

Small Cell Lung Cancer: Progress or Status Quo?

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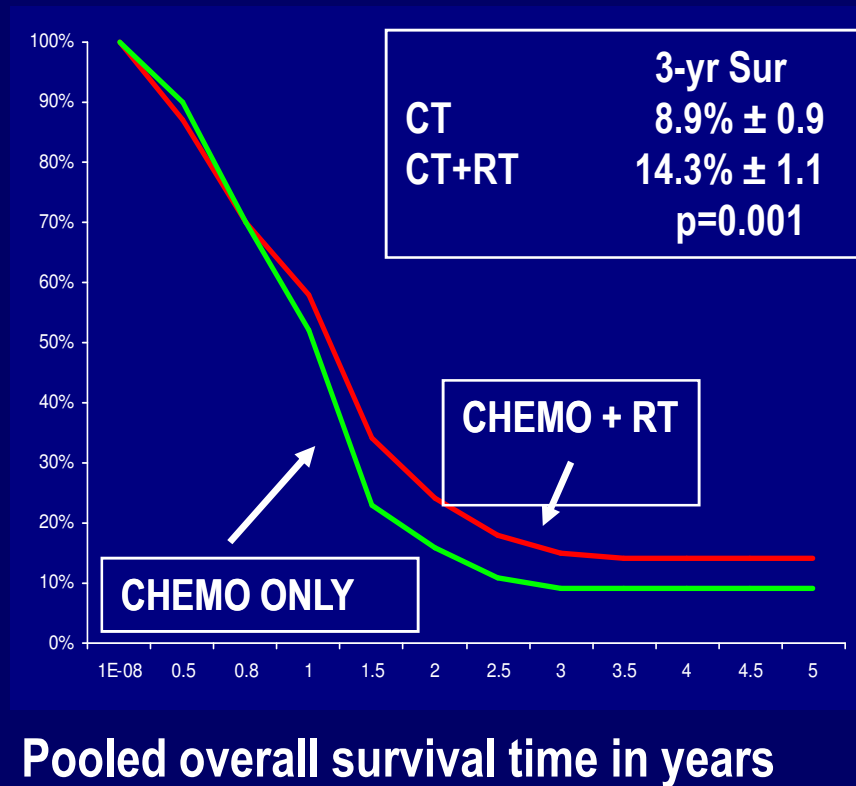
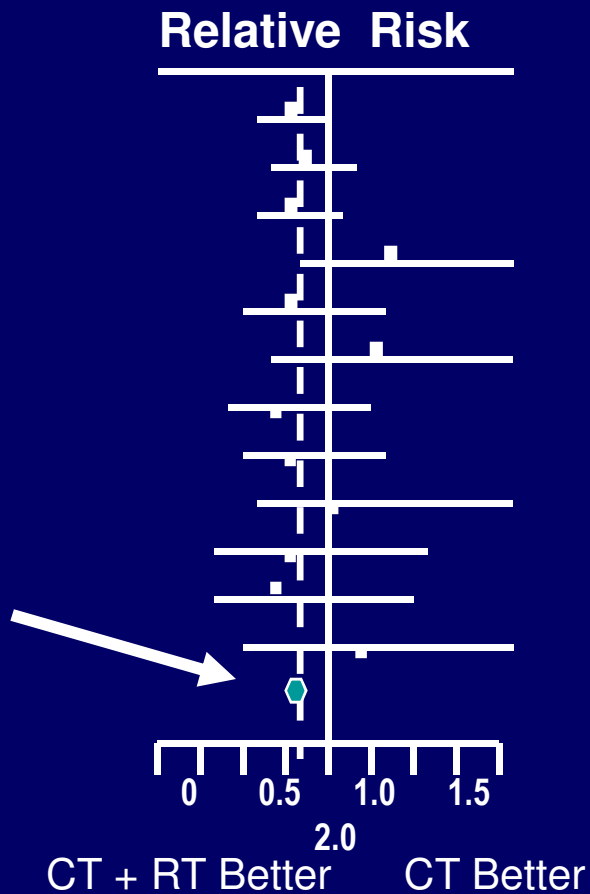
Depends how you define progress

SCLC: More than 1 disease

- Extremely chemotherapy sensitive
- Extremely chemotherapy resistant
- What are the biological differences?
- Many drugs are effective on chemotherapy sensitive cells
- No drugs are highly effective against the resistant clones
- Improved outcomes will come ONLY when we defeat the highly resistant clones

First, let's review the clinical data
and progress to date

Thoracic Irradiation for LS SCLC



2 meta-analysis of thoracic XRT in LS SCLC:

1. Pignon et al. – NEJM '92 : 3-year survival and prognostic factors
2. Warde and Payne – JCO '92: 2-year survival, local control and toxicity

Timing of Thoracic XRT in LD SCLC

Murray et al, JCO 1993;11:336-44

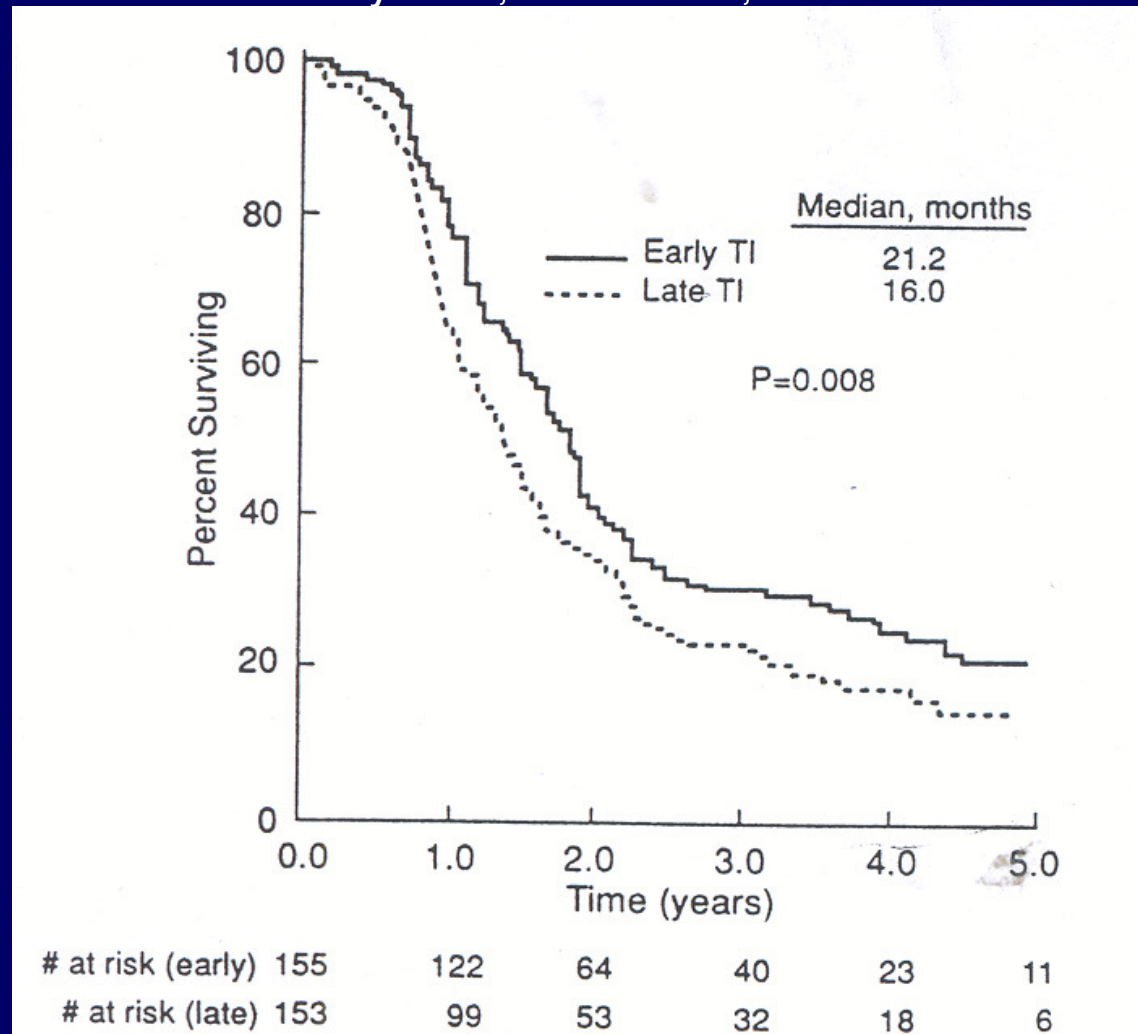


Fig 3. Overall survival: early TI v late TI.

Multivariate Analysis for Survival for Patients with LD SCLC

Giaccone et al, JCO 2005;23:6854-64

Table 5. Multivariate Analysis for Survival

Variable	Hazard Ratio	95% CI	<i>P</i>
Sex			.0066
Male	1		
Female	0.72	0.57 to 0.91	
Chest radiotherapy			.0051
Sequential	1		
Concomittant	0.72	0.57 to 0.91	
PCI			< .0001
No	1		
Yes	0.52	0.41 to 0.65	
Lactate dehydrogenase			.0002
Grade 0	1		
Grade > 0	1.71	1.30 to 2.26	
Platelets			.0019
< 221 10 ⁹ /L	1		
≥ 221 10 ⁹ /L	1.44	1.14 to 1.81	

Abbreviation: PCI, prophylactic cranial irradiation.

