Les populations spéciales

Les sujets âgés

Cours du G.O.L.F.

Strasbourg, 18 novembre 2015

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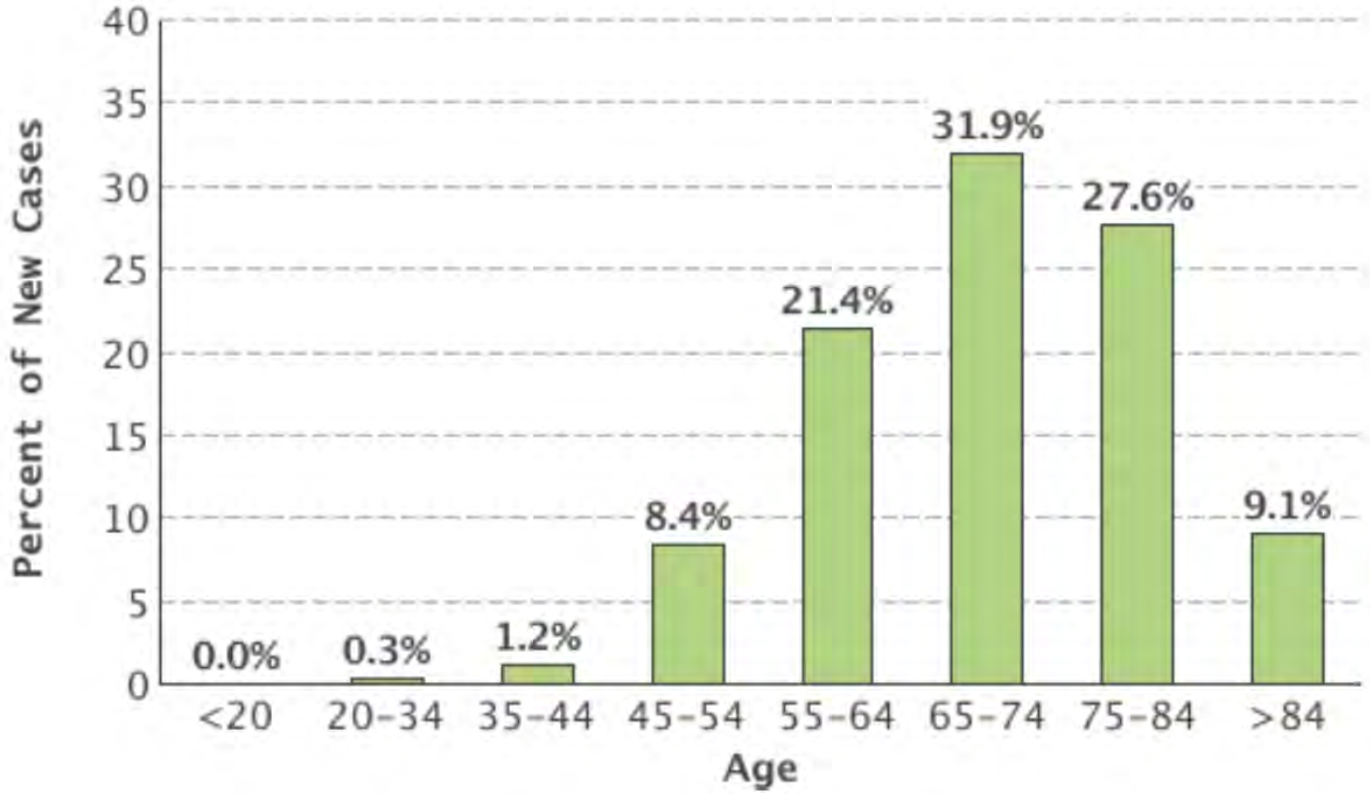
Liens d'intérêt

- Amgen
- Astra Zeneca
- Boehringer Ingelheim
- Bristol Myers Squibb
- Lilly
- Pfizer
- Roche

Sujets âgés

NATIONAL CANCER INSTITUTE

Surveillance, Epidemiology, and End Results Program

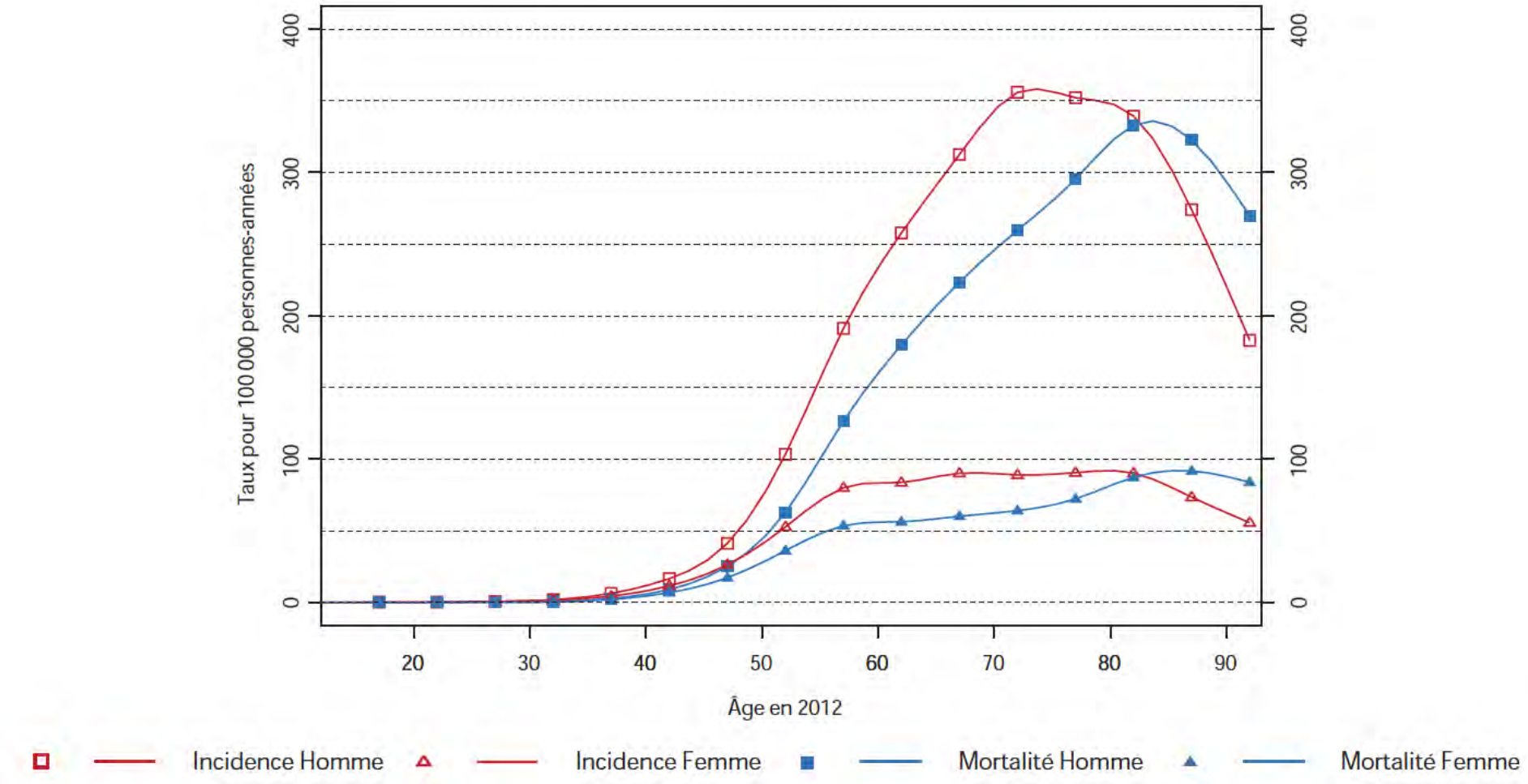


Median Age At Diagnosis
70

SEER 18 2008-2012, All Races, Both Sexes

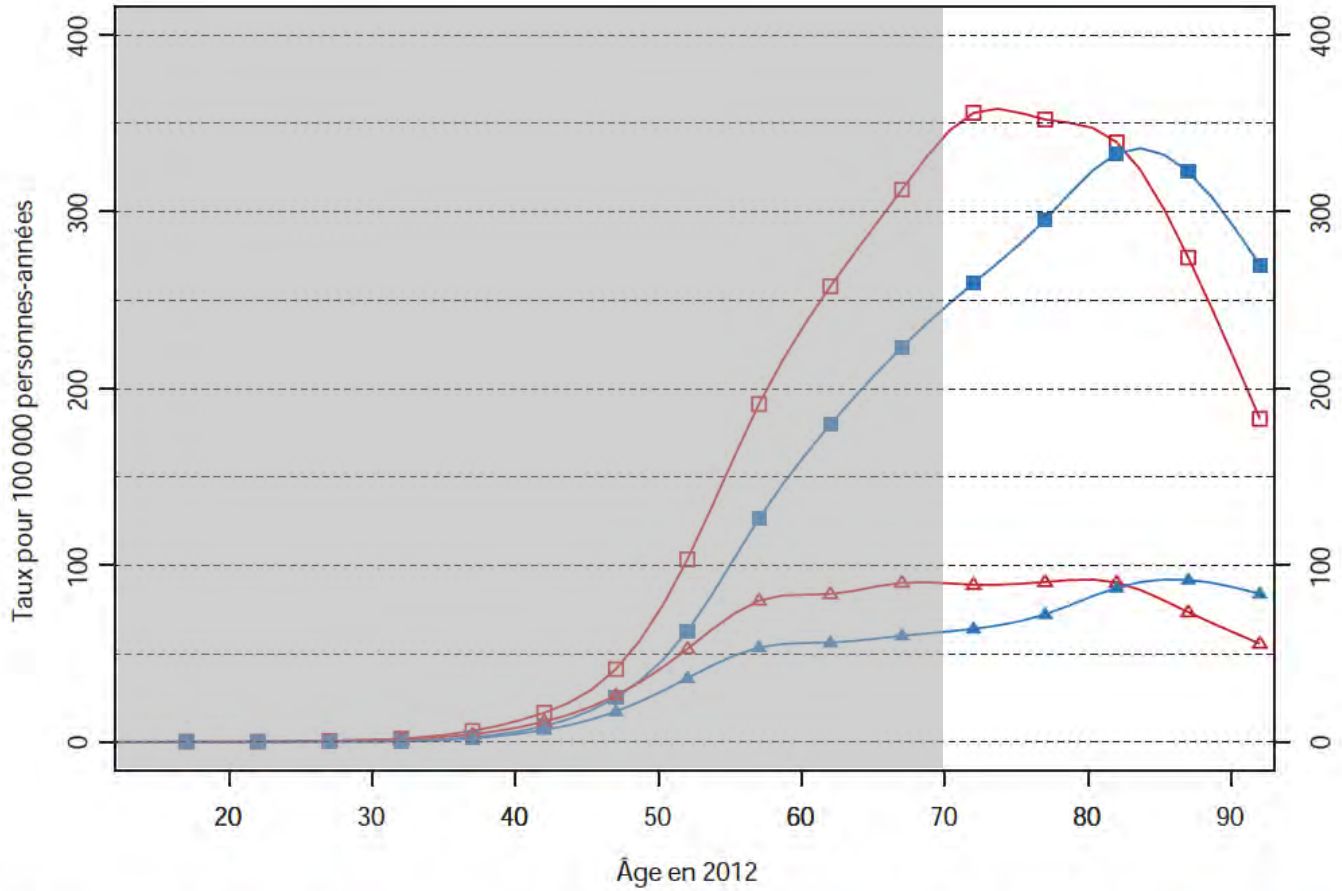
http://seer.cancer.gov

Sujets âgés



www.invs.sante.fr

Sujets âgés



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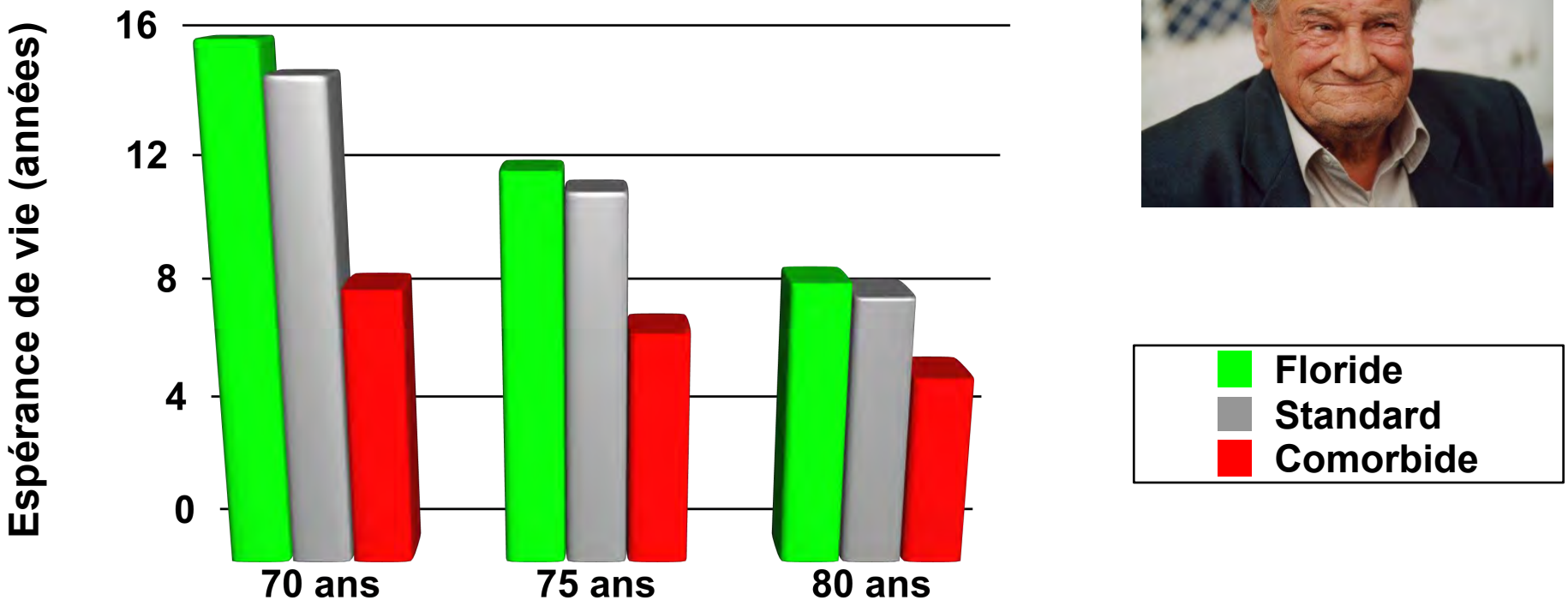
Eviter les préjugés !

