MADRID 2014 ESMO congress

Randomized phase 2 study of investigational, selective Aurora A kinase inhibitor alisertib (MLN8237) with weekly paclitaxel vs paclitaxel alone in patients with recurrent ovarian cancer

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Disclosures

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- Employment: HL, CS, CDU (Takeda)

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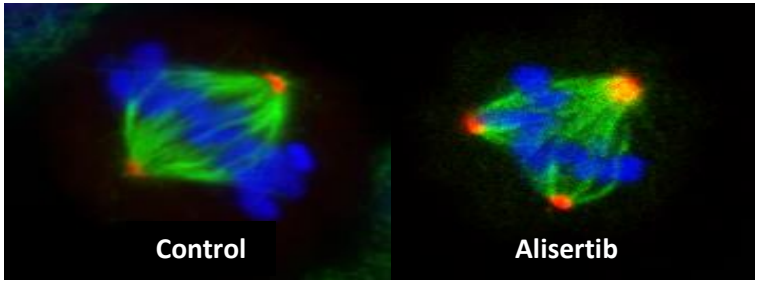
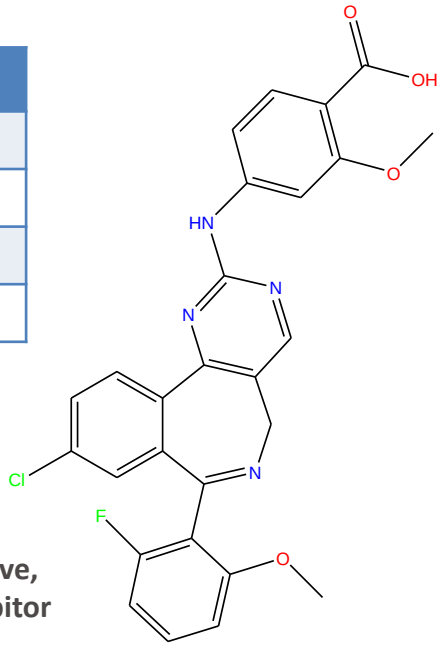
Alisertib (MLN8237) Mechanism of Action

Mechanism of action



α-tubulin DNA Centrosomes

On-target activity[2]	IC_{50} (nM)
Aurora A enzyme	**1**
Aurora B enzyme	397
Aurora A cells	**7**
Aurora B cells	1534



ATP-competitive, reversible inhibitor

Aurora A kinase is a component of the mitotic machinery

Aurora A inhibition results in mitotic defects in proliferating cells[1]

- High incidence of abnormal mitotic spindles often with unseparated centrosomes
- Chromosome alignment defects in metaphase, lagging chromosomes in anaphase, and chromatin bridges in telophase

- **Unique selectivity profile distinct from other pan Aurora inhibitors[2,3]**
- **Orally bioavailable[3,4]**
- **Convenient BID dosing[3,4]**
- **Good PK profile[3]**
- **Predictable and manageable toxicity[3,4]**

1. Hoar K, et al. Mol Cell Biol 2007;27:4513–25
2. Manfredi MG, et al. Clin Cancer Res 2011;17:7614–24
3. Falchook G, et al. Invest New Drugs 2014; Jun 1 [Epub ahead of print]
4. Matulonis U, et al. Gynecol Oncol 2012;127:63–9

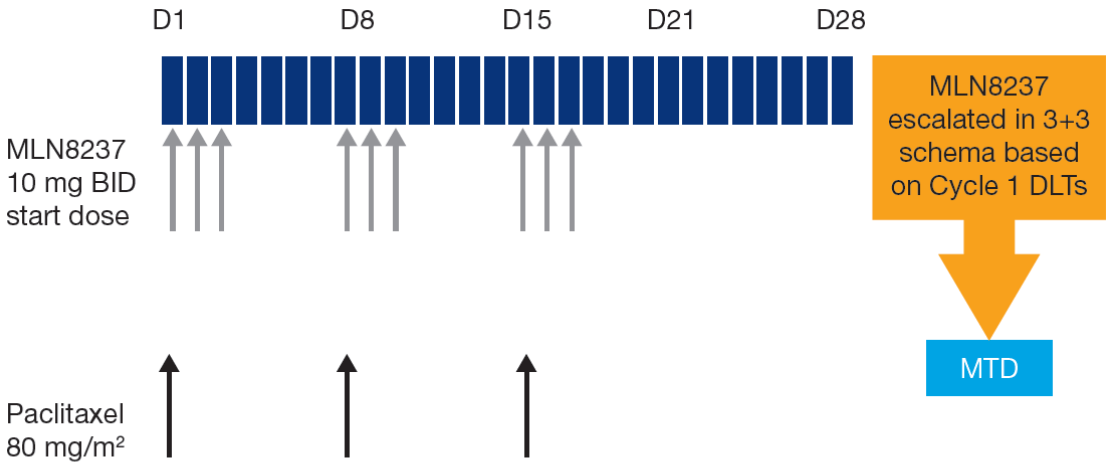
Alisertib Preclinical and Clinical Activity and Toxicity Profile

