
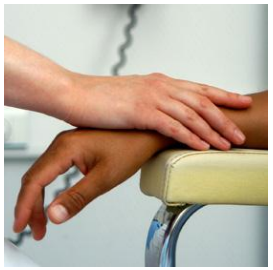
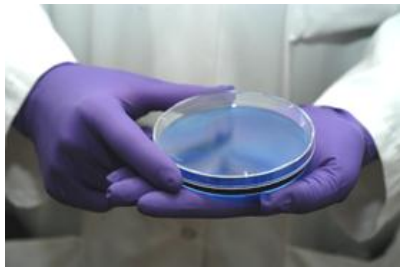
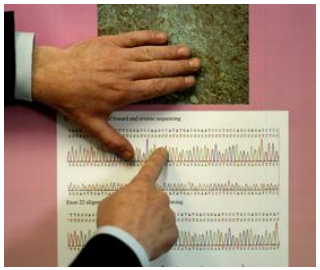

ESMO 2012 NSCLC - IMMUNOTHERAPY, SCLC AND MESOTHELIOMA

Poster Discussion - 31180PD - #1181PD- #1521PD- #1192PD

Benjamin Besse

MD, PhD

VIENNA 2012 ESMO congress

Institut de cancérologie GUSTAVE ROUSSY VILLEJUIF - www.igr.fr

Disclosures

- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
  - **Abbott, Amgen, AstraZeneca, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis**

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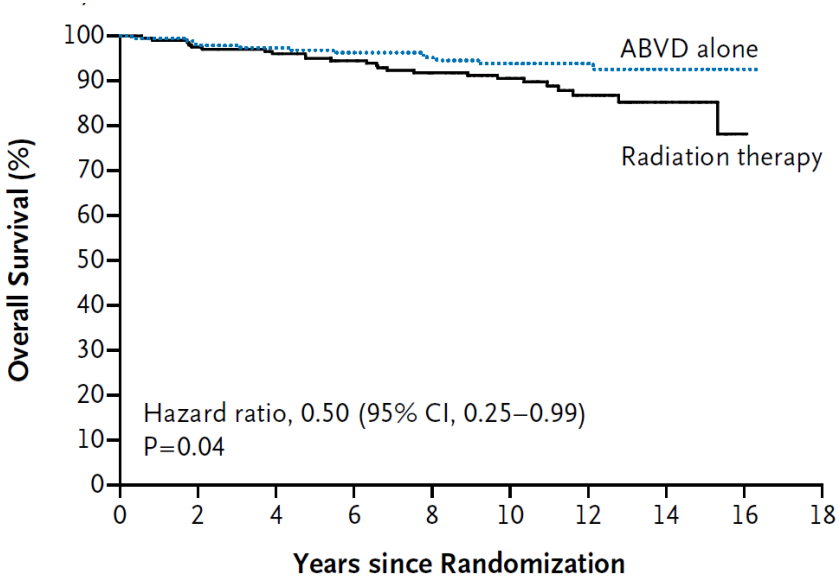
Classical Hodgkin's lymphoma
Standard treatments in adults patients - EORTC

		5 yrs OS
Stages I – II* W/O risk factor	ABVD x 3 + Radiotherapy 30 Gy involved-fields	94-100%
Stages I – II* With Risk factors	ABVD x 4 + Radiotherapy 30 Gy involved-fields	92-95%

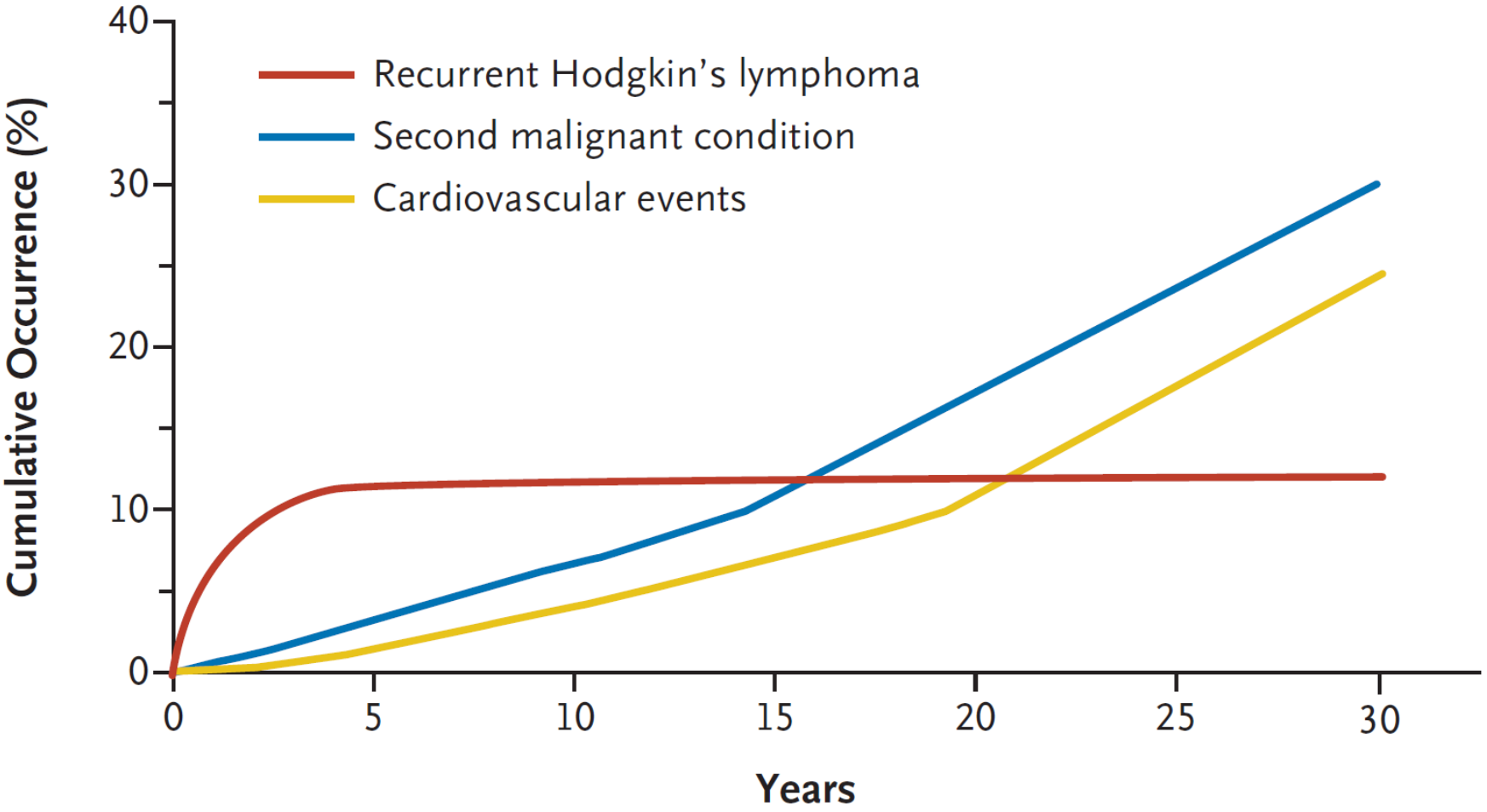
* supra-diaphragmatic stages

EORTC - Risk factors

A - Large mediastinal mass*
B - Age ≥ 50 ans
C - A and ESR ≥ 50 mm
D - ≥ 4 nodal sites
E - B + ESR > 30



Courtesy of Fermé, Meyer NEJM 12


Recurrent Hodgkin's lymphoma
Second malignant condition
Cardiovascular events
Cumulative Occurrence (%)
40
30
20
10
0
0
5
10
15
20
25
30
Years

Hodgkin's lymphoma
Second malignancies in 32591 pts

	Relative risk (95% CI)	Absolute excess risk
All solid tumours	2·0 (1·9–2·4)	33·1
Oesophagus	2·8 (1·8–4·0)	0·7
Stomach	1·9 (1·5–2·4)	1·5
Small intestine	1·5 (0·3–3·5)	0·1
Colon	1·6 (1·4–1·9)	2·0
Lung	2·9 (2·6–3·2)	9·7
Female breast	2·0 (1·8–2·3)	10·5
Leukaemia	9·9 (8·7–11·2)	8·8

Data from Dores and colleagues.[6] All $p<0.05$, except for small intestine.

Hodgkin's lymphoma
Second lung cancer in 5519 pts

BY TIME SINCE TREATMENT (YEARS)

	Number of lung cancers	Relative risk (95% CI)	Absolute excess risk
0–4	18	1·9 (1·1–2·9)	3·9
5–9	25	3·8 (2·5–5·5)	13·8
10–14	21	4·9 (3·1–7·4)	21·5
⩾15	14	5·2 (3·0–8·5)	28·3

Hodgkin's lymphoma
Second lung cancer in 222 pts

- **RELATION WITH PREVIOUS TREATMENT AND CIGARETTE SMOKING**

Treatment		Other*		Moderate to heavy smoker†	
Radiation ⩾5 Gy	Alkylating agents	Relative risk (95% CI)	p	Relative risk (95% CI)	p
No	No	1·0‡		6·0 (1·9–20·4)	0·002
Yes	No	7·2 (2·9–21·2)	<0·001	20·2 (6·8–68·0)	<0·001
No	Yes	4·3 (1·8–11·7)	<0·001	16·8 (6·2–53·0)	<0·001
Yes	Yes	7·2 (2·8–21·6)	<0·001	49·1 (15·1–187)	<0·001