"Une personne âgée de 75 ans veut devenir une personne de 76 ans de manière aussi forte qu'une personne de 55 ans veut devenir une personne de 56 ans"



Sequist and Lynch (editorial), J Clin Oncol 2003

Agenda

- **Une population spéciale…**
- CBNPC localisé
- CBNPC localement avancé
- CBNPC métastatique
  - Addiction oncogénique
  - Hors addiction oncogénique
- Perspectives

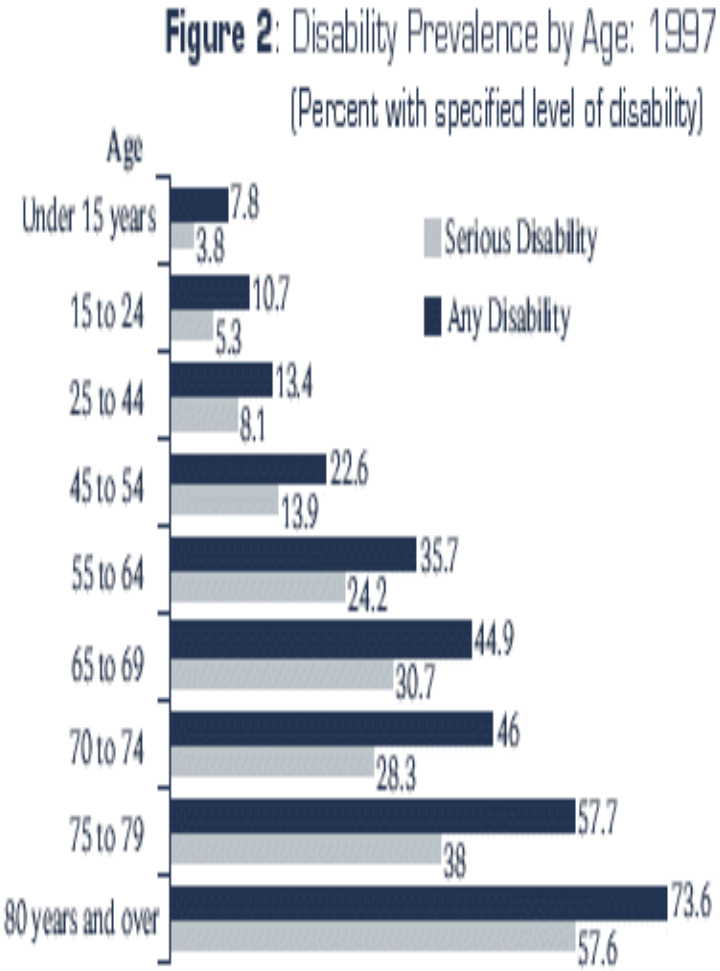
Sujets âgés

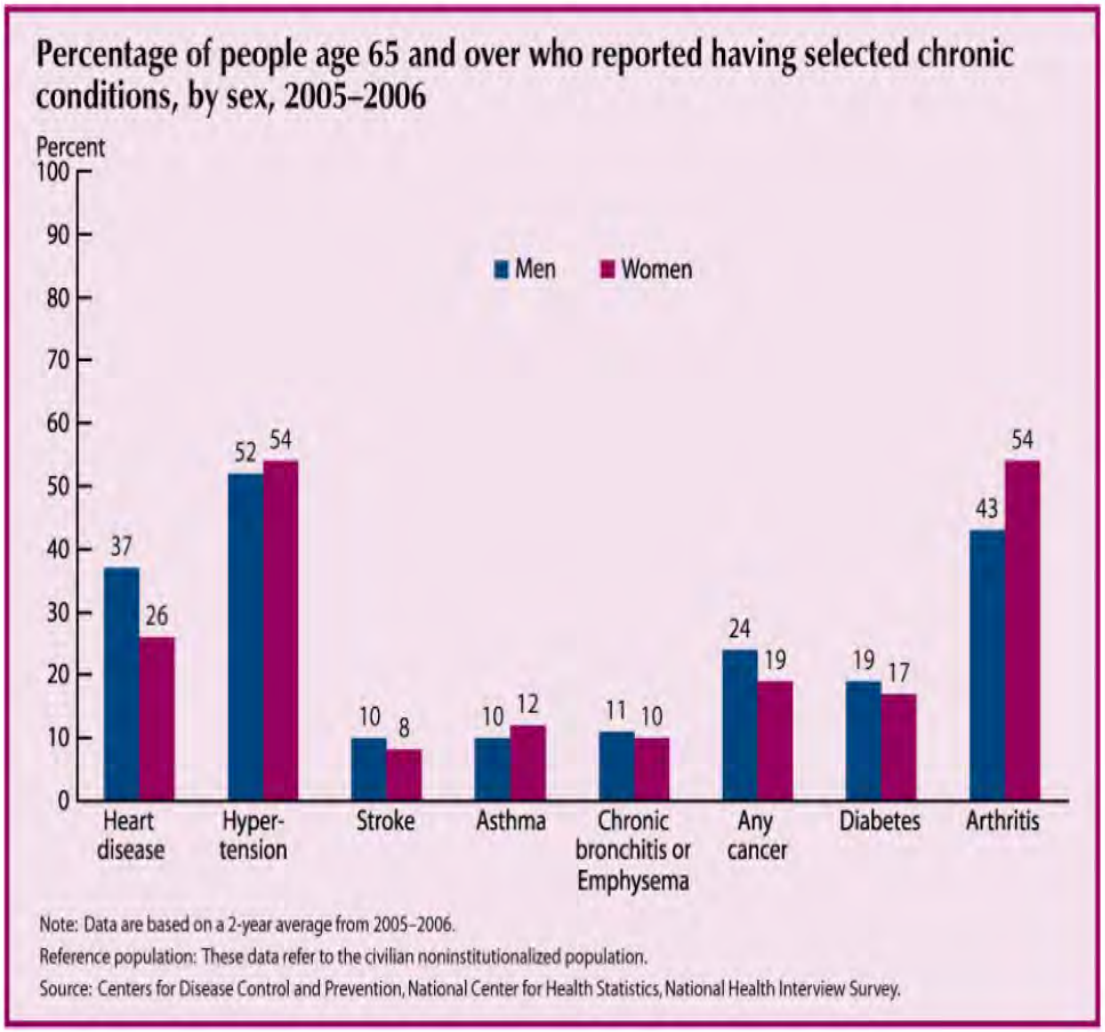
Sujets âgés

- Fonctions physiologiques
- Comorbidités
- Polymédications

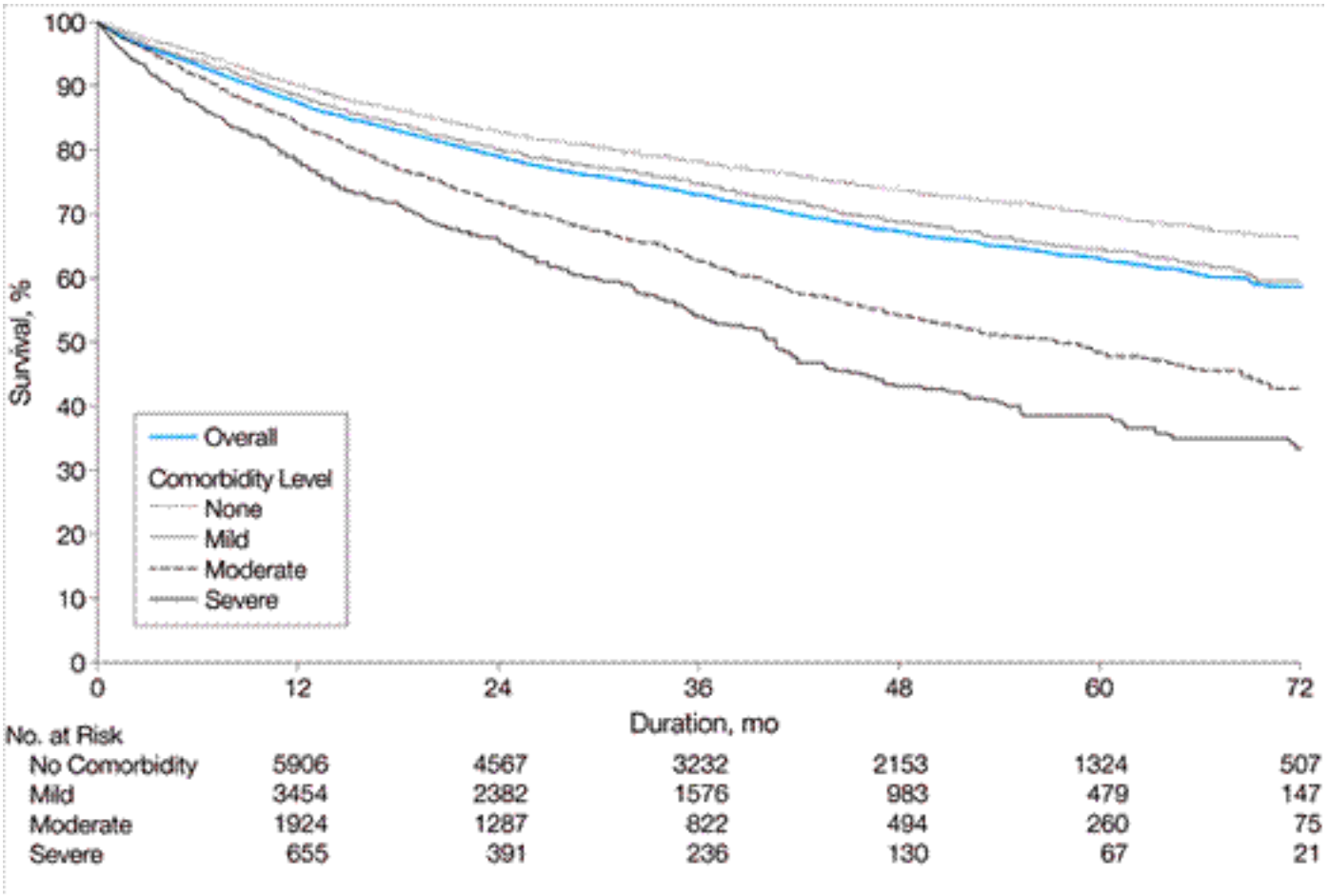
Blanco R et al, Ann Oncol 2015

Comorbidités





Comorbidités



Piccirillo JF et al, JAMA 2004

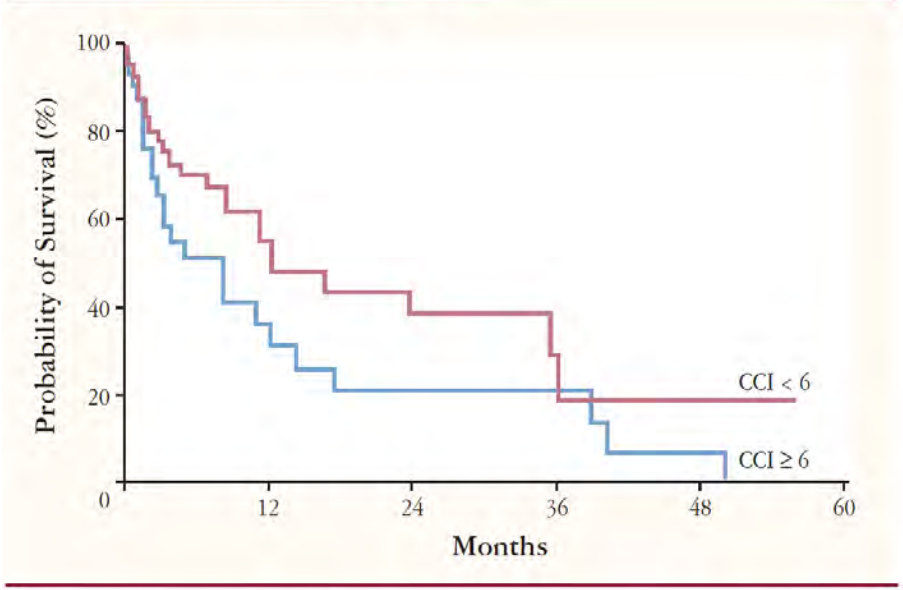
Comorbidités

Table 4 Major Results of Multivariate Analysis for Survival

Characteristics	Median Survival (Months)	*P* Value
Sex (Women vs. Men)	Not reached vs. 8.5	0.0228
Aged 80-85 Years vs. > 85 Years	12.2 vs. 3.84	0.107
CCI < 6 vs. CCI ≥ 6	12.2 vs. 8.2	0.0775
ECOG PS < 2 vs. PS ≥ 2	12.3 vs. 2.8	< 0.00001
Weight Loss ≥ 5% (No vs. Yes)	12.2 vs. 3.2	0.0457
TNM Stage (I/II vs. IIIA/IIIB vs. IV)	40.2 vs. 12.2 vs. 3.1	< 0.00001

Sole factors with a *P* value < 0.2 are reported.
Abbreviation: ECOG = Eastern Cooperative Oncology Group

Figure 1 Median Overall Survival



Survival of elderly patients with NSCLC according to the CCI, showing a better but nonstatistically significant survival for patients with a lower CCI score (12.2 months vs. 8.2 months; *P* = 0.08).

