LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
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New Drugs in Hematology

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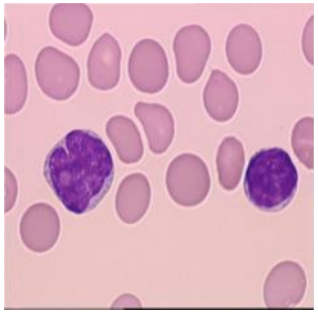
Servizio Sanitario Regionale Emilia-Romagna
Azienda Ospedaliero - Universitaria di Bologna

# *Non Hodgkin Lymphoma*

# *Copanlisib*



European MCL Network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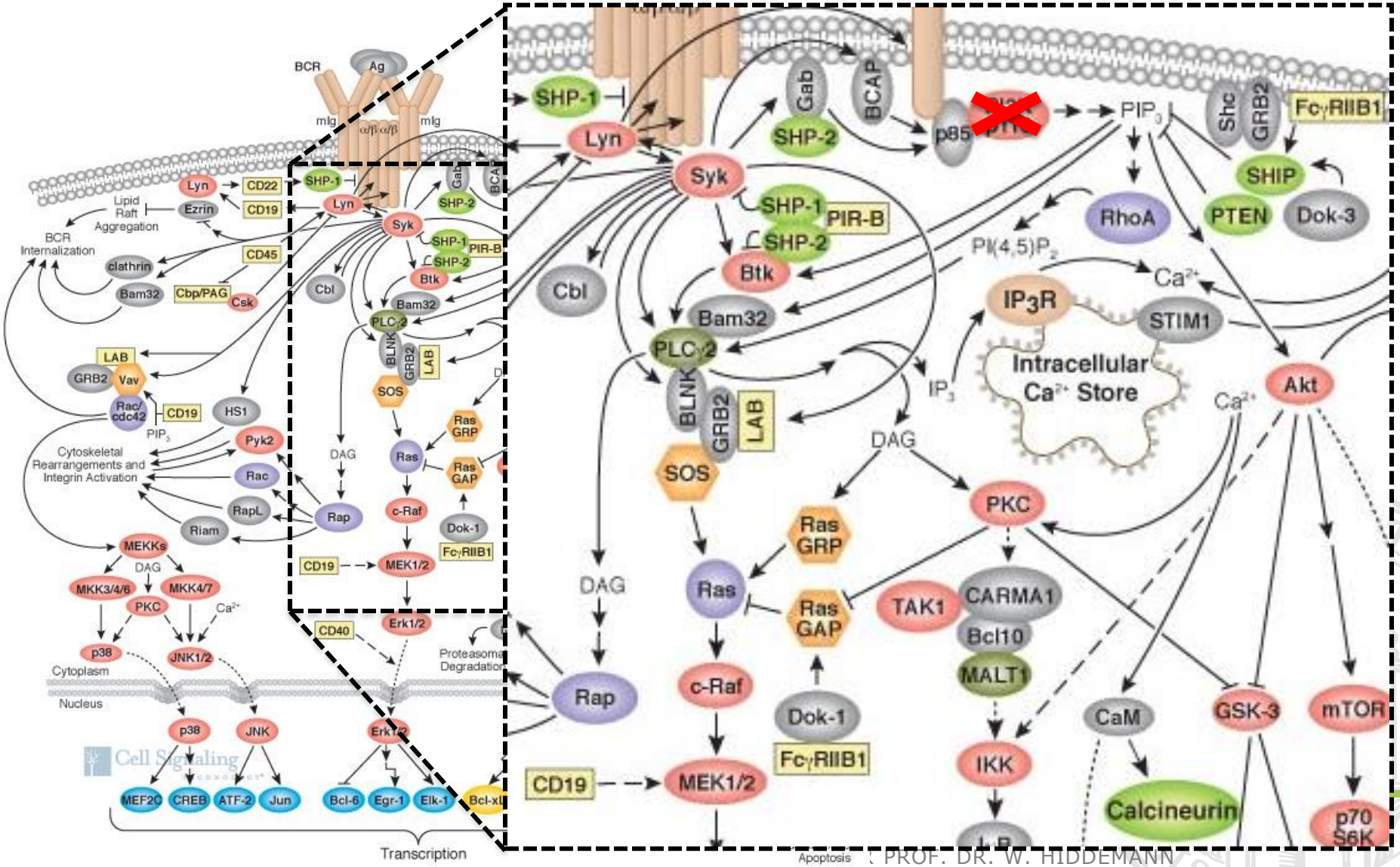
# Disclosures

| | |
|---|---|
| **Research Support (institution)** | **Celgene, Janssen, Mundipharma, Pfizer, Roche** |
| **Employee** | **-** |
| **Major Stockholder** | **-** |
| **Speakers Bureau** | **-** |
| **Speakers Honoraria** | **Celgene, Gilead, Janssen, Mundipharma, Pfizer, Roche** |
| **Scientific Advisory Board** | **Bayer, Celgene, Gilead, Janssen, Pfizer** |

