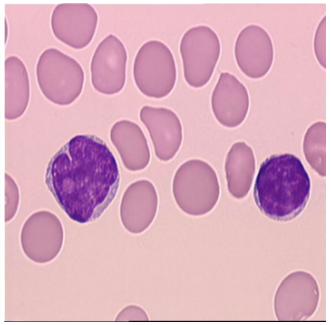
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Medizinische Klinik und Poliklinik III
Direktor: Prof. Dr. W. Hiddemann

*Indolent Lymphoma Workshop * Bologna, May 15 2017*

Copanlisib in patients with relapsed or refractory indolent B-cell lymphoma

primary results of the pivotal CHRONOS-1 study



GLSG

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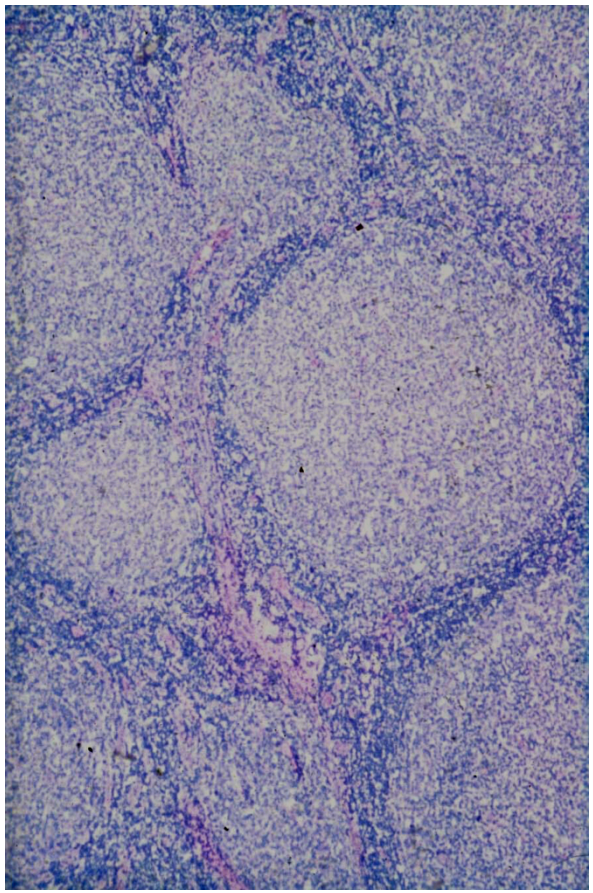
Follicular lymphoma:

