Small cell lung cancer and mesothelioma:
New drugs - 1519PD, 1520PD and 1522PD

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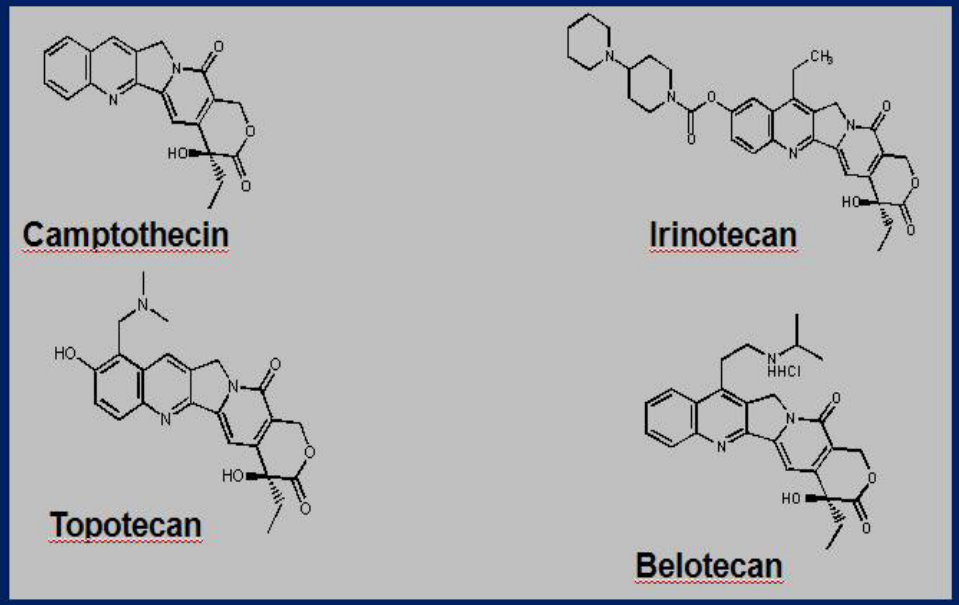
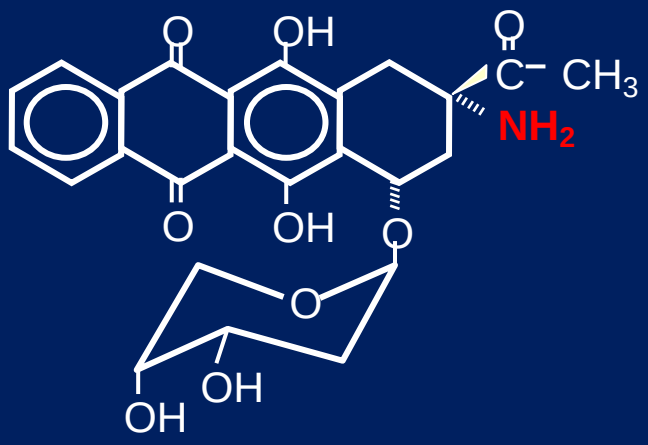
Cytotoxics

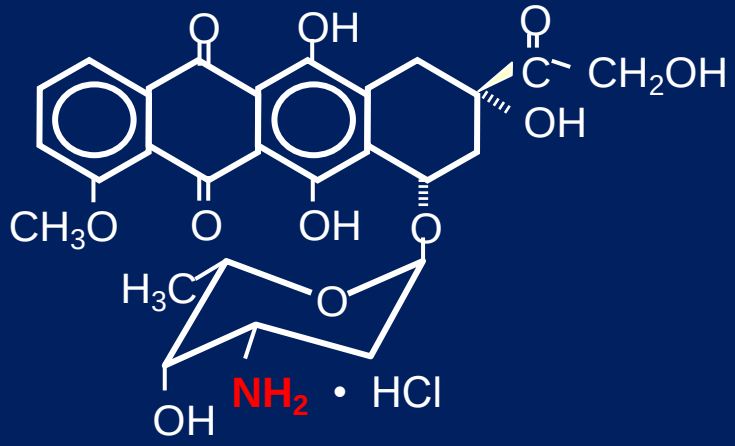
- Irinotecan – topo 1 inhibitor
- Topotecan – topo 1 inhibitor
- Belotecan - topo 1 inhibitor
- Amrubicin – topo 2 inhibitor



Amrubicin (AMR)



Doxorubicin (DXR)



Phase II/III studies of combination chemotherapy in patients with ED-SCLC

Author		n	Experimental regimen		Standard regimen	Outcomes **OS mths – sign**		
Noda *et al*, 2002		**154**	Irinotecan / cisplatin	**I: 60 mg/m^2 day 1, 8, 15** **P: 60 mg/m^2 day 1; q4w**	**E: 100 mg/m^2 day 1, 2, 3** **P: 80 mg/m^2 day 1; q3w**	**12.8** **9.4**	**+ve**	
Hanna *et al*, 2006a		**331**		**I: 65 mg/m^2 day 1, 8** **P: 30 mg/m^2 day 1, 8; q3w**	**E: 120 mg/m^2 day 1,2,3** **P: 60 mg/m^2 day 1; q3w**	**9.3** **10.2**	**NS**	
Lara *et al*, 2009		**641**		**I: 60 mg/m^2 day 1, 8, 15** **P: 60 mg/m^2 day 1; q4w**	**E: 100 mg/m^2 day 1,2,3** **P: 80 mg/m^2 day 1; q3w**	**9.9** **9.1**	**NS**	
Hermes *et al*, 2008		**220**	Irinotecan / carboplati	**I: 175 mg/m^2 day 1** **Ca: AUC 4 day 1; q3w**	**E: 120 mg/m^2 orally day 1–5** **Ca: AUC 4 day 1; q3w**	**8.5** **7.1**	**+ve**	

Pharmacogenomics diarrhoea and neutropenia – UGT 1A1 metabolic enzyme uridine-diphosphate glucuronosyltransferase

