Combining Lurbinectedin and Doxorubicin
The UCLH Experience in Small Cell Lung Cancer

Dr Martin Forster MD PhD
Clinical Senior Lecturer in Experimental Cancer Medicine
Consultant in Medical Oncology
UCL Cancer Institute / UCLH, London, UK

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Pharmamar R&D Day
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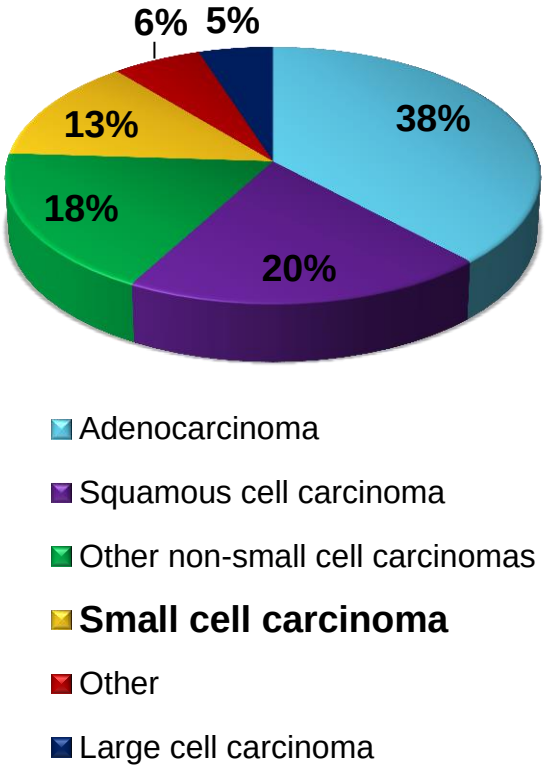
Small Cell Lung Cancer (SCLC)

- Lung Cancer is the most common cancer across men and women globally and the highest cause of cancer mortality
- SCLC accounts for 10-15% of all lung cancer
- Strong association with tobacco use and associated co-morbidities
- ~30% present with ‘limited stage’ disease with only a proportion eligible for ‘radical intent’ treatment, chemo-radiation, associated with ~18 month survival
- >80% treated with palliative chemotherapy with median survival 9-11 months



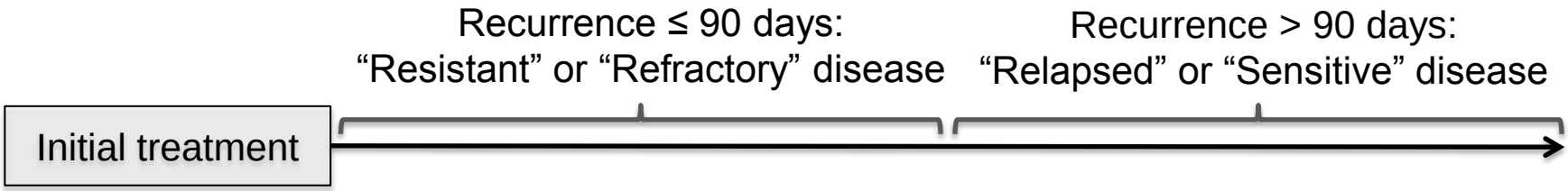
Jackman and Johnson, 2005

Extensive Stage SCLC: First-line therapy

- Combination chemotherapy with cisplatin / carboplatin and etoposide is the mainstay of first-line treatment
  - Response rates 60-70%
  - 4 to 6 cycles
  - Median progression free survival 2-3 months
  - 2-year overall survival < 5%
- Minimal improvement in first line therapy in decades
  - Cisplatin / Irinotecan demonstrated to be superior in Japanese population; not seen in study in Western population
  - Consolidation Thoracic Radiotherapy
  - Prophylactic Cranial Irradiation

Noda et al., NEJM 2002; Hanna et al., JCO 2006; Rossi et al., JCO 2012; Slotman et al., Lancet Onc 2015

