elcc European Lung Cancer Conference

Cabazitaxel vs topotecan in patients with small cell lung cancer (SCLC) with progressive disease during/after first-line treatment with platinum-based chemotherapy

Tracey Evans[1]; Byoung Chul Cho[2]; Katalin Udud[3]; Juergen R. Fischer[4]; Frances A. Shepherd[5]; Pablo Martinez[6]; Rodryg Ramlau[7]; Konstantinos N. Syrigos[8]; Mustapha Chadjaa[9]; Martin Wolf[10]

[1]Abramson Cancer Center, Philadelphia, PA, USA; [2]Yonsei Cancer Center, Yonsei University Health System, Seoul, Republic of Korea; [3]Korányi National Institute of Pulmonology, Budapest, Hungary; [4]Klinikum Loewenstein, Loewenstein, Germany; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Vall d'Hebron University Hospital, Barcelona, Spain; [7]Poznan University of Medical Sciences, Poznan, Poland; [8]Oncology Unit, 3rd Department of Medicine, Athens University School of Medicine, Sotiria General Hospital, Athens; [9]Sanofi, Vitry-sur-Seine, France; [10]Division of Haematology and Oncology, Klinikum Kassel, Kassel, Germany.

26–29 March 2014, Geneva, Switzerland

Organisers

IASLC International Association for the Study of Lung Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Disclosures

- TE; receipt of honoraria or consultation fees from Lilly and Genentech, husband on speakers' bureau for Genentech
- BCC; receipt of grants/research supports from Novartis; receipt of honoraria or consultation fees from Novartis, AstraZeneca and GSK
- FAS; receipt of honoraria or consultation fees from Lilly, AstraZeneca, GSK, Novartis, Roche
- MC; employed by Sanofi
- KU, JRF, PM, RR, KNS, MW; nothing to declare

Background

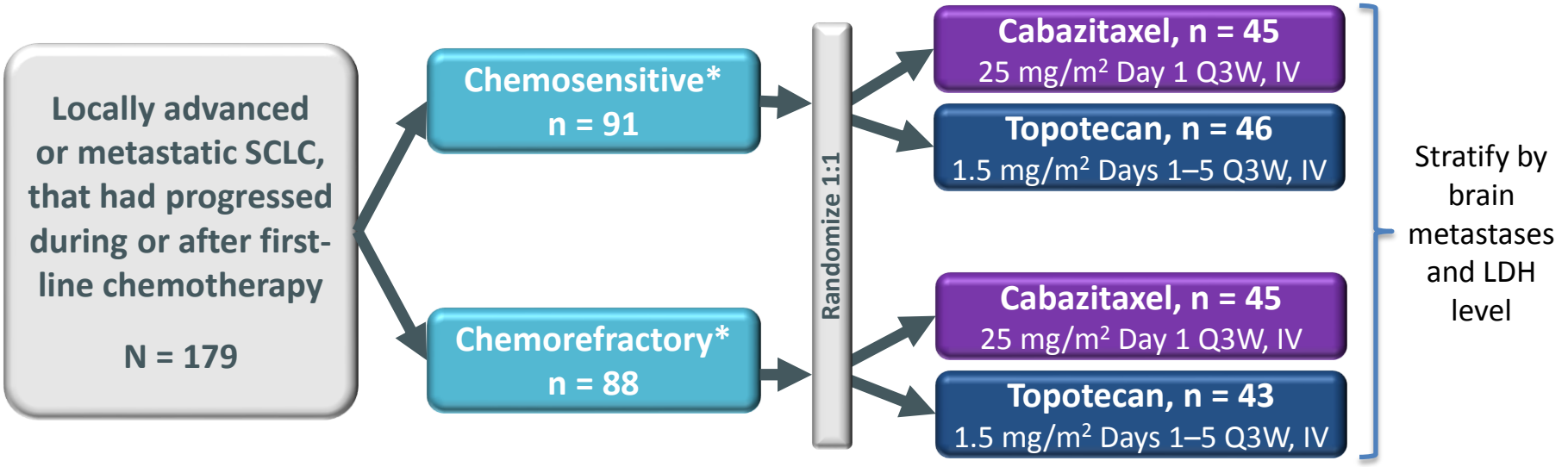
- Platinum-based chemotherapy is the first-line standard of care for SCLC, but most patients experience relapse and death[1]
  - Although several chemotherapy agents have demonstrated activity in SCLC, topotecan is currently the only standard for comparison in relapsed disease[1]
  - Median survival time of patients with relapsed SCLC varies from 14 to 35 weeks[1]
  - More effective second-line treatments are required
- Docetaxel and paclitaxel are effective first or second-line treatments in SCLC[2–4]
  - Cabazitaxel is a next generation taxane with approved safety and efficacy in the second-line treatment of mCRPC and activity in other advanced solid tumors[5–9]
- This study aimed to investigate the efficacy of cabazitaxel compared with topotecan in the second-line treatment of SCLC

