Clinical development of PI3K/AKT/mTOR inhibitors: Toxicity and Metabolic Aspects

ESMO Symposium on Signalling Pathways in Cancer
Targeting the PI3K/AKT/mTor pathway in cancer

Philippe Bedard, MD FRCP(C)

Princess Margaret Cancer Centre – University Health Network

Division of Medical Oncology & Hematology

Bras Drug Development Program

UHN Princess Margaret Cancer Centre

ddp BRAS DRUG DEVELOPMENT PROGRAM

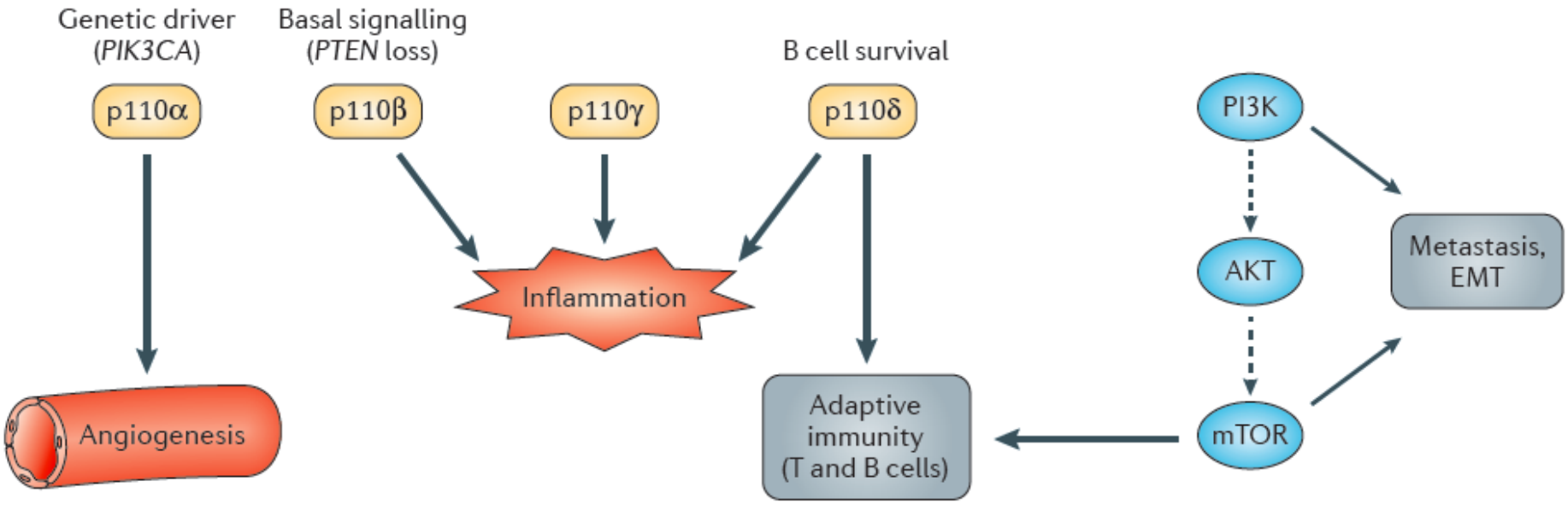
Disclosures

- Research Funding
  - AstraZeneca, BMS, Genentech/Roche, GlaxoSmithKline, Novartis, Sanofi, Servier
- Honoraria/Consultancy (to research account)
  - Novartis, Roche, Sanofi

Learning Objectives

- To provide an overview of toxicities of PI3K-AKT-mTOR signalling pathway
- To differentiate toxicity profiles by class of PI3K-AKT-mTOR inhibitor
- To describe biological basis for metabolic and non-metabolic toxicities observed

Level of Pathway Inhibition and Selectivity Influences Toxicity Profiles



Fruman D et al Nat Rev Drug Discovery 2014 (13): 140-156.

Dose-limiting Toxicities of PI3K-mTOR, pan-PI3K, and isoform specific/sparing PI3K inhibitors

Target	Agents	DLTs
PI3K-mTOR	GSK2126458 GDC-0980 XL765 BEZ235 PF-04691502 PF-05212384 SF1126	Diarrhea Rash, ↑BS ↑LFTs, N/V, rash, fatigue Mucositis, fatigue Fatigue, rash ↑LFTs, ↑BS, rash, mucositis Diarrhea
pan-PI3K	GDC-0941 BKM120 XL147 BAY80-6946 PX-866	Rash, ↑BS, TwI, ↓PLT Mood alteration, rash, ↑BS Rash, hypersensitivity ↑BS, liver/renal failure ↑LFTs, diarrhea
Isoform specific/sparing	BYL719 (α-specific) GDC-0032 (β-sparing) GS-1101 (δ-specific)	↑BS, nausea, vomiting, ↑BS, fatigue, renal failure ↑LFTs

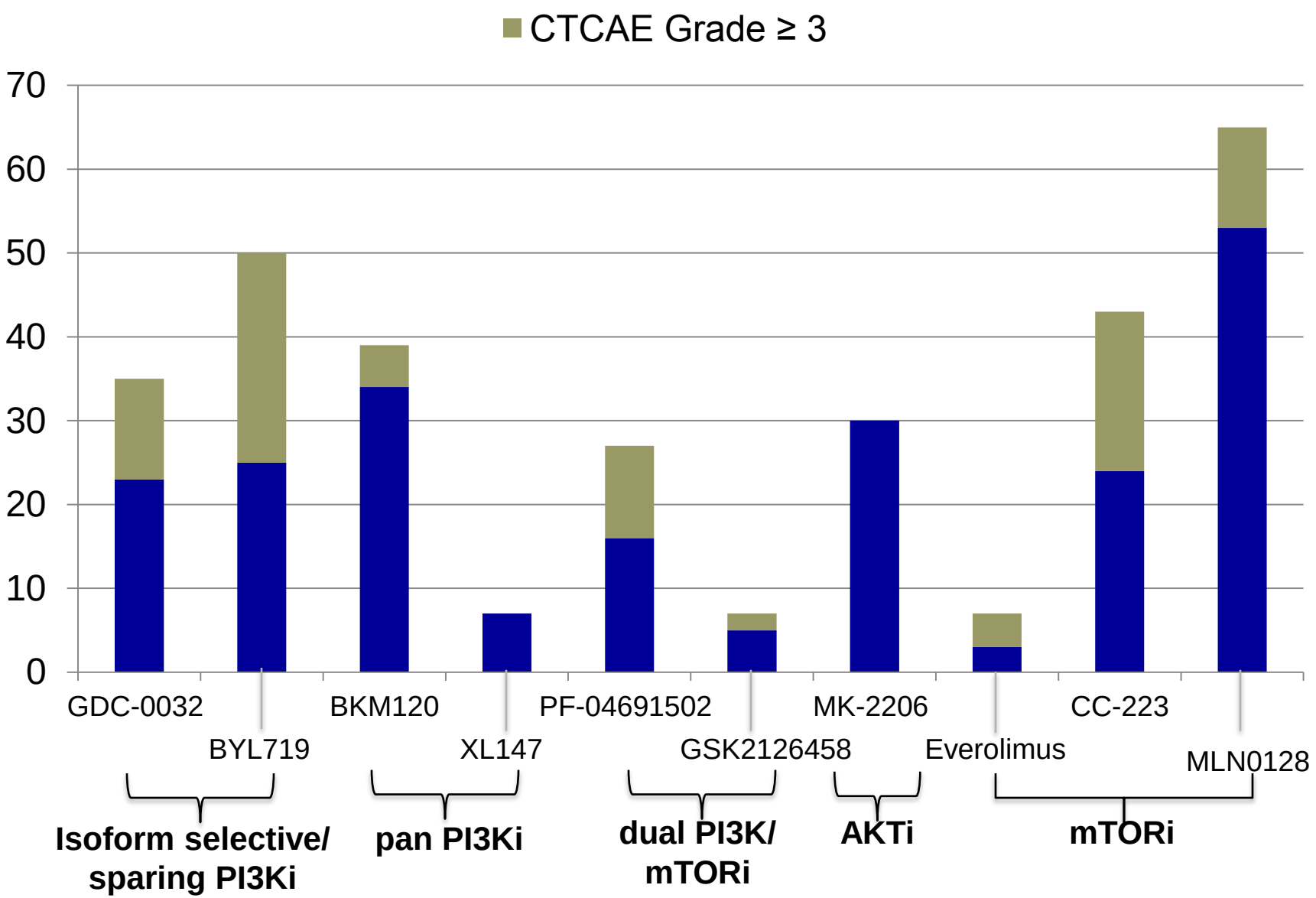
DLT = dose limiting toxicity; BS = blood sugar; N/V = nausea/vomiting; TwI = T-wave inversion; LFTs= transaminases; PLT = platelet