Timing of Thoracic XRT in LD SCLC

Fried et al, JCO 2004;22:4837-45

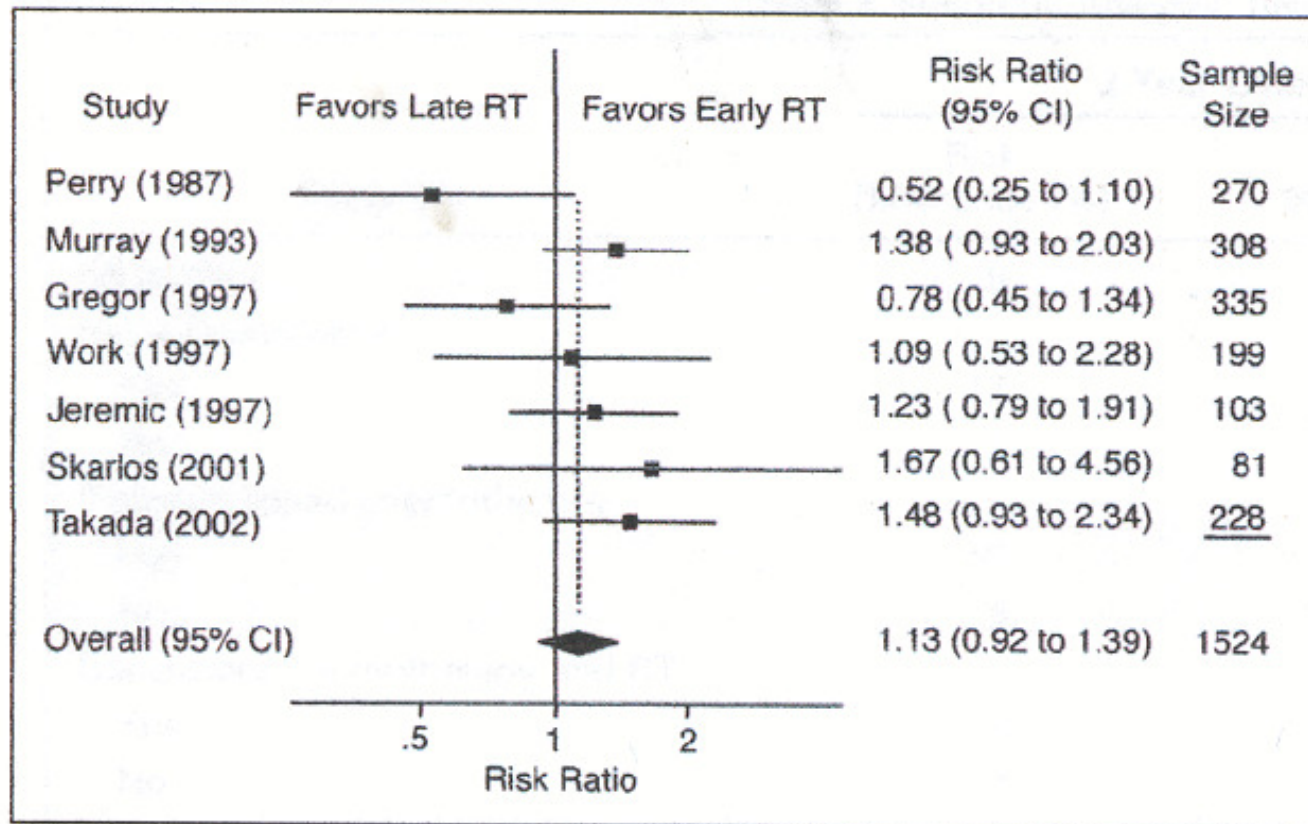
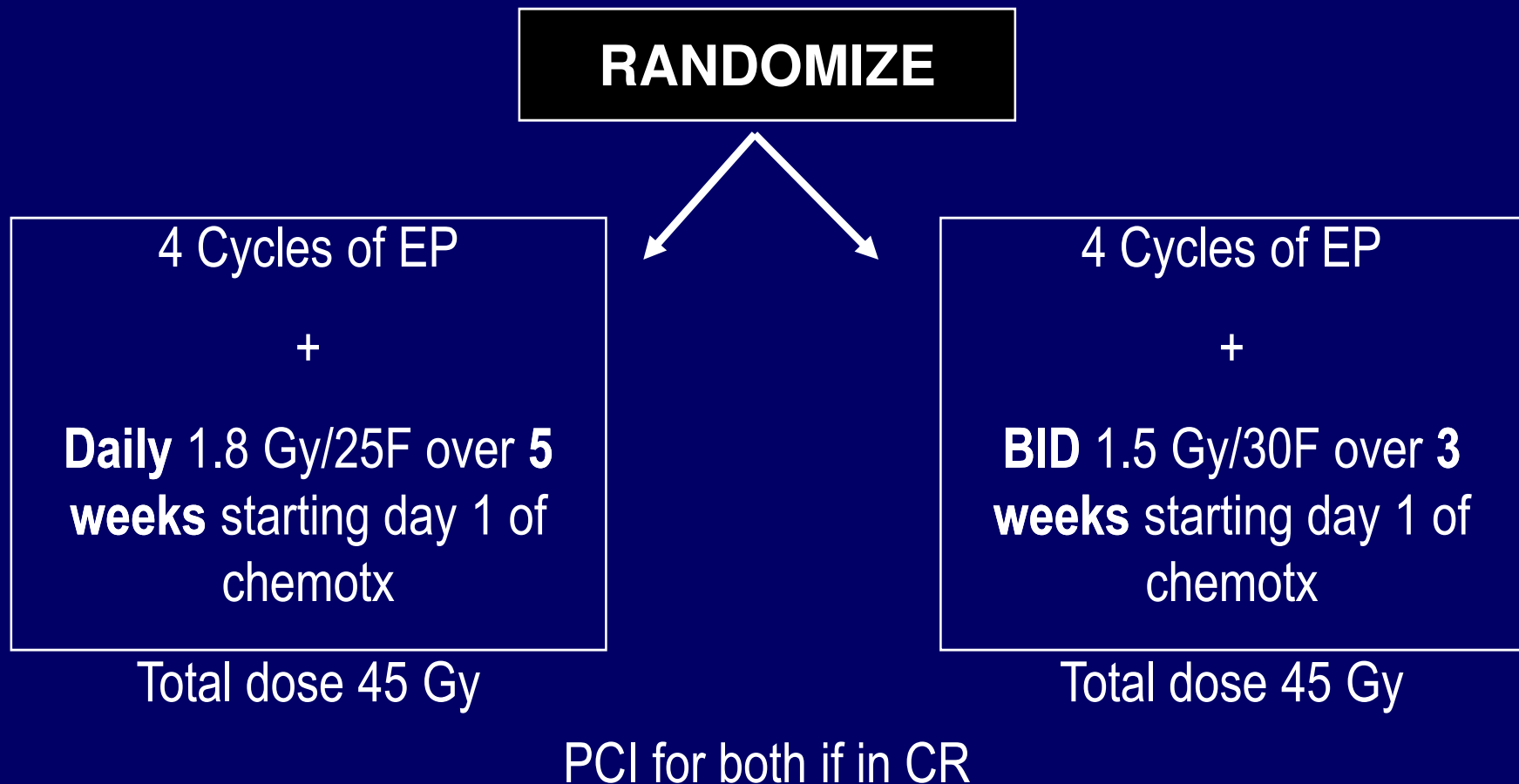


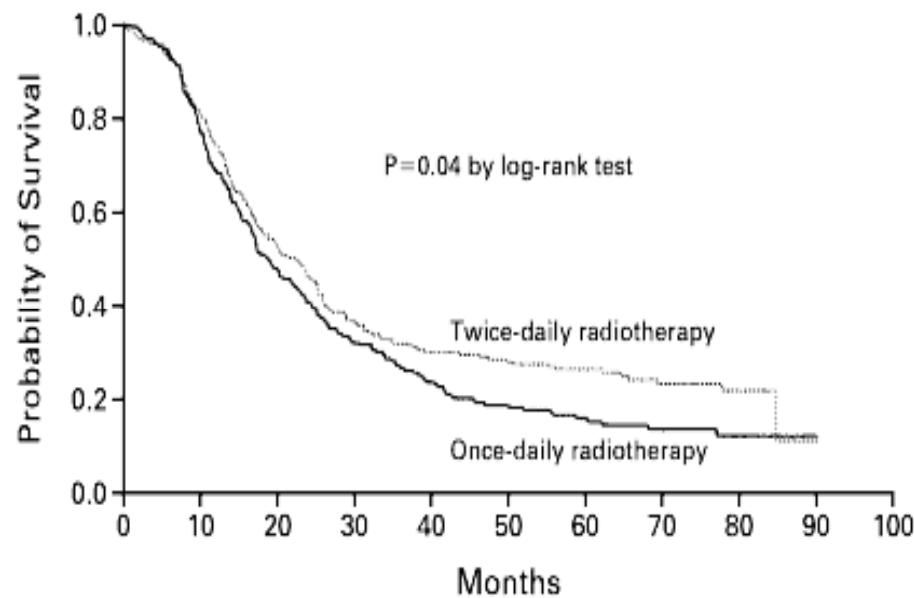
Fig 2. Three-year overall survival risk ratio forest plot for early v late thoracic radiation therapy (RT).