1. Riemsma R *et al*. *BMC Cancer* 2010; **10**:436; 2. Ettinger D *et al*. *J Clin Oncol* 1995; **13**:1430–1435; 3. Jett JR *et al*. *Semin Oncol* 1995; **22**:75–77; 4. Smyth JF *et al*. *Eur J Cancer* 1994; **30A**:1058–1060; 5. de Bono JS *et al*. *Lancet* 2010; **376**:1147–1154; 6. Dieras V, *et al*. *Eur J Cancer* 2013; **49**:25–34; 7. Fumoleau P, *et al*. *BMC Cancer* 2013; **13**:460; 8. Mita AC, *et al*. *Clin Cancer Res* 2009; **15**:723–730; 9. Pivot X *et al*. *Ann Oncol* 2008; **19**:1547–1552.

SCLC, small-cell lung cancer

ARD12166: study design

- Phase II randomized open-label ARD12166 study (NCT01500720)



- Primary endpoint: PFS
- Secondary endpoints: DPFR at 12 weeks, response rate, duration of response, OS, safety and HRQoL
- Other key eligibility criteria: ECOG PS ≤ 1, 1 prior chemotherapy, no prior taxane/topotecan treatment

* Chemosensitive and chemorefractory patient subgroups were assessed both together and separately. Patients were defined as those who progressed (by RECIST 1.1) (A) after ≥ 90 days (chemosensitive) or (B) during or within 90 days (chemorefractory) following the completion of first-line chemotherapy.

DPFR, disease progression-free rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; OS, overall survival; LDH, lactate dehydrogenase; PFS, progression-free survival; SCLC, small-cell lung cancer.

Patient demographics

	Total population		Chemorefractory		Chemosensitive	
	Cabazitaxel (n = 90)	Topotecan (n = 89)	Cabazitaxel (n = 45)	Topotecan (n = 43)	Cabazitaxel (n = 45)	Topotecan (n = 46)
Median age, years (range)	60 (37–82)	62 (27–80)	58 (37–76)	60 (27–80)	62 (40–82)	65 (33–80)
ECOG PS, n (%)						
≤ 1	90 (100)	88 (98.9)	45 (100)	43 (100)	45 (100)	45 (97.8)
2	0	1 (1.1)	0	0	0	1 (2.2)
Patient subgroup, n (%)						
Chemorefractory	45 (50.0)	43 (48.3)	N/A	N/A	N/A	N/A
Chemosensitive	45 (50.0)	46 (51.7)	N/A	N/A	N/A	N/A
LDH level, n (%)						
≤ ULN	46 (51.1)	46 (51.7)	18 (40.0)	17 (39.5)	28 (62.2)	29 (63.0)
> ULN	44 (48.9)	43 (48.3)	27 (60.0)	26 (60.5)	17 (37.8)	17 (37.0)
Brain metastases, n (%)						
Present	25 (27.8)	25 (28.1)	13 (28.9)	12 (27.9)	12 (26.7)	13 (28.3)
Absent	65 (72.2)	64 (71.9)	32 (71.1)	31 (72.1)	33 (73.3)	33 (71.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; N/A, not applicable; ULN, upper limit of normal.

Disease characteristics

	Total population		Chemorefractory		Chemosensitive	
	Cabazitaxel (n = 90)	Topotecan (n = 89)	Cabazitaxel (n = 45)	Topotecan (n = 43)	Cabazitaxel (n = 45)	Topotecan (n = 46)
Median time from initial diagnosis to study treatment, months (range)*	8.7 (3–56)	8.5 (3–36)	6.8 (3–56)	7.1 (3–17)	10.7 (5–22)	10.5 (5–36)
Extent of disease at study entry, n (%)						
Metastatic	87 (96.7)	81 (91.0)	44 (97.8)	41 (95.3)	43 (95.6)	40 (87.0)
Locoregional	3 (3.3)	8 (9.0)	1 (2.2)	2 (4.7)	2 (4.4)	6 (13.0)
Number of organs involved at baseline, n (%)						
1–3	46 (51.1)	35 (39.3)	21 (46.7)	13 (30.2)	25 (55.6)	22 (47.8)
4–5	38 (42.2)	45 (50.6)	19 (42.2)	25 (58.1)	19 (42.2)	20 (43.5)
6–8	6 (6.7)	9 (10.1)	5 (11.1)	5 (11.6)	1 (2.2)	4 (8.7)
Most common sites of metastases†, %						
Lungs	97.8	93.3	97.8	90.7	97.8	95.7
Lymph Nodes	84.4	85.4	86.7	90.7	82.2	80.4
Liver	47.8	50.6	53.3	55.8	42.2	45.7
Bone	31.1	38.2	40.0	44.2	22.2	32.6
Adrenal	26.7	29.2	17.8	32.6	35.6	26.1

