Puma Biotechnology
Clinical Development Strategy in Small-Cell Lung Cancer

August 3, 2023

Phase 2 Study of Alisertib Monotherapy in Solid Tumors

- SCLC Cohorts

Study design:

- Pts had to have undergone ≤ 2 previous cytotoxic regimens, not including adjuvant or neoadjuvant treatments
- Alisertib administration: orally in 21-day cycles at 50 mg twice daily for 7 days followed by a break of 14 days
- 1° Endpoint: Objective Response Rate (RECIST 1.1)

	All (n=48)	Chemotherapy-sensitive relapse (n=36)	Refractory or chemotherapy-resistant relapse (n=12)
Median (range) number of cycles	2·0* (1–17)	3·5 (1–17)	2·0 (2–6)
Best response			
Objective response†	10 (21%) (10–35)	7 (19%)	3 (25%)
Stable disease	16 (33%) (20–48)	13 (36%)	3 (25%)
Stable disease for ≥6 months	2 (4%)	2 (6%)	0
Progressive disease	22 (46%) (31–61)	16 (44%)	6 (50%)
Duration of response (months)	4·1 (3·1–NE)	3·1	4·3
Progression-free survival (months)	2·1 (1·4–3·4)	2·6 (1·4–3·7)	1·7 (1·2–3·9)
Time to progression (months)	2·6 (1·4–3·8)	2·8 (1·4–3·9)	1·4 (1·2–4·4)

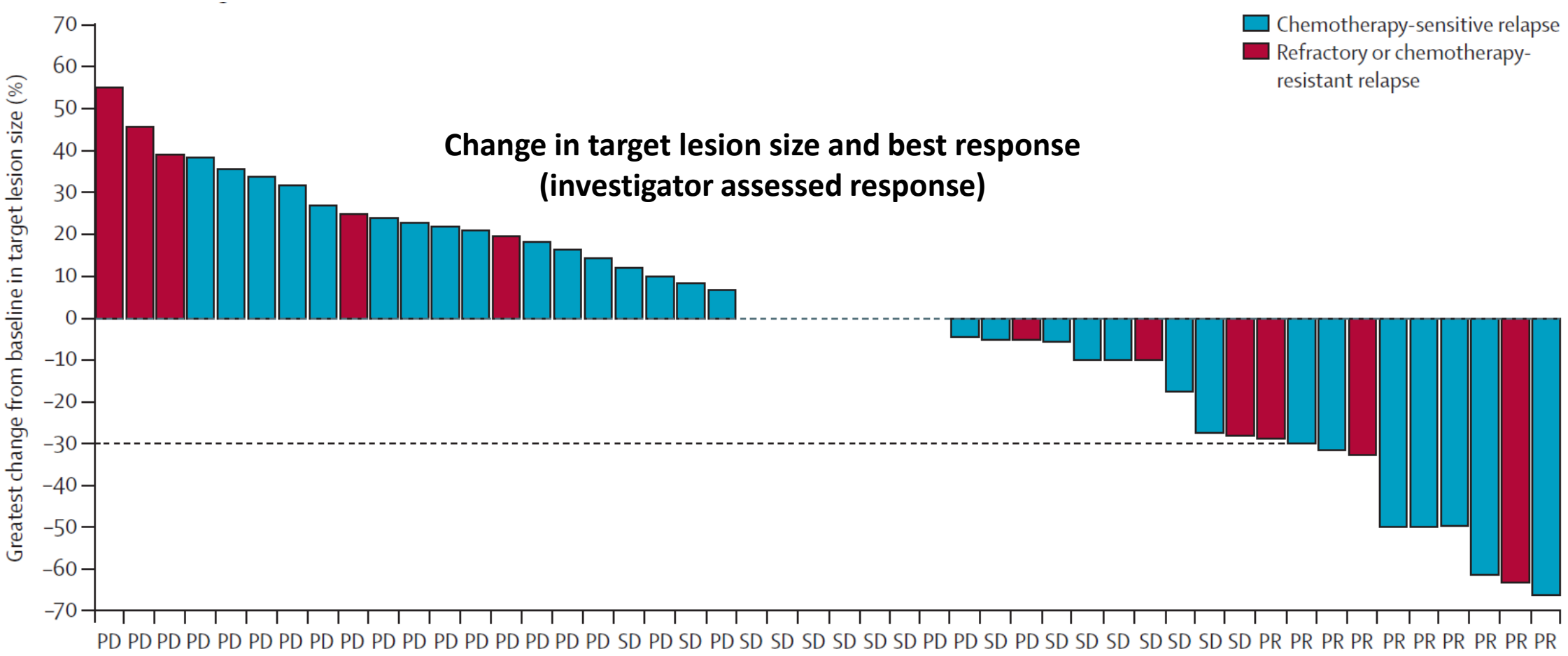
Table adapted from Melichar B Lancet Oncol 2015. Data are either number of patients (%) (95% CI), or median (95% CI), unless otherwise stated. NE=not estimable. *Safety population. †All were partial responses. All responses were based on investigator tumor assessments (RECIST v1.1).

