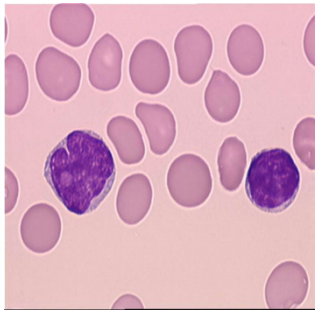
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
Medizinische Klinik und Poliklinik III
Direktor: Prof. Dr. W. Hiddemann

Rome,
March 23-24
2017
VOI Donna Camilla Savelli Hotel

Mantle cell lymphoma:

Front line in young patients

3rd POSTGRADUATE
Lymphoma
Conference



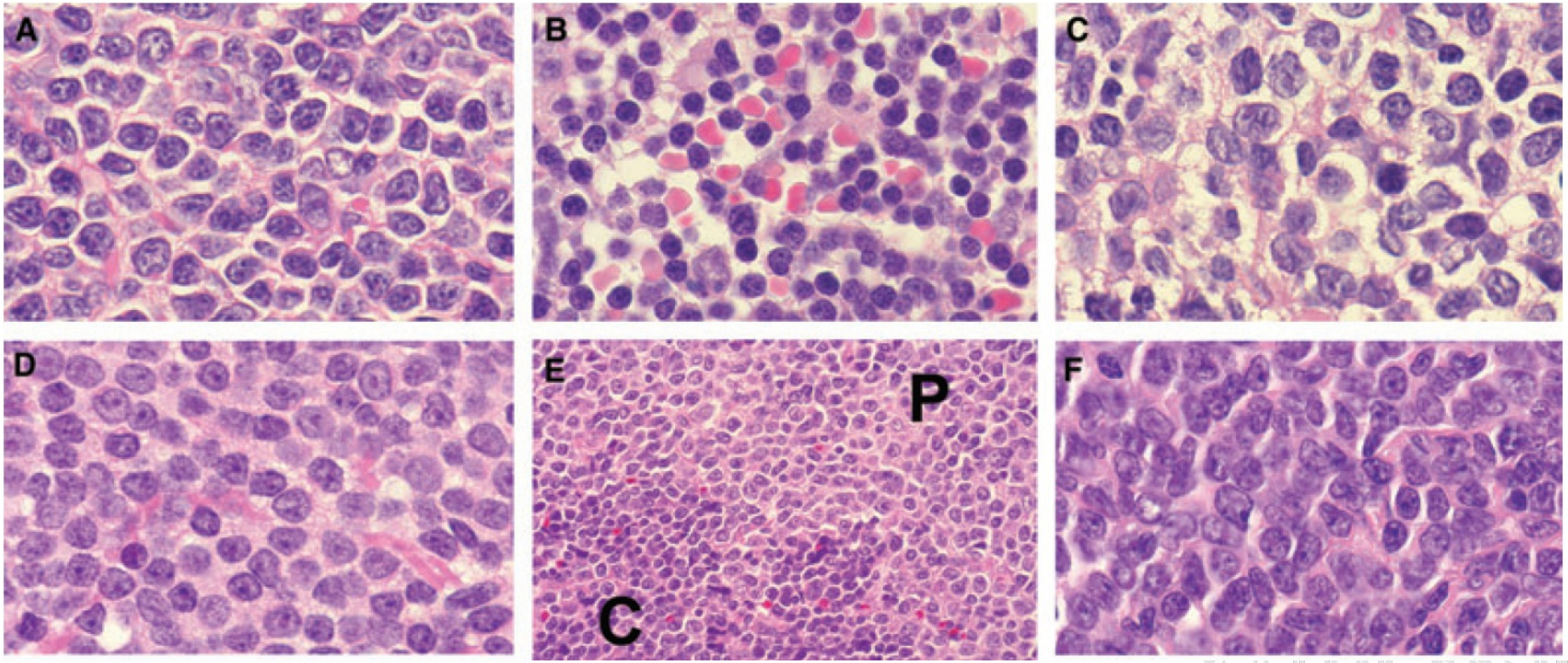
European MCL Network

Prof. Dr. Martin Dreyling
Medizinische Klinik III
LMU München

Mantle cell lymphoma

- molecular pathogenesis
- chemotherapy standards (first line)
- targeted approaches

Mantle cell lymphoma
Histology

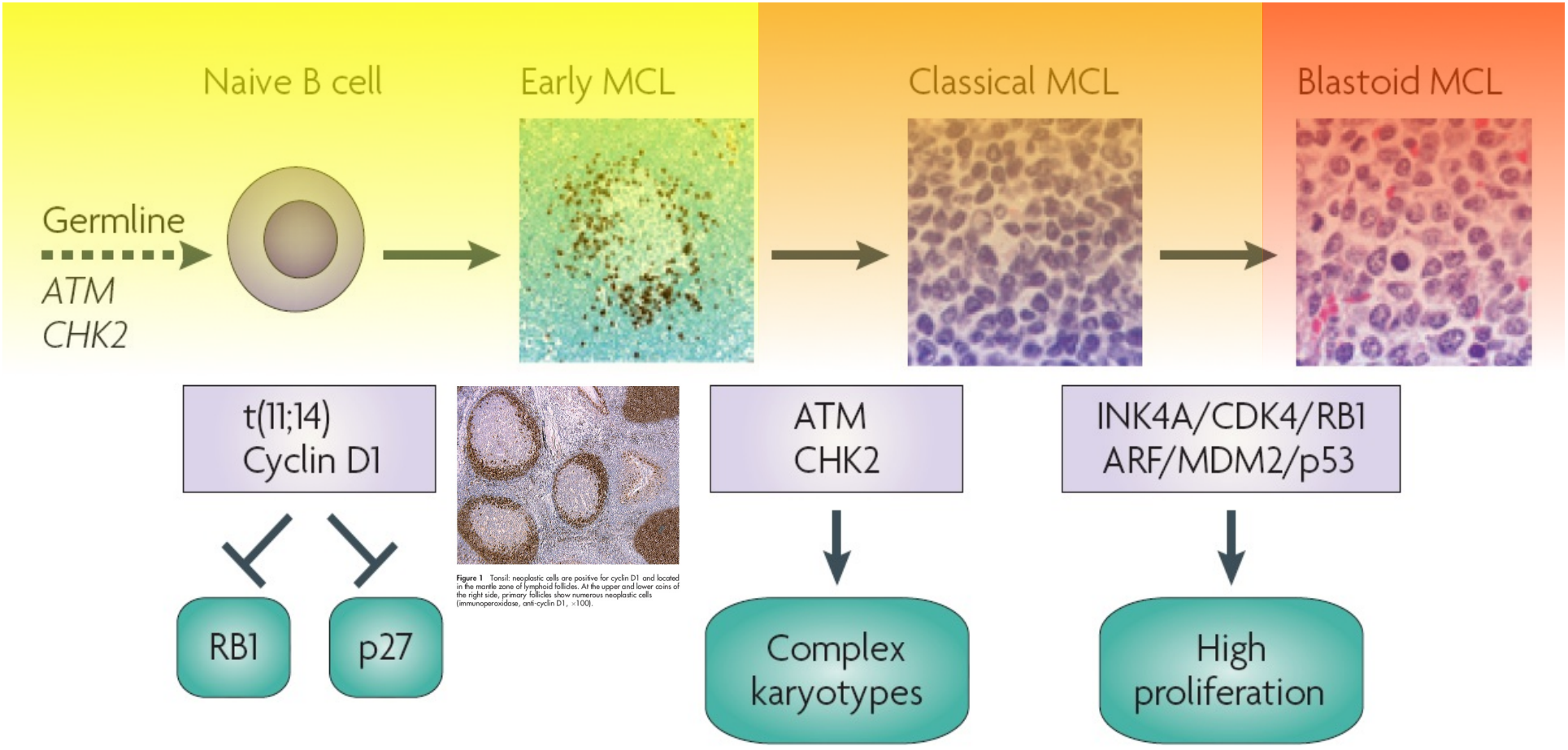


A classical; B small cell; C pleomorphic; D: blastoid; E: classical & pleomorphic; F: classical/pleomorphic

Tiemann, Brit J Haematol 2005

MCL: *a spectrum of disease*

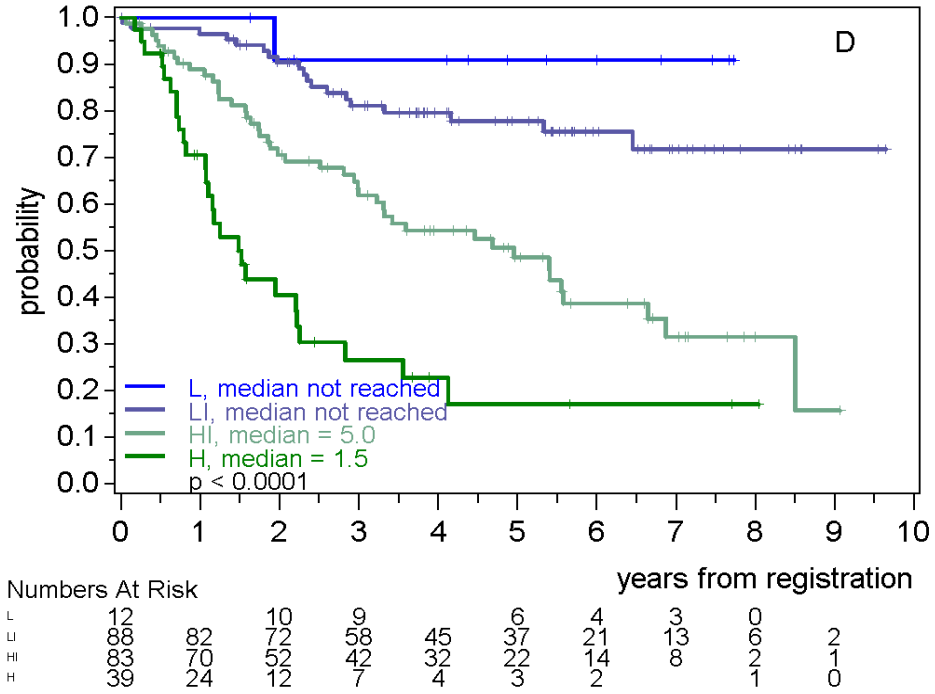
„indolent“ MCL (15%) *„classical“ MCL (80%)* *„transformed“ (5%)*