Dose-limiting Toxicities of mTOR and AKT inhibitors

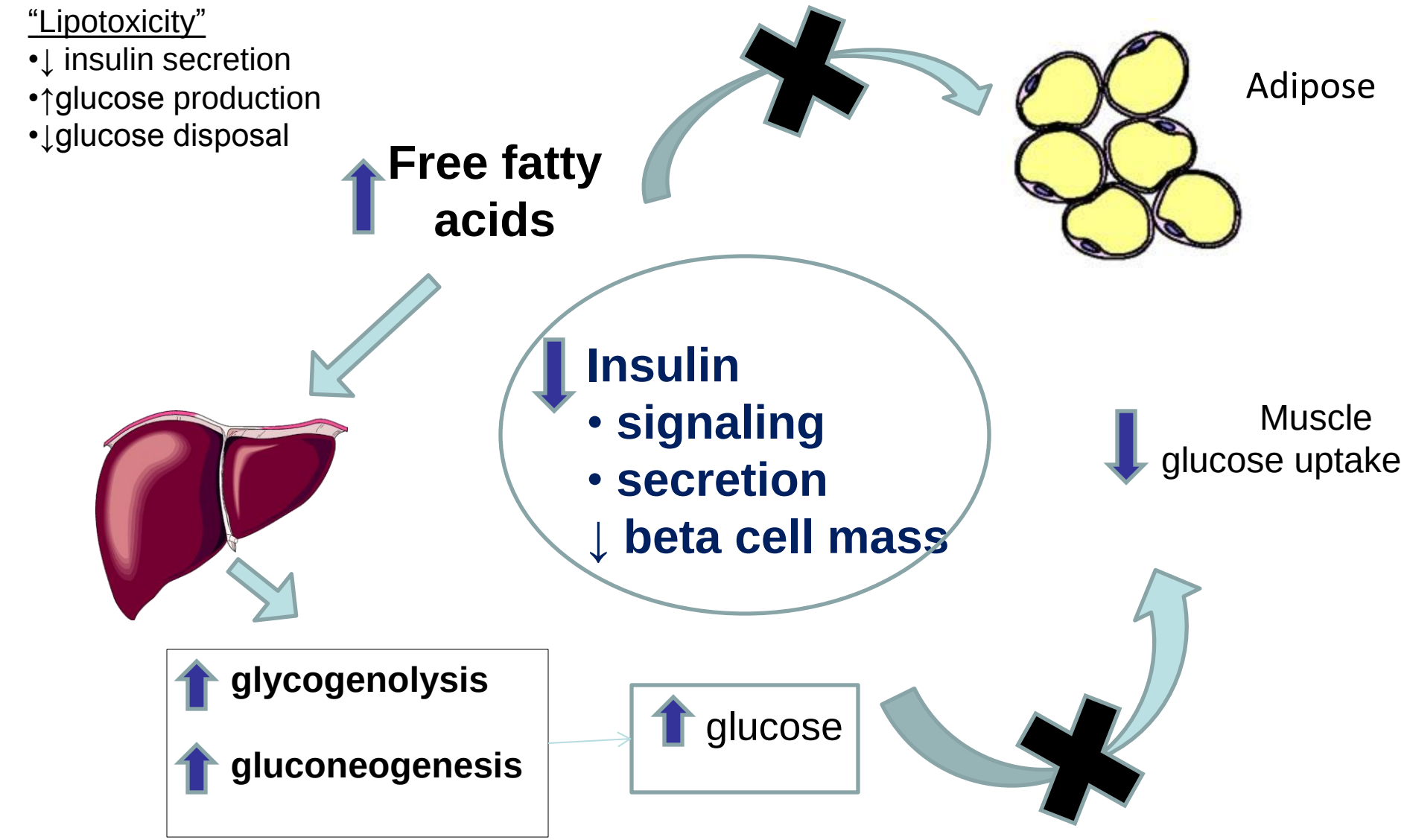
Target	Agents	DLT
mTOR	Temsirolimus	Stomatitis, mood, fatigue, ↓PLT
	Everolimus	Stomatitis, ↑BS, ↓PMN
	Ridaforolimus	Mucositis
	MLN0128	↑BS, rash, anemia
	CC-223	↑BS, rash, mucositis, fatigue
	AZD2014	Mucositis, fatigue
AKT	MK2206	Stomatitis, rash
	GDC-0068	Fatigue
	GSK2141795	↑BS, ↓BS, stomatitis
	AZD5363	↑BS, rash, diarrhea, hypoxemia