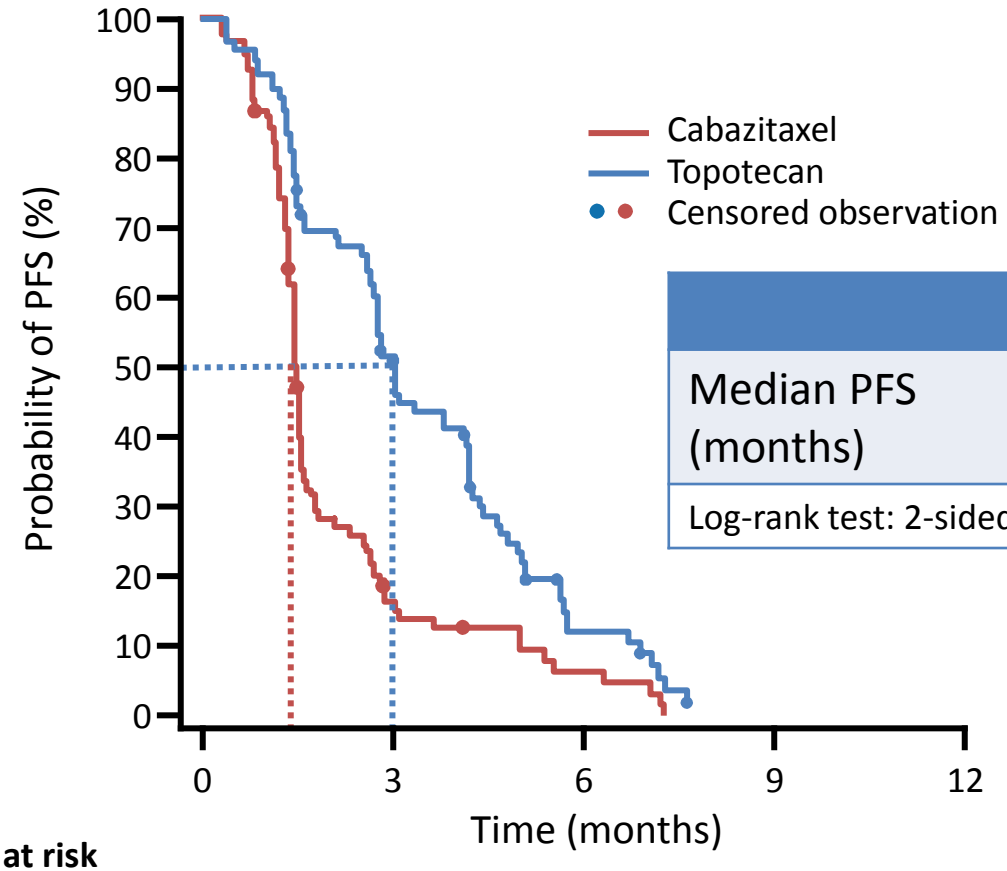
* Total population: cabazitaxel n = 89; topotecan n = 88. Chemosensitive subgroup: cabazitaxel n = 44; topotecan n = 45; †excluding brain

Treatment exposure

	Total population		Chemorefractory		Chemosensitive	
	Cabazitaxel (n = 90)	Topotecan (n = 89)	Cabazitaxel (n = 45)	Topotecan (n = 43)	Cabazitaxel (n = 45)	Topotecan (n = 46)
Median number of treatment cycles (range)*	2.0 (1–14)	4.0 (1–11)	2.0 (1–14)	3.0 (1–8)	2.5 (1–8)	4.0 (1–11)
Median relative dose intensity, % (range)*	98.9 (61.1–103.0)	91.8 (57.6–104.8)	98.9 (72.5–101.7)	93.2 (59.2–104.8)	98.6 (61.1–103.0)	86.8 (57.6–101.6)
Treatment discontinuations, n (%)						
Total	88 (97.8)	87 (97.8)	44 (97.8)	43 (100)	44 (97.8)	44 (95.7)
Disease progression	70 (77.8)	50 (56.2)	38 (84.4)	30 (69.8)	32 (71.1)	20 (43.5)
Adverse event	14 (15.6)	24 (27.0)	4 (8.9)	8 (18.6)	10 (22.2)	16 (34.8)
Other	3 (3.3)	8 (9.0)	1 (2.2)	3 (7.0)	2 (4.4)	5 (10.9)
Patient request	1 (1.1)	5 (5.6)	1 (2.2)	2 (4.7)	0	3 (6.5)

* Total population: cabazitaxel n = 89; topotecan n = 88. Chemosensitive subgroup: cabazitaxel n = 44; topotecan n = 45.