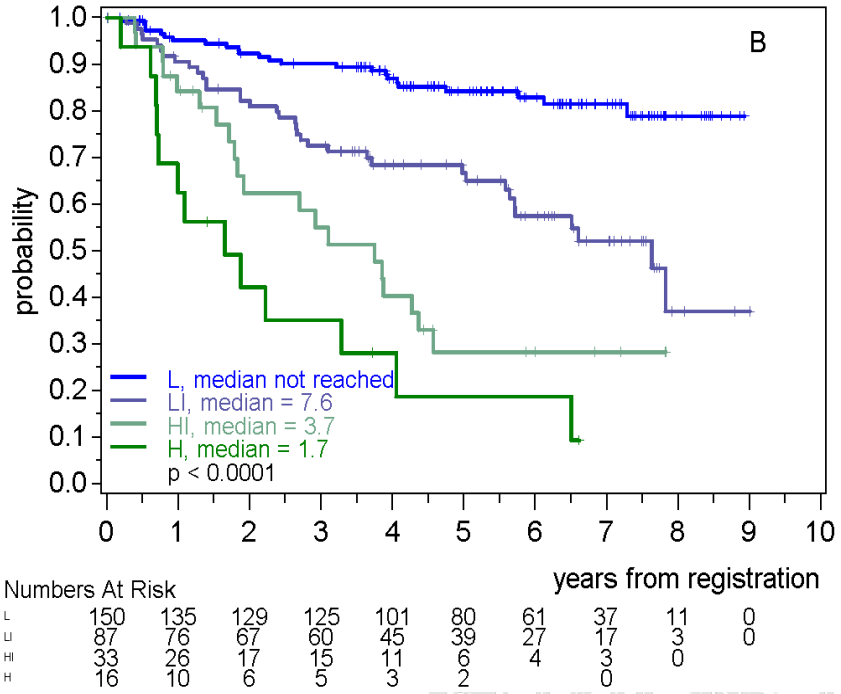
Combined MIPI-c

Overall survival

Patients >65 years



Patients <65 years

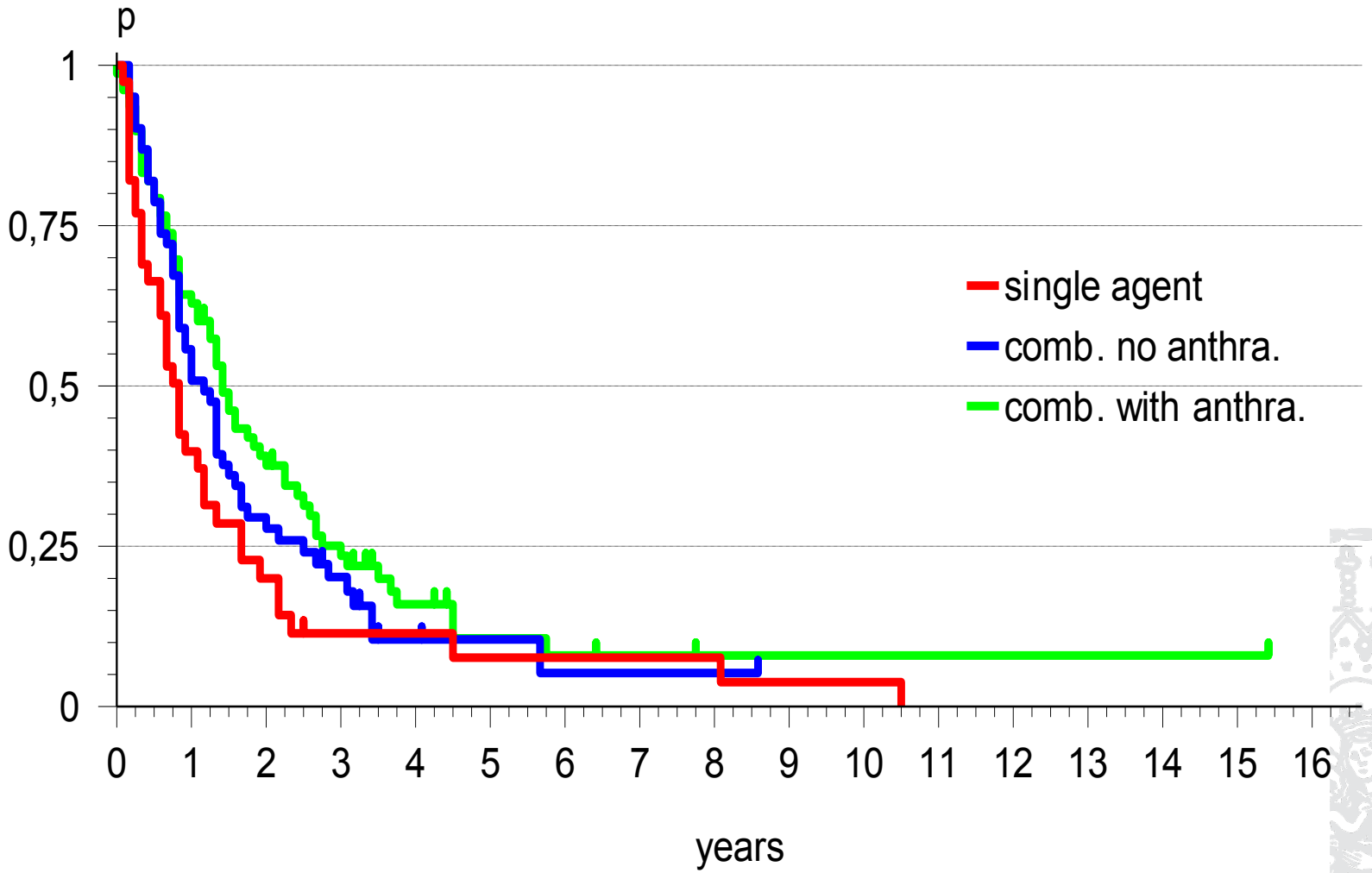


Hoster, JCO 2016

Multicenter Evaluation of MCL

Annexcy Criteria fulfilled

event free interval after chemotherapy in stages III + IV

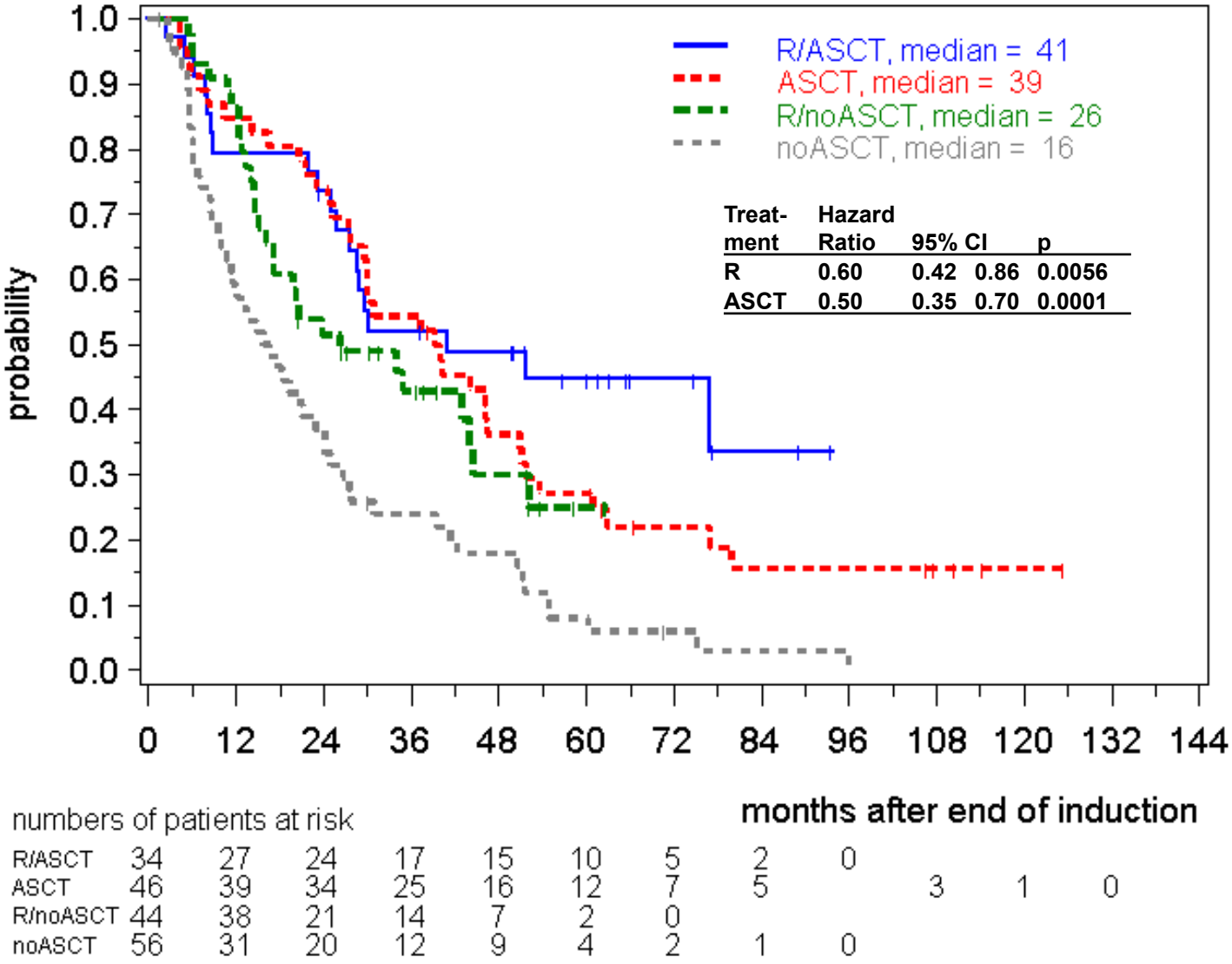


Dreyling, ASCO 1999

young patient (≤65)	elderly patient (>65)	compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (R-CHOP, high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (R-CHOP, VR-CAP, BR) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (e.g. R-BAC, BR) or targeted approaches ↓ discuss: - Rituximab maintenance - allogeneic SCT	immuno-chemotherapy (e.g. BR, R-BAC) or targeted approaches ↓ discuss: - Rituximab maintenance - radioimmunotherapy - autologous SCT	Immuno-chemotherapy (e.g. BR) or targeted approaches
higher relapse		
Targeted approaches: Ibrutinib, Lenalidomide, Temsirolimus, Bortezomib (preferable in combination) Alternatively: repeat previous therapy (long remissions)		

Comparative analysis: ASCT and Rituximab

Response duration



Treat-ment	Hazard Ratio	95% CI		p
R	0.60	0.42	0.86	0.0056
ASCT	0.50	0.35	0.70	0.0001

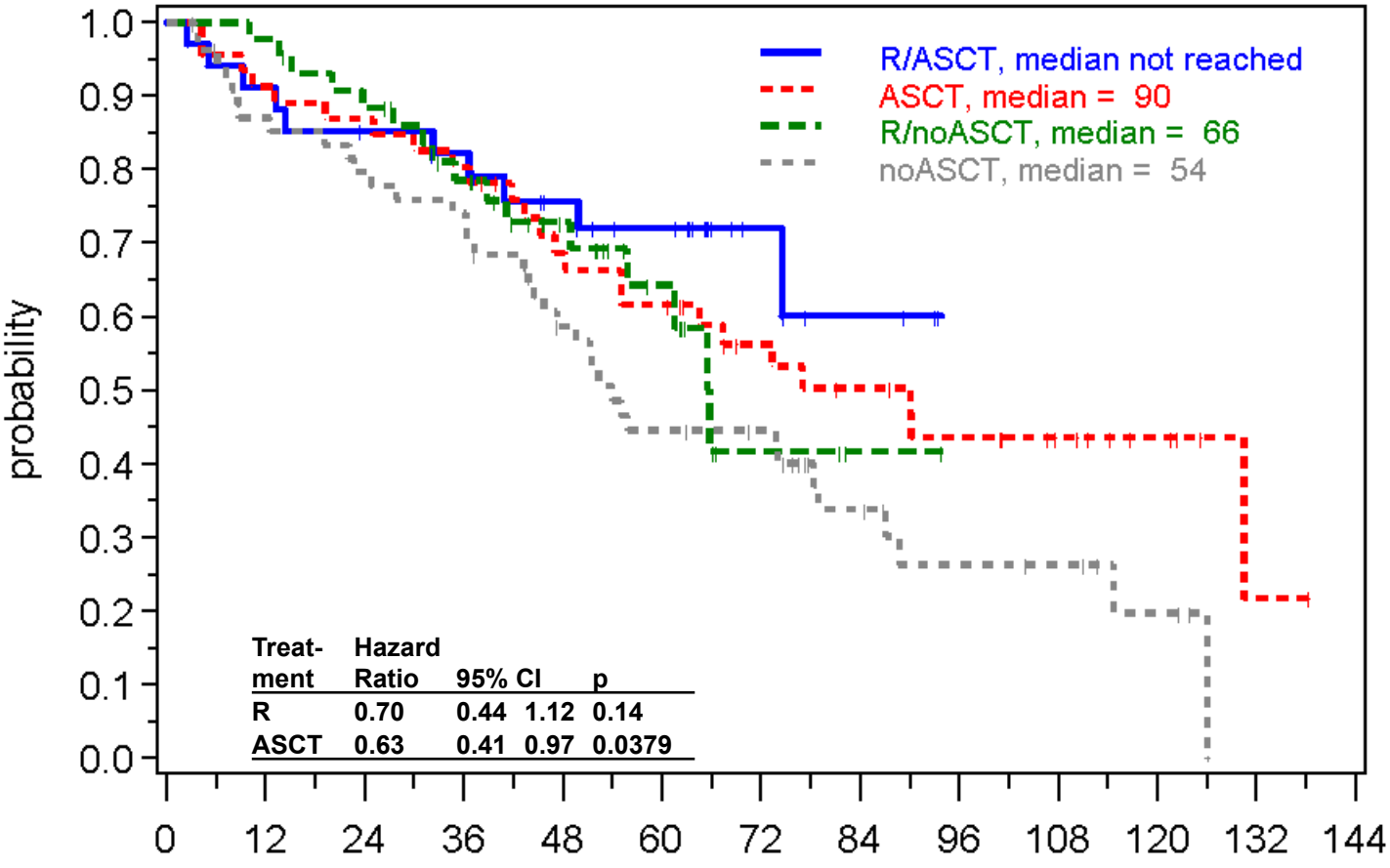
numbers of patients at risk

R/ASCT	34	27	24	17	15	10	5	2	0			
ASCT	46	39	34	25	16	12	7	5		3	1	0
R/noASCT	44	38	21	14	7	2	0					
noASCT	56	31	20	12	9	4	2	1	0			

Hoster, ASH 2009

Comparative analysis: ASCT and IFN

Overall survival



Treatment	Hazard Ratio	95% CI		p
R	0.70	0.44	1.12	0.14
ASCT	0.63	0.41	0.97	0.0379