DLT = dose limiting toxicity; BS = blood sugar; PMN = neutrophil; PLT = platelet

% Patients in Selected Phase I Trials of PAM Inhibitors with Hyperglycemia

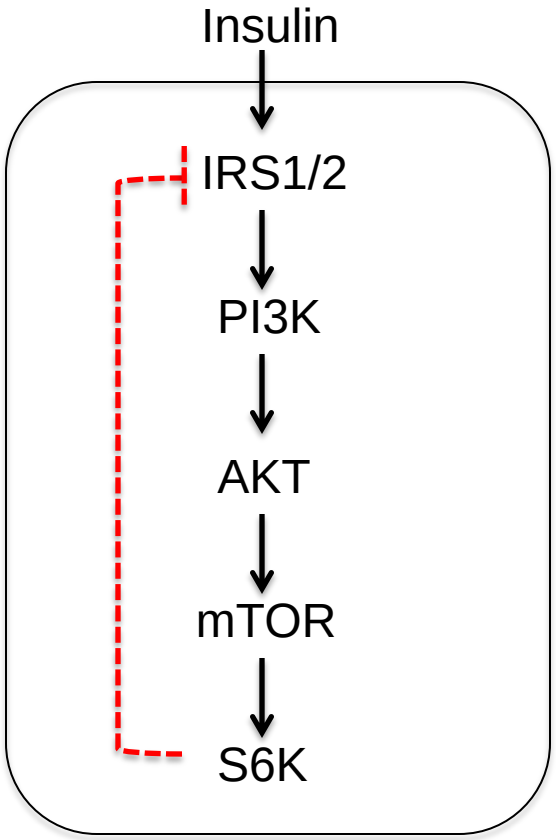


Pathophysiology of PAM pathway inhibitor induced hyperglycemia (primarily mTOR inhibitor)



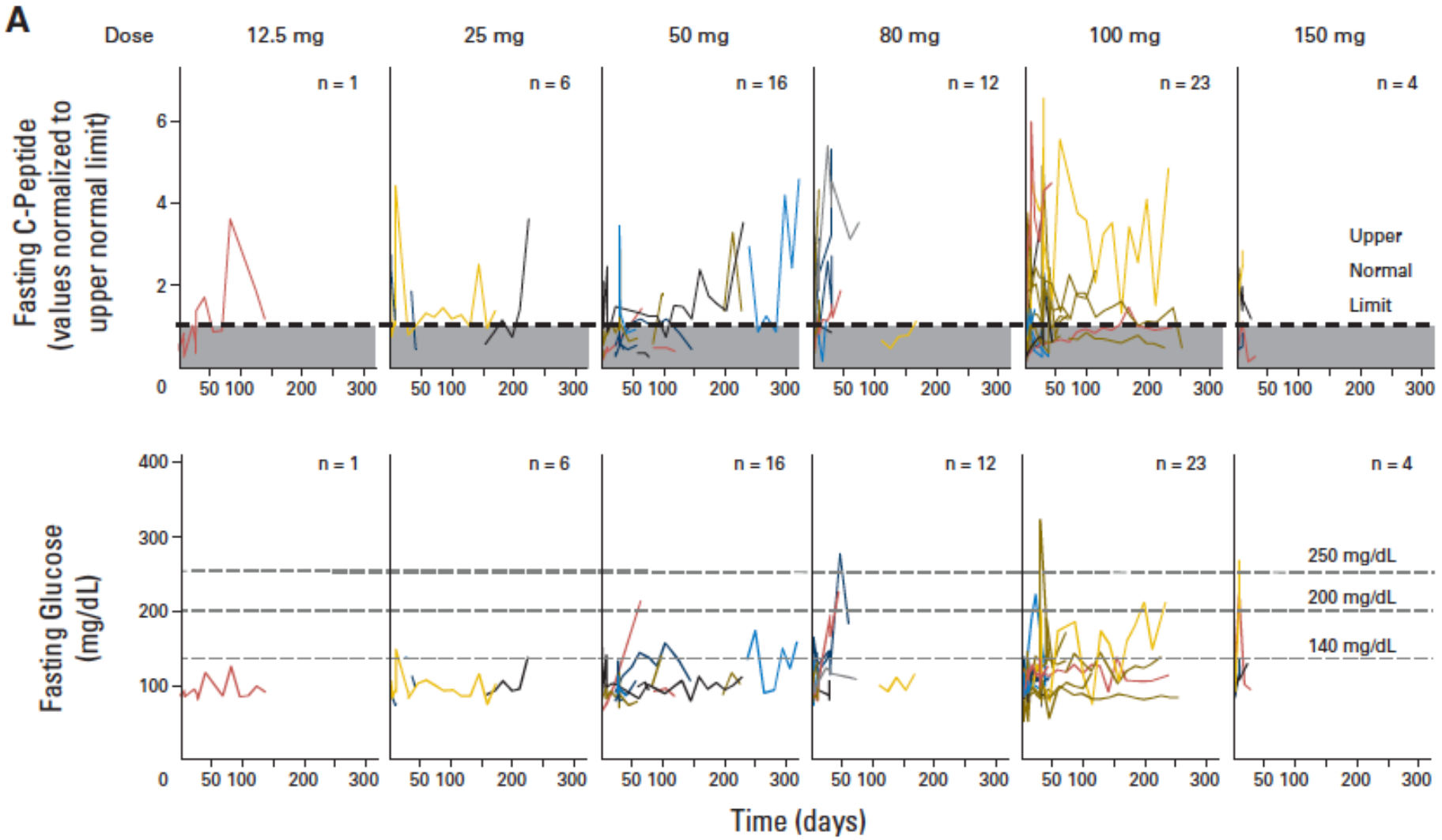
Busaidy N et al J Clin Oncol 2012(30):2919-2928.