Phase II/III studies of combination chemotherapy in patients with ED-SCLC

Author		n	Experimental regimen		Standard regimen	Outcomes **OS mths – sign**		
Heigener *et al*, 2008		**795**	Topotecan/ cisplatin	**T: 1 mg/m^2 day 1–5** **P: 75 mg/m^2 day 5; q3w**	**E: 100 mg/m^2 day 1, 2, 3** **P: 75 mg/m^2 day 1; q3w**	**10.3** **9.4**	**Non inferi**	
Eckardt *et al*, 2006		**784**		**T: 1.7 mg/m^2 oral day 1–5** **P: 60 mg/m^2 day 5; q3w**	**E: 100 mg/m^2 day 1, 2, 3** **P: 80 mg/m^2 day 1; q 3w**	**9.8** **10.1**	**Non inferi**	

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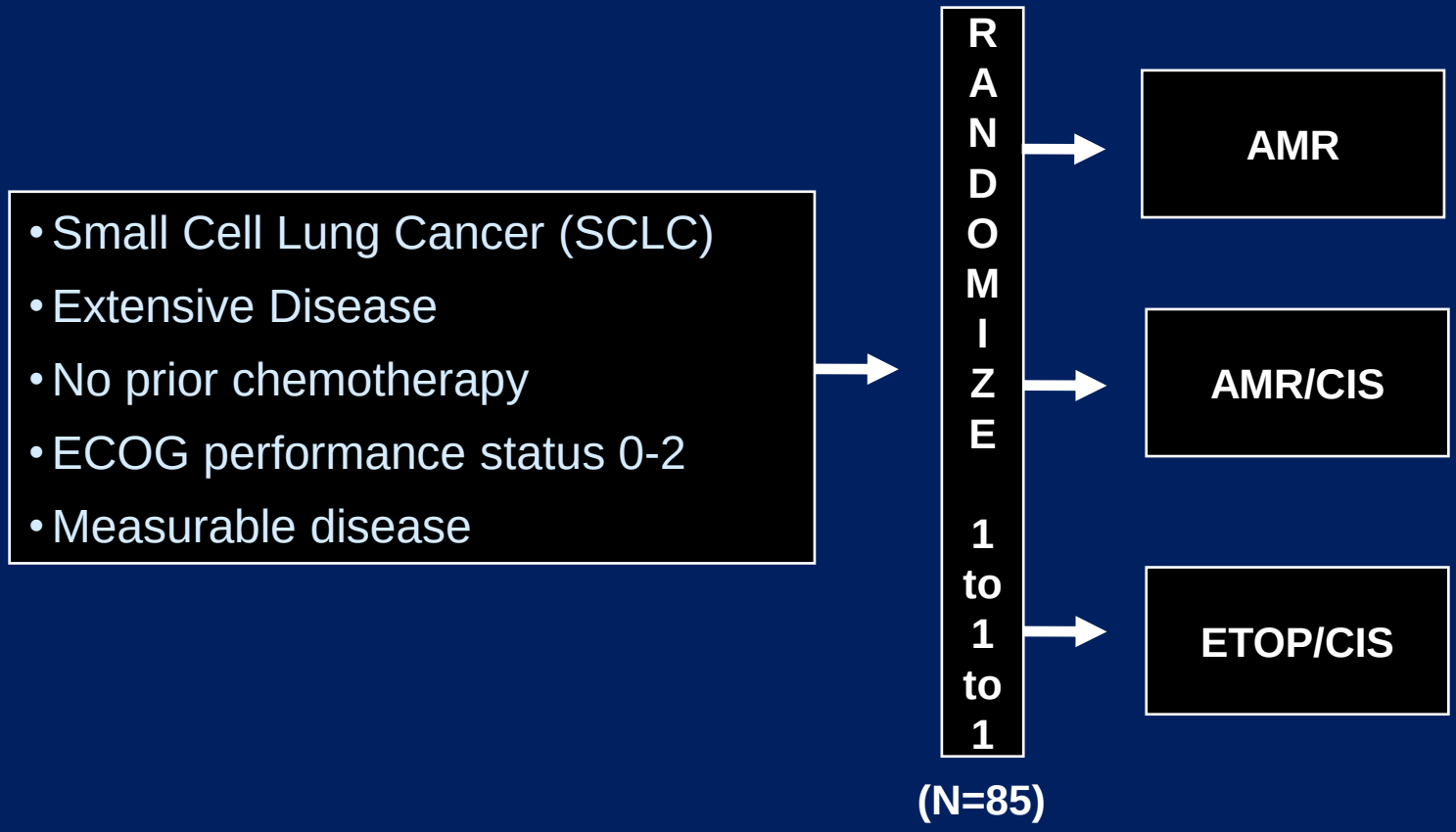
Heigener *et al*, 2008		**795**	Topotecan/ cisplatin	**T: 1 mg/m^2 day 1–5** **P: 75 mg/m^2 day 5; q3w**	**E: 100 mg/m^2 day 1, 2, 3** **P: 75 mg/m^2 day 1; q3w**	**10.3** **9.4**	**Non inferi**	
Eckardt *et al*, 2006		**784**		**T: 1.7 mg/m^2 oral day 1–5** **P: 60 mg/m^2 day 5; q3w**	**E: 100 mg/m^2 day 1, 2, 3** **P: 80 mg/m^2 day 1; q 3w**	**9.8** **10.1**	**Non inferi**	
Kim et al 2012		**129**		**B: 0.5mg/sq.m x 4 days** **P: 60 mg/sq.m**	**E: 100 x 3** **P 60**	**RR 66 v 54%** **OS 16.1 v 11.3mth***		

***more anaemia and thrombocytopenia**

EORTC 08062 – Phase 2 1st Line SCLC



Primary endpoint: Overall Response Rate

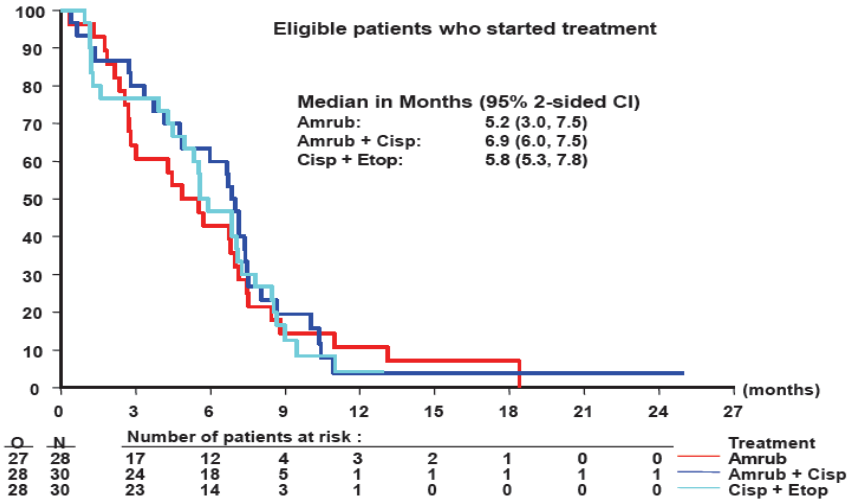
Participating Countries: UK, Netherlands, Poland, Belgium, Italy