Breen D, Barlesi F, et al, Clin Lung Cancer 2007

Polymédications

	Country	Number of patients	Age, years	Number of prescribed drugs	Patients taking over-the-counter drugs (%)	Patients taking complementary and alternative medicines (%)
Cashman et al[3]	UK	100	Median 73·5 (IQR 65–88)	Median 7 (IQR 1–17)	NR	NR
Puts et al[5]	Canada	112	Mean 74·2 (SD 6, IQR 65–92)	Median 5 (IQR 3–9)	NR	NR
Hanigan et al[12]	USA	52	Range 44–85	Mean 5·5 (IQR 0–13)	71%; mean 2·2 drugs (IQR 0–20)	69%; mean 1·9 (IQR 0–11)
Sokol et al[13]	USA	100	Median 78 (IQR 70–90)	Mean 9·1 (prescribed and over the counter)	NR	~50%
Werneke et al[14]	UK	318	NR	NR	NR	>50%

NR=not reported.

Table 1: **Polypharmacy reports of patients with cancer**

Lees J and Chan A, Lancet Oncol 2011

Bénéfice / Risque

Par contre …

- **Examens paracliniques**
  - Pas de différence de tolérance (fibroscopie)
  - Pas de différence d'efficacité
- **Essais thérapeutiques**
  - Moins souvent proposés
  - Taux d'acceptation identique / sujets jeunes

Dissart-Barriol, Barlesi, Rev Mal Respir 2001

Essais spécifiques

Table 4. Adverse Events

	Age-Unspecified (n = 118)		Elderly-Specific (n = 104)		
	No.	%	No.	%	*P*
Patients with any grade 3+ event	112	95	63	61	< .001
Patients with any grade 3+ hematologic event	80	68	10	10	< .001
Patients with any grade 3+ nonhematologic event	95	81	59	57	< .001
Patients with grade 3+ neutropenia	66	56	9	9	< .001
Patients with grade 3+ dyspnea	21	18	20	19	.78
Patients with grade 3+ fatigue	30	25	9	9	.001
Patients with grade 3+ leukopenia	47	40	2	2	< .001
Patients with grade 3+ thrombocytopenia	16	14	1	1	< .001
Patients with grade 3+ febrile neutropenia	15	13	1	1	< .001

NOTE. Throughout Table, adverse events are included only if their frequency was ≥ 10% in either group.

Jatoi A, J Clin Oncol 2005

Essais spécifiques

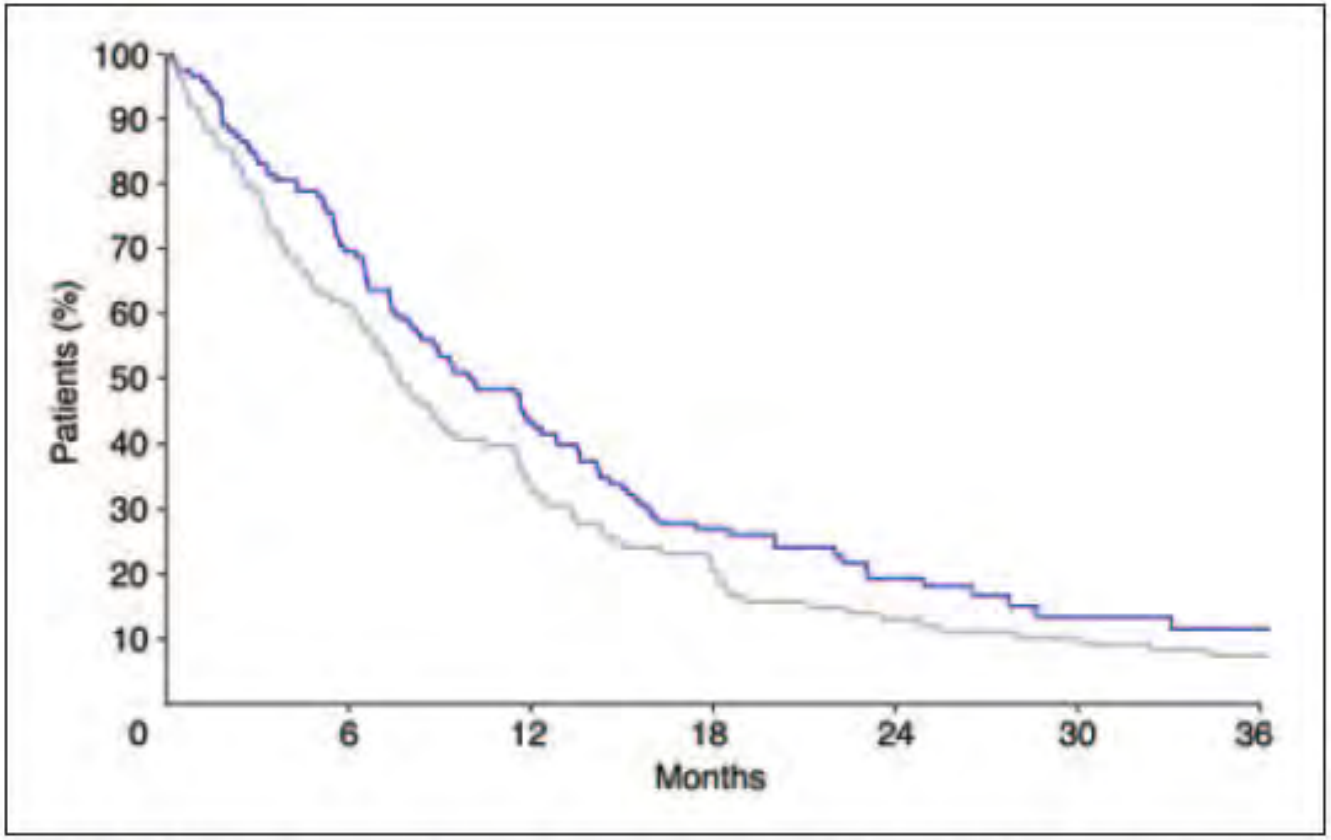


Fig 3. Median survival times in age-unspecified and elderly-specific trials were 302 and 232 days, respectively.

Jatoi A, J Clin Oncol 2005

Facteurs pronostiques

- Performance Status
- Scores ADL et IADL
- Etat nutritionnel
- Etat psychologique

Blanco R et al, Ann Oncol 2015

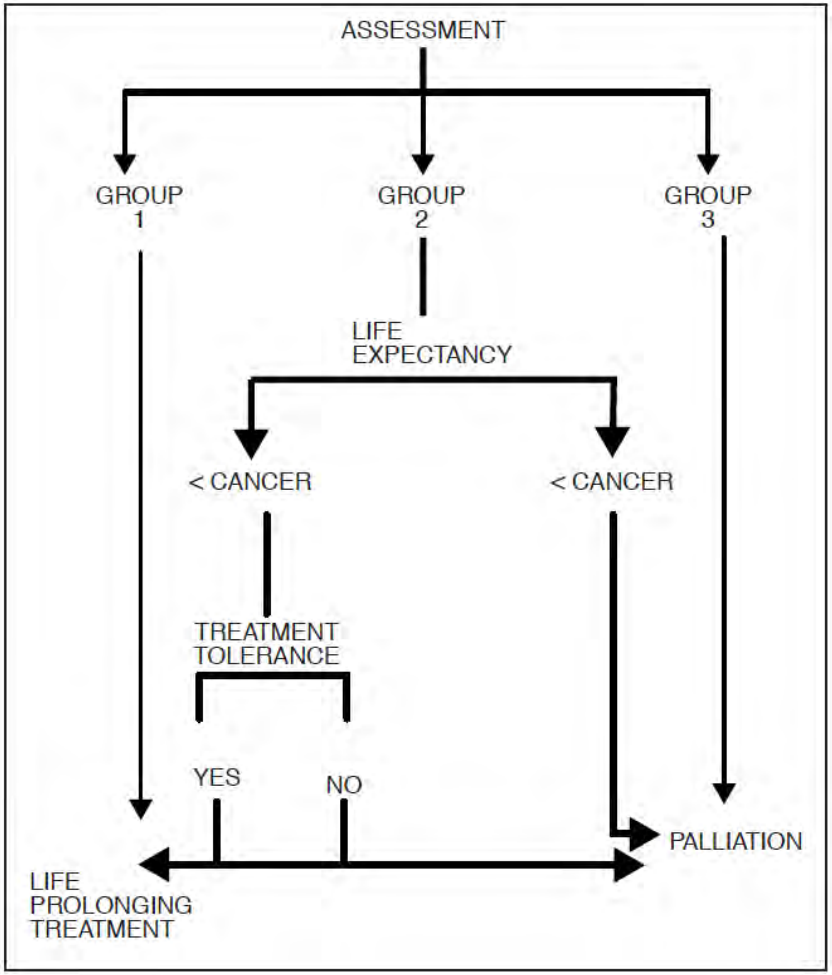
Evaluation Gériatrique Standardisée

Table 5. Elements of a comprehensive geriatric assessment

Parameter assessed	Elements of the assessment
Function	Performance status ADL IADL
Comorbidity	Number of comorbid conditions Severity of comorbid conditions (comorbidity index)
Socioeconomic conditions	Living conditions Presence and adequacy of a caregiver
Cognition	Folstein's minimental status Other tests
Emotional conditions	Geriatric depression scale (GDS)
Pharmacy	Number of medications Appropriateness of medications Risk of drug interactions
Nutrition	Mini-nutritional assessment (MNA)
Geriatric syndromes	Dementia Delirium Depression Falls Neglect and abuse Spontaneous bone fractures

Balducci L and Extermann M, The Oncologist 2000

Evaluation Gériatrique Standardisée



Balducci L and Extermann M, The Oncologist 2000

Outils Gériatriques de Dépistage

Table 2. Alternative instruments to the comprehensive geriatric assessment (CGA), suggested for use in the initial assessment of the health status of elderly cancer patients

Instrument	Description	Sensitivity/specificity	Reference
Abbreviated CGA	Questionnaire covering ADL, IADL, depression and cognitive impairment	Sensitivity 51% Specificity 97%	Overcash et al. [24, 25] Hamaker et al. [26]
Barber screening letter	Questionnaire covering autonomy, health status, hearing, eyesight and hospitalisation	Sensitivity 59% Specificity 79%	Barber et al. [27] Hamaker et al. [26]
Fried frailty criteria	Questionnaire covering weight loss, fatigue, grip strength, gait speed and physical activity	Sensitivity 31% Specificity 91%	Fairhall et al. [28] Hamaker et al. [26]
Geriatric 8	Questionnaire covering ADL, IADL, depression, cognitive impairment, geriatric illness rating and mobility	Sensitivity 87% Specificity 61%	Bellera et al. [29] Hamaker et al. [26]
Groningen Frailty Index	Questionnaire covering mobility, vision, hearing, nutrition, comorbidity, cognition, psychosocial aspects and physical fitness	Sensitivity 57% Specificity 86%	Schuurmans et al. [30] Hamaker et al. [26]
Onco-Geriatric Screening Tool	Questionnaire covering frailty risks	Sensitivity 88% Specificity 44%	Valero et al. [31]
Senior Adult Oncology Program 2	Questionnaire covering availability of caregiving, depression, QoL, ADL, nutrition, sleep and prescription payments	Sensitivity 100% Specificity 40%	Extermann et al. [32]
Triage Risk Screening Tool	Questionnaire covering availability of caregiving, cognitive impairment, ADL, medication use/issues, hospitalisation, nutrition, sensory deficit, incontinence and ability to cope	Sensitivity 92% Specificity 47%	Mion et al. [33] Hamaker et al. [26]
Vulnerable Elders Survey 13	Questionnaire covering age, comparative age-related health and functional status	Sensitivity 68% Specificity 78%	Saliba et al. [34] Hamaker et al. [26]

ADL, activities of daily living; IADL, instrumental activities of daily living; QoL, quality of life.

