ASCT vs. IFN Overall survival

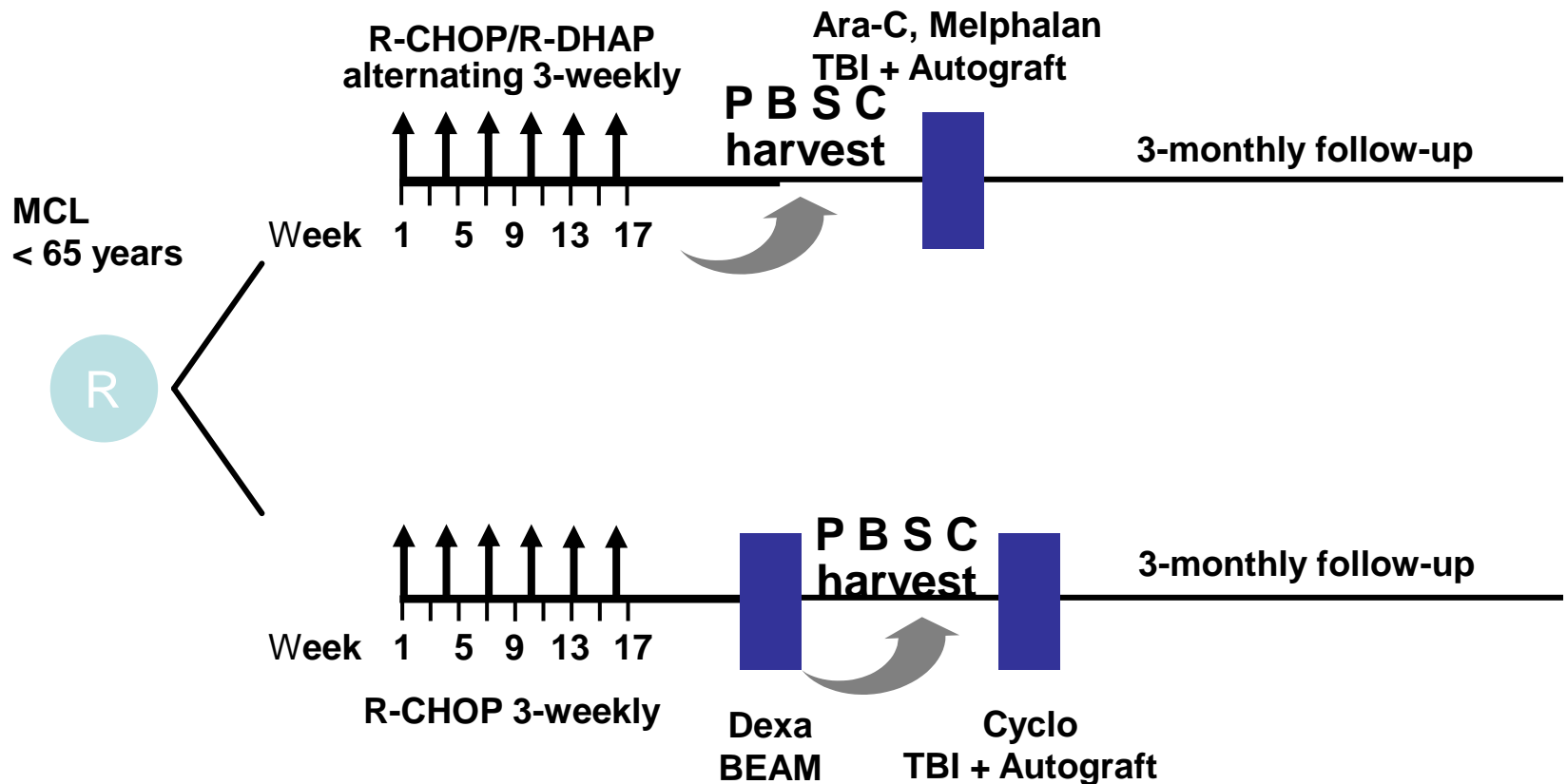


HyperCVAD

- R-Hyper CVAD as per MDACC protocol (first-line)

| | n | CR | RR | 2y PFS |
|-------|----|-----|-----|--------|
| MDACC | 97 | 87% | 97% | 90% |
| SWOG | 49 | 58% | 88% | 63% |

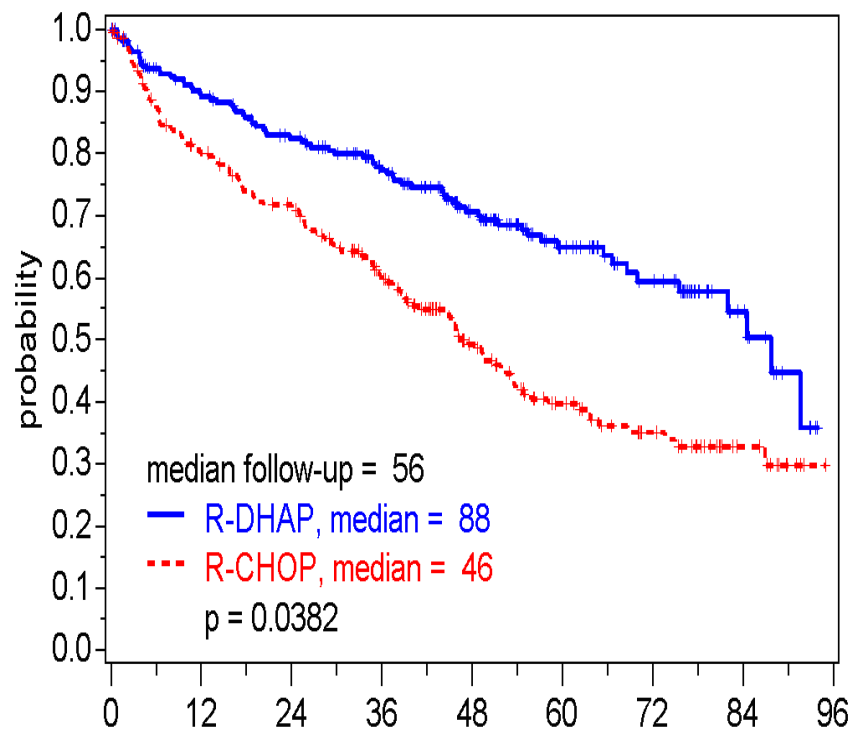
MCL European Network Study



Hermine O, *et al. Blood* 2012; 120:Abstract 151.