Status: 98 enrolled

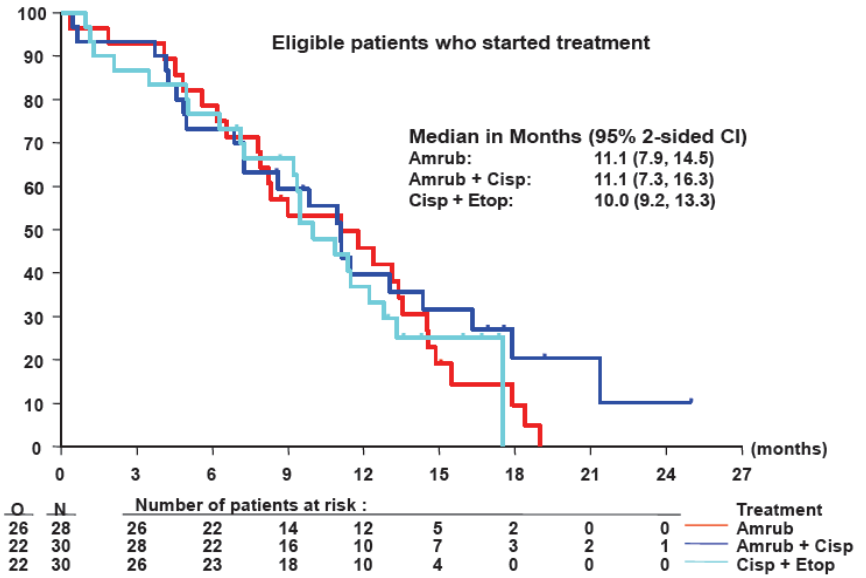
Results

	Amrubicin	amr/cis	cis/etop
N=	33	33	33
No courses	6	6	6
Range	1-22	1- 8	1-17
RR	61%	77%	62
G ¾ neutro	72%	74%	69%
FN	13%	15%	6%

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL

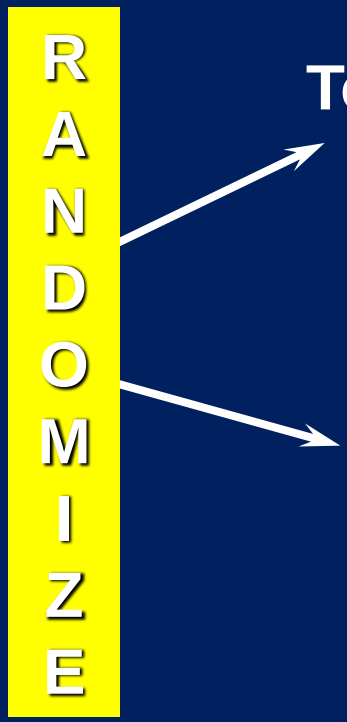


Second line - Study design

Open-Label, Randomized, Multicenter Phase III Trial

Stratification

- Gender
- PS (0/1 or 2)
- Presence of liver metastases at baseline
- TTP from end of prior chemo (≤ 60 or > 60 days)