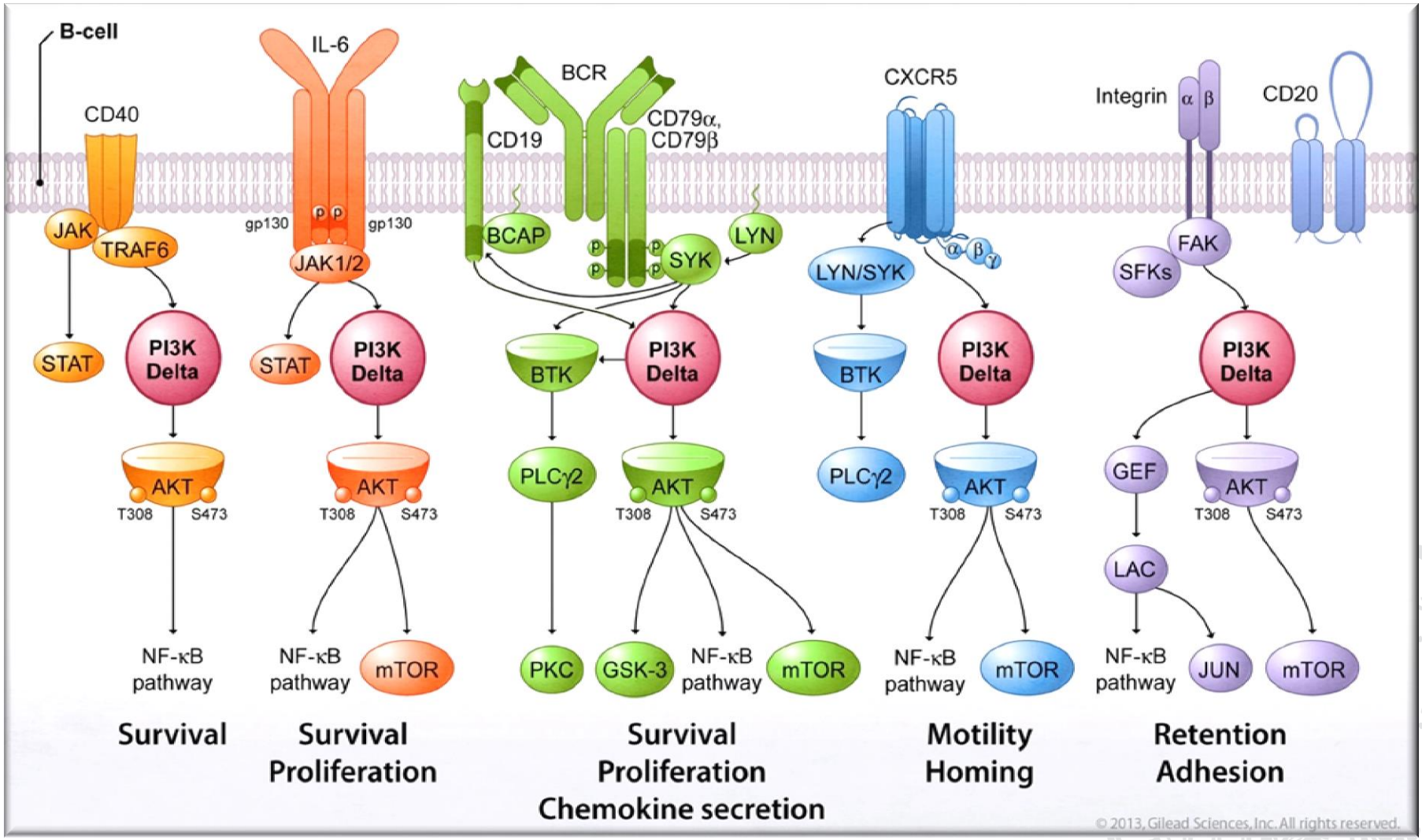
## *B-cell receptor pathway*

# Targeting a critical pathway



# PI3Kδ Inhibition

## *Multiple Critical Pathways in iNHL*



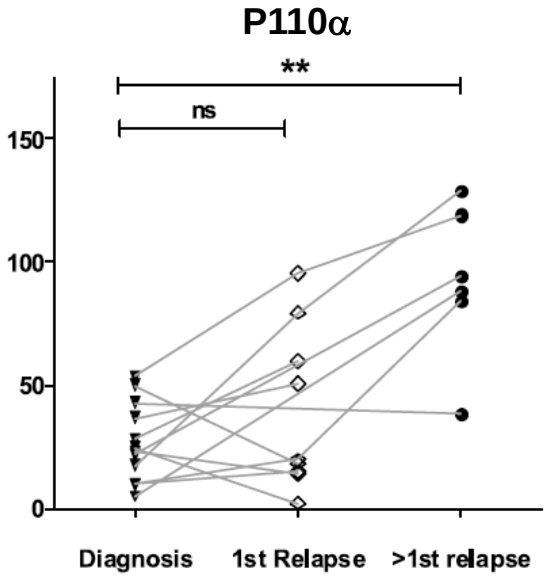

*Lannutti, Blood 2011*

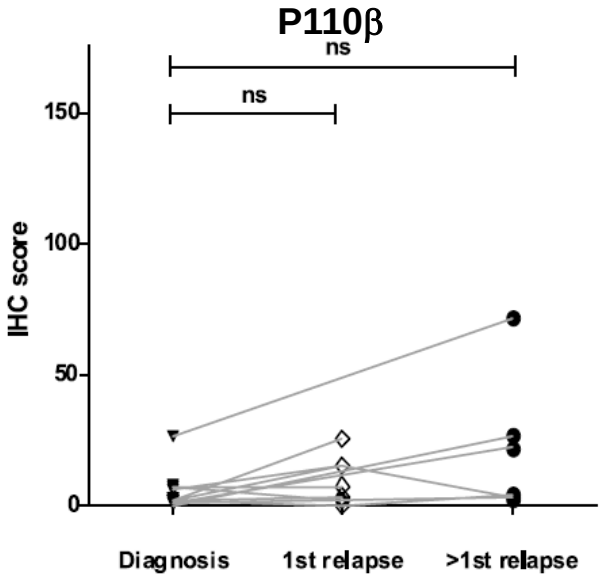
# Class I PI3K isoforms

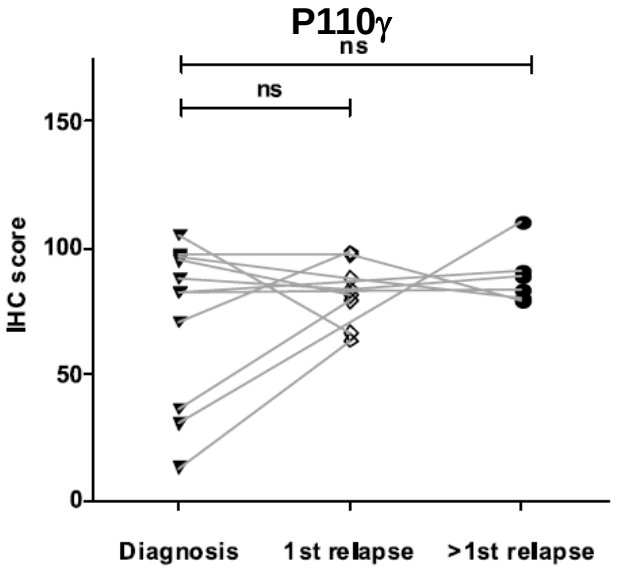
| Class I PI3K isoform | Cellular expression | Primary physiological role |
|---|---|---|
| Alpha (α) | Broad | Insulin signaling and angiogenesis |
| Beta (β) | Broad | Platelet function |
| Gamma (γ) | Leukocytes | Neutrophil and T-cell function |
| Delta (δ) | Leukocytes | B-cell signaling, development,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

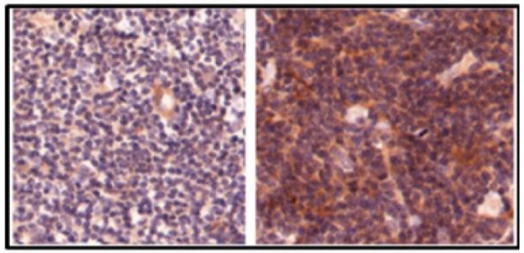

*Okkenhaug, Nat Rev Immunol 2003*

# P110α-mediated constitutive PI3K signaling limits the efficacy of p110δ-selective inhibition in mantle cell lymphoma, particularly with multiple relapse