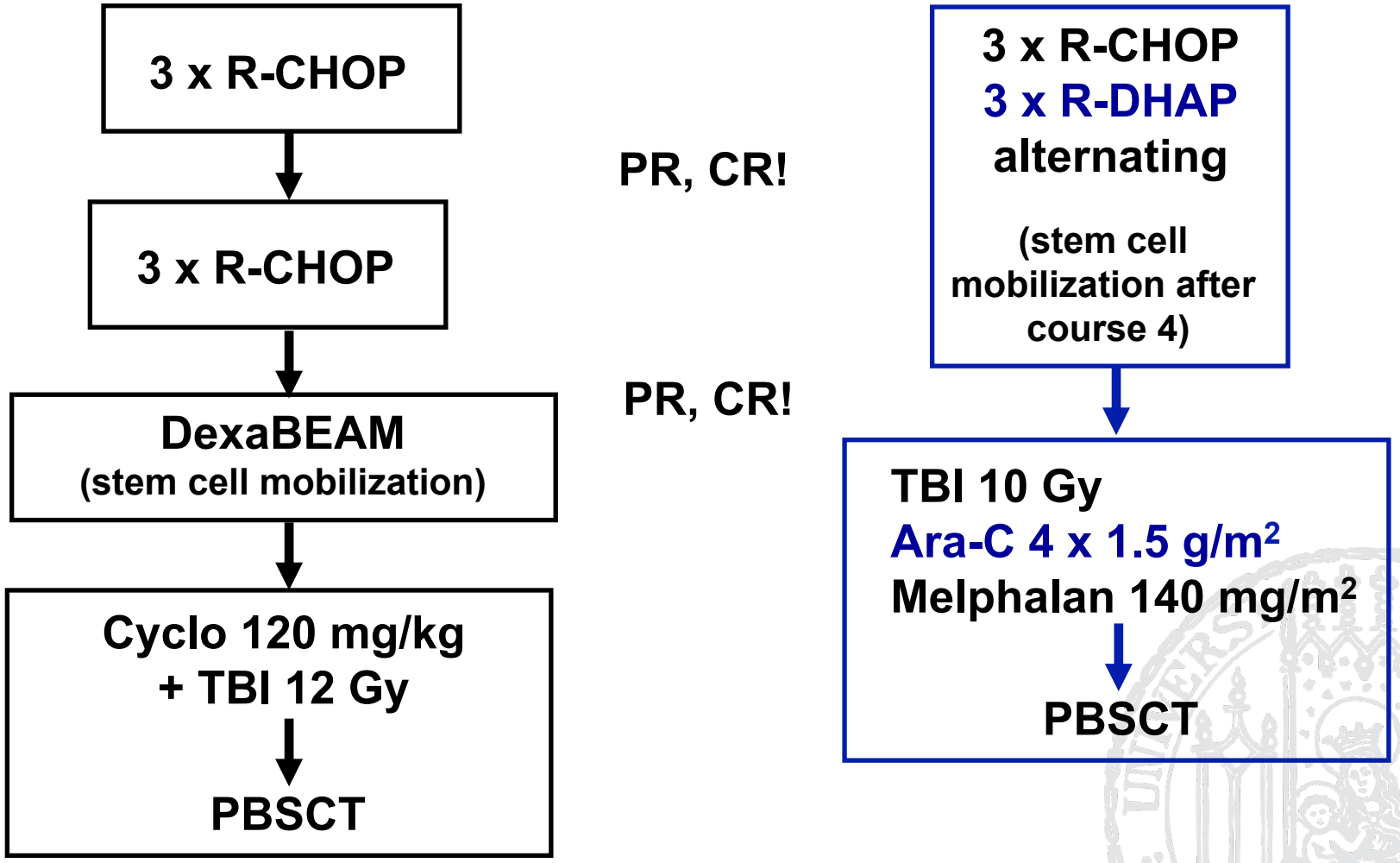
numbers of patients at risk

R/ASCT	34	31	28	26	21	16	6	3	0			
ASCT	46	42	40	37	29	26	19	16	13	9	5	1
R/noASCT	44	43	38	31	20	11	3	1	0			
noASCT	56	47	43	40	29	22	20	11	7	6	3	0