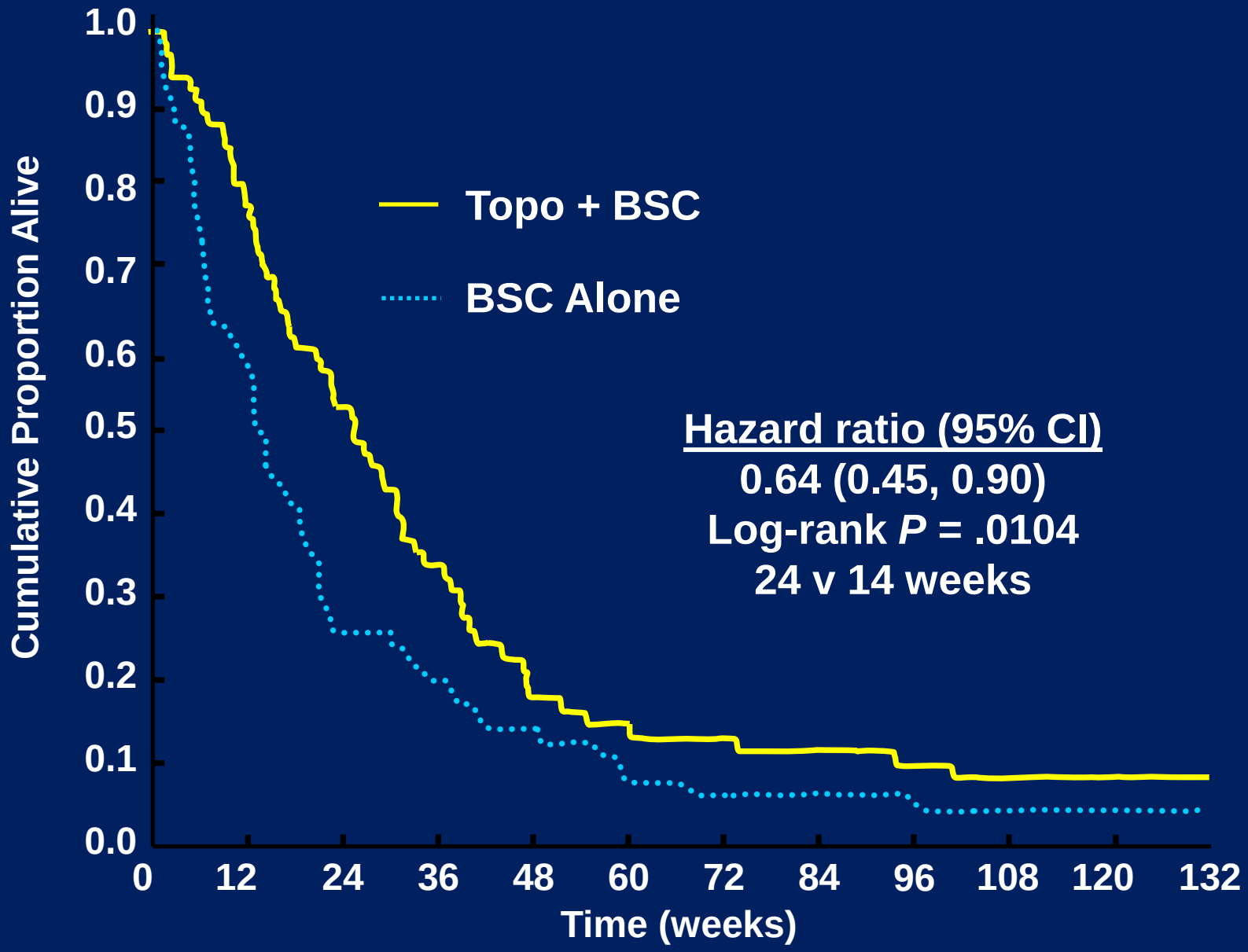


Topotecan 2.3 mg/m^2/day
PO days 1–5 + BSC
N=71

BSC alone
N=70

Cycles repeated q 21 d

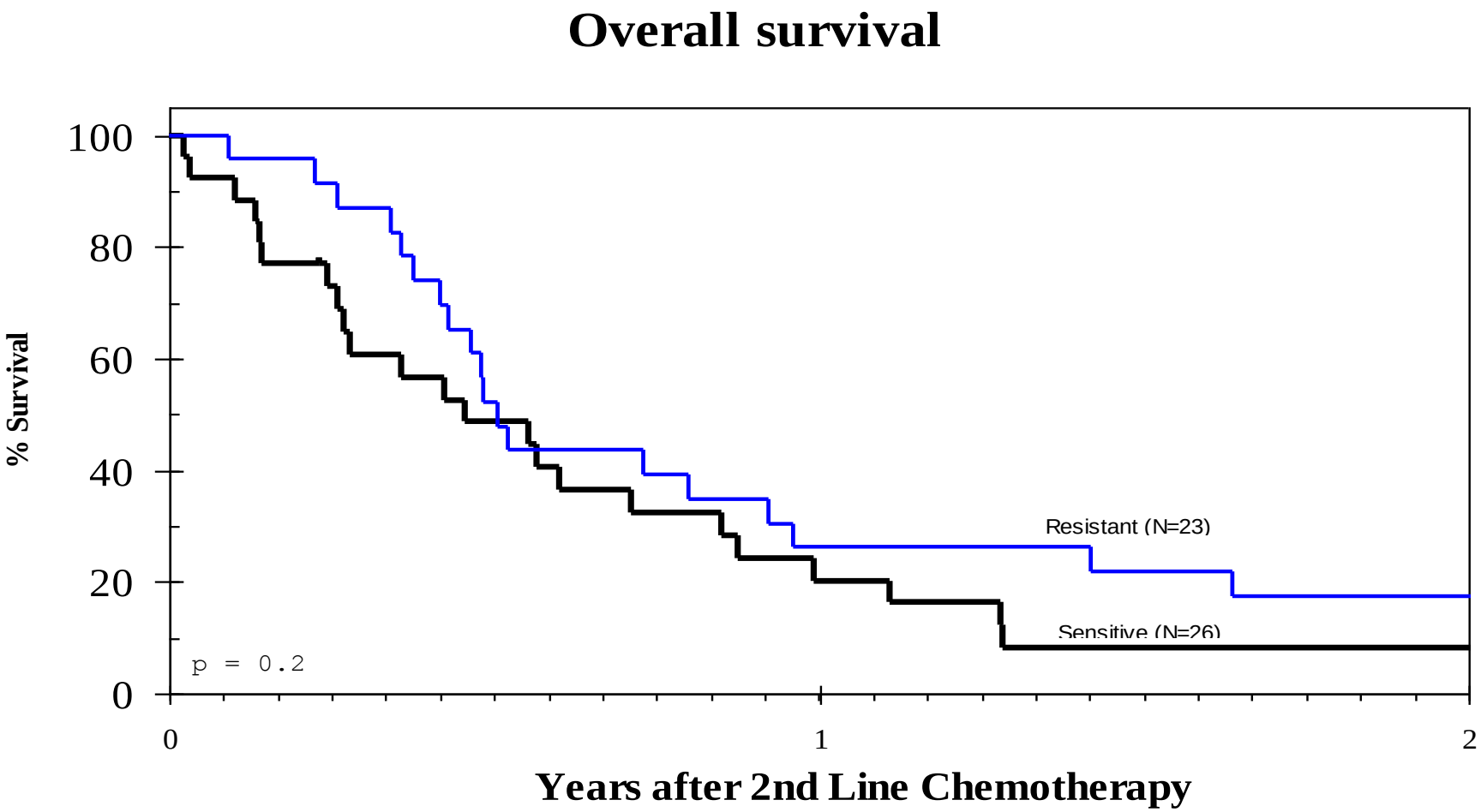
Overall survival (ITT)



Median survival (wk) (ITT)

Factor	Oral Topo + BSC n = 71	BSC Alone n = 70	Log-rank *P* Value
Intrinsic			
Female Median (95% CI)	n = 19 38.7 (16.3, 73.0)	n = 19 14.4 (6.6, 21.1)	.0173
Male Median (95% CI)	n = 52 23.3 (15.9, 29.3)	n = 51 13.3 (10.3, 19.7)	.2702
Extrinsic			
Performance Status 0/1 Median (95% CI)	n = 52 29.2 (21.6, 38.7)	n = 47 18.6 (13.1, 21.4)	.0968
Performance Status 2 *Median (95% CI)*	*n = 19* *20.9 (13.4, 26.9)*	*n = 23* *7.7 (5.3, 13.1)*	*.0146*
Liver metastases absent Median (95% CI)	n = 51 30.9 (23.3, 39.1)	n = 56 14.4 (12.7, 21.0)	.0071
Liver metastases present Median (95% CI)	n = 20 13.3 (9.4, 25.3)	n = 14 7.9 (3.4, 18.6)	.1674
Time to Progression ≤ 60 days *Median (95% CI)*	*n = 22* *23.3 (10.7, 30.9)*	*n = 20* *13.2 (7.0, 21.0)*	*.0357*
Time to Progression > 60 days Median (95% CI)	n = 49 27.7 (17.6, 34.4)	n = 50 14.4 (8.0, 21.1)	.0975