Management of Recurrent Disease



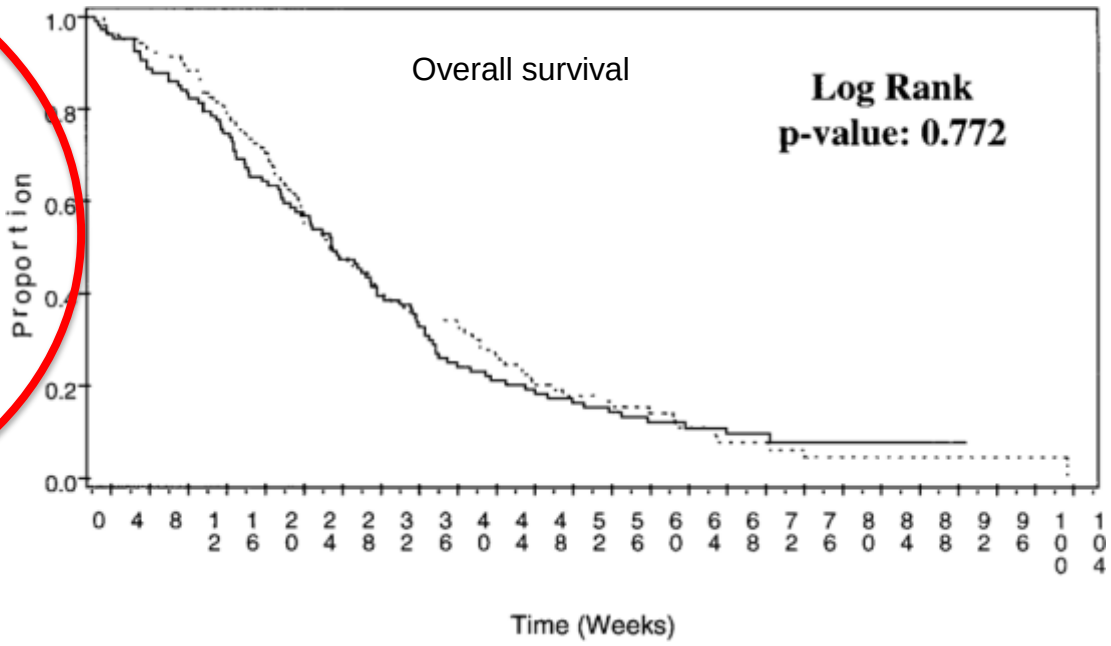
Topotecan as second-line therapy in SCLC

- Three open-label single-arm studies of IV topotecan days 1-5 q3 weekly showed response rates ranging 11% to 31% for 'sensitive' disease and 2% to 7% for 'resistant' disease
- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival.

Ardizzoni et al., 1997; Von Pawel et al., 1999; NCCN guidelines v2.2017

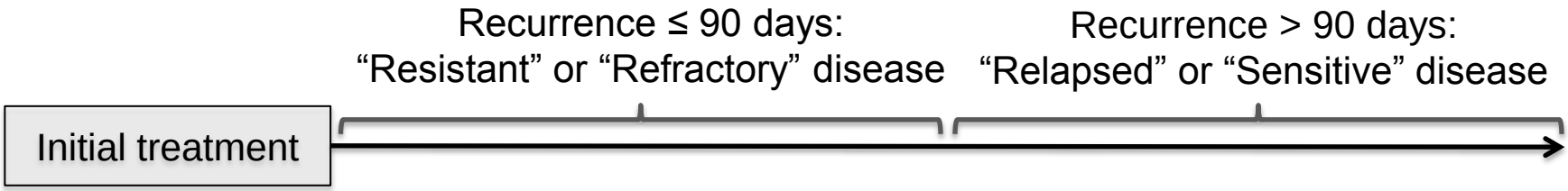
Topotecan vs CAV in second-line setting

- Randomized study in patients with relapse >60 days after completion of first-line therapy
  - Topotecan: 1.5 mg/m^2 IV daily days 1-5 Q21d vs CAV: Cyclophosphamide 1000 mg/m^2, Doxorubicin 45 mg/m^2, Vincristine 2 mg IV day 1 Q21d
- ORR
  - 24 vs 18%
- mTTP:
  - 13.3 vs 12.3 wks
- mOS:
  - 25.0 vs 24.7 wks



Von Pawel et al., JCO 1999

Management of Recurrent Disease



Topotecan is the only FDA- and EMA-approved second-line therapy in SCLC

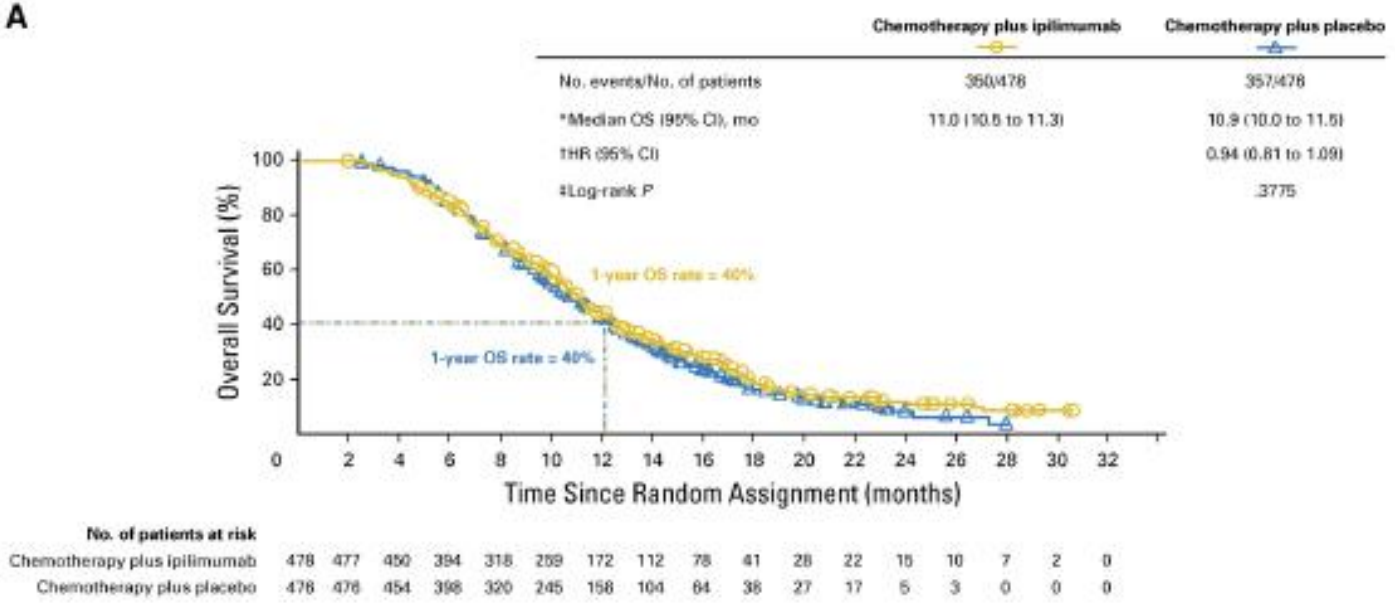
- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival
- Oral topotecan also improved survival compared to BSC