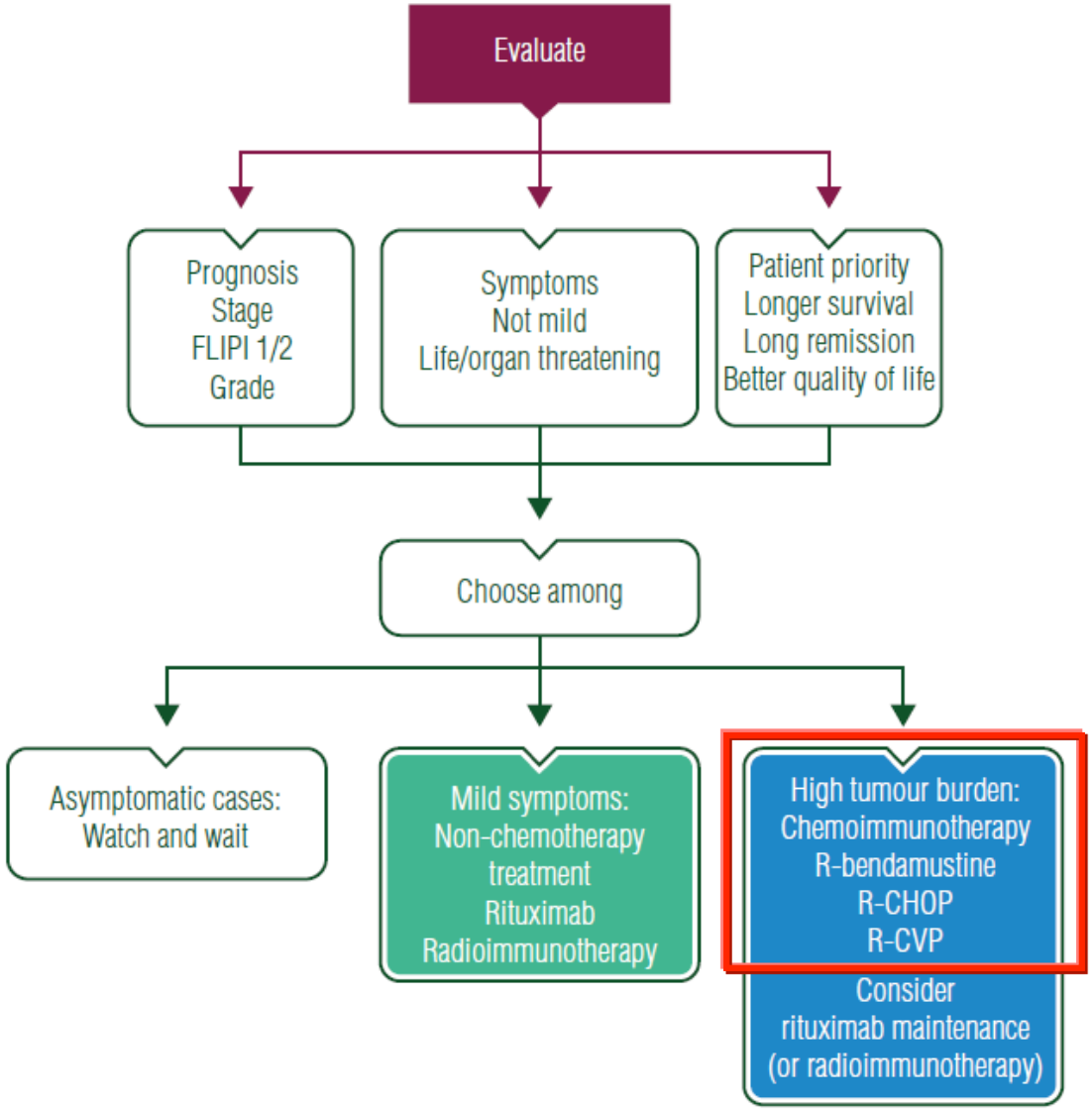
Clinical characteristics



- about 25% of lymphoma
- Median age 60-65 years
- 85% advanced stage III/IV
- Indolent clinical course (median survival 15-20 years)
- In relapse still sensitive to therapy