Hoster, ASH 2009

European MCL Network

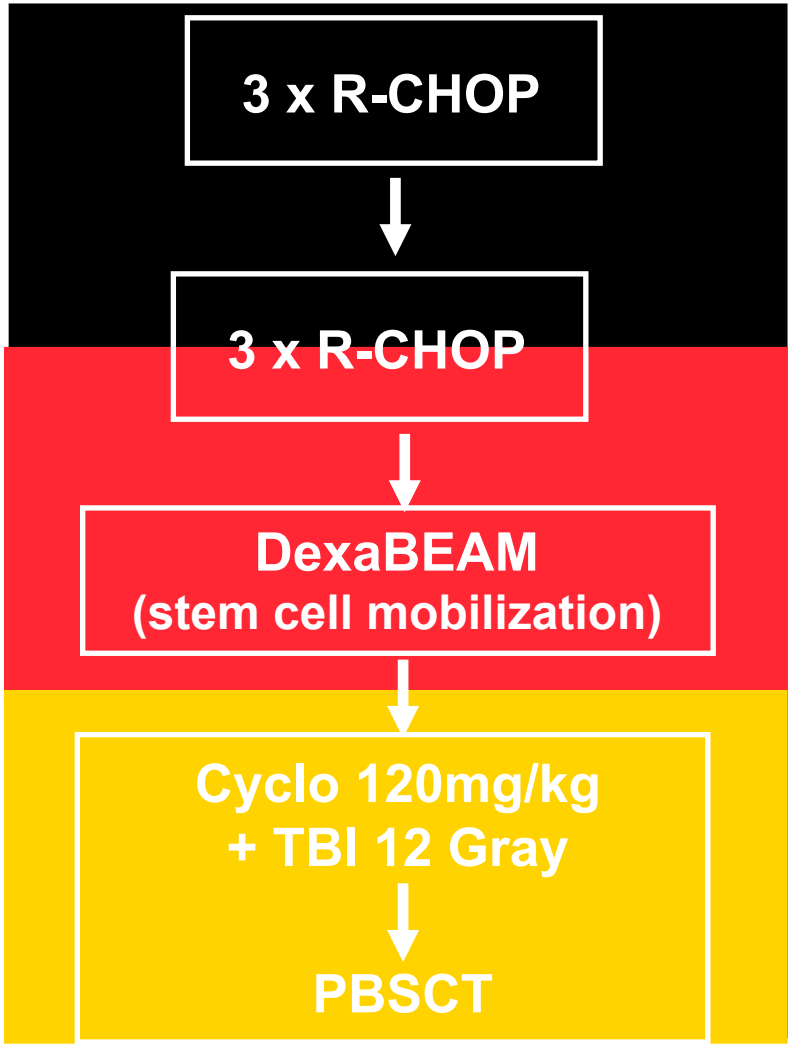
patients <65 years

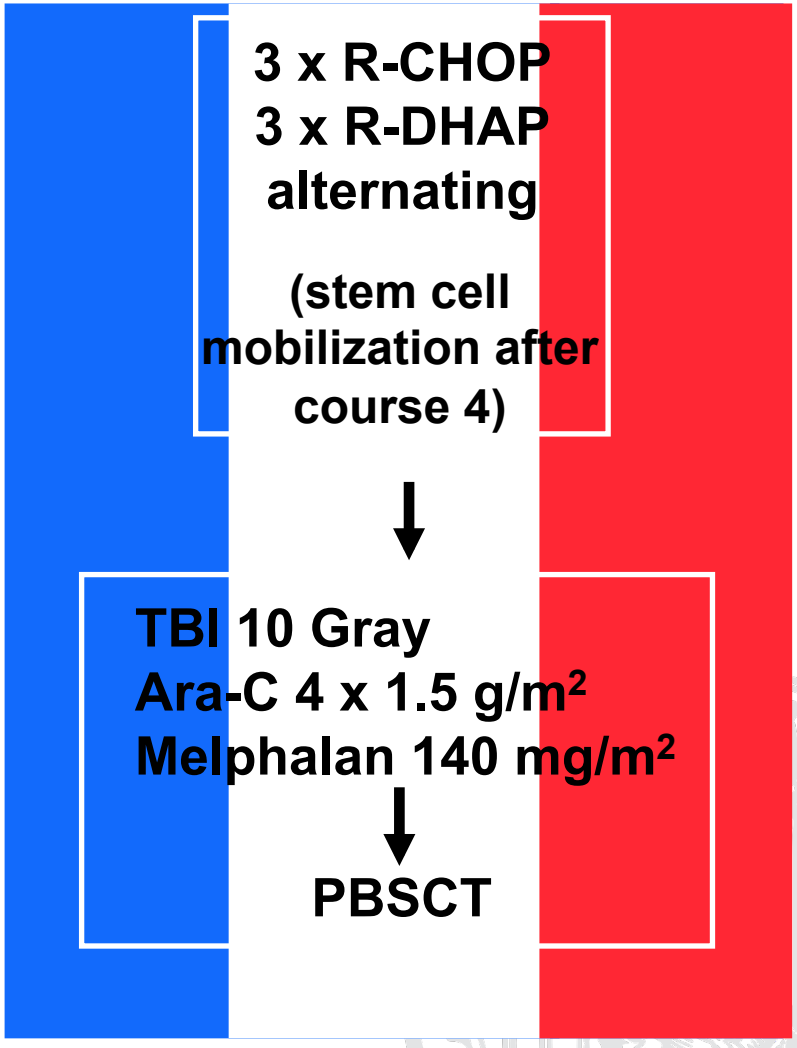


Hermine, Lancet 2016

European MCL Network

patients <65 years

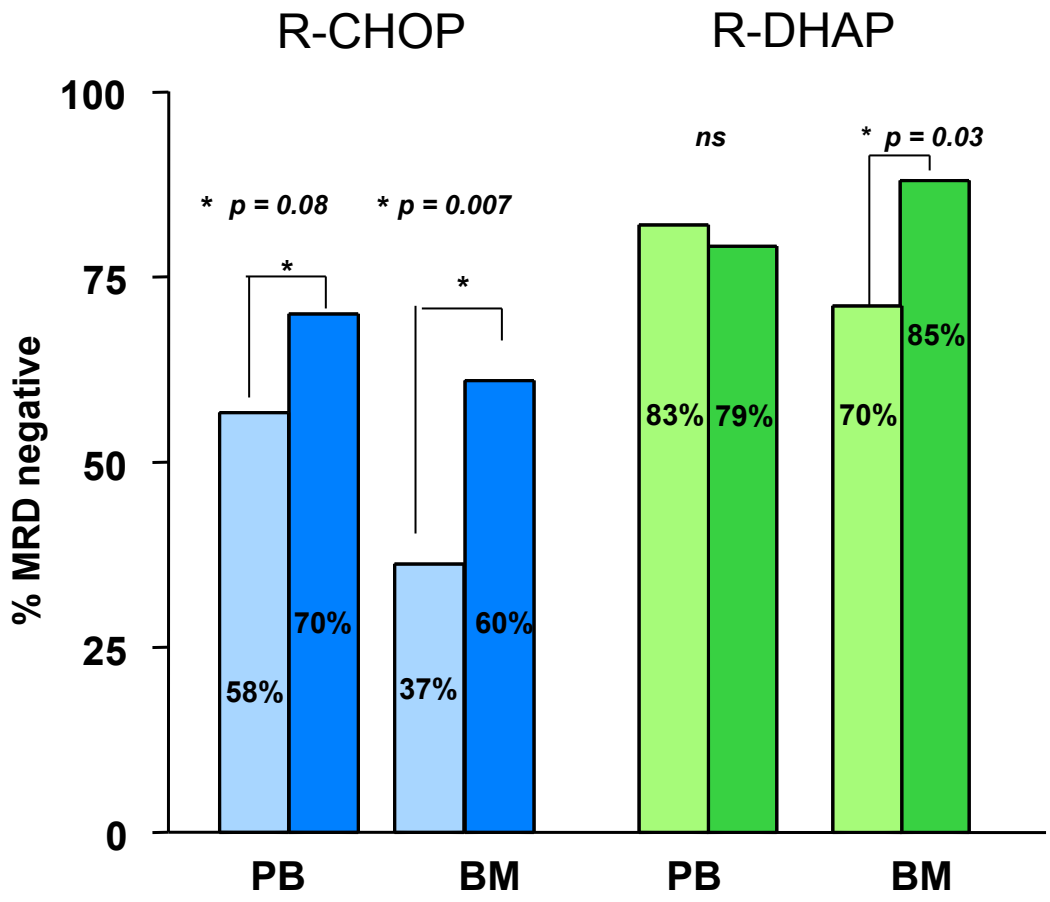




Hermine, Lancet 2016

MRD at end of induction

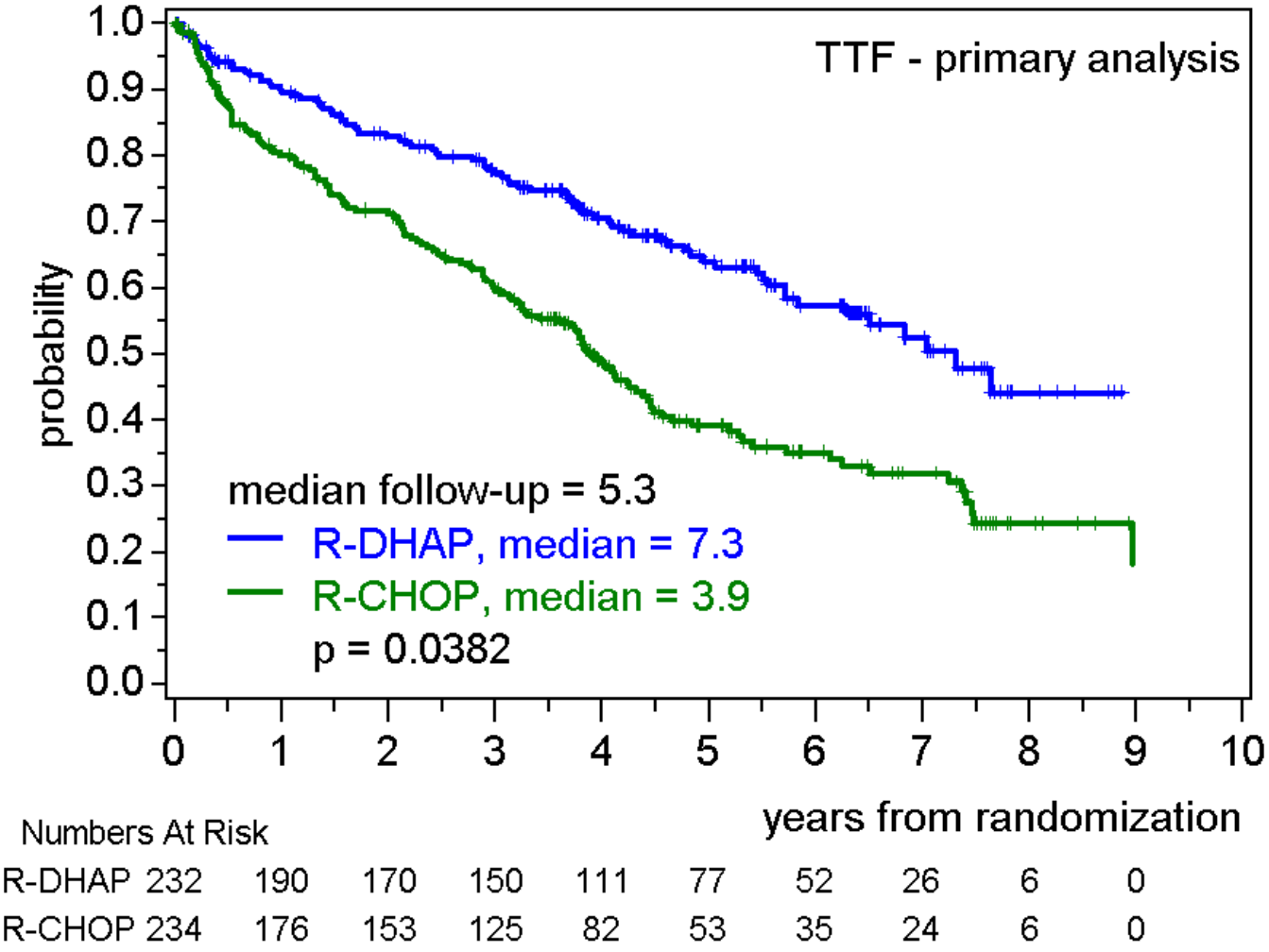
Effect of ASCT



Hermine, Lancet 2016

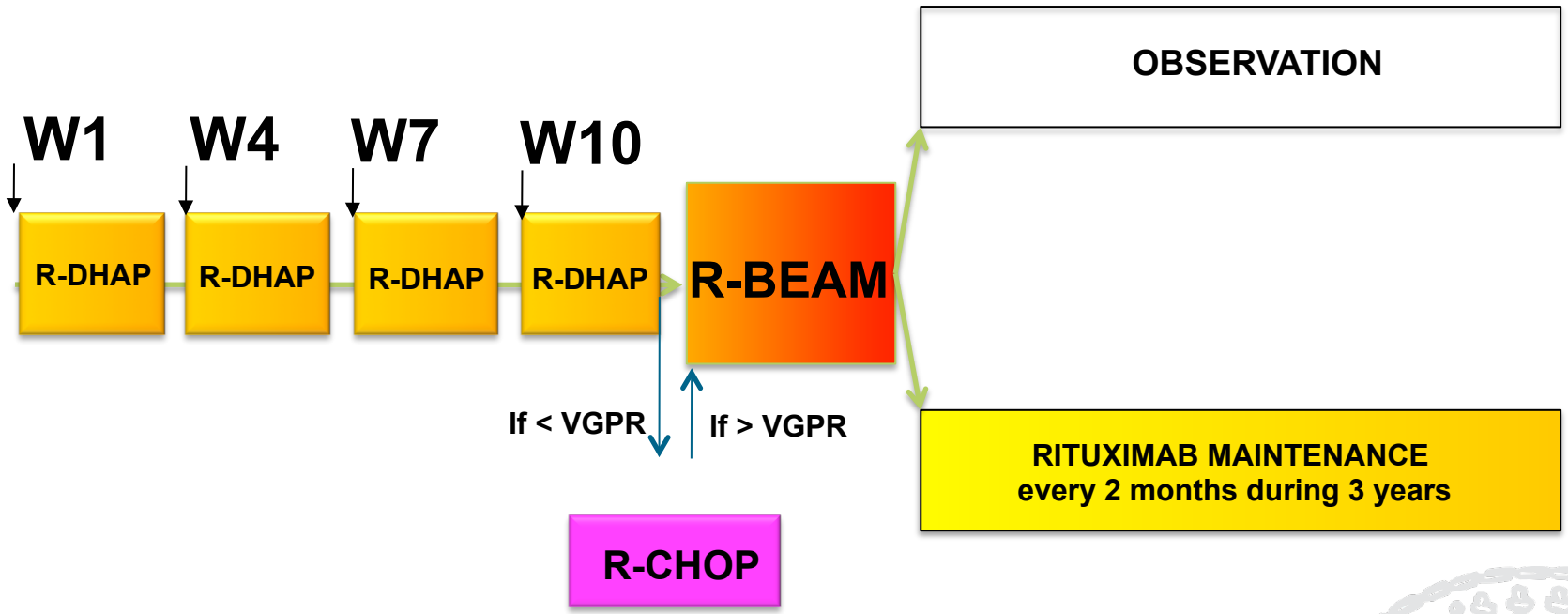
MCL younger

Time to treatment failure



Hermine, Lancet 2016

LyMa trial



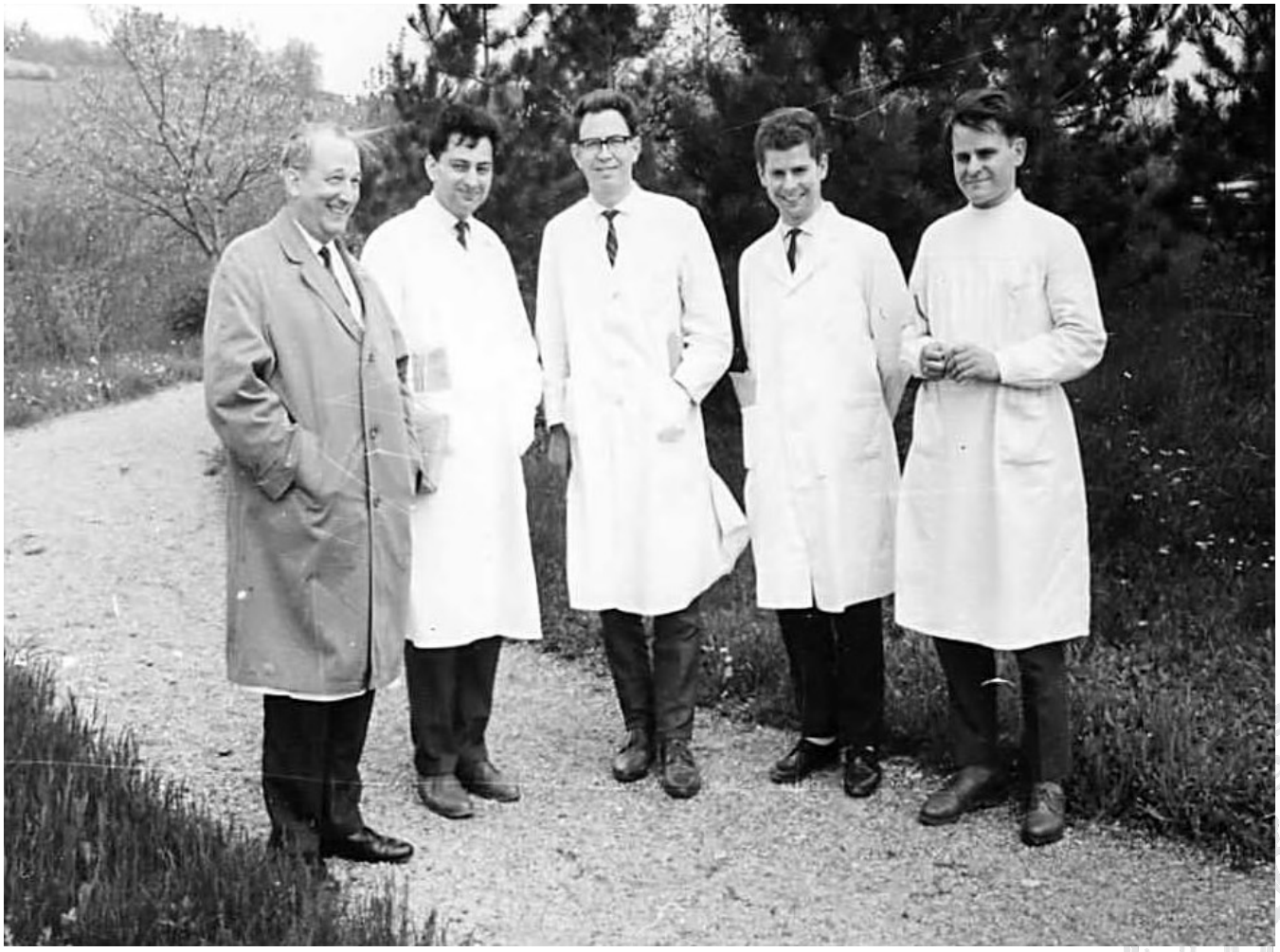
R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

Le Gouill, ASH 2016

Bendamustine:

An ‘agent’ with a long history



- **synthesis : W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)**
- **Published in Journal für Praktische Chemie, Vol. 20, issue 3-4, 1963**
- **IMET 3393 was developed by H. Knöll and later named Cytostasan**