Blanco R et al, Ann Oncol 2015

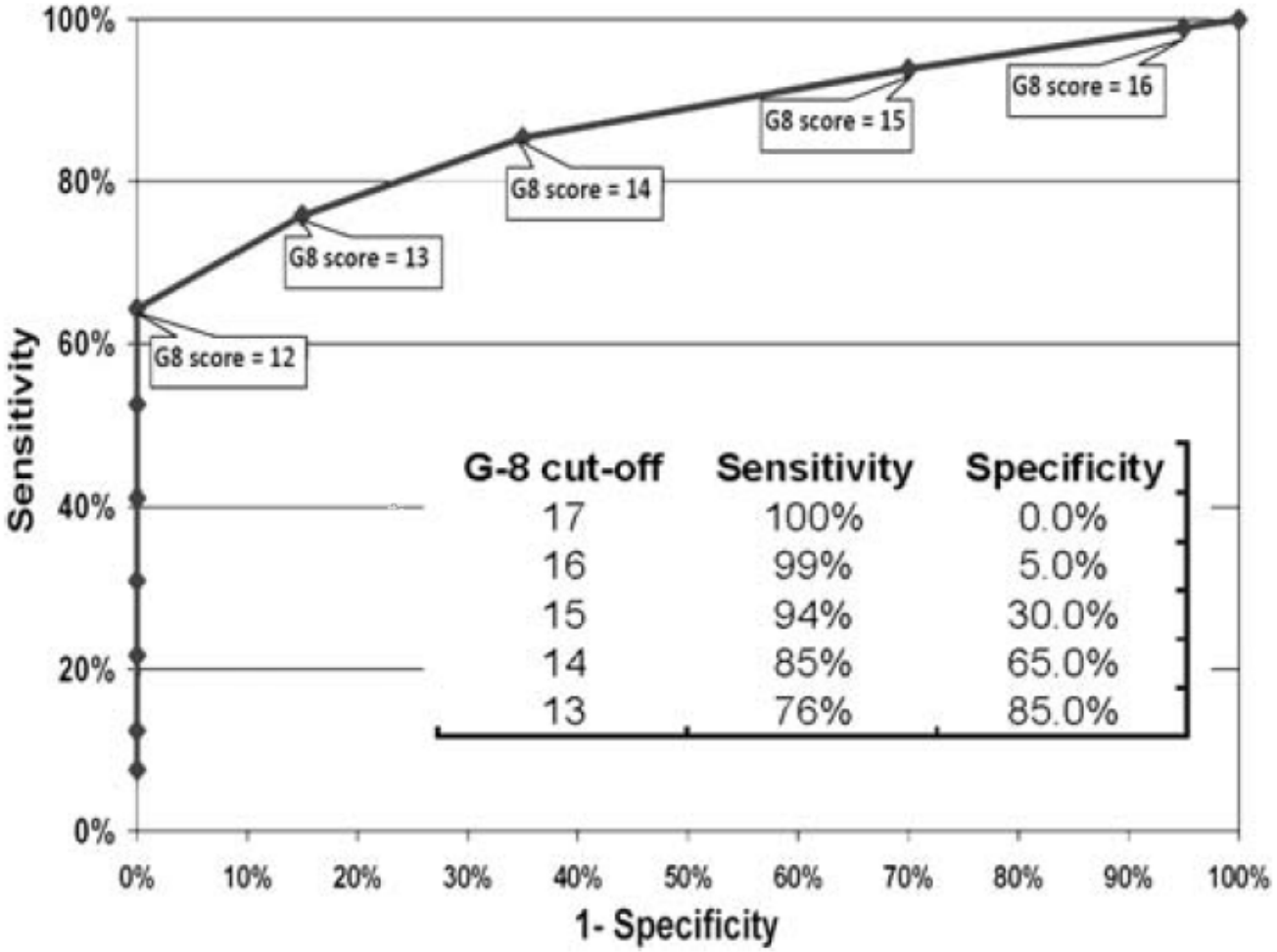
Oncodage (G8)

	Items	Score
A	Le patient présente-t-il une perte d'appétit ? A-t-il mangé moins ces 3 derniers mois par manque d'appétit, problèmes digestifs, difficultés de mastication ou de déglutition ?	0 : anorexie sévère 1 : anorexie modérée 2 : pas d'anorexie
B	Perte récente de poids (< 3 mois)	0 : perte de poids > 3 kilos 1 : ne sait pas 2 : perte de poids entre 1 et 3 kilos 3 : pas de perte de poids
C	Motricité	0 : du lit au fauteuil 1 : autonome à l'intérieur 2 : sort du domicile
E	Problèmes neuropsychologiques	0 : démence ou dépression sévère 1 : démence ou dépression modérée 2 : pas de problème psychologique
F	Indice de masse corporelle	0 : IMC < 19 1 : IMC = 19 à IMC < 21 2 : IMC = 21 à IMC < 23 3 : IMC = 23 et > 23
H	Prend plus de 3 médicaments	0 : oui 1 : non
P	Le patient se sent-il en meilleure ou moins bonne santé que la plupart des personnes de son âge	0 : moins bonne 0,5 : ne sait pas 1 : aussi bonne 2 : meilleure
	Âge	0 : > 85 1 : 80-85 2 : <80
	SCORE TOTAL	**0 – 17**

Un score ≤ à 14 révèle une vulnérabilité ou une fragilité gériatriques devant conduire à une consultation adaptée.

Bellera CA et al, Ann Oncol 2012

Oncodage (G8)



G-8 cut-off	Sensitivity	Specificity
17	100%	0.0%
16	99%	5.0%
15	94%	30.0%
14	85%	65.0%
13	76%	85.0%

Bellera CA et al, Ann Oncol 2012

Agenda

- Une population spéciale…
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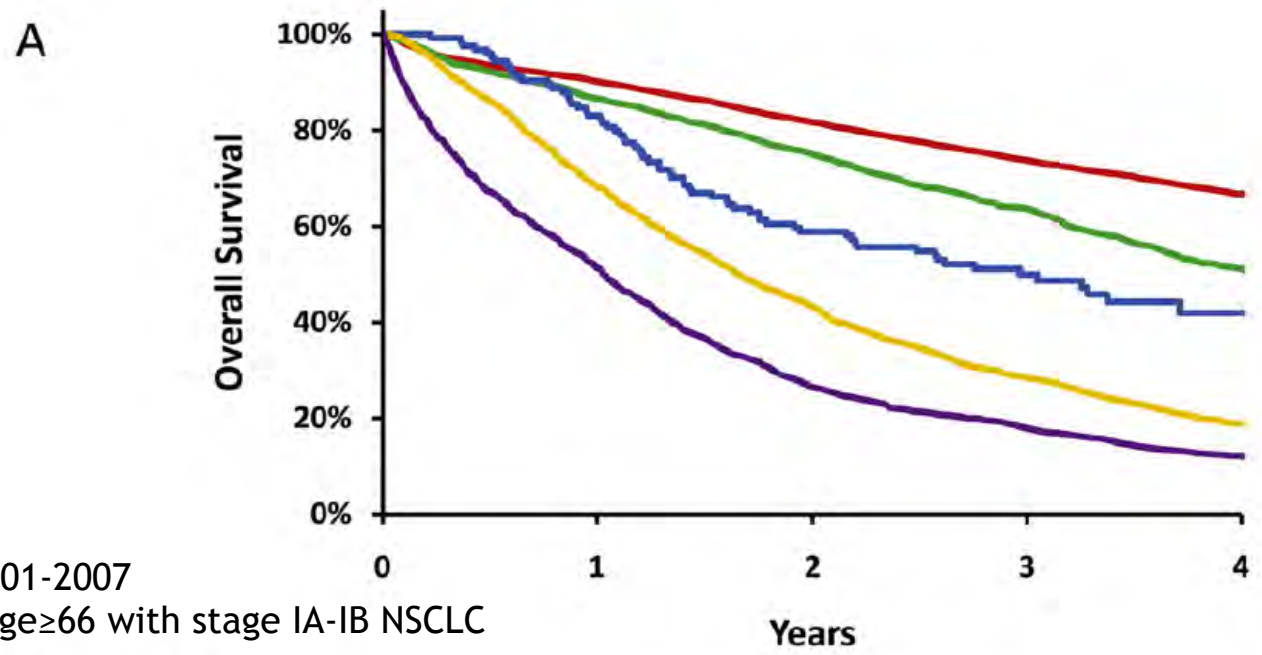
Résection chirurgicale



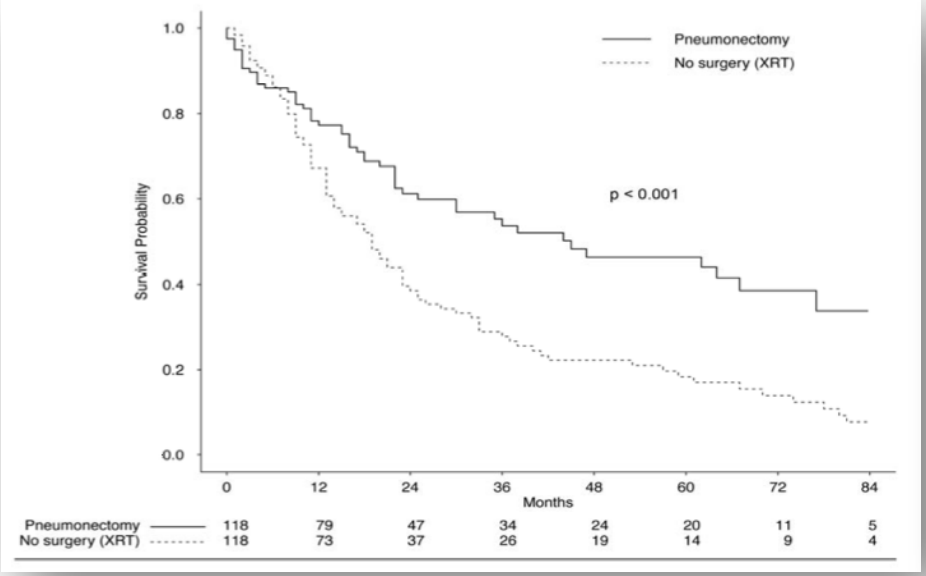
SEER database 2001-2007
10,923 patients age≥66 with stage IA-IB NSCLC

Number at Risk			
Lobectomy	6531	5338	3321
Sublobar Resection	1278	958	488
SBRT	124	73	14
Conventional Rad.	1614	702	229
No Treatment	1378	366	128

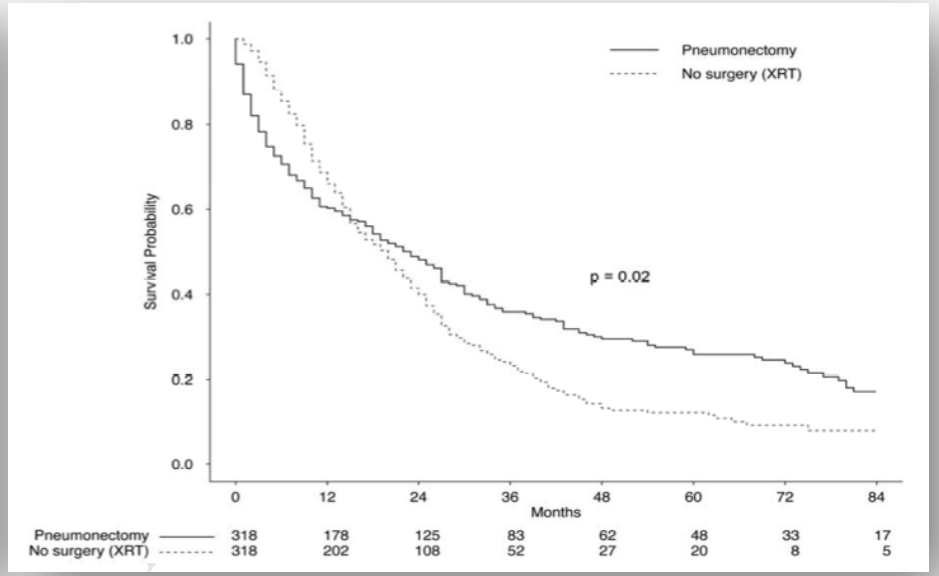
Shirvani SM et al, Int J Radiat Oncol Biol Phys 2003

Résection chirurgicale

<70 ans



≥ 70 ans



SEER database 1988-2010
5701 pneumonectomies dont 1750 age≥70 et stades I-II NSCLC
Score de propension