First line treatment in FL

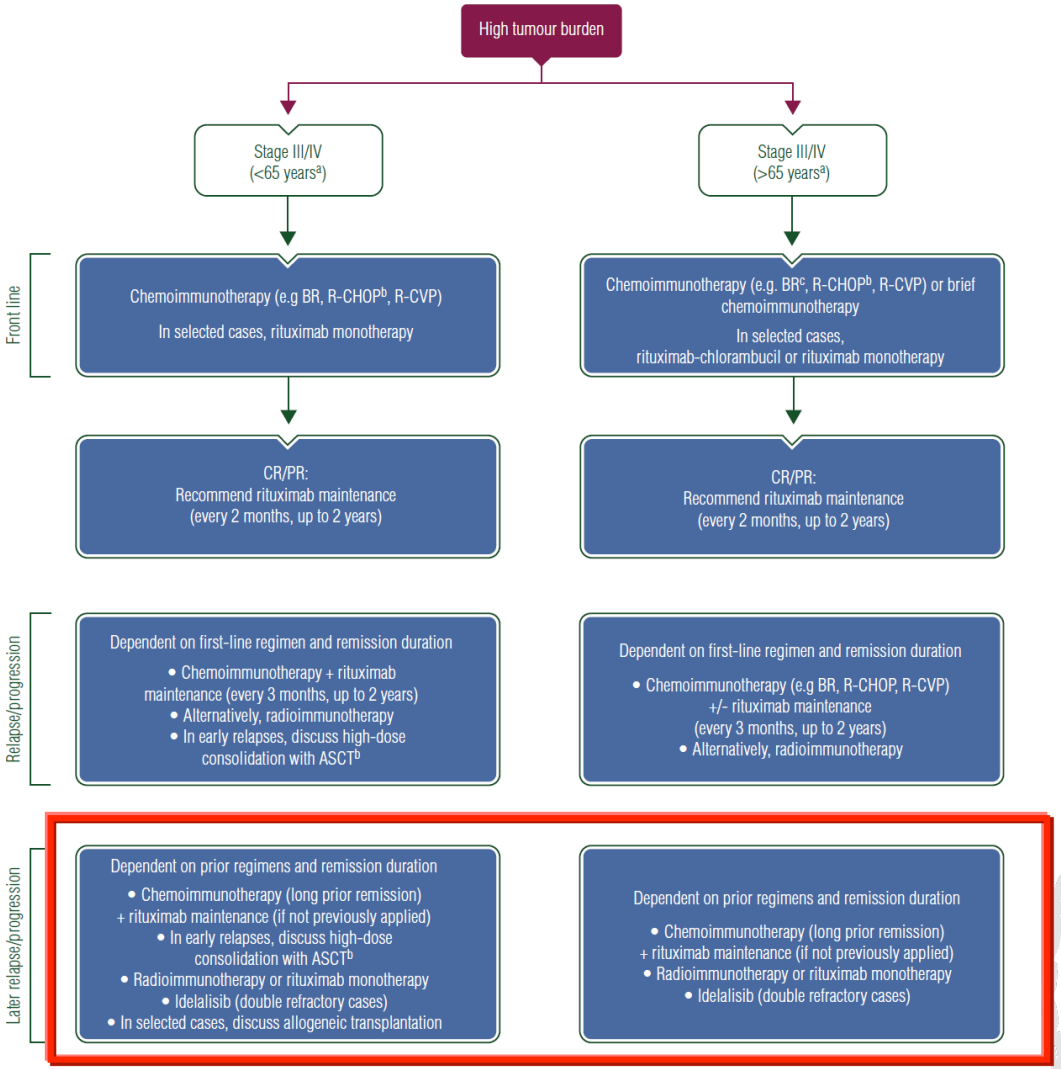
Therapeutic algorithm



Dreyling, ESMO CR 2016

Follicular Lymphoma

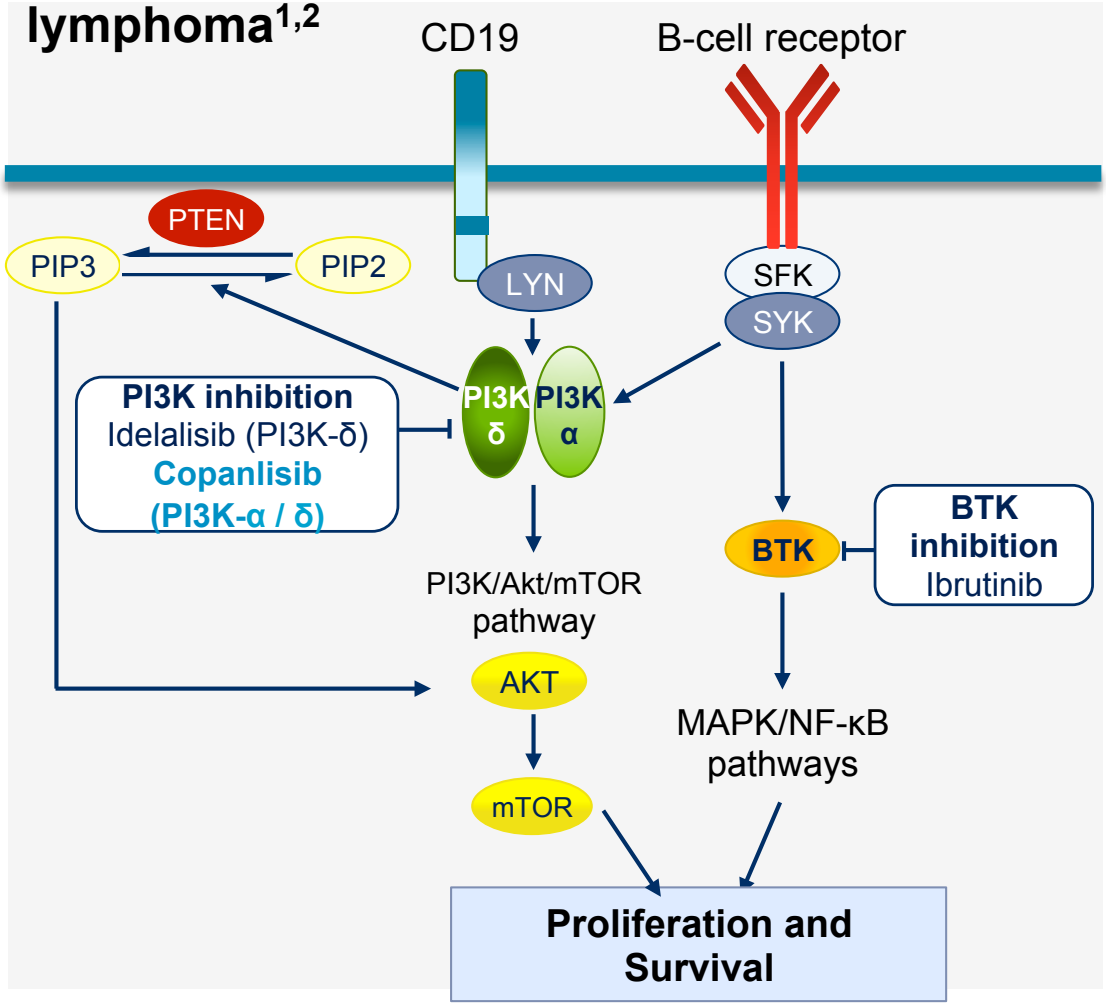
Therapeutic algorithm



Dreyling, ESMO CR 2016

Background (1)

Key signaling pathways in B-cell lymphoma[1,2]



- The B-cell receptor (BCR) and phosphoinositide 3-kinase (PI3K) signaling pathways play a key role in the proliferation and survival of indolent B-cell lymphoma
- Targeted inhibition of BCR / PI3K signaling has emerged as a therapeutic strategy for relapsed / refractory indolent B-cell lymphoma

Roschewski, Nat Rev Clin Oncol 2014; Vaqué, Haematologica 2014; Wiestner, Haematologica 2015; Pongas, Semin Oncol 2016;

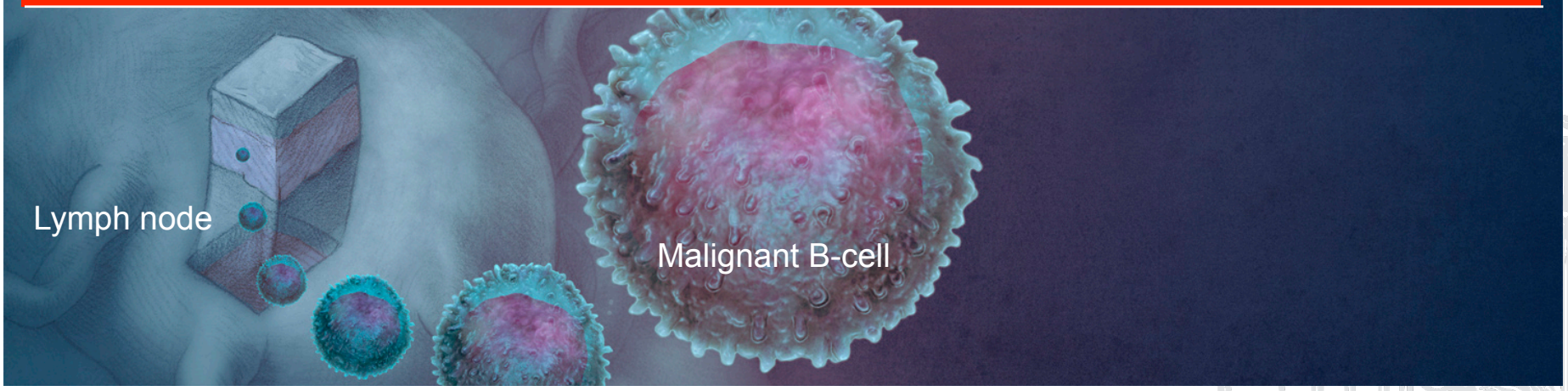
Background (2)