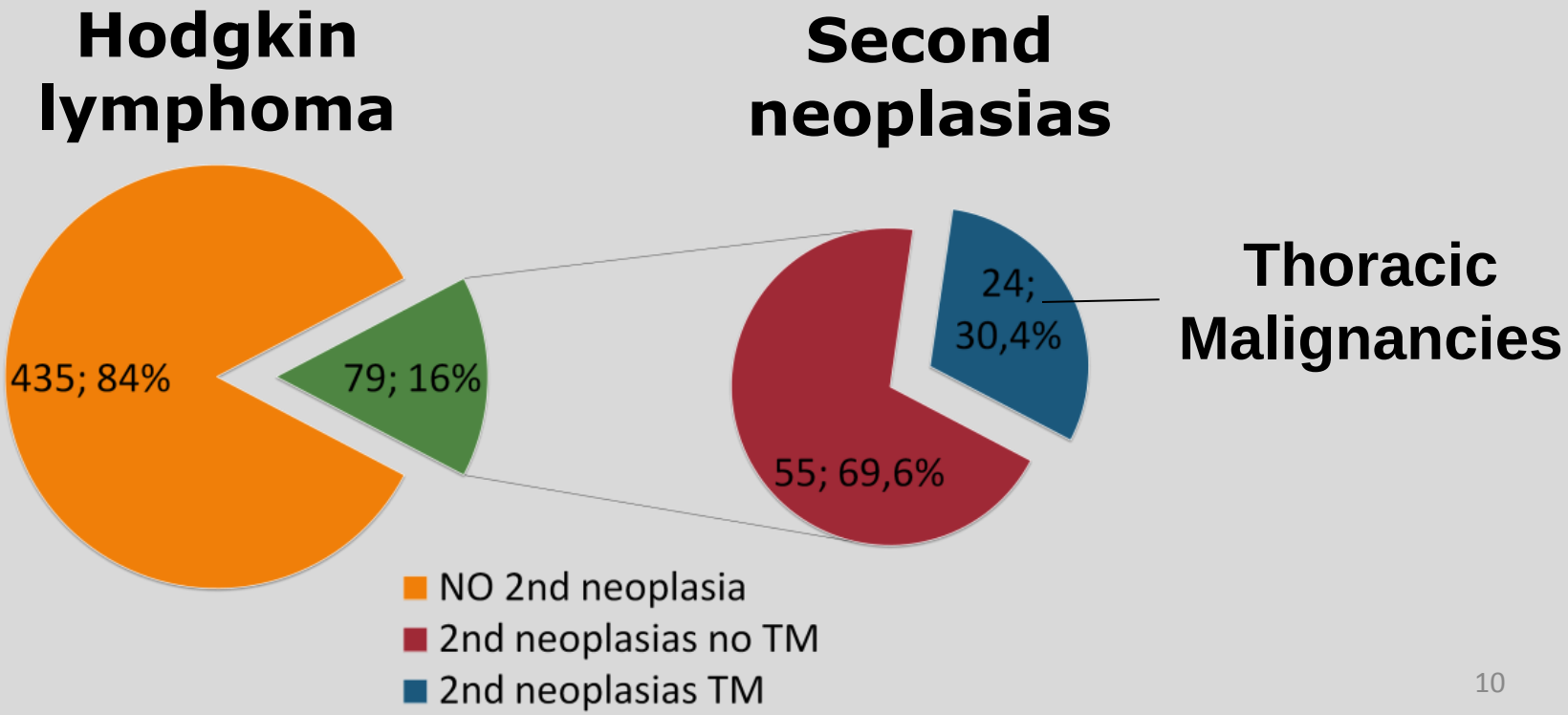
*Includes non-smokers, light cigarette smokers (less than one pack per day), former cigarette smokers, smokers of cigars and pipes only, and patients for whom tobacco smoking habit was not stated. †At least one pack-per-day cigarette smokers. ‡Reference group.

LUNG MALIGNANCIES AND SECOND NEOPLASIAS IN PATIENTS WITH HODGKIN´S LYMPHOMA

E. Almagro-Casado[1], D. Pérez-Callejo[1], A. López-González[3], P. Ibeas[1], A. Ruiz-Valdepeñas[1], M. Palka[1], C. Maximiano[1], M. Méndez García[1], S. Mellor[2], M. Provencio Pulla[1]; [1]Medical Oncology ,Hospital Puerta de Hierro, Majadahonda (Spain), [2]Internal Medicine (idem) [3] Medical Oncology ,Hospital de León (Spain). Corresponding e-mail: e.almagro.c@gmail.com

BACKGROUND AND METHODS

Patients distribution (n=514)



LUNG MALIGNANCIES AND SECOND NEOPLASIAS IN PATIENTS WITH HODGKIN´S LYMPHOMA

RESULTS

YES

- **Thoracic malignancies were more prevalent in men** (88% P=0,001)

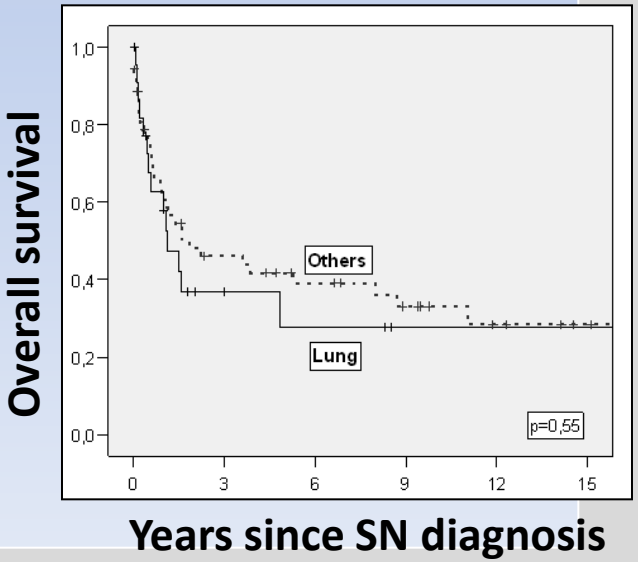
  What is the smoking status ?

- **Treatment with radiotherapy was asociated with increased risk of thoracic malignancies** (0R 2,9 IC 95% 1,1- 7,7 P=0,033)

  Confirmation of previous studies

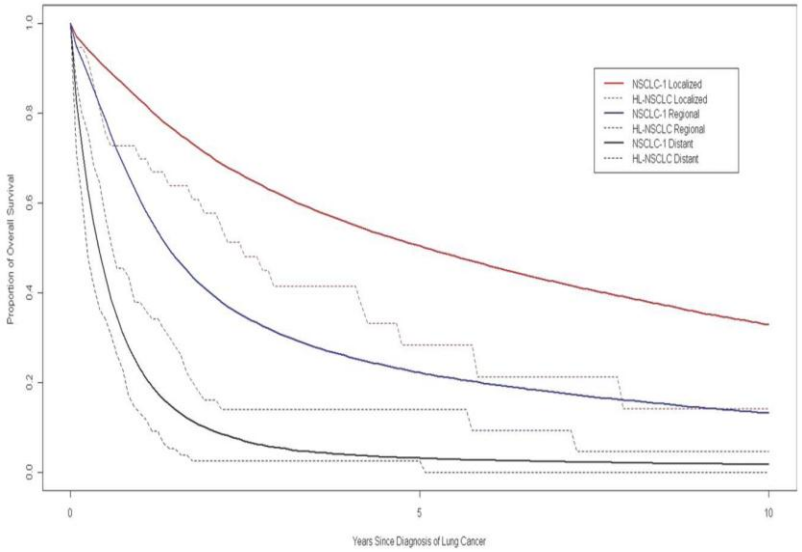
- **Elapsed time to diagnosis of second neoplasia was longer in TM group**
  (median of 16,4 years in TM and 9,7 in HL P=0,03)

  Late screening ?

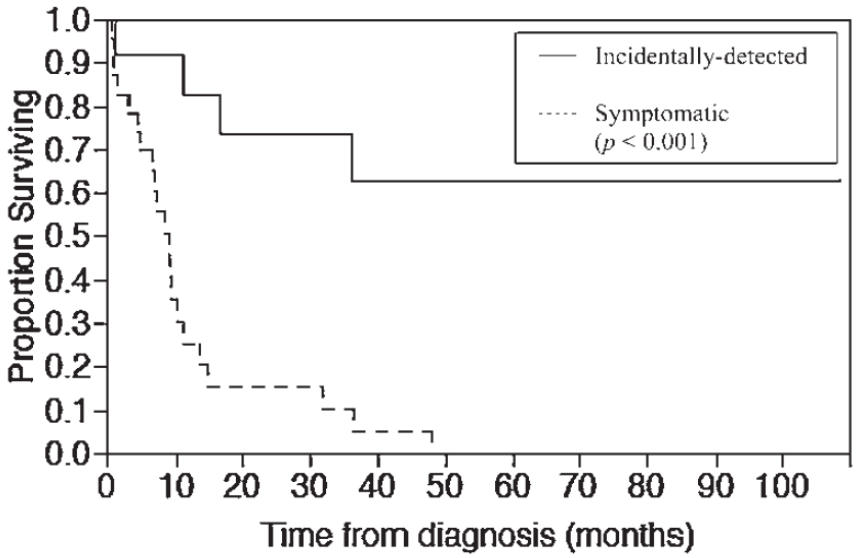


Lung cancer after Hodgkin's lymphoma

Poorer prognosis (SEER database)



Better survival if incidentally-detected



Population to screen ?

Milano, Cancer 2011; Schoenfeld, Ann Oncol 2012

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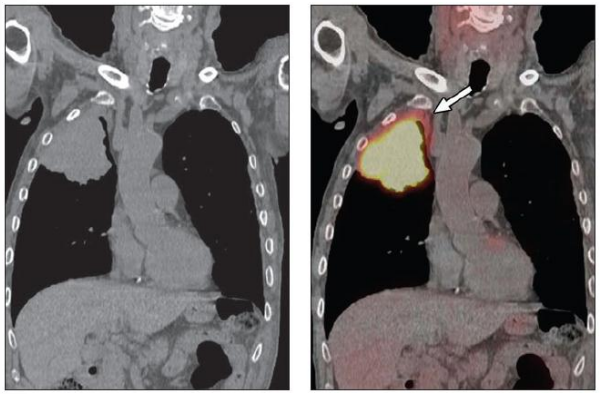
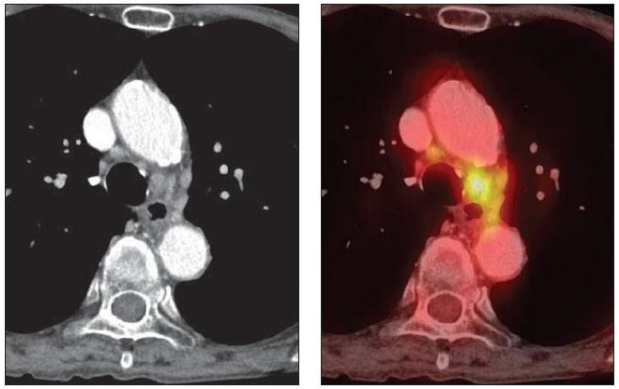
PET/CT in NSCLC staging

T



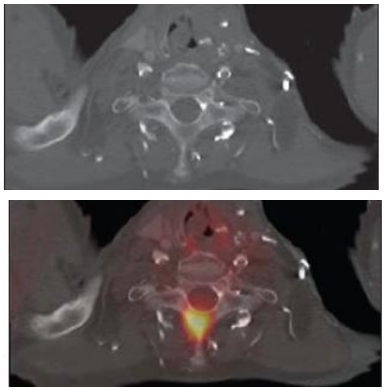
PET/CT accurately predicted the T stage in 82% of cases compared with 68% with CT alone

N



The accuracy of lymph node staging by PET and PET/CT is up to 56% and 78% when compared with surgical staging

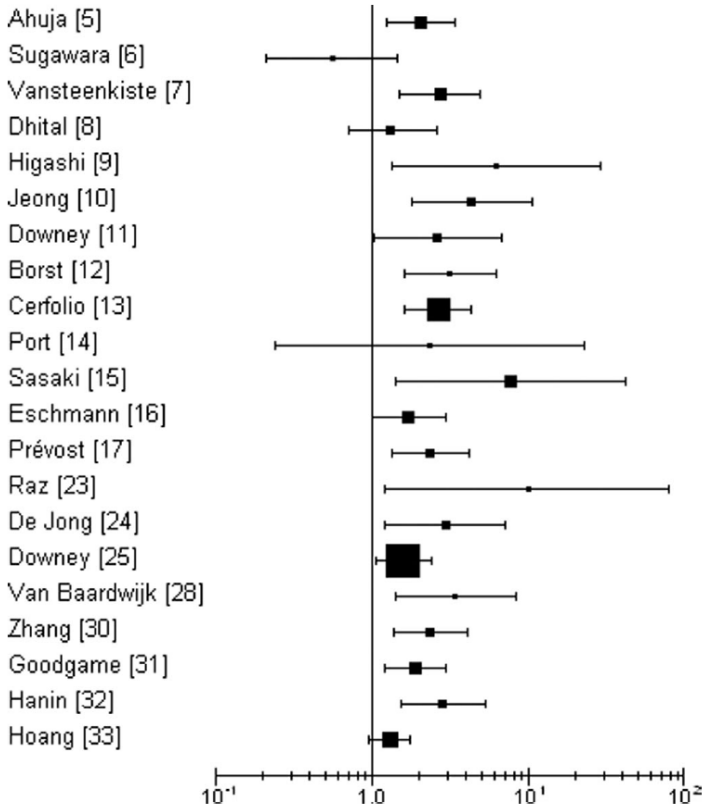
M



PET/CT discovers occult metastatic disease in up to 29% of patients.