Speicher PJ et al, J Am Coll Surg 2014

Résection chirurgicale

Variable	Patients ≥ 70 y (n = 1,969)	Patients < 70 y (n = 1,969)	*P* Value
Hospital LOS, d			.02
Mean (95% CI)	13.0 (12.6-13.4)	12.3 (11.9-12.8)	
Median (IQR)	11.0 (8.0-14.0)	10.0 (8.0-14.0)	
Complications, No. (%)[a]			.07
0	60.0 (1,181)	63.7 (1,255)	
1	24.6 (485)	23.3 (458)	
2	11.3 (222)	9.5 (188)	
≥ 3	4.1 (81)	3.5 (68)	
Complications[b]			.05
None	60.0 (1,181)	63.8 (1,255)	
Minor	23.4 (460)	21.5 (424)	
Major	16.6 (328)	14.7 (290)	
Severity of complications, No. (%)[c]	788	714	.69
Major	41.6 (328)	40.6 (290)	
Minor	58.4 (460)	59.4 (424)	
30-d mortality	3.6 (70)	2.2 (43)	.01
60-d mortality	4.1 (80)	2.4 (47)	.003
90-d mortality	4.7 (93)	2.5 (50)	.0002

Rivera C et al, Chest 2011

Résection chirurgicale

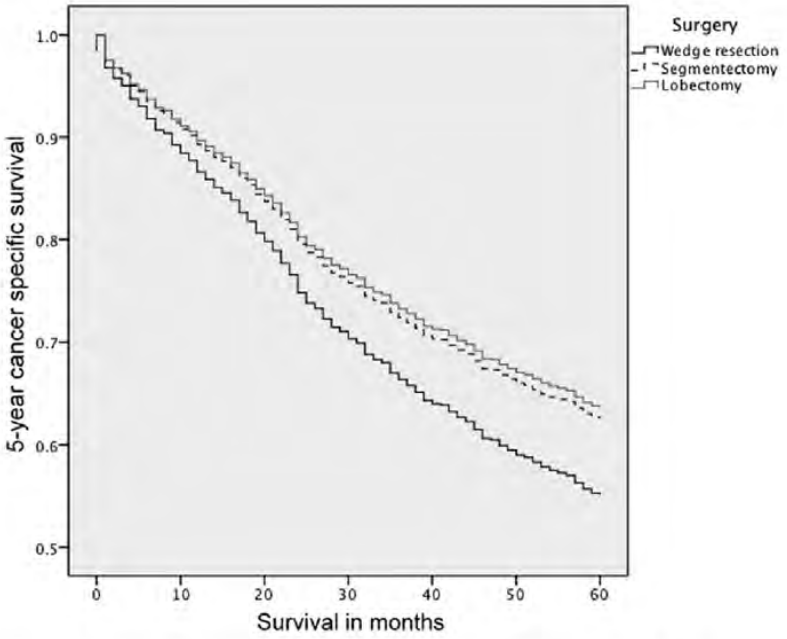


Fig. 2 – Cox proportional hazards regression model illustrating 5-y cancer-specific survival difference among wedge resection, segmentectomy, and lobectomy group in patients with stage IA (T1a/b) NSCLC.

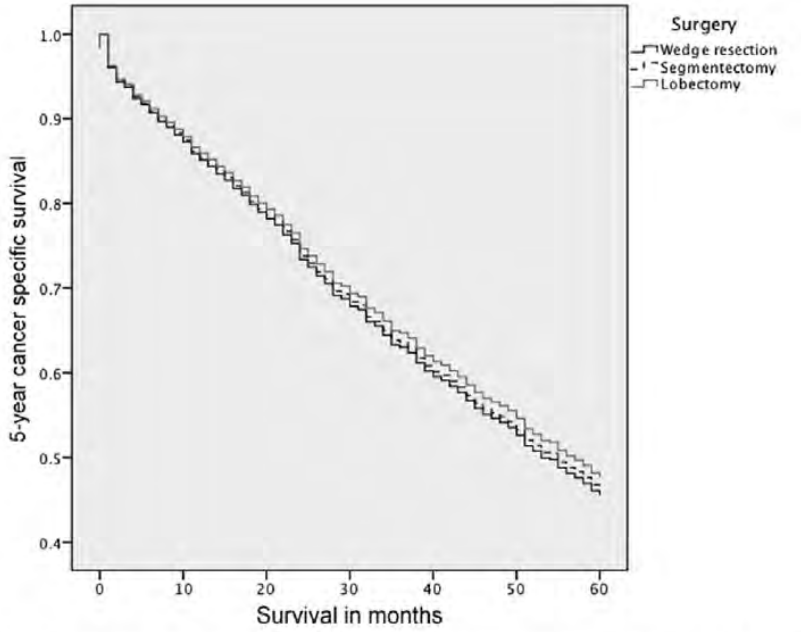


Fig. 3 – Cox proportional hazards regression model did not show any significant 5-y cancer-specific survival difference in patients with T1a NSCLC who underwent wedge resection, segmentectomy, or lobectomy.

SEER database 1998-2007
1640 patients ≥75 ans, stade IA NSCLC

Razi SS et al, J Surg Res 2015

Curage ganglionnaire

Complication	Number of LNs resected		Odds ratio[b]	95% CI	*p*-Value
	≤10 *N* (%)	>10 *N* (%)			
Primary outcome					
30-day mortality	135 (3,6)	43 (3,6)	1,01	0,71−1,43	0,98
Secondary outcomes					
30-Day readmission	301 (8,0)	79 (6,6)	0,82	0,63−1,06	0,12
Prolonged LOS[a]	633 (18,0)	175 (15,5)	0,84	0,70−1,01	0,06
Postoperative ICU stay[a]	2547 (72,4)	843 (74,9)	1,14	0,98−1,33	0,10
Extrapulmonary infections	220 (5,8)	75 (6,3)	1,08	0,83−1,42	0,57
Cardiovascular	64 (1,7)	18 (1,5)	0,89	0,52−1,50	0,65
Thromboembolic	64 (1,7)	34 (2,8)	1,70	1,11−2,59	0,01
Respiratory	1095 (29,0)	319 (26,7)	0,89	0,77−1,03	0,12
Reoperation	48 (1,3)	25 (2,1)	1,66	1,02−2,70	0,04
Transfusion	143 (3,8)	37 (3,1)	0,81	0,56−1,17	0,26

LOS, length of stay; ICU, intensive care unit; LN, lymph nodes; CI, confidence interval.
Some patients may had more than one complication.

[a] $N = 4645$.

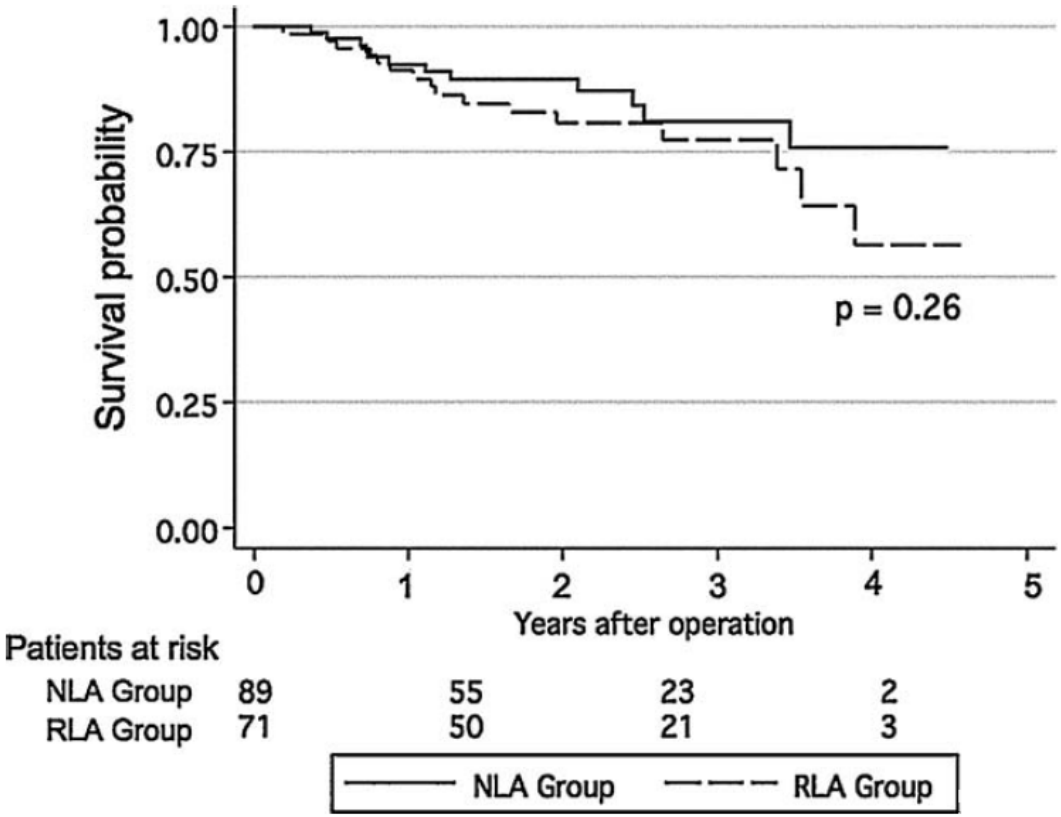
[b] Odds ratio for patients who underwent resection of >10 lymph nodes compared with patients who had ≤10 lymph nodes resected.

SEER database 1992-2002
4975 patients ≥65 ans, stade I NSCLC
Lobectomie +/- curage ganglionnaire

Shapiro M et al, Eur J Surg Oncol 2012

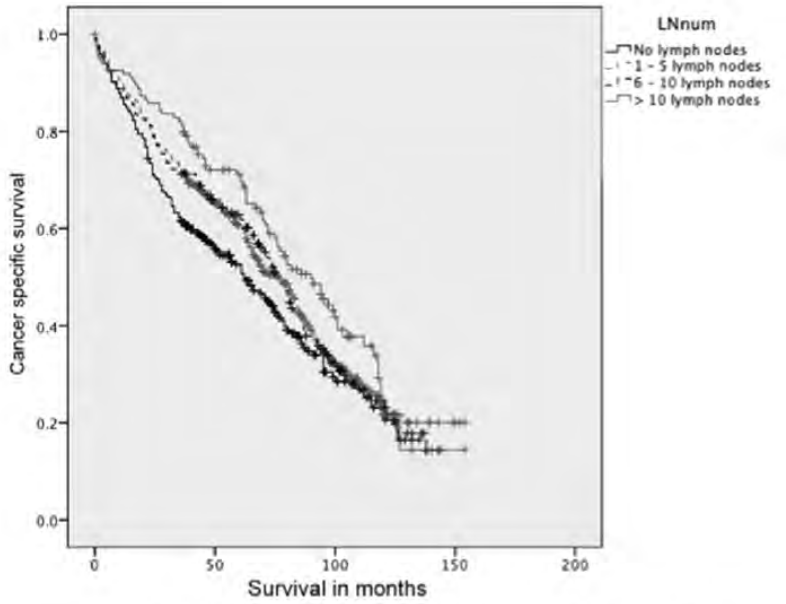
Curage ganglionnaire

Japon 2004-2008
160 patients ≥70 ans
Stade I-III NSCLC



Okasaka T et al, Eur J Cardiothorac Surg Res 2010

Curage ganglionnaire



	Months	0	50	100	150
(n)	No lymph nodes	297	135	29	0
	1-5 lymph nodes	465	272	77	3
	6-10 lymph nodes	212	130	41	0
	> 10 lymph nodes	134	88	34	1

Fig. 4 – Kaplan–Meier survival analysis comparing patient groups based on the number of lymph nodes sampled.

Table 4 – Results of multivariate analysis comparing survival based on the number of lymph nodes examined.

Groups	Median survival	HR	95% CI	P value
No lymph nodes	62	1		
1–5 lymph nodes	77	0.877	0.677–1.135	0.283
6–10 lymph nodes	77	0.838	0.603–1.163	0.267
>10 lymph nodes	90	0.634	0.423–0.951	0.022

SEER database 1998-2007
1640 patients ≥75 ans, stade IA NSCLC

Razi SS et al, J Surg Res 2015

Chirurgie mini-invasive

Table 3. Complications

	VATS	Thoracotomy	*p*
Complication (any severity)	14 (35.0%)	51 (63.0%)	0.004
Complication (significant intervention)	7 (17.5%)	28 (34.6%)	0.051
Cardiac arrhythmia	8 (20.0%)	28 (34.6%)	0.099
Cardiac general	0	2 (2.5%)	0.316
Pulmonary	2 (5.0%)	19 (23.5%)	0.012
Infectious	1 (2.5%)	13 (16.0%)	0.028
Hemorrhagic	3 (7.5%)	7 (8.6%)	1
Neurologic	8 (9.9%)	2 (5.0%)	0.494
Other	0	7 (8.6%)	0.094
Mortality	0	2 (2.5%)	1

VATS = video-assisted thoracic surgery.

Table 5. Clinical Disposition

Variable	VATS	Thoracotomy	*p*
Length of stay (median no. days)	5	6	0.001
ICU admission	1 (2.5%)	12 (14.8%)	0.040
ICU days	2	60	0.001
Discharge to rehabilitation	2 (5.0%)	18 (22.5%)	0.015
Readmission within 30 days	0	7 (8.6%)	0.094

ICU = intensive care unit; VATS = video-assisted thoracic surgery.