- An oral PI3K-δ isoform selective inhibitor (Idelalisib) is approved as 3rd-line treatment for follicular lymphoma (FL) or small lymphocytic lymphoma (SLL)
  - However, US prescribing information contains a black box warning for fatal and / or severe diarrhea or colitis, hepatotoxicity, pneumonitis, and intestinal perforation
  - More recently, reports of a high incidence of serious adverse events associated with idelalisib in combination with standard therapies has led to the early termination of a number of clinical trials
- Copanlisib is an intravenous pan-class I PI3K inhibitor with predominant and potent activity against the PI3K-α and PI3K-δ isoforms
- In Phase I and Phase II studies, copanlisib has demonstrated promising clinical activity and a manageable safety profile in heavily pretreated patients with various subtypes of indolent and aggressive malignant lymphoma

Miller , Clin Cancer Res 2015; Greenwell, Expert Rev Anticancer Ther 2017; Patnaik, Ann Oncol 2016; Dreyling, EHA Congress 2016

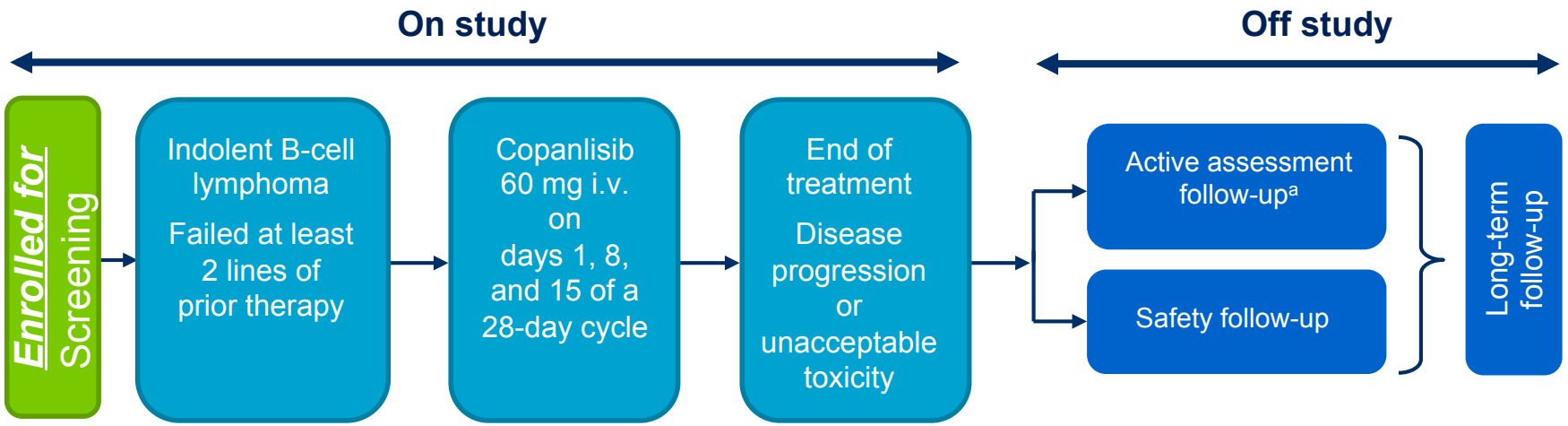
Class I PI3K isoforms

Class I PI3K isoform	Cellular expression	Primary physiological role
Alpha (α)	Broad	Insulin signaling and angiogenesis
Beta (β)	Broad	Platelet function
Gamma (γ)	Leukocytes	Neutrophil and T-cell function
Delta (δ)	Leukocytes	B-cell signaling, development, and survival