Turrisi et al: BID vs QD XRT in LS SCLC with Concurrent EP (*NEJM* 1999; 340(4):265-271)

N = 417 patients with LS SCLC



Hyperfractionated Radiotherapy Improves Survival



TREATMENT GROUP	0-20 Mo	20-40 Mo	40-60 Mo	60-80 Mo	80-100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

	2 year OS (%)	5 year OS (%)
QD XRT	41%	16%
BID XRT	47%	26%

Reduction in local failure:

36% vs 52%

Increased toxicity:

Grade 3 esophagitis

27% vs 11%

But no increase in mortality

Turrisi et al. NEJM 1999; 340(4):265-271

QD vs BID XRT in LD SCLC

Bonner et al, JCO 1999;17:2681-91

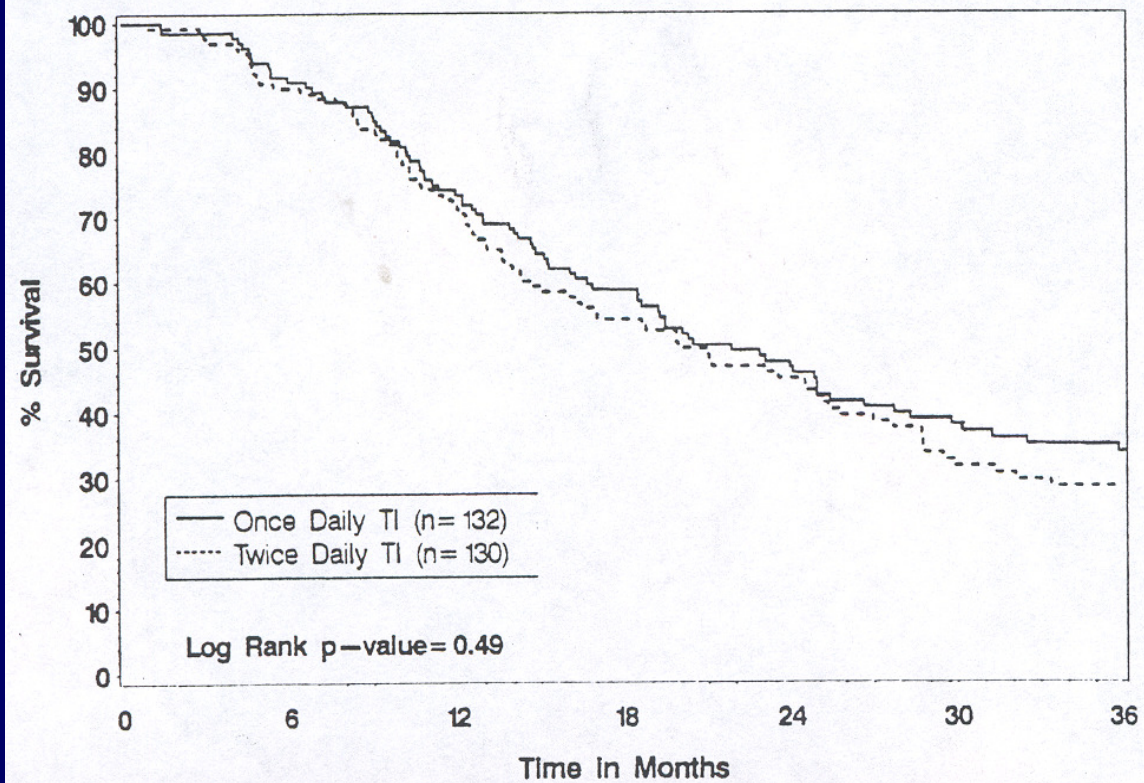


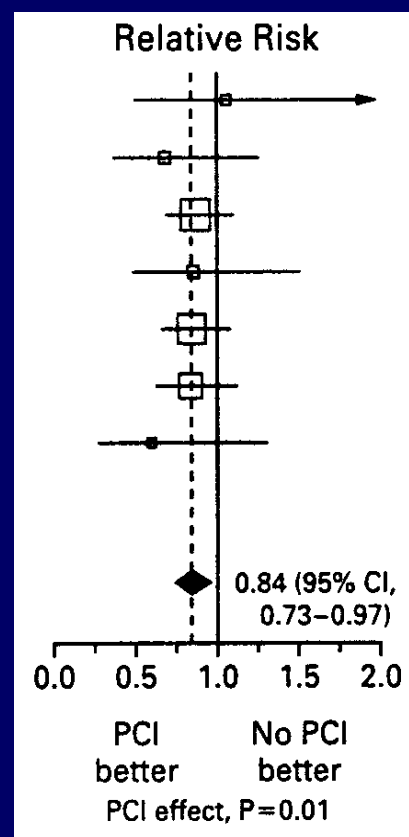
Fig 5. Overall survival with respect to treatment group.

Meta-Analysis of Prophylactic Cranial Irradiation

Auperin et al, NEJM, 1999

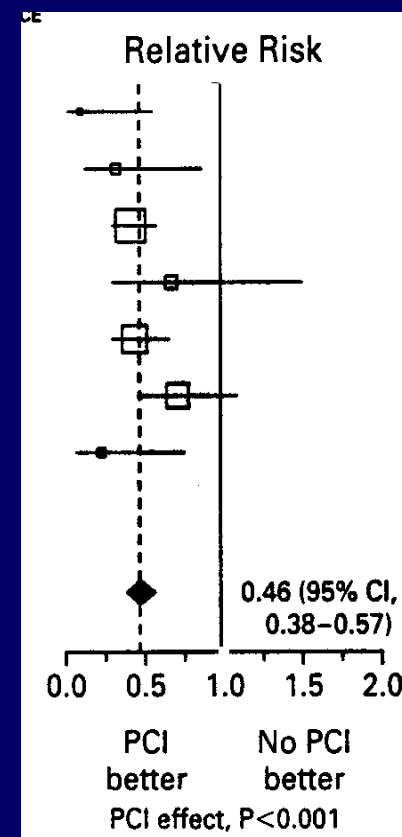
- 7 randomized trials, 987 pts with CR
- 5% increase in survival at 3 yrs
- Higher dose improved local recurrence but no effect on survival

Death



16% ↓ risk

Brain Mets



54% ↓ risk

Extensive Stage SCLC

Chute et al, JCO 1999;17:1794-1801

- 21 phase III trials 1972-1990
- Median survival on control arm from 1972-81 was 7 months
- Median survival on control arm from 1982-90 was 8.9 months

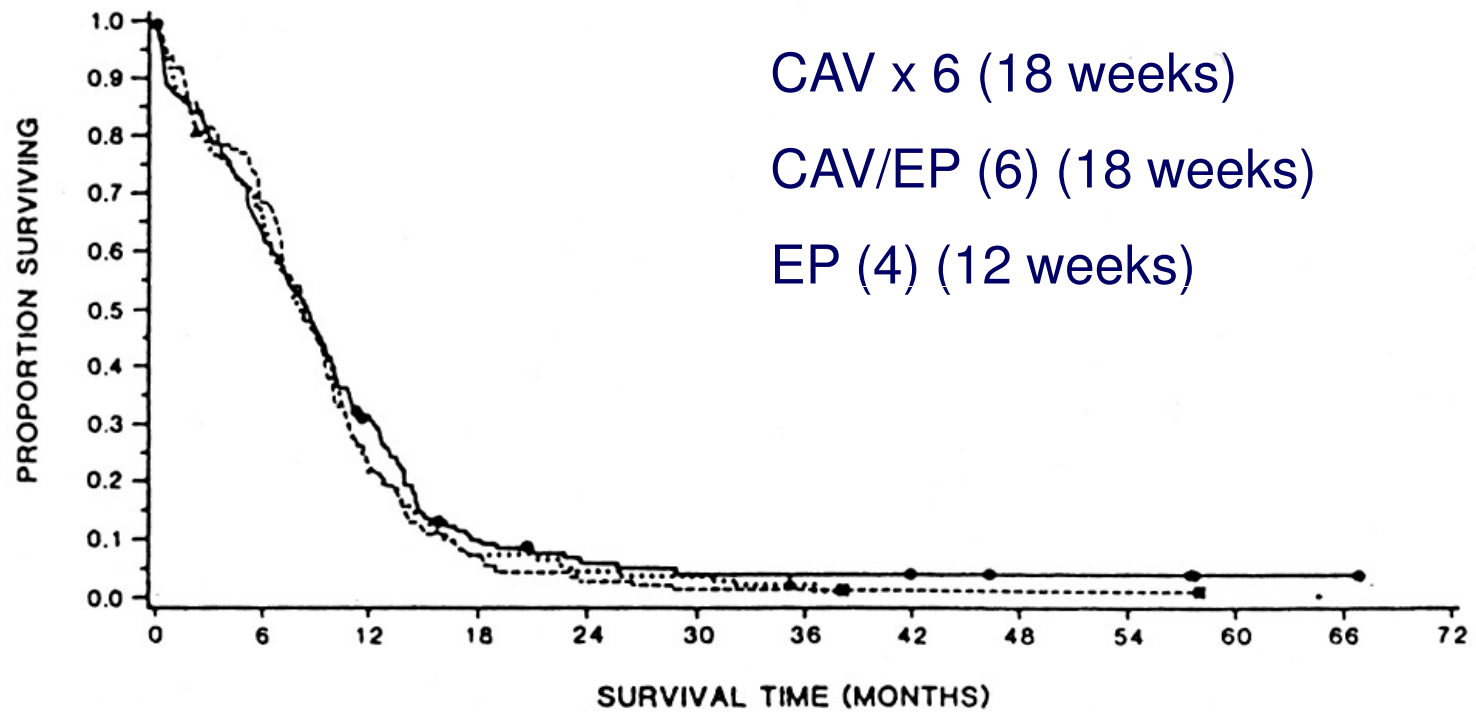
Combination Chemotherapy is Superior to Single Agent

- Cyclophosphamide vs. Cyclophosphamide plus doxorubicin plus DTIC
 - Improved survival for the combination
 - Lowenbraun et al, Cancer 1979;44:406-413
- Etoposide vs. PE/CAV
 - Improved survival for the combination
 - Souhami et al, JNCI 1997;89:577-80

Elderly or Poor PS Patients

- Elderly (age ≥ 70) treated with either:
 - Attenuated dose EP or Full dose EP
 - Primary endpoint is “therapeutic success”:
 - Activity, compliance, toxicity
 - Full dose superior
 - Ardizzoni A, et al. JCO 2005;23:569-75
- WHO PS 2-4
 - Oral etoposide twice daily X 10 days or combination IV chemo (EV or CAV)
 - Combination better
 - MRCLCWP, Lancet 1996;348:563-66

EP is the U.S. Standard



Roth B, et al. J Clin Oncol 1992;10:282-291

Carboplatin can be Substituted for Cisplatin

Okamoto et al, Abstract 7010, ASCO '05

- 220 elderly or poor risk patients randomized to etoposide with either:
 - Carbo AUC 5 d1
 - Cisplatin 25 mg/m² iv d1-3
- Similar toxicity profiles and efficacy
 - (MST ~10 mos; 1 yr 35-40%)

High Dose Therapy

Author	No.	Regimen	Survival
Johnson ¹	298	CAV: High vs Standard	No difference
Lowenbraun ²	293	High dose CAV vs CAVE	No difference
Ihde ³	90	EP: High vs Standard	No difference
Pujol ⁴	125	CEEP: High dose vs Standard	No difference

