Treatment of Lung Cancer: State of the Art

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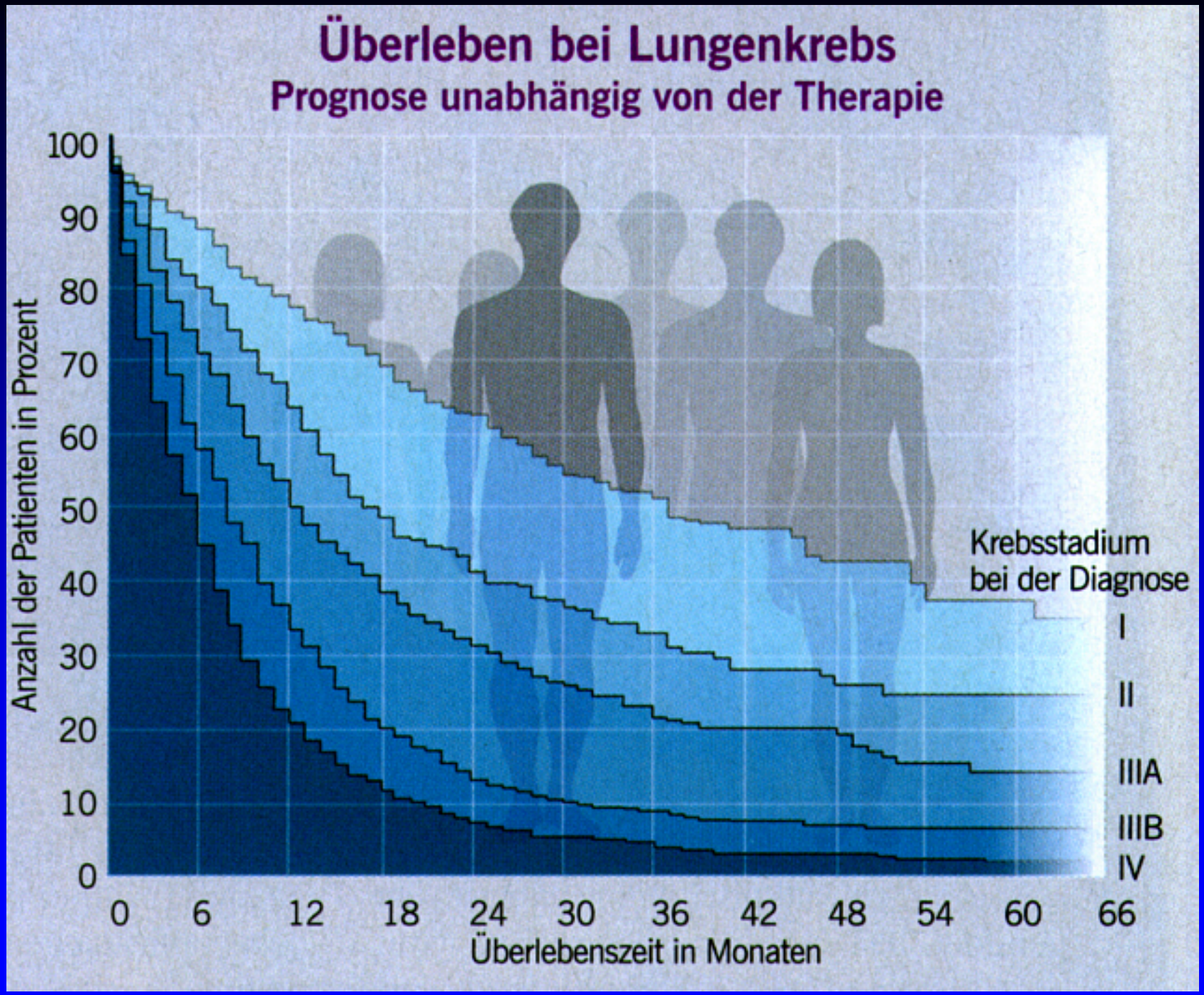
Survival of Patients with Bronchial Carcinoma (n=6097)

1 year	45%
3 years	20%
5 years	14%
7 years	11%
Median (months)	10


Überleben bei Lungenkrebs
Prognose unabhängig von der Therapie
Anzahl der Patienten in Prozent
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
66
Überlebenszeit in Monaten
Krebsstadium bei der Diagnose
I
II
IIIA
IIIB
IV

UICC 1997

Stage I	Stage II	Stage IIIA
A: T1 N0 M0	A: T1 N1 M0	T1 N2 M0
B: T2 N0 M0	B: T2 N1 M0	T2 N2 M0
	T3 N0 M0	T3 N1-2 M0

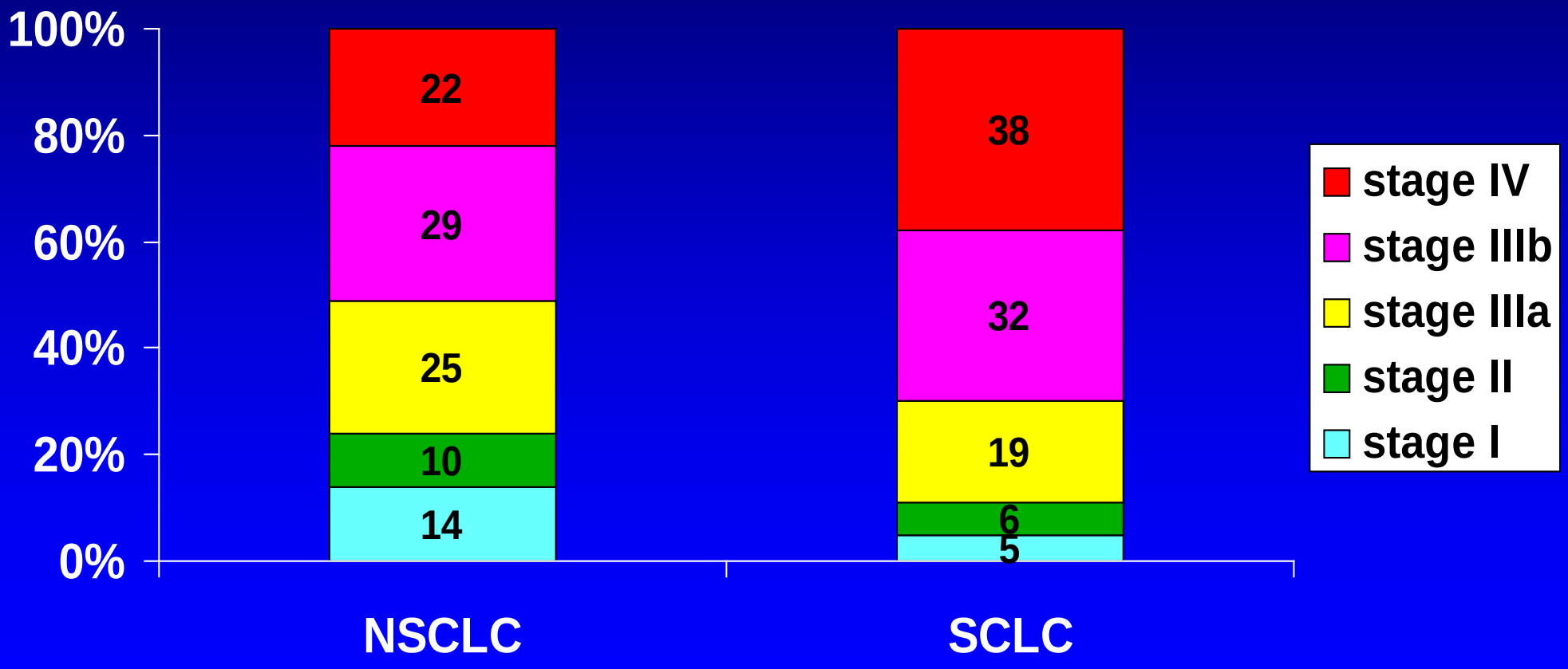
Stage IIIB	Stage IV
any T N3 M0	any T any N M1
T4 any N M0	

Stage (n=6097, stage X: n=128)

	I	II	IIIA	IIIB	IV
n	663	647	1204	1875	1580
1 year	79%	69%	55%	38%	21%
3 years	54%	41%	25%	11%	4%
5 years	43%	31%	18%	7%	2%
7 years	38%	24%	14%	5%	1%
Median (months)	45	27	14	9	6