Okkenhaug, Nat Rev Immunol 2003;
Seiler, Drugs 2016; Iyengar, Blood 2013

Study design



Lymphoma types

- FL (grades 1-3a)
- MZL
- SLL
- LPL / WM

Primary endpoint

- ORR

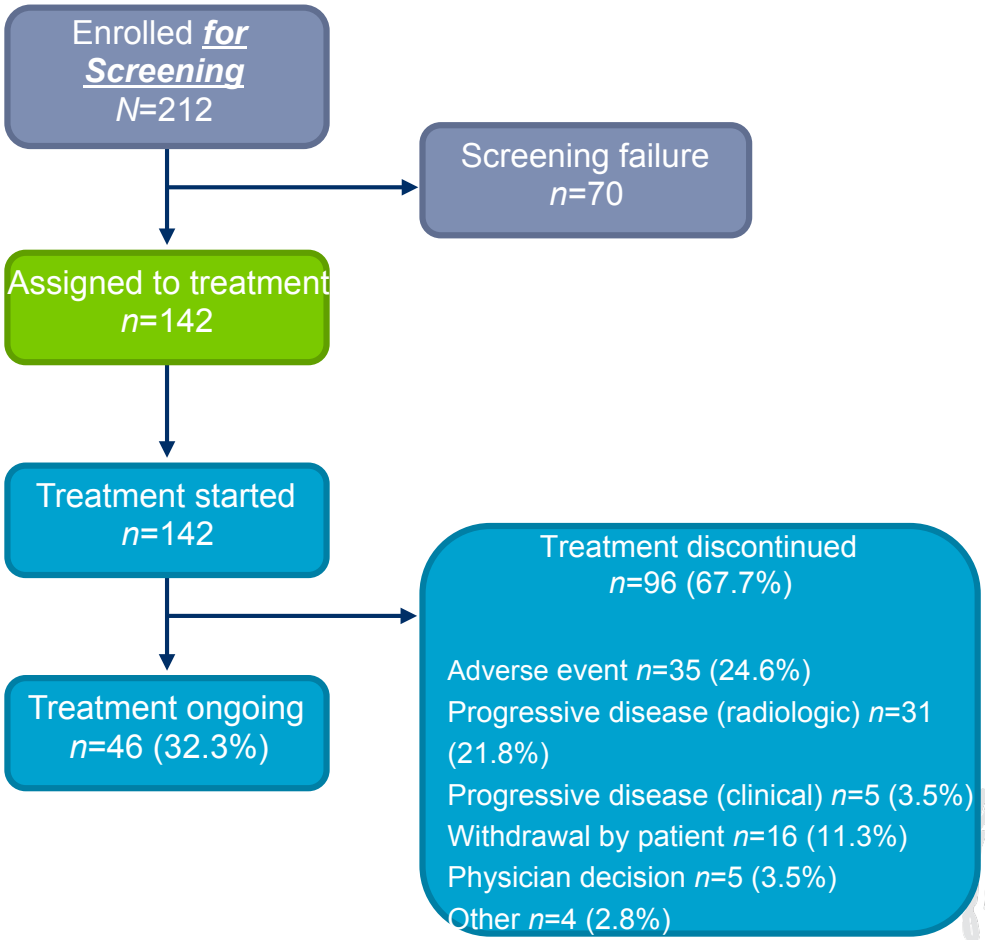
Secondary endpoints

- PFS
- DoR
- OS
- Safety
- Quality of life

Tertiary endpoints

- Disease control rate
- Duration of stable disease
- ECOG scale
- Lesion size
- EQ-5D questionnaire and visual analog scale

Patient Flow



Patient characteristics

	Total (*N*=142)
Males, *n* (%)	71 (50.0%)
Median age, years (range)	63 (25-82)
Median time from most recent progression, months (range)	8.3 (1-73)
Median prior anti-cancer therapy lines (range)	3 (2-9)
Prior rituximab, *n* (%)	142 (100%)
Prior alkylating agents, *n* (%)	142 (100%)

- Most patients (80.3%) had advanced-stage disease at study entry (stage III or IV)
- FL was the most common histology (73.2%)

Copanlisib treatment

	Total (*N*=142)
Median duration of treatment, weeks (range)	22 (1-105)
Median number of cycles (range)	5.5 (0.3-26)
Median percentage of planned dose (range)	96% (51-103%)
Dose interruptions, *n* (%)	105 (73.9%)
Median duration of interruptions, weeks (range)	1 (0-3)
Dose modifications, *n* (%) Dose reduction to 45 mg Dose reduction to 30 mg	 37 (26.1%) 8 (5.6%)

- 91.4% of dose interruptions or delays were due to adverse events
- 54.9% of dose interruptions lasted less than 1 week