¹J Clin Oncol 1987;5:1731-1738; ²Cancer 1984;54:2344-2350

³J Clin Oncol 1994;12:2022-2034; ⁴J Clin Oncol 1997;15:2082-2089

Dose Dense (DD) Therapy

Author	No.	Regimen	Survival
Steward ¹	300	V-ICE q3wk vs 4wk	DD better
Thatcher ²	403	ACE q3wk vs 2wk	DD better
Sculier ³	233	EVI q3wk vs 2wk	Same
Lorigan ⁴	318	ICE q3wk vs 2wk	Same

¹J Clin Oncol 1998;16:642-650; ²J Clin Oncol 2000;18:395-404

³Br J Cancer 2001;85:1441-1451; ⁴JNCI 2005;97:666-674

Three or Four Drug Combinations

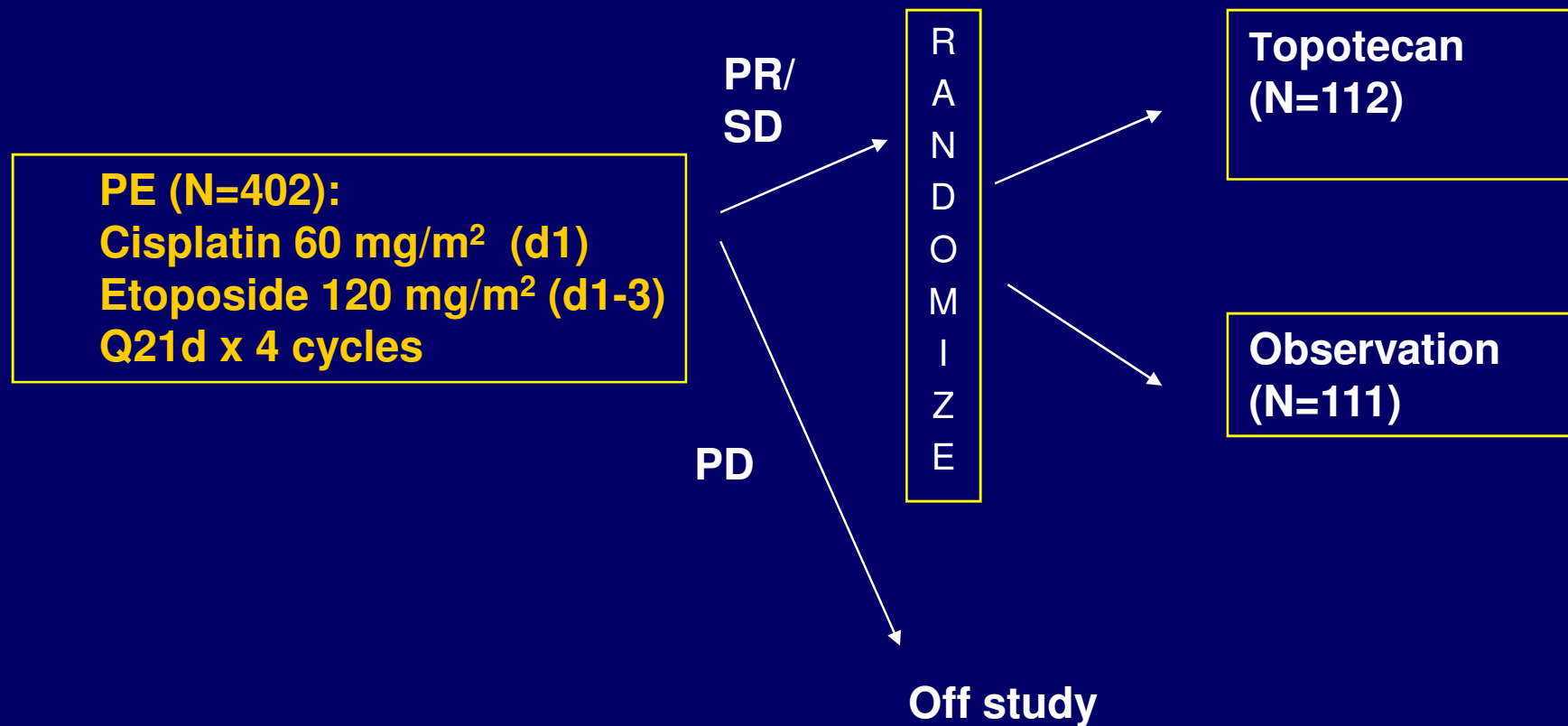
Author	No.	Regimen	Survival
Mavroudis ¹	133	EP vs PET	No difference
Niell ²	587	EP vs PET	No difference
Roth ³	437	EP vs CAV vs CAV/EP	No difference
Sundstrøm ⁴	436	EP vs CEV	EP better
Loehrer ⁵	171	EP vs VIP	VIP better
Pujol ⁶	226	EP vs PCDE	PCDE better

¹Ann Oncol 2001;12:463-470; ²J Clin Oncol 2005;23:3752-3759

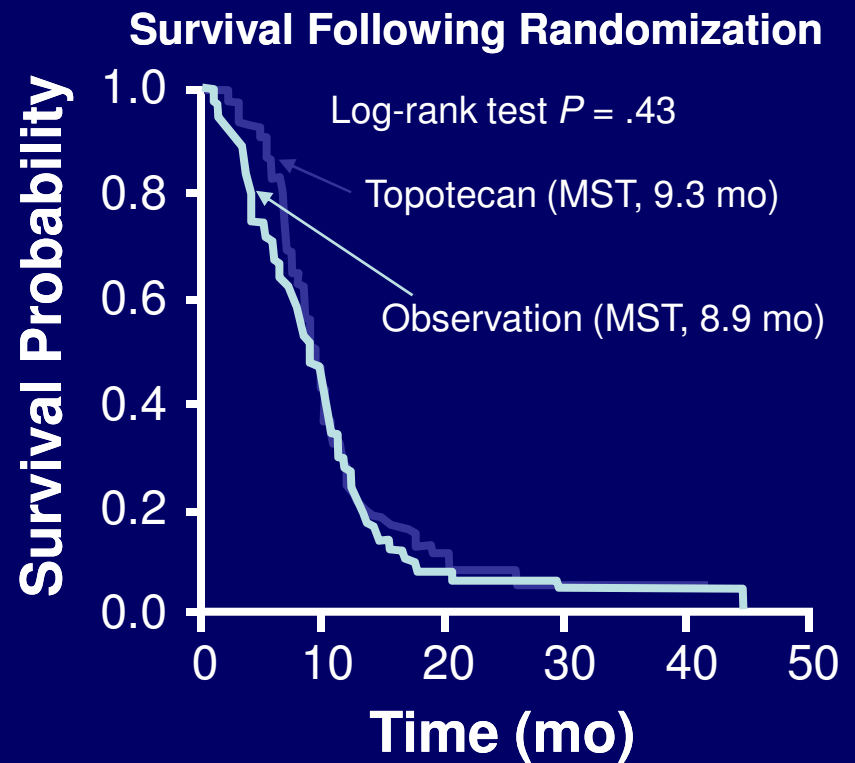
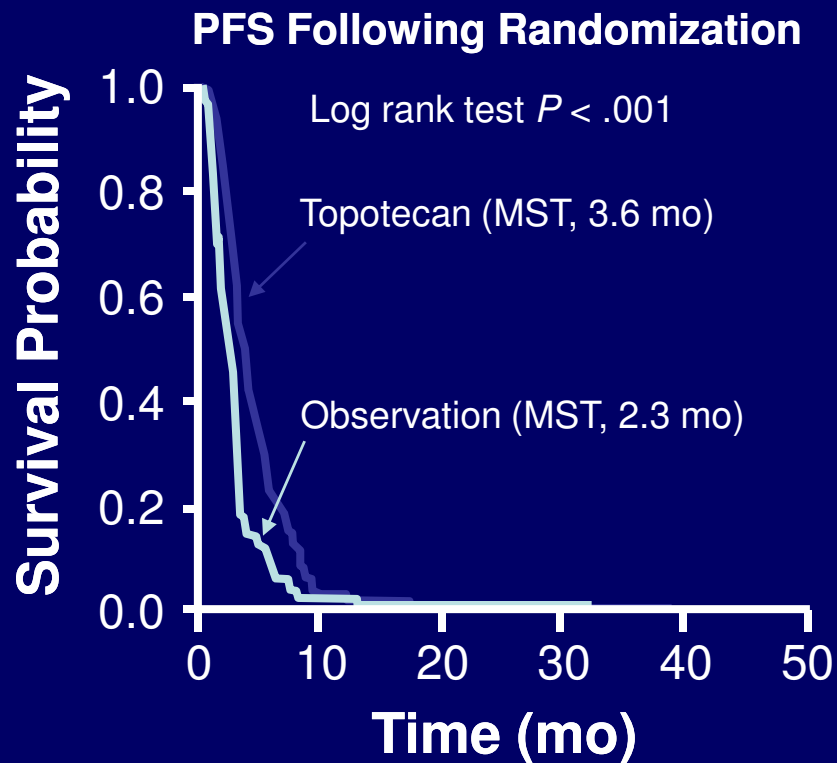
³J Clin Oncol 1992;10:282-291; ⁴J Clin Oncol 2002;20:4665-4672

⁵J Clin Oncol 1995;13:2594-2599; ⁶JNCI 2001;93:300-308

Consolidation with Topotecan after EP in ED SCLC



Topotecan Consolidation in ED SCLC: ECOG Results*



Maintenance Therapy

Author	No.	Regimen	Survival
Ettinger ¹	577	CAV maintenance	No benefit
Cullen ²	61	CAV 6 vs. 12	12 better
Giaccone ³	687	CAE 5 vs. 12	No benefit
Lebeau ⁴	320	CAE 6 vs. 12	No benefit
Spiro ⁵	610	CEV 4 vs. 8	No benefit*
Hanna ⁶	233	VIP 4 vs VIP→V	No benefit
Bleehen ⁷	458	CEMV 3 vs. 6	No benefit