Oral topotecan a new chemotherapy for relapsed SCLC – and a new way of looking at relapse.. Terminology may only serve to support rechallenge with same agent and better prognosis



AMR Phase II trials in 2nd line - Summary

Author [ref]	Study population	Treatment	ORR / medPFS / medOS
Jotte JCO 2011	Sensitive N=76	AMR vs. TOPO	44% / 4.5mo / 9.2mo 13% / 3.3mo / 7.6mo
Ettinger JCO 2010	Refractory N=75	AMR	21% / 3.2mo / 6.0mo
Inoue JCO 2009	Refractory N=36 Sensitive N=23	AMR vs. TOPO	38% / 3.5mo / 8.1mo 13% / 2.2mo / 8.4mo
Onoda JCO 2006	Refractory N=16 Sensitive N=44	AMR	50% / 2.6mo / 10.3mo refr. 52% / 4.2mo / 11.6mo sens.

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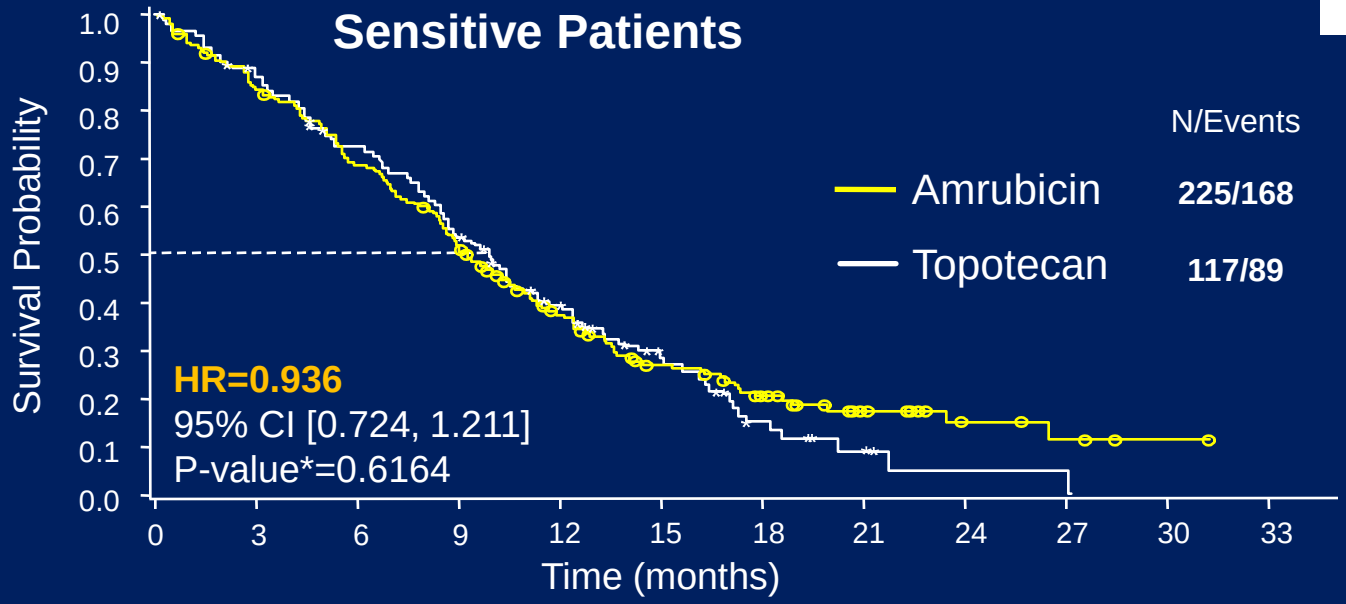
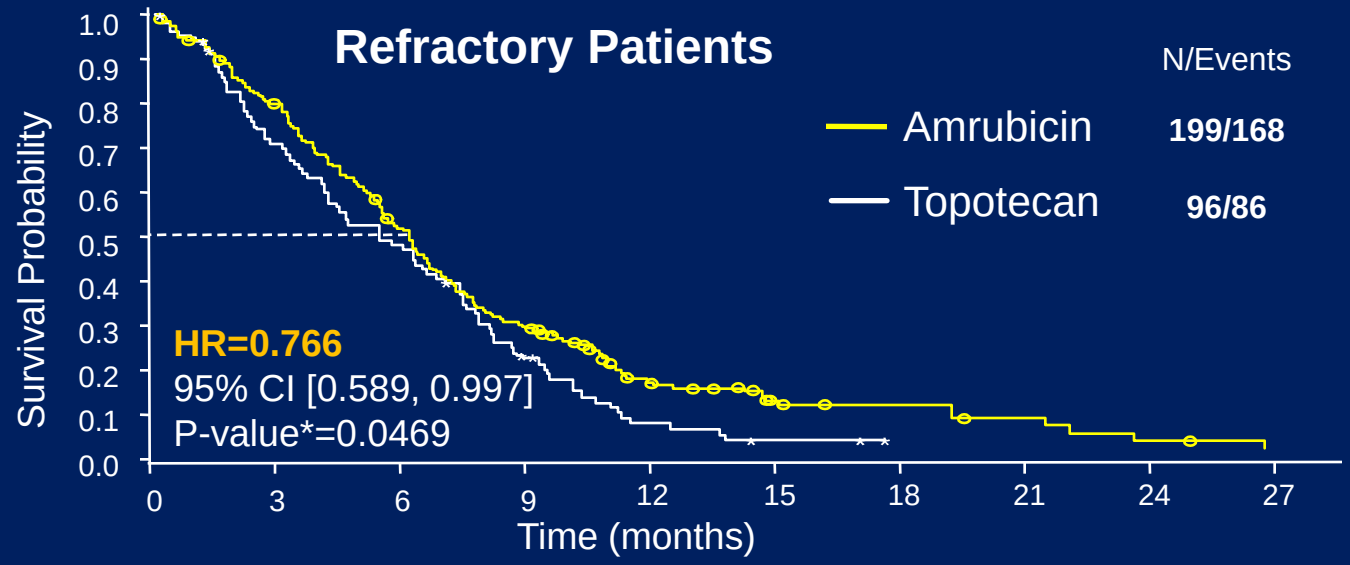
Daga et al 2012	Refractory n=82	AMR	32.9%/3.5 mo/8.9mo