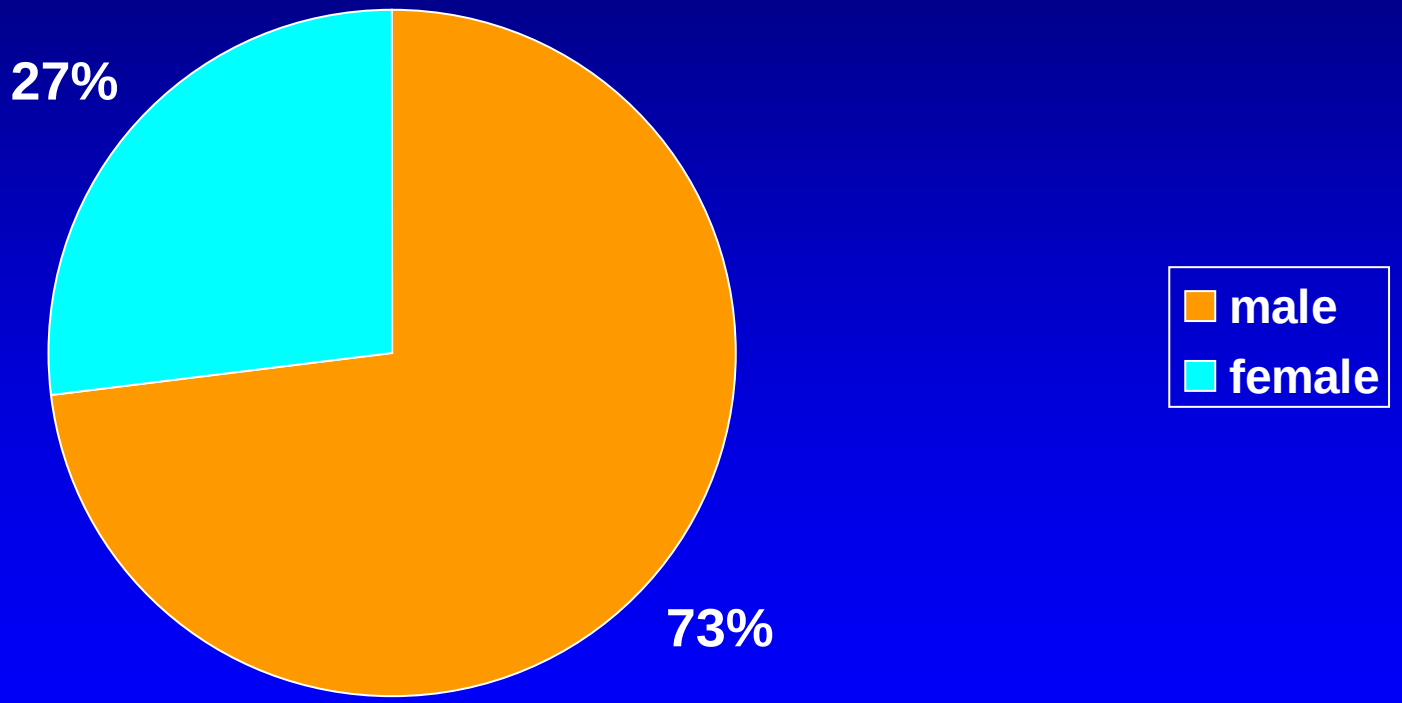
I vs II; II vs IIIA; IIIA vs IIIB; IIIB vs IV : p<0.001

Bronchial Carcinoma
n=6907, 1984 - 1994



Gender

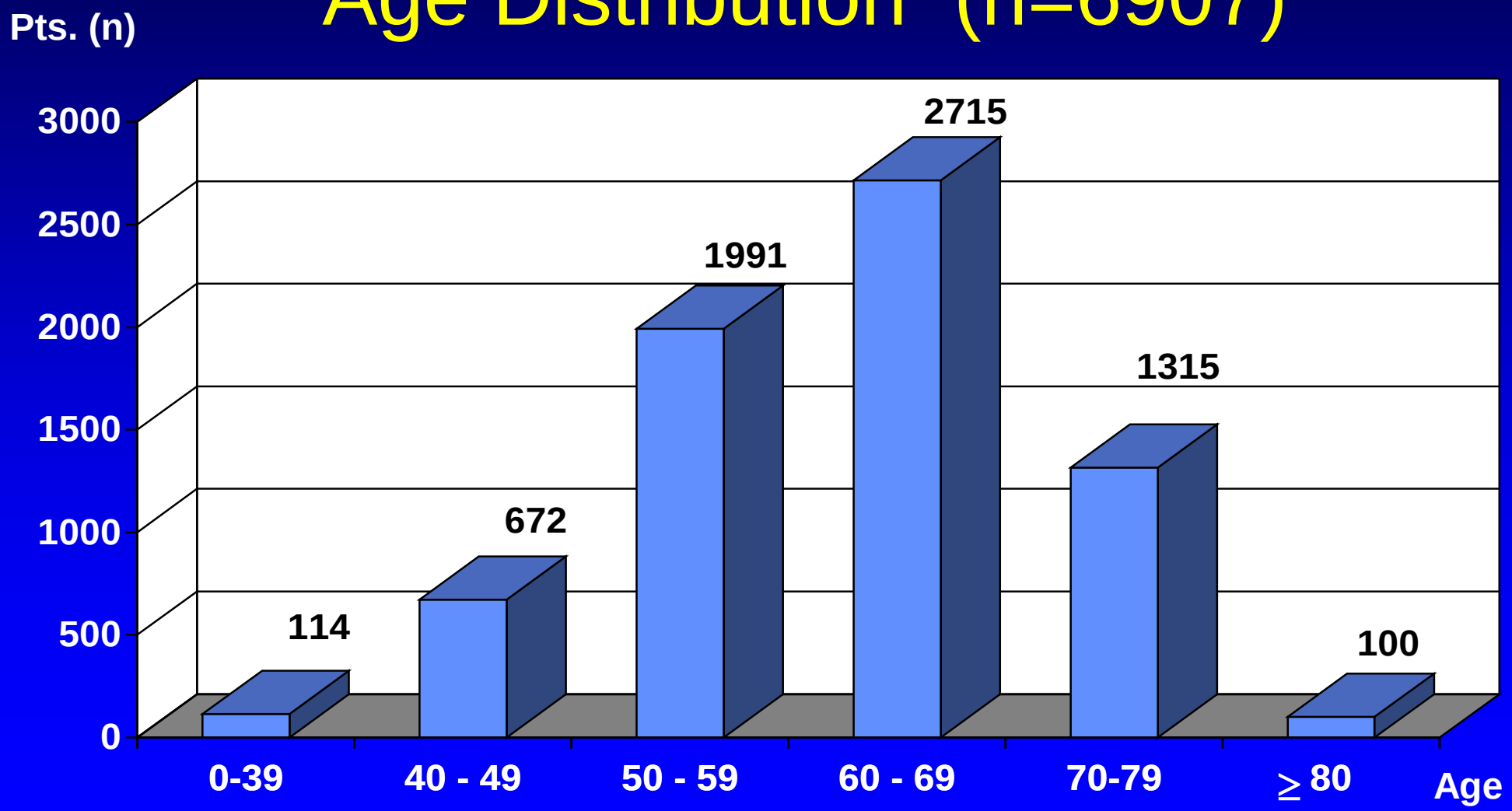
Bronchial Carcinoma 2001 (n=865)



Bronchial Carcinoma
- Histology and Gender (n=6907) -

Histology	Male	Female	total
Squamous cell	2315	223	36.7%
Adeno	1613	616	32.3%
Large cell	383	79	6.7%
SCLC	1134	219	19.6%
Mixed cell	279	46	4.7%
total	5724	1183	(100%)

Bronchial Carcinoma: Age Distribution (n=6907)



Prognostic factors in NSCLC

Variable	Definite	Possible
Stage (TNM)	x	
PS	x	
Weight loss	x	
Sex		x
LDH / albumin		x
Histology		x
HB / PLT / WBC		x
Biologic factors		x
Age		x

Feld et al, Lung Cancer 17 (Suppl. 1) 3-10, 1997

Treatment strategies in NSCLC

Stage	Surgery	Radiotheray	Chemotherapy
I	yes	in case of inoperability	no
II	yes	in case of inoperability	no
III	yes	in case of inoperability; adjuvant	adjuvant, inductive CT/RT
IV	no	palliative	palliative

p-Stage / R0 (n=1750)