- Demonstrates broad anti-tumor activity in solid tumor and heme-lymphatic models[1–3]
- Can be combined with standard of care and targeted agents[1–3]
  - Additive and synergistic effects in multiple tumor models
  - Synergistic effects with taxanes
- Phase I and Phase II single agent trials demonstrate an acceptable safety profile (myelosuppression, mucositits) and modest clinical activity (10% ORR)[4,5]

1. Sehdev V, et al. Cancer 2013;119:904–14
2. Mahadevan D, et al. Clin Cancer Res 2012;18:2210–9
3. Qi W, et al. Biochem Pharmacol 2011;81:881–90
4. Matulonis U, et al. Gynecol Oncol 2012;127:63–9
5. Falchook G, et al. Invest New Drugs 2014; Jun 1 [Epub ahead of print]

Alisertib: Clinical Investigations

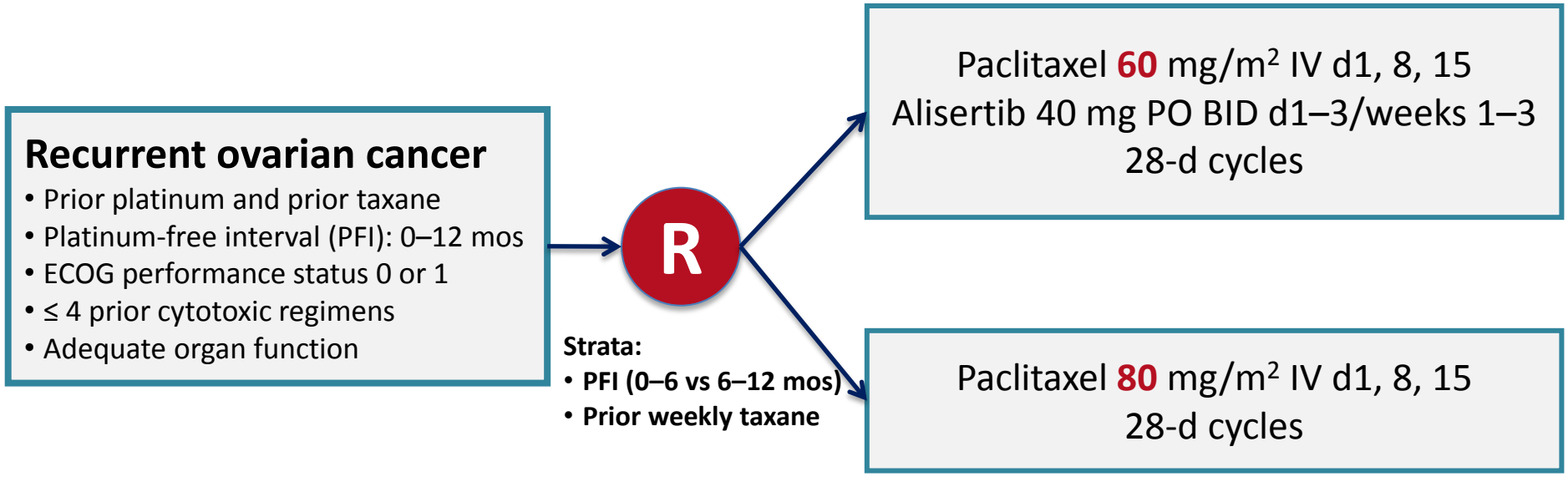
- Phase I: **paclitaxel combination**
  - Ovarian and breast cancer[1,2]
  - DLT: Diarrhea febrile neutropenia stomatitis
  - MTD (28-day cycle):
    - Alisertib 40 mg BID d1–3/weeks 1–3
    - Paclitaxel 60 mg IV weekly
  - ORR (all levels): 47% (1 CR, 9 PRs)



DLTs, dose limiting toxicities; BID, twice daily; MTD, maximum tolerated dose.

1. Falchook G, et al. Int J Gynecol Cancer 2013;23(Suppl):131–2
2. Venkatakrishnan K, et al. J Clin Oncol 2013;31(suppl):2598