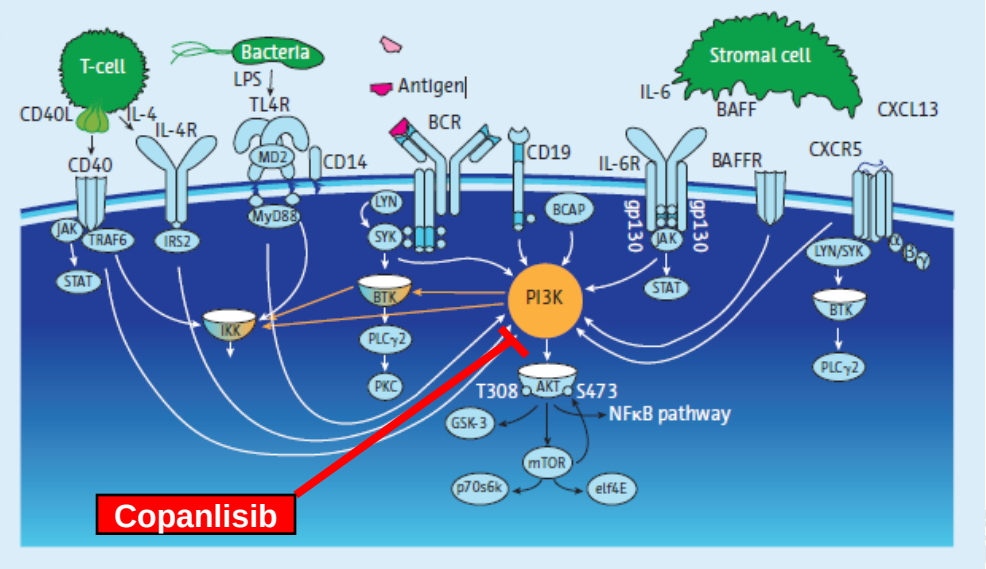



*Iyengar, Blood 20013*

# Introduction:
# copanlisib (BAY 80-6946)

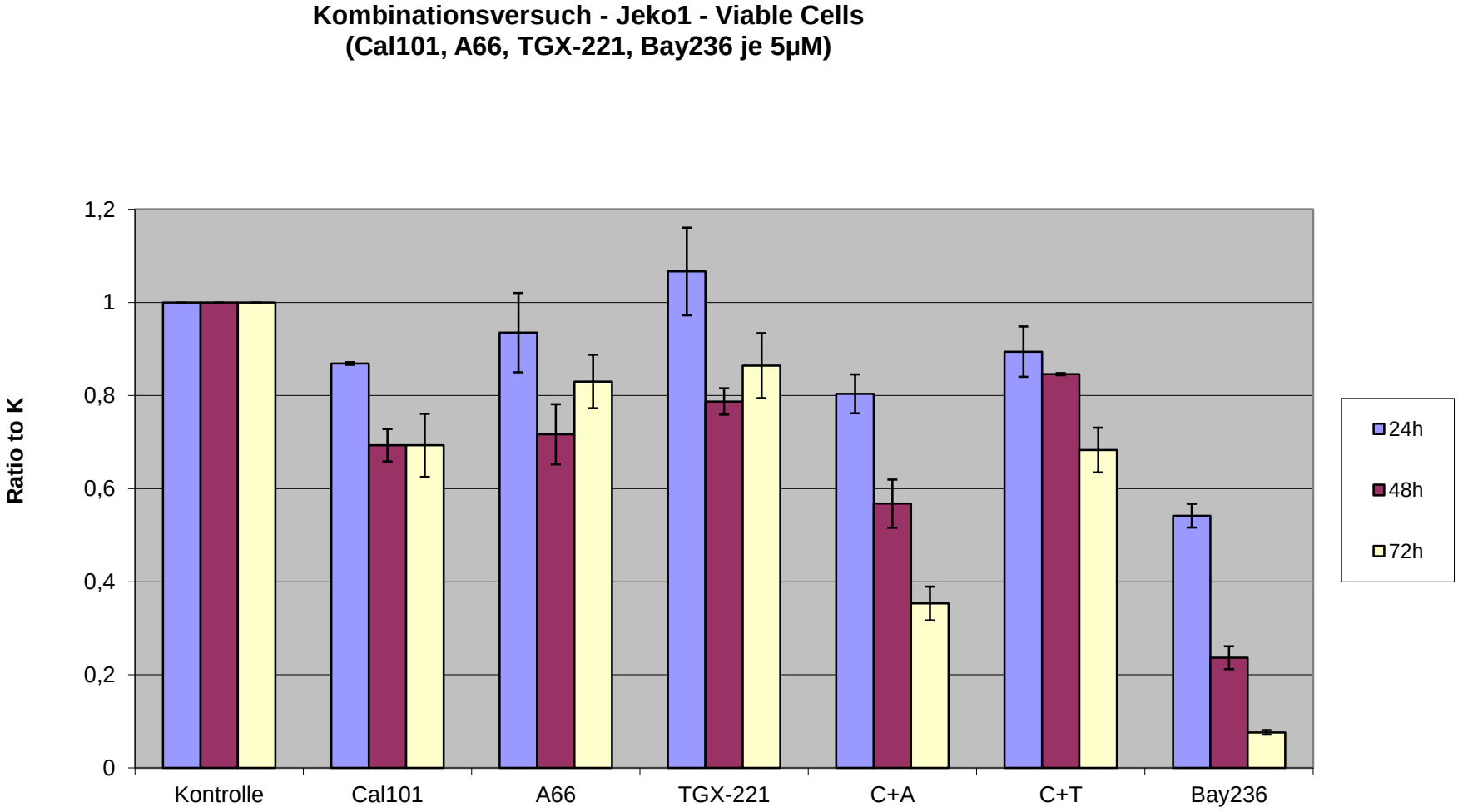
- PI3K inhibitors are effective in PI3K-driven tumors (also combined with chemotherapy)[1]
- Copanlisib is a potent and reversible class I PI3K inhibitor with significant activity against δ- and α-isoforms
- Copanlisib demonstrated efficacy in preclinical tumor models[2]:
  *PIK3CA* mutation
  *PTEN* deletion
  Over-expression of human EGFR






***Yuan, Oncogene 2008; Liu, AACR 2010***

# Inhibition of PI3K isoforms




*Zoellner, EHA 2015*

# Study design

- Open-label, Phase II study
- Patients with histologically confirmed indolent or aggressive lymphoma relapsed / refractory to ≥2 prior lines of treatment
- Patients received copanlisib as an intravenous infusion (1 h); weekly (3 out of a 4-week cycle); starting dose 0.8 mg/kg (maximum dose 65 mg)
- Dose reductions to 0.6 mg/kg (maximum 48 mg) and 0.4 mg/kg (maximum 32.5 mg) if required
- Response evaluation according to the Cheson or iwCLL criteria
- Treatment until PD, toxicity, etc

***Patnaik, ASH 2012 ; Cheson, JCO1999; Hallek, Blood 2008***

# Study objectives

- Primary endpoint
  - Objective response rate (ORR) up to 16 weeks after the last patient has initiated treatment
- Secondary endpoints
  - Safety
  - Progression-free survival, duration of response, and overall survival
  - Pharmacokinetics of copanlisib
  - Potential biomarkers

# Patient characteristics (1)

A total of 67 patients were enrolled and treated

- 33 indolent and 34 aggressive

| **Demographics** | **Indolent (*n*=33)** | **Aggressive (*n*=34)** | **Total (*n*=67)** |
|---|---|---|---|
| Age, median (years) | 68 | 68 | **68** |
| Gender, % female | 55 | 50 | **52** |
| **Histologic subtype, *n* (%)** | | | |
| Follicular lymphoma (G1-G3a) | 16 (48) | 0 | **16 (24)** |
| Chronic lymphocytic leukemia / SLL | 14 (42) | 0 | **14 (21)** |
| Marginal zone lymphoma | 3 (9) | 0 | **3 (5)** |
| Diffuse large B-cell lymphoma | 0 | 15 (44) | **15 (22)** |
| Mantle cell lymphoma | 0 | 7 (21) | **7 (10)** |
| Transformed indolent lymphoma | 0 | 6 (18) | **6 (9)** |
| T-cell lymphoma | 0 | 4 (12) | **4 (6)** |
| Mediastinal B-cell lymphoma | 0 | 1 (3) | **1 (2)** |
| Follicular lymphoma (G3b) | 0 | 1 (3) | **1 (2)** |

# Patient characteristics (2)

| ECOG PS, *n* (%) | Indolent (*n*=33) | Aggressive (*n*=34) | Total (*n*=67) |
|---|---|---|---|
| 0 | 20 (61) | 15 (44) | **35 (52)** |
| 1 | 11 (33) | 17 (50) | **28 (42)** |
| 2 | 2 (6) | 2 (6) | **4 (6)** |
| **B symptoms, *n* (%)** | **Indolent (*n*=33)** | **Aggressive (*n*=32)** | **Total (*n*=65)** |
| Yes | 4 (12) | 7 (22) | **11 (17)** |
| No | 29 (88) | 25 (78) | **54 (83)** |
| **Ann Arbor stage, *n* (%)** | **Indolent (*n*=19)** | **Aggressive (*n*=34)** | **Total (*n*=53)[b]** |
| I | 1 (5) | 0 | **1 (2)** |
| II | 4 (21) | 2 (6) | **6 (11)** |
| III | 6 (32) | 8 (24) | **14 (26)** |
| IV | 8 (42) | 24 (71) | **32 (60)** |