young patient (≤65)	elderly patient (>65)	compromised patient
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higher relapse		
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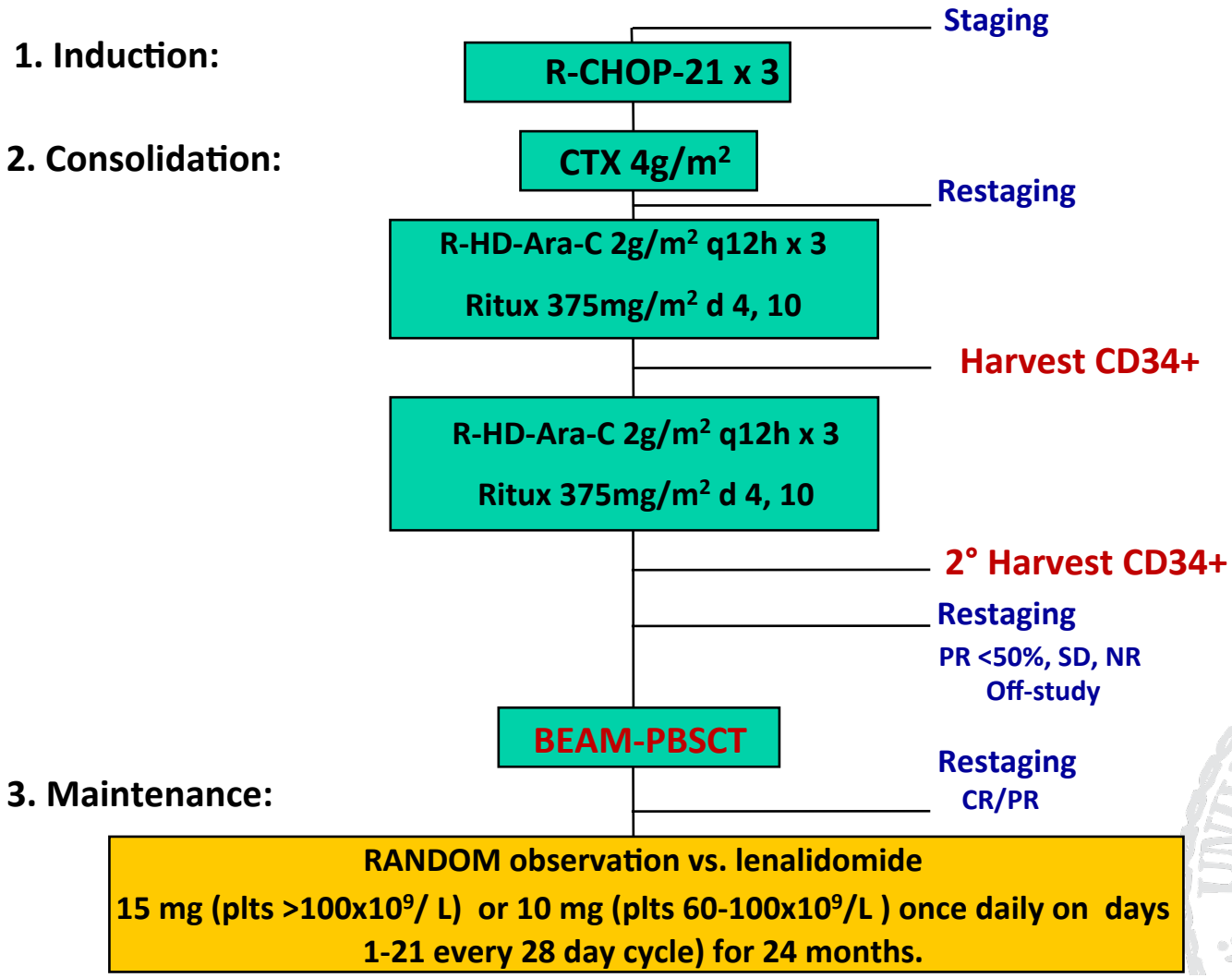
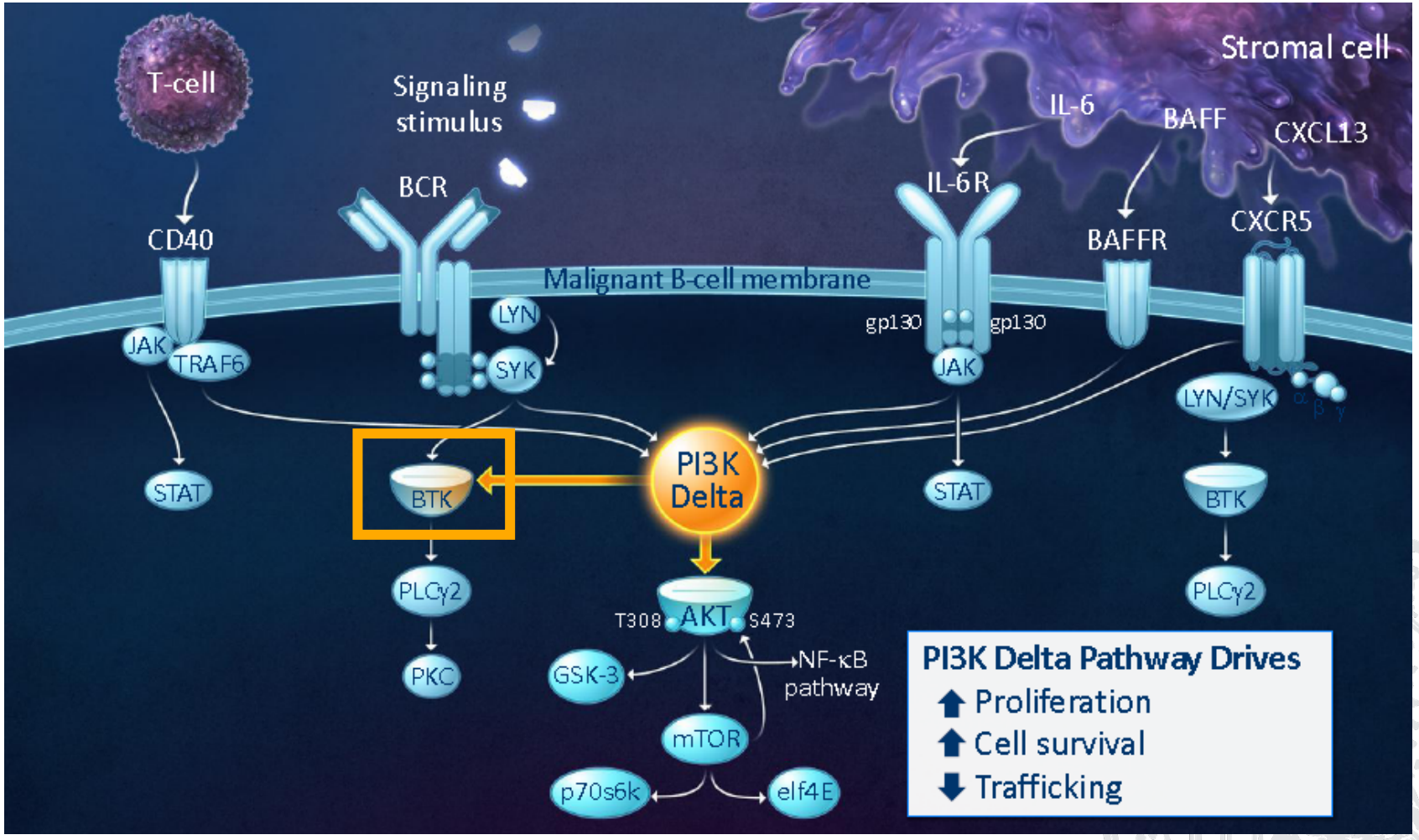
The MCL0208 trial



Mantle cell lymphoma

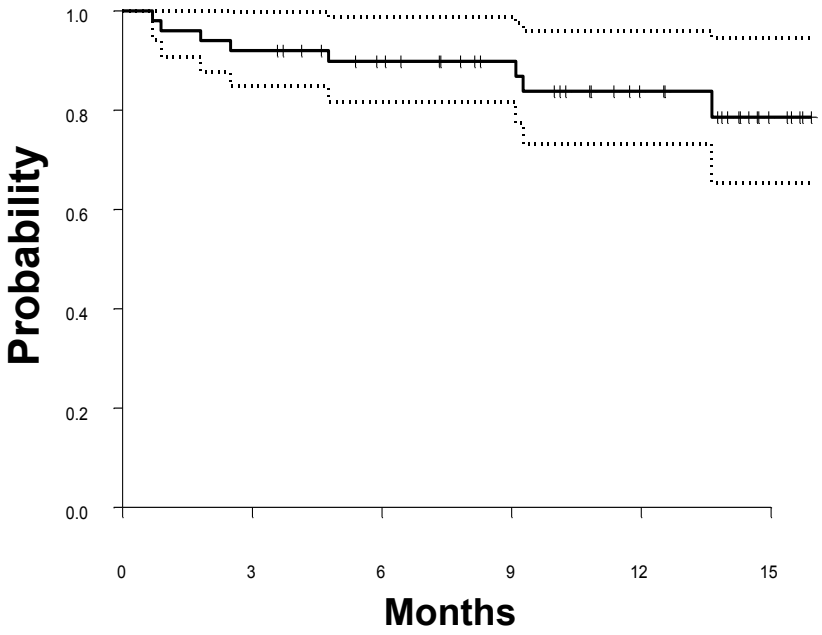
B-cell receptor pathway



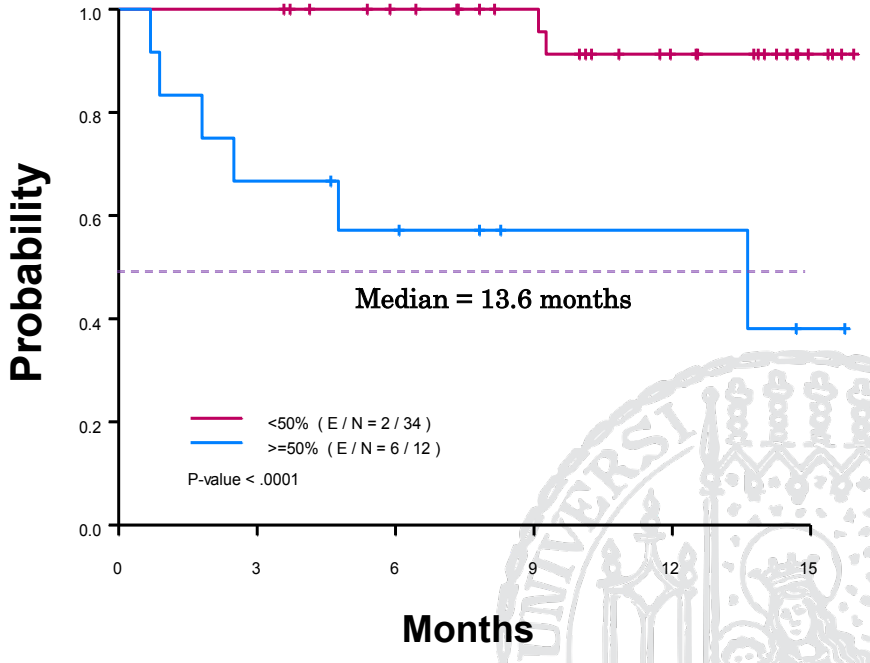
Ibrutinib Rituximab in MCL

Progression-free survival

Overall PFS (n=50)