Oral and IV formulations approved by FDA and EMA

Ardizzoni et al., 1997; Von Pawel et al., 1999; O'Brien et al., 2006; NCCN guidelines v2.2017

Upcoming Interests – Immunotherapy

- Phase 3 Cisplatin & Etoposide +/- Ipilimumab



- Checkmate 032 - Phase 2 Nivolumab monotherapy vs Nivolumab plus Ipilimumab

	Nivolumab-3 (n = 98)	Nivolumab-1 + Ipilimumab-3 (n = 61)	Nivolumab-3 + Ipilimumab-1 (n = 54)
Objective response rate, % (n/N)			
Overall	**10 (10/98)**	**23 (14/61)**	**19 (10/54)**
Platinum-sensitive[a]	11 (6/55)	28 (7/25)	19 (4/21)
Platinum-resistant[a]	10 (3/30)	17 (4/23)	10 (2/21)

Antonia et al., Lancet Onc 2016; Reck et al.; JCO 2016

Upcoming Interests – DLL3 inhibitors

- Rovalpituzumab tesirine (Rova-T) – A delta-like protein 3 Antibody-Drug Conjugate
  - Phase 1 dose escalation study in SCLC (2nd or 3rd line therapy)
    - Maximum tolerated dose 0.4 mg/kg 3 weekly
    - Recommended phase II dose and schedule 0.3 mg/kg 6 weekly
    - 'Active' dose levels: 0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks

	ORR (all patients) N=60	**ORR (DLL3 +ve pts) N=26**
Rova-T 'Active' dose levels	18% (11/60) PFS 2.8m OS 4.6m	38% (10/26) PFS 4.3m OS 5.8m

Rudin et al., Lancet Oncology 2016

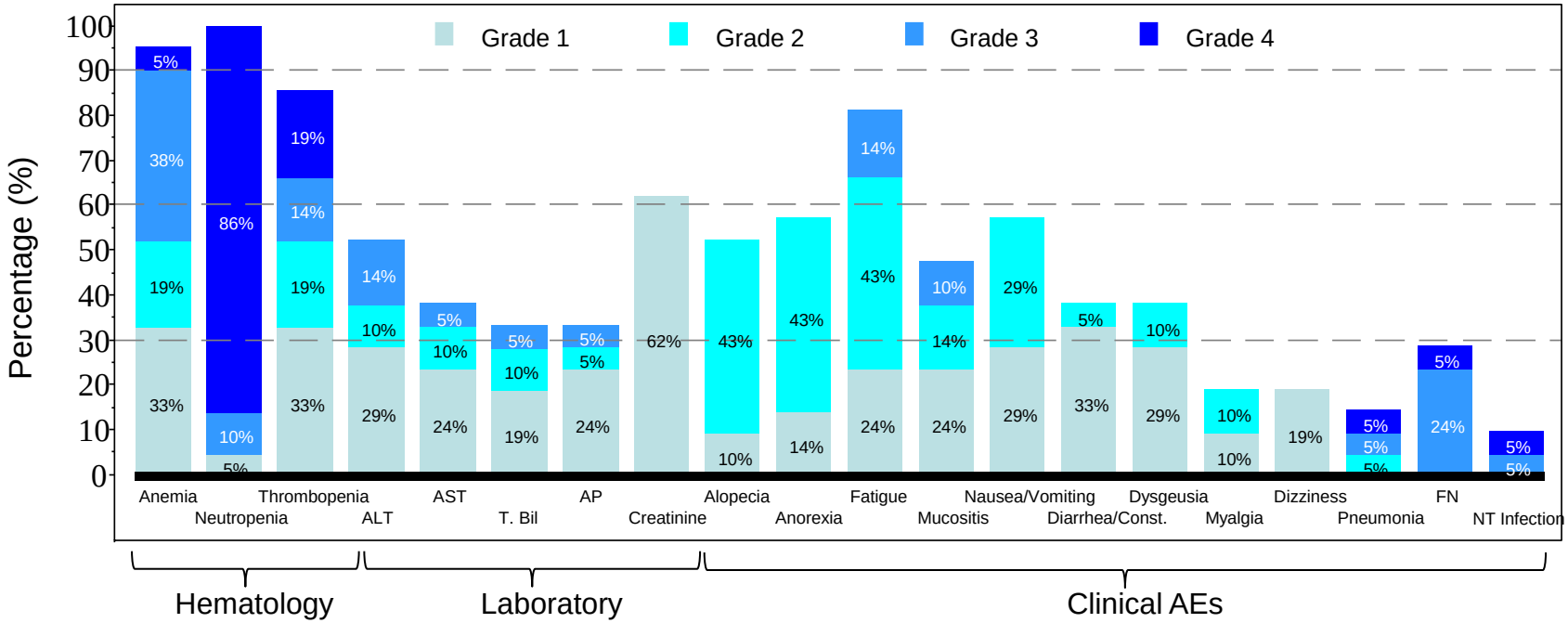
Upcoming Interests – Lurbinectedin & Doxorubicin