	I	II	IIIA	IIIB
n	684	415	299	273
1 year	88%	79%	65%	57%
3 years	70%	51%	37%	26%
5 years	57%	41%	25%	20%
7 years	48%	36%	17%	14%
Median (months)	82	38	22	16

I vs II; II vs IIIA: p<0.001; IIIA vs IIIB : 0,040

BrCa with surgical treatment (n=2137)

Radicality	R0 (n=1750)	R1 (n=181)	R2 (n=206)
1 year	75%	54%	35%
3 years	51%	22%	11%
5 years	40%	16%	5%
7 years	33%	12%	n.d.
Median (months)	38	14	8

R0 vs R1; R1 vs R2: $p<0.001$

Indikationen zur Strahlentherapie beim nicht-kleinzelligen Bronchialkarzinom

- Postoperative Strahlentherapie
- Primäre Strahlentherapie
- Induktionsradiochemotherapie
- Rezidivbestrahlung
- Palliativbehandlung

Optimierung der Strahlentherapie von Bronchialkarzinomen

Gesamtdosis nach individueller Risikoabschätzung
bis zur Toleranzgrenze
(Zielvolumen, LuFu)

Optimierung der Dosisverteilung
(3D-Konformationstherapie, Intensitätsmodulation)

Sequential and concurrent ChemoRadiotherapy for inoperable locally advanced NSCLC: Randomised Study-Results (Selection)

	n	MS (mo)	2-yrs-S (%)	Ref.
RT	77	10	13*	Dillman
CT/RT	78	14	26	(1990)
RT	177	12	14*	Le Chevalier
CT/RT	176	11	21	(1992)
RT	149	11	19*	Sause
CT/RT	151	14	32	(1994)
RT	223	10	16	Cullen
CT/RT	112	12	20	(1999)
RT		12	13*	Schaake-Koning
+CT/RT	331**	13	26	(1992)
CT/RT con.		17*	35*	Furuse
CT/RT sequ.	320	13	27	(1999)

*p <0.05 ** Total No of pts enrolled (3-arm-study) +Cisplatin daily

Zusammenfassung : Gegenwärtiger Stand der Radiochemotherapie in Stadium III NSCLC

Therapie	Med.ÜLZ	1 Jahr	2 Jahre	RT Tox(3-4)
RT	10	40%	15%	10%
CT → RT	14	55%	30%	25%
CT/RT	17	65%	35%	50%
CT → CT/RT	15	60%	40%	35%
CT/RT → CT *	26	78%	54%	< 20%

nach Pisters: ASCO, 2000 * S9504

Clinical Practice Guidelines for Chemotherapy of Stage IV NSCLC

CT is appropriate for selected patients

CT prolongs survival in patient with good PS

CT should be Platinum-based

CT should be initiated while the patient has good PS

CT-Duration should not exceed 8 cycles

JCO 15, 8, 2996-3018, 1997

Cisplatin-containing CT and outcome according to performance status in advanced NSCLC

	MS	1-y-S	Reference
PS 0 - 1	5 - 11 mo	16 - 38 %	Albain (1991) Cullen (1999) Le Chevalier (1999)
PS >1	3 - 5 mo	6 - 16 %	Cullen (1999) Johnson (1999)

Cisplatin-containing CT vs Best supportive care in advanced NSCLC

	n	MST	1-y-s	Ref.
VDS / CIS	44	8 mo*	22 %*	Rapp
CAP	43	6 mo	21 %	(1988)
BSC	50	4 mo	10 %	
ETO / CIS	44	5 mo*	n.r.	Kaasa
BSC	43	4 mo	n.r.	(1991)
MCC	52	9 mo*	38 %*	Cartei
BSC	50	4 mo	12 %	(1993)
MIC	174	7 mo*	28 %*	Cullen
BSC	176	5 mo	18 %	(1997)

*$p \leq .05$

First-line activity of new agents in advanced NSCLC (Phase II)

	n	RR	MS	1-y-s
Paclitaxel	317	26 %	9 mo	41
Docetaxel	300	26 %	10 mo	52
Navelbine	621	20 %	8 mo	24
Gemcitabine	572	21 %	9 mo	39
Irinotecan	161	34 %	10 mo	--
Topotecan	64	11 %	8 mo	30

Gemcitabine (Gem) vs Cisplatin / Etoposide (C/E) in advanced NSCLC: randomized phase II study results

	Europe*		Taiwan**	
	Gem	C/E	Gem	C/E
PR (%)	12 (18.2)	11 (15.3)	5 (19.2)	5 (20.8)
95% CI	(9.8 - 30)	(7.9 - 25.7)	(8.3 - 30.1)	(9.5 - 32.1)
Median TTP	4.2 mo	4.9 mo	8.7 mo	8.5 mo
95% CI	(2.9 - 5.6)	(3.2 - 5.8)	-	-
	p = ns		p = ns	
MS	6.6 mo	7.6 mo	9.2 mo	12 mo
95% CI	(4.9 - 7.1)	(5.6 - 9.6)	-	-
	p = ns		p = ns	

*Manegold et al., Ann Oncol 8, 525-529, 1997

**Perng et al., J Clin Oncol 15, 2097-2102, 1997

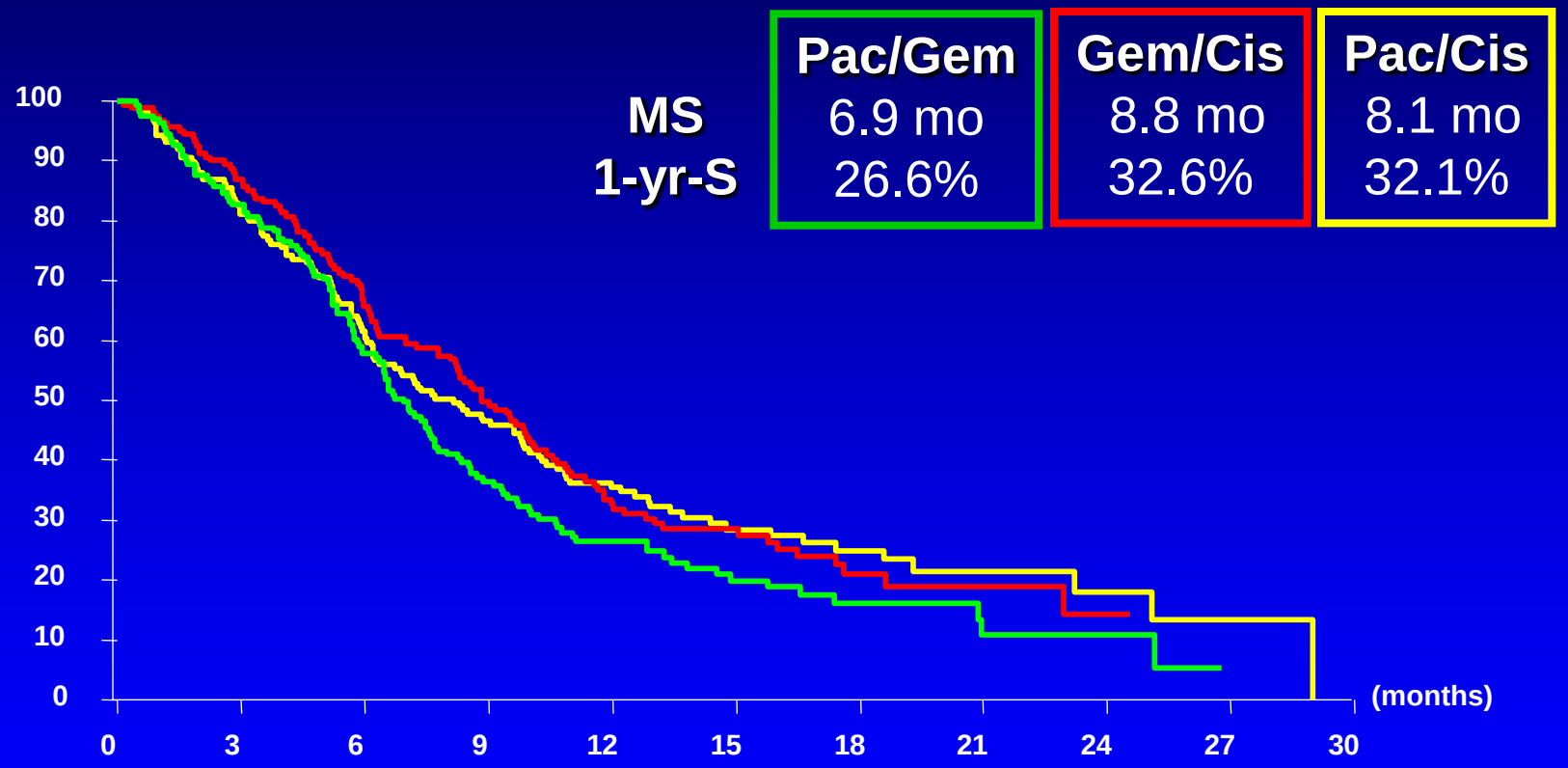
Chemotherapy Stage IV NSCLC: Comparison of regimens containing newer cytotoxic drugs - ECOG 1594: Efficacy