¹J Clin Oncol 1990;8:230-240; ²Ca Chem Pharm 1986;17:157-160

³J Clin Oncol 1993;11:1230-1240; ⁴Eur Respir J 1992;5:286-290

⁵Br J Cancer 1989;59:578-583; ⁶Ann Oncol 2002;13:95-102

⁷Br J Cancer 1993;68:1150-1156

JCOG Study

Noda et al NEJM 2002;346:85-91

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IP Regimen: (n=77)

Cisplatin 60 mg/m² iv d 1

Irinotecan 60 mg/m² iv d 1, 8, 15
cycles repeated every 4 wks X 4

EP Regimen: (n=77)

Cisplatin 80 mg/m² iv d 1

Etoposide 100 mg/m² iv d1,2,3
cycles repeated every 3 wks X 4

Median Survival 12.8 vs 9.4 months

1 yr 58.4% vs 37.7% (P=0.002)

Phase III Study of Cisplatin Plus Etoposide or Irinotecan

Hanna et al, J Clin Oncol 2006;24:2038-2043

Stratified by:

- ◆ Gender
- ◆ LDH \leq vs $>$ ULN
- ◆ Age $<$ vs \geq 65 yrs

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IP Regimen: (N = 221)

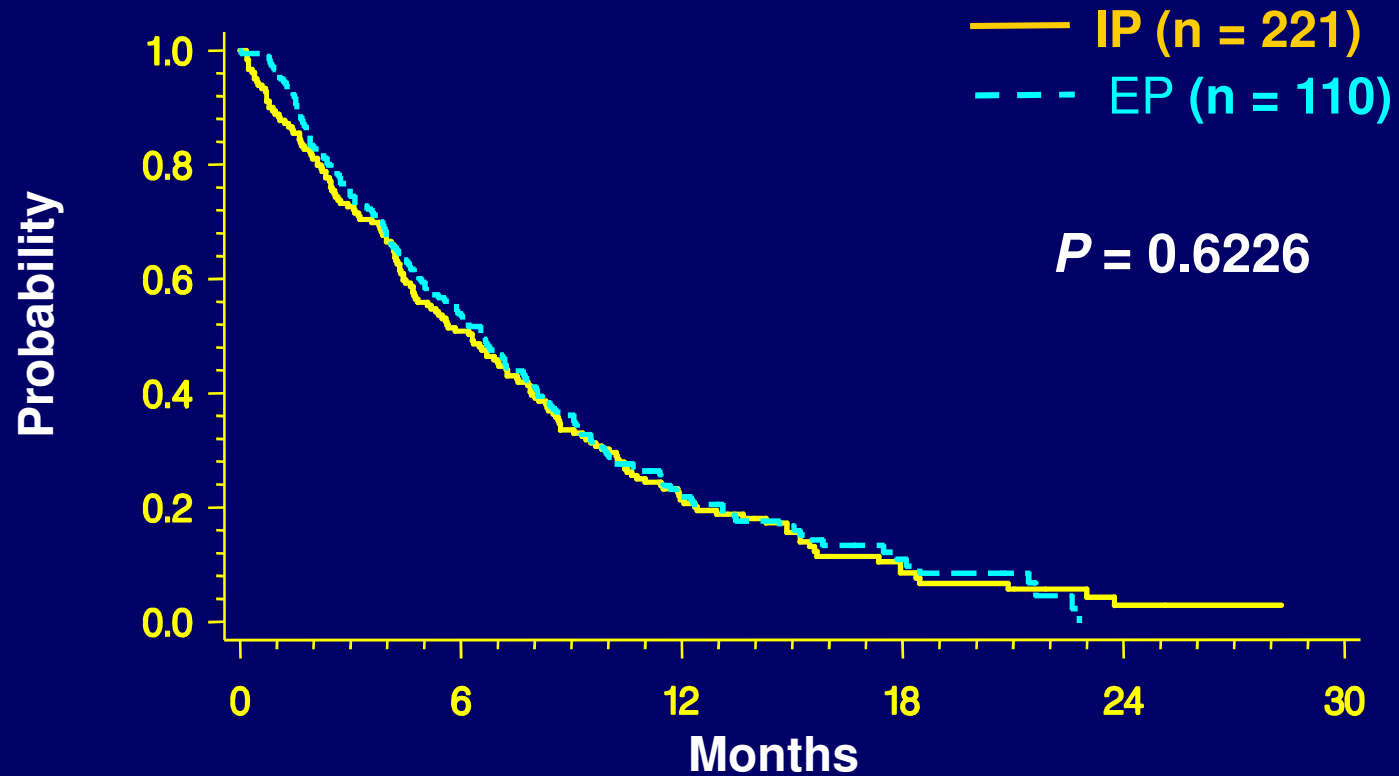
Cisplatin: 30 mg/m², d 1 & 8, q3wk +
Irinotecan: 65 mg/m², d 1 & 8, q3wk
4 cycles or PD or intolerable toxicities

EP Regimen: (N = 110)

Cisplatin: 60 mg/m², d 1, q3wk +
Etoposide: 120 mg/m², d 1–3, q3wk
4 cycles or PD or intolerable toxicities