Lurbinectedin (PM1183) & Doxorubicin (DOX), as a possible new second-line therapy in Small Cell Lung Cancer (SCLC)

- Dose finding part of a Phase Ib study defined a recommended phase II dose of lurbinectedin 4.0 mg flat dose (FD) or 2.0 mg/m^2 + DOX 50 mg/m^2 both on day (D)1 every three weeks (q3w)
- Myelosuppression was dose-limiting regardless of colony stimulating factor (CSF) prophylaxis use
- After DOX withdrawal, treatment could continue with lurbinectedin alone, if clinically appropriate
- Compelling activity was observed during escalation phase with 5 of 7 evaluable 2nd line in SCLC pts (71%) having objective partial response (PR) as per RECIST v.1.1
- Thus, an expansion cohort of 20 2nd line SCLC pts was evaluated

Forster et al., ASCO 2015

Safety (n=21)



AEs, Adverse events; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; Const, constipation; FN, febrile neutropenia; NT, neutropenic; T Bil, Total bilirubin.

Neutropenia time course according to CSF prophylactic use or not (n=109 cycles)

	CSF (n=52)	No CSF (n=57)
Grade 4 neutropenia	25%	33%
Median day of grade 4 nadir (range)	8 (7-11)	14 (10-16)
Time to recovery to rechallenge, in days	4 (2-21)	4 (1-13)
Febrile neutropenia	7.7%	8.8%
Neutropenic infection	None	3.5%
Grade 4 thrombocytopenia	7.7%	None

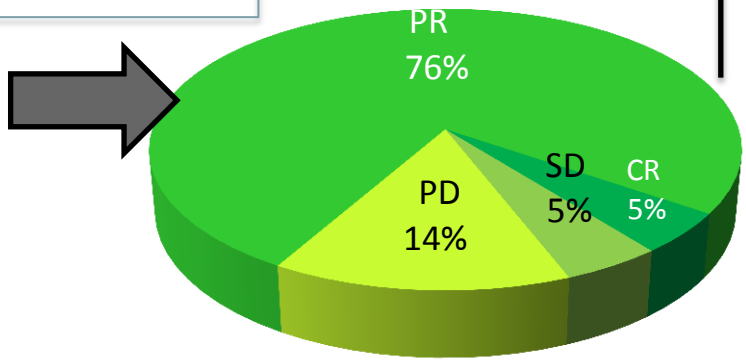
CSF, colony stimulating factor.