Inhibition of PI3K (p110α) or AKT leads to Insulin Resistance



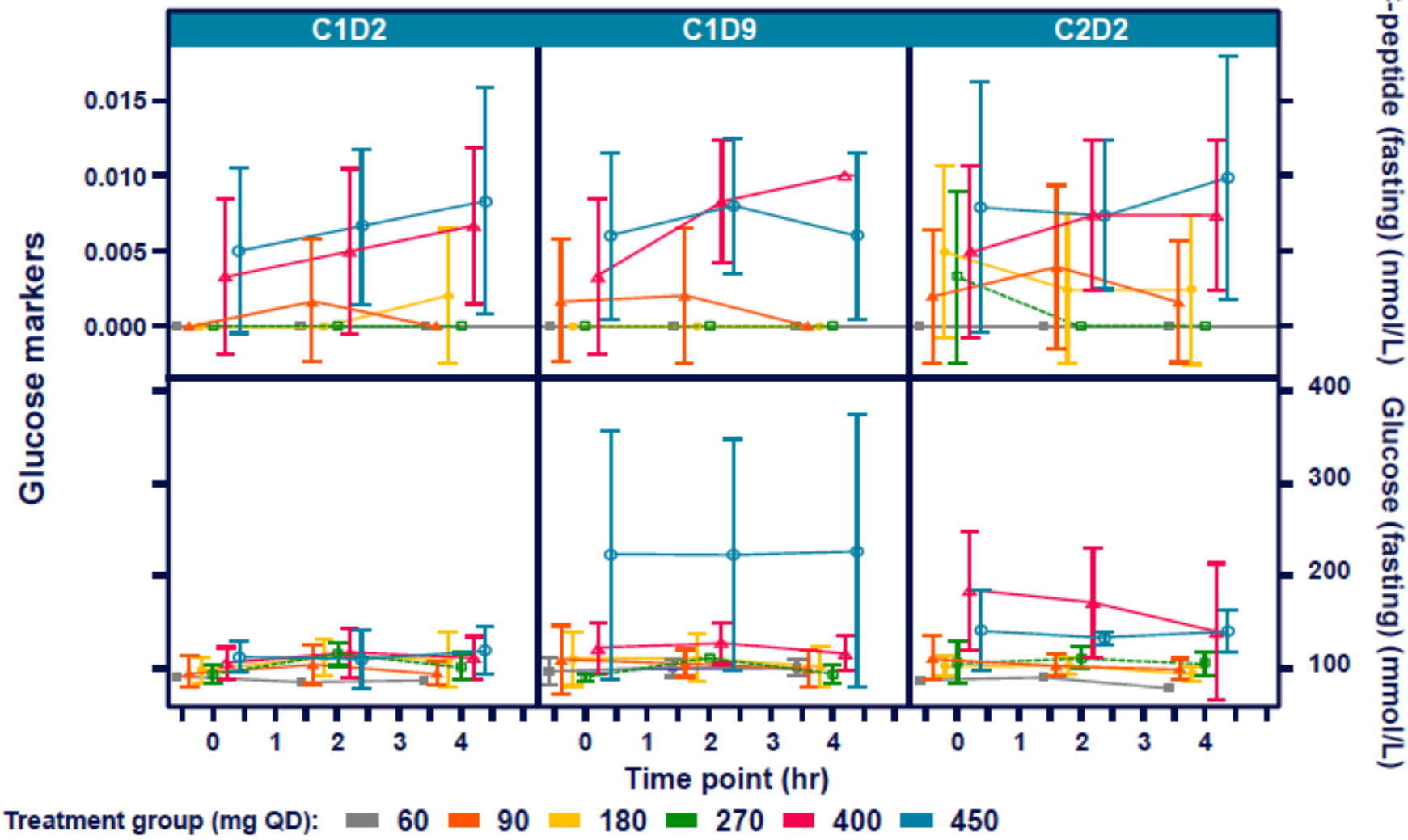
- Decreased peripheral glucose uptake and glycogen synthesis
- Increased levels of circulating glucose
- Triggers release of insulin (and C-peptide)

Elevation of C-Peptide occurs before onset of fasting hyperglycemia with BKM120 (pan PI3Ki)



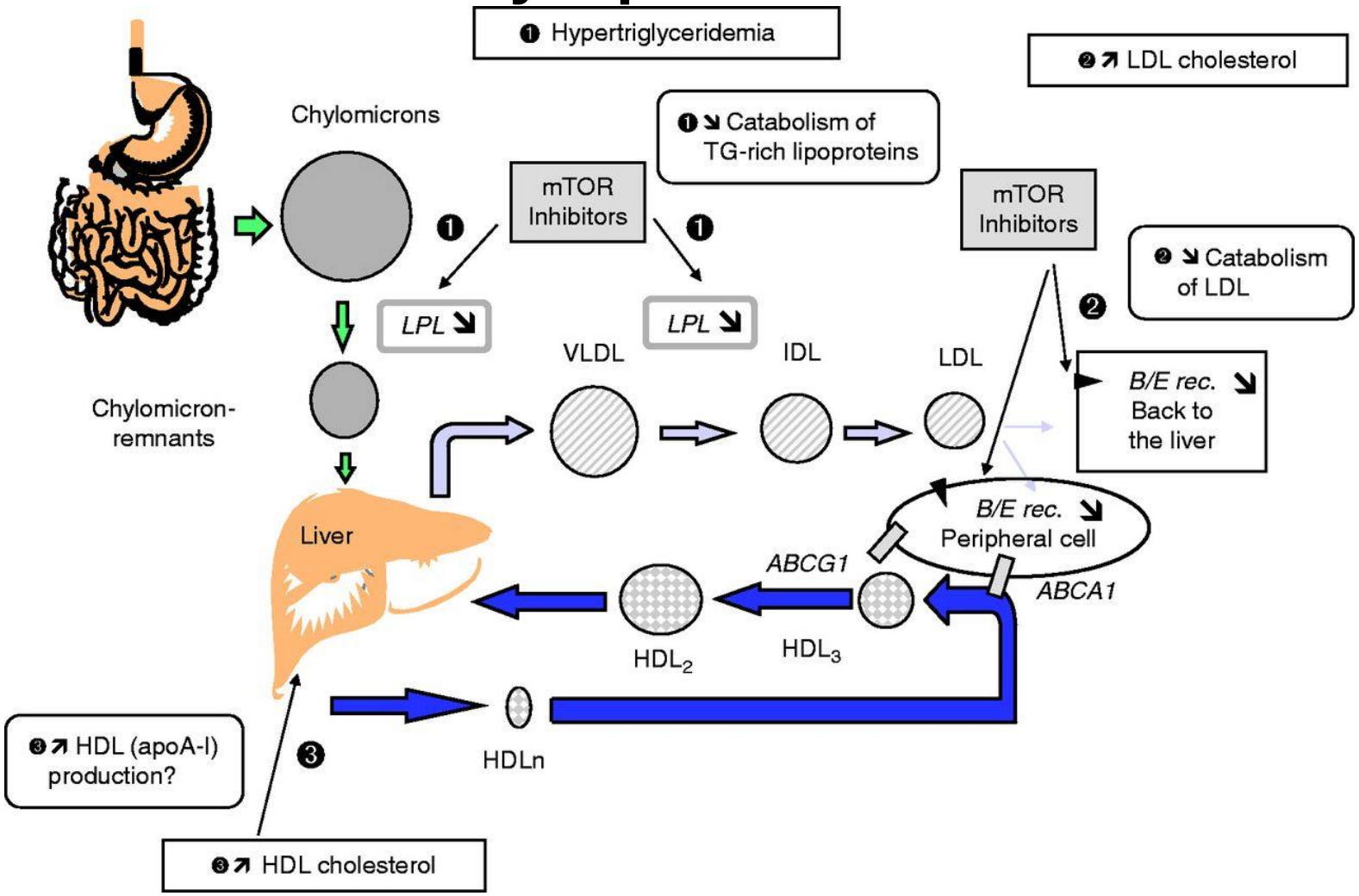
Bendell JC et al J Clin Oncol 2012(30):282-290.