	PAC / CIS 135 (24h) / 75 mg/m²	***GEM / CIS 1000 (1, 8, 15) / 100 mg/m²***	***DOC / CIS 75 / 75 mg/m²***	***PAC / CARBO 225 / AUC6 mg/m²***
n	288	288	289	290
OR	21,3 %	22,0 %	17,3 %	16,3 %
MS	7,8 mo	8,1 mo	7,4 mo	8,1 mo
TTP	3,4 mo	4,2 mo*	3,7 mo	3,1 mo
1-yr-S	31 %	36 %	31 %	34 %

*p = 0.001

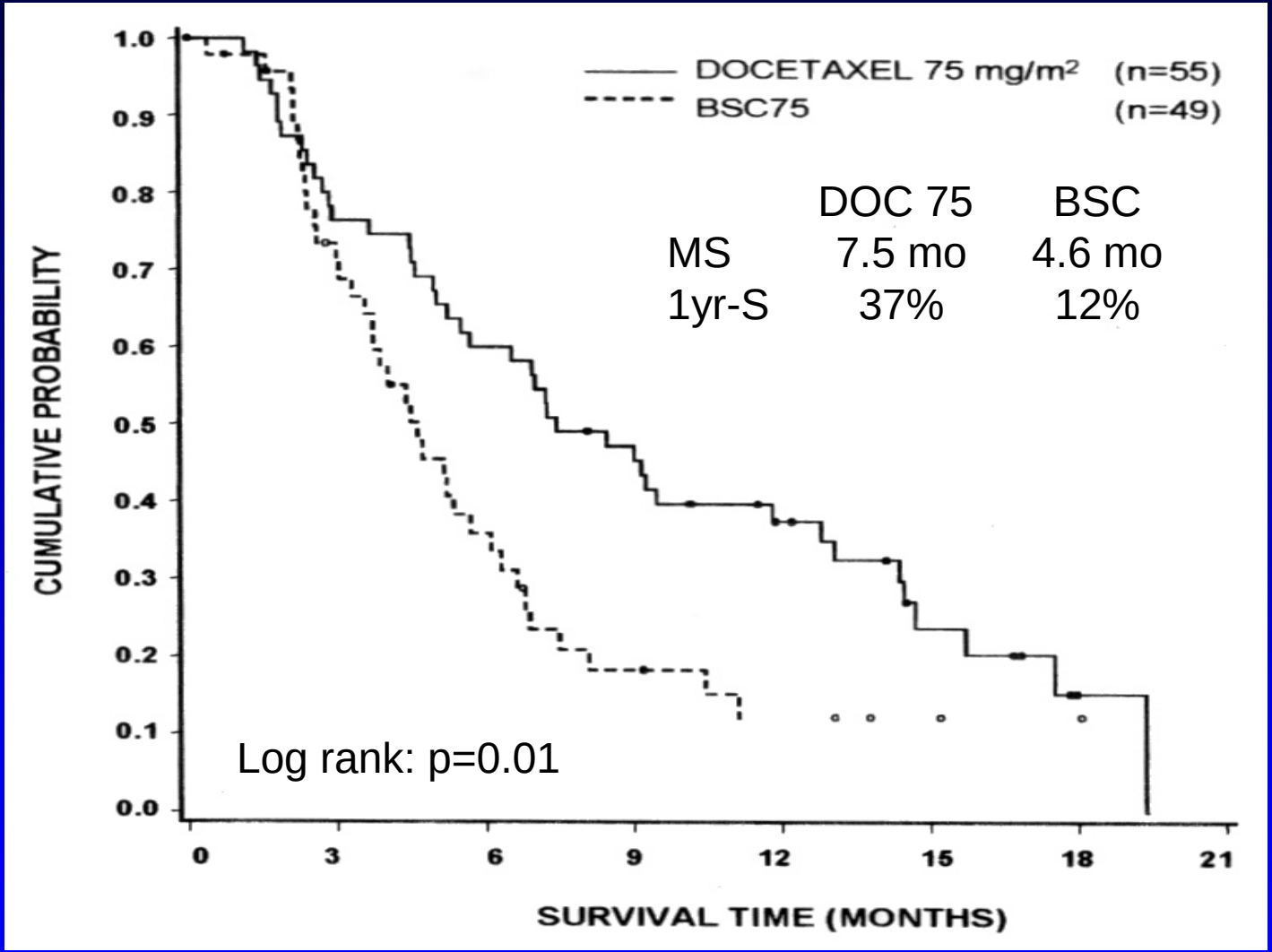
Schiller et al., NEJM, 346:2, 92-98 (2002)

EORTC 08975: Survival (n=480)