# Prior therapies

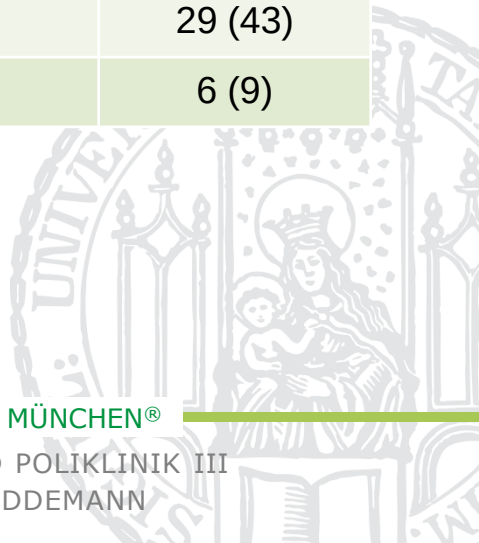
Median number of prior chemotherapy lines was 3

| **Number of prior chemotherapy lines, *n* (%)** | **Indolent (*n*=33)** | **Aggressive (*n*=34)** | **Total (*n*=67)** |
|---|---|---|---|
| 2 | 4 (12) | 10 (29) | **14 (21)** |
| 3 | 8 (24) | 14 (41) | **22 (33)** |
| 4 | 9 (27) | 3 (9) | **12 (18)** |
| ≥5 | 12 (36) | 7 (21) | **19 (28)** |
| **Prior ASCT, *n* (%)** | **Indolent (*n*=33)** | **Aggressive (*n*=34)** | **Total (*n*=67)** |
| Yes | 6 (18) | 6 (18) | **12 (18)** |
| No | 27 (82) | 28 (82) | **55 (82)** |
| **Prior rituximab, *n* (%)** | **Indolent (*n*=33)** | **Aggressive (*n*=34)** | **Total (*n*=67)** |
| Yes | 28 (85) | 28 (82) | **56 (84)** |
| No | 5 (15) | 6 (18) | **11 (16)** |

***Dreyling, ASH 2013***

# Safety overview

| *n* (%) | Indolent (*n*=33) | Aggressive (*n*=34) | Total (*n*=67) |
|---|---|---|---|
| All AEs | 33 (100) | 34 (100) | 67 (100) |
| AEs grade ≥3 | 26 (79) | 30 (88) | 56 (84) |
| Leading to dose reduction | 3 (9) | 3 (9) | 6 (9) |
| Leading to study drug interruption | 13 (39) | 18 (53) | 31 (46) |
| Leading to study drug withdrawal | 8 (24) | 7 (21) | 15 (22) |
| Serious AEs | 10 (30) | 19 (56) | 29 (43) |
| Deaths | 2 (6) | 4 (12) | 6 (9) |



# AEs in ≥10% of patients

| AE, *n* (%) | Indolent (*n*=33) | | | Aggressive (*n*=34) | | | Total (*n*=67) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 1-2 | Grade ≥3 | Total | Grade 1-2 | Grade ≥3 | Total | Grade 1-2 | Grade ≥3 | Total |
| Hyperglycemia | 14 (42) | 7 (21) | 21 (64) | 10 (29) | 8 (24) | 18 (53) | 24 (36) | 15 (22) | **39 (58)** |
| Hypertension | 8 (24) | 12 (36) | 20 (61) | 5 (15) | 13 (38) | 18 (53) | 13 (19) | 25 (37) | **38 (57)** |
| Fatigue | 12 (36) | 2 (6) | 14 (42) | 10 (29) | 3 (9) | 13 (38) | 21 (32) | 5 (8) | **27 (40)** |
| Diarrhea | 9 (27) | 1 (3) | 10 (30) | 13 (38) | 1 (3) | 14 (41) | 22 (33) | 2 (3) | **24 (36)** |
| Nausea | 8 (24) | 0 | 8 (24) | 10 (29) | 1 (3) | 11 (32) | 18 (27) | 1 (2) | **19 (28)** |
| Neutropenia | 2 (6) | 6 (18) | 8 (24) | 1 (3) | 10 (30) | 11 (32) | 3 (5) | 16 (24) | **19 (28)** |
| Anemia | 6 (18) | 2 (6) | 8 (24) | 2 (6) | 5 (15) | 7 (21) | 8 (12) | 7 (11) | **15 (22)** |
| Mucositis oral | 6 (18) | 1 (3) | 7 (21) | 7 (21) | 0 | 7 (21) | 13 (19) | 1 (2) | **14 (21)** |
| Fever | 7 (21) | 1 (3) | 8 (24) | 3 (9) | 0 | 3 (9) | 10 (15) | 1 (2) | **11 (16)** |
| Constipation | 4 (12) | - | 4 (12) | 7 (21) | - | 7 (21) | 11 (16) | - | **11 (16)** |
| Cough | 4 (12) | - | 4 (12) | 5 (15) | - | 5 (15) | 9 (13) | - | **9 (13)** |
| Urinary tract infection | 4 (12) | 0 | 4 (12) | 3 (9) | 1 (3) | 4 (12) | 7 (10) | 1 (2) | **8 (12)** |
| Vomiting | 3 (9) | 0 | 3 (9) | 3 (9) | 1 (3) | 4 (12) | 6 (9) | 1 (2) | **7 (10)** |
| Thrombocytopenia | 1 (3) | 4 (12) | 5 (15) | 0 | 2 (6) | 2 (6) | 1 (2) | 6 (9) | **7 (10)** |
| Infections (other) | 3 (9) | 1 (3) | 4 (12) | 3 (9) | 0 | 3 (9) | 6 (9) | 1 (2) | **7 (10)** |
| Lung infection | 1 (3) | 2 (6) | 3 (9) | 1 (3) | 3 (9) | 4 (12) | 2 (3) | 5 (8) | **7 (10)** |
| Anorexia | 0 | 2 (6) | 0 | 2 (6) | 3 (9) | 5 (15) | 2 (3) | 5 (8) | **7 (10)** |
| Dyspnea | 2 (6) | 1 (3) | 3 (9) | 3 (9) | 1 (3) | 4 (12) | 5 (8) | 2 (3) | **7 (10)** |

***Dreyling, ASH 2013***

# Reasons for treatment discontinuation

A total of 43 patients (64%) discontinued therapy

13 indolent and 30 aggressive

| **Reason for discontinuation, *n* (%)** | **Indolent (*n*=33)** | **Aggressive (*n*=34)** | **Total (*n*=67)** |
|---|---|---|---|
| AE associated with clinical disease progression | 0 | 2 (6) | 2 (3) |
| AE not associated with clinical disease progression | 8 (24) | 5 (15) | 13 (19) |
| PD: clinical progression | 3 (9) | 8 (24) | 11 (16) |
| PD: radiological progression | 0 | 13 (38) | 13 (19) |
| Withdrawal by patient | 1 (3) | 0 | 1 (2) |
| Physician decision | 1 (3) | 2 (6) | 3 (5) |