METHODS: Study design

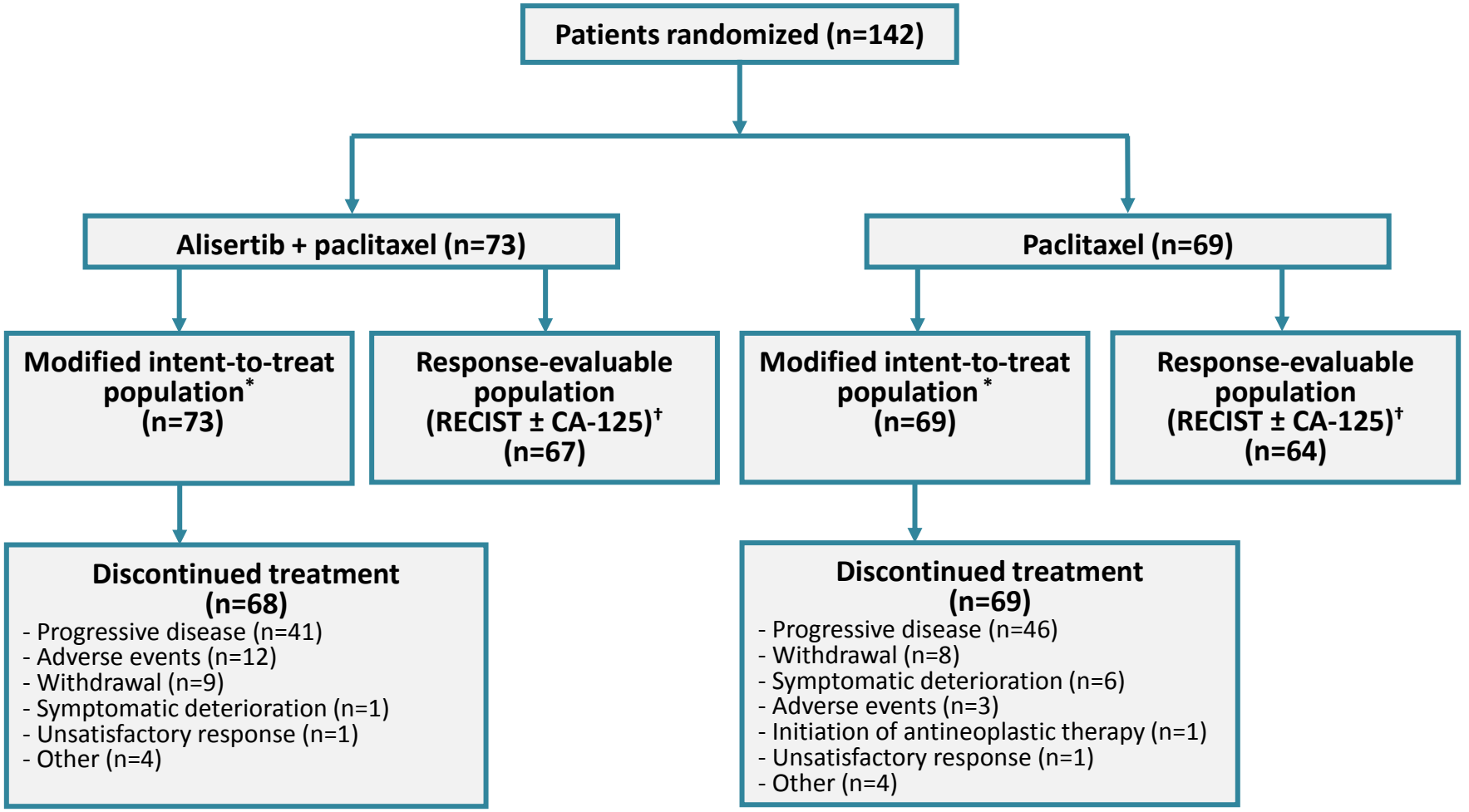


Primary endpoint: PFS
- Based on 'combined' (RECIST 1.1 + CA-125) criteria
- Target: HR 0.67 (median PFS, 4–6 mos)
- N=142 (110 events final)

Secondary endpoints: ORR, safety, PROs
- EORTC QLQ-OV28 (d1 every cycle)
- EORTC QLQ-C30 (d1 every other cycle)

ClinicalTrials.gov Identifier: NCT01091428

METHODS: CONSORT diagram



*Randomized and received at least 1 dose of any study drug
†Measurable disease according to RECIST or assessable disease by CA-125 criteria, received at least 1 dose of study drug, and had at least 1 available post-baseline response assessment by RECIST or CA-125 criteria

Data cut: August 2014

RESULTS: Demographics

Parameter, n (%)	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Disease stage*		
IIIC	41 (56)	36 (52)
IV	18 (25)	23 (33)
Histological subtypes		
Serous carcinoma	**48 (67)**	**44 (64)**
Mucinous carcinoma	2 (3)	0
Carcinoma NOS	16 (22)	10 (14)
Clear cell carcinoma	1 (1)	2 (3)
Endometrioid	3 (4)	7 (10)
Poorly differentiated	2 (3)	3 (4)
Mixed	0	1 (1)
Others	0	3 (4)
Platinum **refractory (during therapy)**	**9 (12)**	**9 (13)**
resistant (>0–6 mos)	**36 (49)**	**35 (51)**
sensitive (>6–12 mos)	28 (38)	25 (36)
ECOG performance status		
0	43 (59)	39 (57)
1	30 (41)	30 (43)

* Disease stage ranged from IA to IVB; only the two most common stages are shown

Data cut: August 2014

RESULTS: Demographics

Parameter, n (%)	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Prior surgery	73 (100)	63 (91)
Prior radiation therapy	2 (3)	5 (7)
Prior lines of therapy (from diagnosis)		
1	14 (19)	20 (29)
2	**29 (40)**	**22 (32)**
3	12 (19)	14 (20)
≥4*	16 (22)	13 (19)
Prior lines of a Taxane		
0	1 (1)	0
1	51 (70)	51 (74)
2	20 (27)	17 (25)
3	1 (1)	1 (1)
Prior bevacizumab (≥ 1 line)	**26 (36)**	**22 (32)**
Response evaluable		
RECIST alone	63 (86)	54 (78)
RECIST and/or CA-125	67 (92)	64 (93)

*Per inclusion criteria, no more than 4 prior therapy lines were allowed for locally recurrent or metastatic disease, not including regimens received in the neoadjuvant and/or adjuvant setting