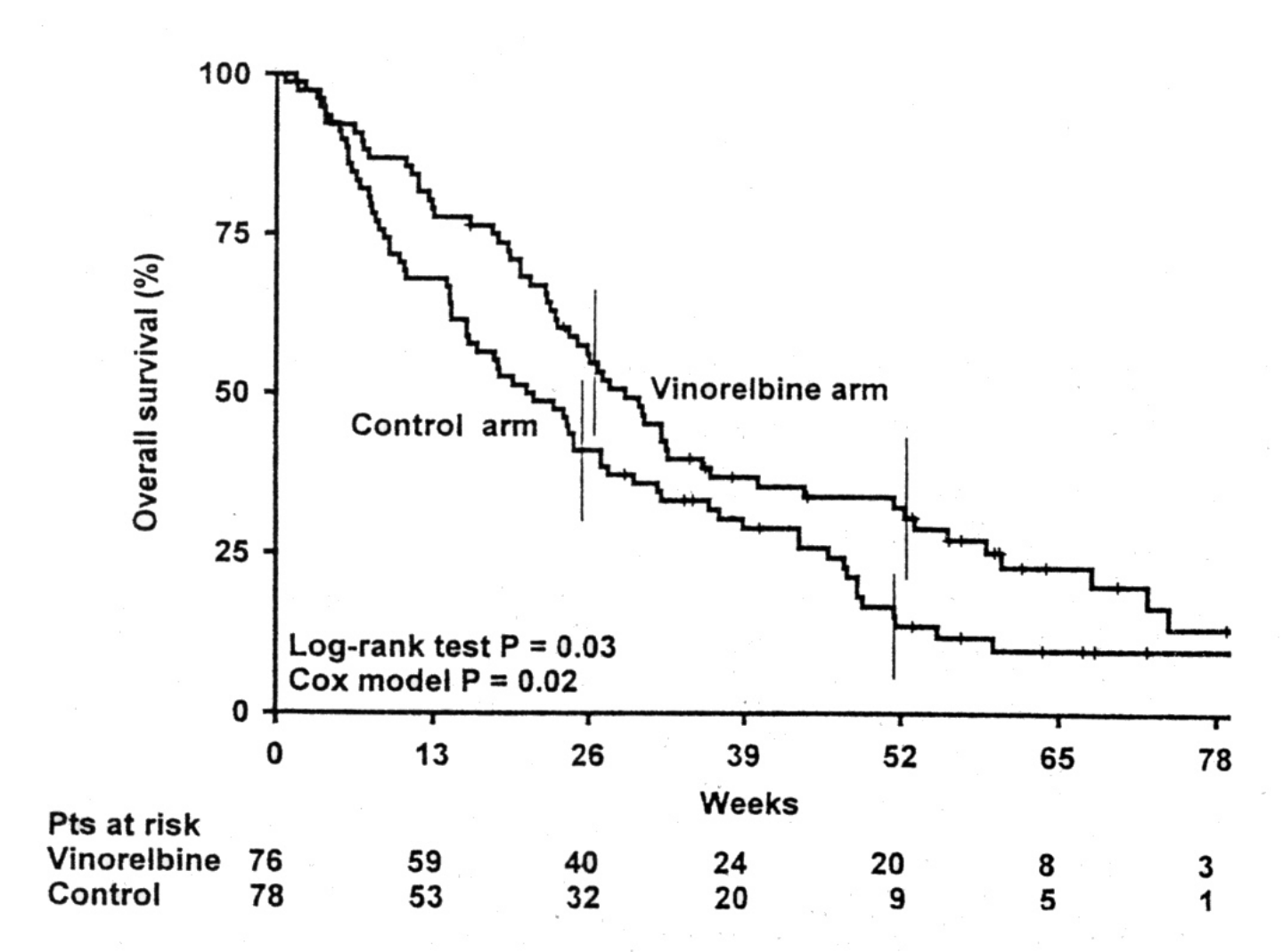
v. Meerbeeck et al. ASCO 2001

Second-line Docetaxel for advanced NSCLC



Shepherd et al. JCO 18,2095,2000

Vinorelbine vs Best Supportive Care in Elderly Patients with advanced NSCLC

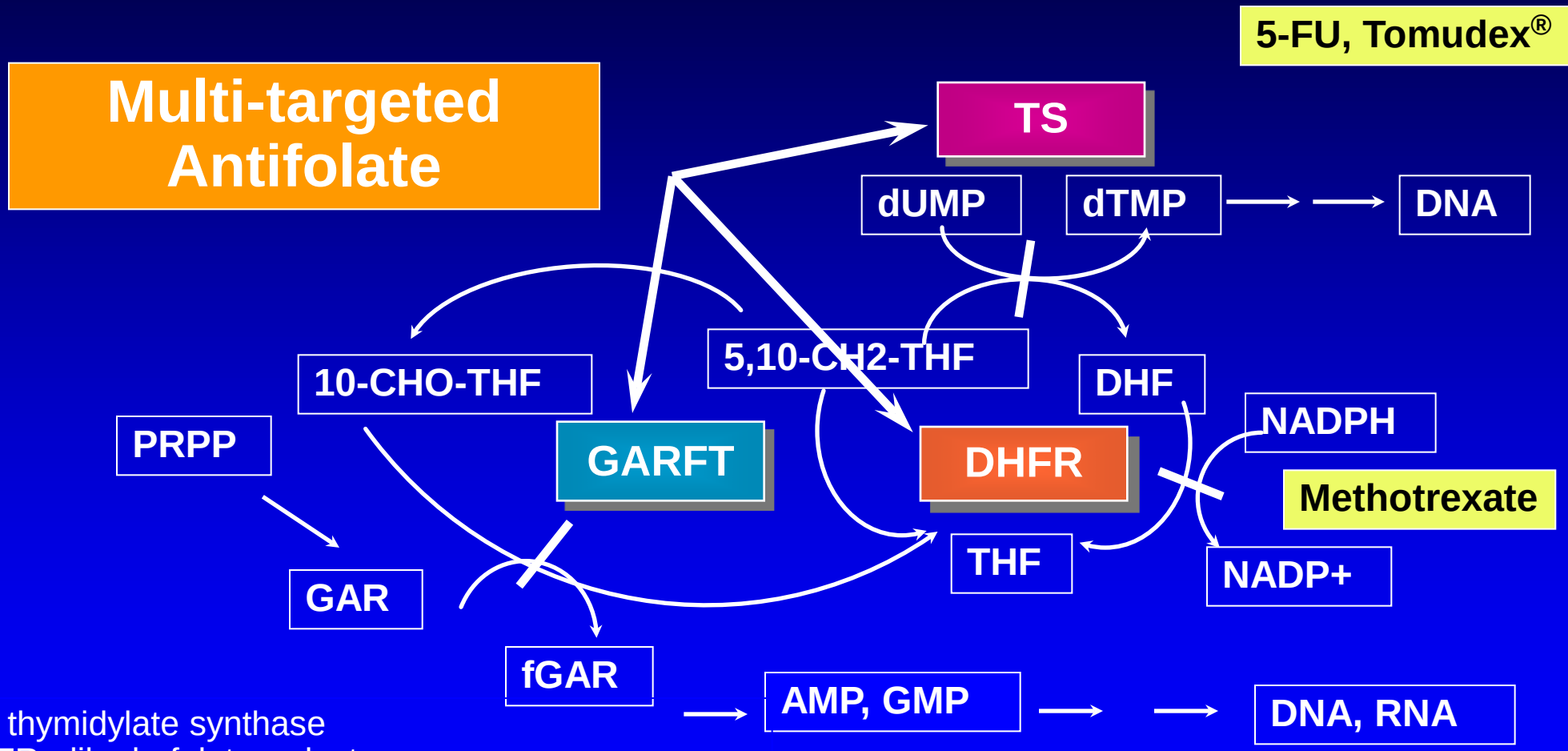


ELVIS-Trial: J Nat Canc Inst 91, 66-72, 1999

New Biologicals for the Treatment of NSCLC

OSI-774	EGFR-tyrosin kinase inhibitor
CI 1033	Pan-Erb-tyrosin kinase inhibitor
ZD1839	EGFR-tyrosin kinase inhibitor
ISIS 3521	Protein kinase C α-antisense inhibitor
PKC 412	Protein kinase C-inhibitor
ISIS 2503	H-ras antisense inhibitor
Bexarotene	Interaction with retinoid x receptor (RxR)

ALIMTA
Folate pathways relevant to the action of ALIMTA



TS: thymidylate synthase
DHFR: dihydrofolate reductase
GARFT: glycinamide ribonucleotide formyltransferase

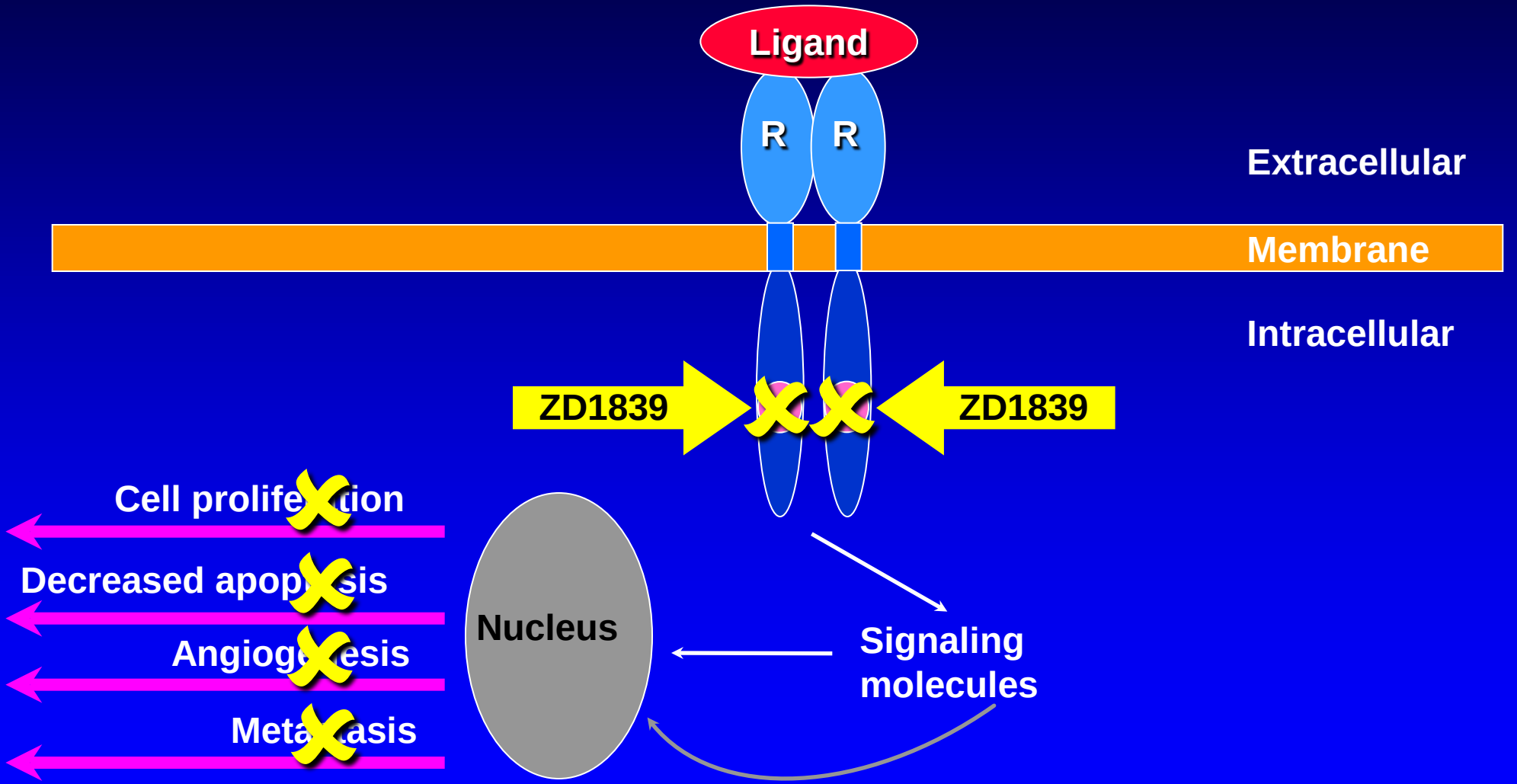
Cisplatin 75 mg/m² and MTA (Alimta™) 500 mg/m² in advanced NSCLC Phase II - Study Results