Progression-free survival: ITT population



	Cabazitaxel	Topotecan
Median PFS (months)	1.4	3.0
Log-rank test: 2-sided $P < 0.0001$; HR = 2.17; 95% CI 1.56–3.01		

Number at risk

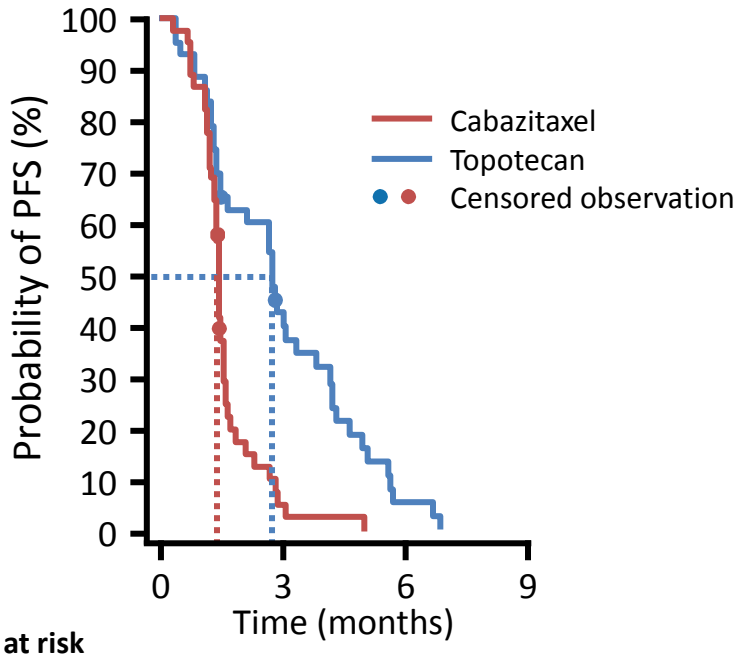
Cabazitaxel	90	4	0	0
Topotecan	89	8	0	0

- The primary objective of PFS improvement with cabazitaxel versus topotecan was not met

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Progression-free survival: subgroups

Chemorefractory

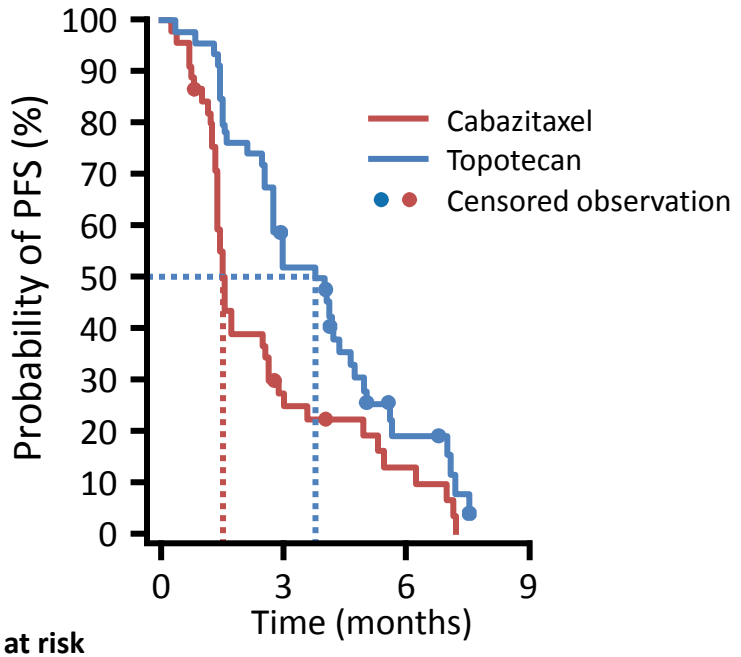


Number at risk

Cabazitaxel	45	0	0
Topotecan	43	2	0

	Cabazitaxel	Topotecan
Median PFS (months)	1.4	2.7
Log-rank test: 2-sided $P < 0.0001$; HR = 3.32 95% CI 1.93–5.73		

Chemosensitive



Number at risk

Cabazitaxel	45	4	0
Topotecan	46	6	0

	Cabazitaxel	Topotecan
Median PFS (months)	1.5	3.8
Log-rank test: 2-sided $P = 0.0045$; HR = 1.94; 95% CI 1.22–3.08		