Phase III 2nd line SCLC N~600



	N/Events	Median OS	95% CI
Amrubicin	**225/168**	**9.2 months**	**8.5-10.6**
Topotecan	**117/89**	**9.9 months**	**8.5-11.5**

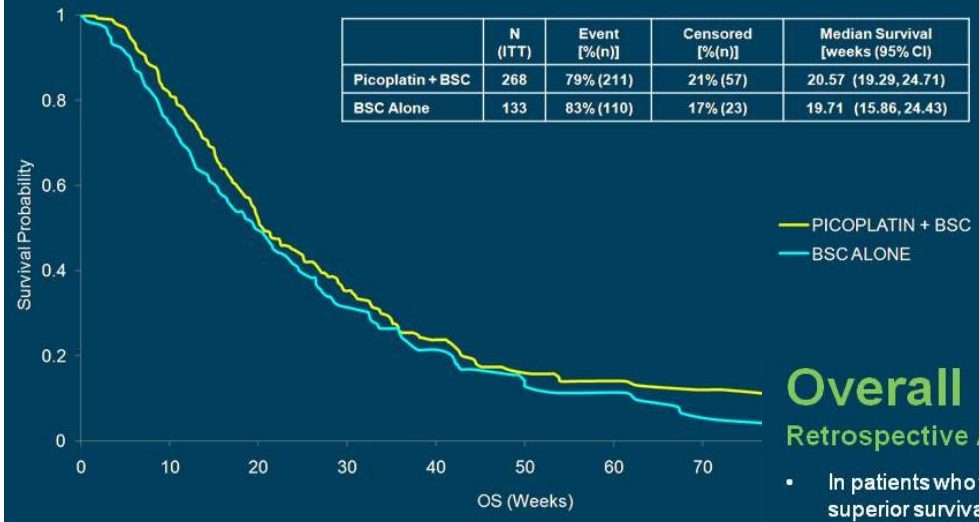


	N/Events	Median OS	95% CI
Amrubicin	**199/168**	**6.2 months**	**5.5-6.7**
Topotecan	**96/86**	**5.7 months**	**4.1-7.0**

* Unstratified log-rank test

Overall Survival

	N (ITT)	Event [%(n)]	Censored [%(n)]	Median Survival [weeks (95% CI)]
Picoplatin + BSC	268	79% (211)	21% (57)	20.57 (19.29, 24.71)
BSC Alone	133	83% (110)	17% (23)	19.71 (15.86, 24.43)



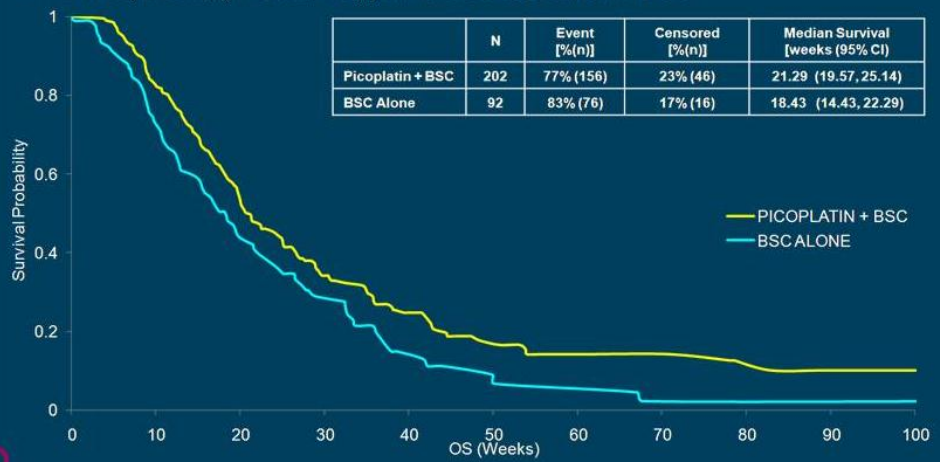
- Stratified log-rank p-value: 0.0895; Hazard Ratio= 0.817 (CI (

Overall Survival

Retrospective Analysis #2: Refractory or Relapsed within 45 Days (n= 294)

- In patients who were refractory or relapsed within 45 days, the picoplatin arm showed significantly superior survival
- Use of post-study chemotherapy was balanced across both arms

	N	Event [%(n)]	Censored [%(n)]	Median Survival [weeks (95% CI)]
Picoplatin + BSC	202	77% (156)	23% (46)	21.29 (19.57, 25.14)
BSC Alone	92	83% (76)	17% (16)	18.43 (14.43, 22.29)



Phase II study of amrubicin in patients with refractory or resistant relapsed small-cell lung cancer: Japan Clinical Oncology Group study (JCOG0901)

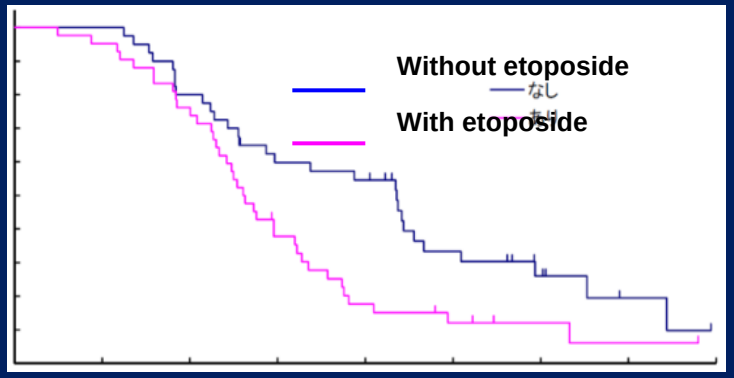
H. Daga, H. Murakami, N. Yamamoto, T. Shibata, M. Endo, H. Watanabe, Y. Ichinose, N. Yamamoto, Y. Ohe, T. Tamura
Lung Cancer Study Group of Japan Clinical Oncology Group (JCOG), Japan