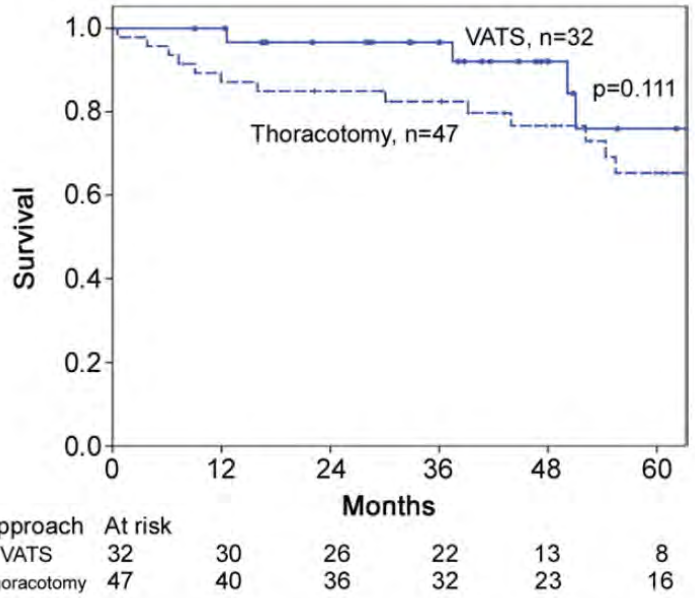


Fig 3. Survival comparison after lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy among stage I patients.

USA, 1998-2009
121 patients ≥85 ans, stade I-III NSCLC
Lobectomie par thoracotomie vs VATS

Port JL et al, Ann Thorac Surg 2011

Radiothérapie

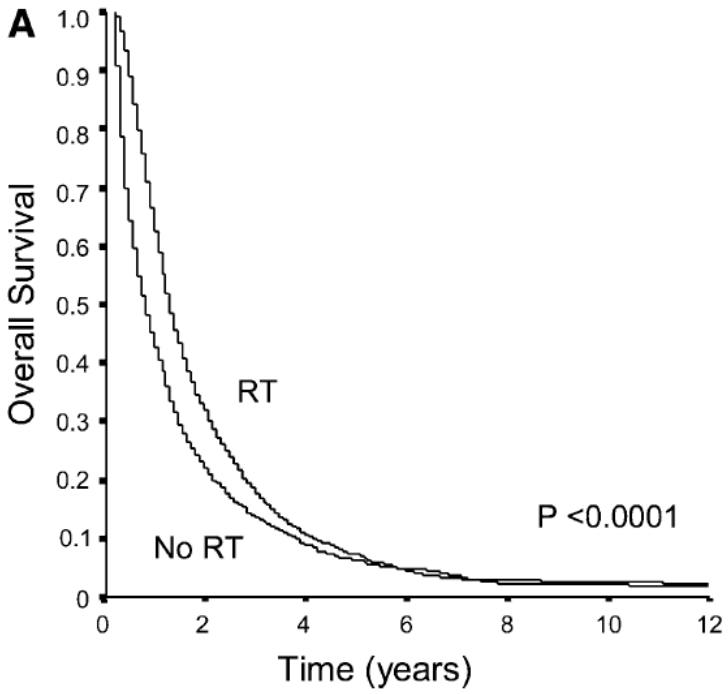


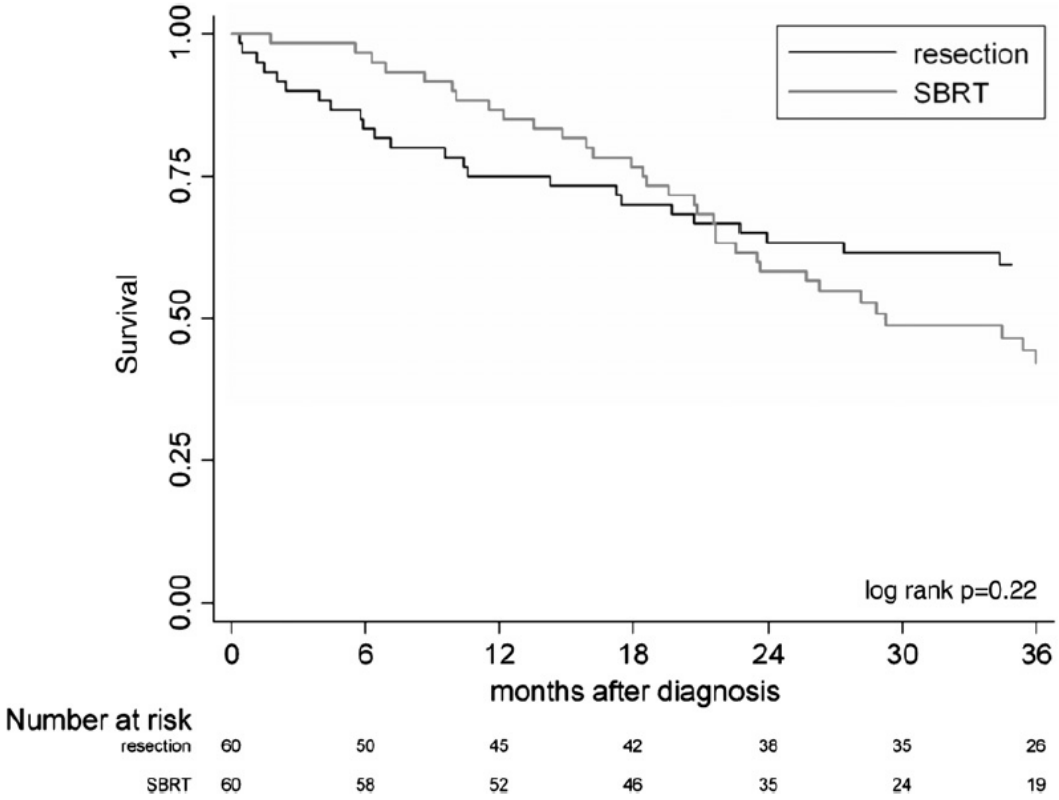
TABLE 2. PROPENSITY SCORE ANALYSIS: RISK OF DEATH FOR PATIENTS TREATED WITH RADIATION THERAPY ACCORDING TO PROPENSITY SCORE QUINTILE

	Overall Survival		Lung Cancer-specific Survival	
Quintile	Hazard Ratio	95% CI	Hazard Ratio	95% CI
1, lowest probability of RT	0.70	0.62–0.79	0.73	0.63–0.84
2	0.72	0.64–0.81	0.71	0.62–0.81
3	0.75	0.66–0.85	0.73	0.64–0.84
4	0.72	0.63–0.81	0.71	0.61–0.81
5, highest probability of RT	0.80	0.70–0.92	0.80	0.69–0.92
Entire sample*	0.74	0.70–0.78	0.73	0.69–0.78

SEER database 1992-2002
6065 patients ≥65 ans, stade I-II NSCLC
Score de propension

Wisnivesky JP et al, Am J Respir Crit Care Med 2010

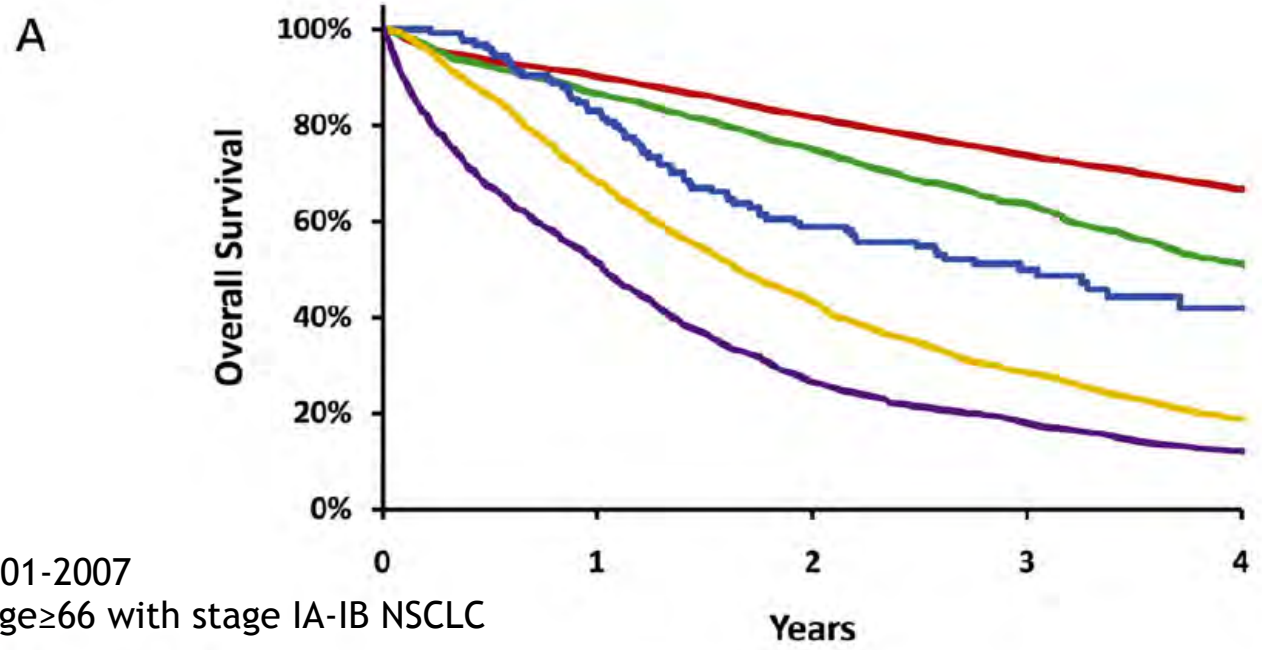
Radiothérapie stéréotaxique



Registre hollandais 2005-2007
120 patients appariés, ≥75 ans, stade I NSCLC

Palma D et al, Radiother Oncol 2011

Radiothérapie stéréotaxique

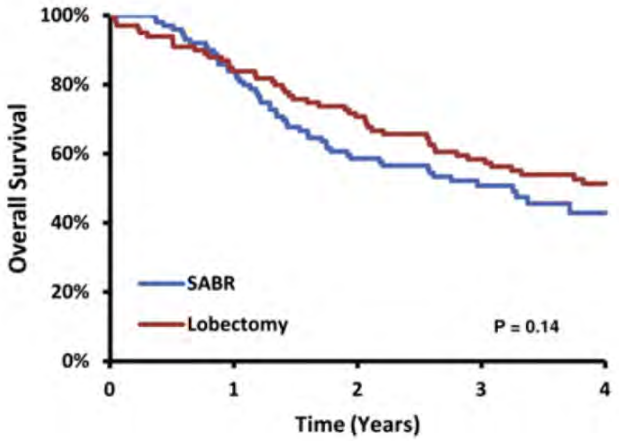


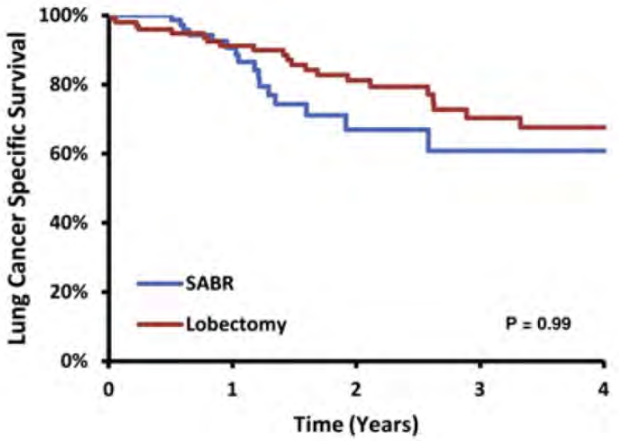
SEER database 2001-2007
10,923 patients age≥66 with stage IA-IB NSCLC

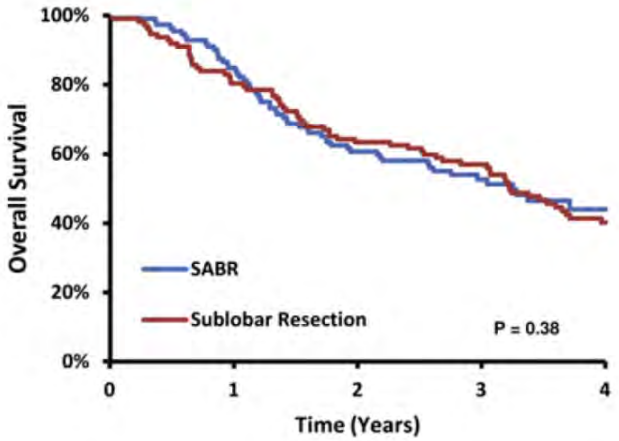
Number at Risk			
Lobectomy	6531	5338	3321
Sublobar Resection	1278	958	488
SBRT	124	73	14
Conventional Rad.	1614	702	229
No Treatment	1378	366	128