***Dreyling, ASH 2013***

# Response rates
## *investigators' assessement*

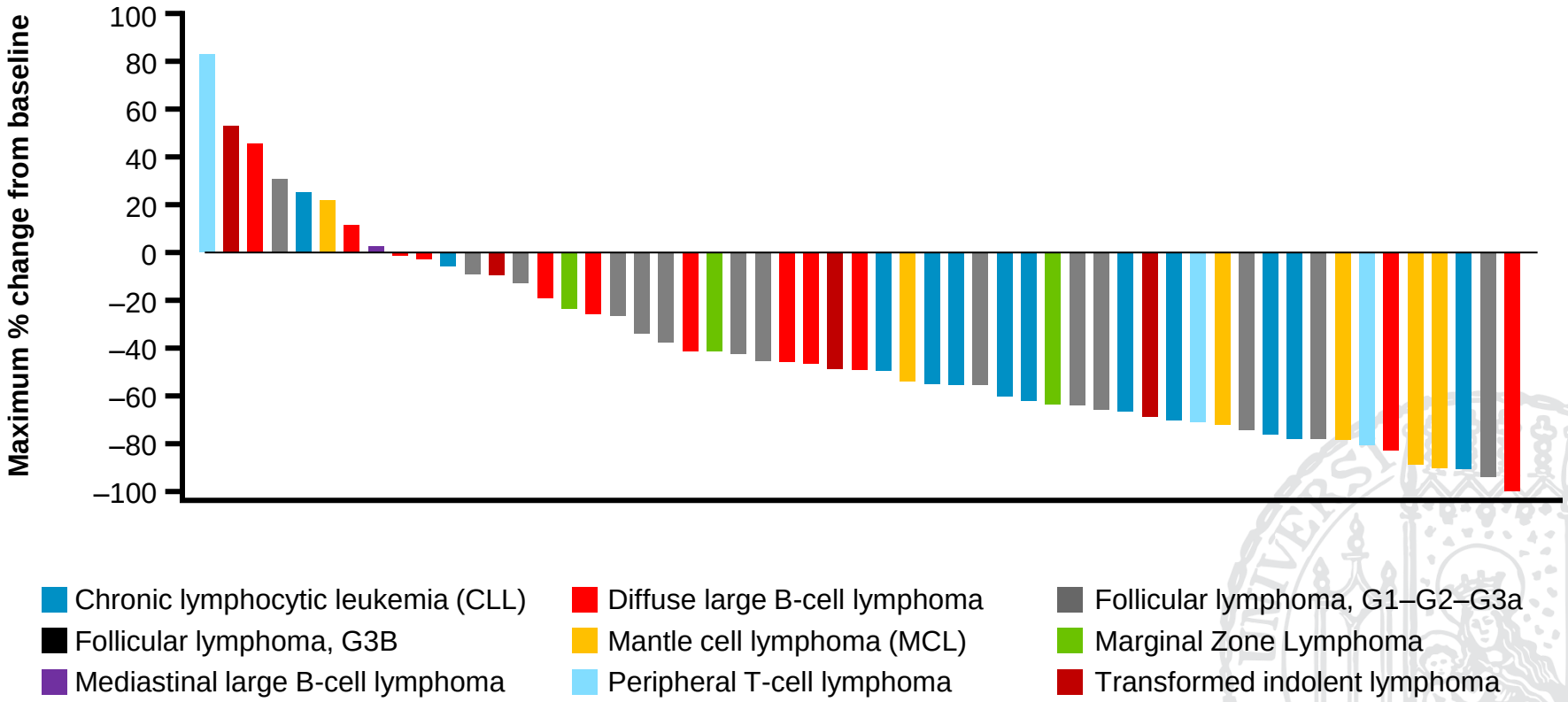
| Histology | *n* | Response |
|---|---|---|
| Diffuse large B-cell lymphoma | 15 | 2 CR / CRu; 3 SD; 10 PD (ORR 13%) |
| Mediastinal large B-cell lymphoma | 1 | 1 PD |
| Transformed indolent lymphoma | 6 | 1 PR; 5 PD (ORR 17%) |
| T-cell lymphoma | 4 | 1 CRu; 1 PR; 2 PD (ORR 50%) |
| Mantle cell lymphoma | 7 | 1 CRu; 4 PR; 2 PD (ORR 71%) |
| Follicular lymphoma G3b | 1 | 1 N/A |
| Follicular lymphoma | 16 | 1 CR; 5 PR; 9 SD; 1 N/A (ORR 40%) |
| Chronic lymphocytic leukemia / SLL | 14 | 6 PR; 6 SD; 1 PD; 1 N/A (ORR 43%) |
| Marginal zone lymphoma | 3 | 2 PR; 1 SD (ORR 66%) |

Median duration of treatment: 3 cycles

***Dreyling, ASH 2013***

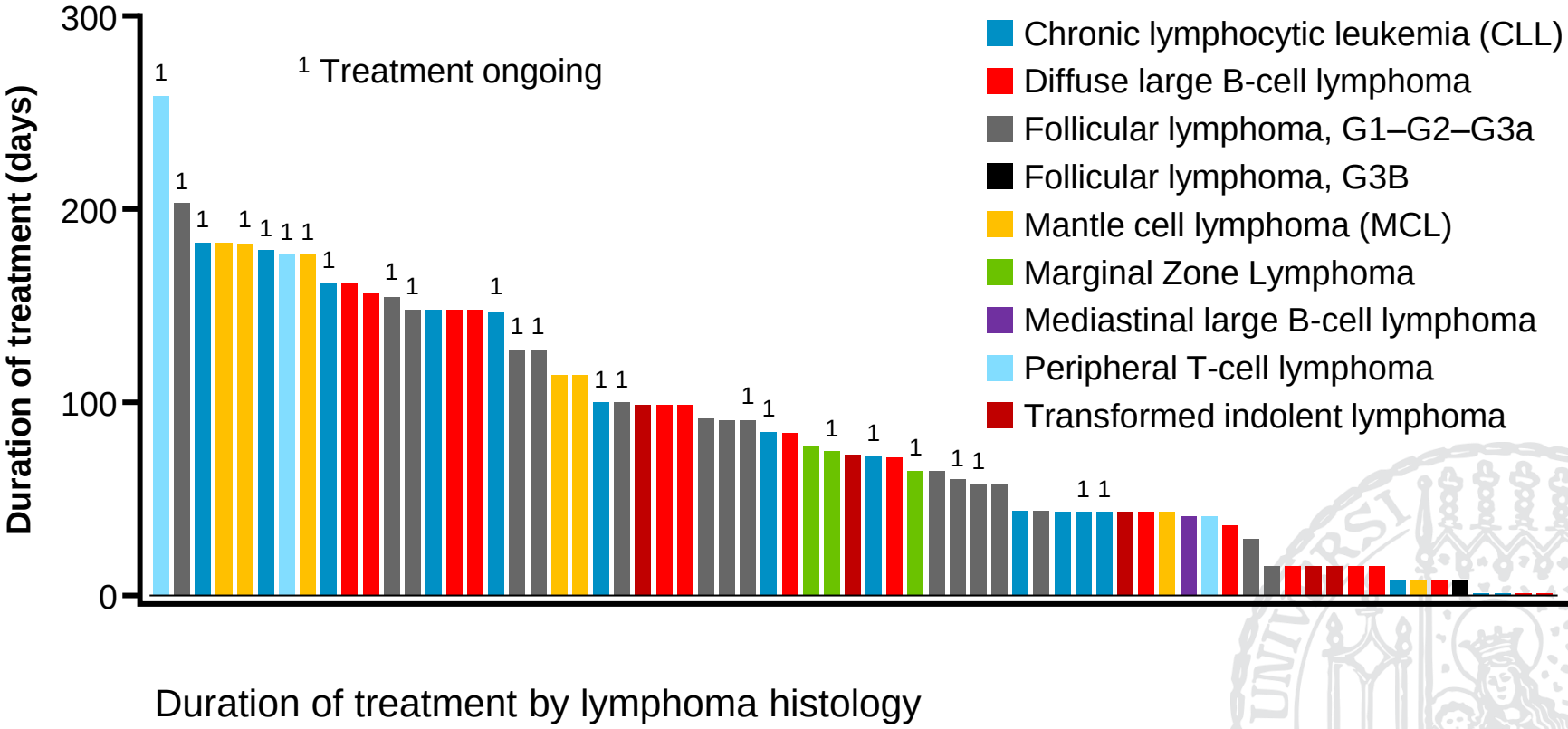
# Response
## *Waterfall Blot*

Best response by lymphoma histology (% change from baseline)