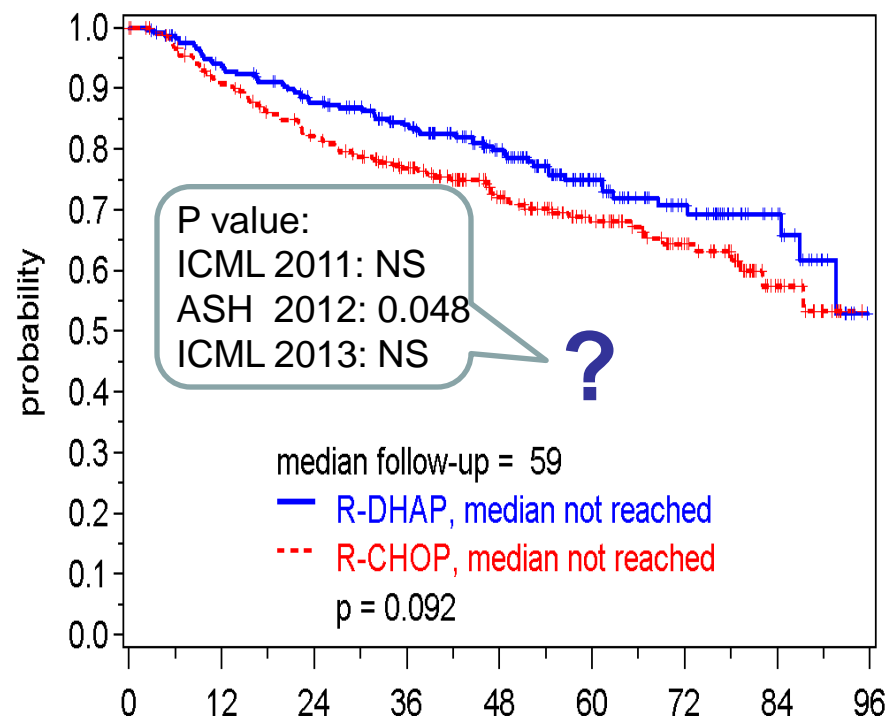
R-CHOP vs R-CHOP alt. R-DHAP in young MCL , first line

Time to treatment failure



| | numbers at risk | | | | | | | | |
|--------|-----------------|-----|-----|-----|-----|----|----|----|---|
| | 234 | 191 | 171 | 143 | 103 | 61 | 41 | 14 | 0 |
| R-DHAP | 234 | 191 | 171 | 143 | 103 | 61 | 41 | 14 | 0 |
| R-CHOP | 235 | 177 | 153 | 116 | 76 | 48 | 32 | 12 | 0 |

Overall Survival



| | numbers at risk | | | | | | | | |
|--------|-----------------|-----|-----|-----|-----|----|----|----|---|
| | 248 | 222 | 201 | 175 | 133 | 81 | 51 | 22 | 0 |
| R-DHAP | 248 | 222 | 201 | 175 | 133 | 81 | 51 | 22 | 0 |
| R-CHOP | 249 | 216 | 188 | 163 | 122 | 90 | 55 | 19 | 1 |

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First line

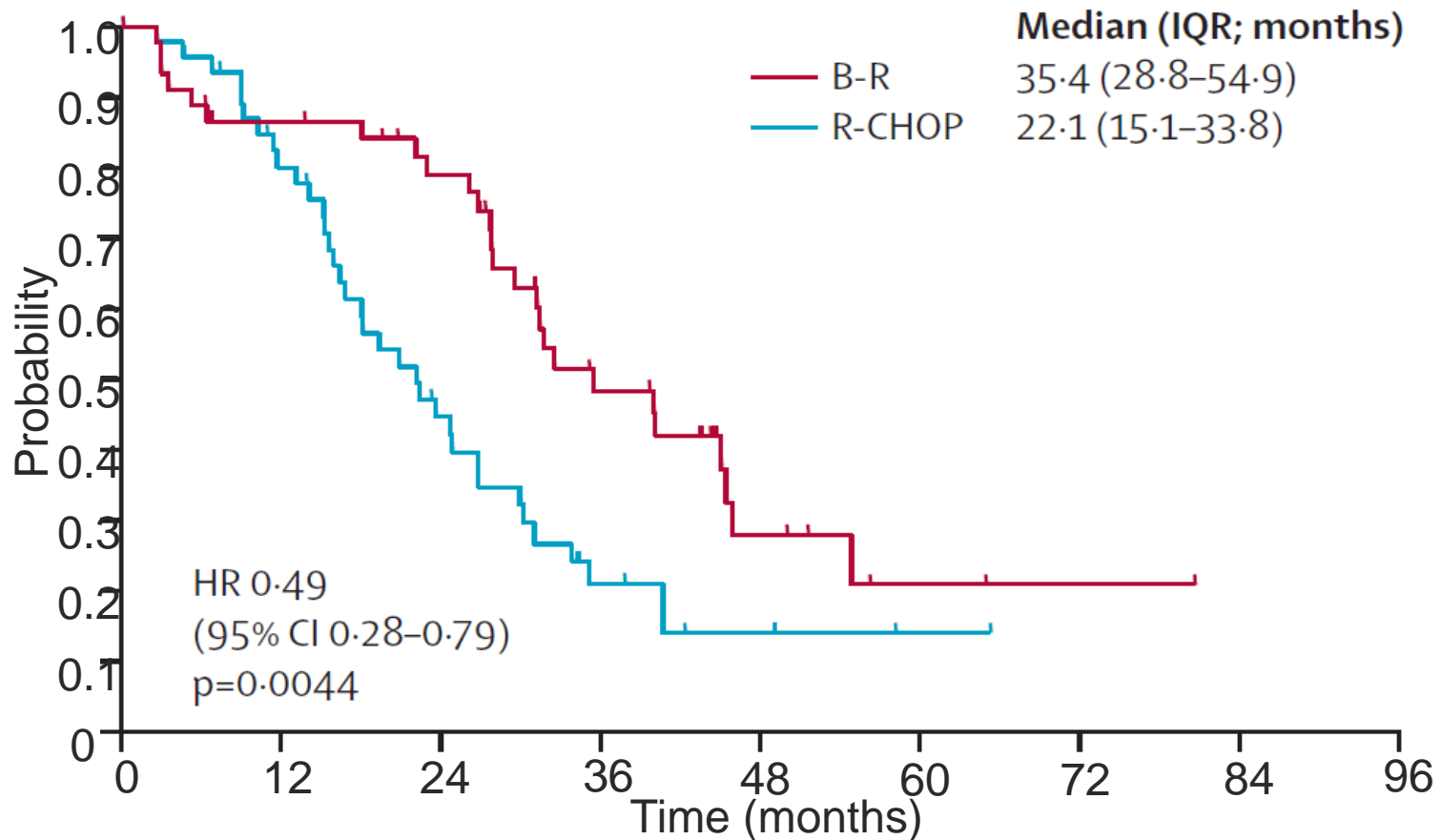
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Relapse

| | | |
|-------------|--|----------------------------|
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Bendamustine in MCL: At least as good as CHOP