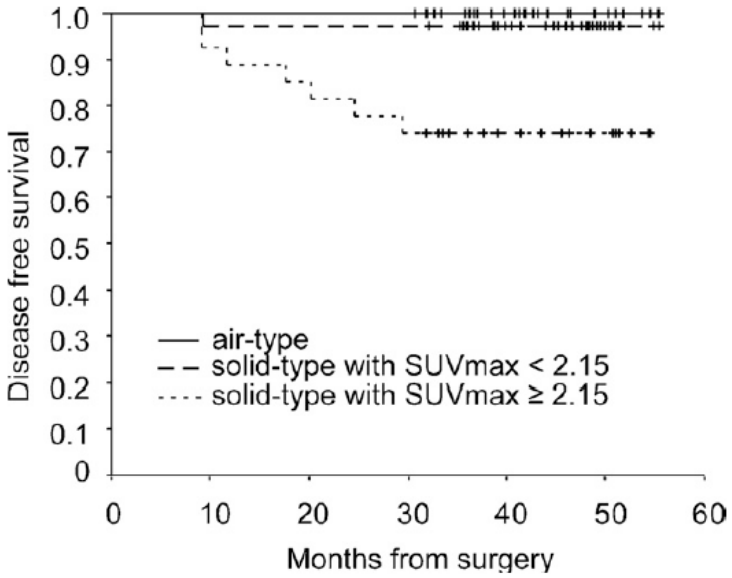
Kligerman, AJR 2009

Tumor (T) FDG uptake is of prognostic value



HR (95% CI) on a logarithmic scale.

By convention, HR 1 means that patients with a higher standard uptake value (SUV) on the primary tumor have a worse prognosis.

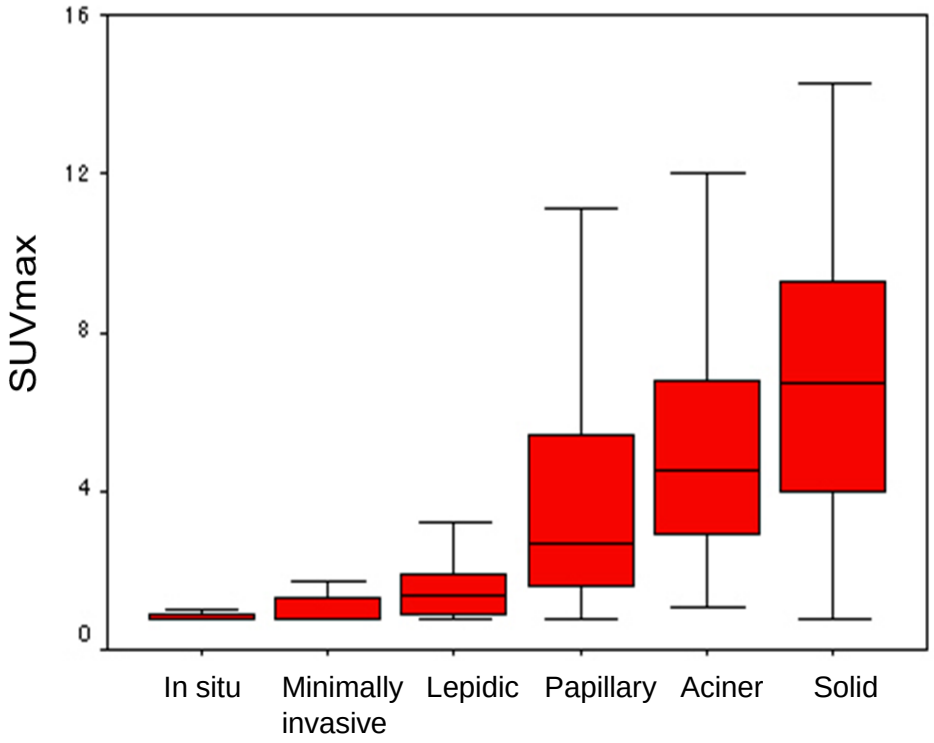


Stage Ia disease, n=100

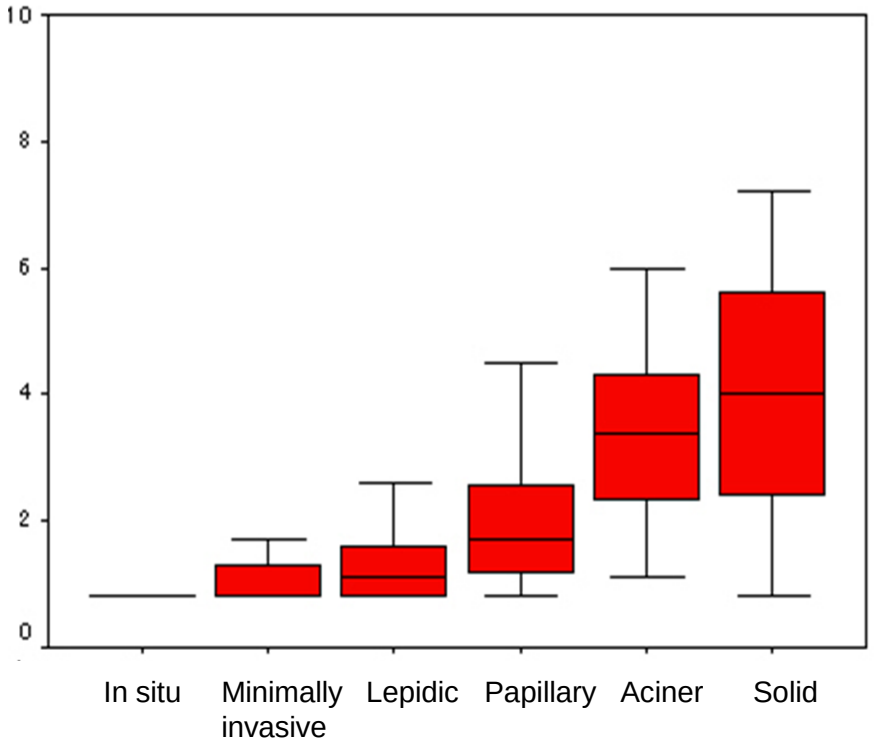
Paesmans JTO 2010, Murakamia EJR 2012

Correlation of different histologic subtypes with SUVmax

【All case (n=287)】



【Stage IA (n=166)】



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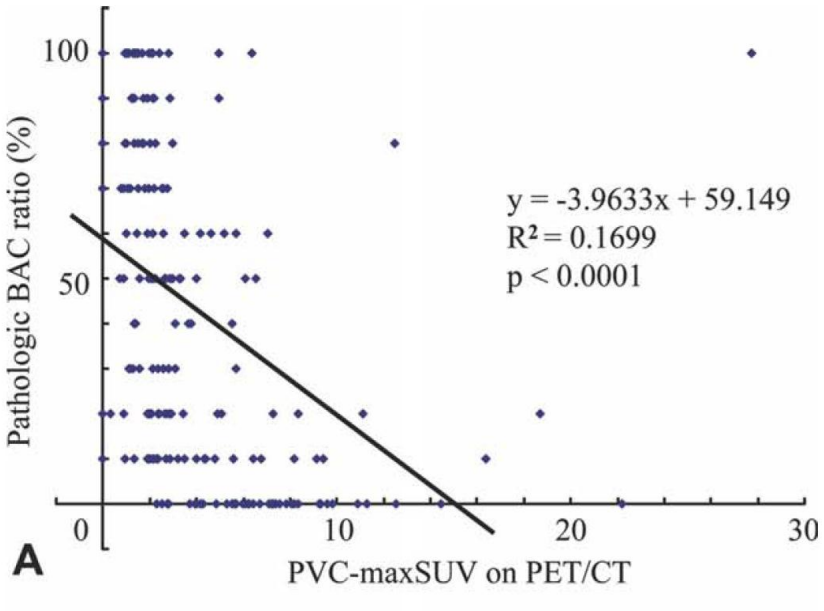
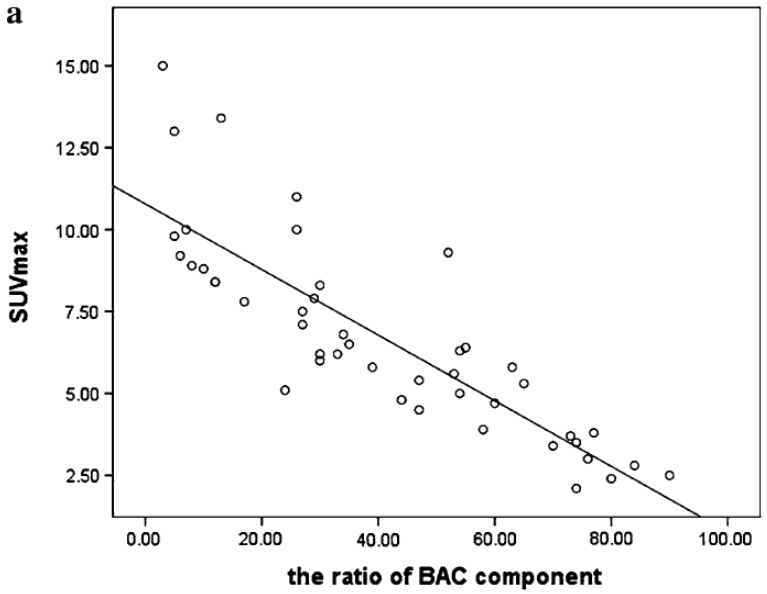
Lepidic (ex-BAC) influences FDG uptake





The SUVmax and the ratio of lepidic component had significant inverse correlation