***Dreyling, ASH 2013***

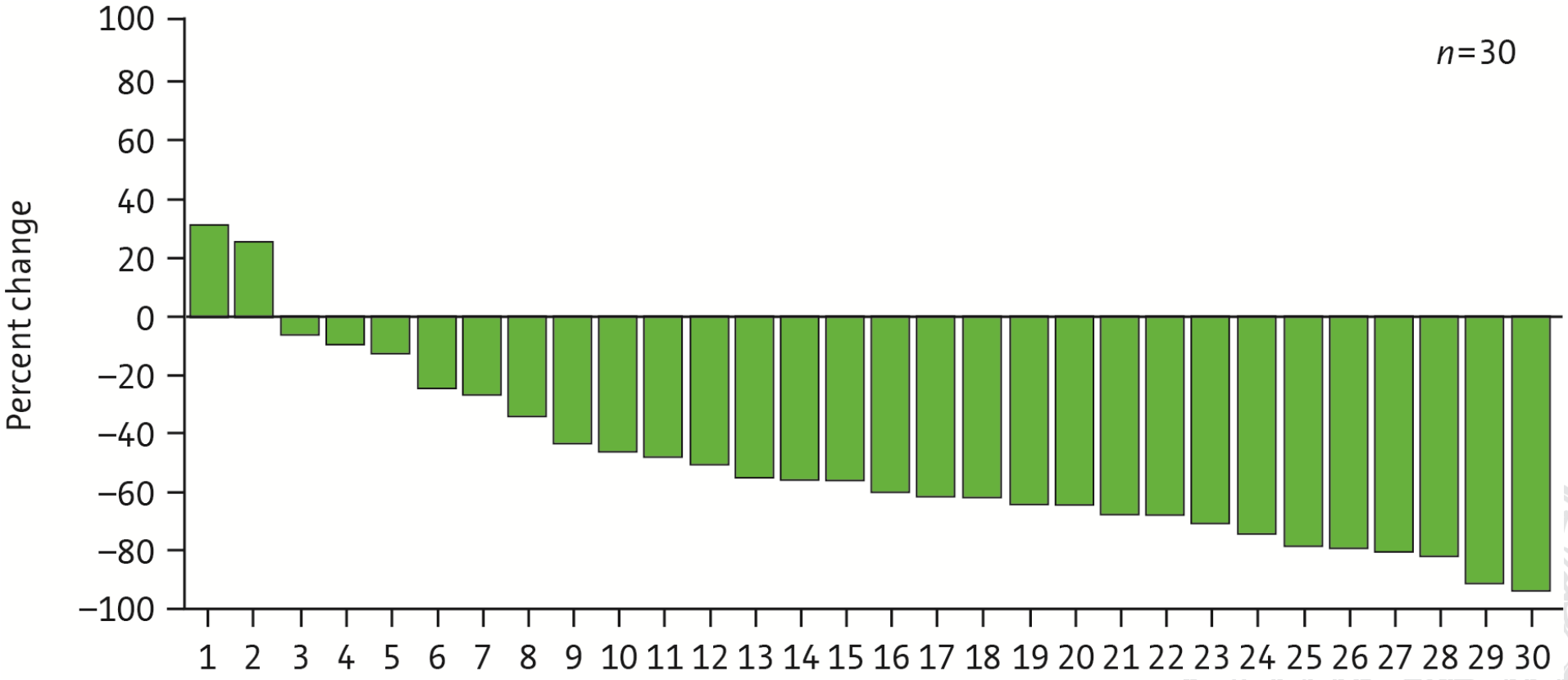
# Treatment duration




Duration of treatment by lymphoma histology

## *Indolent lymphoma*

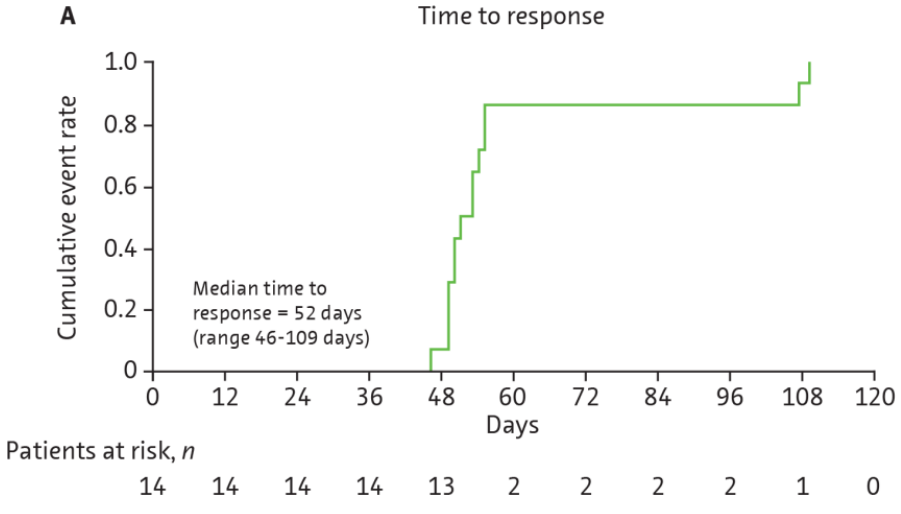
# Best response (% from baseline)

