Non-Hodgkin's Lymphoma (II)

Idelalisib

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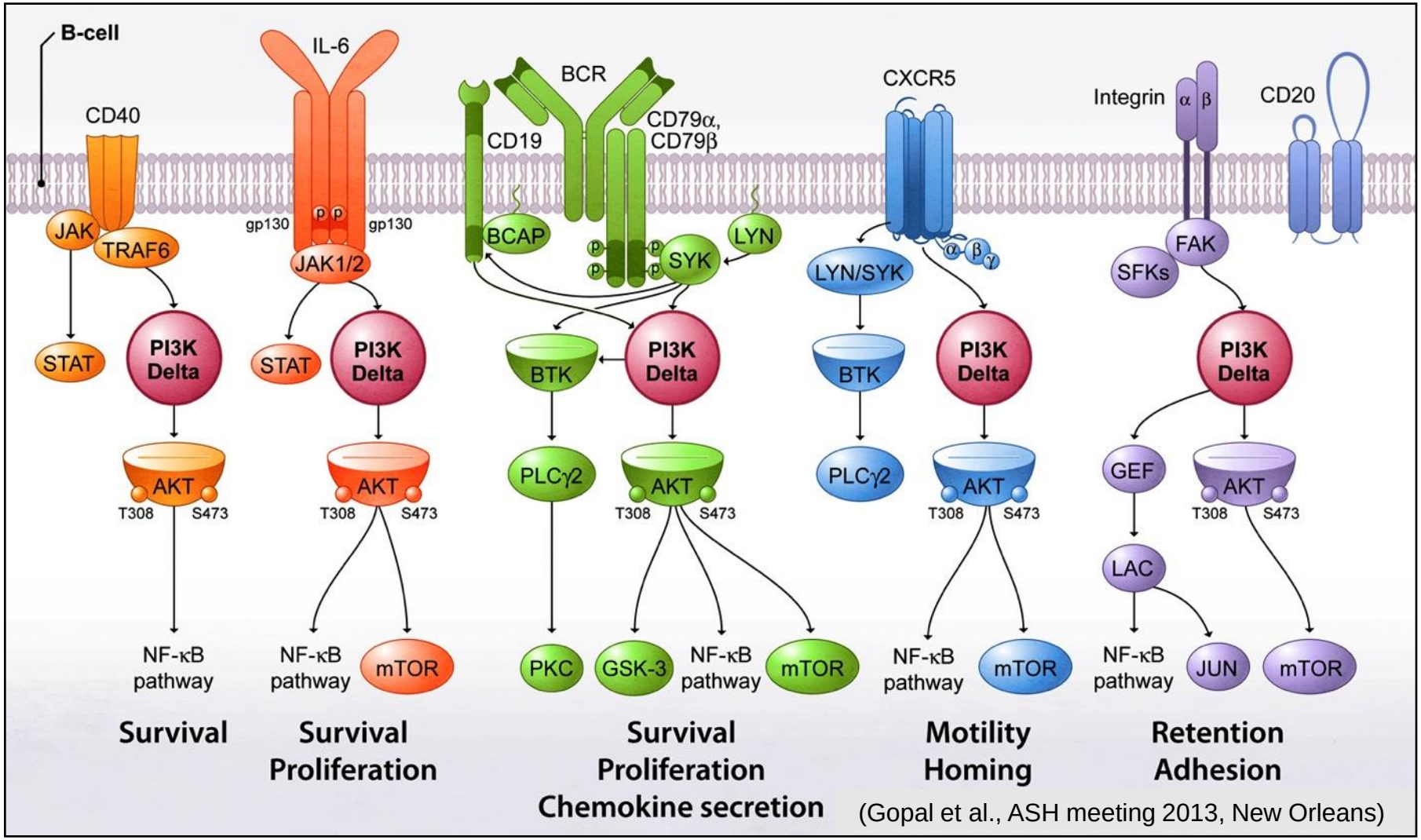
Disclosures

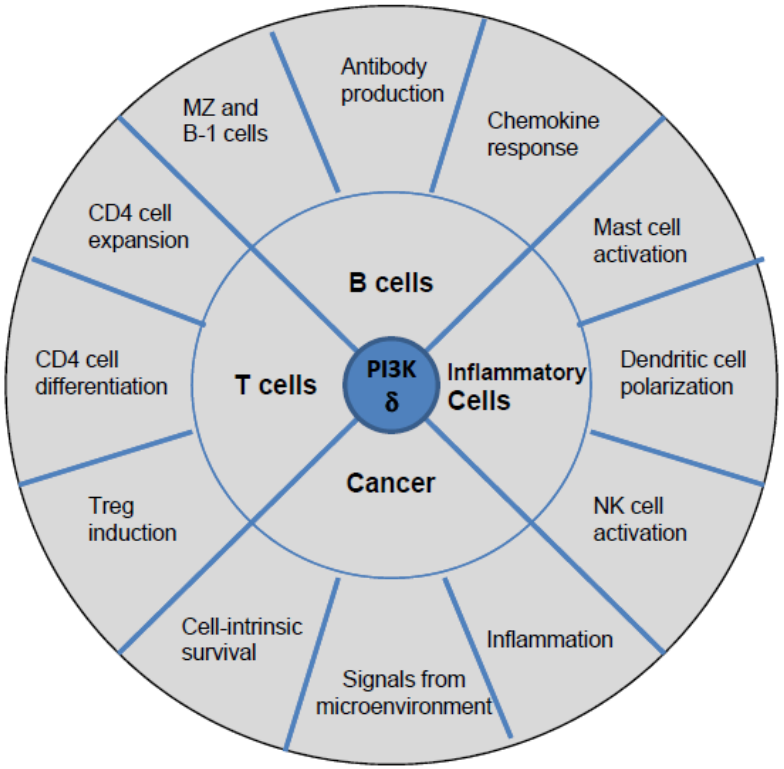
- INCYTE - Advisory board meeting

PI3Kδ Inhibition Impacts Multiple Critical Pathways in iNHL



(Gopal et al., ASH meeting 2013, New Orleans)

PI3K-δ
Expression/Function in B-cells and beyond



(Fruman et al., Cancer Discovery 1:562, 2011)

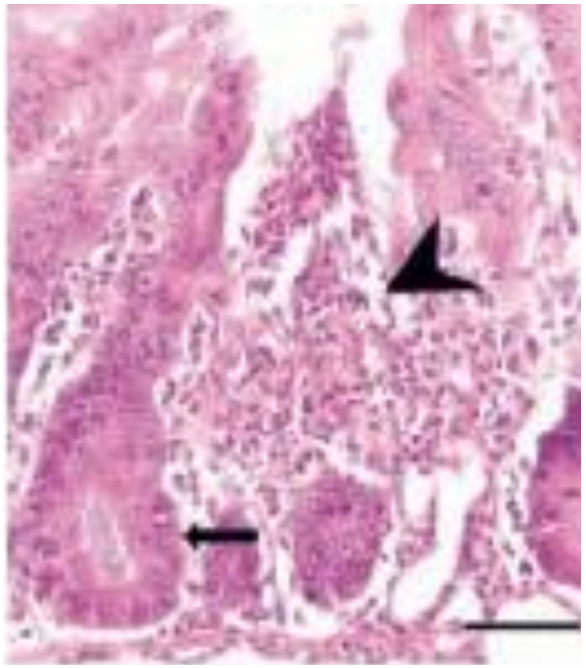
- **Primary role:** - B-cell signaling, development and survival
- **Other functions:** - T-regulatory cell induction
  - CD4 cell differentiation/expansion
  - Mast cell activation, NK cell activation

(Okkenhaug et al., Trends Immunol 28:80–7, 2007; Okkenhaug et al., Curr Top Microbiol Immunol 346:57–85, 2010)

Inflammatory Bowel Disease In PI3K p110dD910A Mutant Mice

WT/WT

PI3K p110δ^{D910A} Mutant Mice



On target effect

(Okkenhaug, et al. Science 297:1031, 2002)

Interim Results From a Phase 1 Study of CAL-101, a Selective Oral Inhibitor of PI3-Kinase p110 delta Isoform, in Patients with Rel/Refr Hematologic Malignancies

Objective Response Rate (N=99 Evaluable)

Population	No. Evaluable	No. with PR	Response Rate	No. SD on Study
Indolent NHL	**23**	**13**	**57%**	**4**
Follicular	11	6	55%	1
Small lymphocytic	6	4	67%	1
Marginal zone	3	2	67%	0
Lymphoplasmacytic	3	1	33%	2
Aggressive NHL				
Mantle cell	**12**	**8**	**67%**	**1**
Diffuse large B cell	9	0	0%	0
CLL	**33**	**10**	**30%**	**11***
AML	11	0	0%	0
MM	11	0	0%	0

PR=partial response, SD=stable disease
***CLL patients with lymph node response but not peripheral lymphocyte response**

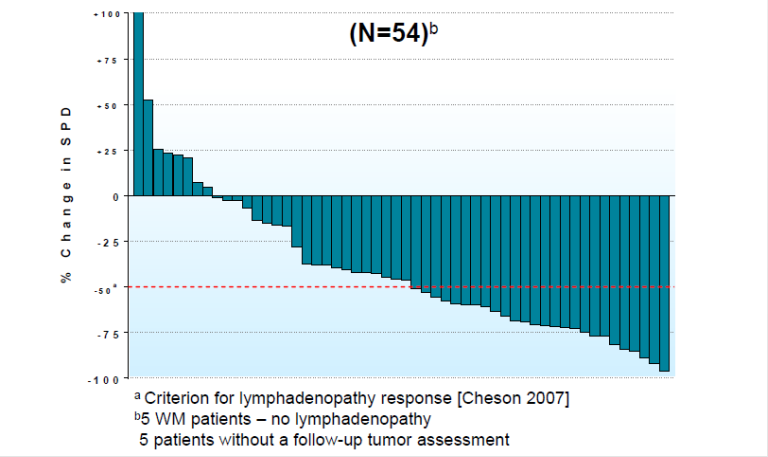
Duration of response
- **>6 months n=12, with 8 continuing on study**
- **<6 months thus far, continuing on study n=6**

(Furman et al., ASCO 2010)

Final report of a phase I study of Idelalisib, a selective inhibitor of PI3K-δ, in patients with rel/refr indolent NHL