Pharmacodynamic effects of BYL719 on glucose metabolism: Increase of C-peptide to compensate drug-induced glucose elevation at ≥400 mg



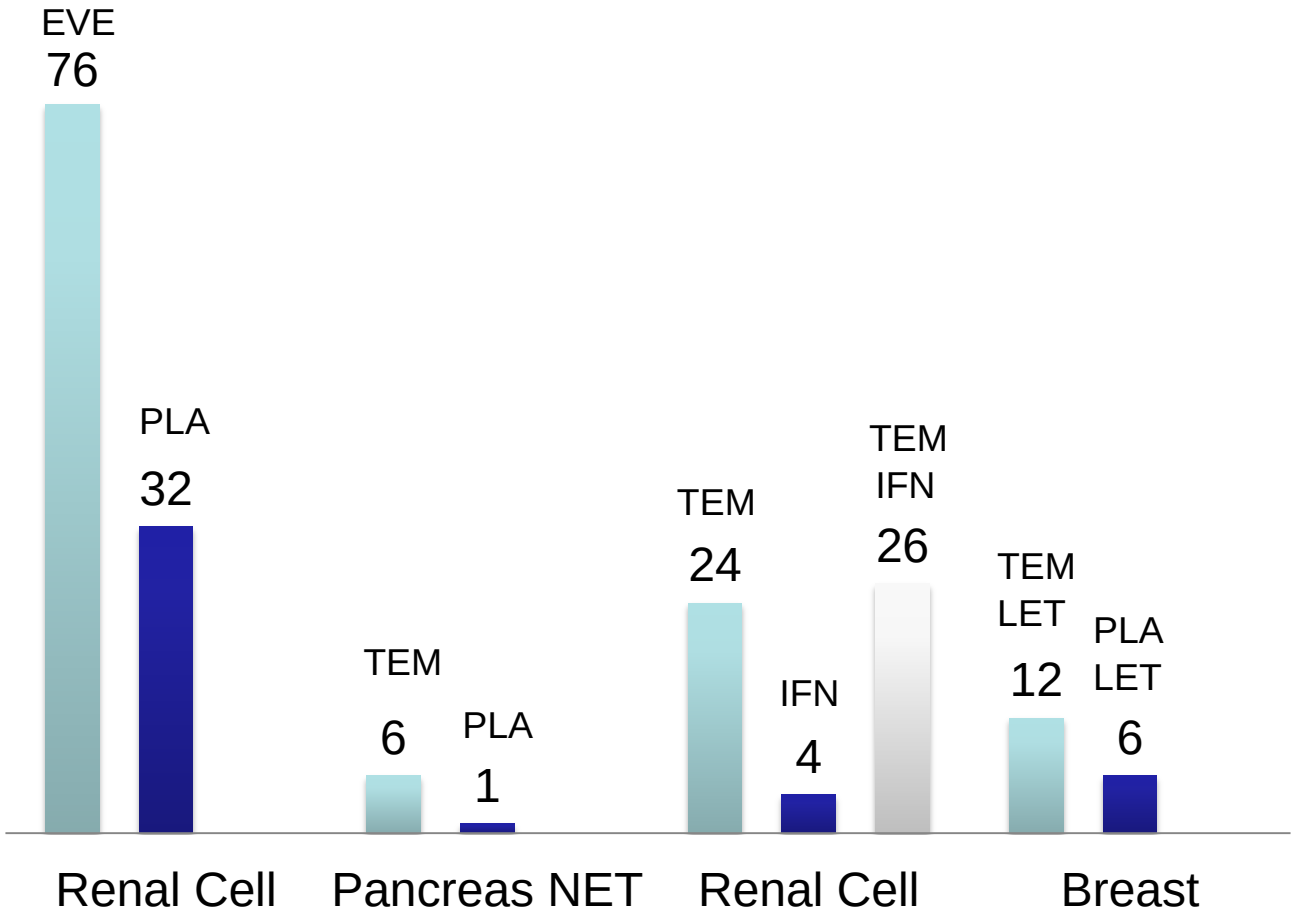
Juric D, et al. Presented at AACR Annual Meeting, March 31 – April 4, 2012

Pathophysiology of mTOR inhibitor induced dyslipidemia



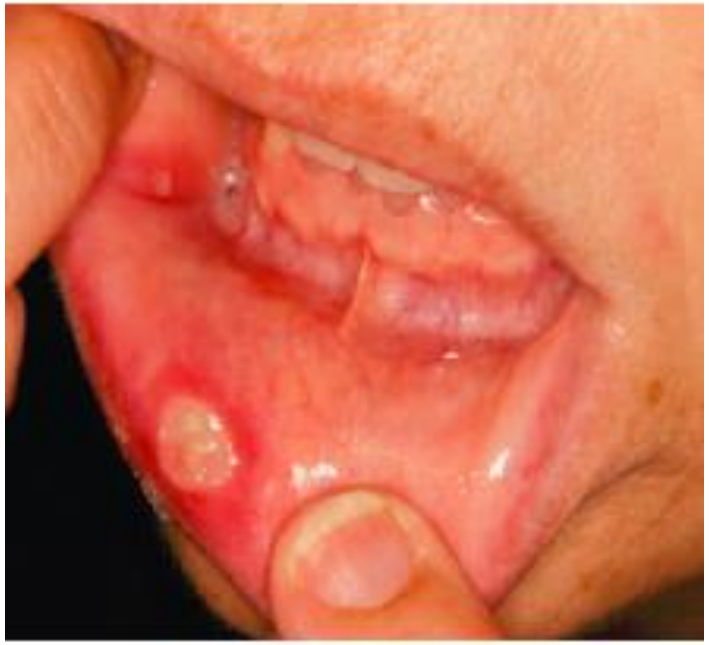
Vergès B et al. Eur J Endocrinol 2014;170:R43-R55

% Patients in Selected mTOR Inhibitor Trials with Hypcholesterolemia (CTCAE grade ≥ 1)



EVE = everolimus; PLA = placebo; TEM = temsirolimus; IFN = interferon; LET = letrozole; NET = neuroendocrine tumor