Nakayama Cancer 2010, Liu Ann Nucl Med 2010

Correlation of different histologic subtypes with GLUT1 and HIF1α

【GLUT1】

	in situ:13	Lepdic:36	Papillary: 52	Acinar:34	Micropapillary: 9	Solid:3
0	11	34	20	14	1	0
1	2	1	17	5	3	0
2	0	0	10	9	4	0
3	0	1	5	6	1	3
mean ± SD	0.15±0.36	0.11±0.52	1.0±0.98	1.2±1.2	1.6±0.83	3

P=0.019

【HIF1α】

	in situ:13	Lepdic:36	Papillary: 52	Acinar:34	Micropapillary: 9	Solid:3
0	13	35	45	26	8	0
1	0	1	5	3	1	1
2	0	0	1	2	0	0
3	0	0	1	3	0	2
mean ± SD	0	0.028±0.16	0.19±0.56	0.47±0.95	0.11±0.31	2.3±0.94

P=0.010

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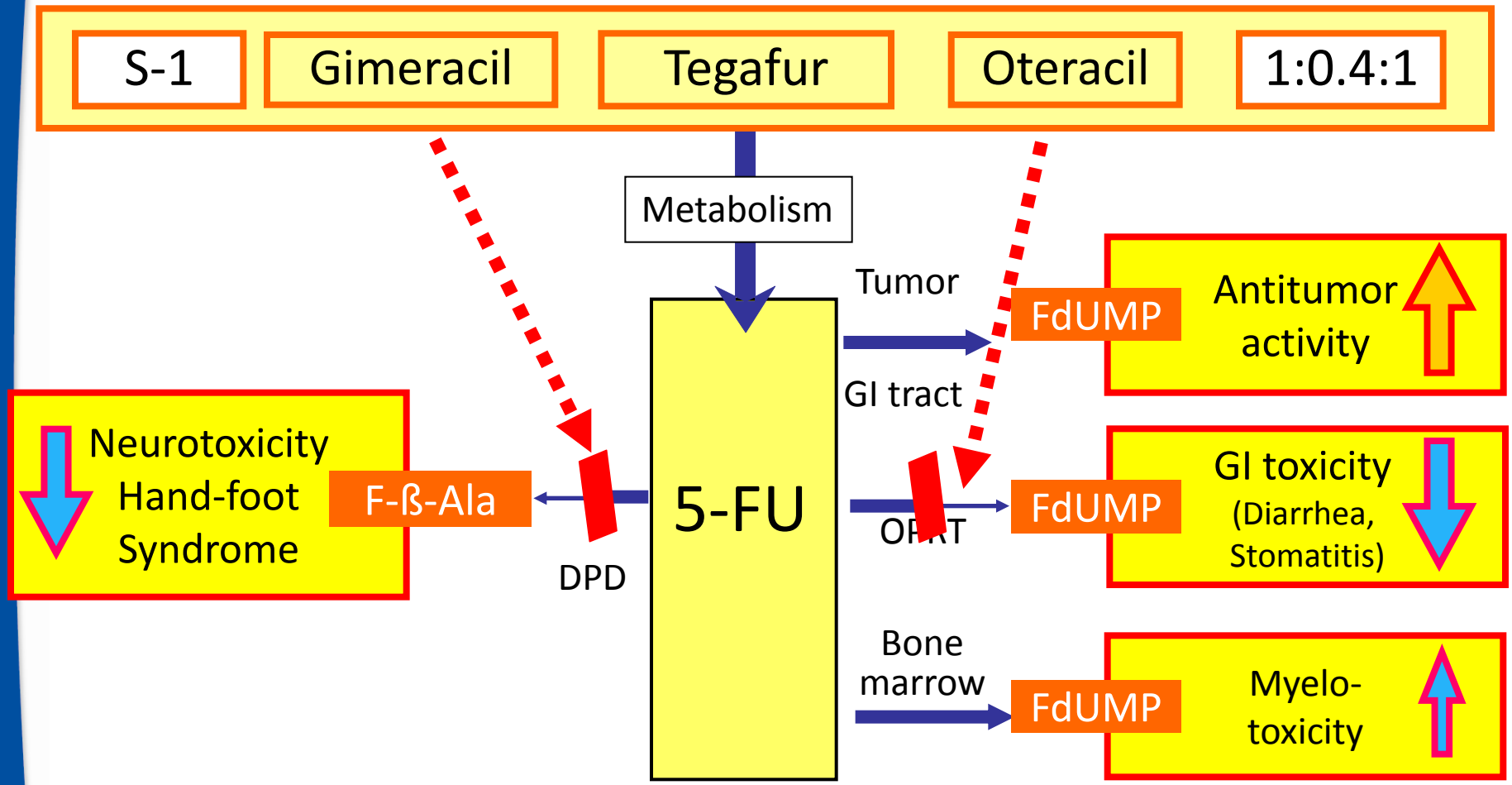
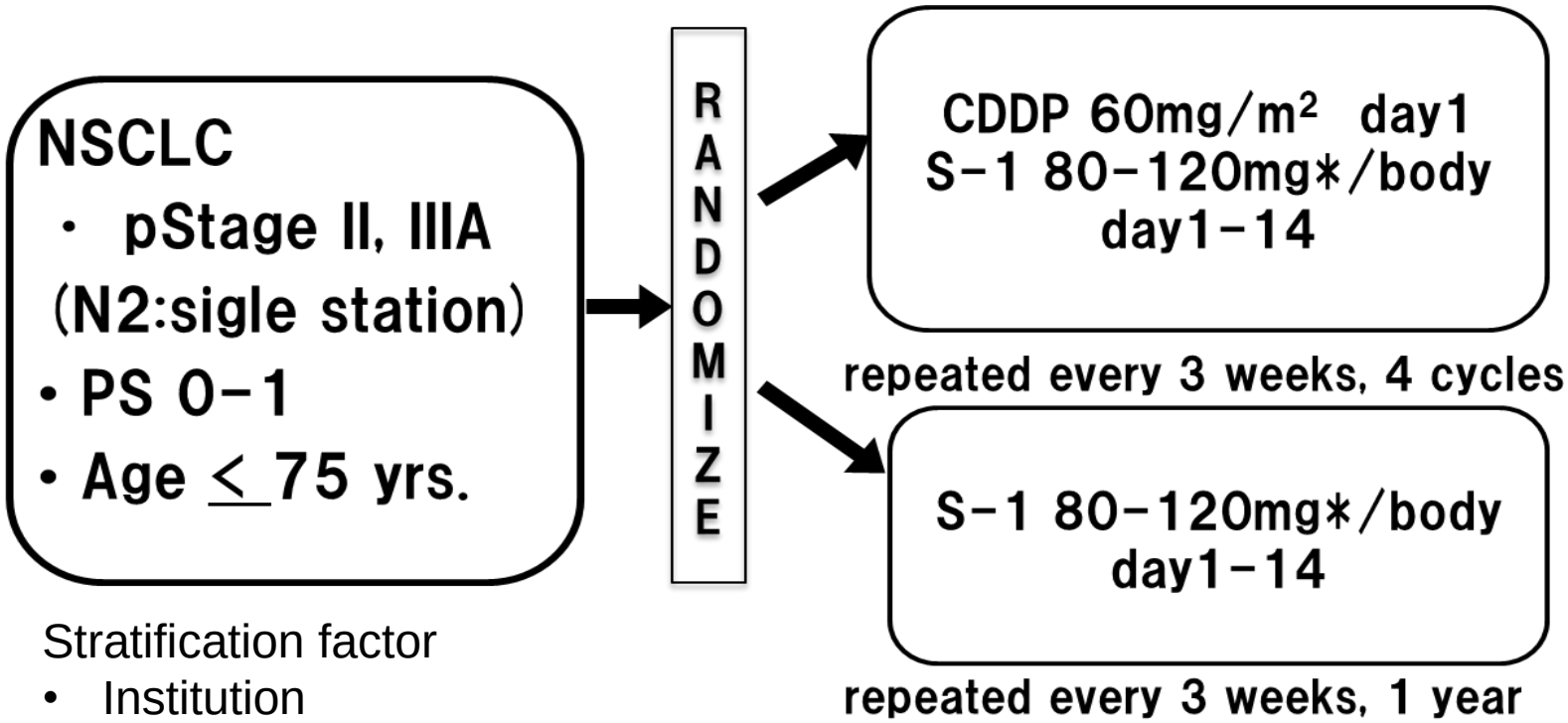
Biochemical Action of S-1



Shirasaka T, et al. Anti-Cancer Drugs 7: 548-557, 1996.

Design



Stratification factor
- Institution
- Histology
- pStage: II or IIIA

Sample size 200 pt

*According to body surface area,
BSA < 1.25 m2, 80 mg/day
1.25=<BSA <1.5, 100 mg/day
BSA >=1.5, 120 mg/day