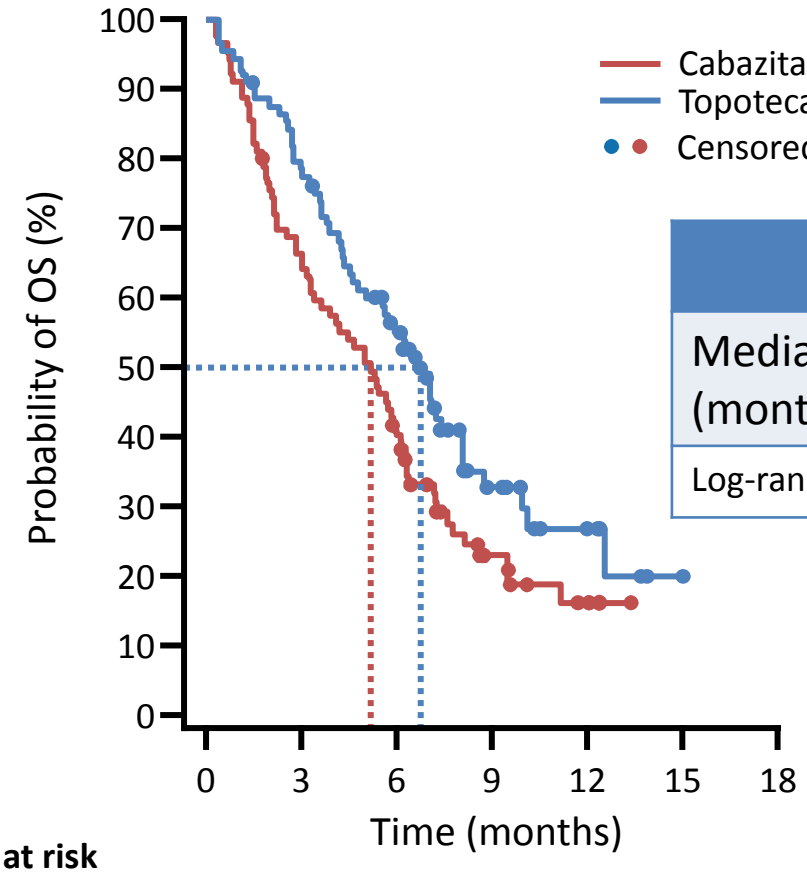
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Objective tumour response rate: ITT population

Response, n (%)	Overall		Chemorefractory		Chemosensitive	
	Cabazitaxel (n = 73)	Topotecan (n = 79)	Cabazitaxel (n = 35)	Topotecan (n = 37)	Cabazitaxel (n = 38)	Topotecan (n = 42)
Complete response	0	0	0	0	0	0
Partial response	0	8 (10.1)	0	3 (8.1)	0	5 (11.9)
Stable disease	16 (21.9)	50 (63.3)	5 (14.3)	21 (56.8)	11 (28.9)	29 (69.0)
Disease progression	51 (69.9)	18 (22.8)	28 (80.0)	11 (29.7)	23 (60.5)	7 (16.7)
Not evaluable/ missing data	6 (8.2)	3 (3.8)	2 (5.7)	2 (5.4)	4 (10.5)	1 (2.4)

ITT, intent-to-treat.

Overall survival: ITT population



	Cabazitaxel	Topotecan
Median OS (months)	5.2	6.8
Log-rank test: 2-sided *P* = 0.0125; HR = 1.57; 95% CI 1.10–2.25		