	Europe*	Canada**
No pts (eval.)	36	29
Partial Response	14 (39 %)	13 (45 %)
Response duration		
median	10 mos	6 mos
range	1 - 15 mos	2 - 9 mos
Overall Survival		
median	11 mo	10 mos
range	1 - 18 mos	1 - 15* mos
1-year-survival	50 %	49 %

*Manegold et al., Ann Oncol 11, 435-440, 2000

** Shepherd et al., Proc ASCO 19, 507a (abstr. 1984), 2000

ZD1839 - mode of action



ZD1839 (IRESSA™) as 2nd/3rd-line Therapy for Advanced NSCLC: Phase II-Results (IDEAL I)

Pts (n): total/eval	210/208		
Response rate	18.7%	(95%CI: 13.7-24.0%)	
Overall disease control	52.9%	(95%CI: 45.9-59.8%)	
Progression-free survival	3 mos	(34% of pts ≥ 4 mos)	
Symptom improvement	38.7%	(95%CI: 30.5-47.4%)	
Adverse events	250 mg	500 mg	
Grade 3/4	32.0%	50.9%	
Diarrhea	1.0%	8.5%	
Rash	1.0%	6.6%	
Pts withdrawn	1.9%	9.4%	

Baselga et al. (2001) NCI-EORTC-AACR (Miami)

NSCLC: Site of first relapse by histology

	squamous	non-squamous	total
locally only	39 %	25 %	30
distant	61 %	75 %	70
brain only	20 %	25 %	23

Feld et al (1984)

Randomized Trials of Chemotherapy after Surgical Resection for NSCLC

Author	Stage	Treatment	pts (n)	MS (mo)	1-y-S	2-y-S	3-y-S (%)
Holmes	Stage II - III	CAP	62	23	75	41	--
	R0 - Res.	BCG	68	16	64	30	--
Lad	Stage I - III	CAP-RT	78	20	60	41	24
	R1 - Res.	RT	86	13	54	32	20
Feld	T2N0, T1N1	CAP	136	76	89	80	60 (5-y)
	R0 - Res.	No Rx	133	83	88	73	52 (5-y)
Ohta	Stage III	VdsP	91	37	--	--	41 (5-y)
	R0 - Res.	No Rx	90	31	--	--	35 (5-y)
Dautzenberg	Stage I - III	COPAC-RT	138	1.3/1.2 y	--	38/36	17/19
	R0 - Res.	RT	129	2.1/0,8 y	--	54/22	34/6
Wada	Stage I - III	CVUFT	115	--	--	--	61 (5-y)
	R0 - Res.	UFT	108	--	--	--	64 (5-y)
		No Rx	100	--	--	--	49 (5-y)
Nijranen	T1-3 N0	CAP	54	7+ y	--	--	67 (5-y)
	R0 - Res.	No Rx	56	5+ y	--	--	56 (5-y)

Induction Chemotherapy in Stage III NSCLC
- selected non-randomized studies -

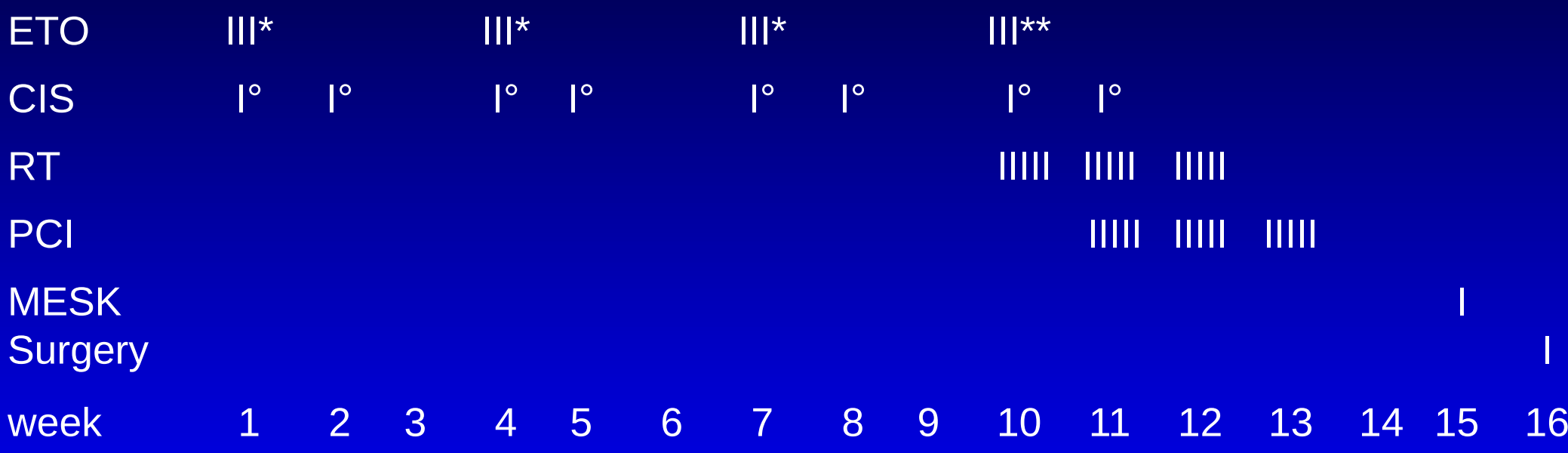
Reference		n pts	Remission (%)	Resection-rate
Bitran	(1986)	20	70	3 / 3
Bonomi	(1986)	20	60	4 / 12
Kris	(1987)	20	65	8 / 19
Martini	(1988)	41	73	21 / 28
Burkes	(1989)	39	70	21 / 35
Pujol	(1990)	30	53	14 / 30
Chapman	(1990)	33	67	23 / 33
Takita	(1993)	40	60.5	23 / 40
Rebello	(1993)	34	65	17 / 34
Fischer	(1994)	60	52	37 / 60

Induction Chemotherapy in Stage III NSCLC
- randomized trials -

	n	Regimen	Survival median	Survival 2-year	Survival 5-year	p
Roth	28	CT (3) + S + RT*	64 mo	60 %	40 %	<.05
	32	S + RT*	11 mo	25 %	18 %	
Rosell	30	CT (3) + S + RT	26 mo	25 %	13 %	<.001
	30	S + RT	8 mo	8 %	0 %	
Pass	13	CT (2) + S + CT (4)	29 mo	46 %	--	NS
	14	S + RT	16 mo	21 %	--	
Elias	24	RT + S + RT	23 ml	--	--	NS
	23	CT (2) + S + CT (2) + RT	19 mo	--	--	