Melichar B Lancet Oncol 2015

Phase 2 Study of Alisertib Monotherapy in Solid Tumors

- SCLC Cohorts

10 (21%; 95% CI 10–35) of 48 patients had an objective response; all responders achieved a partial response



PD=progressive disease. SD=stable disease. PR=partial response. Dotted line at –30% represents a partial response, according to RECIST 1.1 (investigator tumor assessments).

Melichar B Lancet Oncol 2015

Phase 2 Study of Alisertib Monotherapy in Solid Tumors

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All-cause adverse events in safety evaluable SCLC cohort (n=60)

	Grade 1–2	Grade 3–4
Any adverse event	14 (23%)	43 (72%)
Neutropenia	5 (8%)	22 (37%)
Fatigue	23 (38%)	5 (8%)
Anaemia	9 (15%)	10 (17%)
Alopecia	16 (27%)	NA
Diarrhoea	16 (27%)	2 (3%)
Nausea	18 (30%)	0
Leukopenia	4 (7%)	8 (13%)
Stomatitis	9 (15%)	4 (7%)
Decreased appetite	18 (30%)	0
Vomiting	10 (17%)	1 (2%)
Thrombocytopenia	5 (8%)	6 (10%)
Somnolence	8 (13%)	1 (2%)
Dyspnoea	10 (17%)	0
Constipation	5 (8%)	0
Pyrexia	4 (7%)	0
Peripheral oedema	4 (7%)	0
Headache	8 (13%)	1 (2%)
Insomnia	7 (12%)	0
Cough	5 (8%)	0
Asthenia	6 (10%)	1 (2%)
Dehydration	3 (5%)	3 (5%)

Table adapted from Melichar B Lancet Oncol 2015. Data are number of patients with AE (%) for AEs of any grade in at least 10% of patients overall. NA = not applicable

Melichar B Lancet Oncol 2015

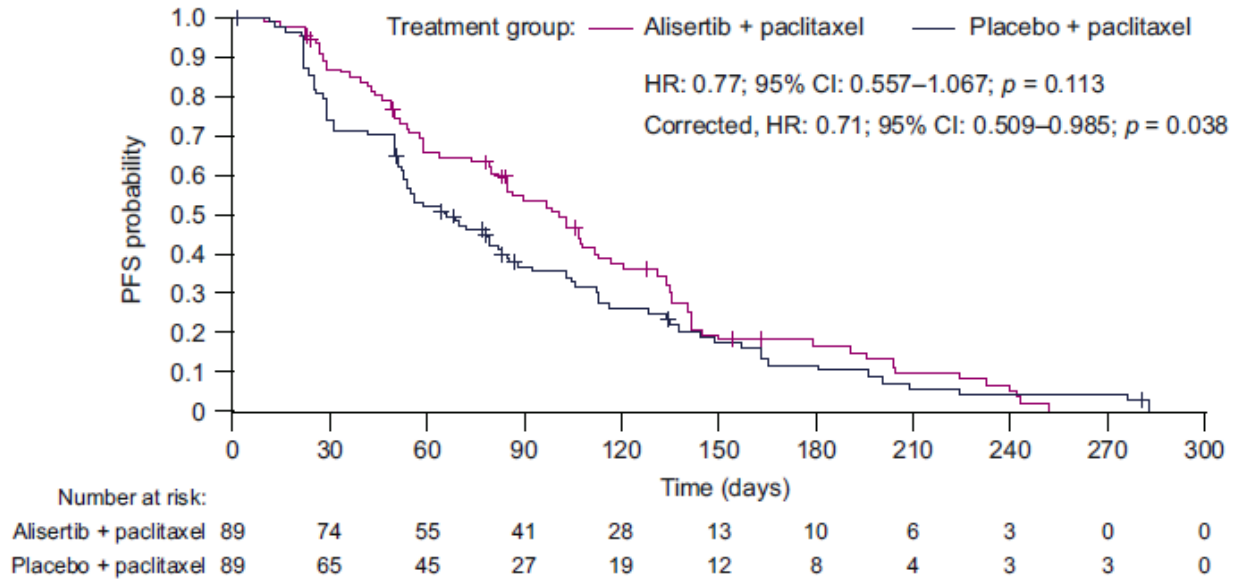
Randomized Phase 2 Study of Paclitaxel plus Alisertib vs Paclitaxel plus Placebo as Second-Line SCLC: Primary Analysis