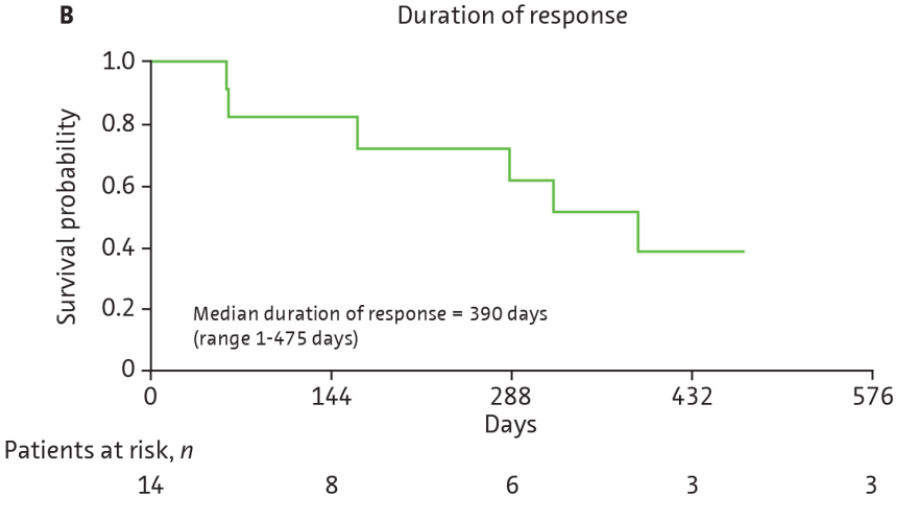


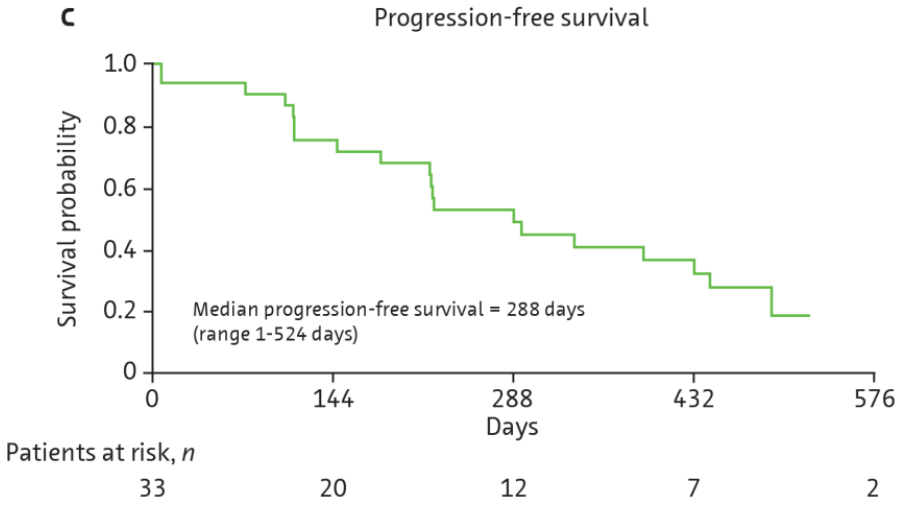

***Dreyling, ASH 2014***

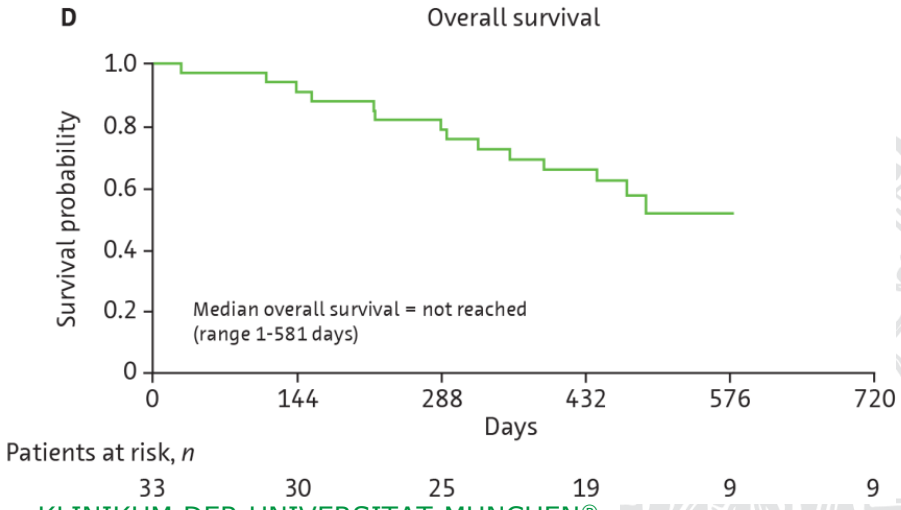
# *Indolent lymphoma*

# Survival rates



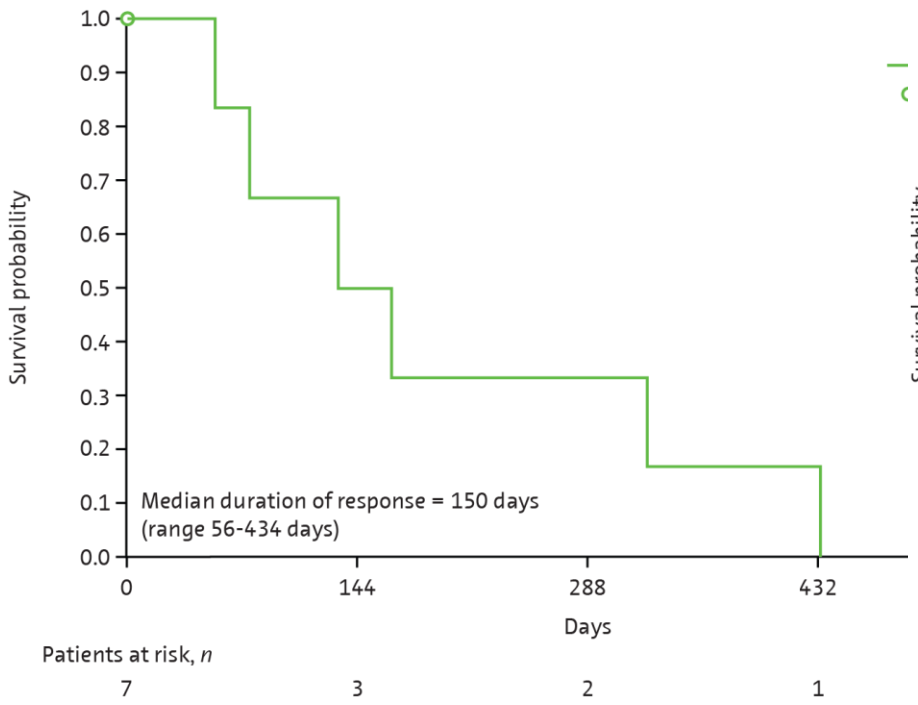

*Dreyling, ASH 2014*

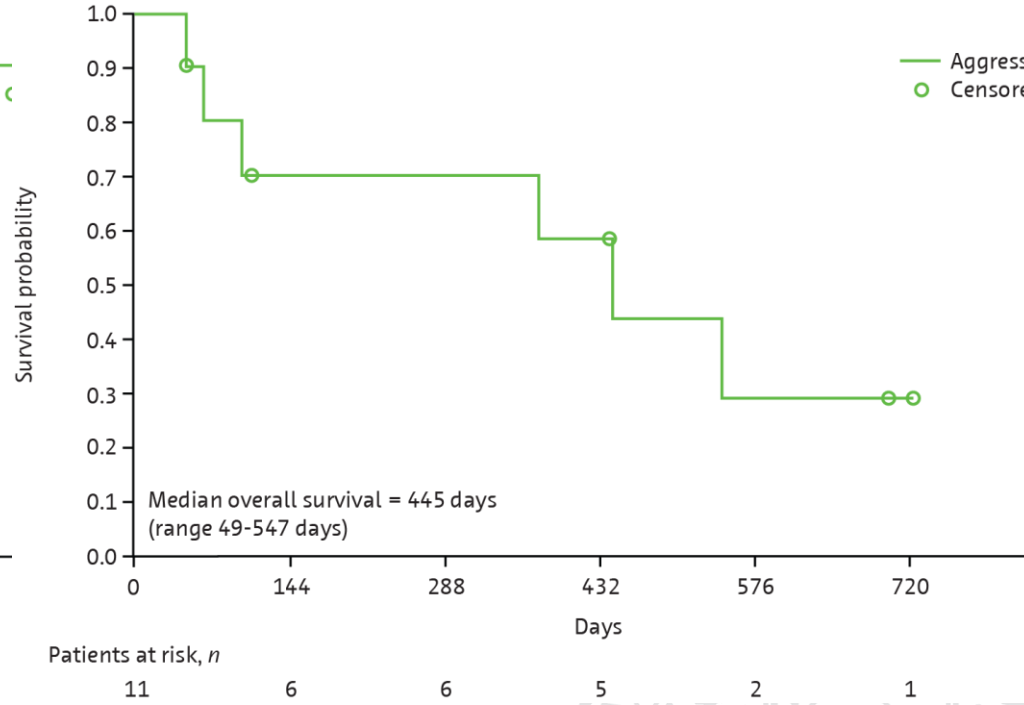
# *Mantle cell lymphoma*
# Best Response

| *n* (%) | MCL patients (*n*=11) |
|---|---|
| Best response | |
| Unconfirmed complete response | 2 (18.2) |
| Partial response | 5 (45.5) |
| Stable disease | 0 |
| Progressive disease | 3 (27.3) |
| Not available | 1 (9.1) |
| Objective response rate | 7 (63.6) |