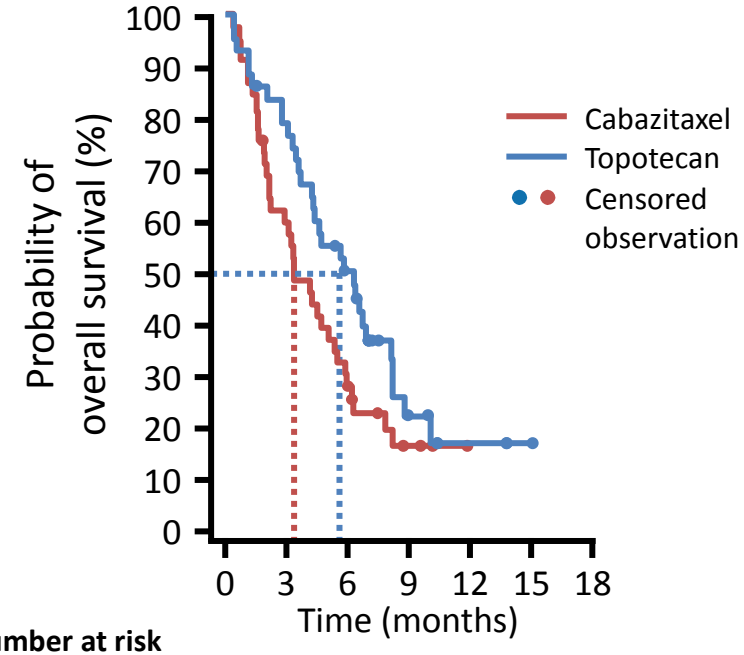
Number at risk

Cabazitaxel	90	35	12	2	0
Topotecan	89	45	14	6	0

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

Overall survival: subgroups

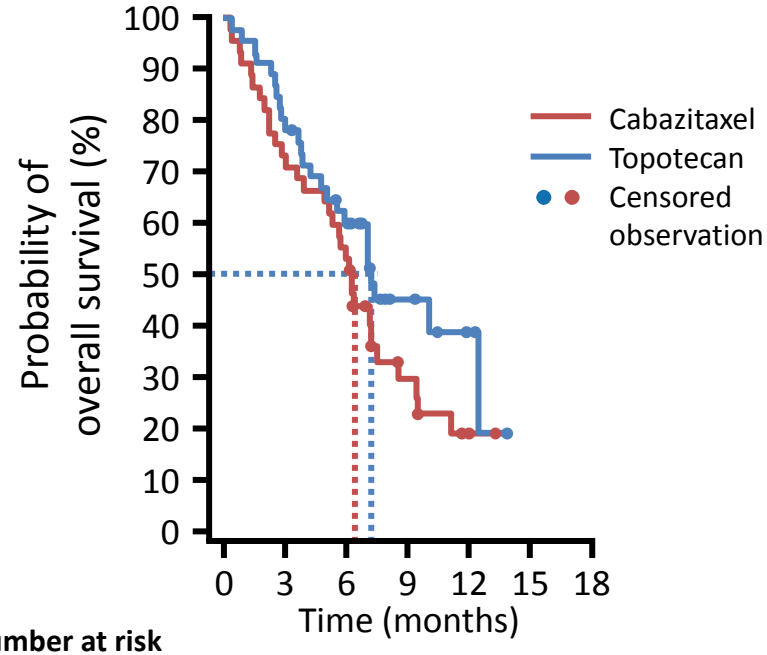
Chemorefractory



Number at risk					
Cabazitaxel	45	11	3	0	0
Topotecan	43	19	5	2	0

	Cabazitaxel	Topotecan
Median OS (months)	3.4	5.7
Log-rank test: 2-sided *P* = 0.035; HR = 1.70 95% CI 1.03–2.80		