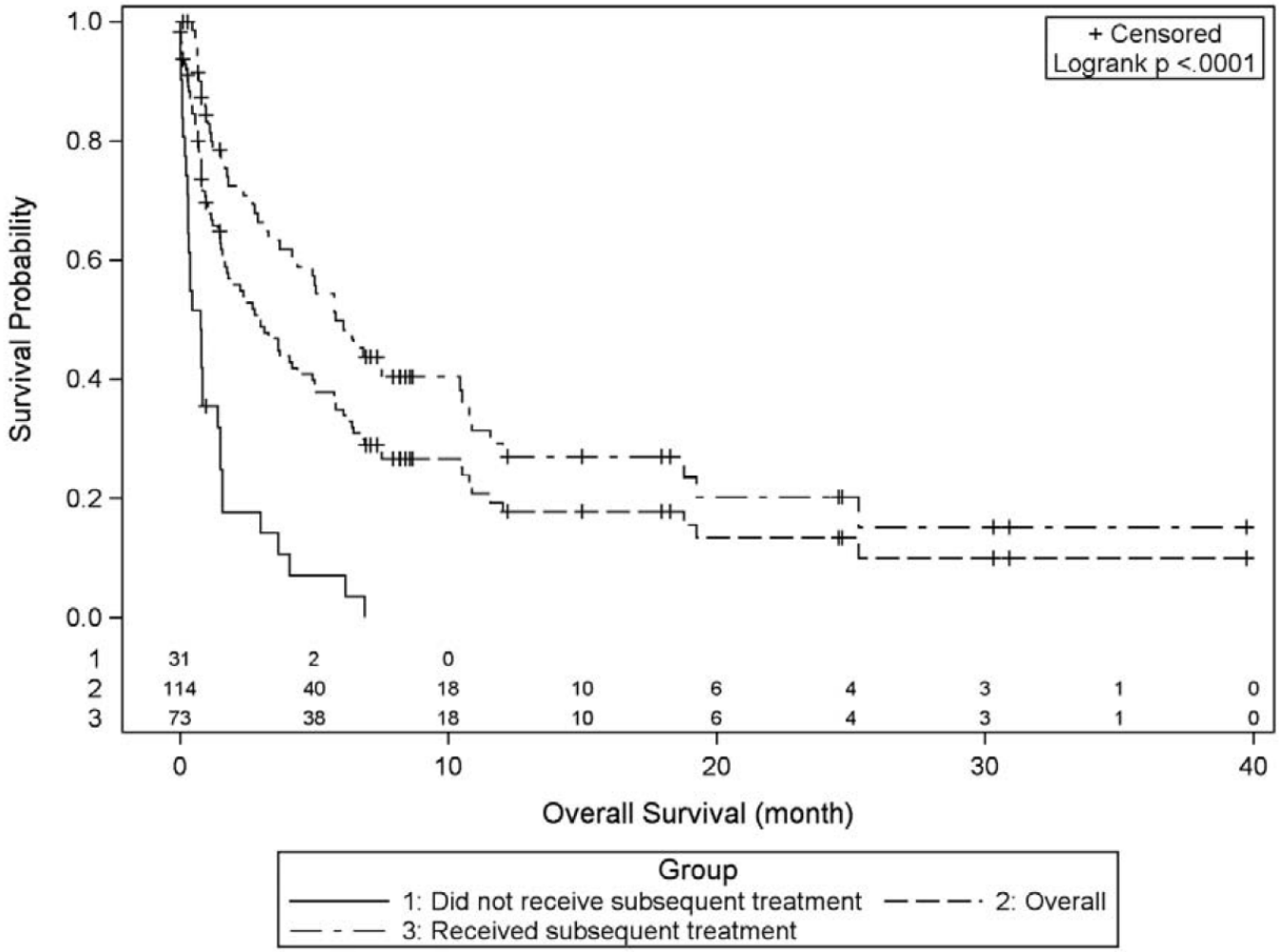
PFS by Ki67



Wang, Lancet Oncology 2016

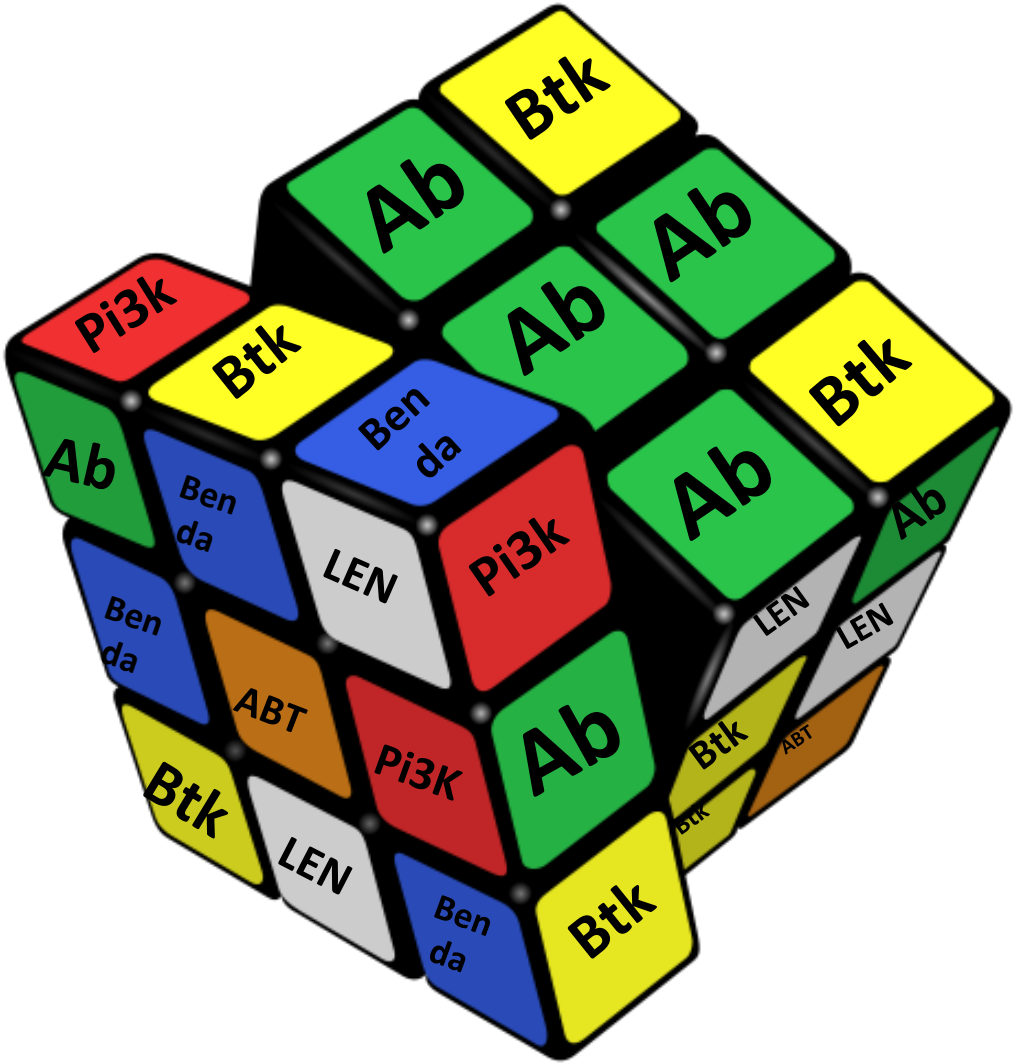
Relapsed mantle cell lymphoma

Failure under ibrutinib



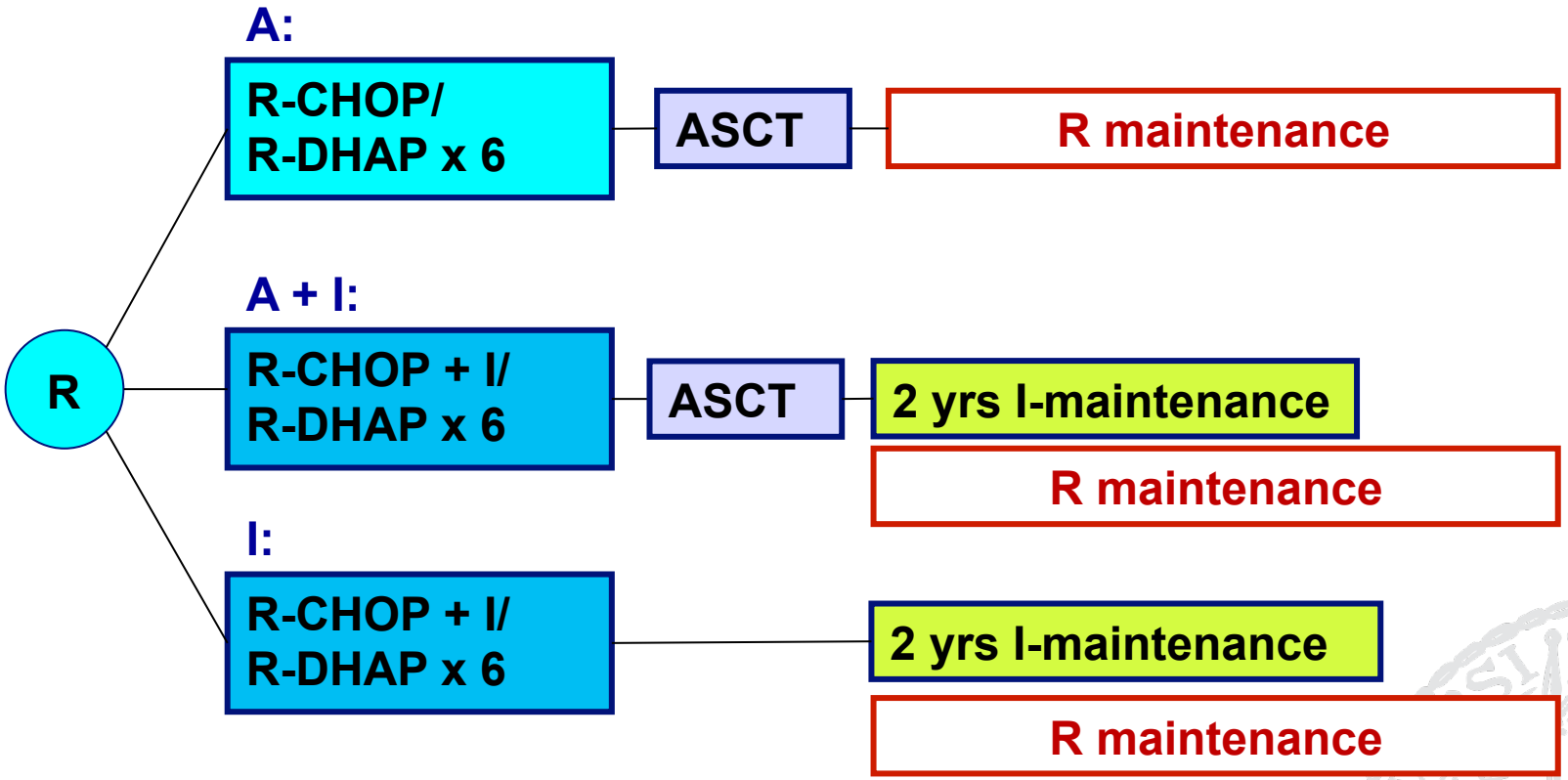
Martin, Blood 2016

The era of combinations



Triangle (from 5/2017)

add on vs head to head comparison



superiority/non-inferiority: time to treatment failure
HR: 0.60; 65% vs. 77% vs. 49% at 5 years

Planned Countries & sites

1) Sponsor

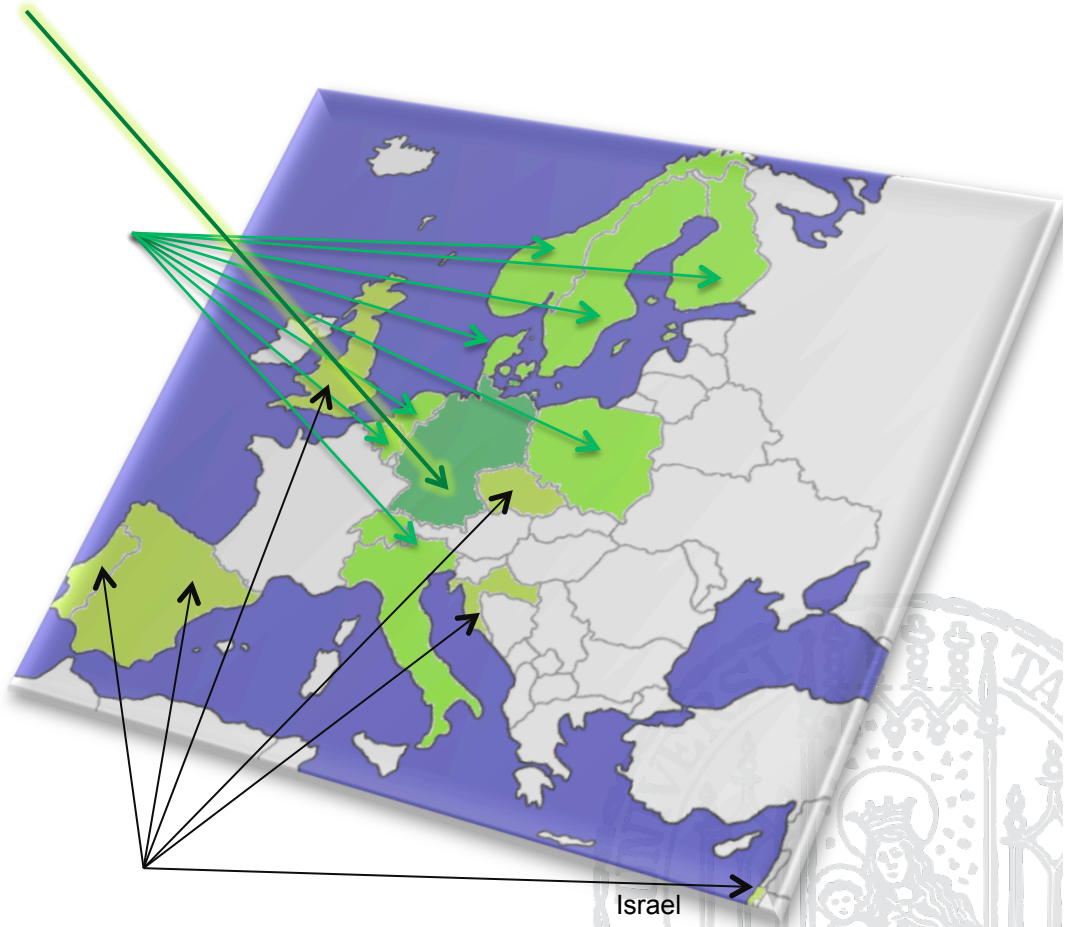
Germany	→	60 sites

2) Countries in safety run-in

Sweden	→	8 sites
Norway	→	5 sites
Denmark	→	6 sites
Finland	→	3 sites
The Netherlands	→	25 sites
Belgium	→	8 sites
Italy	→	34 sites
Poland	→	7 sites
UK	→	25 sites

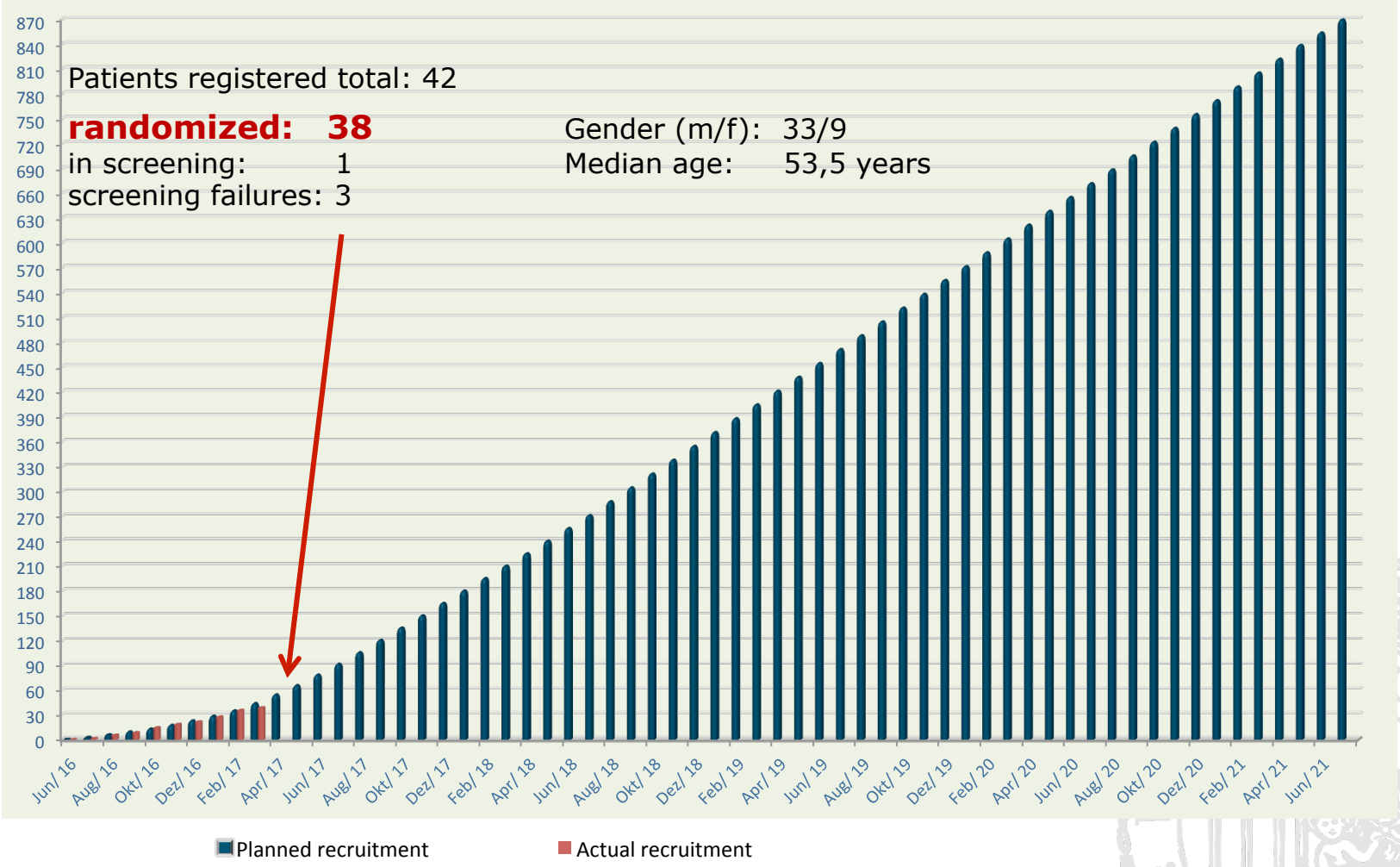
3) Countries following after safety run-in