Primary endpoint: Two year relapse free survival

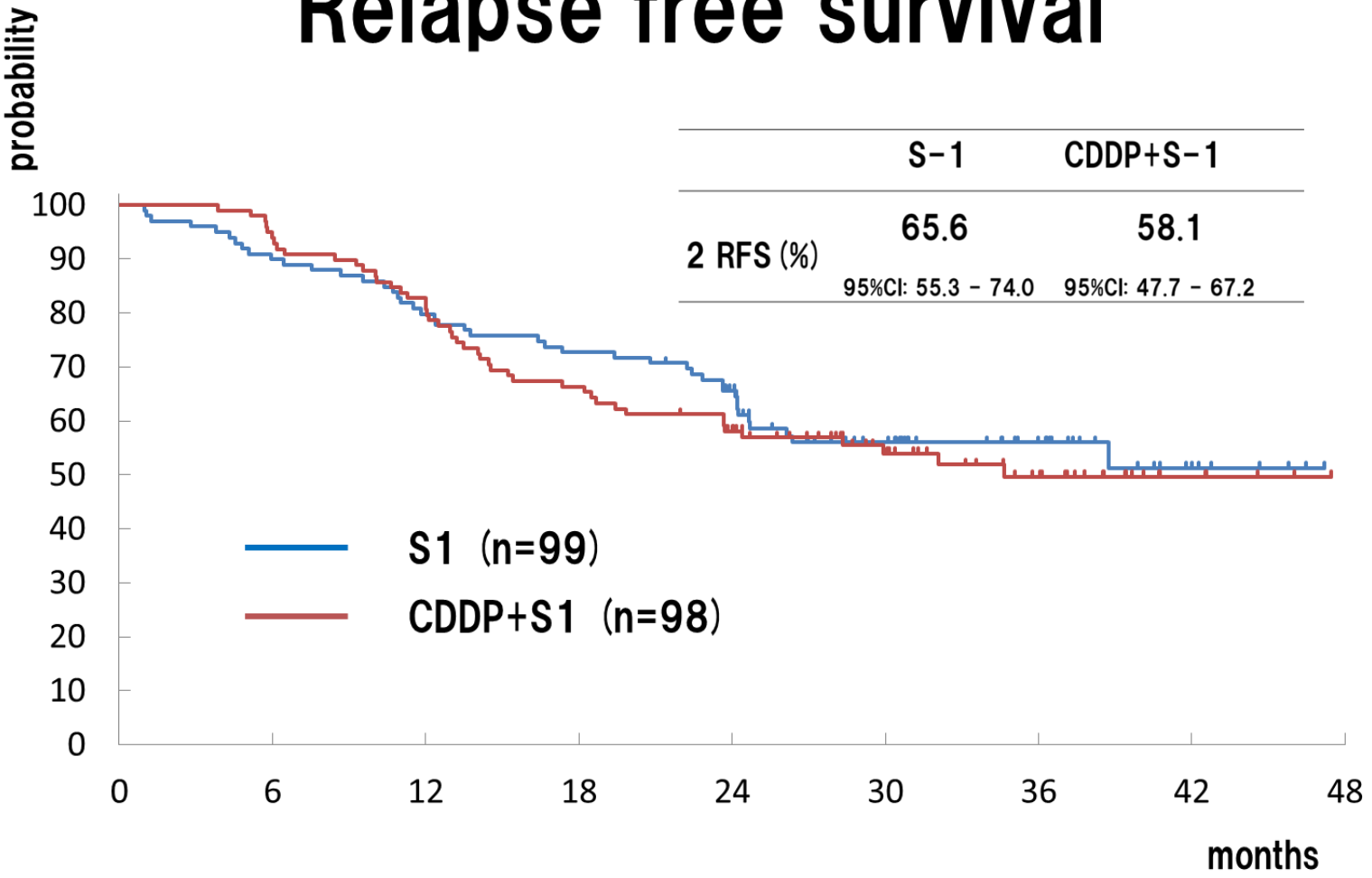
Adverse events

	S-1 (n=97) % Grade 3 or 4	CDDP+S-1 (n=95) % Grade 3 or 4	P
General			
Fatigue	1	4.2	0.209
Anorexia	2.1	9.5	0.032
Nausea	0	6.3	0.014
Vomiting	0	2.1	0.244
Erruption	0	0	
Febrile neutropenia	0	5.3	0.028
Hematological			
Anemia	1	8.4	0.018
Neutropenia	13.4	27.4	0.020
Thrombocytopenia	0	2.1	0.244
Biochemical			
ALT elevation	1	0	1.000
Creatinin elevation	0	1.1	0.495

Completion of protocol treatment

S-1	CDDP+S-1
52.6%	74.7%

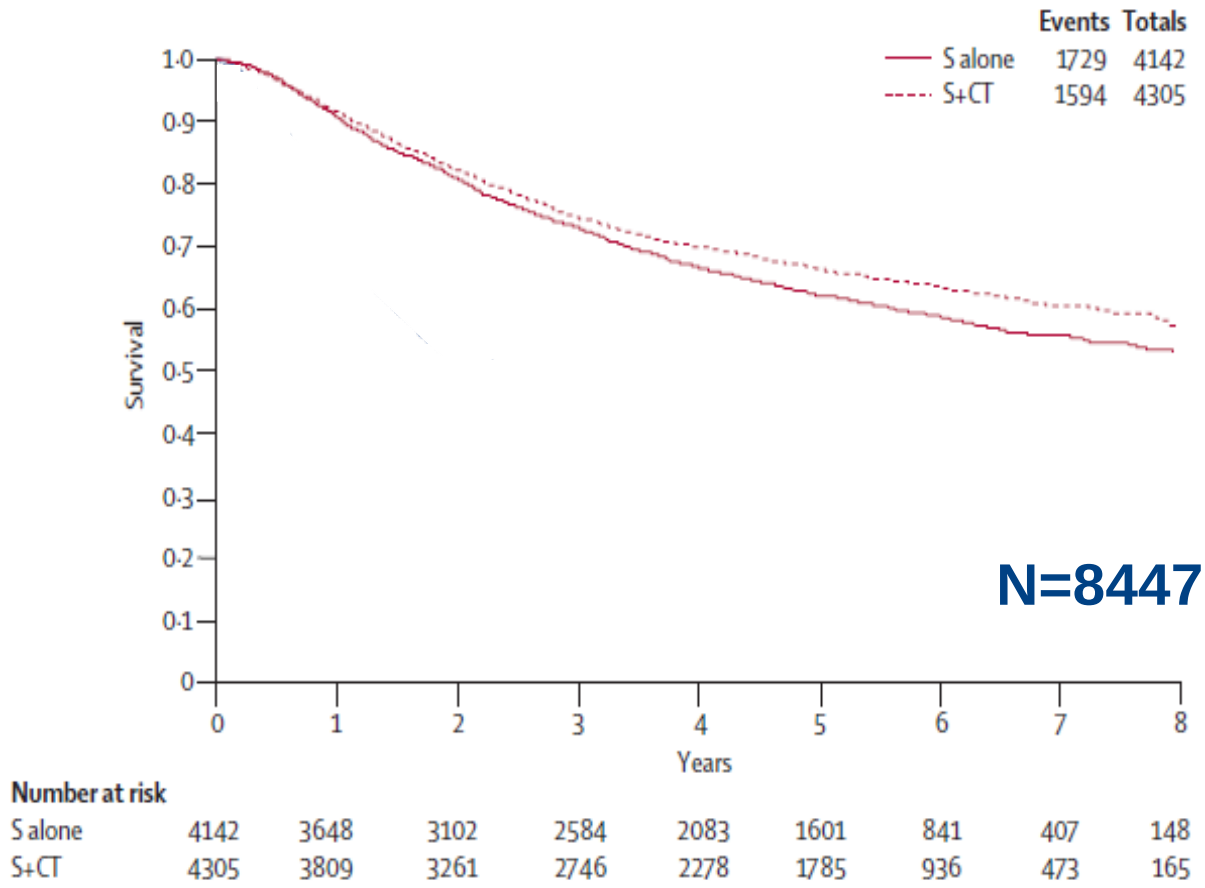
Relapse free survival



	S-1	CDDP+S-1
2 RFS (%)	65.6	58.1
	95%CI: 55.3 - 74.0	95%CI: 47.7 - 67.2

Conclusion: S-1 and CDDP+S-1 demonstrated a promising activity with a favorable 2-year relapse free survival and safety as an adjuvant chemotherapy in patients with completely resected NSCLC.

NSCLC Meta-analyses Collaborative Group



N=8447

HR = 0.87 (0.81-0.93) p<0.000001

Absolute benefit of 4% at 5 years

***Lancet* 2010; 375: 1267–77**

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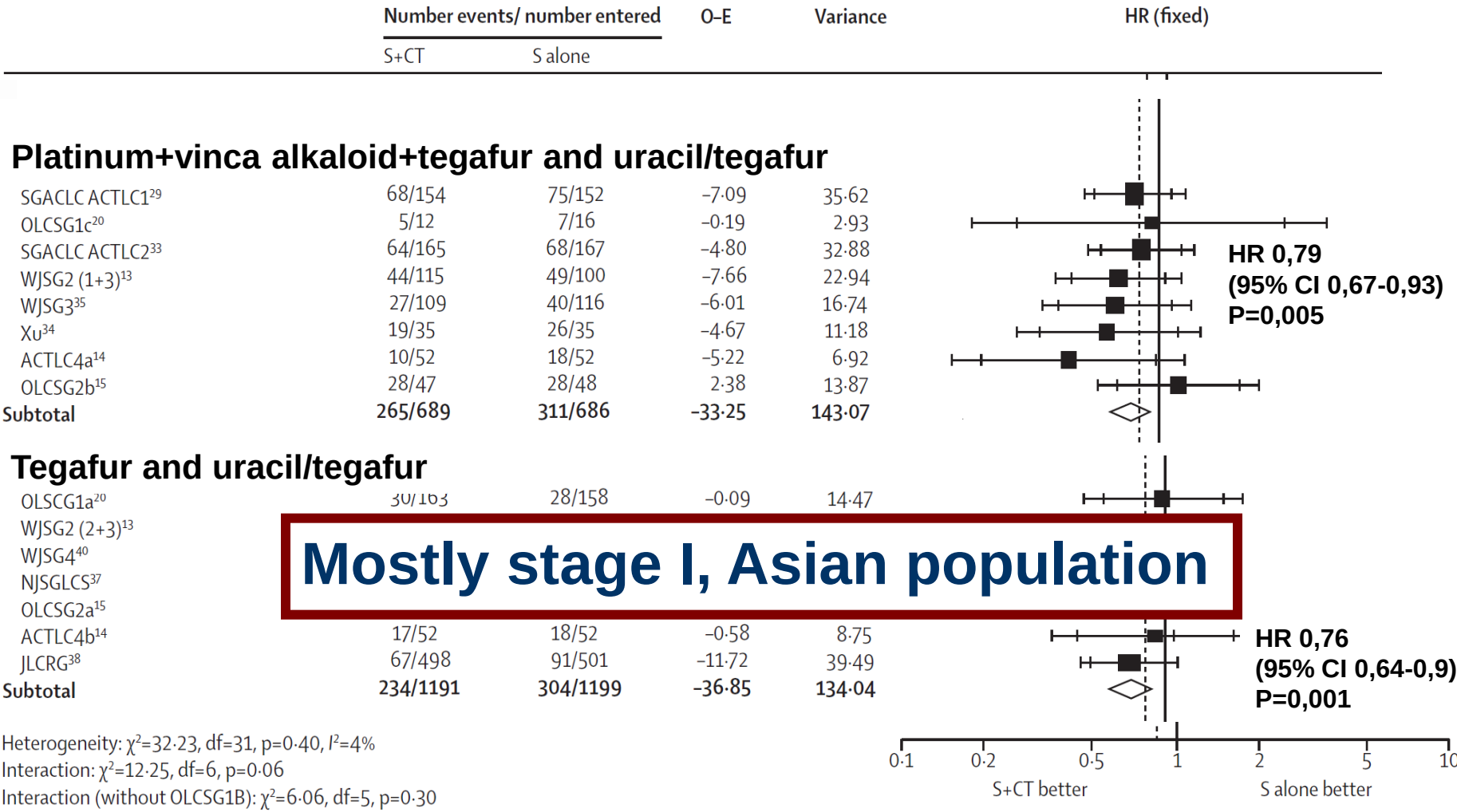
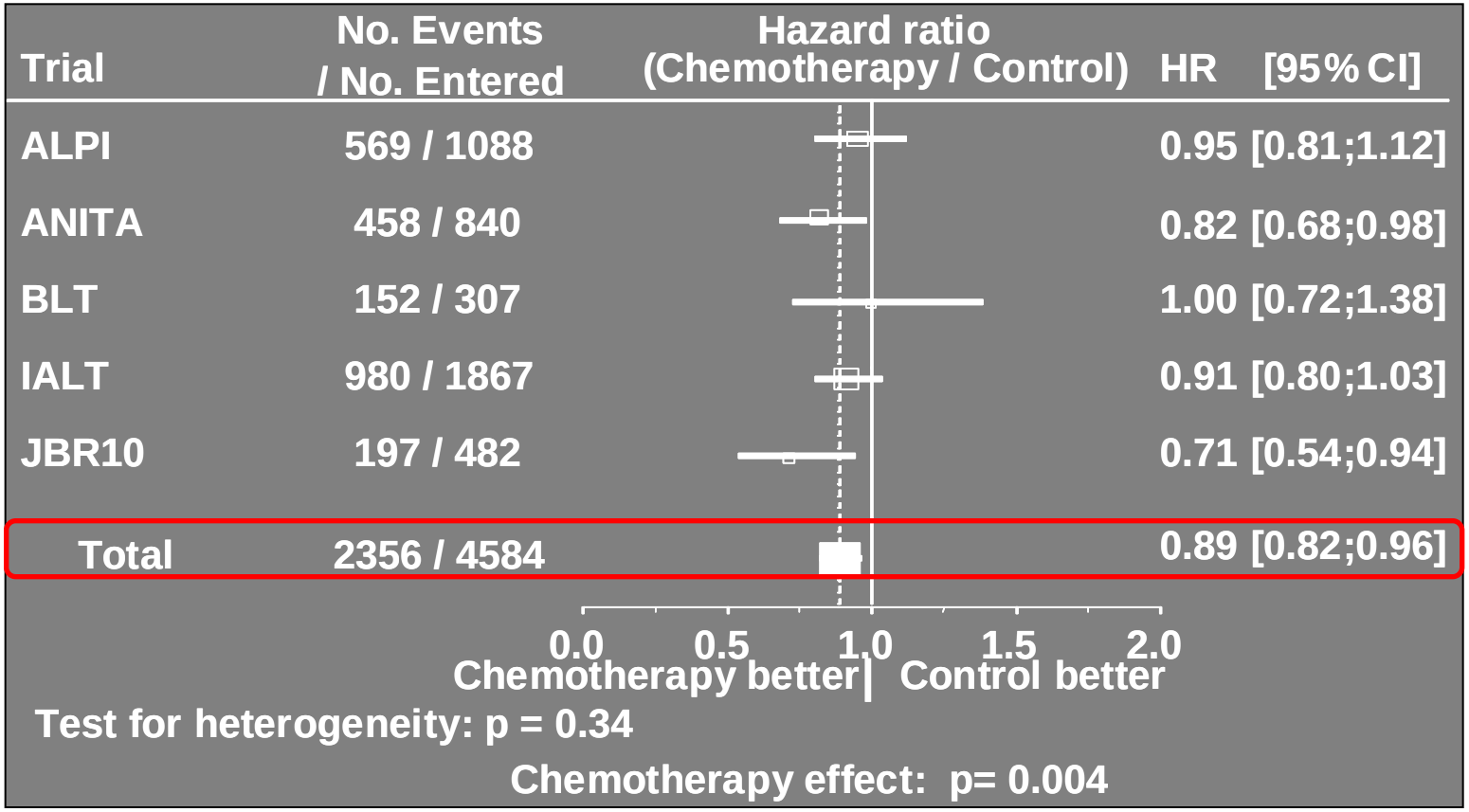