Study design:

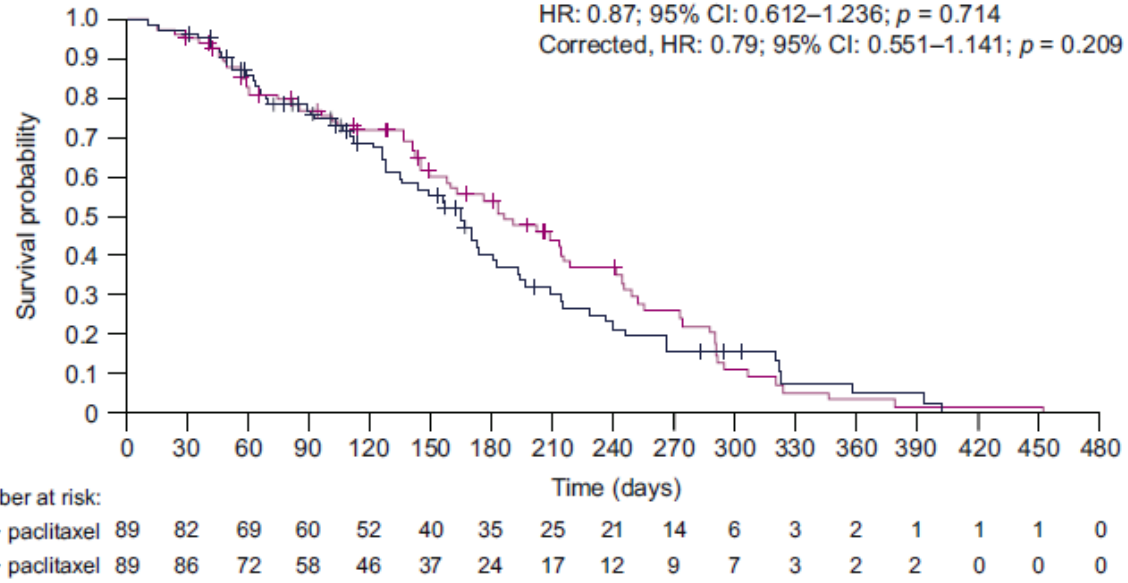
- Patients with relapsed or refractory SCLC stratified by relapse type (sensitive vs resistant or refractory)
- Randomized 1:1 to alisertib + paclitaxel or placebo + paclitaxel in 28-day cycles
- Alisertib (40 mg BID for 3 weeks on days 1–3, 8–10, and 15–17) plus paclitaxel (60 mg/m2 intravenously on days 1, 8, and 15) or placebo plus paclitaxel (80 mg/m2 intravenously on days 1, 8, and 15) in 28-day cycles
- 1° endpoint PFS

Biomarkers: associations between c-Myc expression in tumor tissue (prespecified) and genetic alterations in ctDNA (retrospective) with clinical outcome