Data cut: August 2014

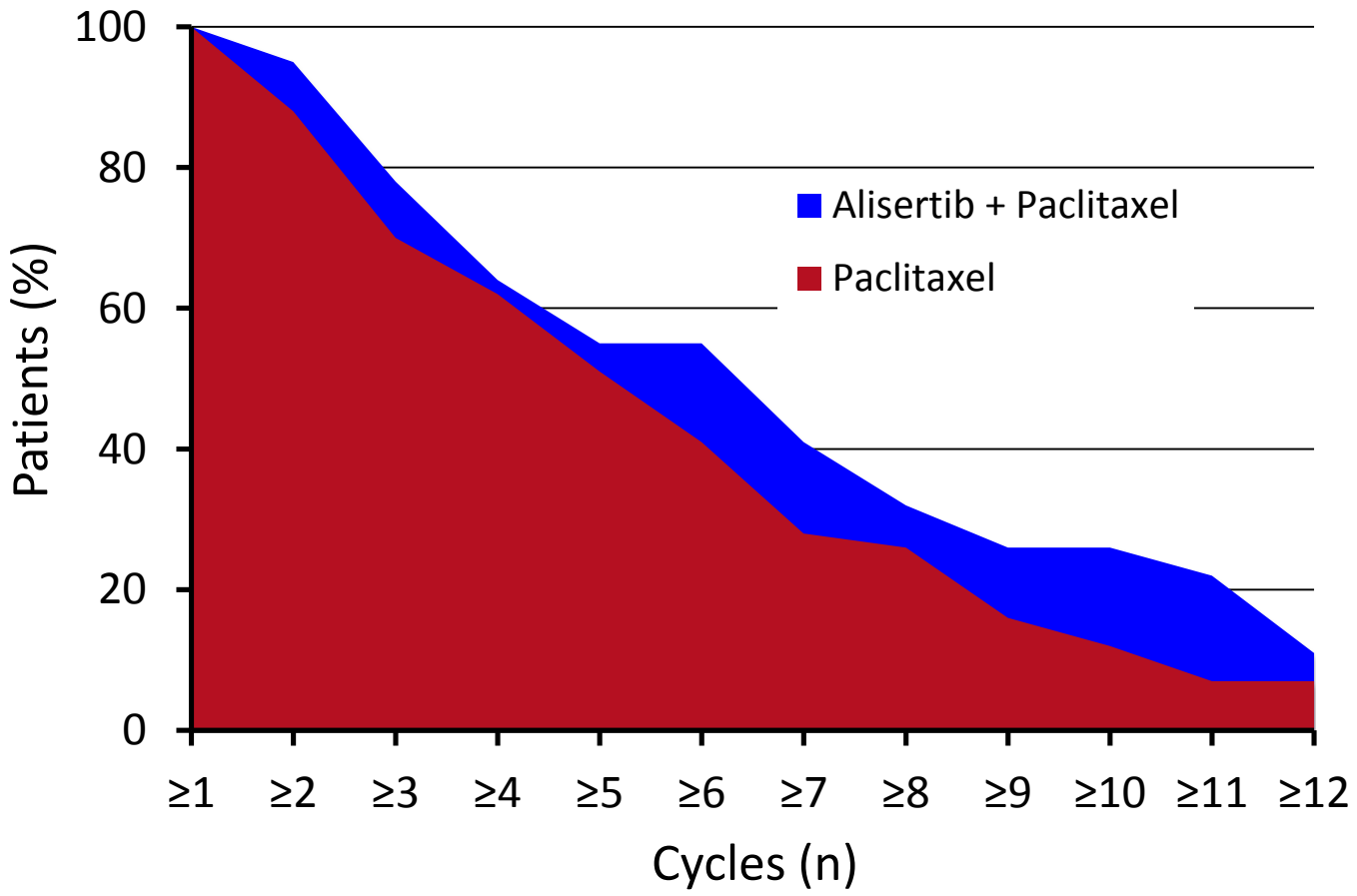
RESULTS: Exposure

Parameter	Alisertib + Paclitaxel (n=73)		Paclitaxel (n=69)
	Alisertib	Paclitaxel	Paclitaxel
Median cycles received, n (range)	6 (1–28)		5 (1–14)
Received ≥ 6 cycles, n (%)	40 (55)		28 (41)
Median total amount of dose taken	3120 mg	824 mg/m^2	970 mg/m^2
Median relative dose intensity, %*	78	82	95

* Relative dose intensity = total amount of dose taken / total amount of dose prescribed at study entry