Forster et al., ASCO 2015

Efficacy

1st line Platinum-based combination

N=21



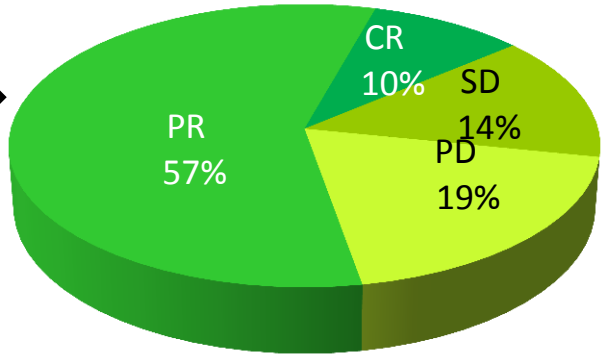
ORR
81%
95% CI: 58-95%

PD

median CTFI
3.1 months

2nd line Lurbinectedin /DOX

N=21

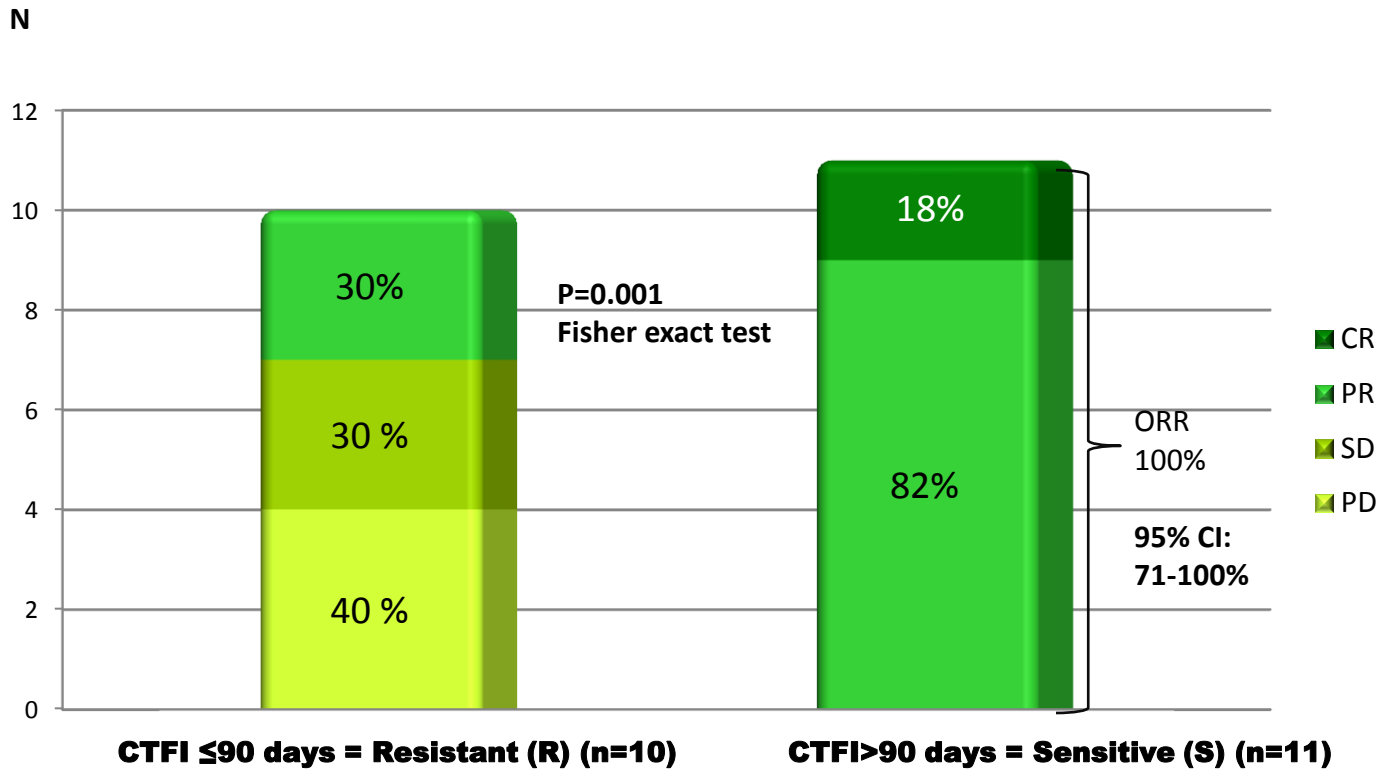


ORR
67%
95% CI: 43-85%

CI, confidence interval; CR, complete response; CTFI, chemotherapy-free interval; DOX, doxorubicin; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Forster et al., ASCO 2015

Best RECIST v.1.1 response according to chemotherapy free interval (CTFI)



Exceptional activity with significant but manageable toxicity led to a further expansion cohort of Lurbinectedin (2mg/m^2) and Doxorubicin (40mg/m^2) and plans for a randomised study

Forster et al., ASCO 2015

Patient Characteristics

- Dose escalating phase I study in patients with different tumour types
- 9 patients with metastatic small cell lung cancer treated at UCLH

Number of patients	9
Male	7
Female	2
Median Age	63 (58-78)

Lurbinectedin combination dose (mg)	**Dox (mg/m^2)**	**# patients**
3	50	1
4	50	3
5	50	1
$2mg/m^2$	40	4

# Lines prior systemic therapy	
0	0
1	9
2	0
Platinum Sensitivity	
Sensitive	6
Resistant	3
Platinum Free interval (weeks)	
Median	17
Range	8 to 55