Croatia	→	4 sites
Czech Republic	→	5 sites
Israel	→	7 sites
Portugal	→	1 site
Spain	→	14 sites
Switzerland	→	12 sites



TRIANGLE Recruitment:

20. March 2017



TRIANGLE Recruitment:

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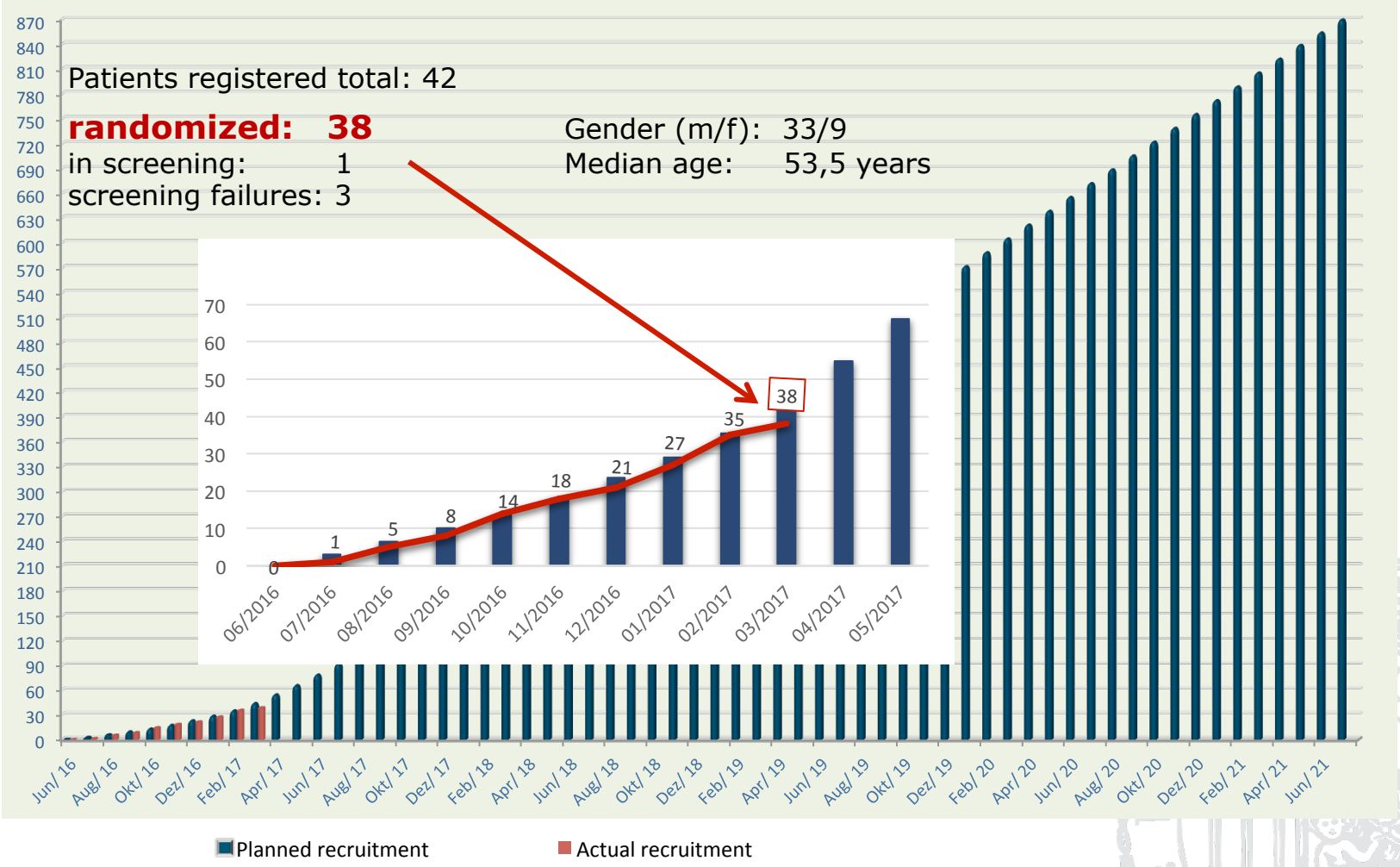
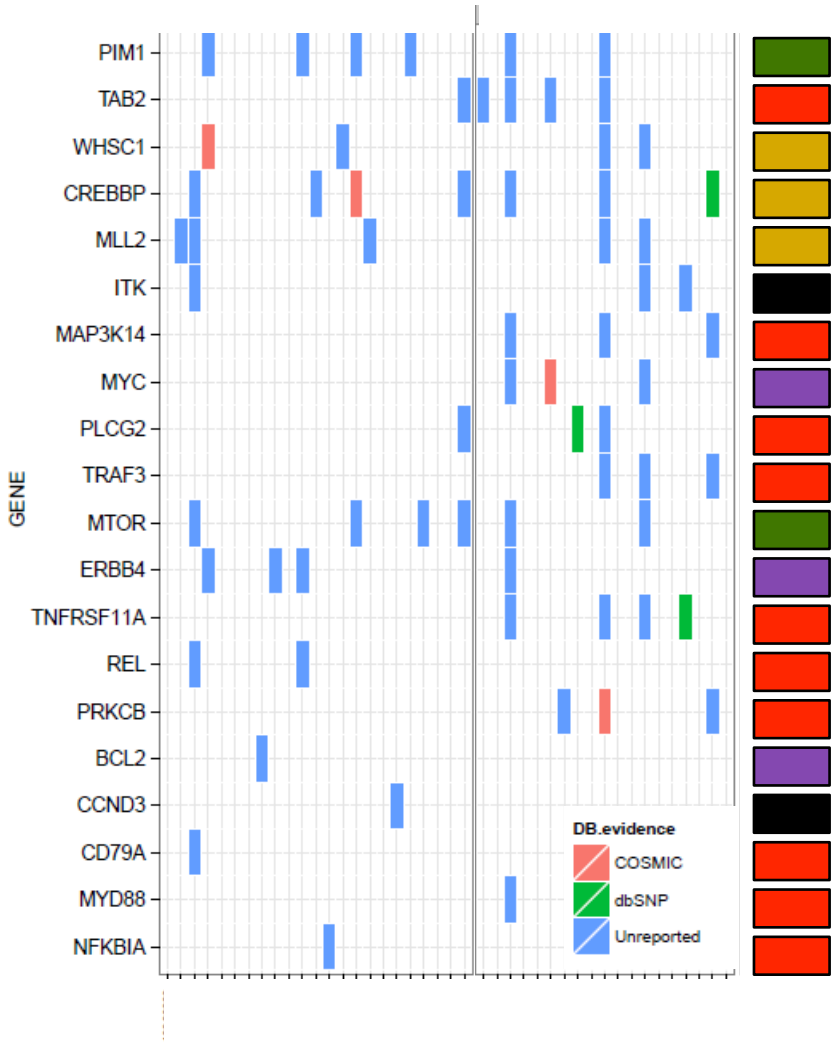
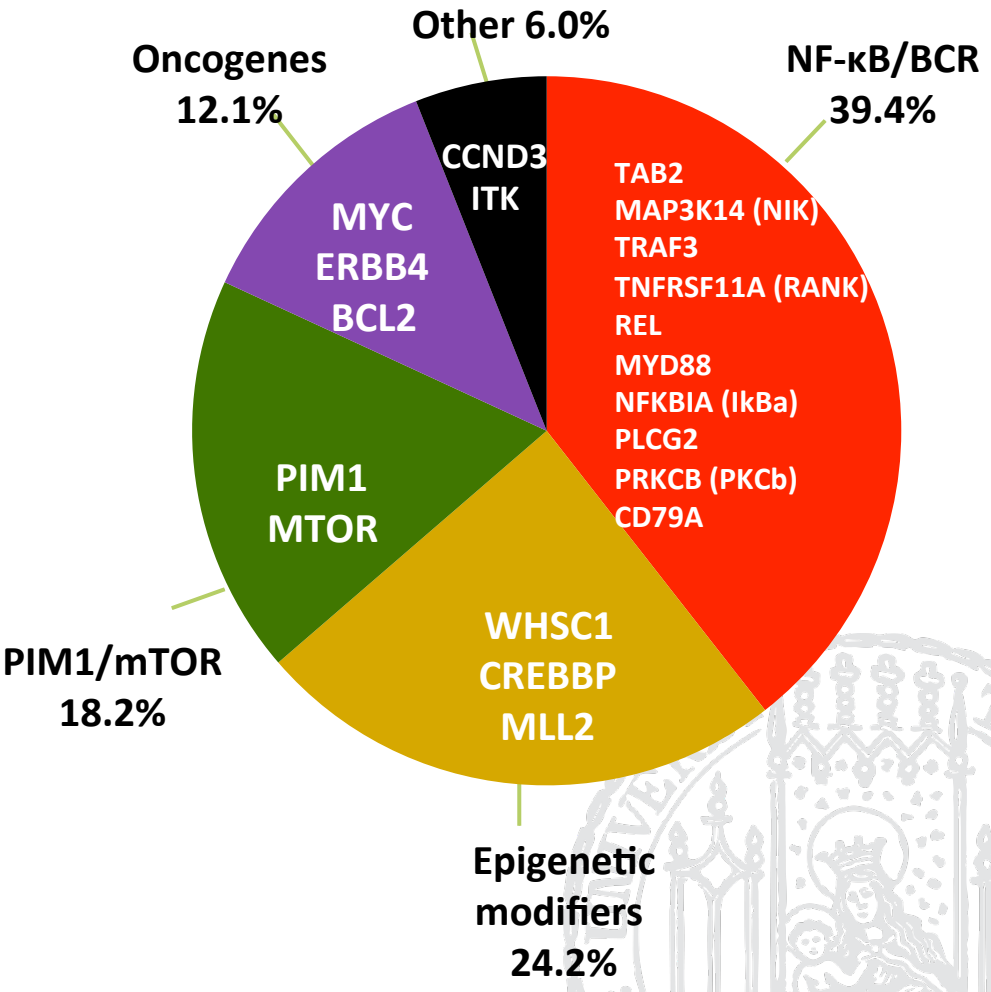


NF-κB, PIM / mTOR, and Epigenetic Modifiers

Differential mutations





Balasubramanian, ASH 2014

P316

The Combination of Ibrutinib and Venetoclax (ABT-199) Rapidly Achieves Complete Remissions in Patients with Relapsed / Refractory Mantle Cell Lymphoma

Preliminary Results of the Phase II AIM Study

Constantine S. Tam, Andrew Roberts, Mary Ann Anderson, Sarah Jane Dawson, Rodney Hicks, Christiane Pott, David Westerman, Glenda Burke, Sarah Kamel, Martin Dreyling, Mark Dawson, John F. Seymour

Peter MacCallum Cancer Center and Royal Melbourne Hospital, Melbourne, Victoria, Australia

BACKGROUND

- Both Ibrutinib and venetoclax (ABT-199) have single-agent activity in relapsed / refractory Mantle Cell Lymphoma (MCL).
- Although monotherapy achieves response rates of 68 – 75%, complete remissions (CR) are uncommon at <25%, and median PFS is limited to <18 months.
- The combination of ibrutinib and venetoclax is supported by multiple preclinical models.
- We report the preliminary results of the first-in-human combination of ibrutinib and venetoclax given at full doses.

METHODS

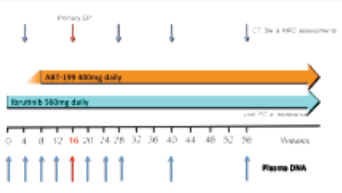
- The ABT-199 & Ibrutinib in MCL (AIM) Study is a Phase II, investigator-initiated study conducted at 2 Melbourne hospitals.
- Patients must have MCL and at least 1 prior line of systemic therapy.
- Primary endpoint = CR rate at 4 months.

Ibrutinib Phase II in MCL : CR Rates

- We also evaluated responses using PET scans, gastro / colonoscopy (as appropriate), and assessed MRD using multi-parameter marrow flow cytometry (sensitivity $<10^{-4}$), ASO-PCR and circulating tumour DNA testing.