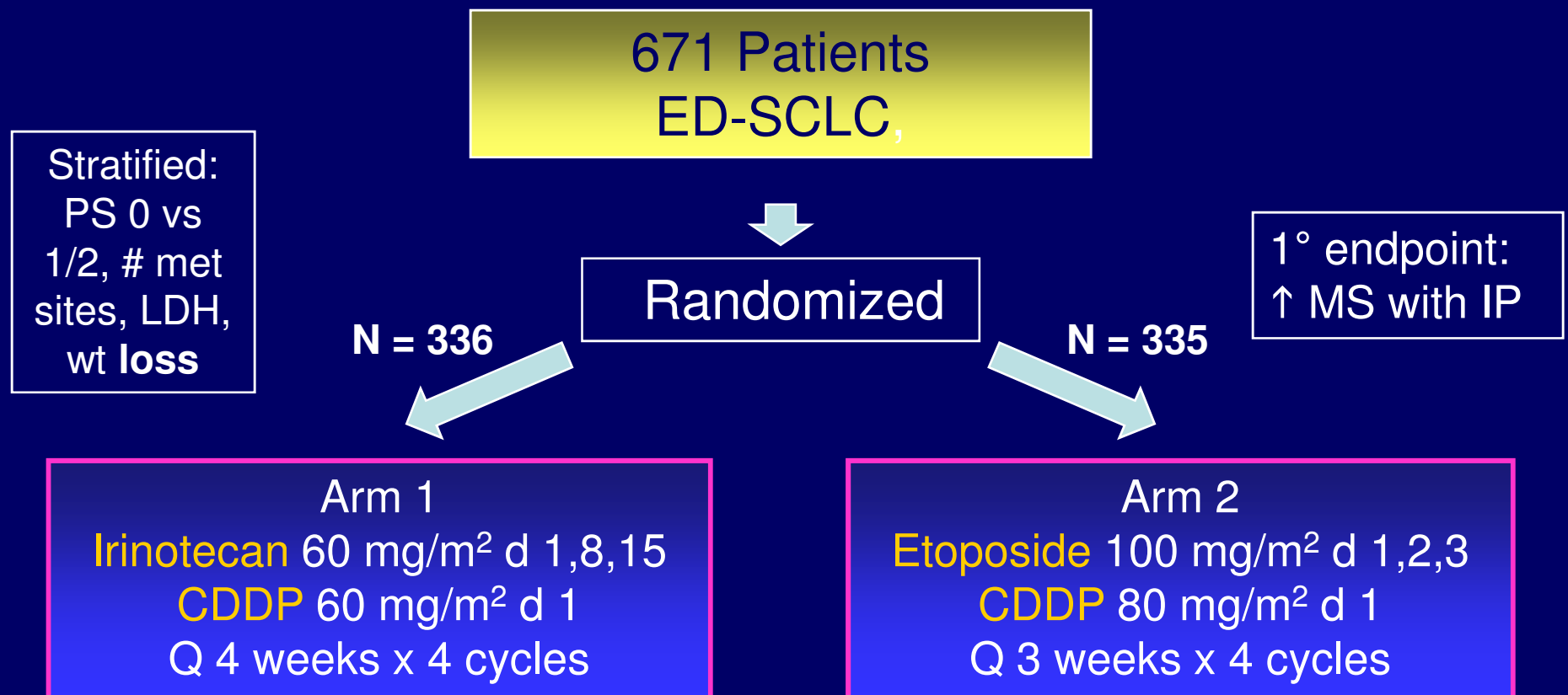
Overall Survival

Hanna et al, J Clin Oncol 2006;24:2038-2043



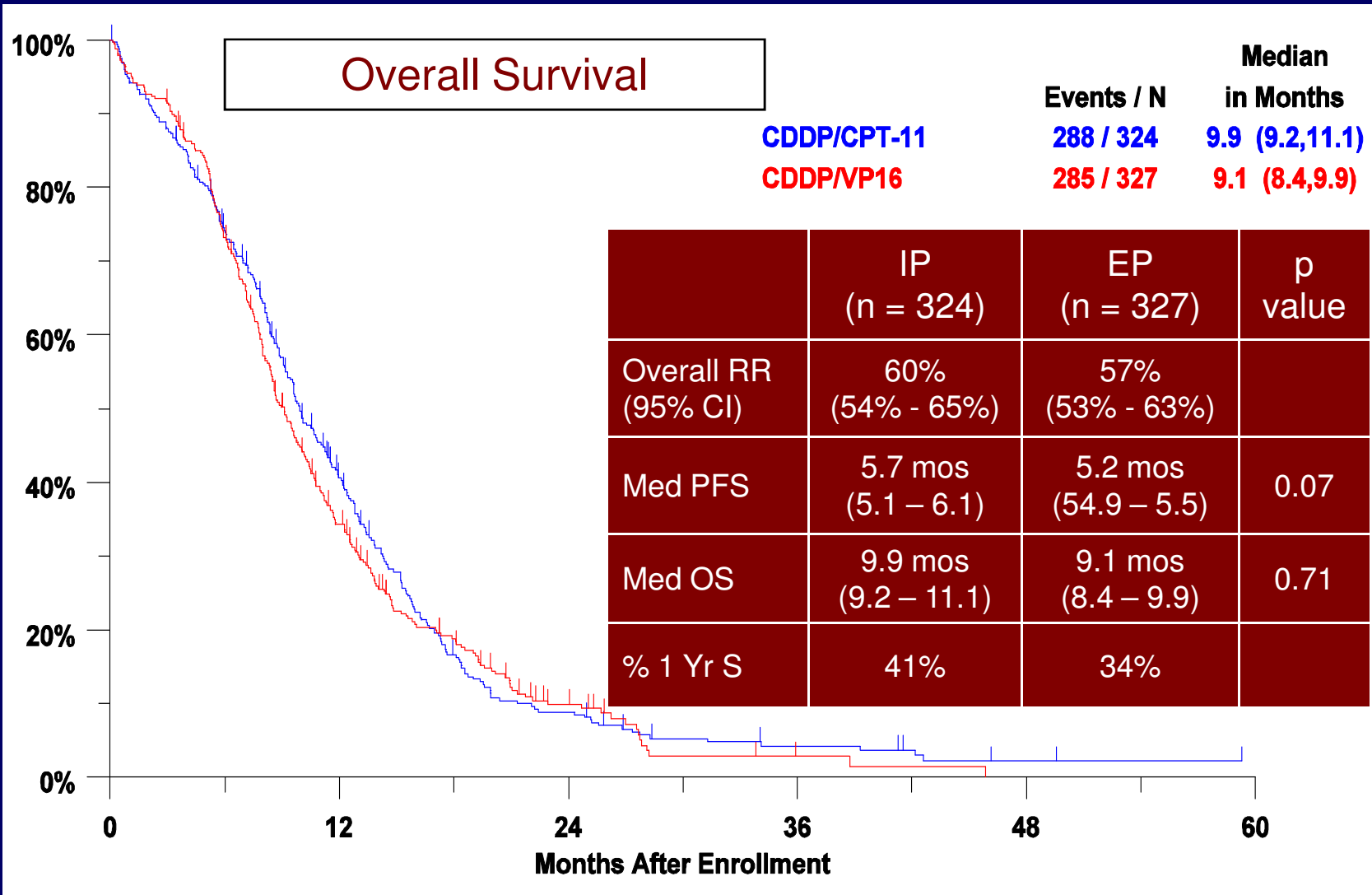
S0124: IP vs EP

Natale et al, ASCO 2008, Abst 7512



S0124: Survival

Natale et al, ASCO 2008, Abst 7512



Relapsed SCLC: Topotecan vs BSC

O'Brien M, et al; Lung Ca 2005;49:S54 (abstract O-157)

Stratification

Gender

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

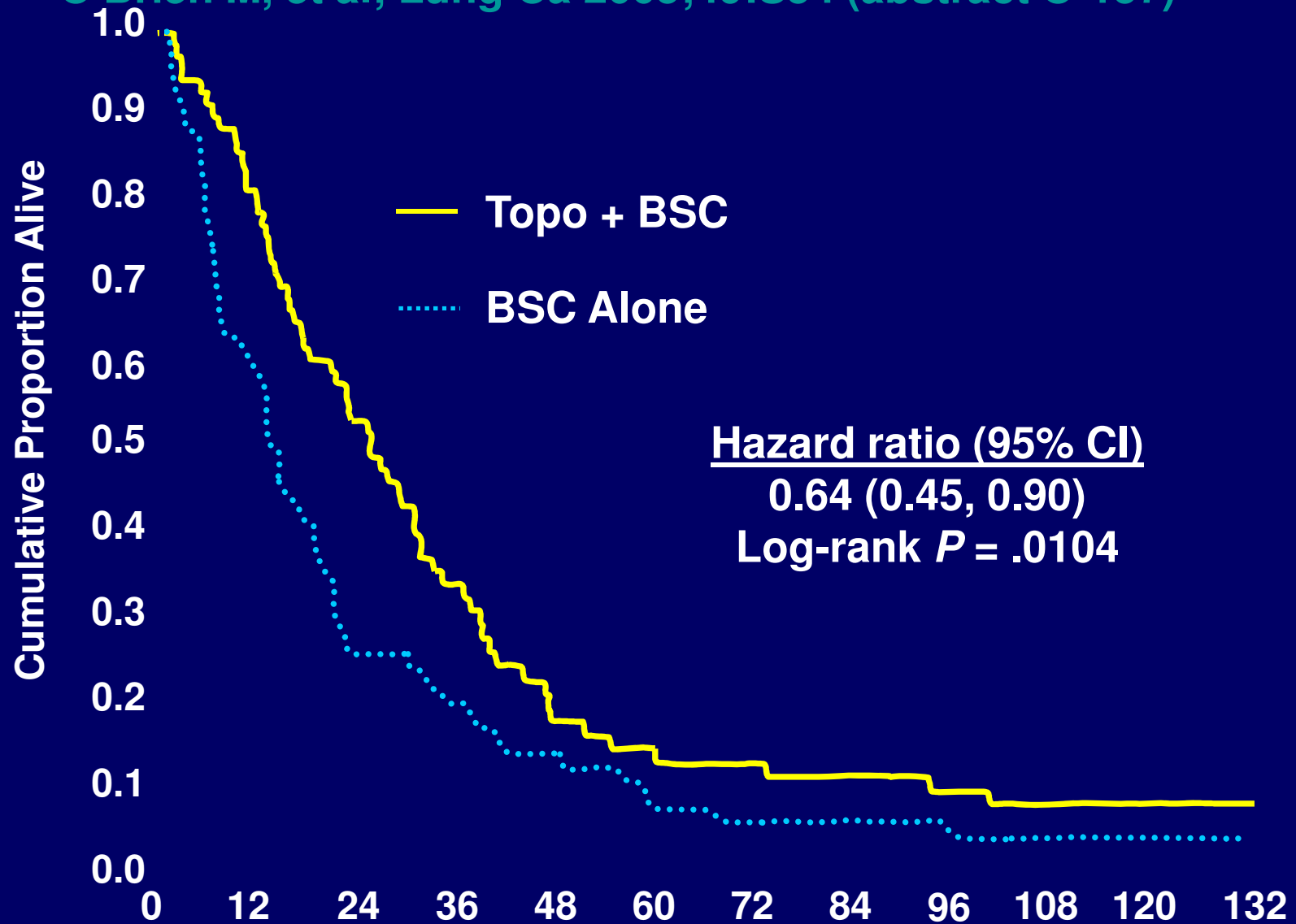
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Topotecan 2.3 mg/m²/day
PO days 1–5 + BSC

BSC alone

Overall Survival

O'Brien M, et al; Lung Ca 2005;49:S54 (abstract O-157)



Relapsed SCLC: Topotecan vs CAV

Stratification

Performance status
Extent of disease at relapse

Cycles repeated every 21 days

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Topotecan

1.5 mg/m²/day IV day x 5

CAV

Cyclophosphamide:
1.0 g/m²

Doxorubicin: 45 mg/m²

Vincristine: 2 mg

Topotecan Versus CAV

	Topotecan N=107	CAV N=104
PR rate (%)	24%	17%
MST (weeks)	25	25
6 mo survival	47%	45%
1yr survival	14%	14%

von Pawel J, et al. J Clin Oncol 1999;17:658-667

Amrubicin in 2nd line SCLC

Study	Refractory/ Sensitive	N	RR (%)
Jotte	Sensitive	75	40
Ettinger	Refractory	75	17
Sugawara	Both	29	38
Hasegawa	Sensitive	9	56
	Refractory	17	41
Onoda	Sensitive	44	52
	Refractory	16	50
Kato	Sensitive	24	50
	Refractory	10	60

PCI in ED SCLC

Slotman et al, ASCO 2007, Abst 4

- ED SCLC, PS 0-2
- Response following 4-6 cycles chemo
- Randomized to PCI vs Observation
 - PCI: 20-30 Gy in 5-12 fractions
- Baseline brain imaging **NOT** mandated unless symptoms warranted imaging

PCI in ED SCLC: Patient Characteristics

Slotman et al, ASCO 2007, Abst 4

Variable	PCI	Control
N	143	143
PS 0-1	92.3%	89.5%
Persistent 1° disease	75.5%	76.9%
Bone mets	22%	26%
Lymph nodes	50%	47%
“Other sites of mets”	64%	82%
No mets present	30.8%	27.3%
Received 20 Gy in 5 fx	~67%	-----