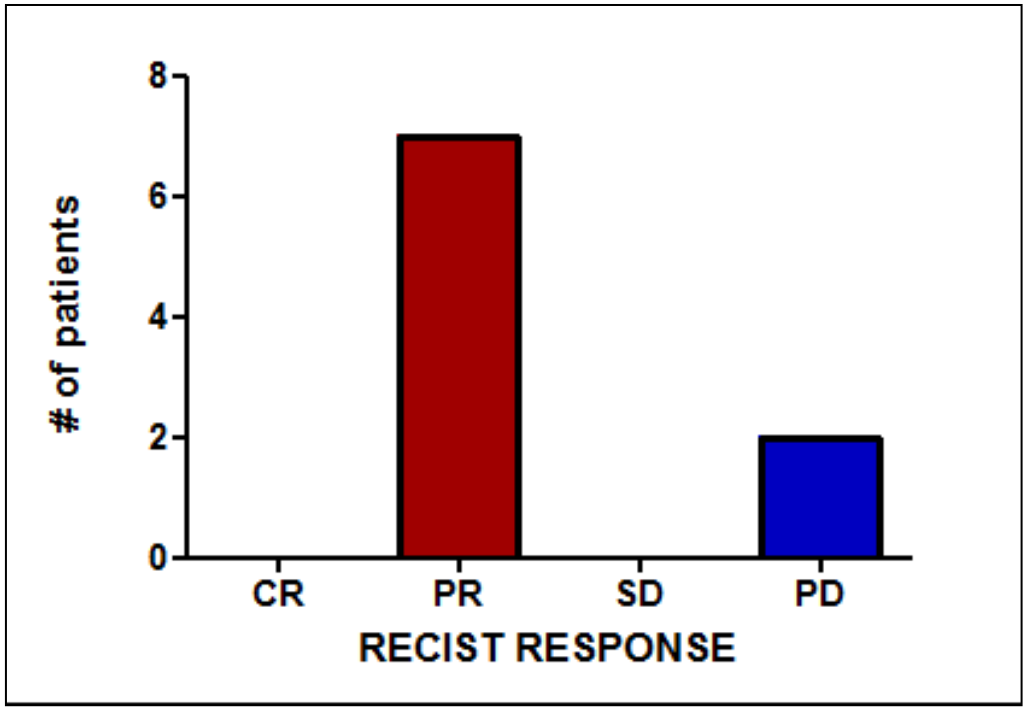
Toxicity

Patient #	PM Dose (mg)	Dox Dose (mg/m²)	#Dox/PM combo	#PM single agent	DR in combo	DR single agent	Reason for DR
1*	3 mg	50	4	0	no	NA	
2	**3.5 mg**	**40**	**2**	**0**	**no**	**NA**	
3	**3.75 mg**	**40**	**6**	**2**	**no**	**yes**	G4 neut/ G3 plts
4	**3.75 mg**	**40**	**10**	**4**	**no**	**yes**	G4 neut/ G3 plts
5	4 mg	50	8	4	no	no	
6	**4 mg**	**40**	**2**	**0**	**no**	**NA**	
7	4 mg	50	8	7	yes	yes	G4 neut
8*	4 mg	50	4	0	no	no	
9**	5 mg	50	3	1	yes	yes	G4 neut

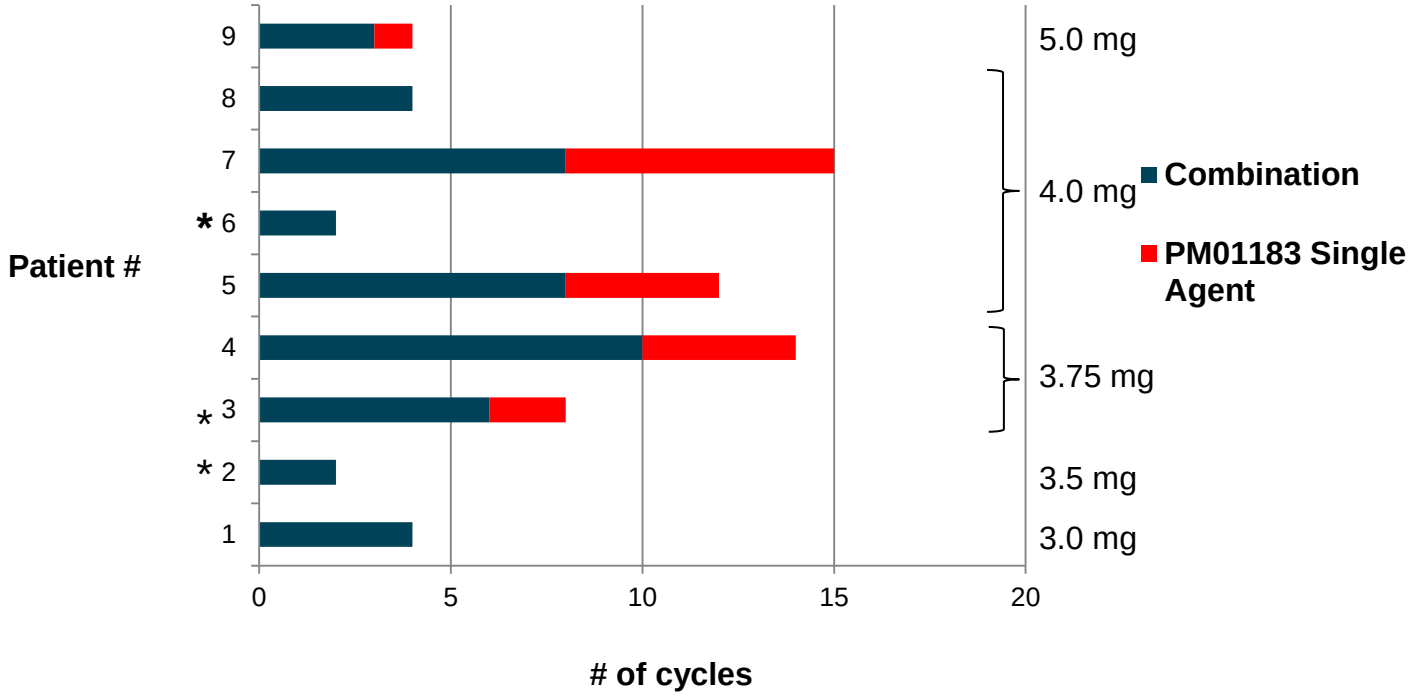
* Discontinued treatment due to fatigue / decline in PS without evidence of PD