Category, n, %	All (N=64)	<150 mg BID (N=40)	≥150 mg BID (N=24)[b]
ORR	**31 (48)**	**17 (43)**	**14 (58)**
CR	1 (1.6)	1 (2.5)	0
PR	26 (41)	14 (35)	12 (50)
MR[a]	4 (6.3)	2 (5)	2 (8.3)
SD	24 (38)	17 (43)	7 (29)
PD	4 (6.3)	4 (10)	0
NE	5 (7.8)	2 (5)	3 (12.5)

[a]Category for Waldenstroms Macroglobulinemia only, (IgM ≥25% decrease)
[b]150 mg BID, 200 mg BID, 350 mg BID



[a] Criterion for lymphadenopathy response [Cheson 2007]
[b]5 WM patients – no lymphadenopathy
5 patients without a follow-up tumor assessment

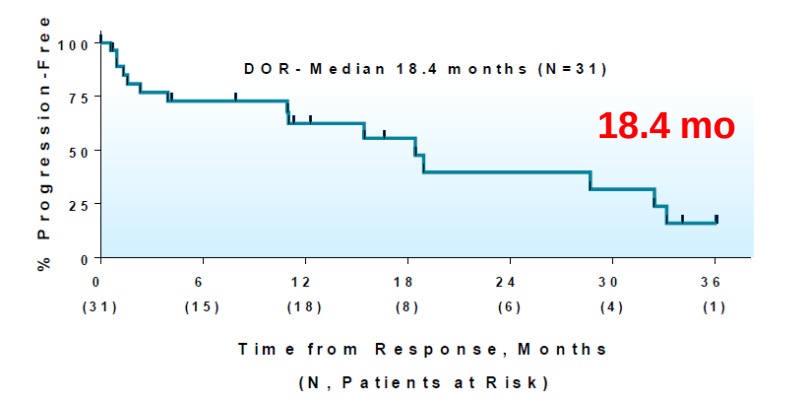
- 38 FL, 11 SLL, 9 LPL/WM, 6 MZL
- Median duration of thx 3.8 mo (0-41)
- Extension protocol: 19 pts (30%)

Lymph node Reduction in 85% of evaluable patients (46/54)

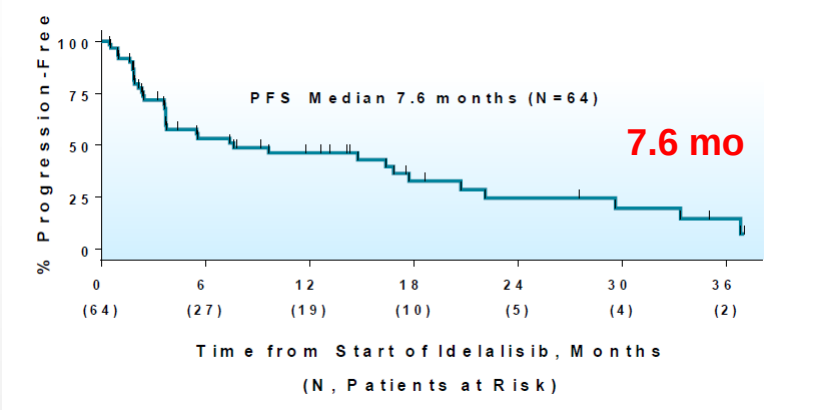
(Kahl et al., ICML 2013)

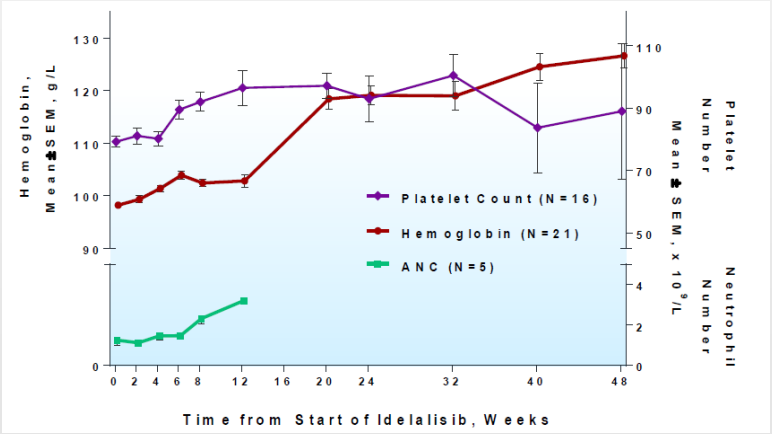
Final report of a phase I study of Idelalisib, a selective inhibitor of PI3K-δ, in patients with rel/refr indolent NHL

Duration of response (Study 02+99)



Progression Free Survival (Study 02+99)





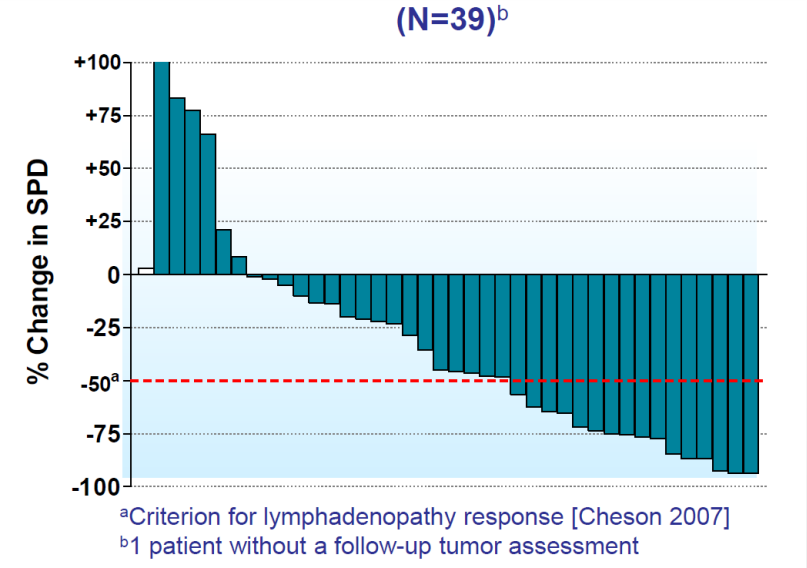
Improvement of baseline cytopenias during treatment

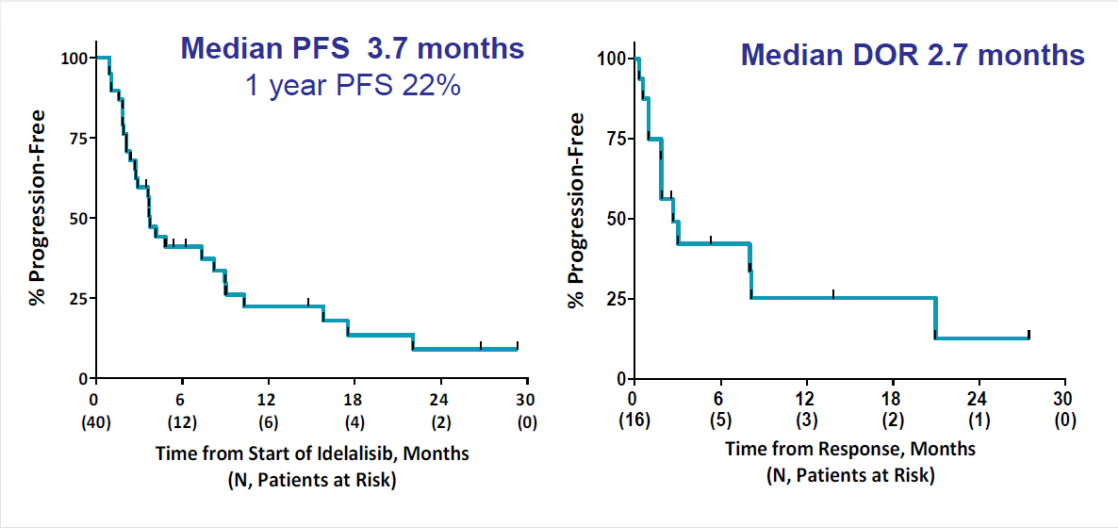
(Kahl et al., ICML 2013)

Final report of a phase I study of Idelalisib, a selective inhibitor of PI3K-δ, in patients with rel/refr MCL

Category	n, %
ORR	**16 (40)**
CR	3 (7.5)
PR	13 (32.5)
SD	19 (47.5)
PD	4 (10)
NE	1 (2.5)