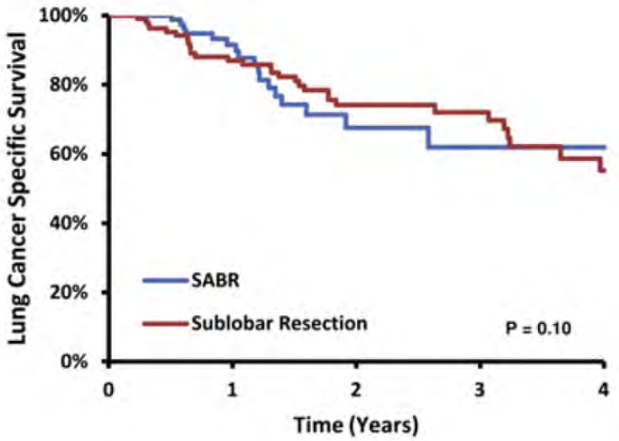
Shirvani SM et al, Int J Radiat Oncol Biol Phys 2003

Radiothérapie stéréotaxique



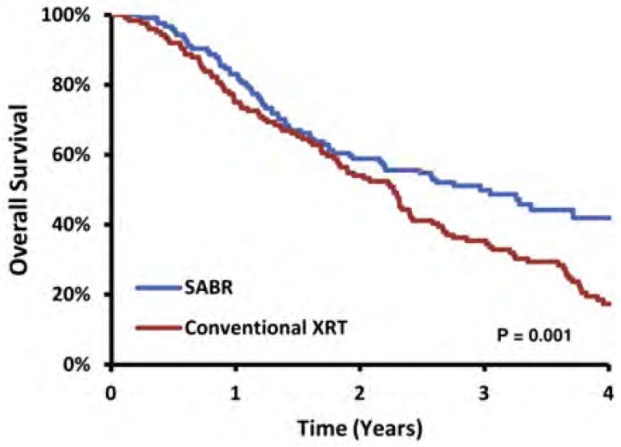


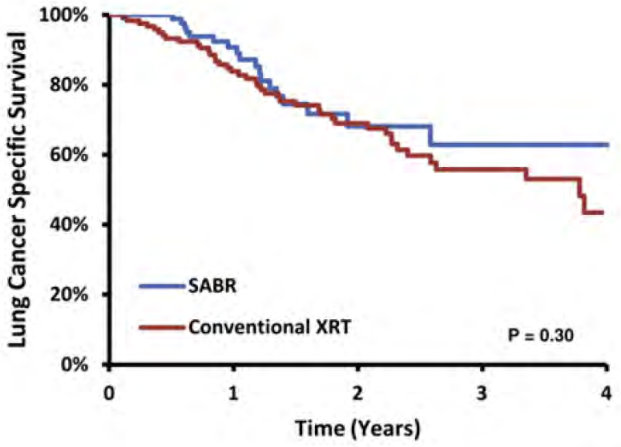


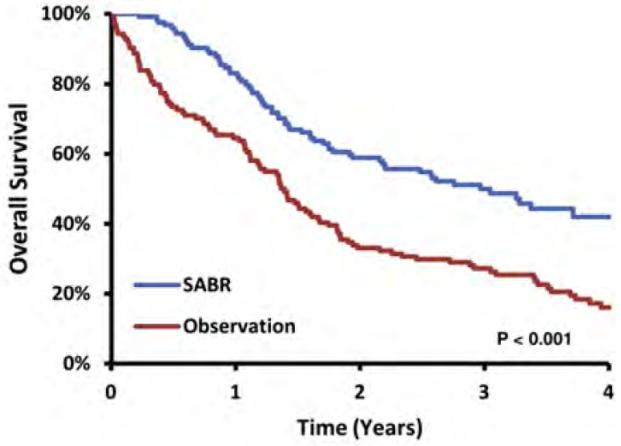


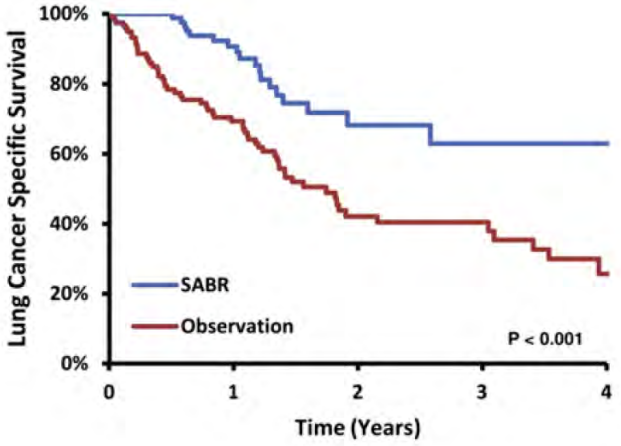
Shirvani SM et al, Int J Radiat Oncol Biol Phys 2003

Radiothérapie stéréotaxique









Shirvani SM et al, Int J Radiat Oncol Biol Phys 2003

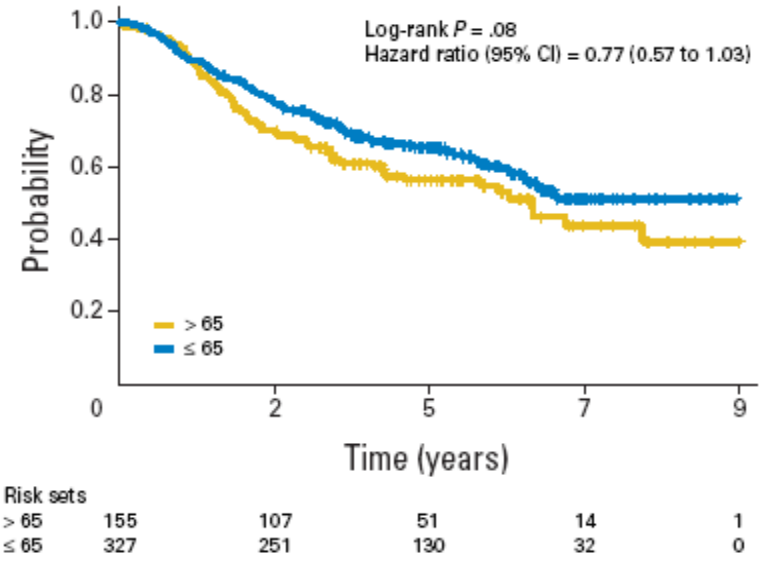
Chimiothérapie adjuvante

- Pts ≥ 65 ans JBR10 (n=155)
- EG (PS>0) plus altéré: 64 *vs* 43%, p=0.004
- Traitement (n=77)
  - Compliance moins bonne: 40 vs 56%, p=0.025
  - Refus Cx plus fréquent: 40 vs 23%, p=0.01
  - Toxicités comparables

Pepe C et al., J Clin Oncol 2007

Analyse de sous groupe (JBR10)

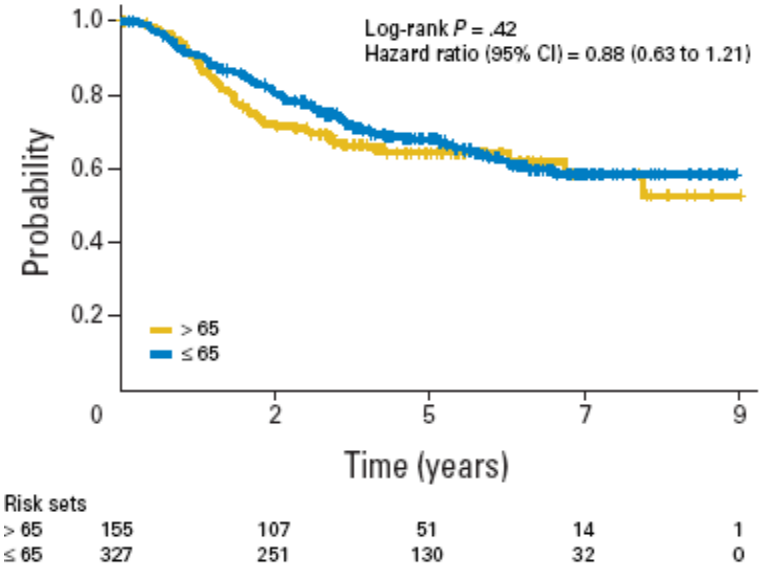
Survie globale



Risk sets

> 65	155	107	51	14	1
≤ 65	327	251	130	32	0

Survie spécifique



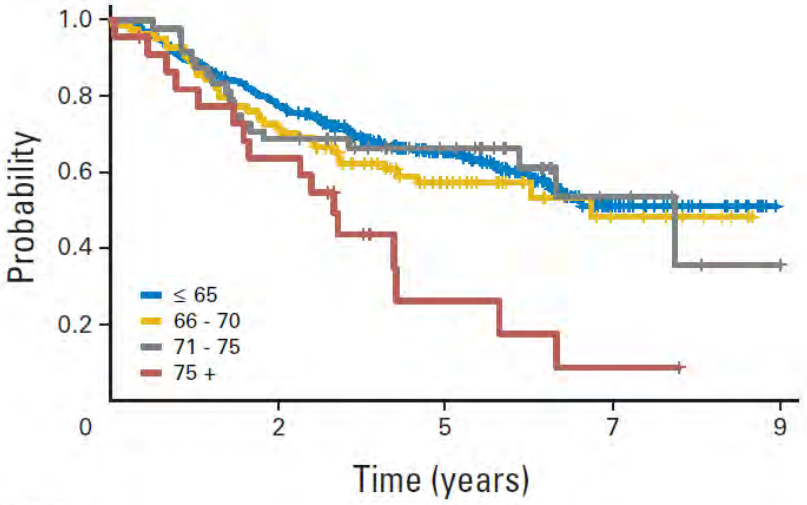
Risk sets

> 65	155	107	51	14	1
≤ 65	327	251	130	32	0

Pepe C et al., J Clin Oncol 2007

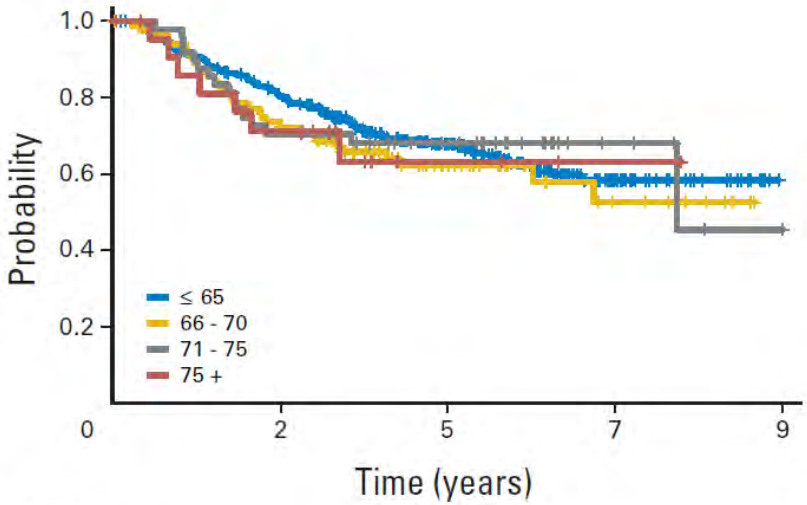
Analyse de sous groupe (JBR10)

Survie globale



Risk sets					
≤ 65	327	251	130	32	0
66 - 70	84	60	27	8	0
71 - 75	48	33	21	5	1
75 +	23	14	3	1	0

Survie spécifique

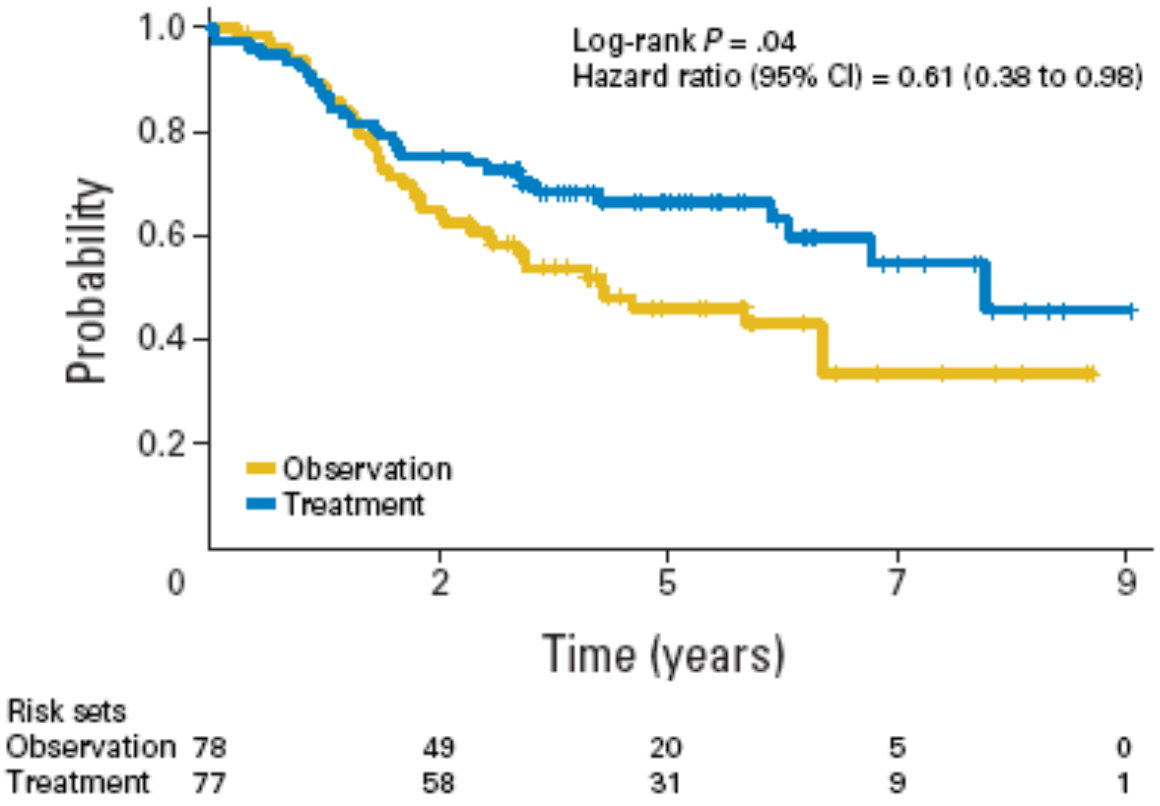


Risk sets					
≤ 65	327	251	130	32	0
66 - 70	84	60	27	8	0
71 - 75	48	33	21	5	1
75 +	23	14	3	1	0