#1519
PD

- **The hypothesis of this study is that if the response rate of amrubicin is high enough compared with topotecan, amrubicin will be a standard treatment.**

			RR	
Previously treated with irinotecan	No	35	25.7	0.25
	Yes	47	38.3	
Previously treated with etoposide	No	40	45.0	0.034
	Yes	42	21.4	
Response to previous chemotherapy	CR, PR	61	36.1	0.42
	SD, PD	21	23.8	

OS: previously treated with or without etoposide



	With etoposide (n = 42)	Without etoposide (n = 40)
Median	7.9 months	13.1 months
(95% CI)	(6.9-9.6)	(7.7-14.0)

HR (95% CI) = 1.86 (1.13-3.06), $p = 0.0128^{\#}$

7003: A phase III study comparing amrubicin and cisplatin (AP) with irinotecan and cisplatin (IP) for the treatment of extended-stage small cell lung cancer (ED-SCLC): JCOG0509 – *Kotani Y et al*

- **aged 20 to 70, and ECOG PS 0–1: IP: I (60 mg/m^2) iv on days 1, 8, and 15, and P (60 mg/m^2) iv on day 1, every 4 weeks; or AP: A (40 mg/m^2) iv on day 1–3, and P (60 mg/m^2) iv on day 1, every 3 weeks**
  - **initial dose of A decreased from 40 to 35 mg/m^2 due to increased FN**

Study endpoints:	AP n=142	IP n=142
median OS	**15.0**	**18.3 m ***
HR (1.41; 96.3% CI, 1.03-1.93)		
Median PFS	**5.2**	**5.7 m**
(HR 1.43, 95% CI, 1.13-1.82)		
RR was	**77.9%**	**69.5% p=0.14**
Grade 4 neutropenia	**78.6%**	**22.5%**
G3-4 FN	**32.1**	**10.7%**
G3-4 diarrhea	**1.4%**	**7.1%**

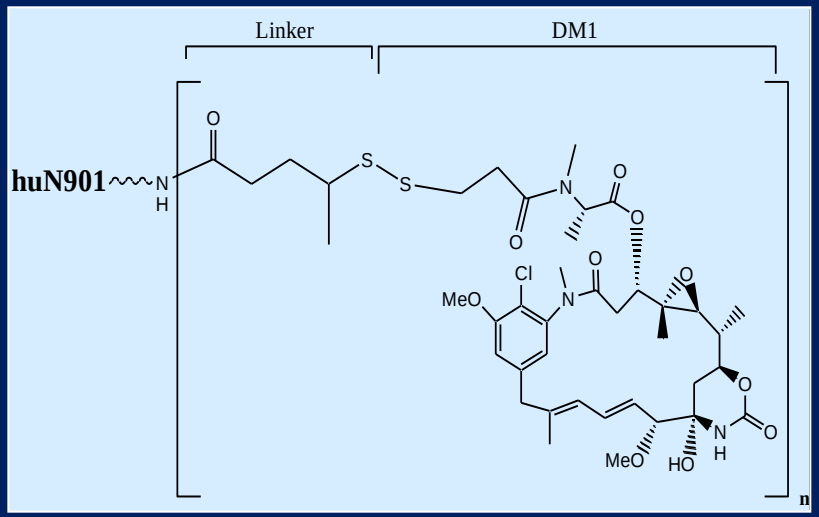
***>50% received secondline amrubicin**

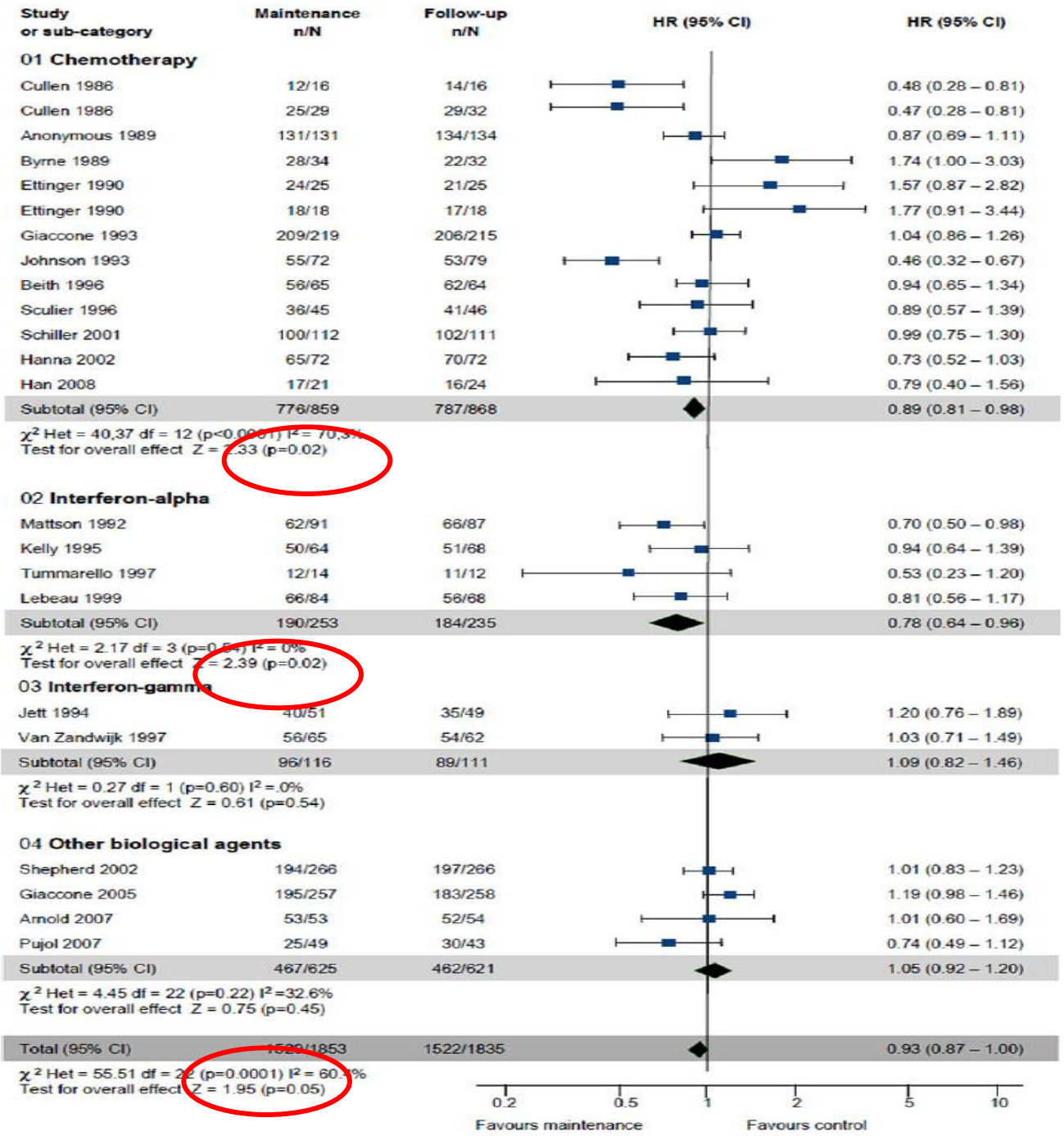
Kotani et al. J Clin Oncol 30, 2012 (suppl; abstr 7003)