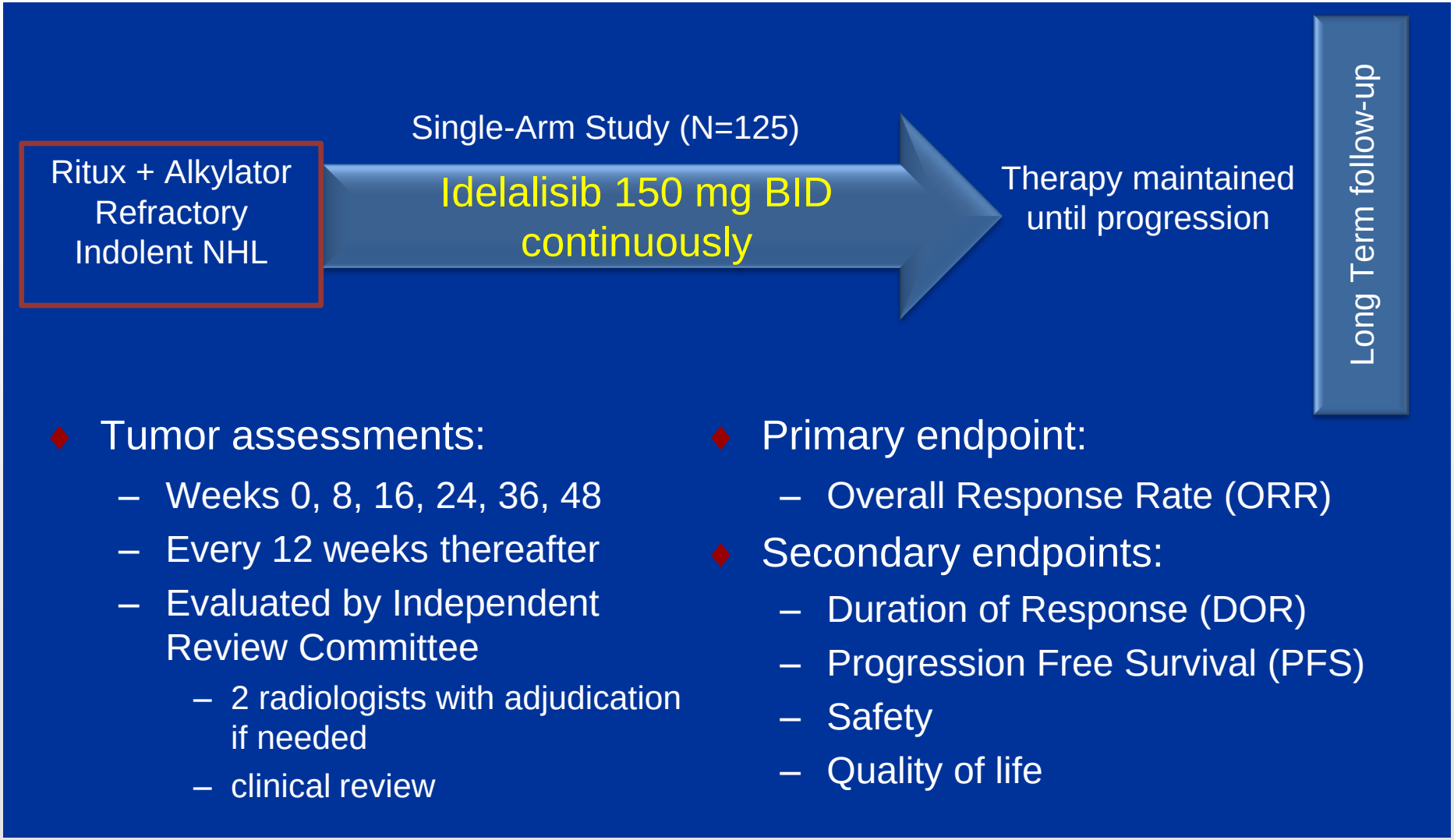
ORR for ≥ 150 mg BID was **67%** (8/12)
ORR for < 150 mg BID was **29%** (8/28)





(Spurgeon et al., ASCO 2013)

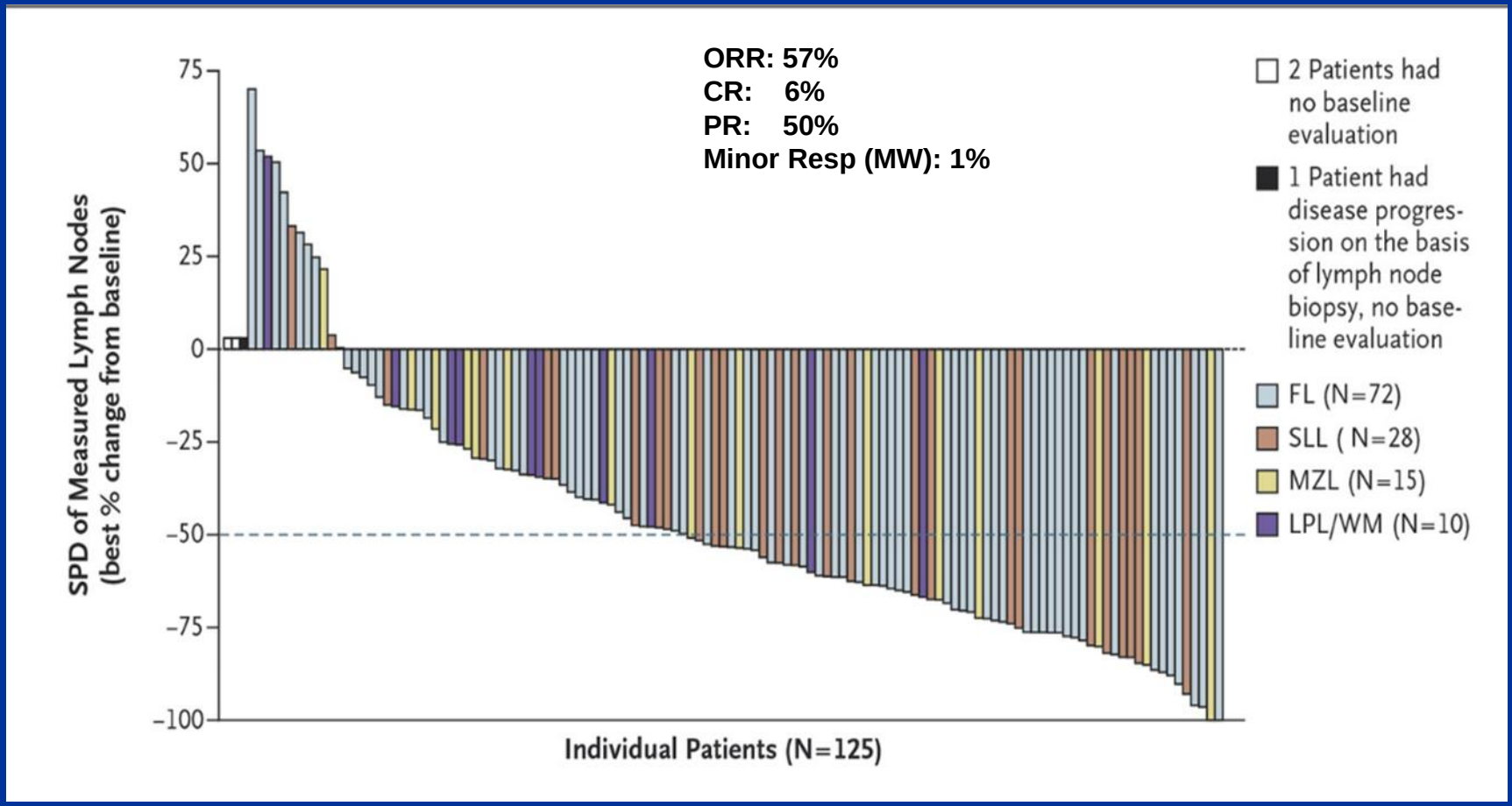
Idelalisib: Selective PI3K Inhibitor Phase II in Refractory iNHL



- Tumor assessments:
  - Weeks 0, 8, 16, 24, 36, 48
  - Every 12 weeks thereafter
  - Evaluated by Independent Review Committee
    - 2 radiologists with adjudication if needed
    - clinical review
- Primary endpoint:
  - Overall Response Rate (ORR)
- Secondary endpoints:
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)
  - Safety
  - Quality of life

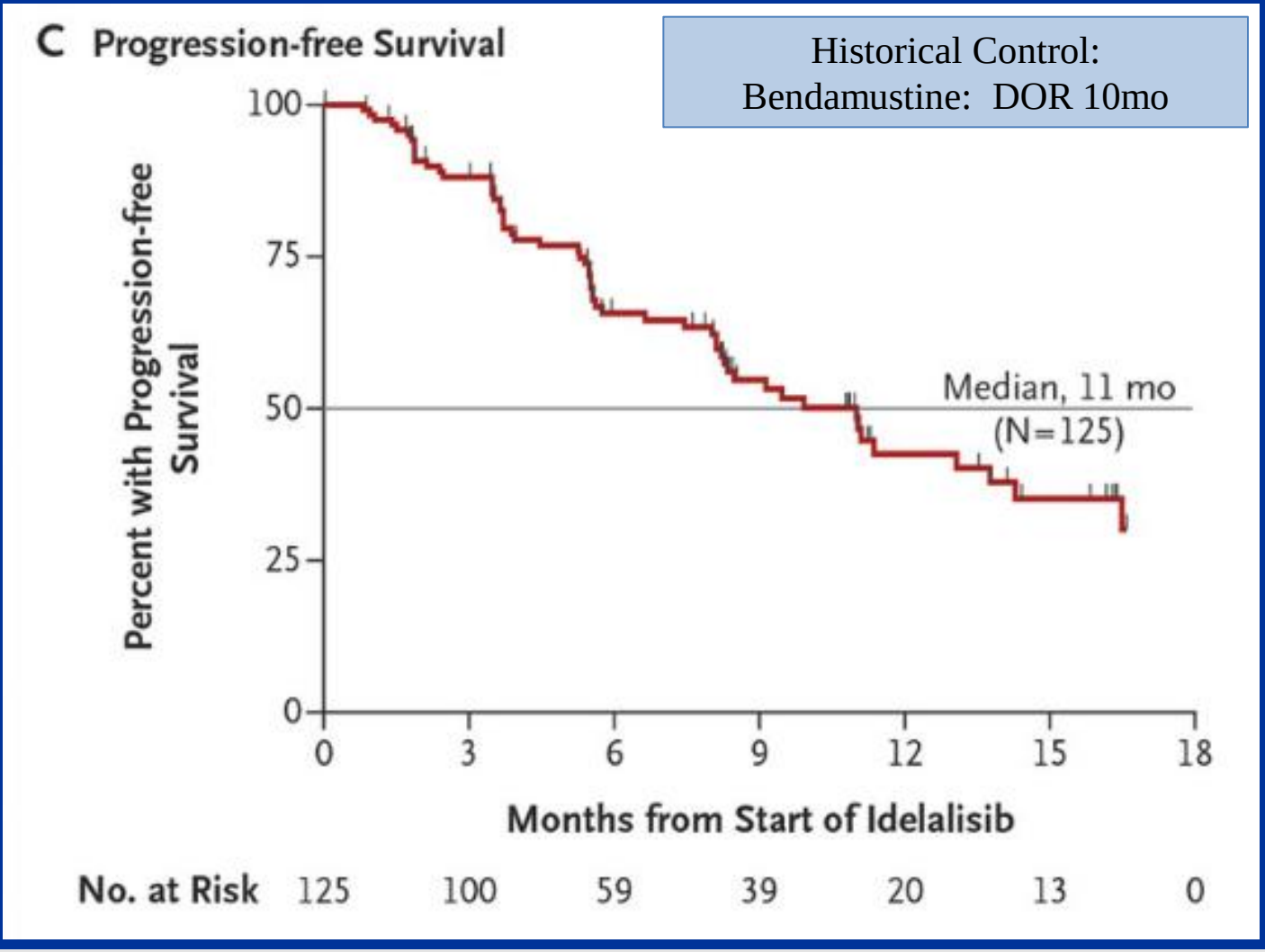
(Gopal A, et al. NEJM 2014)