Chemosensitive

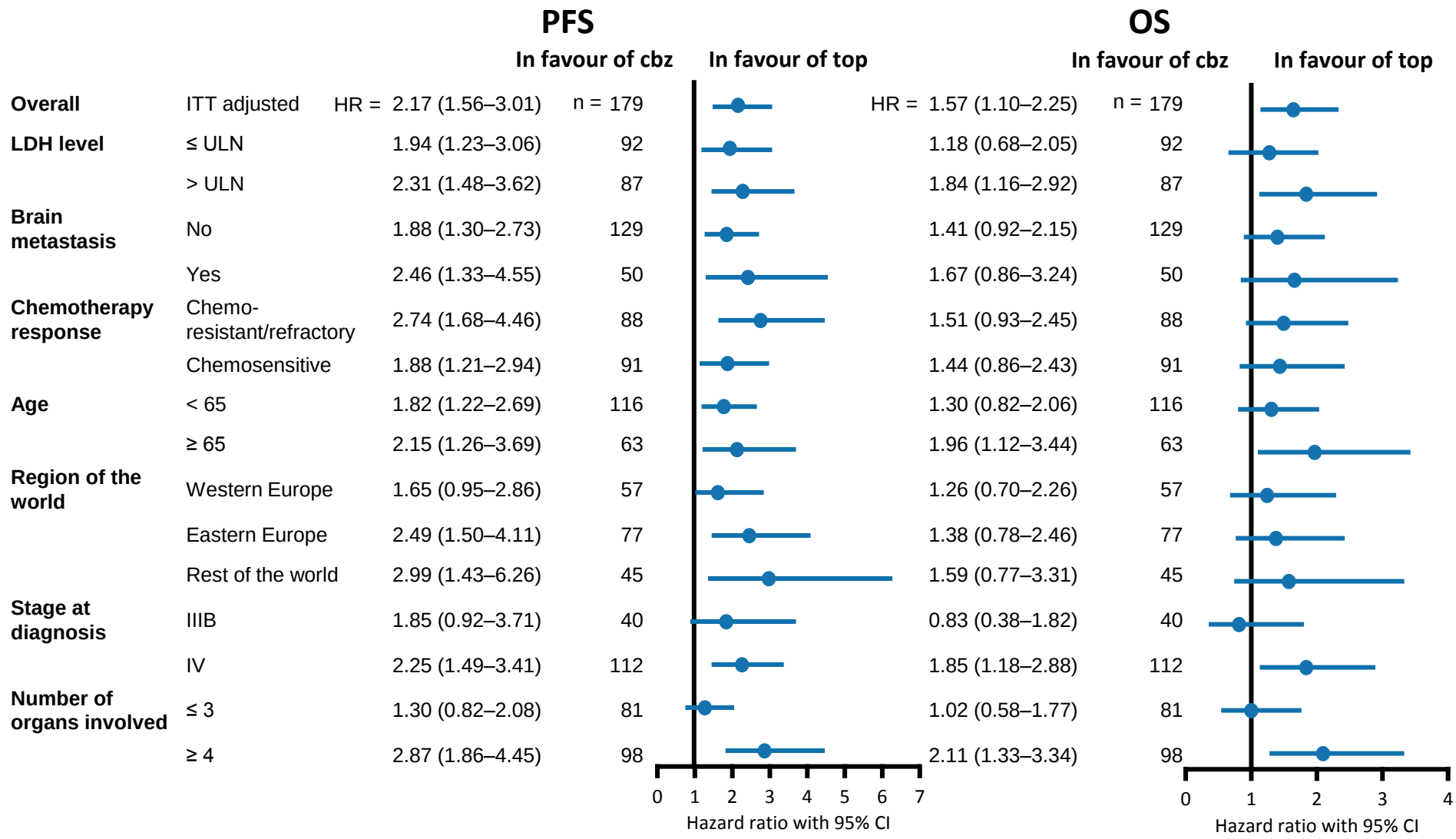


Number at risk					
Cabazitaxel	45	24	9	2	0
Topotecan	46	26	9	4	0

	Cabazitaxel	Topotecan
Median OS (months)	6.3	7.2
Log-rank test: 2-sided *P* = 0.116; HR = 1.53 95% CI 0.90–2.62		

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Subgroup analysis



Cox model for Overall stratified for brain metastases and LDH level as specified at the time of randomization. Cox models for all subgroups were run without using strata. Hazard ratios (HR) < 1 favour cabazitaxel group and > 1 favour the topotecan group.

Cbz, cabazitaxel; CI, confidence interval; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; Top, topotecan; ULN, upper limit of normal.

Most frequently reported TEAEs regardless of relationship to study treatment: safety population

TEAEs*	Cabazitaxel (n = 89)		Topotecan (n = 88)	
	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3
Any TEAE	79 (88.8)	52 (58.4)	83 (94.3)	63 (71.6)
Fatigue	26 (29.2)	7 (7.9)	22 (25.0)	7 (8.0)
Diarrhoea	17 (19.1)	2 (2.2)	9 (10.2)	0
Decreased appetite	16 (18.0)	2 (2.2)	13 (14.8)	1 (1.1)
Vomiting	16 (18.0)	1 (1.1)	7 (8.0)	0
Nausea	14 (15.7)	2 (2.2)	11 (12.5)	0
Asthenia	11 (12.4)	2 (2.2)	18 (20.5)	7 (8.0)
Abdominal pain	10 (11.2)	2 (2.2)	3 (3.4)	0
Cough	10 (11.2)	1 (1.1)	8 (9.1)	0
Febrile neutropenia	10 (11.2)	10 (11.2)	14 (15.9)	14 (15.9)

- Overall, 29 patients died as a result of TEAEs (in 10 patients, the event was listed as ‘disease progression’ or ‘death’)
  - 7 deaths were considered possibly related to study treatment[†]

* TEAEs in > 11% of patients (cabazitaxel group, all-grade). TEAE, treatment-emergent adverse event. Red box represents TEAE of interest.
[†] TEAEs leading to death and considered possibly related to treatment included neutropenic infection (n = 3), febrile neutropenia (n = 2), neutropenic sepsis (n = 1) and cardiopulmonary failure (n = 1).

Most frequently reported TEAEs regardless of relationship to study treatment: subgroups

TEAEs*	Chemorefractory (n = 88)				Chemosensitive (n = 89)			
	Cabazitaxel (n = 45)		Topotecan (n = 43)		Cabazitaxel (n = 44)		Topotecan (n = 45)	
	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3
Any TEAE	40 (88.9)	29 (64.4)	39 (90.7)	31 (72.1)	39 (88.6)	23 (52.3)	44 (97.8)	32 (71.1)
Fatigue	15 (33.3)	4 (8.9)	8 (18.6)	3 (7.0)	11 (25.0)	3 (6.8)	14 (31.1)	4 (8.9)
Diarrhoea	7 (15.6)	0	3 (7.0)	0	10 (22.7)	2 (4.5)	6 (13.3)	0
Decreased appetite	8 (17.8)	1 (2.2)	5 (11.6)	1 (2.3)	8 (18.2)	1 (2.3)	8 (17.8)	0
Vomiting	7 (15.6)	0	2 (4.7)	0	9 (20.5)	1 (2.3)	5 (11.1)	0
Nausea	5 (11.1)	1 (2.2)	4 (9.3)	0	9 (20.5)	1 (2.3)	7 (15.6)	0
Asthenia	10 (22.2)	2 (4.4)	8 (18.6)	5 (11.6)	1 (2.3%)	0	10 (22.2)	2 (4.4)
Abdominal pain	4 (8.9)	0	0	0	6 (13.6)	2 (4.5)	3 (6.7)	0
Cough	7 (15.6)	1 (2.2)	2 (4.7)	0	3 (6.8)	0	6 (13.3)	0
Febrile neutropenia	6 (13.3)	6 (13.3)	7 (16.3)	7 (16.3)	4 (9.1)	4 (9.1)	7 (15.6)	7 (15.6)

* TEAEs in > 11% of patients (cabazitaxel group, **total** safety population, all-grade TEAEs). TEAE, treatment-emergent adverse event.