Ongoing studies

- Pravastatin may stop the growth of tumour cells and make tumour cells more sensitive to chemotherapy – phase III in UK
- enoxaparin in SCLC (Fragmatic)
- Chemo +/- bev IFCT-0802 French Phase II/III: recruiting
- NGR-hTNF in Combination With Doxorubicin in Patients Affected by Metastatic Small Cell Lung Carcinoma (NGR007): MolMed
- Secondline +/- valproic acid
- CE + anti-NCAM

BB 10901 Immunogen





Maintenance chemotherapy

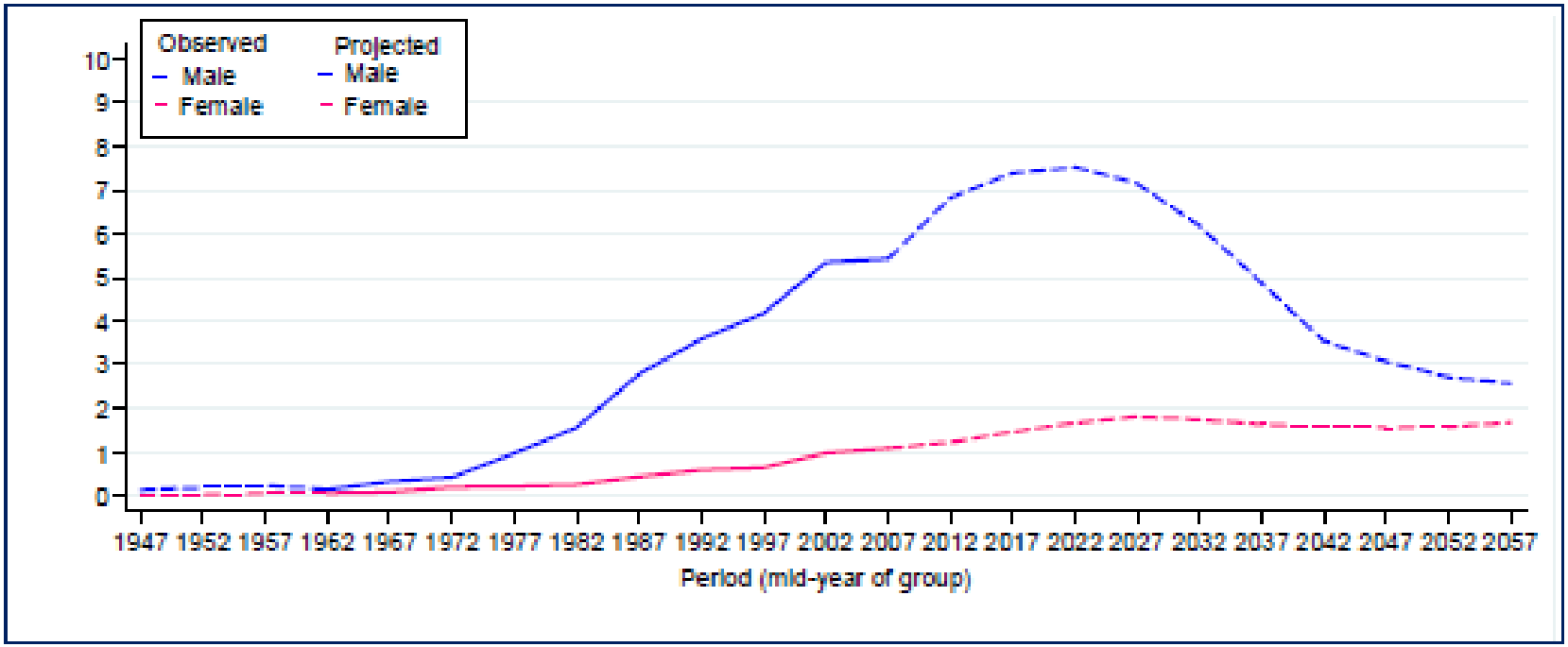
21 RCTs
PFS neg
OS +

Rossi et al

Genome analyses - 2012

- 29 SCLC exomes
- Inactivation of P53 and RB1
- Mutations in 3 genes encoding for histone modifiers
- PTEN mutations
- Focal amplifications of FGFR TK gene

Figure 6: Observed (thick lines) and predicted (dashed lines) age-standardised rates (per 100,000 European standard population) of mesothelioma, South East England, 1947-2057, by sex and period.



Data on chemotherapy in first line MM available to date:

	Nb patients	PS	RR (%)	TTP/PFS Mths	OS mths	1yr OS (%)
Pemetrexed/Cisplatin	456	**0-1**	**41.3%**	**5.7**	**12.1**	**47%**
Cisplatin alone			**16.7%**	**3.9**	**9.3**	**37%**
Raltitrexed/Cisplatin	250	**0-1/2**	**24.0%**	**5.6**	**11.2**	**45.5%**
Cisplatin alone			**14%**	**4.1**	**8.8**	**39.4%**
Bortezomib/Cisplatin	82	**0-2**	**27.4%**	**5.6**	**13.5**	**56%**

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Bortezomib/Cisplatin	82	**0-2**	**27.4%**	**5.6**	**13.5**	**56%**
AMATUXIMAB + pem cis	89		**39%**	**6.1**	**14.8**	

Was there any correlation with mesothelin expression?