Tumor Response



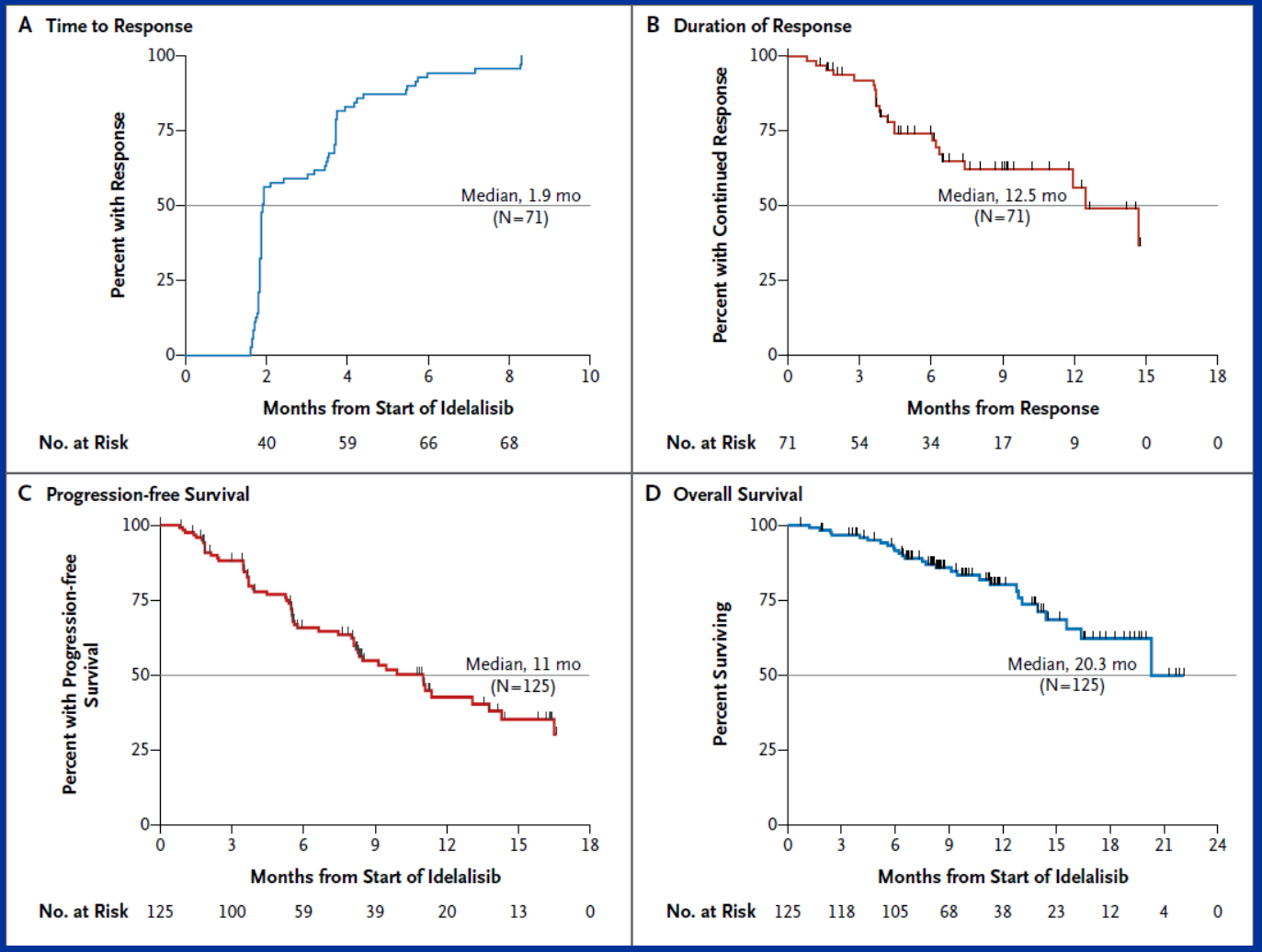
(Gopal A, et al. NEJM 2014)

Progression Free Survival



(Gopal A, et al. NEJM 2014)

Progression Free Survival



(Gopal A, et al. NEJM 2014)

Adverse Events

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

(Gopal A, et al. NEJM 2014)

SAEs and AEs Leading to Discontinuation

Serious Adverse Event*, n (%)	
Pyrexia	10 (8.0%)
Pneumonia	8 (6.4%)
Diarrhea	7 (5.6%)
Dehydration	4 (3.2%)
Fever/Neutropenia	4 (3.2%)
Colitis	3 (2.4%)
Acute Renal Failure	3 (2.4%)

*SAE occurring in more than 2 subjects

AE leading to Discontinuation	
Transaminase elevations	4 (3%)
Infections	3 (2%)
Diarrhea	2 (1.6%)
Colitis	2 (1.6%)
Neutropenia	2 (1.6%)
Pneumonia	2 (1.6%)
Pneumonitis	2 (1.6%)
ARDS	1 (0.8%)
Failure to Thrive	1 (0.8%)
Mucositis	1 (0.8%)

(Salles et al., ICML 2013)

Idelalisib Efficacy and Safety in Follicular Lymphoma Patients From a Phase 2 Study - Post hoc analysis

Patient Disposition

- At the time of data cutoff (June 11, 2014, vs June 25, 2013, for core study publication), 7 patients (9.7% of 72 FL patients) were still on treatment and 65 had discontinued
- The most frequent reason for discontinuation was PD (52.8% [n=38/72])

Disposition	Patients (n=72)
Ongoing, n (%)	7 (9.7)
Discontinued, n (%)	
PD	38 (52.8)
AE*	15 (20.8)
Investigator request	4 (5.6)
Death†	5 (6.9)
Withdrew consent	3 (4.2)

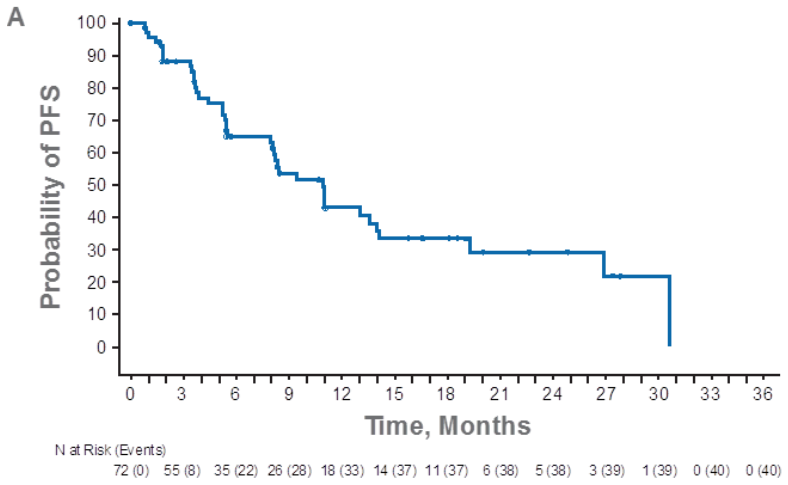
AE=adverse event; PD=progressive disease.

*Colitis (n=4); liver transaminase elevation (n=2); diarrhea (n=2); pneumonitis (n=1), rash/pneumonia (n=1); septic shock (n=1); fever (n=1); mucositis (n=1); pulmonary infiltrates (n=1); and hepatic cytolysis (n=1).
†Cause of death: heart failure, cardiac arrest, splenic infarct/acute abdomen, drug-induced pneumonitis, and unknown (n=1 each).

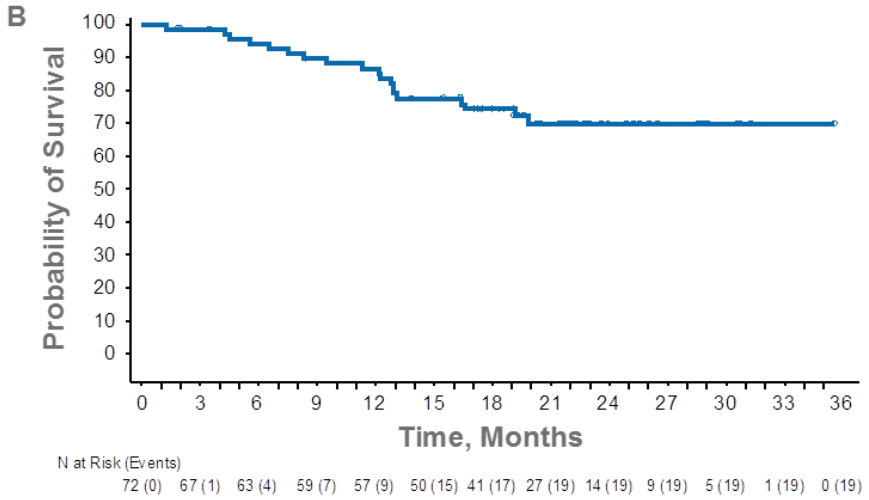
(Salles et al., ASCO 2015)