PFS in ITT



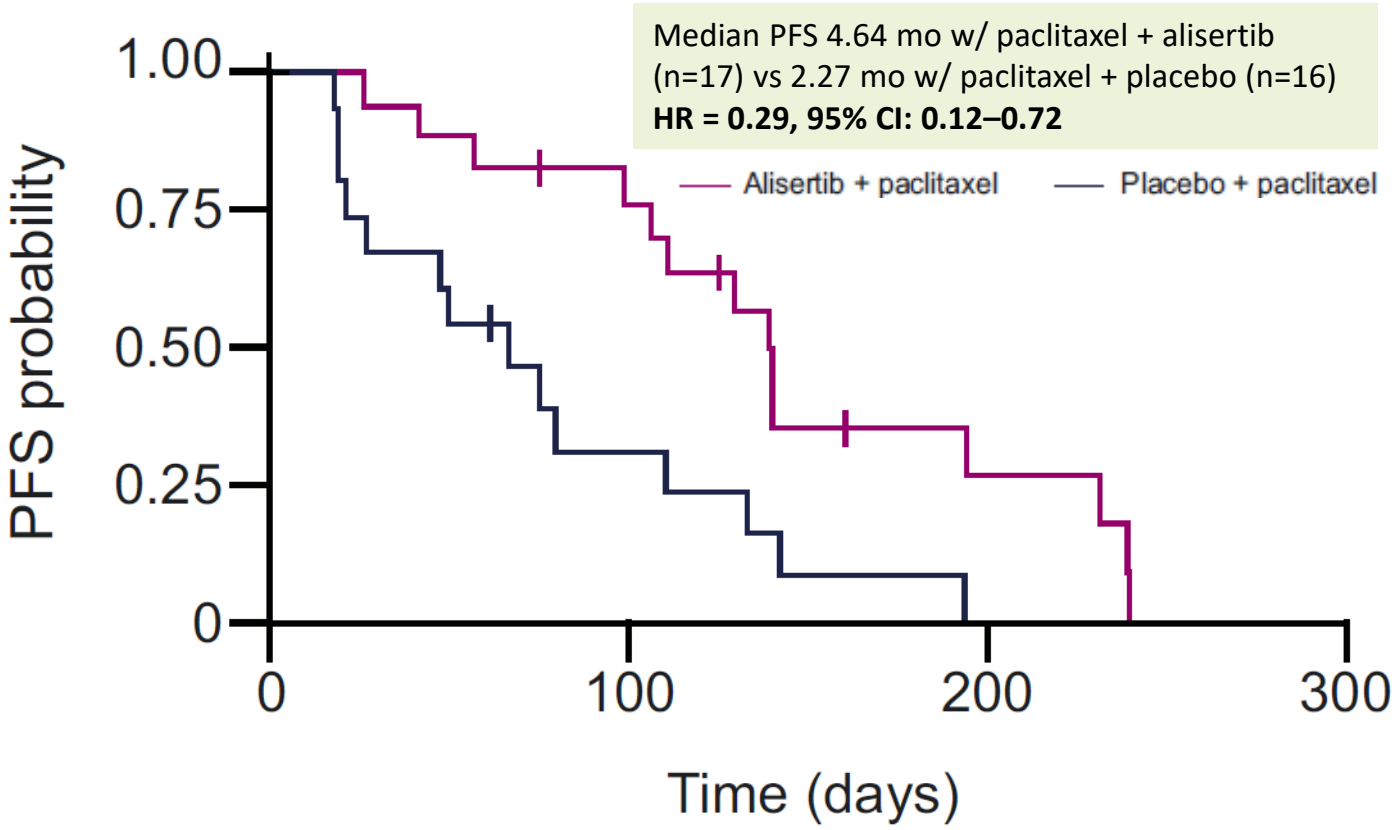
OS in ITT



Randomized Phase 2 Study of Paclitaxel plus Alisertib vs Paclitaxel plus Placebo as Second-Line SCLC: Correlative Biomarker Analysis