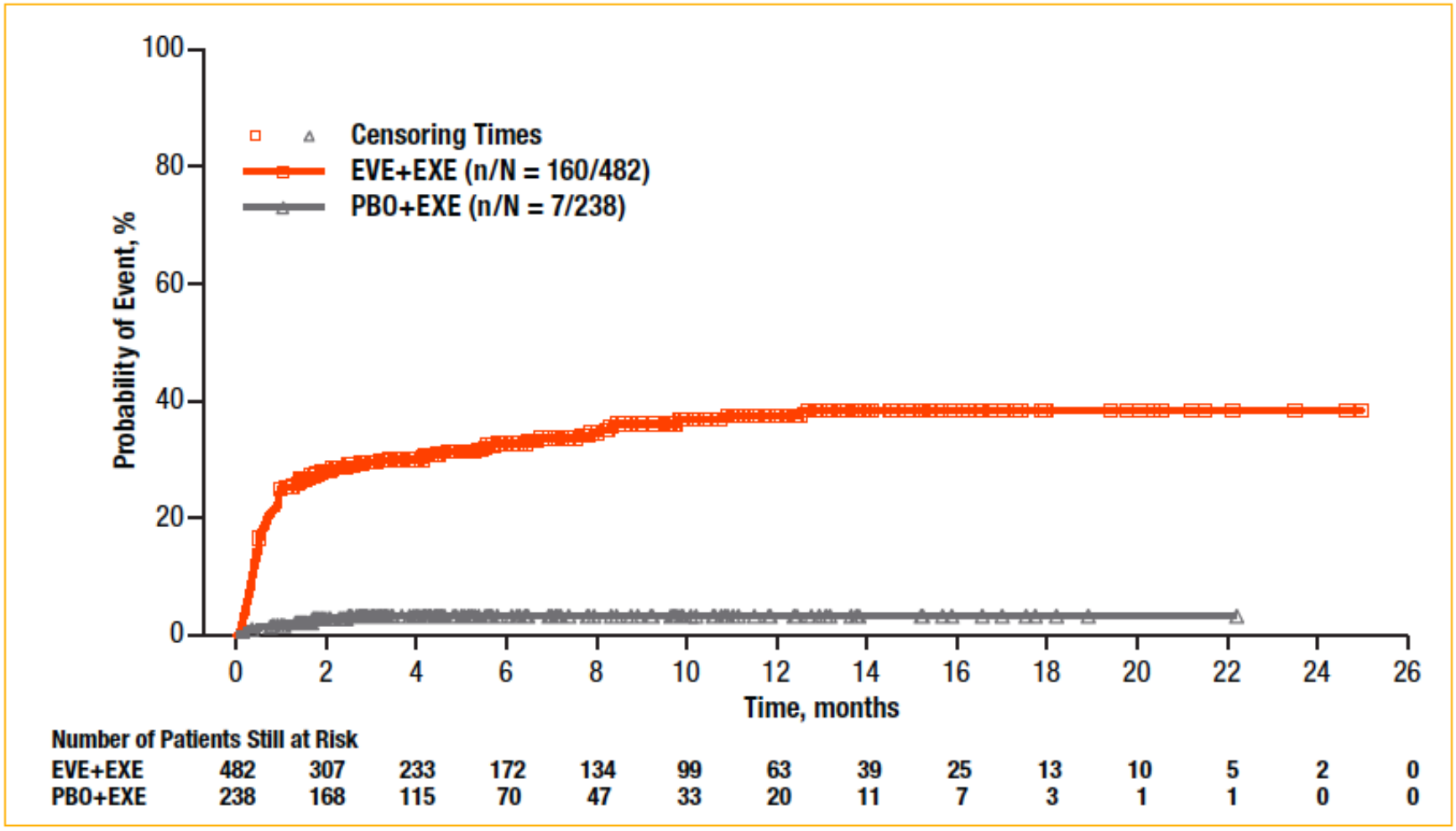
mTOR Inhibitor Induced Stomatitis



- Small ovoid ulcers with gray halo & erythematous ring
- Non-keratinized, movable oral surfaces
  - buccal & labial mucosa, lateral tongue, soft palate
- Early onset, often painful
- Severity often peaks within first cycle
- Similar presentation with PI3K inhibitor stomatitis

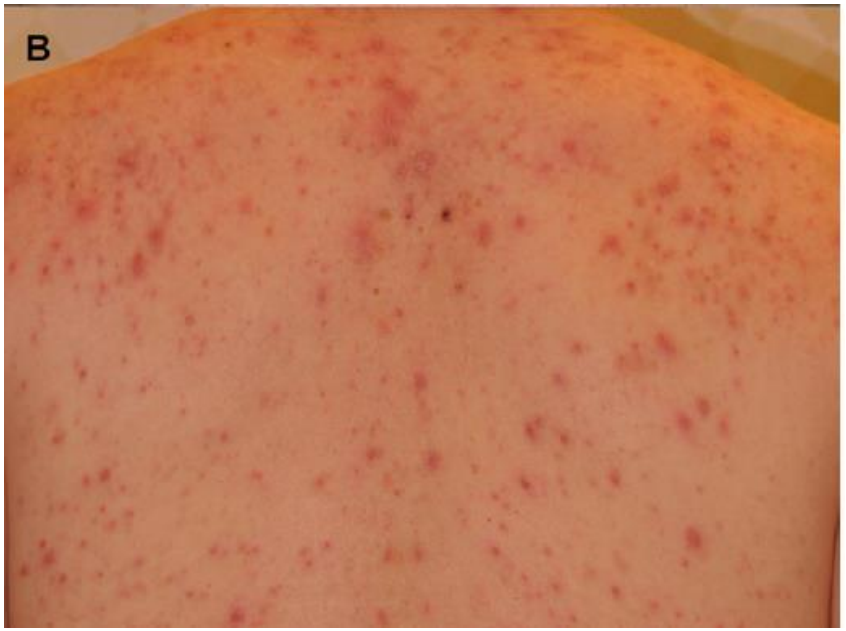
Sonis S, et al. Cancer. 2010;116(1):210-215.