Results

Median PFS 11.0 mo



Median OS was not reached

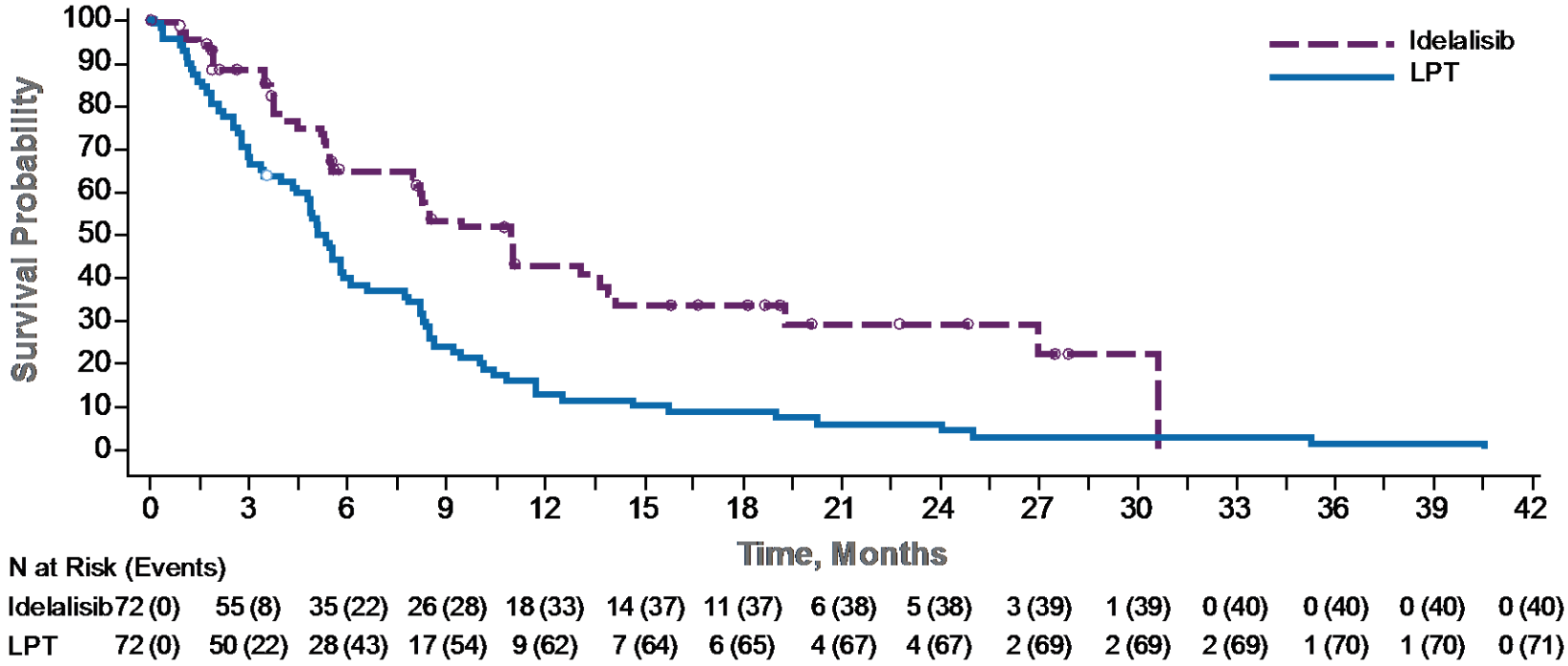


- Time to first CR ranged from 1.9 to 19.2 months

(Salles et al., ASCO 2015)

Comparison of PFS With Previous Line of Therapy Before Study

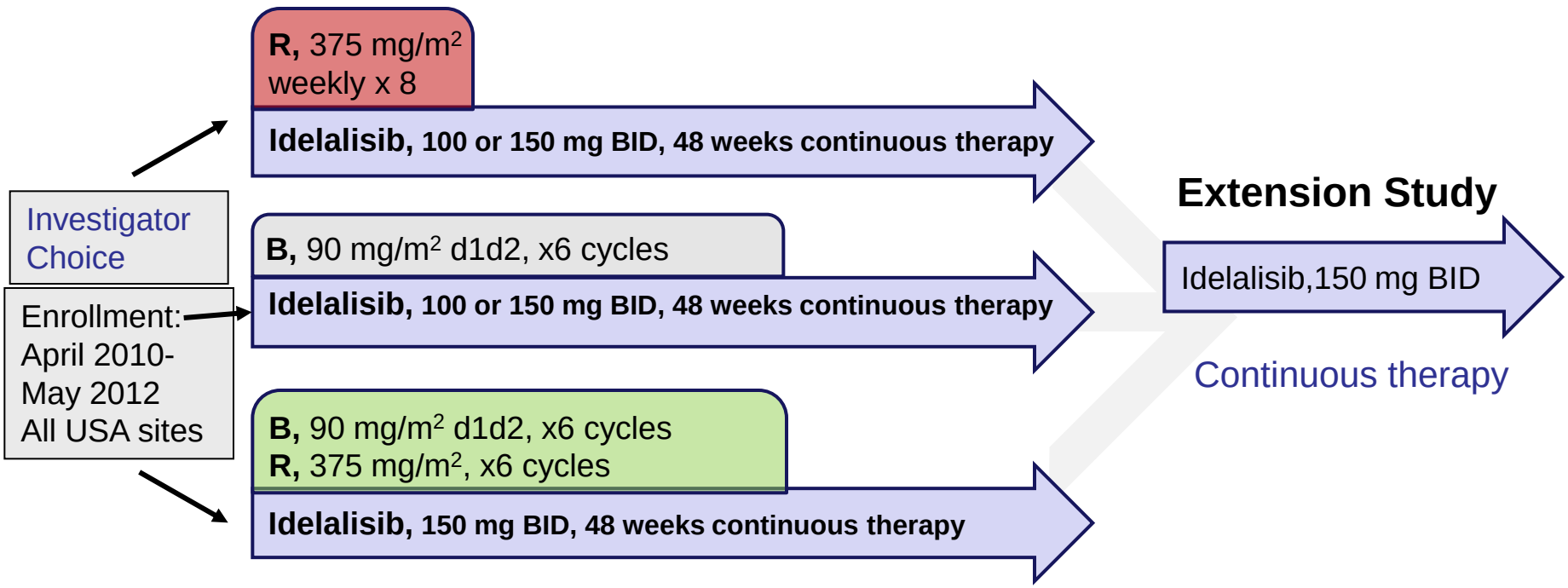
Median PFS of the most recent regimen: was 5.1 (4.4–6.0) mo



N at Risk (Events)															
Idelalisib	72 (0)	55 (8)	35 (22)	26 (28)	18 (33)	14 (37)	11 (37)	6 (38)	5 (38)	3 (39)	1 (39)	0 (40)	0 (40)	0 (40)	0 (40)
LPT	72 (0)	50 (22)	28 (43)	17 (54)	9 (62)	7 (64)	6 (65)	4 (67)	4 (67)	2 (69)	2 (69)	2 (69)	1 (70)	1 (70)	0 (71)

(Salles et al., ASCO 2015)

101-07: Idelalisib Phase 1b Combination Study in iNHL
3 groups, non-randomized



Disease assessments:

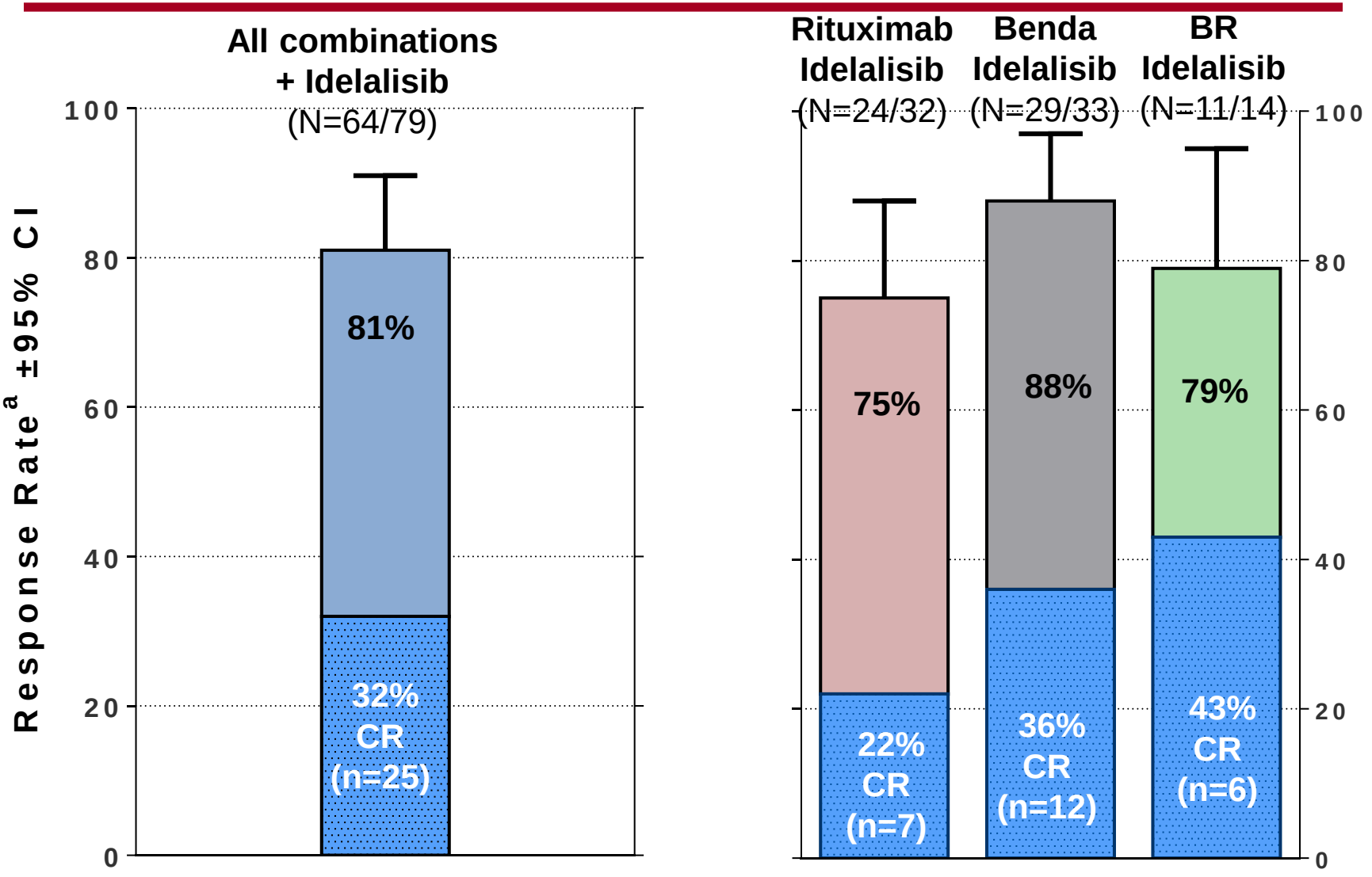
- **Weeks 0, 8, 16, 24**
- **Every 12 weeks thereafter**
- **Investigator determined**

Endpoints:

- **Safety (Primary)**
- **Dose selection**
- **Pharmacokinetics**
- **Pharmacodynamics**
- **Efficacy**

(de Vos et al., ASH 2014)