Data cut: August 2014

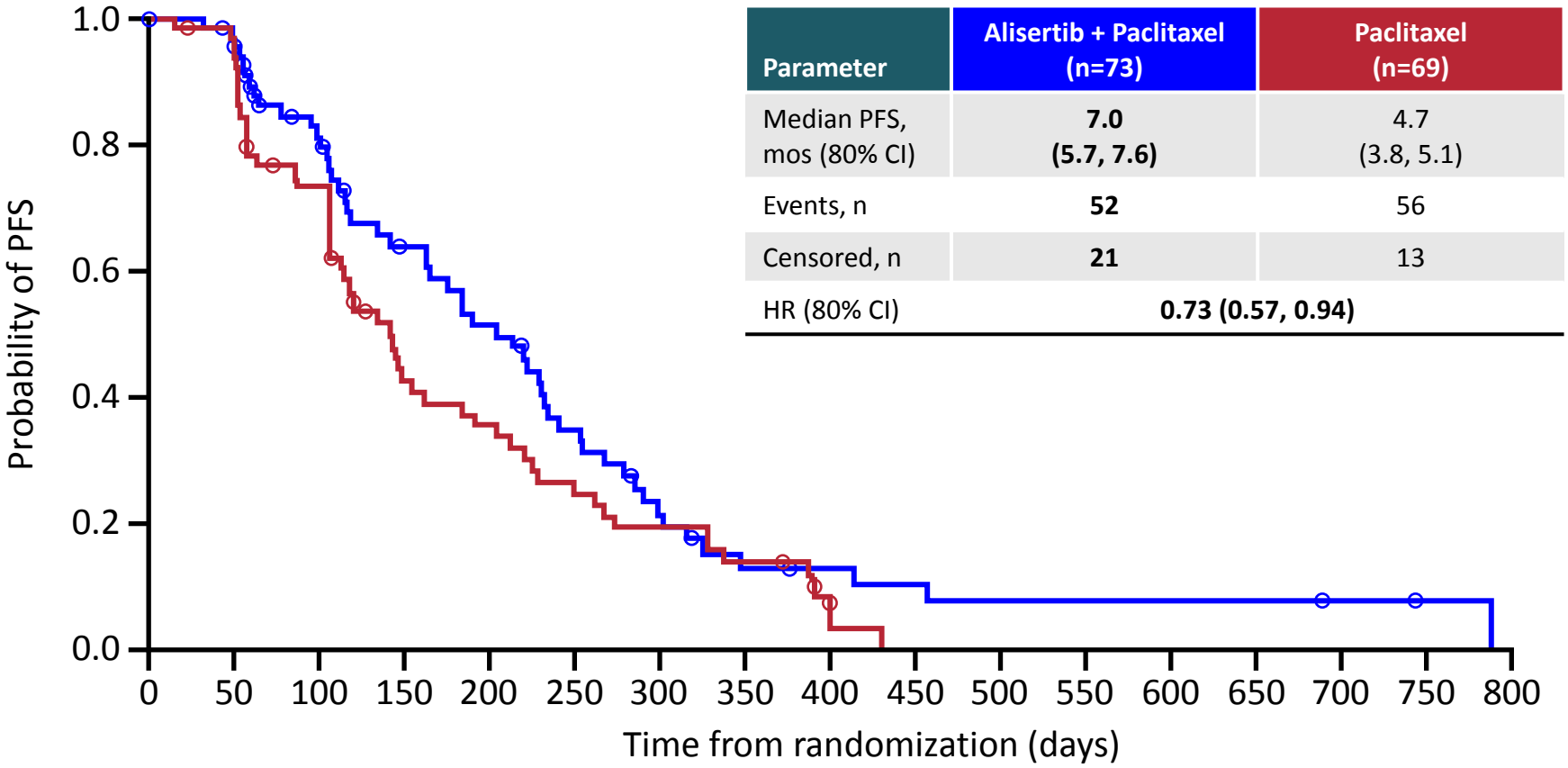
RESULTS: Exposure



Treated cycles	Patients (%)	
	A+P (n=73)	P (n=69)
≥ 1	100	100
≥ 2	95	88
≥ 3	78	70
≥ 4	64	62
≥ 5	55	**51**
≥ 6	**55**	41
≥ 7	41	28
≥ 8	32	25
≥ 9	26	16
≥ 10	22	12
≥ 11	15	7
≥ 12	11	7