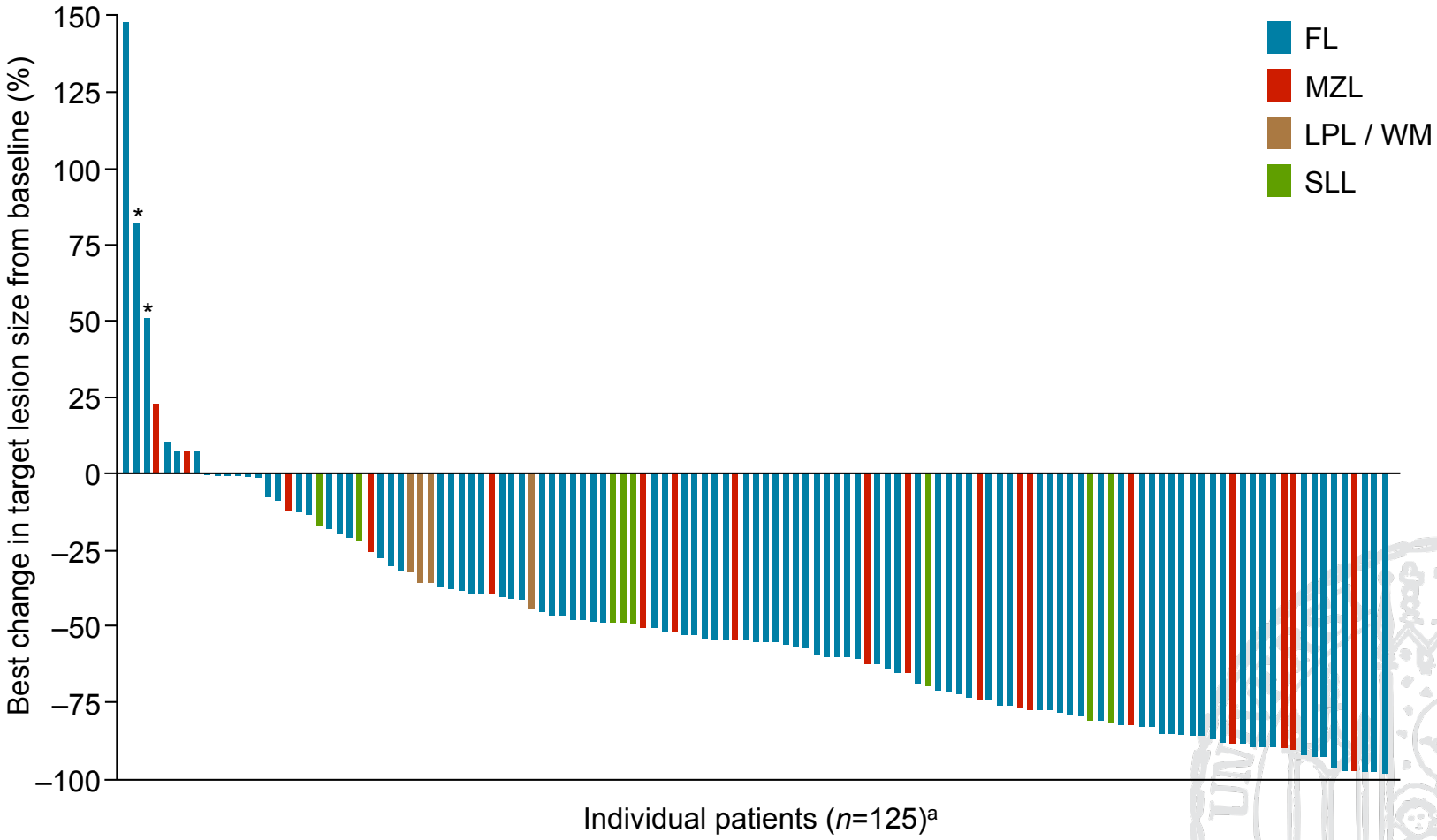
Safety profile

Most common TEAEs (≥15% incidence), *n* (%)	Total (*N*=142)		
Grade	**All**	**3**	**4**
Any TEAE	140 (98.9%)	75 (52.8%)	38 (26.7%)
Hyperglycemia	71 (50.0%)	48 (33.8%)	10 (7.0%)
Diarrhea	48 (33.8%)	7 (4.9%)	0
Fatigue	43 (30.3%)	3 (2.1%)	0
Hypertension	43 (30.3%)	34 (23.9%)	0
Decreased neutrophil count	42 (29.6%)	11 (7.7%)	23 (16.2%)
Fever	36 (25.4%)	6 (4.2%)	0
Nausea	33 (23.2%)	1 (0.7%)	0
Lung infection	30 (21.1%)	18 (12.7%)	3 (2.1%)
Decreased platelet count	29 (20.4%)	9 (6.3%)	1 (0.7%)
Oral mucositis	28 (19.7%)	4 (2.8%)	0
Upper respiratory infection	26 (18.3%)	4 (2.8%)	0
Cough	23 (16.2%)	0	0
Anemia	22 (15.5%)	6 (4.2%)	0

2 patients (1.4%) had grade 3 pneumonitis and 1 patient had grade 4 colitis (0.7%)

- Three deaths (2.1%) were considered drug-related (2.1%): lung infection, respiratory failure, and a thromboembolic event (0.7% each)

Best Response (target lesions)