MCL: PFS



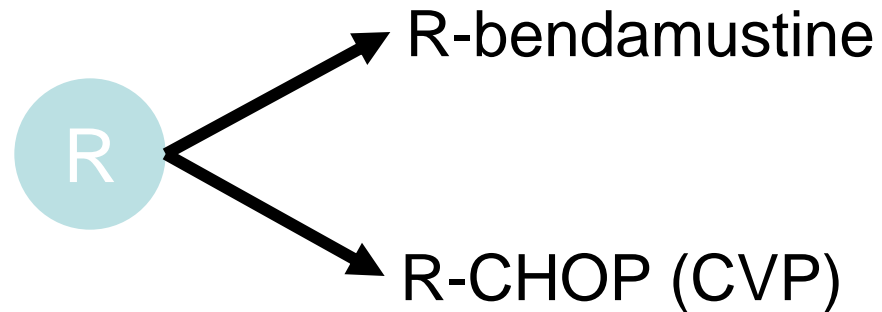
R-benda vs R-CHOP (CVP): BRIGHT

Study design

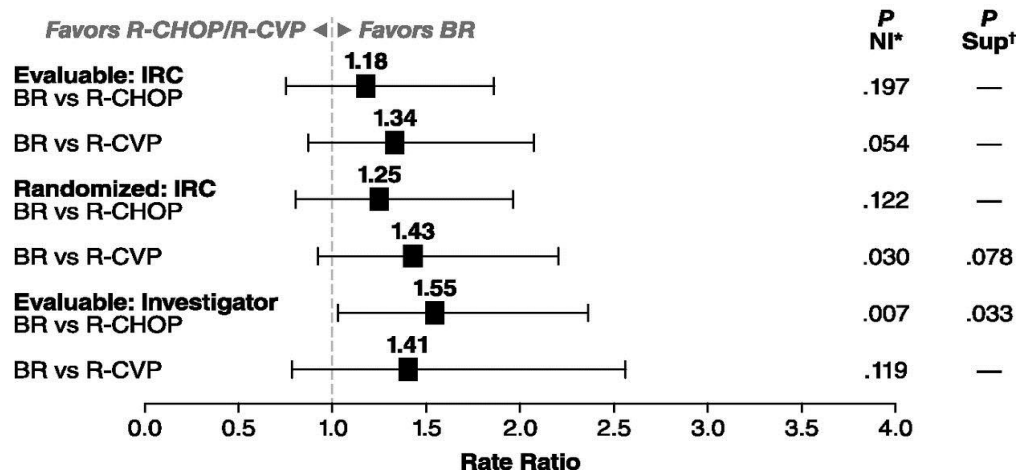
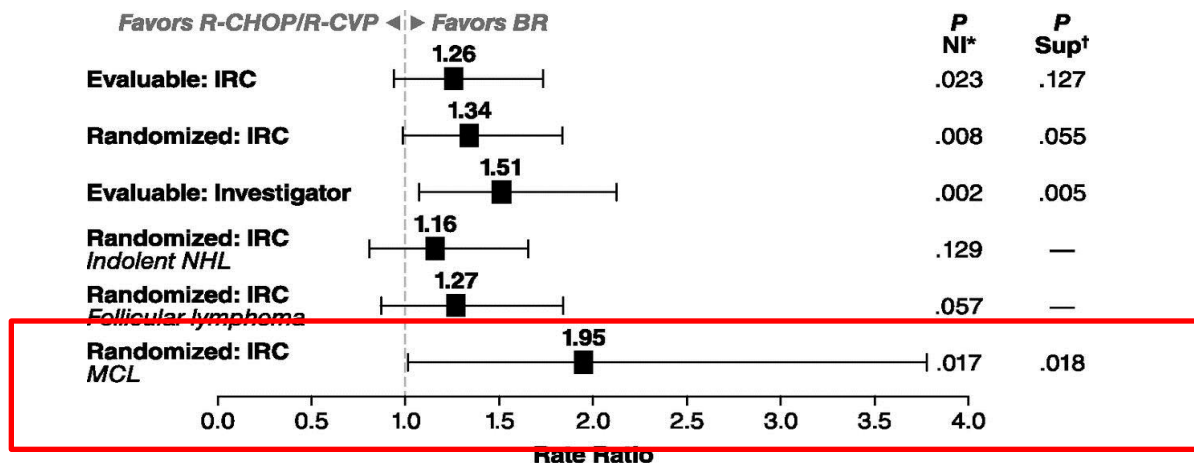
n = 447