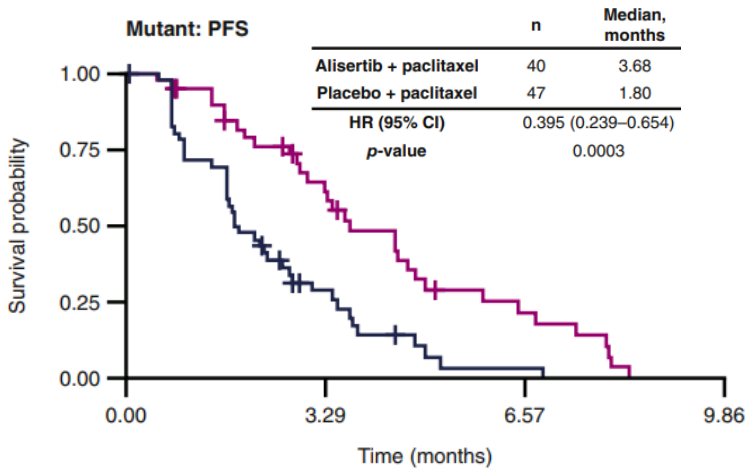
Improved PFS observed among patients positive versus negative for *c-Myc* expression

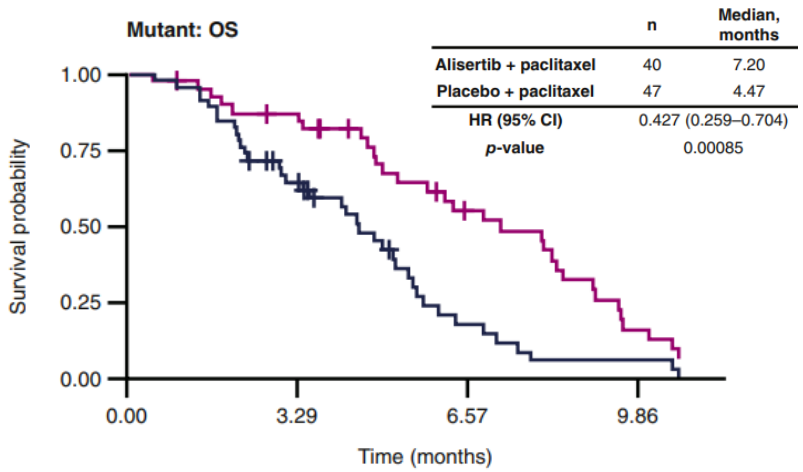
PFS in patients positive for *c-Myc* expression

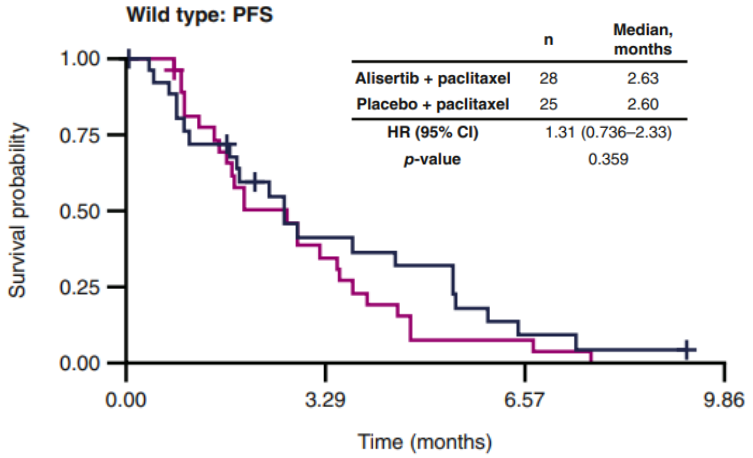


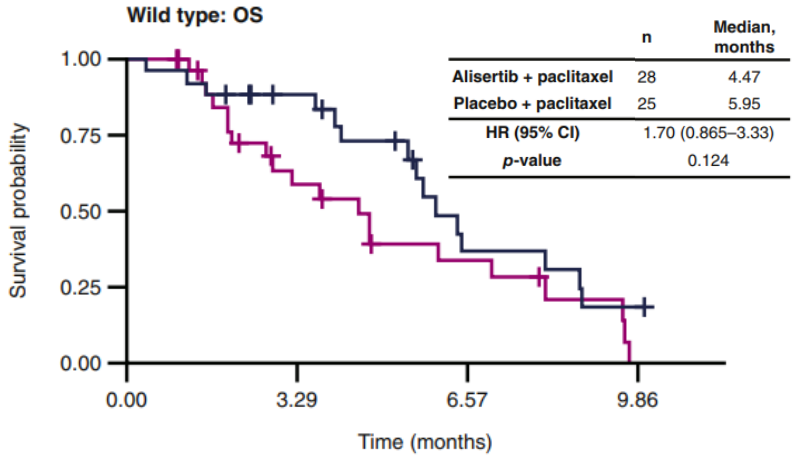
Randomized Phase 2 Study of Paclitaxel plus Alisertib vs Paclitaxel plus Placebo as Second-Line SCLC: Correlative Biomarker Analysis