Data cut: August 2014

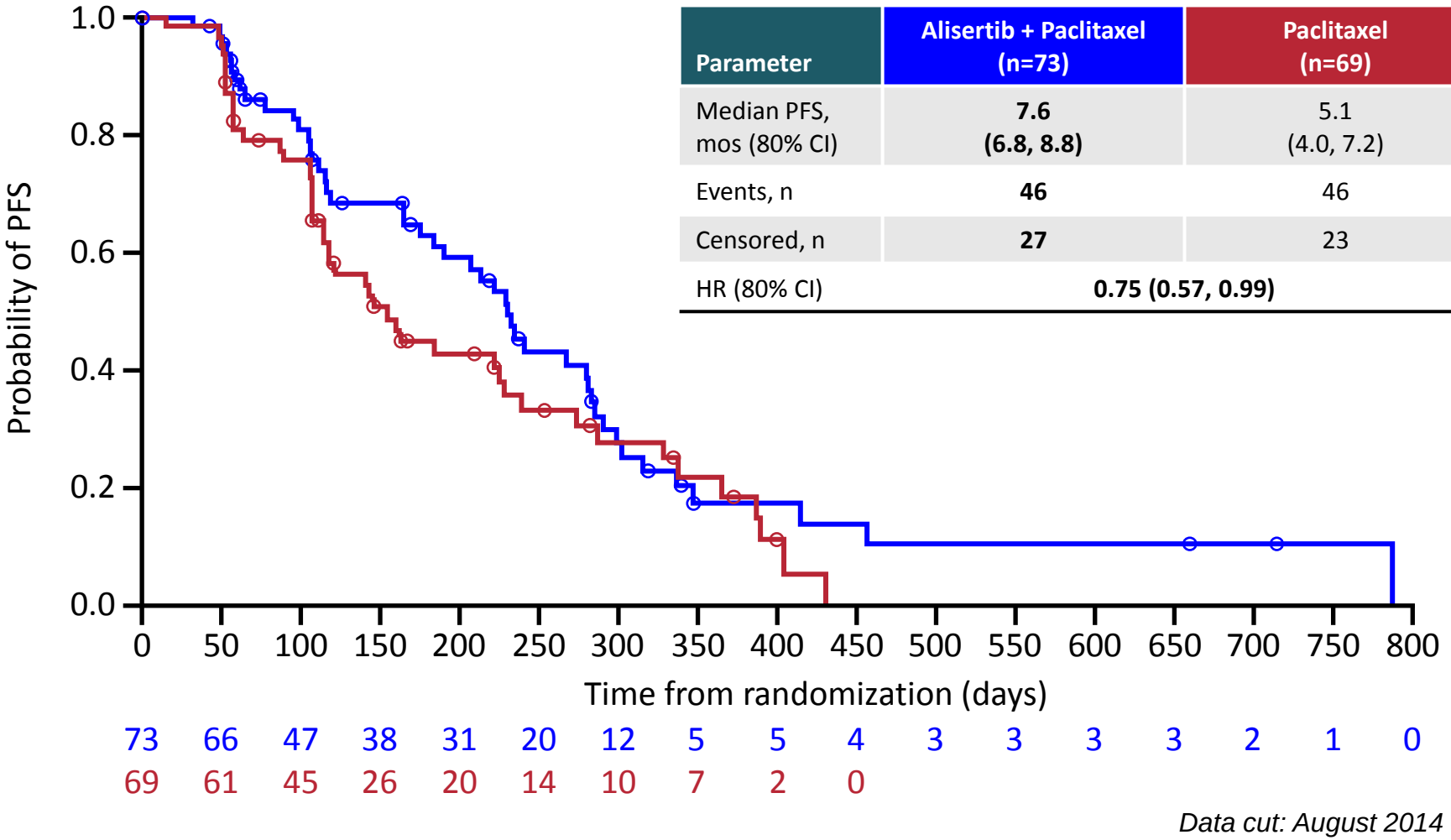
Modified ITT population (RECIST ± CA125)



Parameter	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Median PFS, mos (80% CI)	**7.0 (5.7, 7.6)**	4.7 (3.8, 5.1)
Events, n	**52**	56
Censored, n	**21**	13
HR (80% CI)	**0.73 (0.57, 0.94)**	

Data cut: August 2014

Modified ITT population (RECIST)



Parameter	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Median PFS, mos (80% CI)	**7.6 (6.8, 8.8)**	5.1 (4.0, 7.2)
Events, n	**46**	46
Censored, n	**27**	23
HR (80% CI)	**0.75 (0.57, 0.99)**	

Data cut: August 2014

RESULTS: Best response

RECIST ± CA-125	Alisertib + Paclitaxel (n=67)		Paclitaxel (n=64)	
	n	% (80% CI)	n	% (80% CI)
ORR*	41	**61** (53, 69)	31	**48** (40, 57)
Median DOR, mos	**6.6**		**5.6**	

RECIST only	Alisertib + Paclitaxel (n=63)		Paclitaxel (n=54)	
	n	% (80% CI)	n	% (80% CI)
ORR*	31	**49** (40, 58)	20	**37** (28, 47)
Median DOR, mos	**6.0**		**7.6**	

* By investigator assessment

Data cut: August 2014

RESULTS: PFS and response by platinum sensitivity

RECIST ± CA-125	Resistant / Refractory (n=89)		Sensitive (n=53)	
	Alisertib + Paclitaxel (n=45)	Paclitaxel (n=44)	Alisertib + Paclitaxel (n=28)	Paclitaxel (n=25)
Events, n	28	36	24	20
Median PFS, mos (80% CI)	**6.2** (3.9, 7.3)	**4.4** (3.7, 4.9)	**7.6** (6.0, 9.1)	**4.8** (3.5, 10.8)
HR (80% CI)	**0.65 (0.47, 0.91)**		**0.92 (0.61, 1.37)**	

Data cut: August 2014

RESULTS: PFS and response by platinum sensitivity

RECIST alone	Resistant / Refractory (n=89		Sensitive (n=53)	
	Alisertib + Paclitaxel (n=45)	Paclitaxel (n=44)	Alisertib + Paclitaxel (n=28)	Paclitaxel (n=25)
Events, n	25	30	21	16
Median PFS, mos (80% CI)	**7.0** (3.9, 7.9)	**4.7** (3.8, 6.0)	**9.3** (7.5, 9.5)	**7.5** (3.5, 12.7)
HR (80% CI)	**0.71 (0.50, 1.01)**		**0.85 (0.55, 1.31)**	
Response	n=39	n=33	n=24	n=21
ORR	**39%**	**33%**	**67%**	**43%**
SD	49%	45%	21%	38%

Data cut: August 2014

RESULTS: Safety overview

AE, n (%)	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Any AE	73 (100)	66 (96)
Grade ≥3 AE	67 (92)	35 (51)
Drug-related AE	73 (100)	59 (86)
Drug-related Grade ≥3 AE	64 (88)	14 (20)
SAE	30 (41)	19 (28)
Drug-related SAE	22 (30)	3 (4)
AE leading to drug discontinuation	12 (16)	2 (3)
On-study deaths*	1 (1)*	1 (1)†