FL = 83%

MCL = 17%



BRIGHT study: results

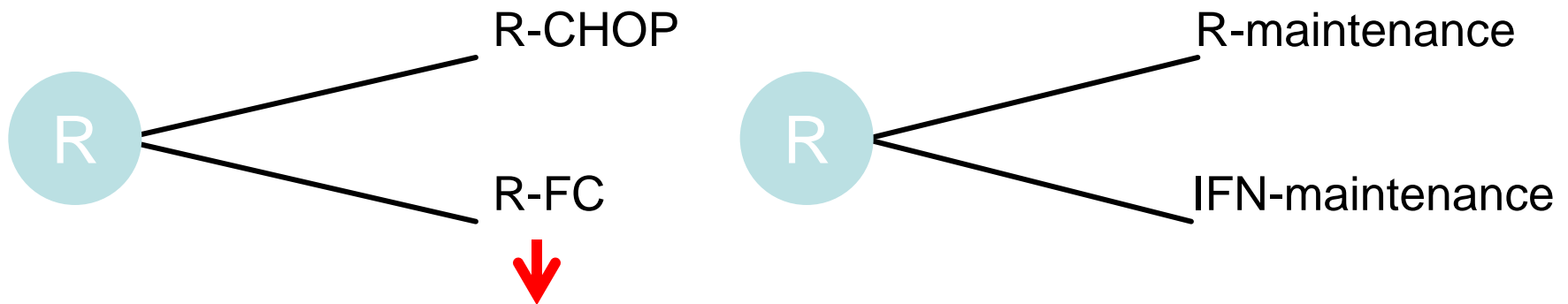


Ian W. Flinn et al. Blood 2014;123:2944-2952

R-maintenance in MCL

559 MCL aged > 60 years

2 RANDOMISATIONS

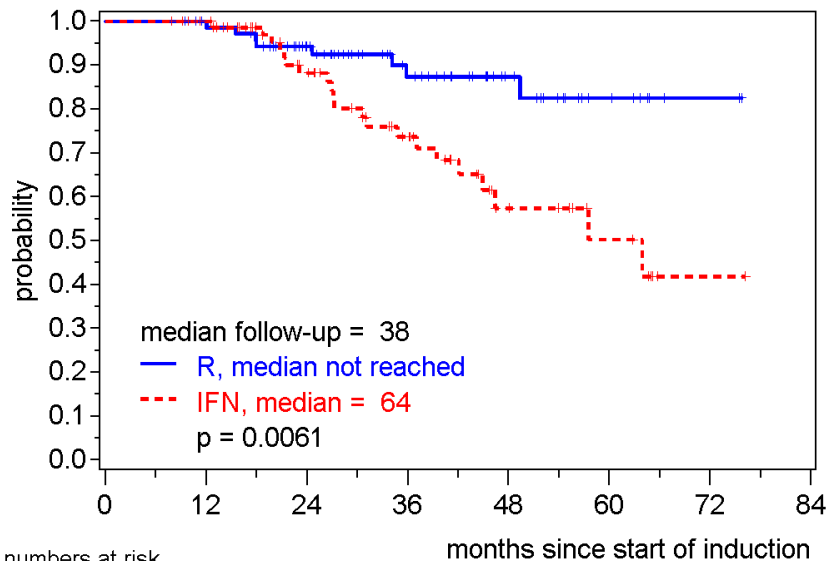


R-CHOP better than R-FC

The effect of R-maintenance depends on the induction regimen

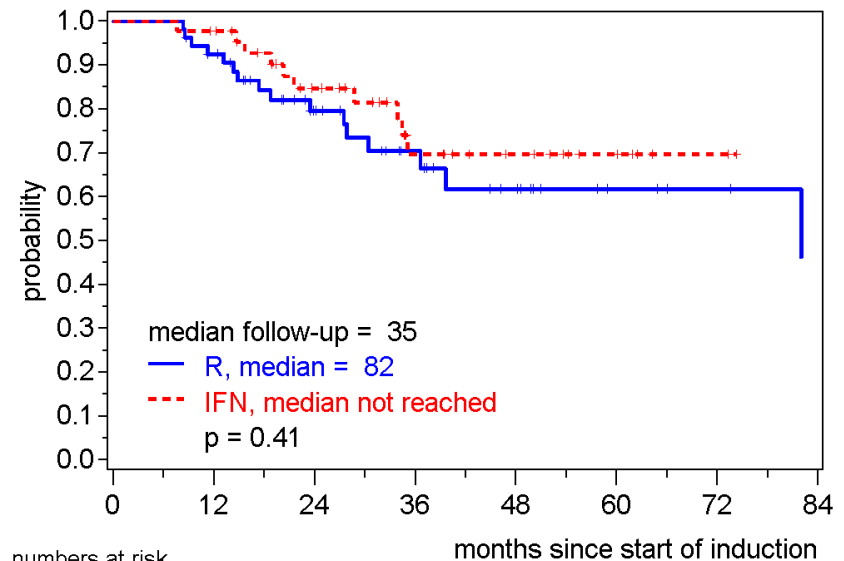
OS

After R-CHOP



| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|-----|----|----|----|----|----|----|----|----|
| R | 74 | 70 | 53 | 34 | 19 | 8 | 2 | 0 |
| IFN | 76 | 72 | 49 | 31 | 13 | 7 | 1 | 0 |