TREATMENT PLAN

- Patients received 4 weeks of ibrutinib (560mg) and were then restaged.
- Venetoclax is added to ibrutinib from week 5 and stepped up weekly (daily dosages of 50/100/200/400mg) with tumour lysis syndrome monitoring.
- Patients then receive both drugs at full doses until intolerance or disease progression.



RESULTS

Study Status Overview

- 15 (of target 24) subjects enrolled.
- 11 started venetoclax after 4-week ibrutinib induction.
- 9 fully escalated to venetoclax 400mg/day; no patient to date has failed to escalate fully.
- 8 patients are fully evaluable for primary endpoint (4 months), and their results are reported in detail here.

Patient Characteristics (n = 8)

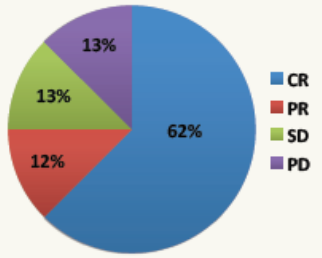
Characteristic	Value
Age in years (median, range)	72 (53 – 77)
Male / Female	7 / 1
Performance Status (ECOG) ≥ 1	6
MIPI • High / Intermediate	6 / 2
Prior Lines of Therapy • Chemorefractory (%) • Prev hyperCVAD or autoSCT (%)	2 (1 – 7) 63 25
Current Status • Died of progressive disease • Alive and continuing therapy • Time on therapy (days)	 1 7 120 (85 – 285)

Drug Related Adverse Events (n = 8)

Adverse Event	All Grades N (%)	Grade 3-4 N (%)
Diarrhoea	5 (63)	0
Bruising / bleeding	4 (50)	0
Nausea / vomiting	4 (50)	0
Dyspepsia	2 (25)	0
Fatigue	2 (25)	0
Oral candidiasis	2 (25)	0
Respiratory Tract Infection	1	0
Mouth ulcer	1	0
Peripheral oedema	1	0
Cramps	1	0
Sensitive tongue	1	0
Urinary tract infection	1	0
Cellulitis	1	0
Anaemia	1	0
Atrial fibrillation	1	1
Irregular heart beat	1	0
Fever (possible TLS)*	1	1

- One possible case of TLS (* in table): 66 yo female, chemorefractory MCL with rapid growth kinetics and bulky (15cm) disease, no response to ibrutinib induction, developed fever and elevated LDH on day 3 of venetoclax 50mg. Did not meet formal TLS criteria. Successfully restarted venetoclax and fully escalated to 400mg venetoclax, with stable disease.

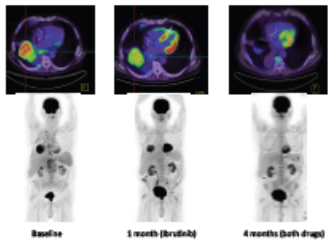
Response Rates (n = 8)



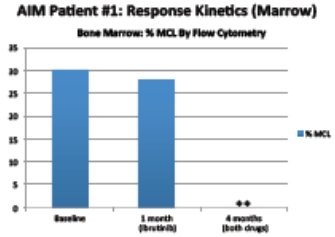
- Complete remissions in 5 (62%) patients – 4 had assessable disease in marrow, all 4 were MRD-negative at <0.01% by flow cytometry in the marrow.
- ASO-PCR results available in 2 complete responders – MRD detectable at 0.01% and 0.0001% at 4 months.
- 1 patient was classified as PR due to low-volume, non-FDG avid disease that was poorly visualized by PET.
- 1 patient had stable disease at 4 months (44% ↓ SPD) after progressing through ibrutinib induction (23% ↑ SPD).
- 1 patient (blastic MCL) progressed through ibrutinib and venetoclax, and died of progressive disease at 54 days.

Examples of Response Kinetics

AIM Patient #1: Response Kinetics (PET)



AIM Patient #1: Response Kinetics (Marrow)



**MRD Negative at < 10^{-4} (660,000 events counted)

CONCLUSIONS

- The combination of ibrutinib and venetoclax is feasible and highly active.
- The major toxicities are gastrointestinal.
- Achievement of deep responses of <0.01% MRD opens up possibilities for treatment cessation.

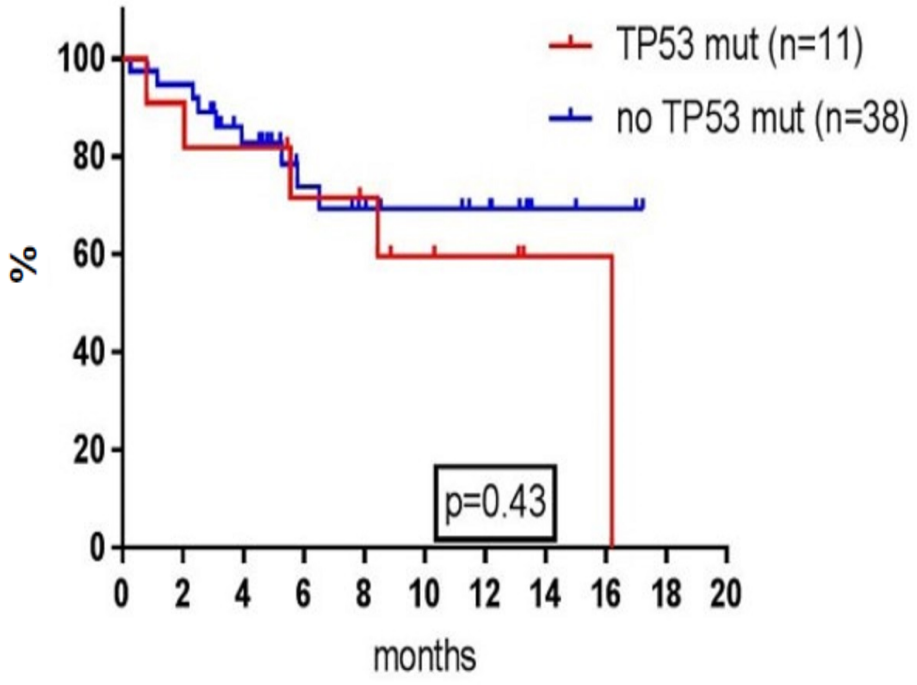
Disclosures

CST: Janssen and AbbVie (honoraria and research funding); AWR: AbbVie and Genentech (research funding); JFS: AbbVie, Genentech, Janssen and Roche (honoraria). This study is supported by Janssen, AbbVie and the Victorian Cancer Agency.

Relapsed mantle cell lymphoma

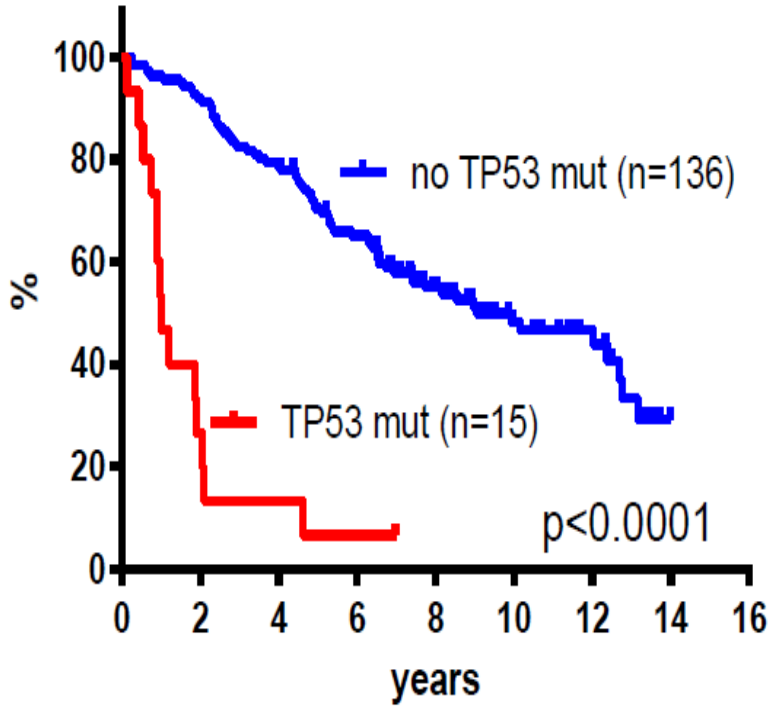
Ibrutinib-Lenalidomid-R

NORDIC MCL6 PHILEMON



Jerkeman, ASH 2016

NORDIC MCL2/3



Eskelund, ASH 2016

European MCL Network

Study generation 2017

< 65 years	> 60 years	> 65 years
MCL younger: R-CHOP/DHAP =>ASCT R-CHOP/DHAP+I =>ASCT => I R-CHOP/DHAP + I => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/-Lenalidomide	*MCL elderly I:* BR +/- Ibrutinib => Rituximab M +/- Ibrutinib

1. Relapse

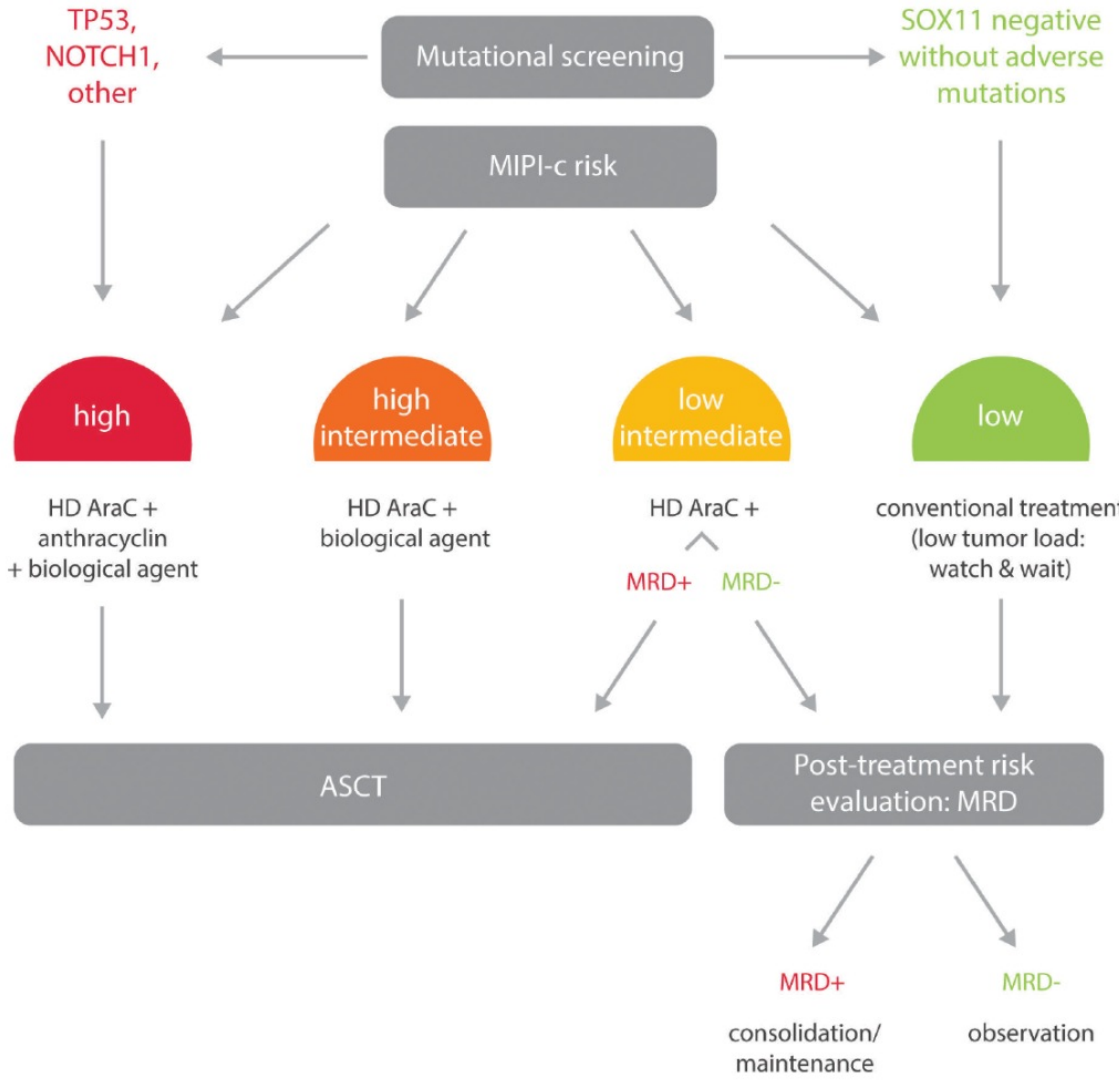
R-HAD +/- Bortezomib

2. Relapse (or not qualifying for R-HAD)

Ibrutinib vs Temsirolimus	*BeRT* BR-Temsirolimus

First line MCL

Suggested therapeutic algorithm



Dreyling, Haematologica 2016

Annual conference 2015 in Vicenza

www.european-mcl.net

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