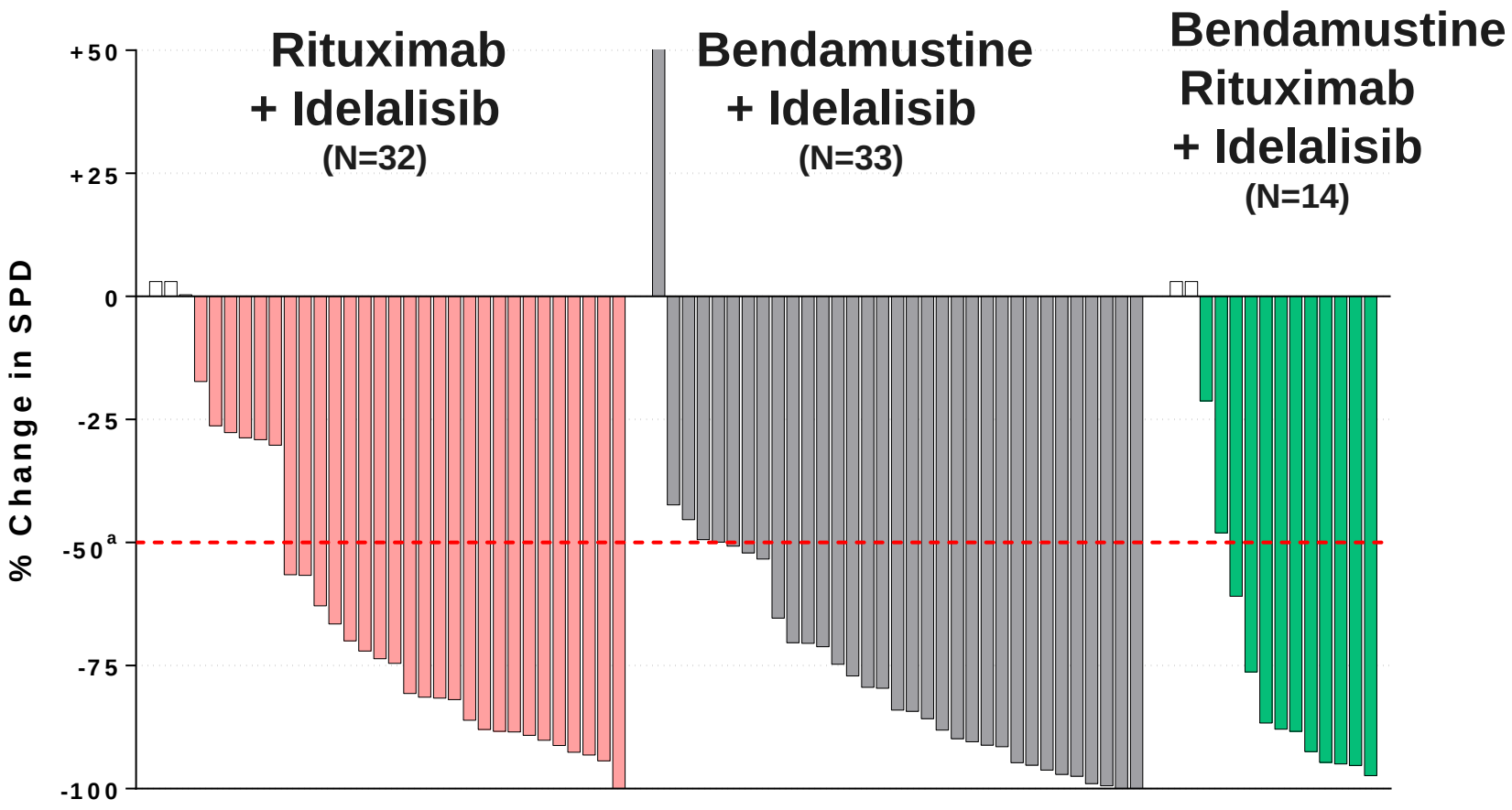
Overall Response Rates



[a] Criterion for response [Cheson 2007]

(de Vos et al., ASH 2014)

Best Response in Tumor Area

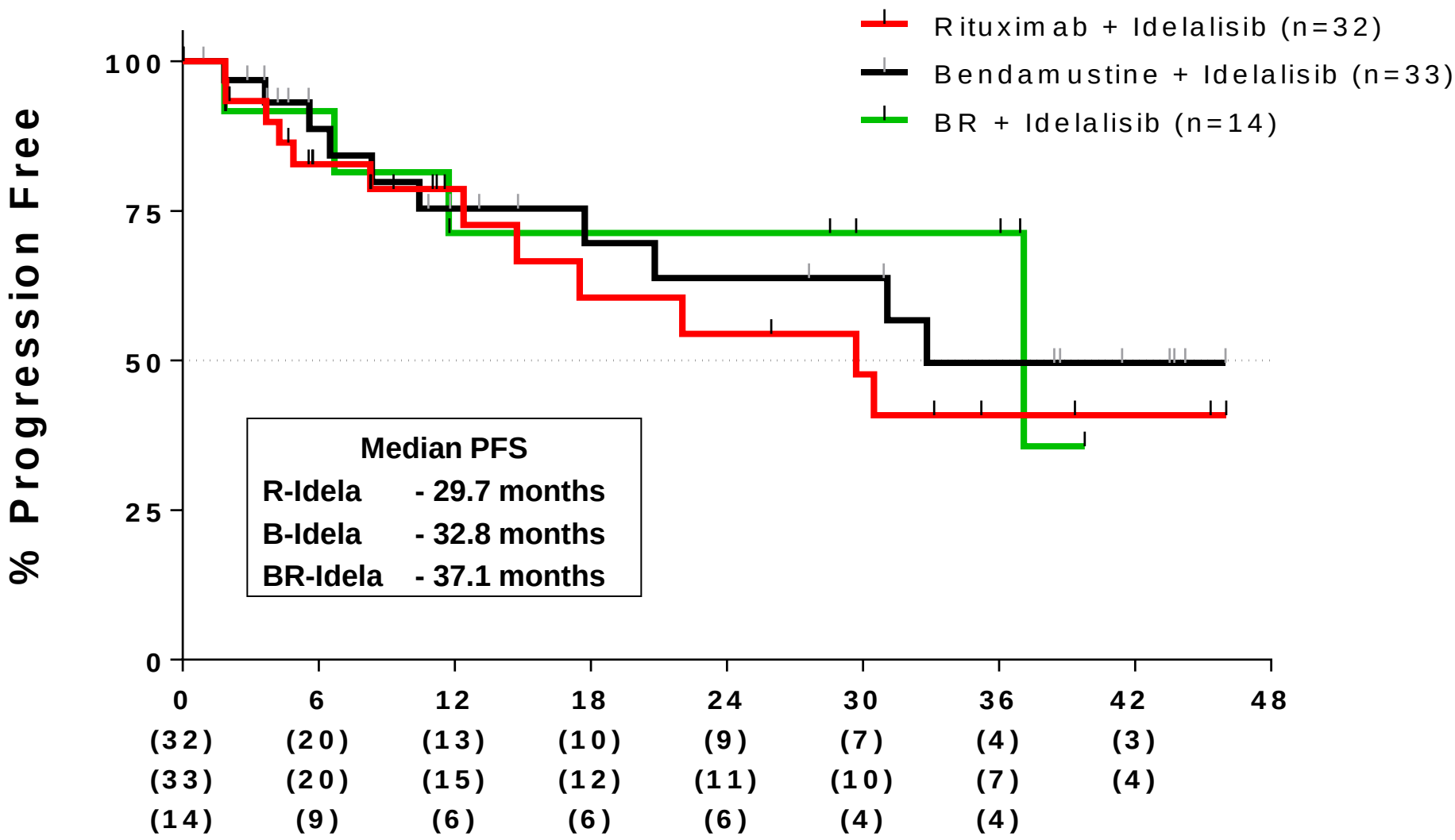


□ Non-evaluable (patients without a follow-up tumor assessment)

[a] Criterion for response [Cheson 2007]

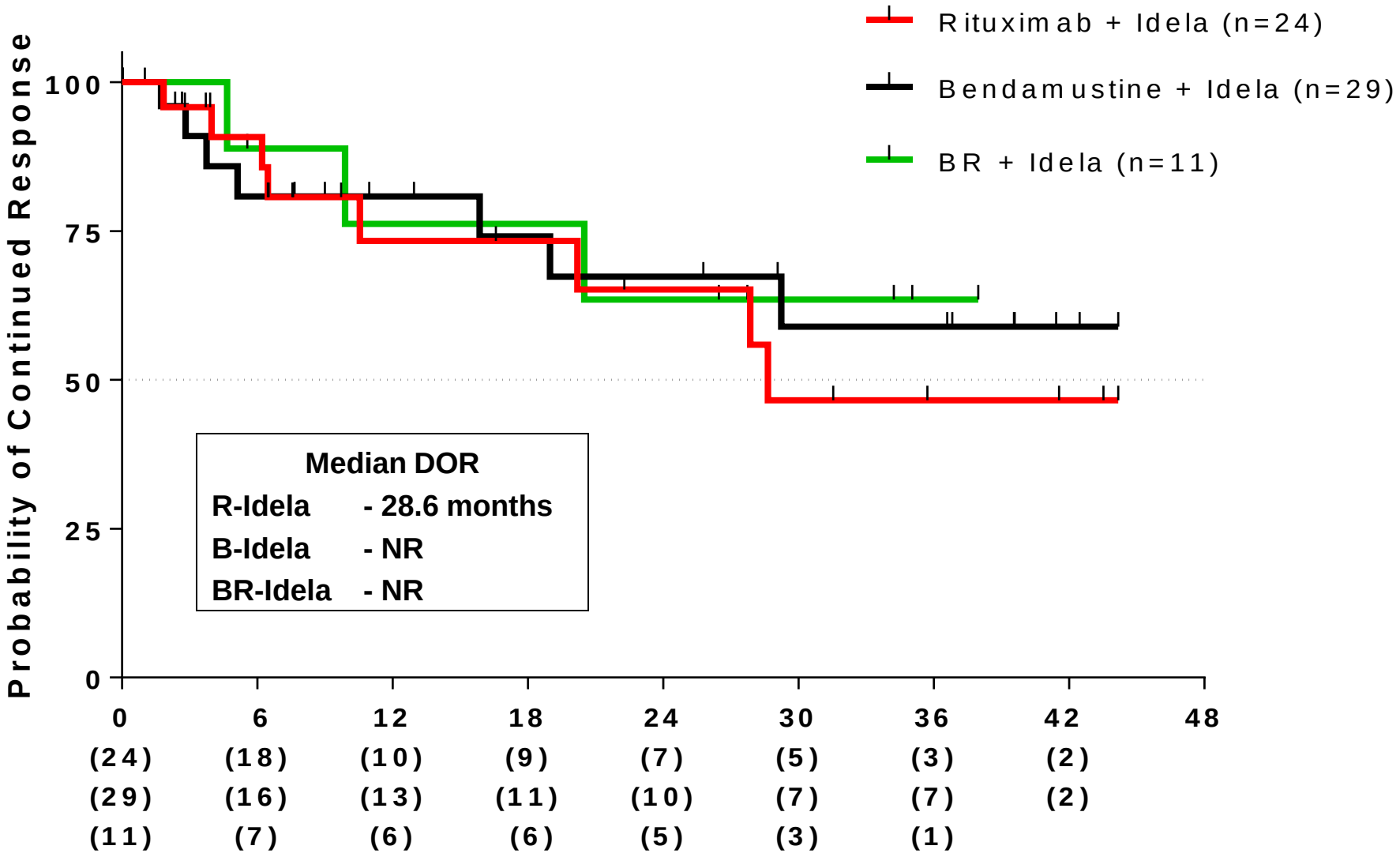
(de Vos et al., ASH 2014)