* in case of positive margins

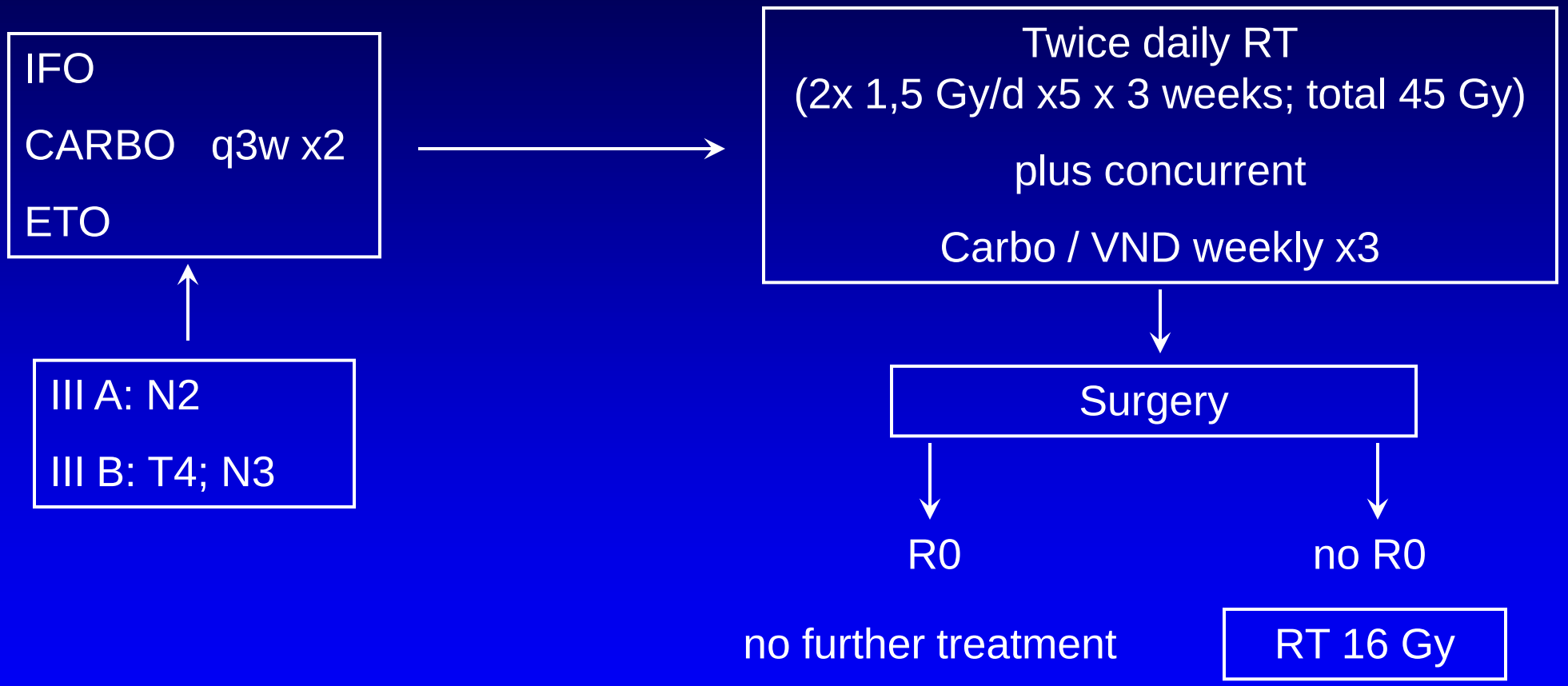
Induction Chemo/Radiotherapy in Stage III A/B NSCLC
Treatment plan



ETO	150* / 100 ** mg/m²/d x 3
CIS	60° / 50°° mg/m²
RT	1,5 Gy twice daily, 5x a week for 3 weeks (total 45 Gy)
PCI	2 Gy daily, 5x a week for 3 weeks (total 30 Gy)

Eberhardt et al, JCO 16, 622-634, 1998

Induction Chemo/Radiotherapy in Stage III A/B NSCLC
Treatment plan



Thomas et al, JCO 17, 1185-1193, 1999

Induction-Therapy in Stage III A/B NSCLC
Results of non-randomized studies

	CT/RT → Surgery						CT → Surgery	
	Albain (1995)		Eberhardt (1998)		Thomas (1999)		Fischer (1994)**	
Survival	III A	III B	III A	III B	III A	III B	III A	III B
median	13 mo	17 mo*	20 mo	18 mo*	25 mo	17 mo*	39 mo	17 mo
1-year	--	--	--	--	--	--	78 %	85 %
2-year	37 %	39 %*	--	--	52 %	30 %*	68 %	45 %
3-year	27 %	24 %*	--	--	35 %	26 %*	31 %	n.r.
4-year	--	--	31 %	26 %*	--	--	--	--

* not significant ** not tested

Albain et al, JCO 13, 1880, 1995
Eberhardt et al, JCO 16, 622, 1998
Thomas et al, JCO 17, 1185, 1999
Fischer et al, Sem Oncol 21 (suppl. 4) 20, 1994

Induction Chemotherapy in operable NSCLC

Questions to be answered

Type, duration, and time of CT

Role of radiotherapy

Role of surgery

Target tumor stage

Staging procedures

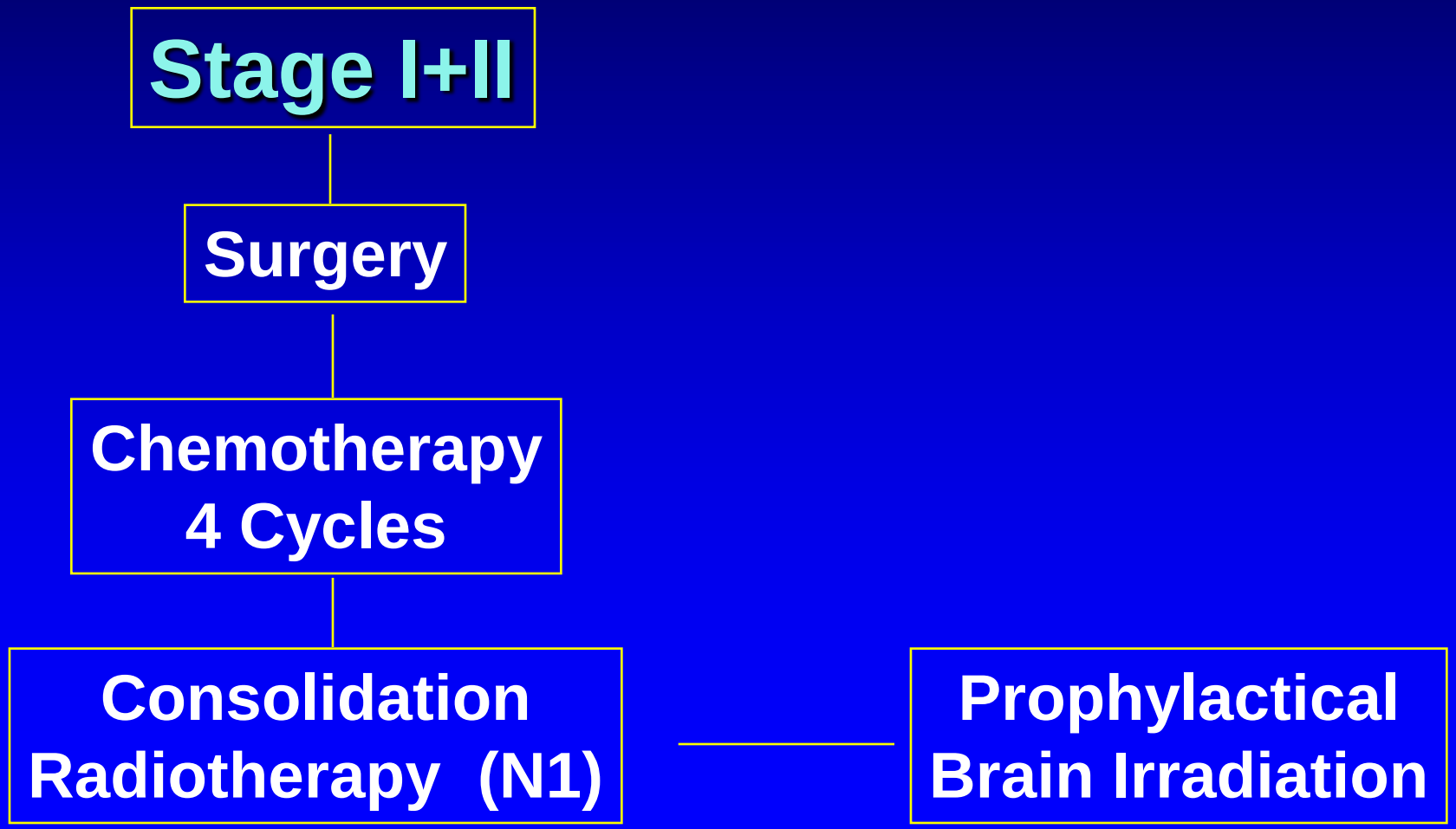
Limited disease

- Primärtumor auf ein Hemithorax begrenzt
- Ipsilaterale LK
- Ipsi- und kontralaterale mediastinale LK
- Rekurrensparese und/oder Phrenikusparese
- Kleiner Erguß ohne maligne Zellen