*Small bowel obstruction, not related
† Sepsis, not related

Data cut: August 2014

RESULTS: TEAEs (all grades)

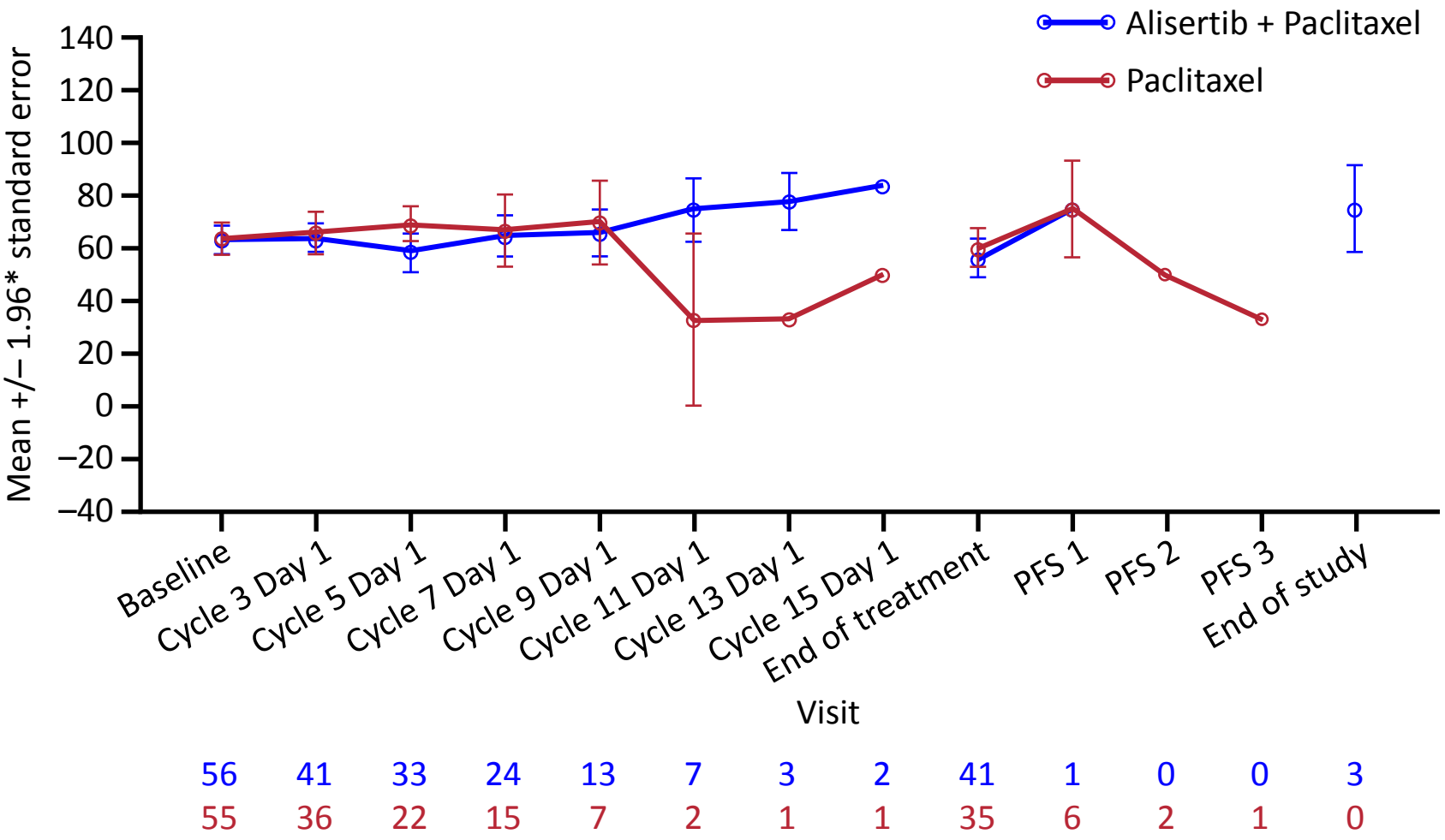
Preferred term, n (%)	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Neutropenia	**55 (75)**	10 (14)
Diarrhea	**47 (64)**	16 (23)
Stomatitis	**46 (63)**	6 (9)
Fatigue	42 (58)	31 (45)
Anemia	**34 (47)**	21 (30)
Nausea	34 (47)	32 (46)
Alopecia	28 (38)	22 (32)
Constipation	26 (36)	18 (26)
Abdominal pain	21 (29)	20 (29)
Vomiting	21 (29)	19 (28)
Peripheral neuropathy (sensory)	**20 (27)**	**20 (29)**
Cough	**17 (23)**	4 (6)
Decreased appetite	**15 (21)**	8 (12)
Edema peripheral	12 (16)	**19 (28)**

RESULTS: Grade ≥3 TEAEs

Primary system organ class / preferred term, n (%)	Alisertib + Paclitaxel (n=73)	Paclitaxel (n=69)
Blood and lymphatic disorders		
Neutropenia	51 (70)	6 (9)
Anemia	12 (16)	3 (4)
Neutrophil count decreased	11 (15)	1 (1)
Febrile neutropenia	10 (14)	0
Leukopenia	10 (14)	0
GI disorders		
Stomatitis	18 (25)	0