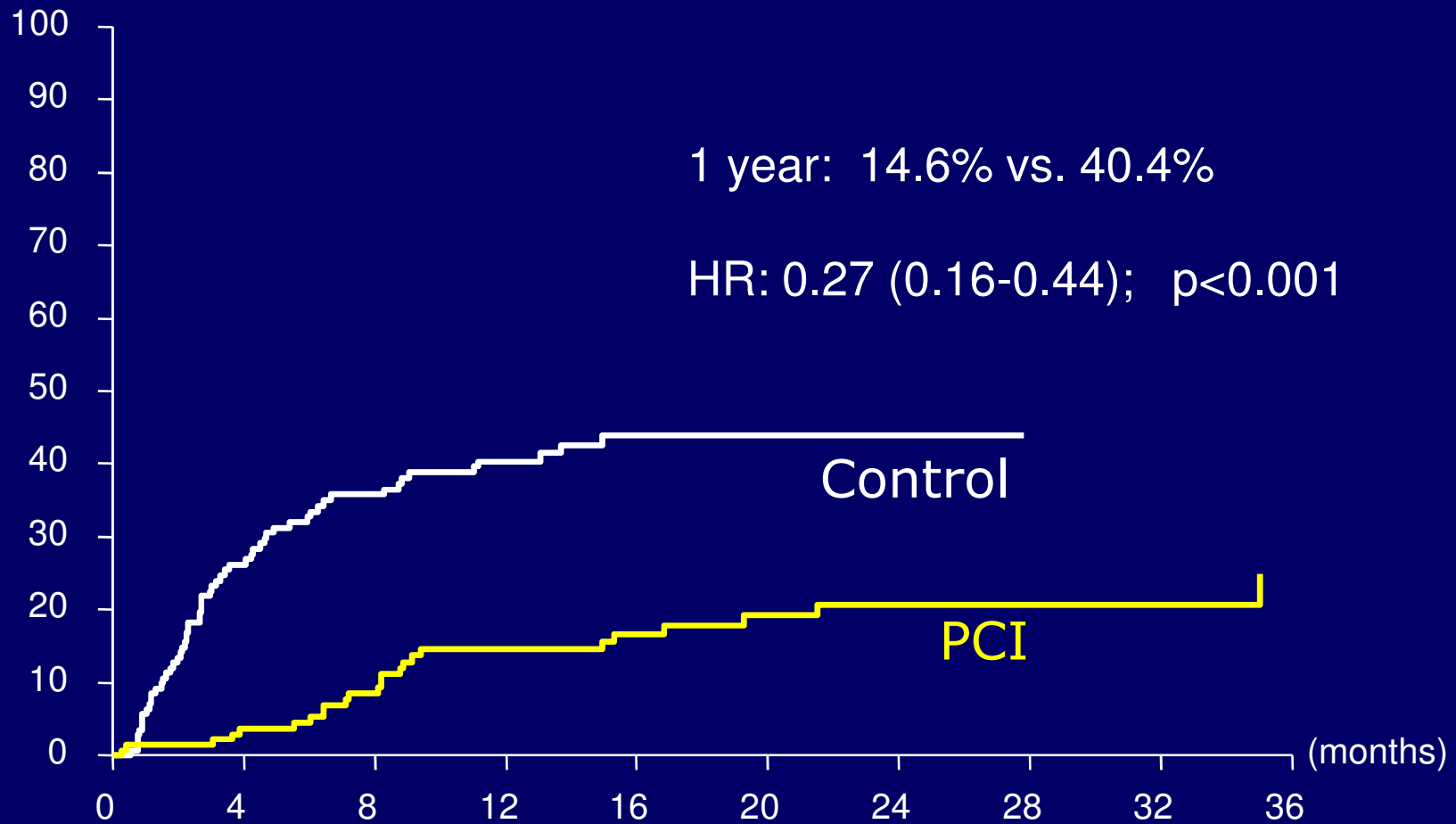
PCI in ED SCLC: Toxicity

Slotman et al, ASCO 2007, Abst 4

Variable	PCI
Headache	>40%
Nausea/Vomiting	>35%
Fatigue	~10%
Late Headache	35%

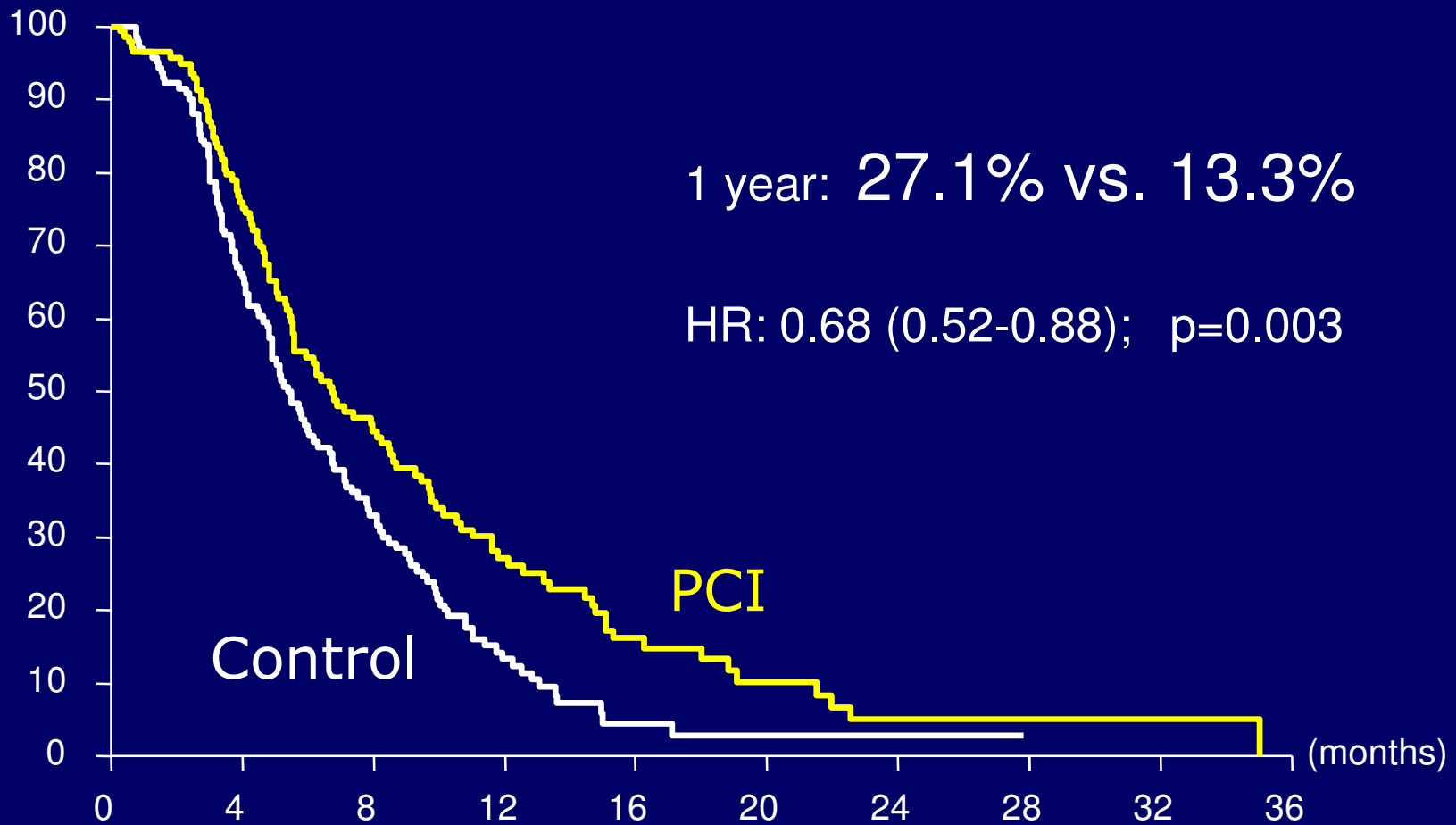
Symptomatic Brain Metastases

Slotman et al, ASCO 2007, Abst #4



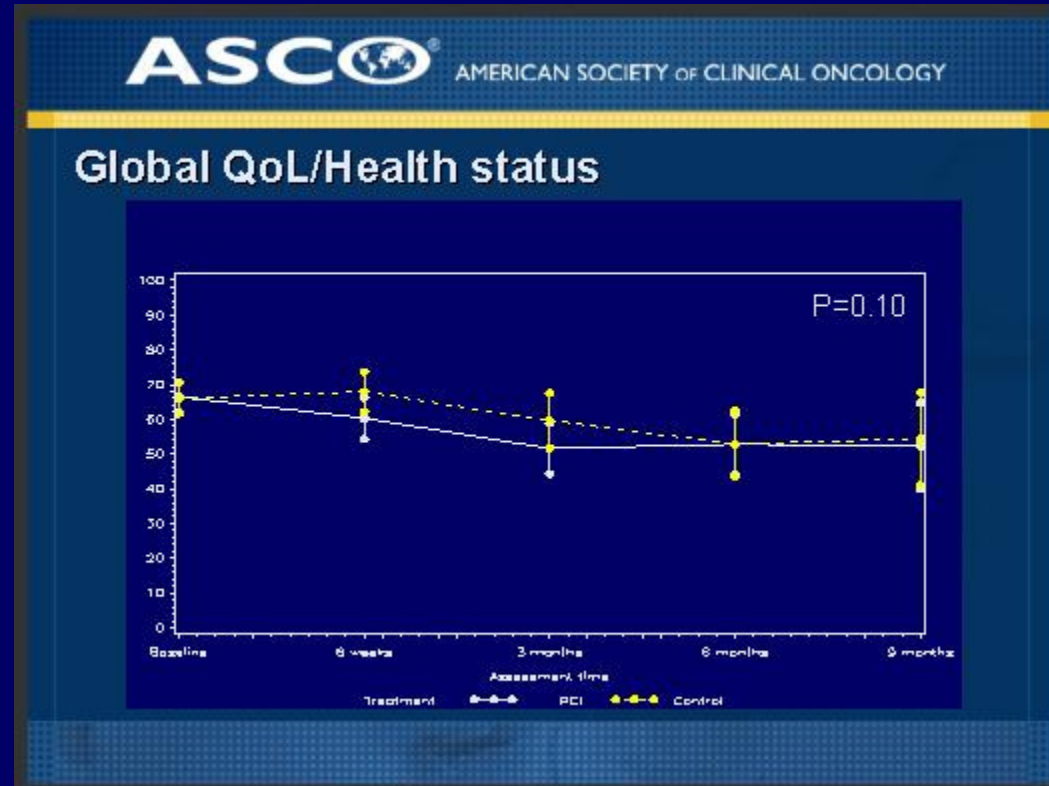
Survival from Randomization

Slotman et al, ASCO 2007, Abst #4



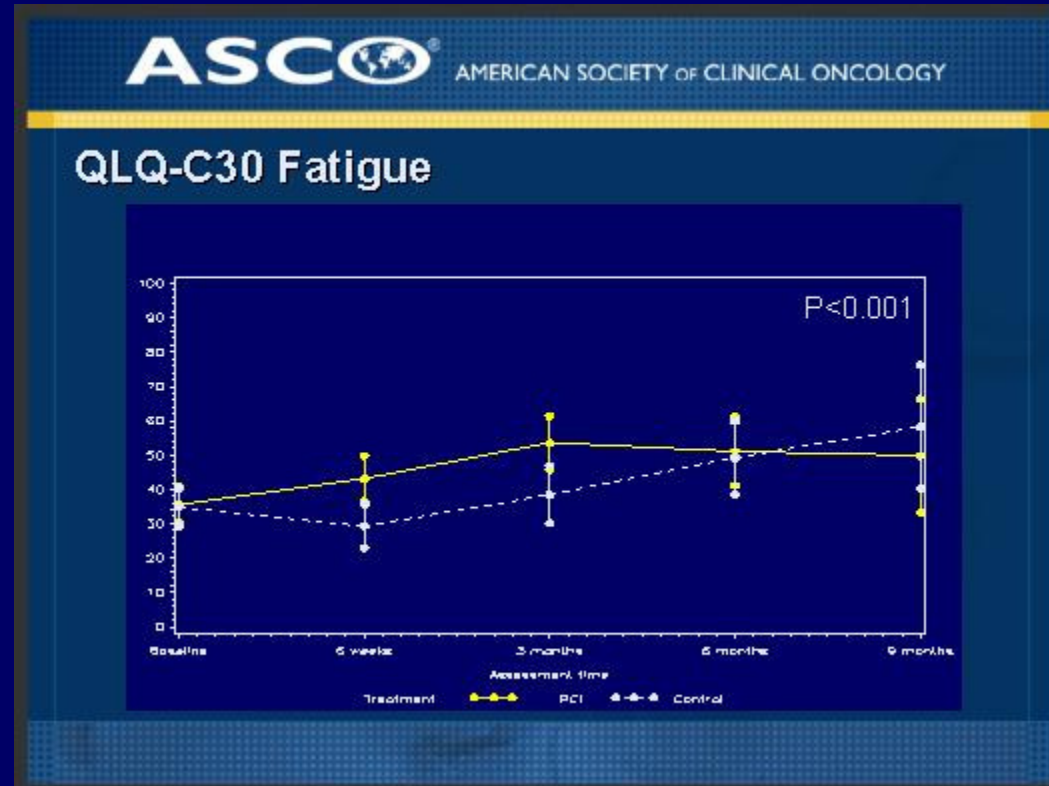
Quality of Life with PCI in ED SCLC

Slotman et al, ASCO 2007, Abst 4



Fatigue with PCI in ED SCLC

Slotman et al, ASCO 2007, Abst 4



Comments on PCI in ED SCLC

- Definition of ED not explicit
 - Lymph nodes only? 30% had **NO** mets at randomization
- Imbalance in “other” sites of mets favoring PCI arm
- Were arms balanced for type of response: PR vs. SD?
- Baseline brain imaging **NOT** required
 - May have been treating asymptomatic brain mets in “PCI” arm and delay in Rx of brain mets in control arm
 - What was time interval on control arm from randomization until detection of brain mets?

Comments on PCI cont'd

- Fatigue scores significantly lower on PCI arm for 6 months ($p < 0.001$)
 - Other side effects, even Grade 1/2 are clinically significant
- QoL scores trended lower as well on PCI arm ($p = 0.1$)
- Makes sense **for some patients**---minimal disease, good PS, but clearly **does not make sense for other patients**---PS 2, advanced disease (liver, adrenal mets), SD to prior therapy

How do we move forward from here?

SCLC and Anti-angiogenic Trials

Study	Target	Agent	Schema	Result
NCI-C/ EORTC Bayer	MMP	Marimastat BAY 12-9566	+/- Maintenance +/- Maintenance	Negative Negative
ECOG CALGB HOG	VEGF	BEV (B)	Chemo + B Chemo + B Chemo + B	Positive Negative Negative
United Kingdom	Vascular stabilizer	Thalidomide	Chemo +/- T	Negative
NCI-C	VEGFR TKi	ZD 6474	+/- Maintenance	Negative
SWOG	VEGFR Tki	Sorafenib	Monotherapy	Negative

SCLC and Targeted Agents

Study	Target	Agent	Schema	Result
Rudin	Bcl-2	Oblimersen	Chemo +/-	Negative
ECOG	MTOR	CCI-779	+/- Maintenance	Negative
HOG	EGFR	Gefitinib	Monotherapy	Negative