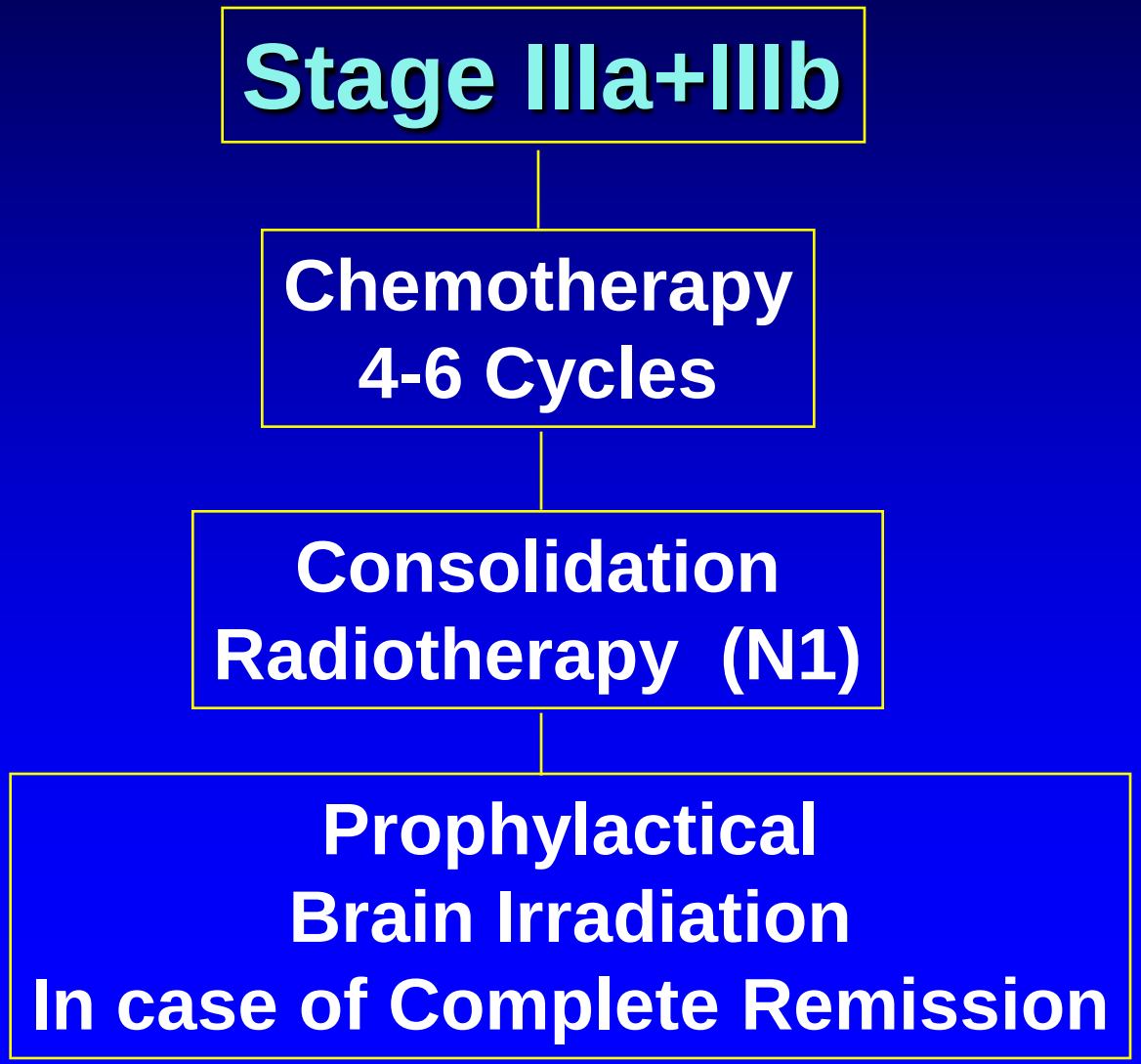
Extensive disease

- Kontralaterale hiläre LK
- Thoraxwandinfiltration
- Pleuritis carcinomatosa
- Lymphangiosis carcinomatosa
- V. cava superior-Syndrom
- Fermetastasen

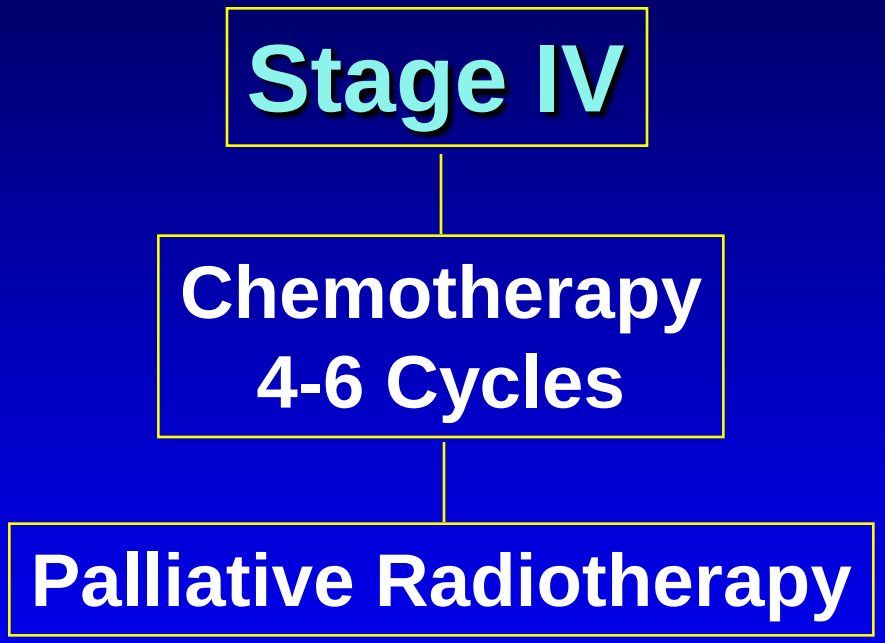
Treatment Strategies in SCLC Stage I + II



Treatment Strategies in SCLC
Stage IIIa and IIIb



Treatment Strategies in SCLC Stage IV



SCLC Chemotherapy

Cyclophosphamid
Adriamycin
Etoposid
Vincristin
Vindesin
Iphosphamid
Carboplatin
Cisplatin
Epirubicin

Paclitaxel
Docetaxel
Irinotecan
Topotecan
Gemcitabin

SCLC - Chemotherapie

Adriamycin	(A)	4-Epirubicin	(Epi-CO)
Cyclophosphamid	(C)	Iphosphamid	(AIO)
Vincristin	(O)	Etoposid	(ACE)

SCLC - Chemotherapie

Cis-Platin
Etoposid

Vincristin
Etoposid

Iphosphamid
Etoposid

Carboplatin
Etoposid

SCLC – Results of Therapy

Results:	limited disease	extensive disease
Remission rates	50-90%	50-90%
Complete Remission	50%	20%
Median Survival	12-15 Mo	6-9 Mo
2-year – recurrence free	6-10%	some cases

SCLC Chemotherapie-Intensivierungsstrategien

sequentiell - alternierende CT
wöchentliche CT
Dosiseskalation
konventionell
mittels G (GM) -CSF
mittels late intensification
mittels early intensification
Multimodale Behandlung
neue Medikamente

PCI beim SCLC (limited disease) in CR nach CTx
Metaanalyse (Auperin et al. 1999)

	mit PCI	ohne PCI
Hirnmetastasen (3J)	33%	59%
	RR=0,46 (0,38-0,57)	
Überleben (3J)	20,7%	15,3%
	RR=0,84 (0,73-0,97)	