Data cut: August 2014

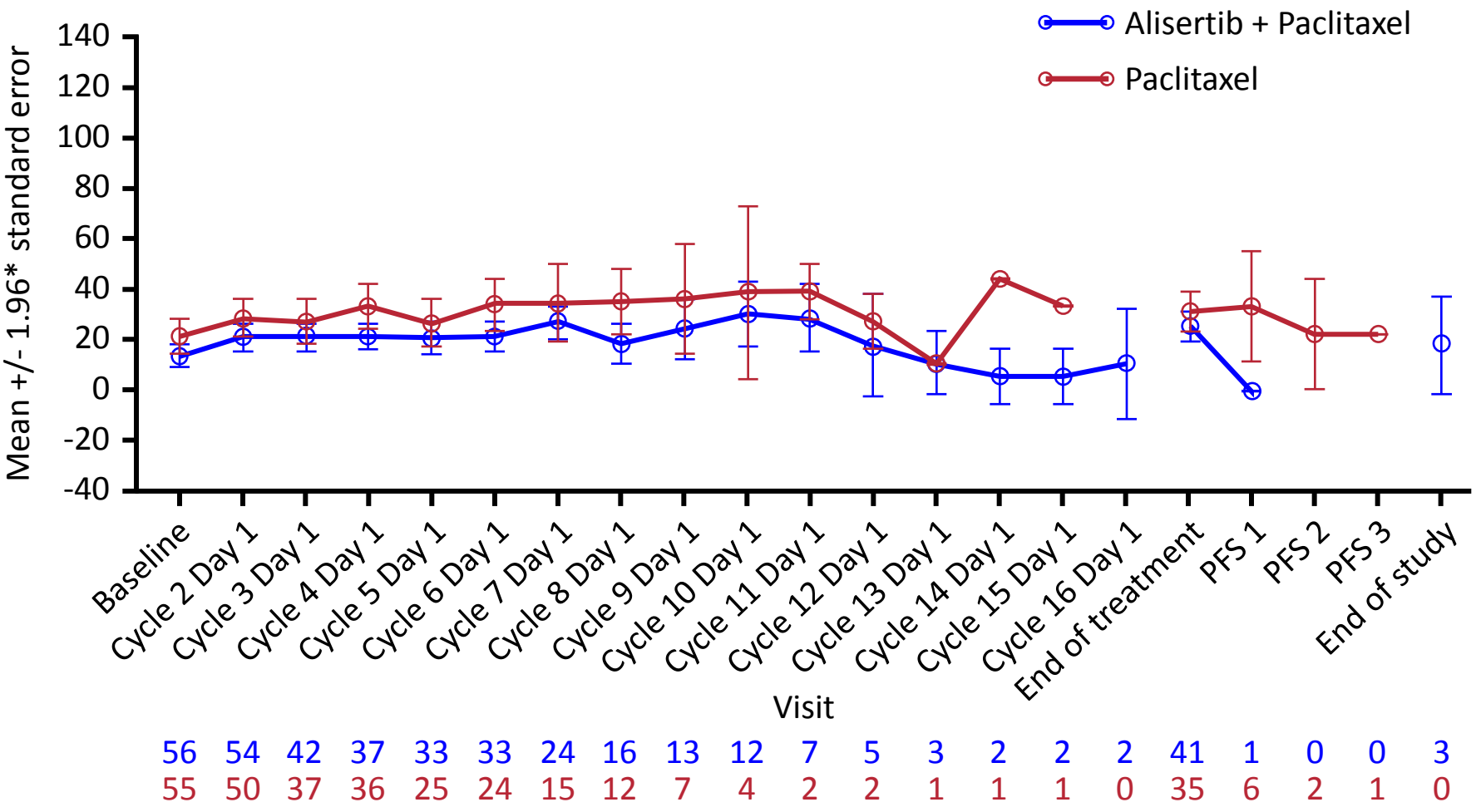
RESULTS: QLQ-C30 overall QoL



Note: Higher scores represent improved QoL

Data cut: August 2014

RESULTS: QLQ-OV28 peripheral neuropathy



56	54	42	37	33	33	24	16	13	12	7	5	3	2	2	2	41	1	0	0	3
55	50	37	36	25	24	15	12	7	4	2	2	1	1	1	0	35	6	2	1	0

Note: Higher scores represent higher level of symptoms

Data cut: August 2014

Summary

- Alisertib/paclitaxel significantly reduced the risk for progression by GCIG criteria
  - HR: 0.73, Median 7.0 vs 4.7 months
- Similar AE profile but increased incidence of some drug-related AEs in the combination arm, as expected by the addition of alisertib: neutropenia, diarrhea, and stomatitis
- No new or unanticipated toxicities in the combination arm and no increase in rate of peripheral neuropathy
- Relevant grade ≥3 drug-related AEs were neutropenia and stomatitis
- Toxicities were generally manageable with standard medical intervention and dose reductions as needed
- Data continue to mature (biomarkers, metabolomics)

Acknowledgments

- Patients and families who generously participated
- Co-investigators and study teams who worked hard to develop this interim data set
- You, for your attention