Lancet 2010; 375: 1267–77

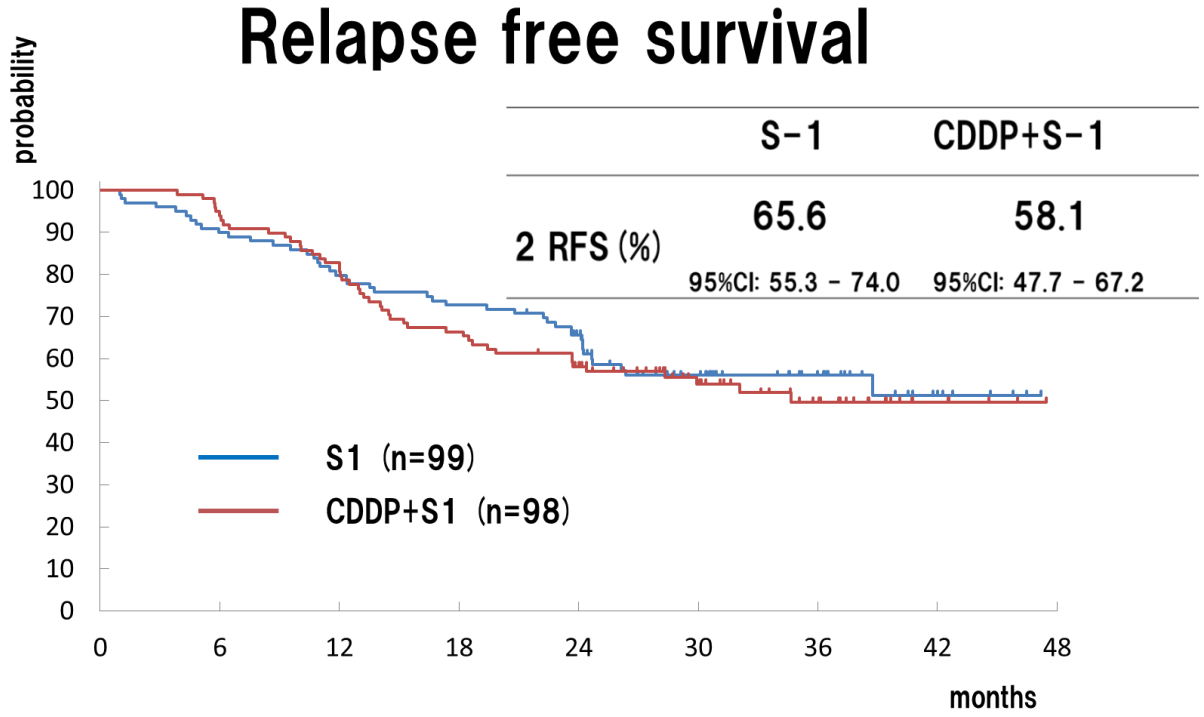
LACE : adjuvant cisplatin-based regimens



Absolute OS benefit at 5 years = 5.3% ±1.6%

Toxic death = 0.8 to 2 %

J Clin Oncol 2008; 26:3552-3559.



- **No implication for clinical pratice**
- **Both arms may be evaluated vs. standard treament**
  - **in larger population**
  - **in western population**

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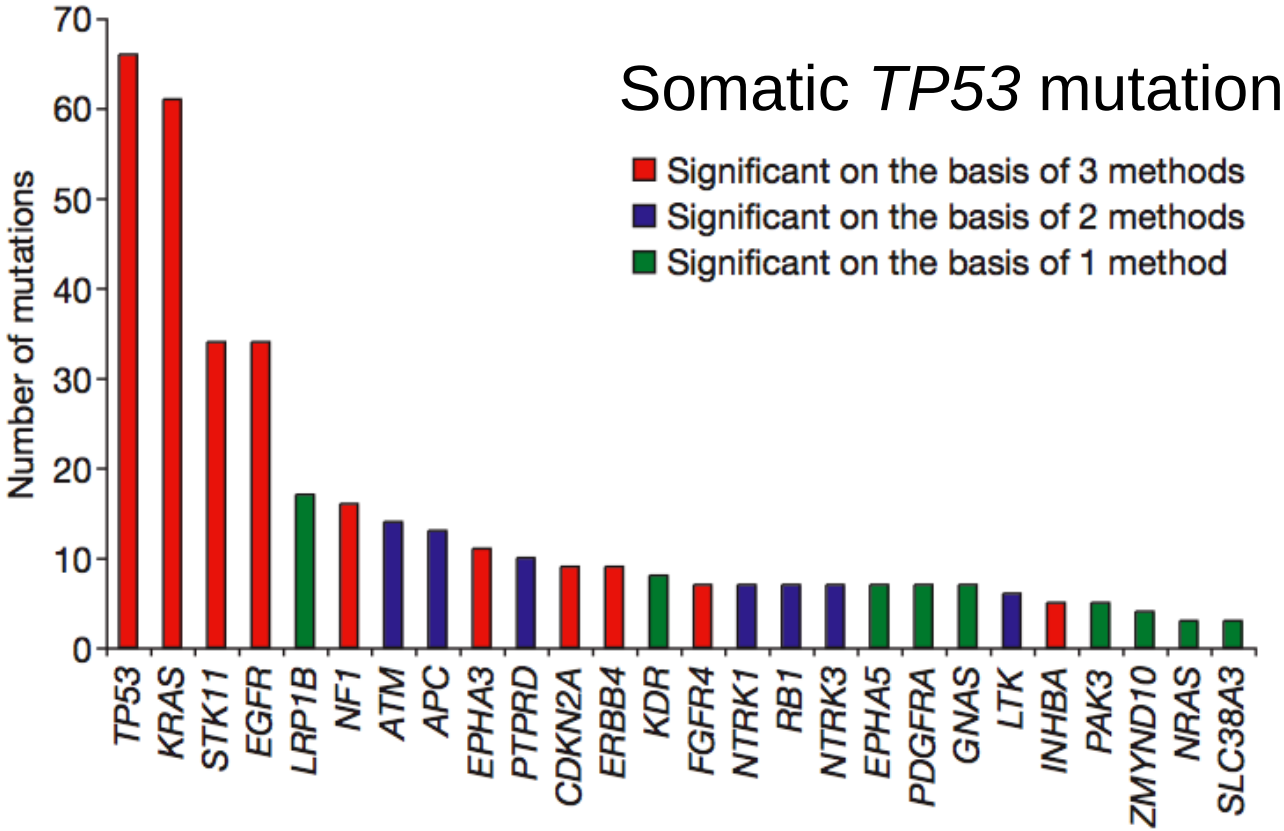
TP53 mutation in NSCLC : the most frequent