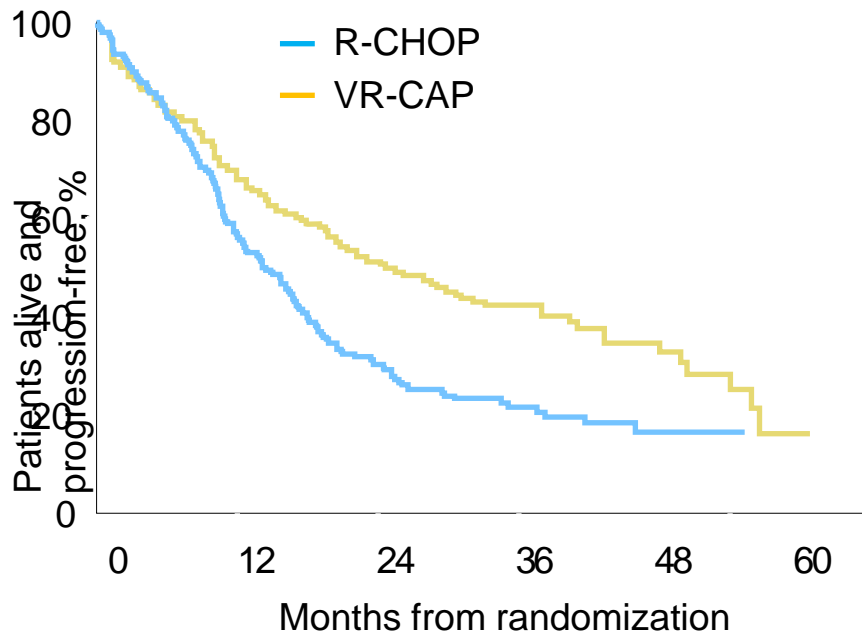
After R-FC



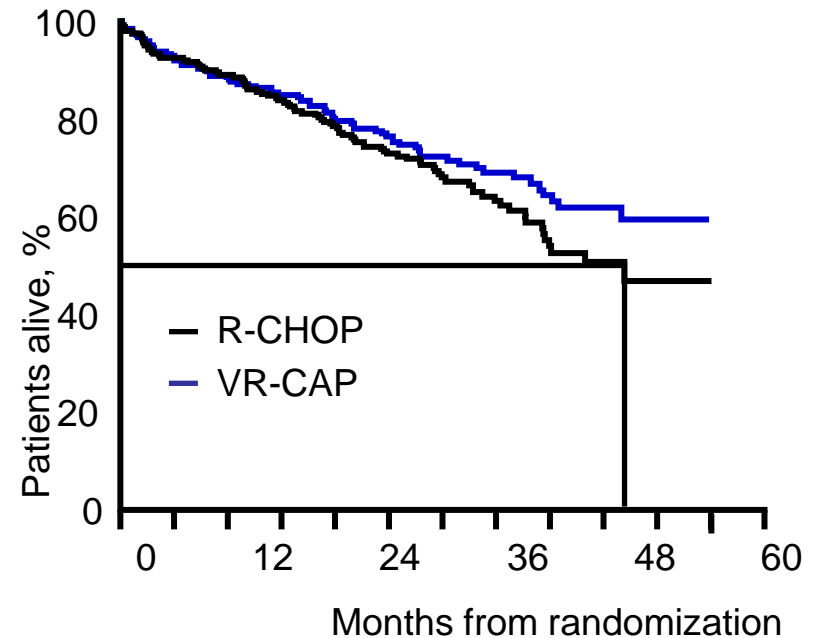
| | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 |
|-----|----|----|----|----|----|----|----|----|
| R | 54 | 48 | 30 | 18 | 11 | 4 | 2 | 0 |
| IFN | 44 | 42 | 29 | 16 | 11 | 6 | 2 | 0 |

● What about maintenance after R-bendamustine?

Superior PFS but not OS with VR-CAP vs R-CHOP



| | R-CHOP | VR-CAP |
|--------------------|-------------------|--------|
| Median PFS, months | 14.4 | 24.7 |
| HR (95% CI) | 0.63 (0.50, 0.79) | |
| P-value | <0.001 | |



| | R-CHOP | VR-CAP |
|-------------------|-------------------|-------------|
| Median OS, months | 56.3 | Not reached |
| HR (95% CI) | 0.80 (0.59, 1.10) | |
| P-value | 0.173 | |

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Ibrutinib

Dreyling M et al, *Ann. Oncol.* 2013



Published series of allo-transplant in relapsed MCL

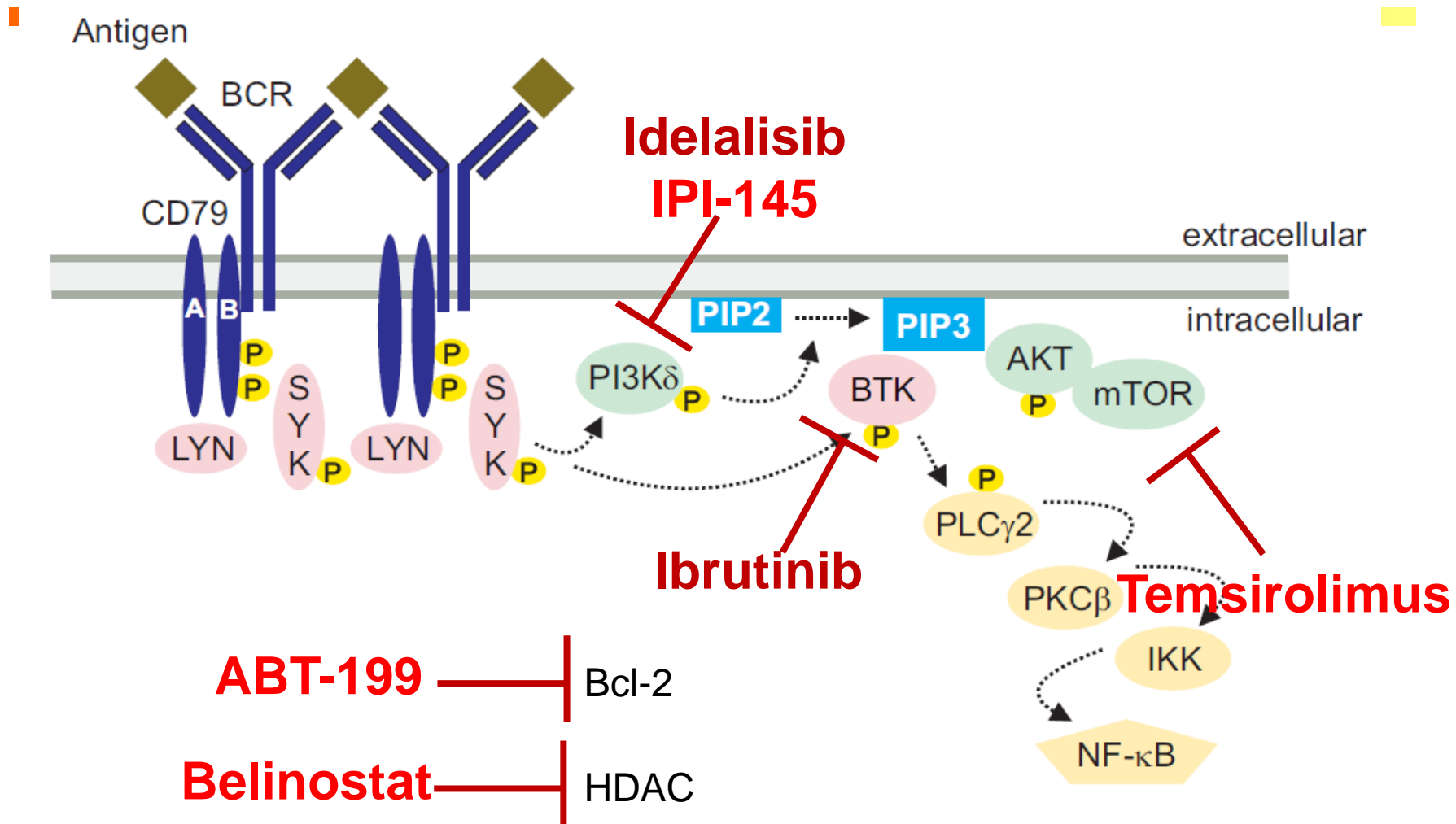
| | <u>N</u> | <u>3-5 y PFS</u> |
|---------------------------|----------|------------------|
| 4 studies (myeloablative) | 10-18 | 42-55% |
| 4 studies (RIC) | 35-180 | 14-46% |
| CIBMTR registry (2011) | 105 | 20% |
| EBMT registry (2011) | 325 | 32% |