Time to Onset of Grade ≥ 2 Stomatitis in BOLERO-2 Trial



Perez A al ASCO 2013 Abstract #558

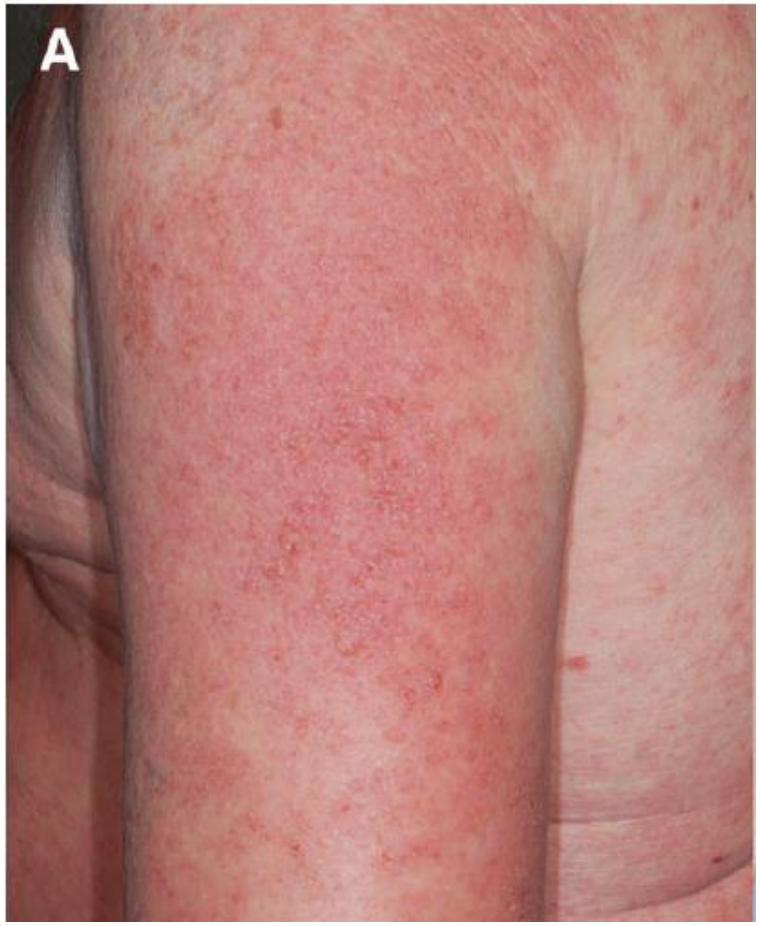
PAM Inhibitor Induced Rash

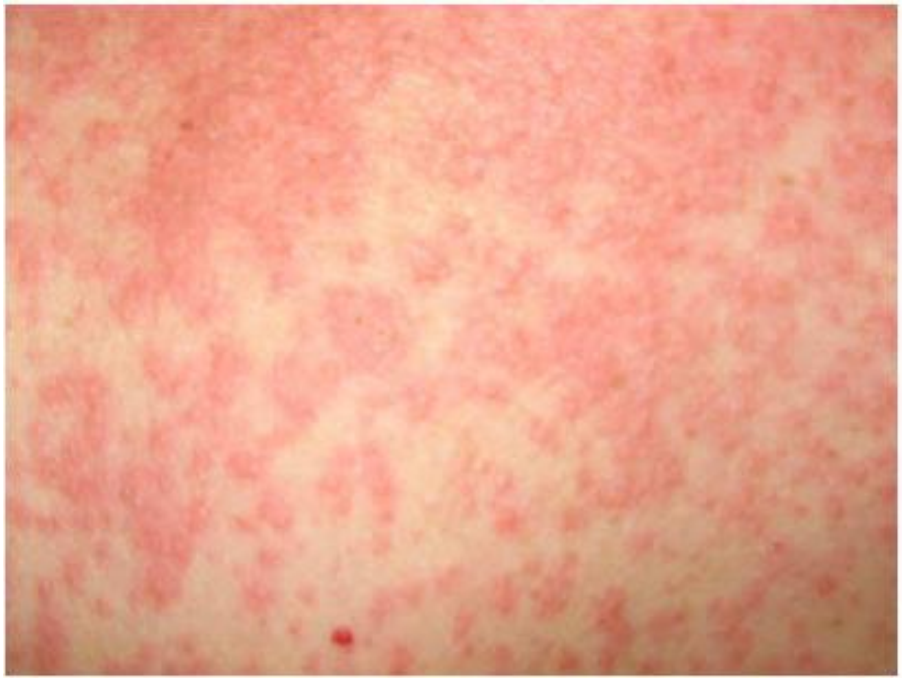


- Often presents as pruritic, erythematous maculopapular
  - Face, trunk, scalp, abdomen, extremities
- May coalesce into large plaque-like areas
- Skin biopsies = spongiotic dermatitis & perivascular infiltrate
- Other presentations (mTOR)
  - Pustules, nodular lesions, eosinophilic-hypersensitivity