** Discontinued treatment due to persistent pancytopenia despite dose reductions

Best Imaging Response



Treatment Duration



Median # cycles of Dox/Lurbinectedin = 4, range 2-10

Five patients on single agent lurbinectedin, median 4, range 1-7

Median # total cycles 4, mean 7.2, range 2-15

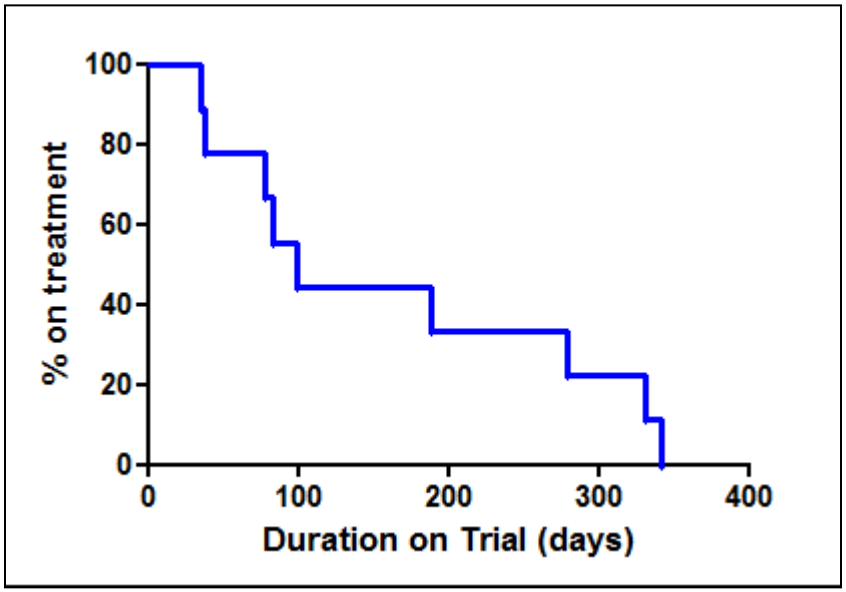
* Platinum refractory patients

Treatment Duration

Patient #	Dose PM	Dose Dox	#Dox/ PM	#PM single agent	Best response	Reason for discontinuation
1	3 mg	50 mg/m^2	4	0	PR	Pneumonia and decline in PS*
2	**3.5 mg**	**40 mg/m^2**	**2**	**0**	**PD**	**Disease Progression**
3	**3.75 mg**	**40 mg/m^2**	**6**	**2**	**PR**	**Disease Progression (Brain)**
4	**3.75 mg**	**40 mg/m^2**	**10**	**4**	**PR**	**Disease Progression (Brain)**
5	4 mg	50 mg/m^2	8	4	PR	Disease Progression
6	**4 mg**	**40 mg/m^2**	**2**	**0**	**PD**	**Disease Progression**
7	4 mg	50 mg/m^2	8	7	PR	Disease Progression
8	4 mg	50 mg/m^2	4	0	PR	Toxicity, fatigue and decline in PS**
9	5 mg	50 mg/m^2	3	1	PR	Persistent pancytopenia despite DR***

* PD 4 months after trial discontinuation
** Death 2 months after trial discontinuation
*** New brain mets 2 months after trial discontinuation

Duration on study drug



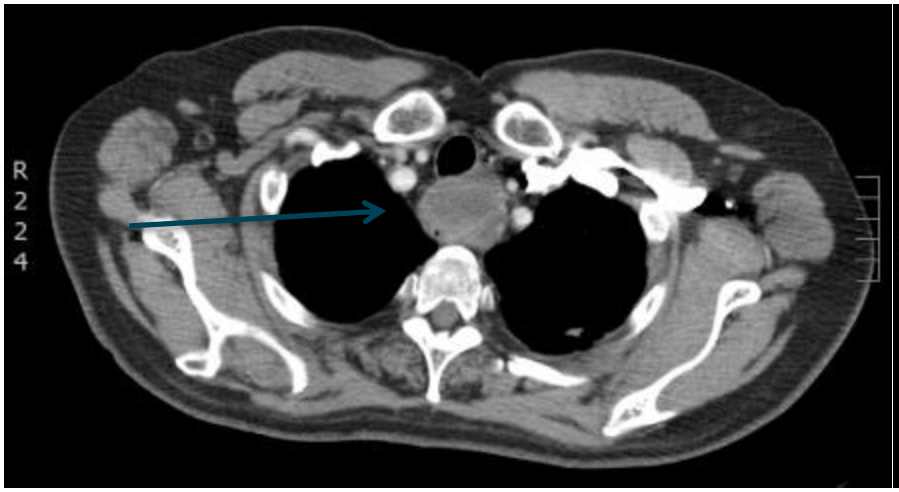
Median duration on IMP 99 days (35-341)