Conclusions: Allo-BMT cures 1/3
of transplant eligible relapsed MCL

Promising targeted drugs

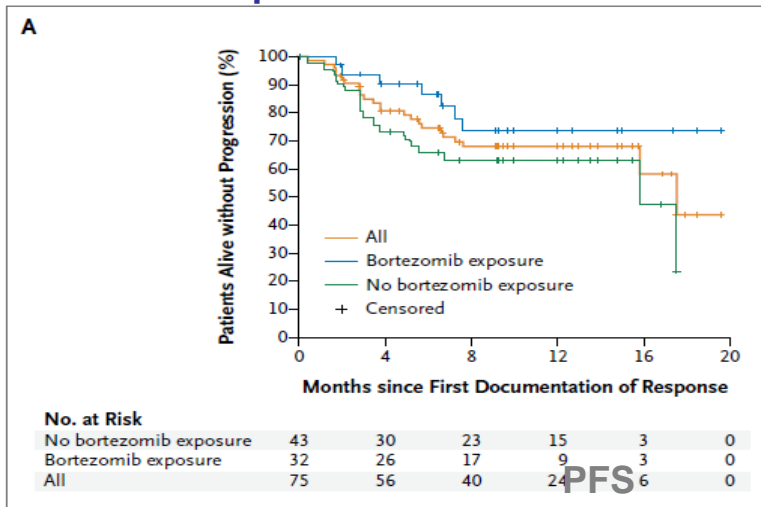
| Phase I-II data (caution!) | RR in relapse |
|----------------------------|---------------|
| Bortezomib | 30% |
| Everolimus / Temsirolimus | 20% |
| Lenalidomide | 50% |
| Ibrutinib (PCI 32765) | 60% |
| Idelalisib (CAL 101) | 50% |

Small molecules



Ibrutinib in Relapsed MCL

Response duration



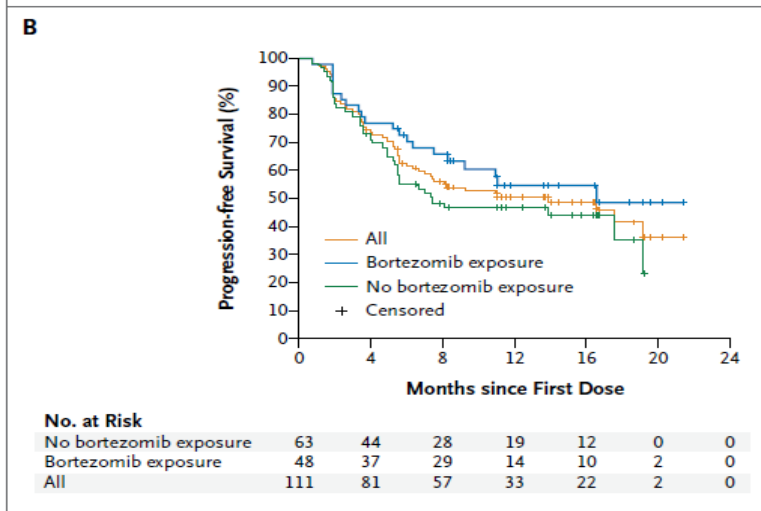
111 cases

Median 3 previous regimens

68% RR (22% CR)

Over time: 75% (35% CR)

Median PFS 1 year

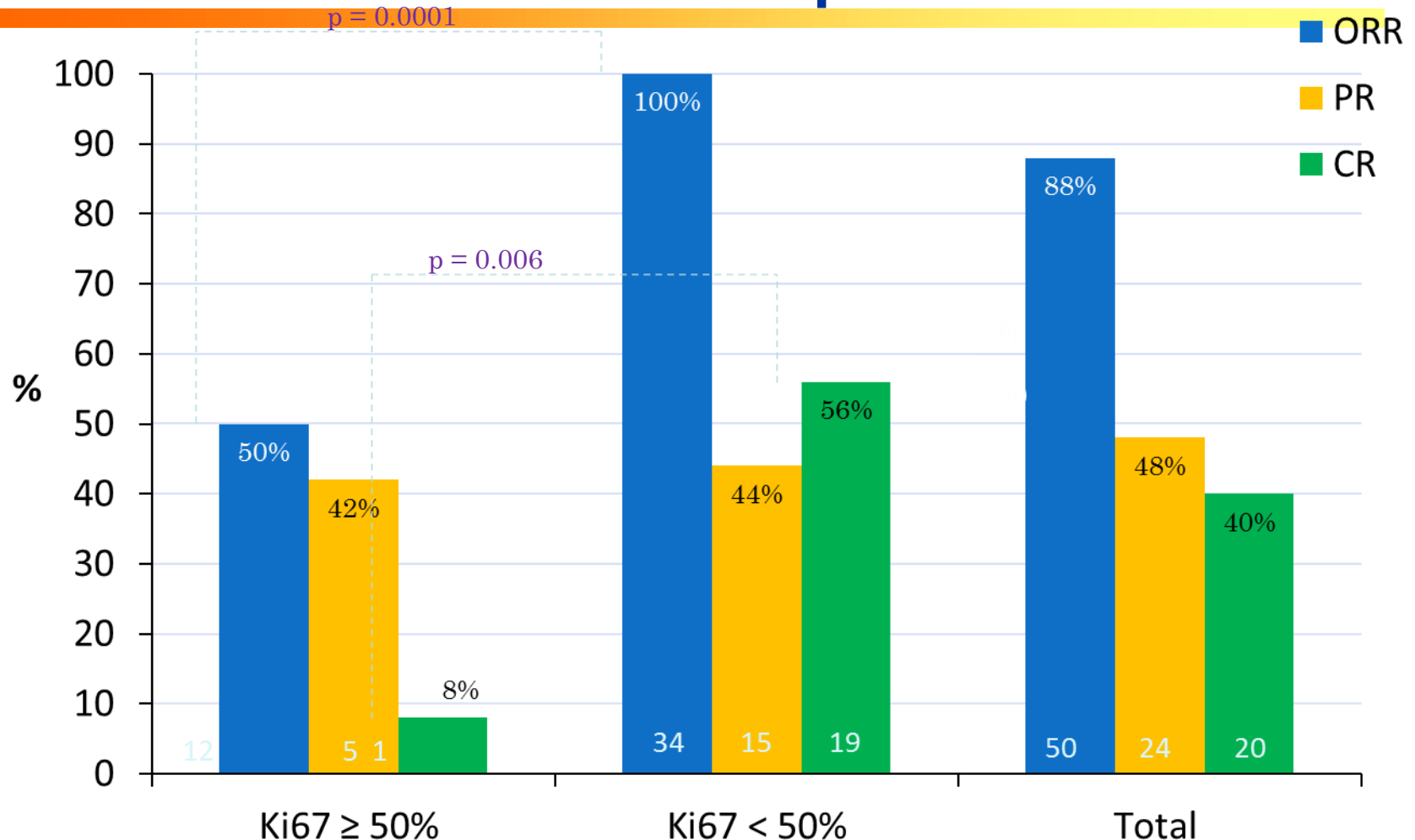


Side effects mild:

Diarrhea, fatigue, nausea

Wang ML, et al. *N Engl J Med*. 2013;369(6):507-516.