Balagula Y et al Cancer 2012;118:5078–83

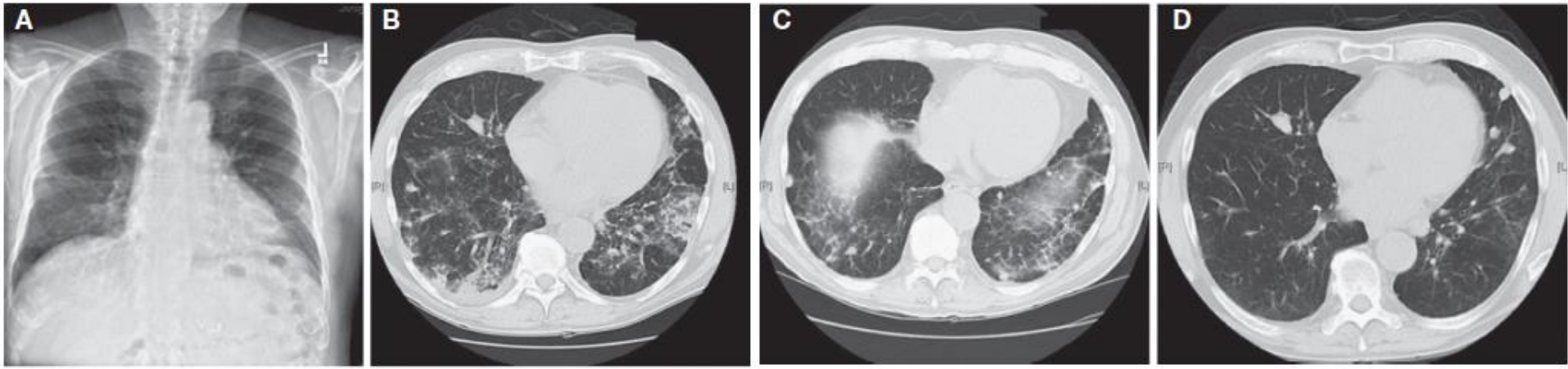
PAM Inhibitor Induced Rash





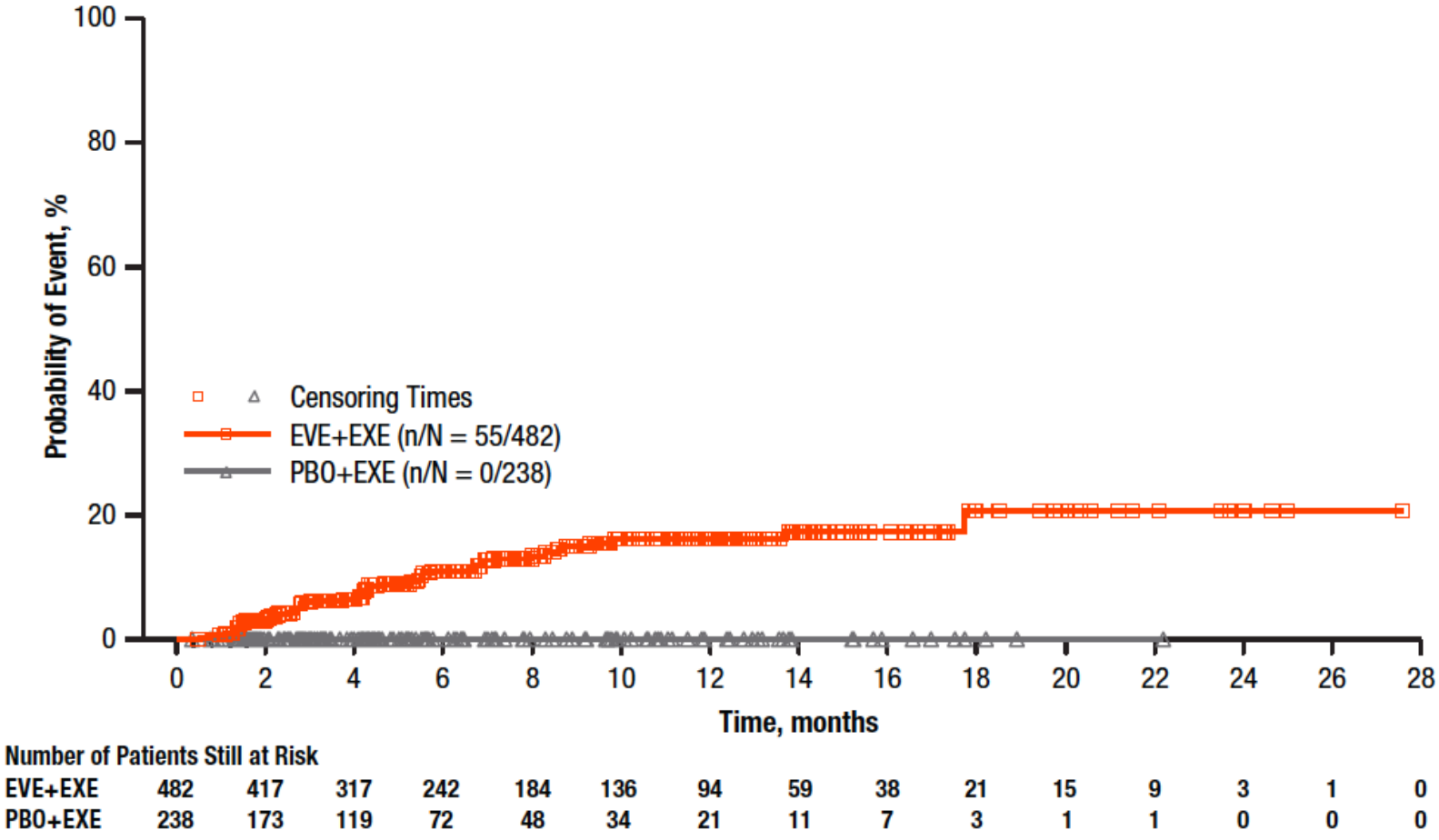
PAM Non-Infectious Pneumonitis

- New radiographic interstitial lung infiltrates
  - Symptoms may include cough or dyspnea
  - Negative blood, sputum, and broncho-alveolar (BAL) cultures
- Biopsies may show organizing pneumonia, granulomatous inflammation or lymphocytic infiltrate
- Most well-described with mTOR inhibitors, but also seen with PI3K and PI3K/mTOR dual inhibitors



White DA, et al. Am J Respir Crit Care Med. 2010;182(3):396-403

Time to Onset of Grade ≥ 2 Pneumonitis in BOLERO-2 Trial



Ito Y al ASCO 2013 Abstract #561

Non-Infectious Pneumonitis in BOLERO-2 Trial

NIP and Related Events Characteristics	EVE+EXE n=482	PBO+EXE n=238
Any grade, (n)	20%	0%
Grade 3	4%	0%
Grade 4	0.2%	0%
Percentage (n) of patients and median time for complete resolution from grade 3	75% (15); 5.4 weeks	Not applicable
Percentage (n) of patients and median time for complete resolution from grade 2	83% (29); 5.1weeks	Not applicable
Dose interruptions, % (n)	10% (48)	Not applicable
Treatment discontinuation related to NIP, % (n)	7% (33)	Not applicable

Ito Y al ASCO 2013 Abstract #561

Comparing Adverse Event Profiles of PI3K-mTOR inhibitors, Pan-PI3K inhibitors, and BYL719

Drug-related AE (%)	Grades	Drug			
		PI3K-mTOR inhibitors		Pan-PI3K inhibitors	PI3K alpha specific inhibitor
		GSK2126458 (at MTD) n=44	GDC-0980 (all dose levels) n=33	BKM120 (all dose levels) n=81	BYL719 (all dose levels) n=35
Hyperglyceamia	All	7	83	30	49
	3–4	2	14	5	14
Nausea	All	11	36	30	37
	3–4	0	0	0	6
Fatigue/Asthenia	All	18	58	24	31
	3–4	0	3	1	3
Decreased appetite	All	-	36	30	31
	3–4		0	0	0
Diarrhea	All	16	45	30	26
	3–4	2	6	4	0
Vomiting	All	5	18	NR	17
	3–4	0	0		0
Rash	All	5	36	27	17
	3–4	0	6	5	3

Munster PN et al. J Clin Oncol 29: 2011 (suppl; abstr 3018); Wagner AJ et al. J Clin Oncol 29: 2011 (suppl; abstr 3020); Grana et al. J Clin Oncol 29: 2011 (suppl; abstr 3043)/Bendell JC, et al. J Clin Oncol 30: 282-90; 2012; Juric D et al. Abstract #7551, AACR 2012

Safety Profile of Idelasilib in Refractory CLL (δ-selective inhibitor)

Event (n = 54)	Any grade	Grade ≥3
Fatigue	31.5%	1.9%
Diarrhea	29.6%	5.6%
Pyrexia	29.6%	3.7%
Pneumonia	20.4%	18.5%
Neutropenic fever	11.1%	11.1%
Vomiting	11.1%	1.9%
Increased AST*	24.1%	1.9%
Increased ALT*	18.5%	1.9%

* In total, 15 patients experienced elevated transaminases.

- Serious AEs included cellulitis (6%), colitis (6%), bronchitis (4%), infection (4%) and sepsis (4%).

Brown JR et al. ASCO 2013;Abstract 7003.

Safety Profile of GDC-0032 in Advanced Solid Tumors (β-isoform sparing PI3K inhibitor)

Table 2. AEs (≥ 10% or Any Grade ≥ 3) Potentially Related to GDC-0032

Adverse Event, n (%)	Grades	3 mg (n=6)	5 mg (n=3)	8 mg (n=4)	9 mg Expan. (n=23)	12 mg (n=10)	16 mg (n=11)	All Patients (N=57)
Diarrhea	All	1 (17)	1 (33)	1 (25)	11 (48)	5 (50)	7 (64)	26 (46)
	≥3	-	-	-	1 (4)	-	2 (18)	3 (5)
Hyperglycemia	All	-	-	2 (50)	7 (30)	3 (30)	8 (73)	20 (35)
	≥3	-	-	-	2 (9)	2 (20)	3 (27)	7 (12)
Fatigue	All	2 (33)	1 (33)	1 (25)	7 (30)	5 (50)	5 (46)	21 (37)
	≥3	-	-	-	-	-	2 (18)	2 (4)
Nausea	All	2 (33)	1 (33)	1 (25)	9 (39)	3 (30)	6 (55)	22 (39)
	≥3	-	-	-	-	-	-	-
Rash*	All	-	-	-	5 (22)	4 (40)	6 (55)	15 (26)
	≥3	-	-	-	-	3 (30)	3 (27)	6 (11)
Decr. appetite	All	1 (17)	1 (33)	1 (25)	7 (30)	5 (50)	5 (46)	20 (35)
	≥3	-	-	-	-	-	-	-
Stomatitis*	All	-	-	-	-	6 (60)	4 (36)	10 (18)
	≥3	-	-	-	-	1 (10)	-	1 (2)
Vomiting	All	-	1 (33)	-	4 (17)	-	4 (36)	9 (16)
	≥3	-	-	-	-	-	-	-
Colitis		-	-	-	1 (4)	1 (10)	-	2 (4)

Juric D et al. ESMO 2013;Abstract P017.

Summary

- Frequently observed toxicities of PAM inhibitors
  - Hyperglycemia, hyperlipidemia
  - Rash, stomatitis
  - Pneumonitis
  - Diarrhea, nausea/vomiting
  - AST/ALT elevation
  - Fatigue
- Mechanism of action, potency, and schedule of administration may influence toxicity profile
- Early recognition of toxicities is important to ensure optimal medical management