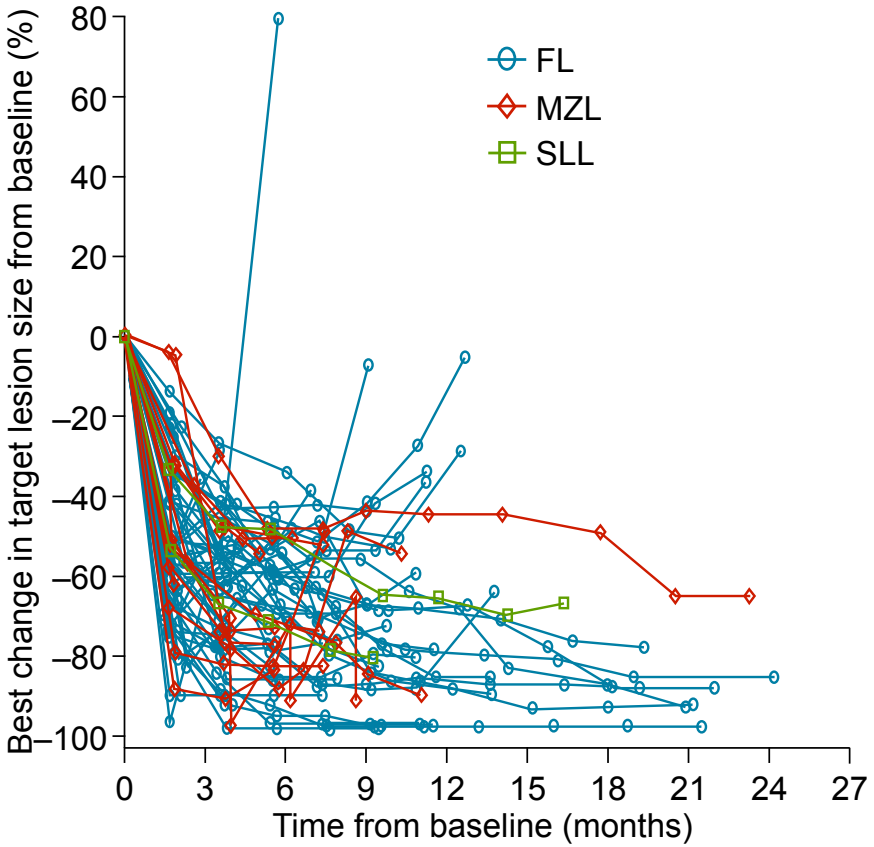


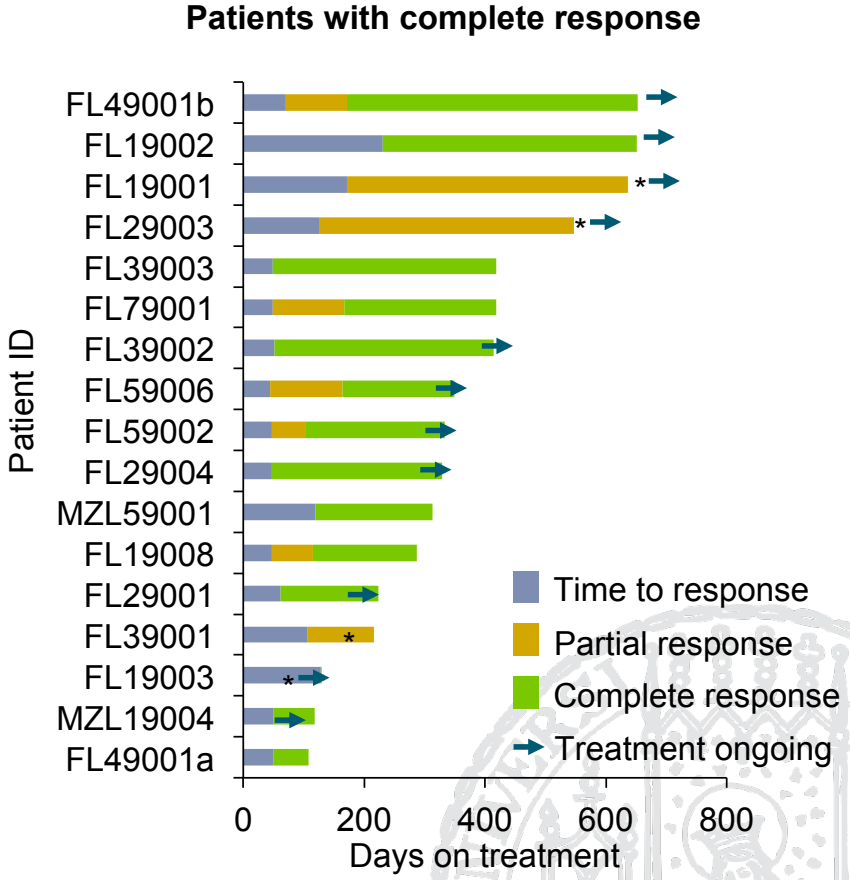
***Patient was assessed as having stable disease by independent review**

Primary endpoint: ORR

	FL (*n*=104)	MZL (*n*=23)	SLL (*n*=8)	LPL / WM (*n*=6)	Total (*N*=142)
Best response, *n* (%)					
Complete response	15 (14.4)	2 (8.7)	0	0	17 (12.0)
Partial response	46 (44.2)	14 (60.9)	6 (75.0)	1 (16.7)	67 (47.2)
Stable disease	35 (33.7)	4 (17.4)	1 (12.5)	3 (50.0)	42 (29.6)
Progressive disease	2 (1.9)	0	1 (12.5)	0	3 (2.1)
NE / NA	6 (5.8)	3 (13.0)	0	2 (33.3)	12 (8.5)
ORR, *n* (%)	61 (58.7)	16 (69.6)	6 (75.0)	1 (16.7)	84 (59.2)
95% CI	48.6-68.2	47.1-86.8	34.9-96.8	0.4-64.1	50.6-67.3
Disease control rate, *n* (%)	91 (87.5)	20 (87.0)	7 (87.5)	4 (66.7)	122 (85.9)
95% CI	79.6-93.2	66.4-97.2	47.4-99.7	2.3-95.7	79.1-91.2