Ibrutinib + rituximab in 50 R/R MCL Best Response



** Ki67 N/A for 4 patients **

Wang et al, ASH 2014, abstr. 627

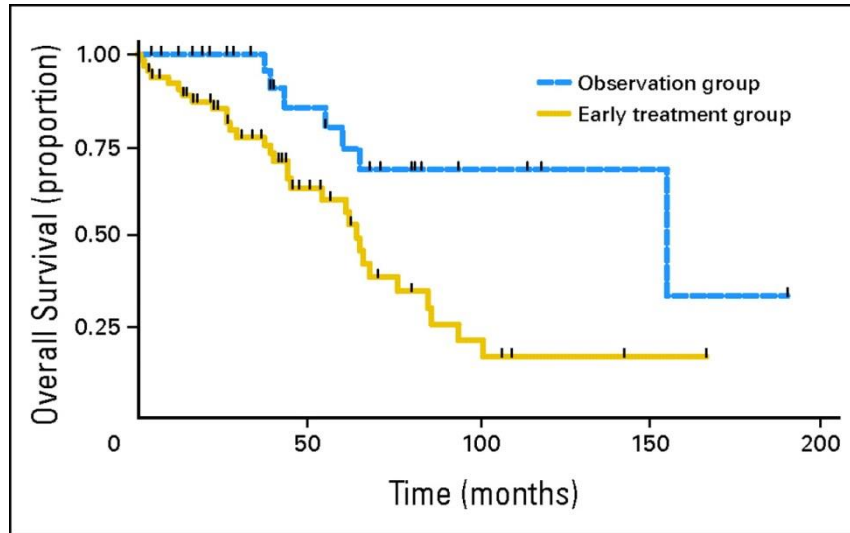
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Weill-Cornell experience

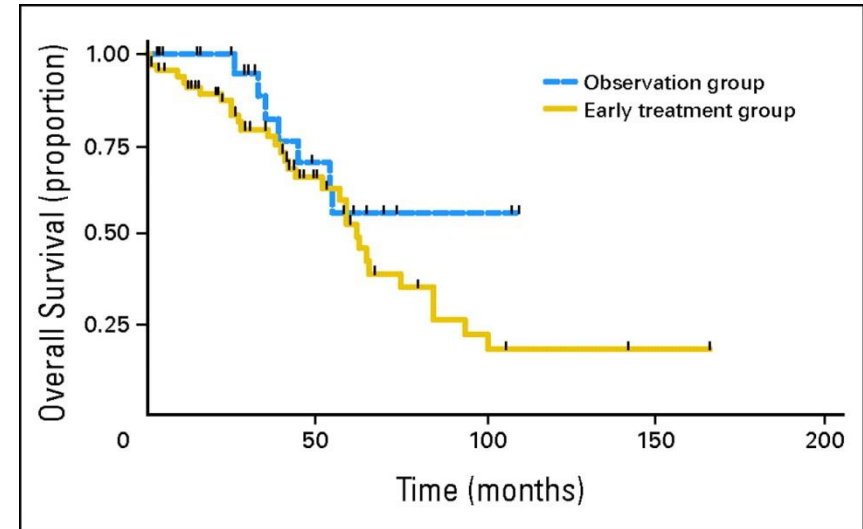
97 MCL over 10 years
66 Immediate treatment
31 Observed (median TTT = 1 y)

The observation group had a less aggressive MCL



OS from diagnosis

Deferring treatment did not compromise efficacy

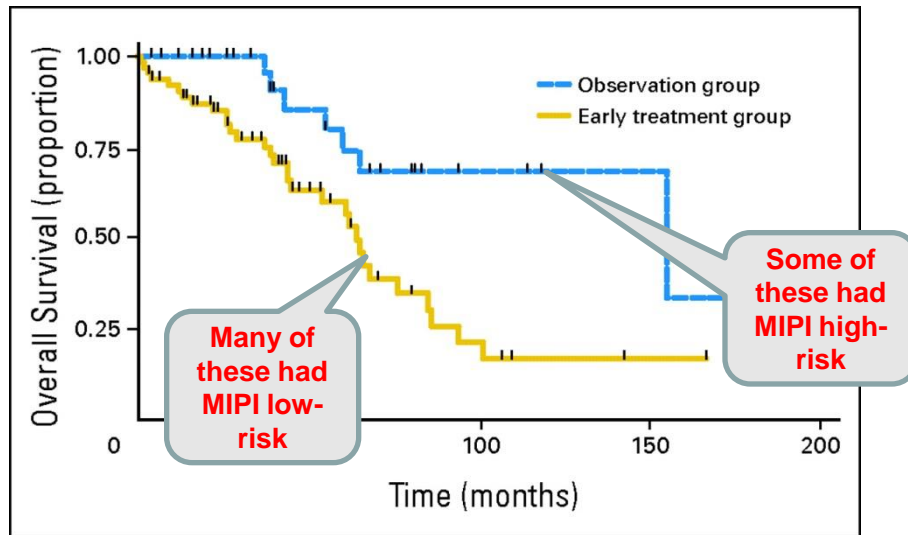


OS from start of treatment

Weill-Cornell: MIPI is not predictive of indolent course!