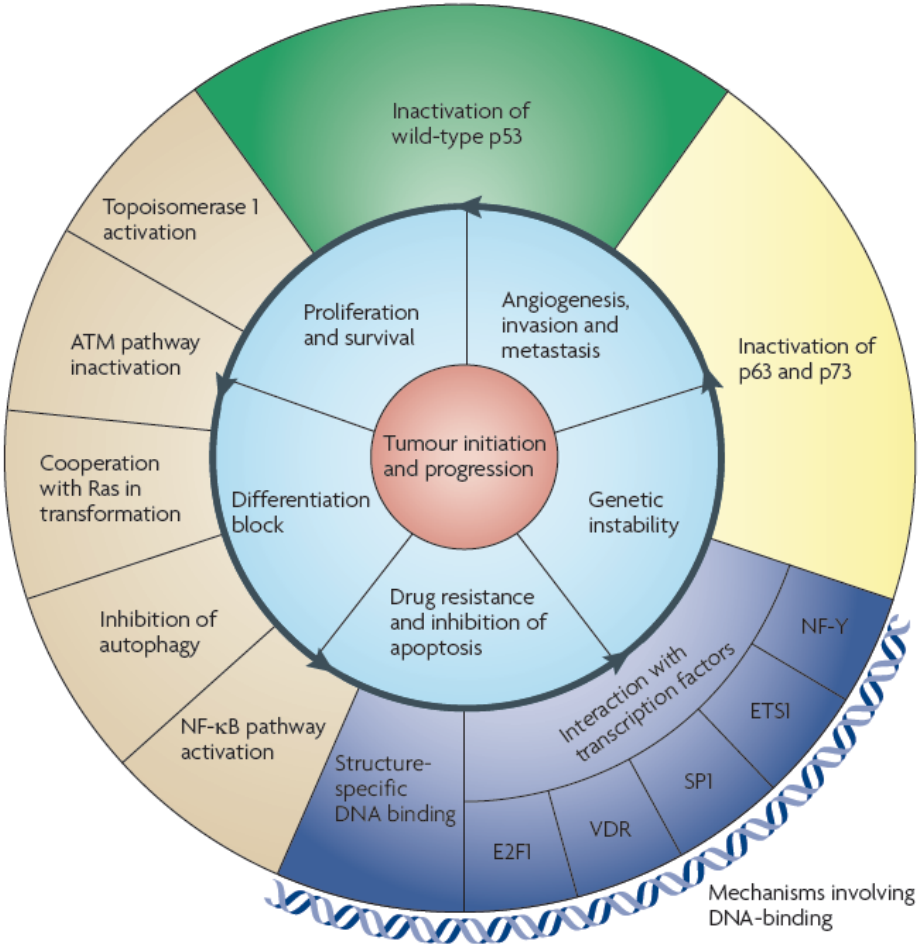


Germline *TP53* mutations : Li–Fraumeni Syndrome

Ding et al. Nature 455, 1069, 2008

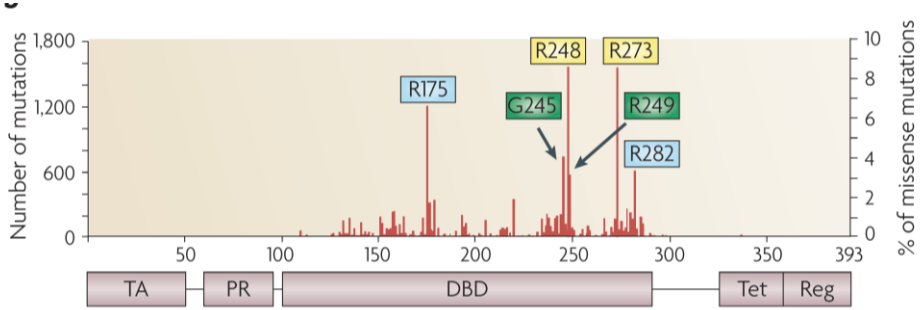
⇢ p53 role

Decision making by p53: life, death and cancer

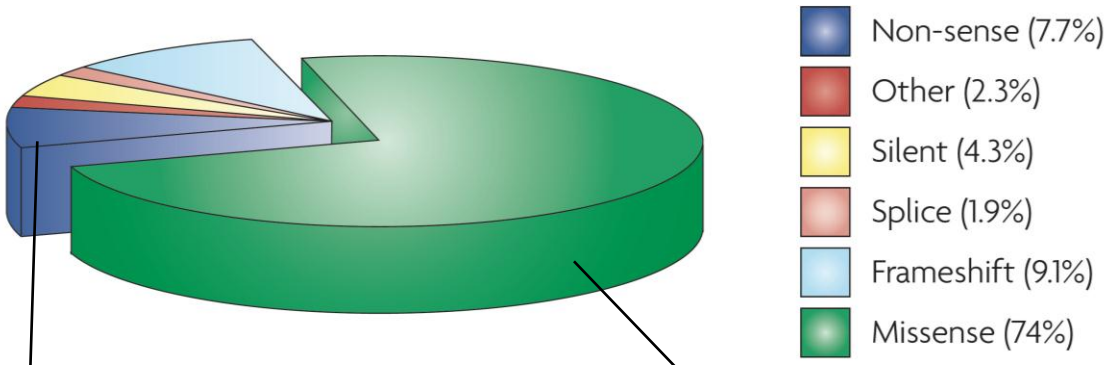


Oren Cell Death Diff 2003, Brosh Nat R

⇢ *TP53* vs. p53



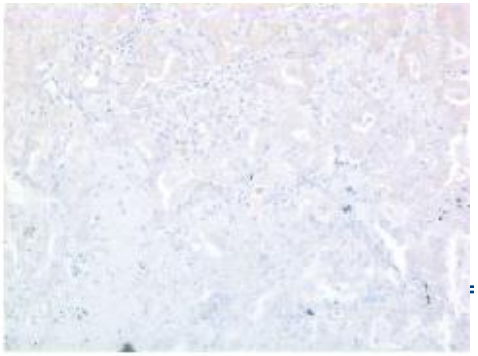
TP53 gene
(mutations)

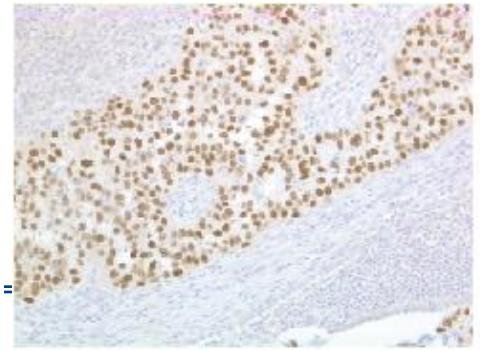


Truncated protein

Accumulation of abnormal p53

P53 protein
(IHC)





Brosh Nat Rev Cancer 2009

TP53 Mutation Description

Four Mutation Classification systems were tested:

Classification 1: WT/MT

Classification 2: WT/3 classes of MT based on measured residual p53 transactivation activity in a standard functional assay

Classification 3: WT/ 3 classes of MT based on effects of mutation on p53 protein structure

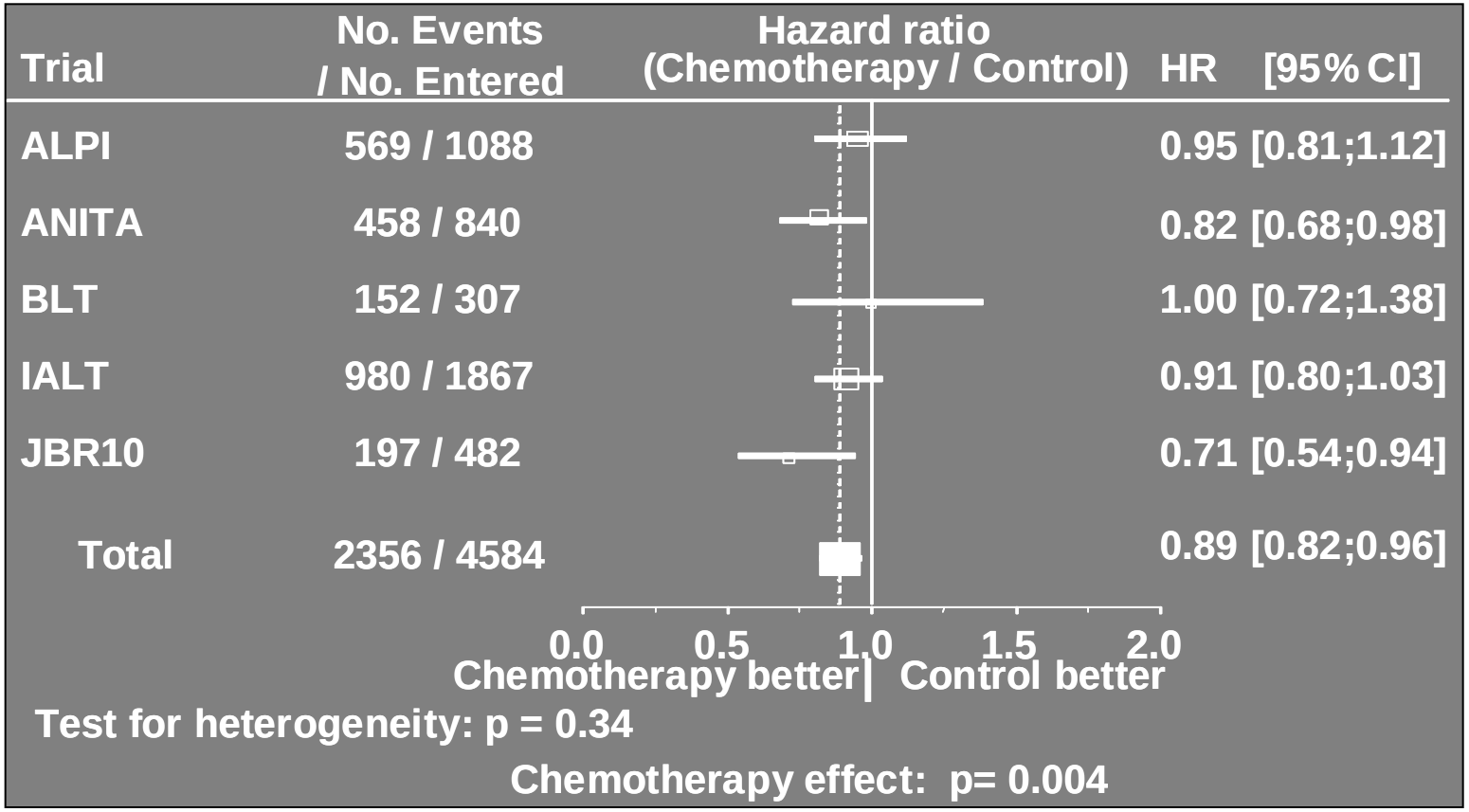
Classification 4: WT/ 3 classes of MT based on interpolating classifications 2 and 3 above.

Data are presented for classifications 1 and 3 only. Classifications 2 and 4 do not add to the message.

Analysis of classification 1 was presented before. However, in present analysis, all datasets were reviewed using the same criteria. Silent mutations were reclassified as WT, a well as mutations not previously found in TP53 database and predicting no functional/structural effects

IPRI International Prevention Research Institute

LACE : adjuvant cisplatin-based regimens



Absolute OS benefit at 5 years = 5.3% ±1.6%

Toxic death = 0.8 to 2 %

J Clin Oncol 2008; 26:3552-3559.