Patient JB

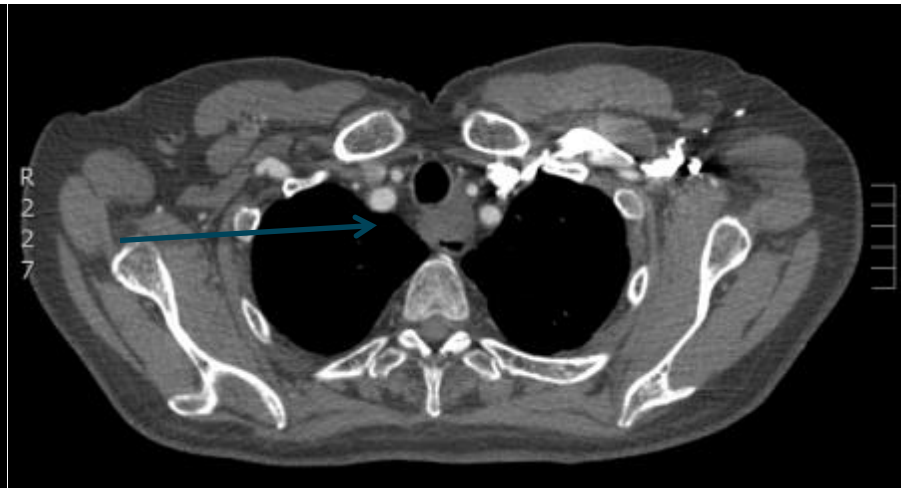
- 71 year old male
  - Ex smoker
  - COPD; CVD (TIAs); Depression
- April 2014 – T4N2M1b Extensive Stage Small Cell Lung Cancer with left suprahilar mass invading mediastinum, mediastinal LNs and a liver metastasis
- October 2014 – completed 6 cycles of carboplatin and etoposide with partial response
  - Had persisting respiratory symptoms and declined PCI but received palliative RT to left lung and mediastinum (20Gy in 5#) in Feb 2015
- March 2015 (~4 months PFI) developed disease progression in lungs and bone

- Referred to UCLH
  - Grade 1 cough; grade 1 SOB; grade 1 lethargy
  - ‘PS 1’
  - Intrathoracic disease (47mm mediastinal mass)
- May 2015 – commenced lurbinectedin 2mg/m^2 (3.75 mg) and doxorubicin 40mg/m^2
  - Minimal toxicity (G1 lethargy)
  - Partial response in June 2015 post 2 cycles (40% reduction in target lesions; 28mm)
- Incremental response until complete response of target lesion (post 4 cycles) and very good partial response of non target disease
- January 2016 – completed 10 cycles combination chemotherapy

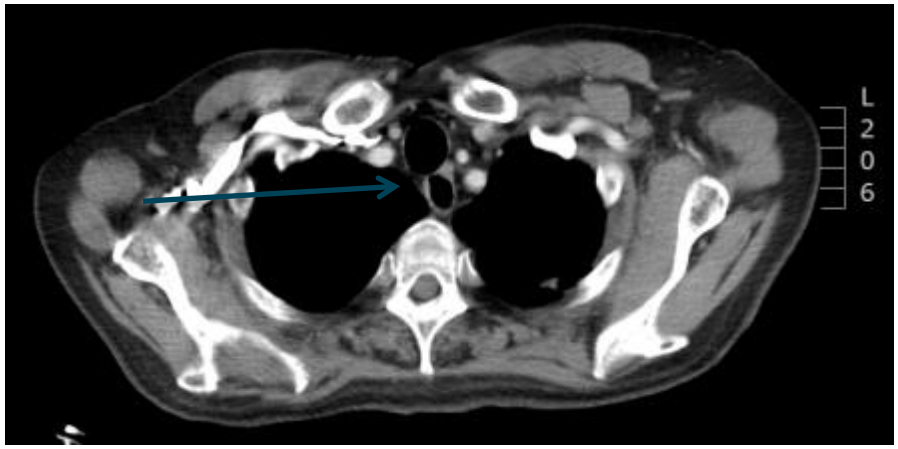
Baseline



Post 2 cycles



6 months



- Jan 2016 started onto single agent lurbinectedin (4mg/m^2; 7mg)
  - Dose reduced to 3mg/m^2 (5.25mg) due to pancytopenia after cycle 2
  - maintained PR on CT after 2 cycles
- April 2016 – complaining of blurred vision and unsteadiness
  - CT brain – multiple brain metastases
  - No extra-cranial progression
  - Off study
- April 2016 - RIP

Summary

- Tolerability across multiple dose levels driven by myelosuppression
  - Much better tolerated on expansion ‘phase III’ schedule
  - Side effects are manageable, with option for dose delays or modification if required
  - Maintenance monotherapy also feasible
- Very impressive responses
  - Some longer duration than with 1st line therapy!
- Phase III registration study ongoing with hopes to define a new standard second line SCLC treatment and improves outcomes for this patient population

Thanks

- UCLH CRF staff
  - Rebecca Kristeleit
  - Michael Flynn and other Clinical Fellows
  - David Leader and other research nurses
  - Aaron Clarke and other data managers
- NIHR UCH Clinical Research Facility
- Patients and their families

Any Questions?