Progression Free Survival:



(de Vos et al., ASH 2014)

Duration of Response:



(de Vos et al., ASH 2014)

101-07: Summary and Conclusions

- High response rates with Idelalisib in combination
  - ORR 81% overall
- Durable response
  - **Median PFS 37 months**
  - **DOR at 36 months 55%**
- Manageable safety profile with treatment up to >3 years with no unexpected toxicities in combination
- Data provide strong support for Phase 3 trials in combination with R or BR
  - **Rituximab +/- Idelalisib (313-0124)**
  - **Rituximab/Bendamustine+/- Idelalisib (313-0125)**

Yosemite

Bridalveil

(de Vos et al., ASH 2014)

Idelalisib: Side effects of special interest

- Transaminase elevations
  - Occur within 4-12 weeks of drug initiation
  - Resolve spontaneously over 2-4- weeks
  - Generally asymptomatic and transient
  - Successful re-challenge at lower dose after resolution
- Severe diarrhea
  - Occurs after several months of drug exposure
  - Watery diarrhea, unresponsive to anti-diarrheals
  - Resolution within ~1 month
  - Treatments included: budesonide, systemic steroids, mesalamine
- Rash
  - Usually maculopapular rash, occasionally associated with fever and pruritus
  - Responsive to diphenhydramine, topical or systemic steroids
  - Pathogenic mechanism?
    - Biopsies: ~ delayed type hypersensitivity reaction
- Pneumonia/pneumonitis
  - Occurred in some patients with no infectious agent identified
  - Some events required mechanical ventilation or have been fatal

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

Clinical Trials Included in Analysis

Study No.	N	Drug Regimen	ClinicalTrials.gov
101-02	191	Dose-ranging monotherapy	NCT00710528[1-3]
101-07	232	Dose-ranging combination therapies	NCT01088048
101-08	64	Idelalisib 150 mg BID + rituximab	NCT01203930
101-09	125	Idelalisib 150 mg BID	NCT01282424[4]
101-10	13	Idelalisib 150 mg BID	NCT01306643
101-11	25	Idelalisib 150 mg BID	NCT01393106
101-99	NA*	Continued idelalisib after parent study	NCT01090414
312-0116	110	Idelalisib 150 mg BID + rituximab	NCT01539512[5]

- 760 patients with CLL, indolent non-Hodgkin lymphoma, or other B-cell malignancy
- 101-99 = long-term extension study (no double counting)

(Zelenetz et al., BSH/ISH 2016)

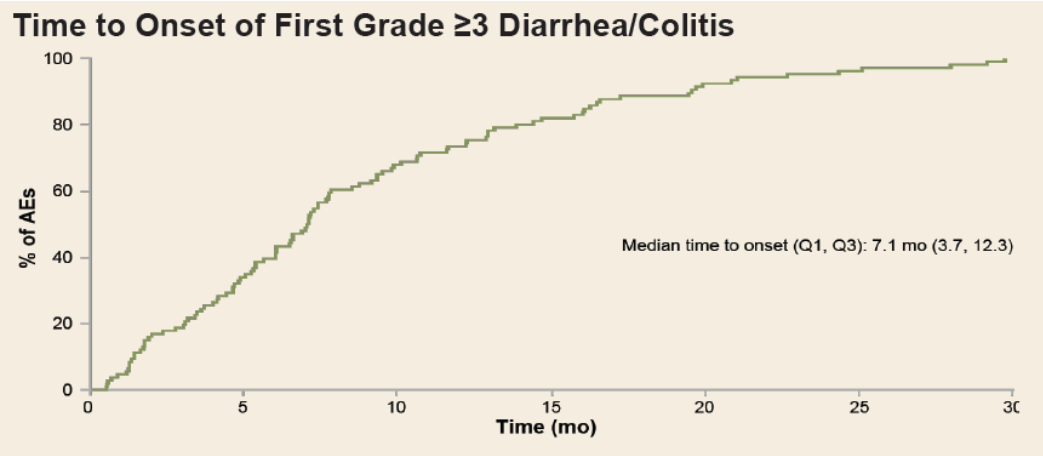
Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

Common Adverse Events (≥15% of Patients)

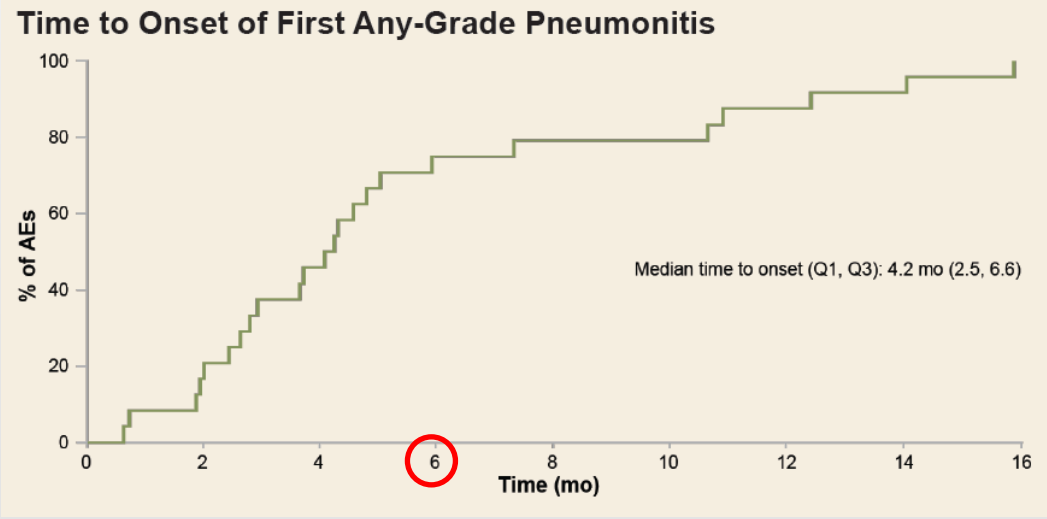
AE, n (%)	Idelalisib Monotherapy n=354		Idelalisib Combination Therapy n=406	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Pyrexia	96 (27)	7 (2)	169 (42)	47 (12)
Diarrhea/colitis	131 (37)	38 (11)	161 (40)	68 (17)
Fatigue	112 (32)	6 (2)	130 (32)	13 (3)
Nausea	91 (26)	5 (1)	125 (31)	30 (7)
Cough	80 (22)	3 (1)	118 (29)	21 (5)
Rash	60 (17)	7 (2)	99 (24)	30 (7)
Chills	49 (14)	0	86 (21)	23 (6)
Pneumonia	47 (13)	40 (11)	74 (18)	56 (14)
Constipation	39 (11)	0	68 (17)	1 (<1)
Dyspnea	43 (12)	7 (2)	68 (17)	10 (3)
Abdominal pain	40 (11)	4 (1)	37 (17)	5 (1)
Vomiting	53 (15)	5 (1)	60 (15)	18 (4)
Decreased appetite	46 (13)	8 (2)	62 (15)	2 (<1)

(Zelenetz et al., BSH/ISH 2016)

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials



- Grade ≥3 diarrhea occurred in 106 patients (14%)
- Generally a late-onset AE



- Pneumonitis occurred in 24 patients (3%)
- Most AEs within first 6 months of treatment

(Zelenetz et al., BSH/ISH 2016)

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

Management of Selected Adverse Events With Dose Modifications

	Total With AE (all grades)	Patients With AEs Requiring*:		
		Dose Reduction	Dose Interruption	Treatment Discontinuation
ALT/AST elevation	366 (48)	50 (7)	59 (8)	25 (3)
Diarrhea/colitis	302 (40)	20 (3)	64 (8)	34 (5)
Rash	159 (21)	13 (2)	30 (4)	18 (2)
Pneumonitis	24 (3)	4 (1)	7 (1)	8 (1)
Neutropenia	396 (52)	10 (1)	27 (4)	2 (<1)

*An individual patient may have had multiple dose modifications (%s may be overlapping).

(Zelenetz et al., BSH/ISH 2016)

Safety of Idelalisib in B-Cell Malignancies: Integrated Analysis of Eight Clinical Trials

Success of Rechallenge Following Dose Interruptions

Patients, n (%)	N=760
Grade ≥3 diarrhea/colitis	106 (14)
Rechallenged	71/106 (67)
Successful rechallenge	41/71 (58)
Grade ≥3 ALT/AST elevation	109 (14)
Rechallenged	82/109 (75)
Successful rechallenge	63/82 (77)
Grade ≥3 rash	45 (6)
Rechallenged	34/45 (76)
Successful rechallenge	27/34 (79)
Any-grade pneumonitis	24 (3)
Rechallenged	13/24 (54)
Successful rechallenge	9/13 (69)

Drug was interrupted until AE resolved to Grade ≤1.