Improved outcomes among pts with genetic alternations in cell cycle genes *CDK6*, *RBL1*, *RBL2*, and *RB1* (collectively referred to as "mutant")









Randomized Phase 2 Study of Paclitaxel plus Alisertib vs Paclitaxel plus Placebo as Second-Line SCLC: Safety

Table 3. Most Frequently Reported All-Cause and Drug-Related Treatment-Emergent AEs, Occurring in at Least 15% (All-Cause) or at Least 10% (Drug-Related) of Patients Overall (Any Grade) in Either Arm, Respectively, with the Corresponding Grade 3 or higher AEs (Safety Population), and All Drug-Related Fatal AEs

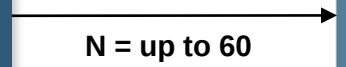
	Alisertib/Paclitaxel (n = 87)		Placebo/Paclitaxel (n = 89)	
AE	Any Grade	Grade ≥3	Any Grade	Grade ≥3
All-cause AE, n (%)	86 (99)	66 (76)	85 (96)	45 (51)
Diarrhea	51 (59)	14 (16)	18 (20)	1 (1)
Fatigue	38 (44)	9 (10)	29 (33)	5 (6)
Nausea	29 (33)	2 (2)	30 (34)	4 (4)
Anemia	38 (44)	12 (14)	18 (20)	3 (3)
Neutropenia	43 (49)	35 (40)	7 (8)	5 (6)
Vomiting	28 (32)	2 (2)	21 (24)	3 (3)
Decreased appetite	29 (33)	3 (3)	19 (21)	3 (3)
Dyspnea	21 (24)	4 (5)	19 (21)	2 (2)
Stomatitis	29 (33)	12 (14)	6 (7)	2 (2)
Cough	17 (20)	0	17 (19)	0
Constipation	8 (9)	1 (1)	21 (24)	0
Asthenia	14 (16)	3 (3)	11 (12)	0
Dizziness	14 (16)	0	8 (9)	0
Alopecia	14 (16)	0	5 (6)	0
Leukopenia	13 (15)	7 (8)	5 (6)	2 (2)
Decreased neutrophil count	14 (16)	11 (13)	4 (4)	1 (1)
Weight decreased	13 (15)	0	5 (6)	0
Drug-related fatal AE, n (%)				
Neutropenic sepsis	–	1 (1)	–	0
Sepsis	–	1 (1)	–	0
Febrile neutropenia	–	1 (1)	–	0
Septic shock	–	1 (1)	–	0

AE, adverse event

PUMA-ALI-4201 study design

Key inclusion criteria

- Pathologically confirmed ES-SCLC
- Progression on or after first-line platinum-based chemo; must have prior immunotherapy
- Measurable disease per RECIST v1.1
- Must provide tissue biopsy, archival tissue acceptable; if unavailable, fresh tissue biopsy required
- Treated, stable brain mets allowed
- ECOG PS 0-1



Alisertib
50 mg po BID on days 1-7 of every 21-day cycle

Efficacy and safety objectives and endpoints

Objective
Primary Endpoint
• Proportion of patients with confirmed complete responses (CR) or partial responses (PR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
Secondary Endpoints
• Duration of response (DOR) • Disease control rate (DCR) • Progression free survival (PFS)
• Overall survival (OS)
• Adverse events (AEs) and serious adverse events (SAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v.5.0)
• Plasma alisertib concentrations on Cycle 1 Day 1 and Day 8
Exploratory Endpoints
• ORR, DOR, DCR, PFS, and OS within selected biomarker subgroups from formalin-fixed paraffin-embedded (FFPE) tissue and/or from plasma (circulating tumor DNA [ctDNA])

Parallel Clinical and Biomarker Development

- Comprehensive biomarker strategy supports clinical development and commercialization