Dataset/Classification 1

TRIAL		WT	MT	TOTAL
IALT	Nb	303	221	524
	%	58	42	
JBR10	Nb	286	111	397
	%	72	28	
ANITA	Nb	74	31	105
	%	70	30	
CALGB	Nb	112	71	183
	%	61	339	
TOTAL		775	434	1209

Analysis

Cox model used in LACE-BIO

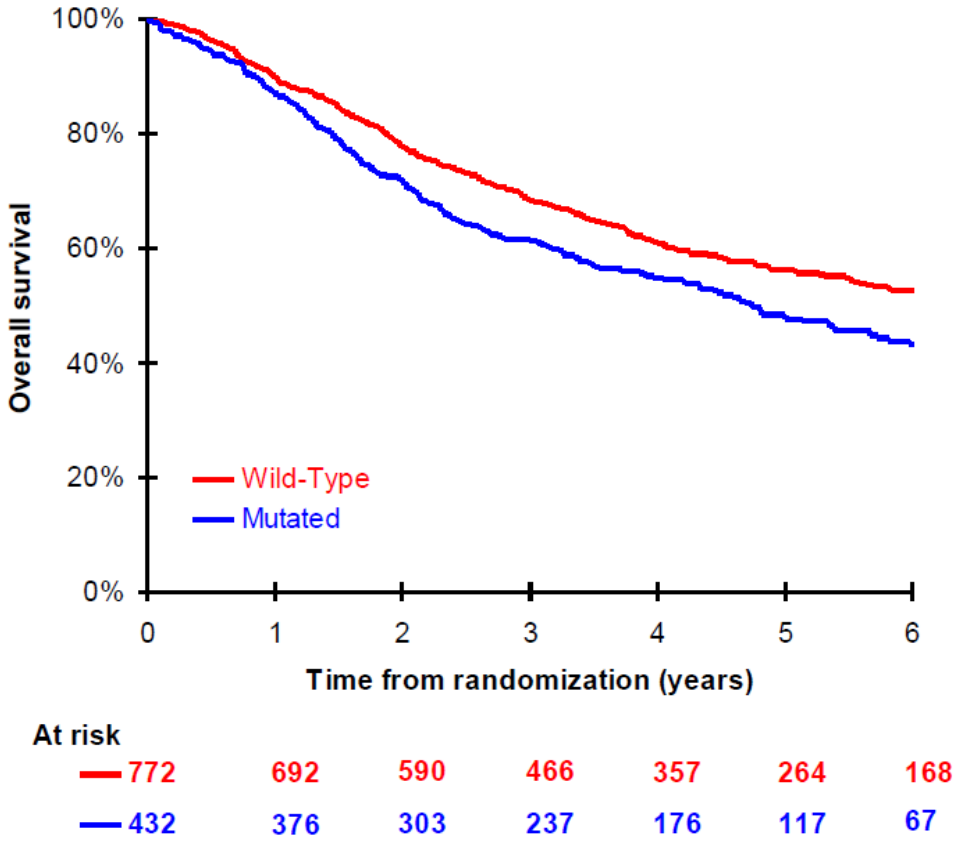
stratified on trial
adjusted on :
- **Attributed treatment (no chemotherapy, chemotherapy)**
- **Sex (male, female)**
- **Age (<55, 55-64, ≥65)**
- **Histology (squamous cell carcinoma, adenocarcinoma, other)**
- **T (T1, T2, T3-4)**
- **N (N0, N1, N2)**

A test was considered significant if p-value ≤ 0.01

Test for heterogeneity will not be presented: Tthey all are non-significant

Classification 1

Prognostic analysis : unadjusted Kaplan-Meier survival curves



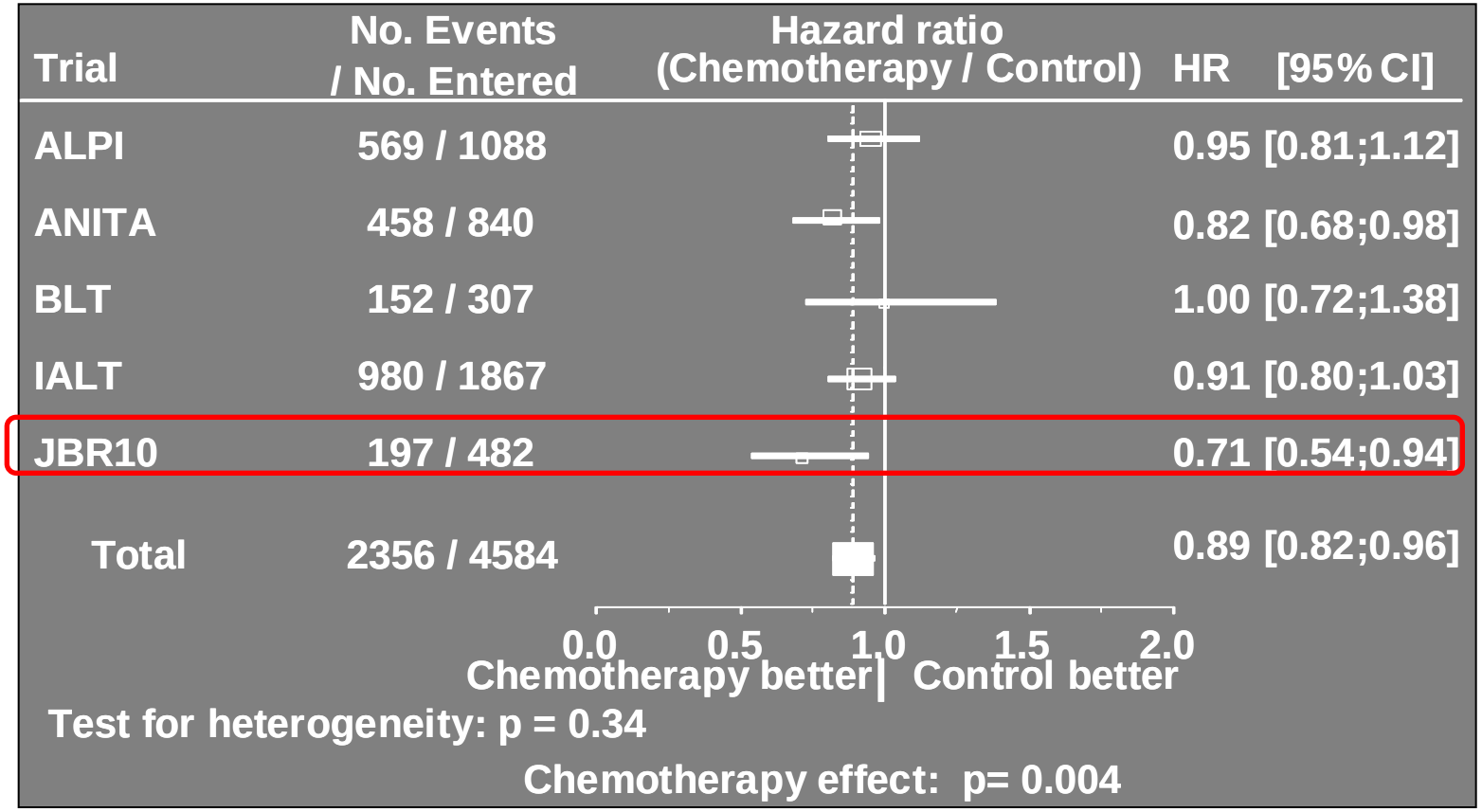
Classification 1 – Overall Survival

Predictive analysis

***P53* mutation**	**Chemotherapy group** (Nb deaths / Nb patients)	**Control group** (Nb deaths / Nb patients)	**HR for event CT vs. no CT** [95% CI]
Wild-Type n=772	153/377	190/395	0.77 [0.62;0.96] p=0.02
Mutant n=432	127/233	100/199	1.05 [0.81;1.37] p=0.71
HR for event Mutant vs. WT [95% CI]	1.39 [1.09;1.77] p=0.008	1.02 [0.79;1.30] p=0.90	Test for interaction p53*treatment **p=0.07**

TP53 mutation (classification 3)	**CT group** (Nb events / Nb patients)	**No CT group** (Nb events / Nb patients)	HR for event CT vs. no CT [95% CI]
Wild-type n=772	179/377	218/395	0.75 [0.62;0.92] p=0.005
Non-missense n=91	34/56	18/35	1.12 [0.63;1.98] p=0.71
HR for event Non-missense vs. WT	1.31 [0.90;1.90] p=0.16	0.88 [0.54;1.44] p=0.62	1.48 [0.81;2.72] p=0.21
Missense-nonDBM n=153	48/78	45/75	1.03 [0.69;1.55] p=0.88
HR for event Missense-nonDBM vs. WT	1.52 [1.10;2.10] p=0.01	1.11 [0.80;1.54] p=0.53	1.37 [0.87;2.16] p=0.18
Missense-DBM n=188	56/99	52/89	0.88 [0.60;1.29] p=0.50
HR for event Missense-DBM vs. WT	1.15 [0.85;1.56] p=0.36	0.99 [0.73;1.34] p=0.94	1.17 [0.76;1.79] p=0.48

LACE : adjuvant cisplatin-based regimens



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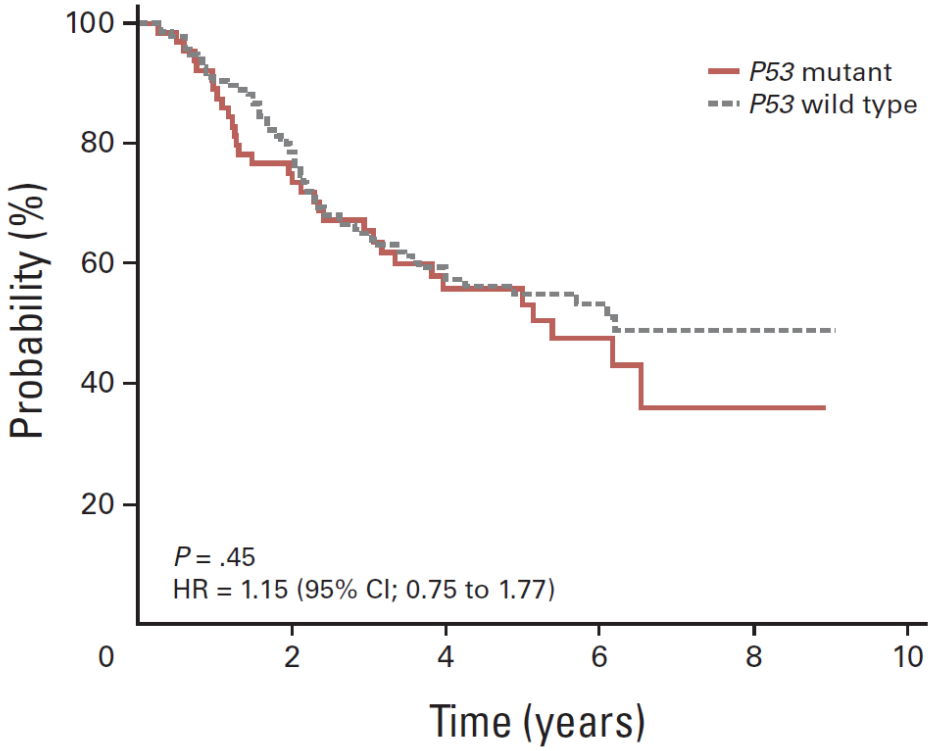
P53 in BR10



. at risk						
3 mutant	64	48	26	14	3	0
3 wild type	136	106	55	27	10	0

- **Neither prognostic or predictive**

- **Many biomarkers analyzed in LACE-BIO (KRAS, EGFR, ERCC1…)**
- **Pathway analysis > single biomarker analysis ?**
  - **Pasi Janne : KRAS & P53 correlation in LACE-BIO - 17:15 Hall D**
- **Validation in prospective trial**
- **P53**
  Discovered 33 yrs ago, still so much to learn !