Response over time

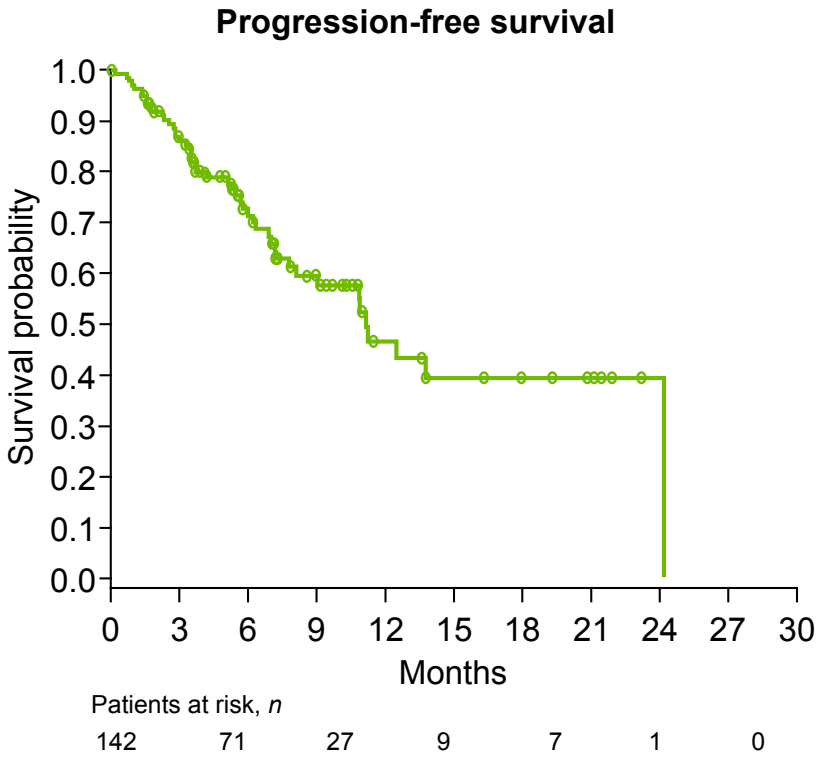


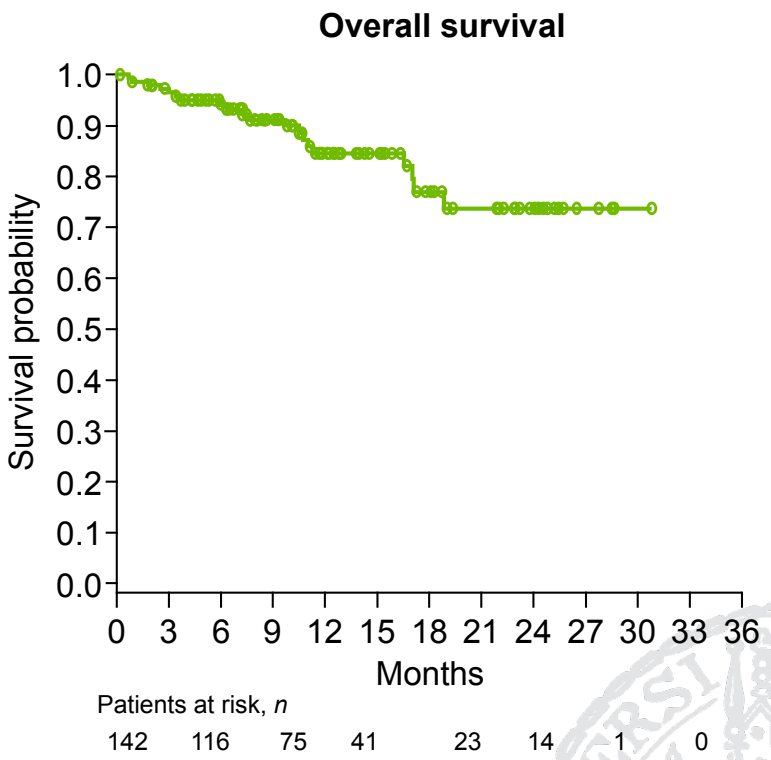


- **Median DoR was 22.6 months (range, 0-22.6; 95% CI 7.4-22.6)**

*Patient was assessed as having a complete response at the last assessment

Additional efficacy endpoints





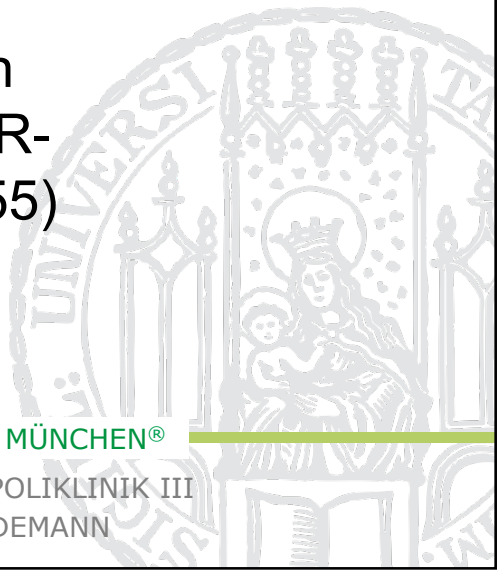
- Median PFS was 11.2 months (95% CI 8.1-24.2)

Summary

- Copanlisib demonstrated promising anti-tumor efficacy in a heavily pretreated patient population with indolent B-cell lymphoma
- ORR was 59%, (complete responses 14%),
  Median DoR 22.6 months, median PFS 11.2 months
- low rates of severe hepatic enzymopathy, diarrhea, or pneumonitis:
  - transient hyperglycemia and hypertension were the most common TEAEs
  - serious TEAEs: pneumonitis (1.4%, grade 3), colitis (0.7%, grade 4)
  - Rates of opportunistic infections or fatal TEAEs were low

Conclusions

- ✓ Copanlisib demonstrated promising antitumor activity in relapsed or refractory indolent lymphoma
- ✓ The safety profile for copanlisib was manageable and distinct compared with that of oral PI3K inhibitors, possibly due to the intermittent schedule and intravenous route of administration
- ✓ Current Phase III studies investigate copanlisib in combination with rituximab (NCT02367040) and R-CHOP / rituximab + bendamustine (NCT02626455)



Acknowledgements

German Lymphoma Alliance

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DIREKTOR PROF. DR. W. HIDDEMANN