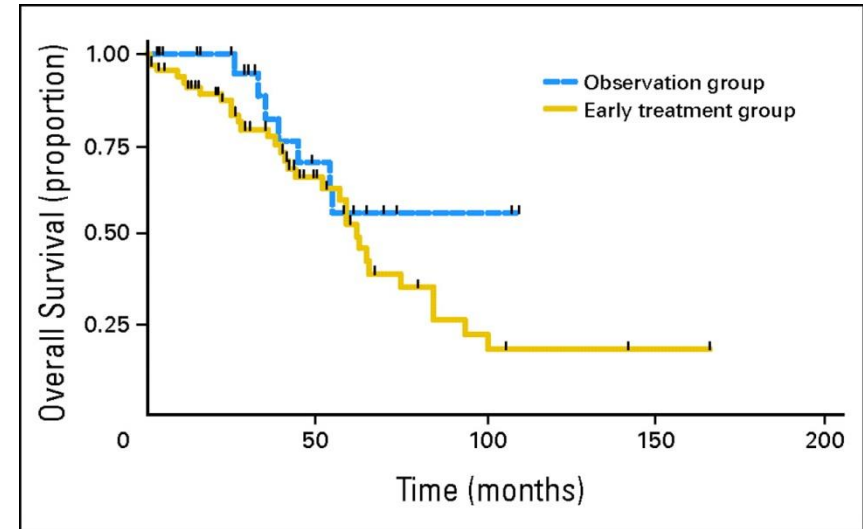
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OS from diagnosis

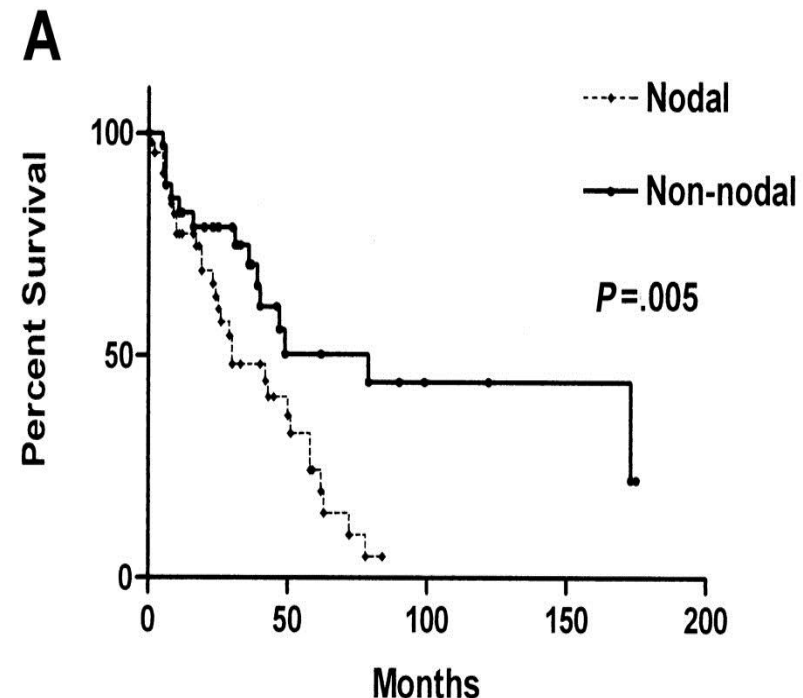
Deferring treatment did not compromise efficacy



OS from start of treatment

Nodal vs non-nodal leukemic MCL

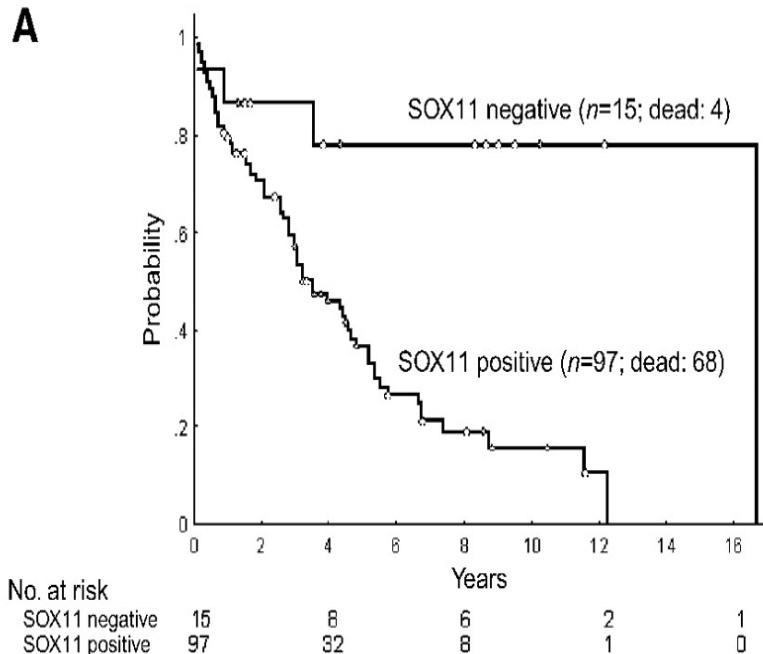
| % | Nodal (n=43) | Non-nodal (n=37) |
|---------------------|-----------------|---------------------|
| Splenomegaly | 58 | 76 |
| GI tract | 19 | 5 |
| CD38+ | 94 | 48 |
| IgVH unmutated | 90 | 44 |
| Complex karyotype | 100 | 53 |
| Immediate treatment | 95 | 49 |
| Median OS | 30m | 79m |



Negative SOX11 associated with indolent MCL ?

GEP identifies 13 genes expressed in cMCL and not in iMCL
For one of these, SOX11, the protein can be stained in IHC.

112 MCL cases



iMCL cases were:

- Non-nodal
- Hypermuted IGVH
- No genomic complexity
- SOX11 neg

Indolent mantle cell leukemia: a clinicopathological variant

Cleveland Clinic, 2000-2010: 8 cases

- morphology and immunophenotype of MCL
- no symptoms
- lymphocytosis
- Kappa light-chain restriction
- low-level BM involvement
- SOX-11 neg

Equivalent of MBL (monoclonal B-lymphocytosis) ?

In the majority of MCL you can consider watch and wait.

useful for decision

- GELF/BNLI criteria as
- absence of symptoms
 - no rapidly progressive LN
 - no altered blood counts
 - ...

(MIPI ?)

not useful for decision

Ki 67
IGHV mutation
SOX11
Genetic abnormalities

Conclusions

- MCL is neither an indolent nor a curable disease
- Few randomized trials give clear hint on the best treatment strategy
- Several studies **suggest** that
 - Bendamustin is superior to CHOP
 - Rituximab improves the effect of chemo
 - HD-AraC and HDCT improve OS
 - Rituximab maintenance is good after R-CHOP
- Ibrutinib and lenalidomide offer new perspectives
- Consider W+W in very selected cases