Johnson Krug Dy	C-Kit	Imatinib	Monotherapy Monotherapy Monotherapy	Negative Negative Negative
EORTC	GD-3	BEC2/BCG	+/- Maintenance	Negative
SWOG	Proteo- some	Bortezomib	Monotherapy	Negative
SWOG	RAF/VEGF	Sorafenib	Monotherapy	Negative

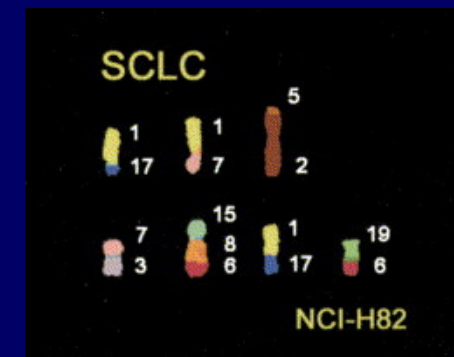
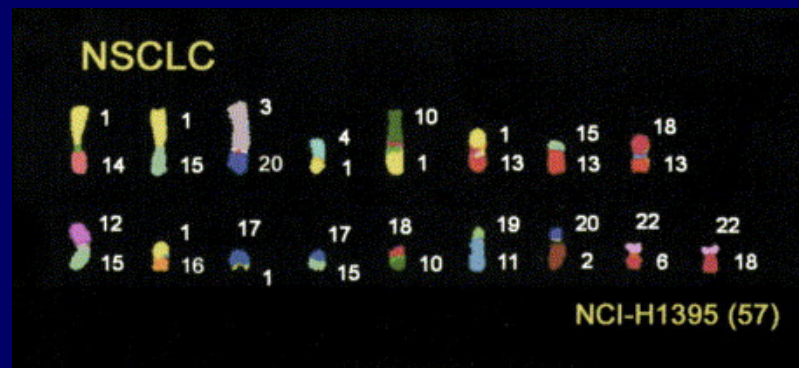
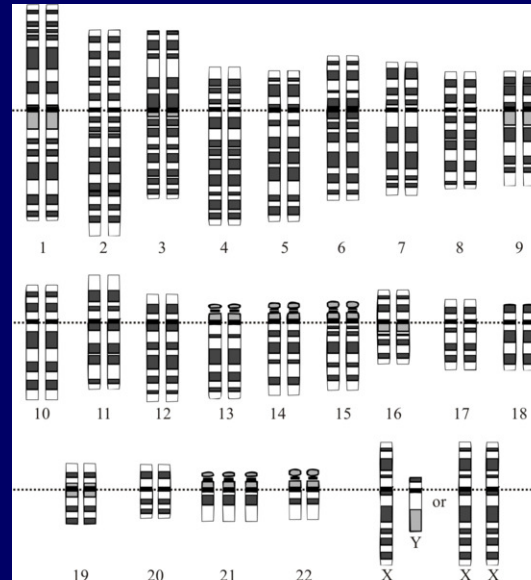
Somatic Mutations of Protein Kinase Gene Family in Lung Cancer

Davies et al, Cancer Res 2005;65:7591-5

- 26 lung neoplasms and 7 lung cancer cell lines evaluated
- 188 somatic mutations detected in 141 genes
 - Majority are passenger mutations (vs. dominant driver)
- Considerable variation between individual lung cancers in the number of mutations
 - Mutations in each kinase was infrequent
 - Therefore, may be a significant challenge to exploit the same target for a large number of patients

Complexity of Lung Cancer defined by chromosomal painting

- Complex disease
 - Not a single agent responsible for disease as in polio or small pox.
 - Not a single gene responsible like cystic fibrosis or sickle cell anemia

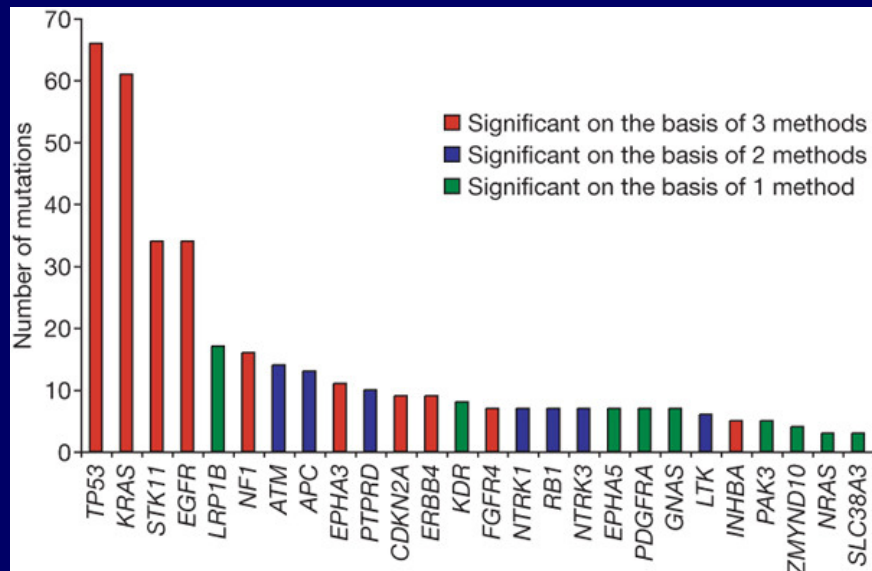


Lung cancer research:

- Cancer Genetics (Genomics)
 - Human genome sequenced 2001.
 - 2004 through last week, lung cancer genome analyses published.



Significantly mutated genes in lung adenocarcinomas.



- Identified factors and pathways know to be important in lung cancer (Very good)
- Identified new factors and pathways that may be important in lung cancer (Potential to be very good)

Optimal Treatment of ED SCLC: Summary

- Combination chemotherapy is superior to single agent in 1st line therapy, even in elderly or poor PS patients
- Platinum agent + Etoposide X 4 cycles remains standard in the U.S.
- Dose intensification, consolidation or maintenance therapy does not substantially improve survival, but adds significantly more toxicity
- Carefully consider PCI in select patients w/ ED SCLC
- Single agent therapy is standard in 2nd line treatment
- We must understand the biology to improve Rx
- Reducing tobacco consumption remains key to reducing the suffering from SCLC