(Zelenetz et al., BSH/ISH 2016)

FDA Alerts Healthcare Professionals About Clinical Trials with Idelalisib in Comb. with other Cancer Medicines (March 14, 2016)

- Six randomized phase 3 trials have been terminated.
- Important safety signal was seen in phase 3 trials of Idelalisib, due to reports of an increased rate of AEs, including deaths, in Idelalisib combination studies in patients with CLL, SLL and other iNHL.
- It is noted that infectious issues in the Idelalisib-containing arms are likely a contributing factor (including sepsis/pneumonias).
- Serious and fatal infections have occurred with idelalisib, including infections from PJP and CMV. These infections have most frequently occurred within the first 6 months of idelalisib treatment for patients with CLL and iNHL.
- These trials are currently undergoing detailed analyses by Gilead and regulators (EMA/FDA).

Combined Studies 123/124/125	ZYDELIG (N = 664)	Control (N = 402)
All Deaths	49 (7.4%)	14 (3.5%)
Hazard Ratio (95% CI[1])	2.29 (1.26, 4.18)	

[1] stratified by study

Current GILEAD/FDA recommendations

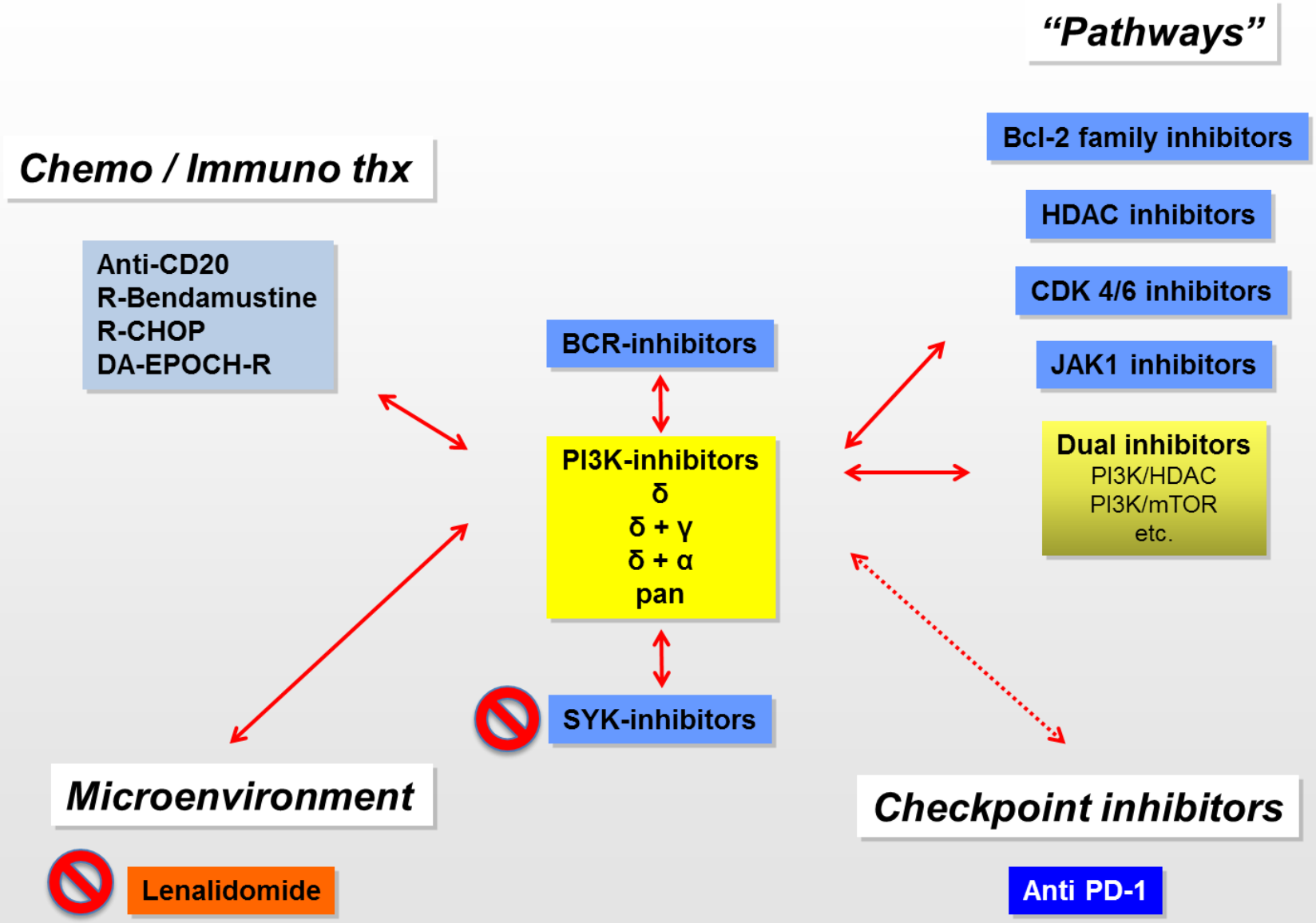
- Subjects must receive trimethoprim-sulfamethoxazole or other established prophylaxis for PJP throughout the course of idelalisib treatment.
- Prophylaxis will continue until the CD4+ T-cell count is documented to be >200 cells/mcL after idelalisib treatment ends.
- Subjects must permanently discontinue idelalisib upon diagnosis of PJP.

- CMV surveillance must be conducted approximately every 4 weeks throughout the course of idelalisib treatment.
- If unequivocal clinical or laboratory evidence of CMV infection is present, the subject must permanently discontinue idelalisib treatment and undergo effective antiviral treatment according to established clinical guidelines.

In my opinion…

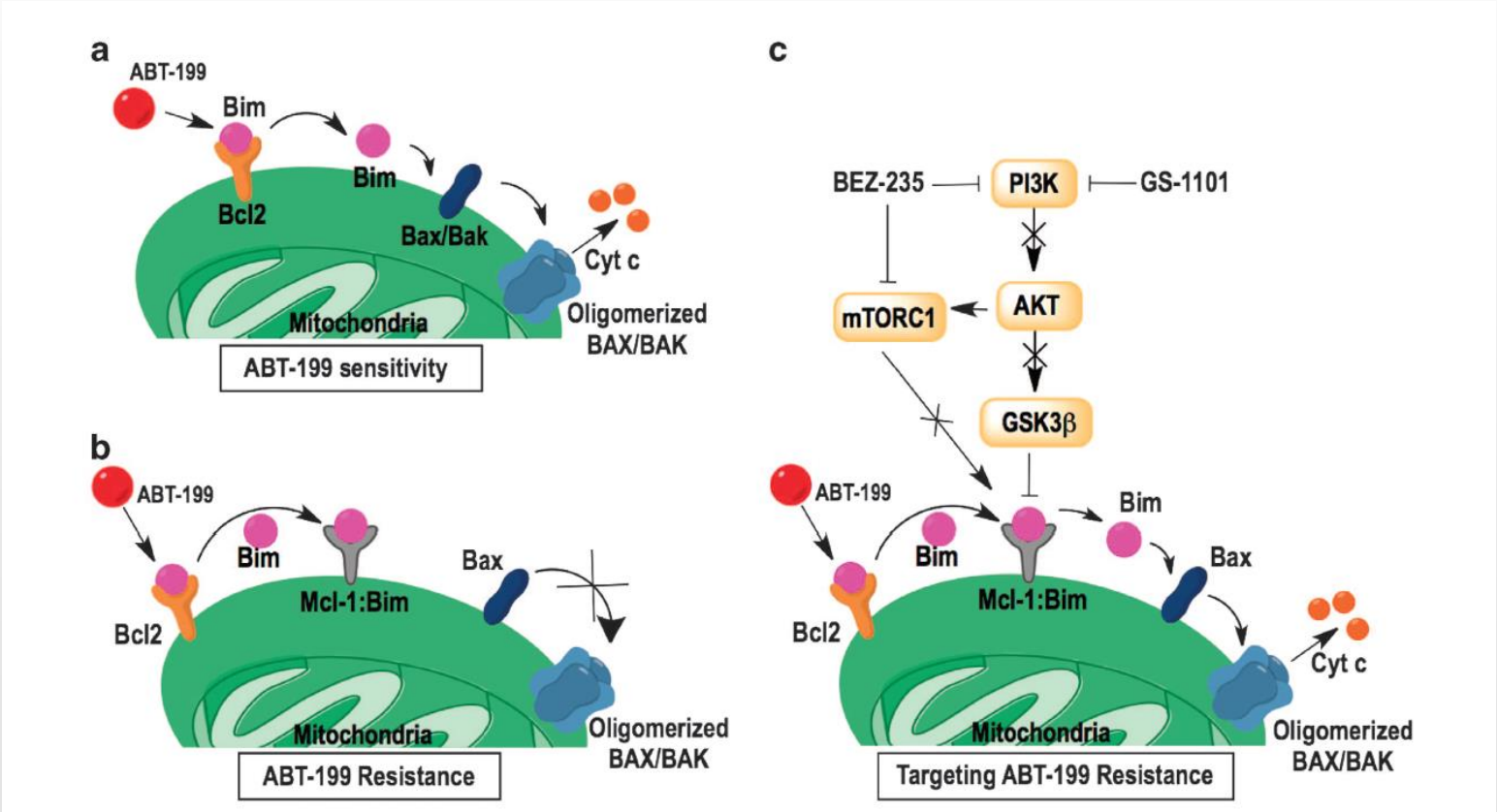
- Difficult to speculate on the similarities and differences between the patient populations across studies and other factors that may account for different outcomes of individual trials.
- Await further information from these trials.
- Idelalisib is approved for relapsed CLL in combination with rituximab and for relapsed follicular lymphoma or SLL patients who have received at least two prior systemic therapies.
- <u>Role of idelalisib in combination therapies for relapsed iNHL remains to be determined</u>
  - Balancing efficacy and toxicity
  - Factors
    - Treatment dosing and schedule
    - Supportive care and infection prophylaxis
    - Monitoring

PI3K-inhibitor combinations



ABT-199 – Mechanisms of resistance
in vitro model

- MCL-1 and BCL-XL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies



(Choudhary et al., Cell Death and Disease (2015) 6, e1593; doi:10.1038/cddis.2014.525)

Idelalisib: Conclusions

- Highly selective PI3K delta inhibitor
- Significant activity in iNHL (single agent or combination thx)
- Open questions:
  - Effects on immune-system/Long term immunosuppression
  - Immune deregulation (Tregs, etc.)
- Clinical trials with correlative studies
  - Biomarkers
  - Immune system deregulation
  - Biopsies (GI, Skin, disease at relapse)
- Mechanism(s) of resistance?
  - Expression of other PI3K isoforms can contribute to relative resistance