***Cunningham, ASH 2015***

# *Mantle cell lymphoma*
# Survival rates



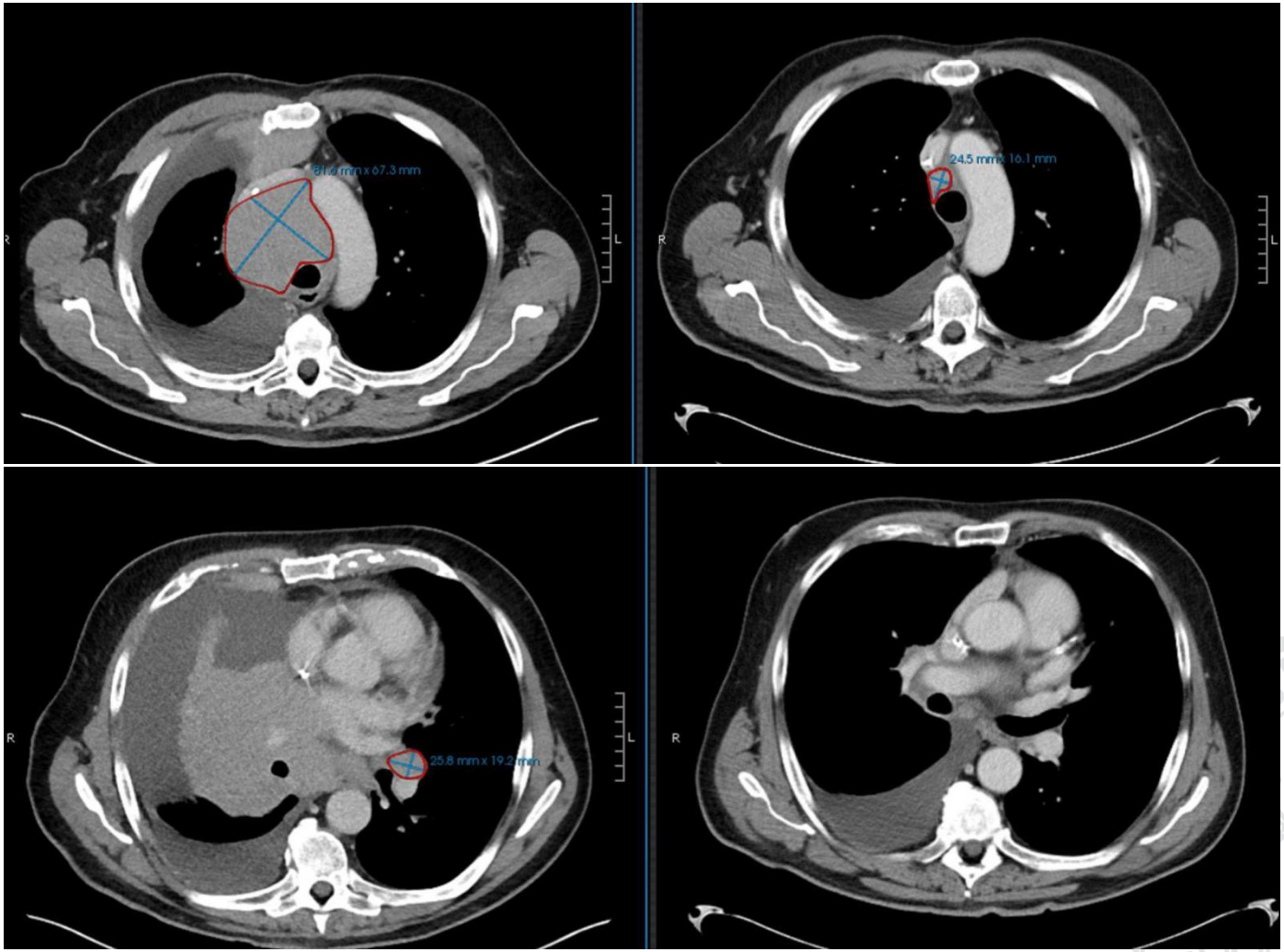

***Cunningham, ASH 2015***

## *Case report MCL*

# Clinical characteristics

- Male, 79 years
- Mantle cell lymphoma stage IV: pleural effusion, mediastinal bulk (cava suppression), bone marrow
- Prior therapy
  - 6 × R-CHOP 2004
  - Blinatumomab 2007
  - 4 × Bendamustin-R 2009
  - R-HAD + Bortezomib 2012, 2013
- High MIPI, orthopnea, regular pleural punctures
- Concomitant disease: renal insufficiency, polyneuropathy, restless legs

# *Case report MCL*
# radiological course



# Conclusions

## *copanlisib in malignant lymphoma*

- Acceptable / no unexpected toxicity in r/r lymphoma
- Preliminary efficacy results are encouraging
  - Significant activity in FL, CLL, MCL, peripheral T-cell lymphoma, and DLBCL
  - Complete responses in FL, MCL, peripheral T-cell lymphoma, and DLBCL
- Further phase II/III studies (combinations) in indolent/ aggressive lymphoma

# Copanlisib

## *Ongoing trials in lymphoma*

### Indolent NHL

- CHRONOS-1(16349B): Ph II, C single arm, relapsed/refractory third line
  *NCT016604551; enrollment completed*
- CHRONOS-2(17322) : Ph III, randomized, C vs placebo, third line
  *NCT02369016; enrollment ongoing*
- CHRONOS-3 (17067) : Ph III, randomized, rituximab ± C, second line
  *NCT02367040; enrollment ongoing*
- CHRONOS-4 (17833) : Ph III, randomized, RB/R-CHOP ± C, second line
  *NCT02626455*; dose escalation cohorts are open

### Aggressive NHL

- DLBCL (17119) : Ph II, C single arm, relapsed/refractory DLBCL
  *NCT02391116; enrollment completed*
- MCL (17120) : Ph II, C single arm, ibrutinib pretreated
  *NCT02455297; enrollment ongoing*

# Hyperglycemia

- 13 of 67 patients (19%) received insulin
  - 1 serious AE of hyperglycemia (grade 3); long-term insulin and oral antidiabetics (metformin)
  - 9 patients: short-acting insulin for 2 days ≤3 times
  - 3 patients: short-acting insulin after most infusions
  - 1 patient: prophylactic insulin per investigator's decision

# Hypertension

- 19 patients with prior hypertension;
  17 with antihypertensive medication
  - Additional medication in 5 of 19 patients (26%)
- 1 SAE of hypertension (grade 3):
  amlodipine, losartan, and hydrochlorothiazide
- Medication in 7 patients without hypertension (15%)
  - 5 naïve patients: medication on day of infusion only
  - 2 naïve patients started continuous medication (amlodipine)

# Drug-related AEs in ≥10% of patients

| | Indolent (*n*=33) | | | Aggressive (*n*=34) | | | Total (*n*=67) | | |
|---|---|---|---|---|---|---|---|---|---|
| **AE, n (%)** | **Grade 1-2** | **Grade ≥3** | **Total** | **Grade 1-2** | **Grade ≥3** | **Total** | **Grade 1-2** | **Grade ≥3** | **Total** |
| Hyperglycemia | 14 (42) | 7 (21) | 21 (64) | 9 (27) | 8 (24) | 17 (50) | 23 (34) | 15 (22) | **38 (57)** |
| Hypertension | 8 (24) | 10 (30) | 18 (55) | 5 (15) | 12 (35) | 17 (50) | 13 (19) | 22 (33) | **35 (52)** |
| Diarrhea | 8 (24) | 1 (3) | 9 (27) | 10 (29) | 1 (3) | 11 (32) | 18 (27) | 2 (3) | **20 (30)** |
| Neutrophils decreased | 2 (6) | 4 (12) | 6 (18) | 1 (3) | 9 (26) | 10 (29) | 3 (5) | 13 (19) | **16 (24)** |
| Fatigue | 7 (21) | 2 (6) | 9 (27) | 5 (15) | 1 (3) | 6 (18) | 12 (18) | 3 (5) | **15 (22)** |
| Nausea | 6 (18) | - | 6 (18) | 5 (15) | - | 5 (15) | 11 (16) | - | **11 (16)** |
| Mucositis oral | 5 (15) | 1 (3) | 6 (18) | 2 (6) | 0 | 2 (6) | 7 (11) | 1 (2) | **8 (12)** |
| Lung infection | 1 (3) | 2 (6) | 3 (9) | 1 (3) | 3 (9) | 4 (12) | 1 (2) | 5 (8) | **7 (10)** |

Hyperglycemia and hypertension were the most common AEs

No grade 4 hypertension or hyperglycemia was observed

***Dreyling, ASH 2013***