Red box represents TEAE of interest.

Haematological abnormalities*: safety population

Laboratory abnormality	Cabazitaxel (n = 88)		Topotecan (n = 88)	
	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3
Anaemia	83 (94.3)	3 (3.4)	87 (98.9)	23 (26.1)
Leukopenia	70 (79.5)	46 (52.3)	82 (93.2)	57 (64.8)
Neutropenia	60 (68.2)	50 (56.8)	77 (87.5)	69 (78.4)
Lymphopenia	68 (77.3)	34 (38.6)	63 (71.6)	28 (31.8)
Thrombocytopenia	52 (59.1)	4 (4.5)	81 (92.0)	40 (45.5)

Haematological abnormalities*: subgroups

Laboratory abnormality	Chemorefractory				Chemosensitive			
	Cabazitaxel (n = 45)		Topotecan (n = 43)		Cabazitaxel (n = 44)		Topotecan (n = 45)	
	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3
Anaemia	41 (93.2)†	0†	42 (97.7)	7 (16.3)	42 (95.5)	3 (6.8)	45 (100)	16 (35.6)
Leukopenia	35 (79.5)†	22 (50.0)†	38 (88.4)	21 (48.8)	35 (79.5)	24 (54.5)	44 (97.8)	36 (80.0)
Neutropenia	28 (62.2)	23 (51.1)	35 (81.4)	31 (72.1)	32 (74.4)‡	27 (62.8)‡	42 (93.3)	38 (84.4)
Lymphopenia	38 (84.4)	17 (37.8)	27 (62.8)	7 (16.3)	30 (69.8)‡	17 (39.5)‡	36 (80.0)	21 (46.7)
Thrombocytopenia	25 (56.8)†	0†	40 (93.0)	14 (32.6)	27 (61.4)	4 (9.1)	41 (91.1)	26 (57.8)

* Based on laboratory abnormalities. † n = 44. ‡ n = 43. TEAE, treatment-emergent adverse event. Red boxes represent TEAEs of interest.

Conclusions

- In the late 1990s, randomized studies of topotecan demonstrated efficacy in the treatment of relapsed SCLC[1,2]
  - No other agent has since shown superior clinical activity
- Cabazitaxel did not demonstrate an improved PFS vs topotecan in patients with SCLC that had progressed during or after first-line platinum-based chemotherapy
- The reported safety profile is consistent with previous cabazitaxel studies and no new safety concerns were identified[3–7]

1. Ardizzoni A *et al*. *J Clin Oncol* 1997; **15**:2090–2096;
2. Von Pawel *et al. J Clin Oncol* 1999; **17**:658–667;
3. de Bono JS *et al*. *Lancet* 2010; **376**:1147–1154;
4. Dieras V, *et al*. *Eur J Cancer* 2013; **49**:25–34;
5. Fumoleau P, *et al*. *BMC Cancer* 2013; **13**:460;
6. Mita AC, *et al*. *Clin Cancer Res* 2009; **15**:723–730;
7. Pivot X *et al*. *Ann Oncol* 2008; **19**:1547–1552.

PFS, progression-free survival; SCLC, small-cell lung cancer.

Acknowledgements

- The authors would like to thank participating patients and their families
- The authors would also like to thank the study investigators, research coordinators and study sites
- The study was sponsored by Sanofi
- Statistical analyses were performed by Laurent Kassalow, Sanofi
- The authors received editorial support from Paul Scutt of MediTech Media, funded by Sanofi

Questions?

Back-up

TEAEs leading to death

- Overall 29 patients died as a result of TEAEs (in 10 patients, the event was listed as ‘disease progression’ or ‘death’)
  - 7 deaths were considered possibly related to study treatment

- TEAEs leading to death and considered possibly related to treatment included neutropenic infection (n = 3), febrile neutropenia (n = 2), neutropenic sepsis (n = 1) and cardiopulmonary failure (n = 1).

- Treatment-related TEAEs leading to death per treatment arm:
  - Cabazitaxel/chemosensitive patients: neutropenic sepsis (n = 1)
  - Cabazitaxel/chemorefractory patients: neutropenic infection (n = 2)
  - Topotecan/chemosensitive patients: febrile neutropenia (n = 1), neutropenic infection (n = 1)
  - Topotecan/chemorefractory patients: febrile neutropenia (n = 1), cardiopulmonary failure (n = 1)