Pepe C et al., J Clin Oncol 2007

Analyse de sous groupe (JBR10)

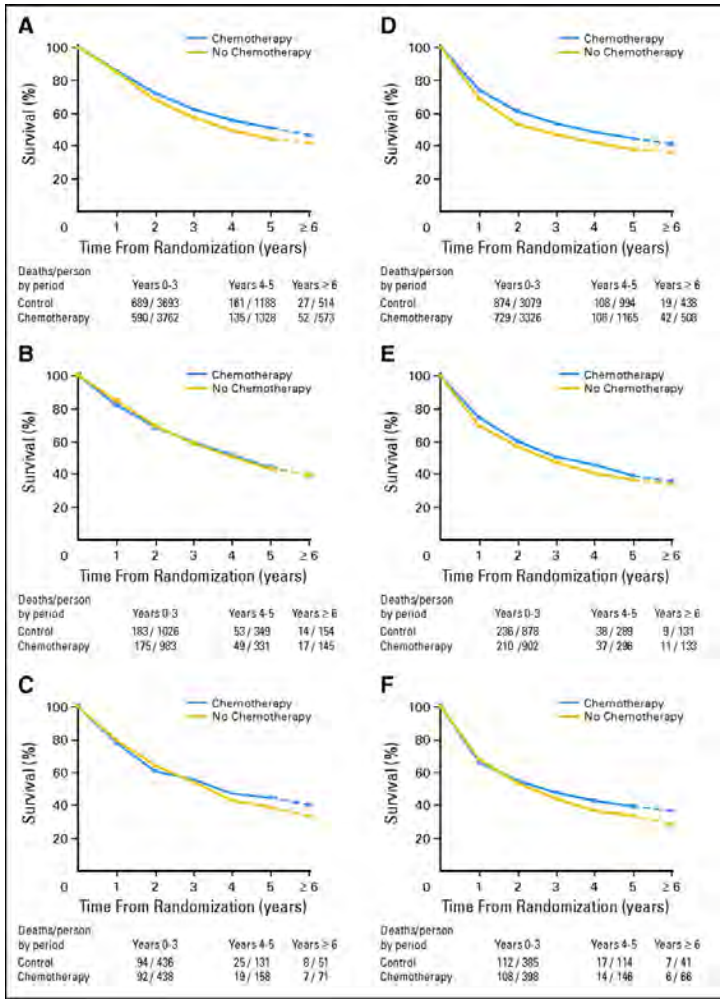
Survie globale par bras de traitement



Pepe C et al., J Clin Oncol 2007

Méta-analyse LACE

- LACE database
- <65 / 65-69 / ≥70 ans
- Efficacité comparable
- Toxicités comparables
- Doses CDDP reçues plus faibles
- Décès autre cause: **22** vs 12% (p<0.0001)



Fruh M et al., J Clin Oncol 2008

Radiothérapie adjuvante

Model	HR (95% CI)[a] Without Adjustment for Chemotherapy Receipt	Adjusting for Chemotherapy Receipt
Primary analysis: Entire cohort		
Adjusting for propensity scores	1.11 (0.97-1.27)	1.13 (0.99-1.30)
Stratified by propensity score quintiles	1.12 (0.98-1.28)	1.14 (1.00-1.30)
Matched analysis	1.10 (0.95-1.27)	1.12 (0.97-1.29)
Stratified analyses		
Limited to patients who received chemotherapy[b]		
Adjusting for propensity scores	1.17 (0.88-1.56)	—
Stratified by propensity score quintiles	1.18 (0.89-1.58)	—
Matched analysis	1.22 (0.88-1.67)	—
Limited to patients who did not receive chemotherapy		
Adjusting for propensity scores	1.13 (0.97-1.32)	—
Stratified by propensity score quintiles	1.14 (0.98-1.33)	—
Matched analysis	1.25 (0.96-1.32)	—
Limited to patients who received intermediate-complexity RT planning		
Adjusting for propensity scores	1.09 (0.94-1.26)	1.10 (0.94-1.27)
Stratified by propensity score quintiles	1.09 (0.94-1.27)	1.10 (0.95-1.28)
Matched analysis	1.05 (0.91-1.21)	1.06 (0.91-1.22)
Limited to patients who received high-complexity RT planning		
Adjusting for propensity scores	1.09 (0.87-1.38)	1.17 (0.92-1.48)
Stratified by propensity score quintiles	1.13 (0.89-1.43)	1.20 (0.95-1.54)
Matched analysis	1.09 (0.95-1.27)	1.12 (0.97-1.29)
Adjusting for time trends		
Adjusting for propensity scores	1.06 (0.92-1.22)	1.07 (0.93-1.24)
Stratified by propensity score quintiles	1.07 (0.93-1.22)	1.10 (0.95-1.25)
Matched analysis	1.05 (0.91-1.21)	1.07 (0.93-1.24)

Wisnivesky JP et al., Cancer 2012

Agenda

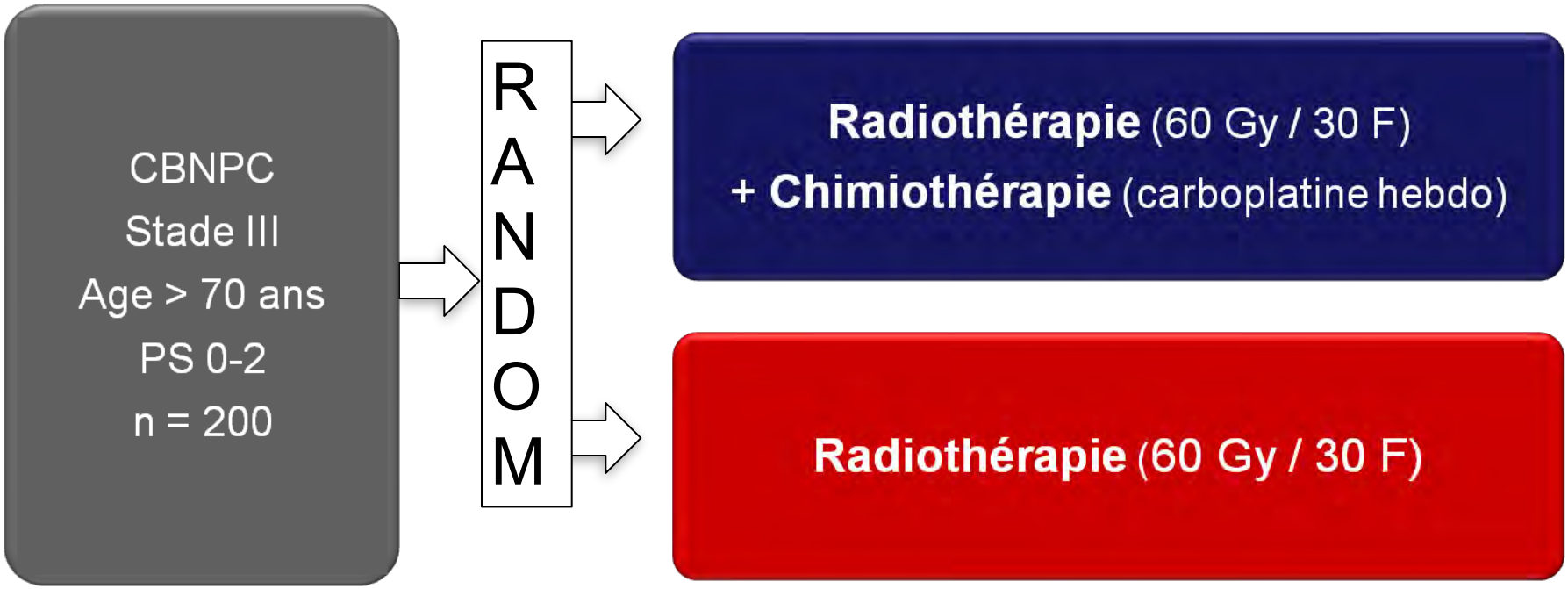
- Une population spéciale…
- CBNPC localisé
- **CBNPC localement avancé**
- CBNPC métastatique
  - Addiction oncogénique
  - Hors addiction oncogénique
- Perspectives

CBNPC localement avancé

- Radiothérapie thoracique exclusive
- Radio-chimiothérapie séquentielle
- Radio-chimiothérapie concomitante ?

Hayakawa et al., Lung Cancer 2001; Blanco R et al., Ann Oncol 2015

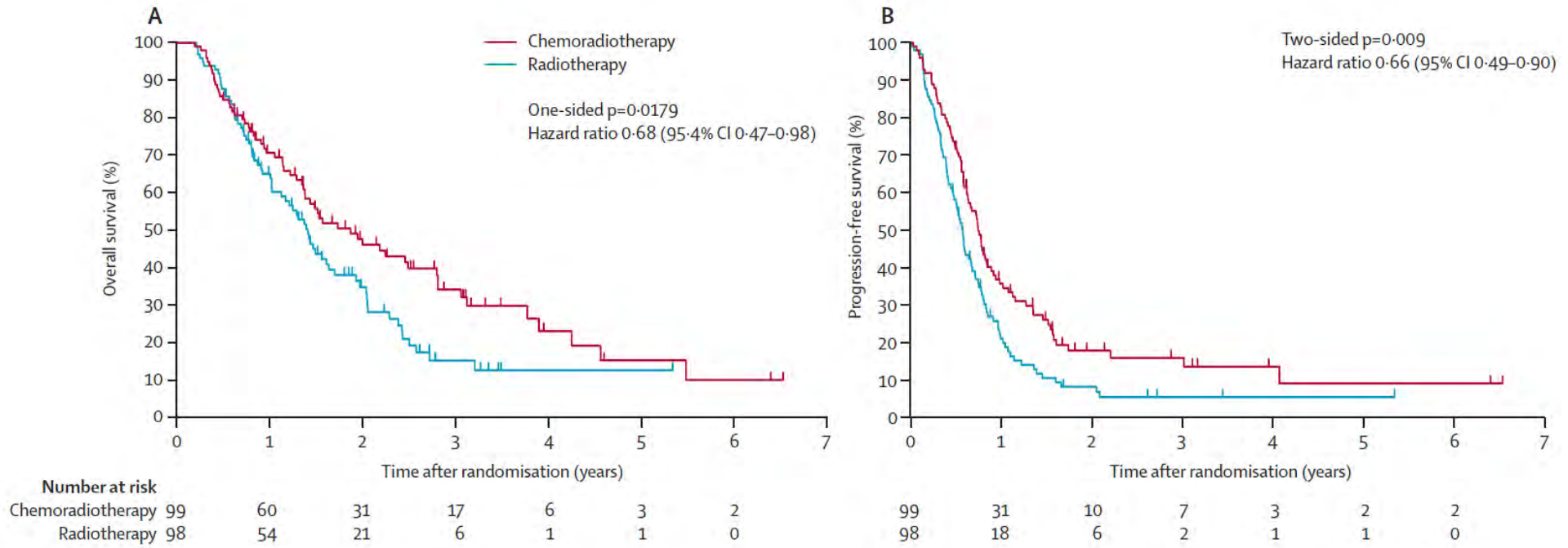
CBNPC localement avancé



Stratification par centre, PS (0 vs.1 vs. 2), et stade (IIIA vs. IIIB)

Atagi S et al, Lancet Oncol 2012

CBNPC localement avancé



Atagi S et al, Lancet Oncol 2012

CBNPC localement avancé

	Chemoradiotherapy (n=96)					Radiotherapy (n=98)*				
	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3–4	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3–4
Leucopenia	7	25	49	12 (12·5%)	63·5%	35	18	0	0	0
Neutropenia	10	20	33	22 (22·9%)	57·3%	10	3	0	0	0
Anaemia	26	33	4	1 (1·0%)	5·2%	22	15	0	0	0
Thrombocytopenia	18	23	28	0	29·2%	3	0	2	0	2·0%
Ventricular arrhythmia	4	1	0	0	0	2	0	0	0	0
Cardiac ischaemia or infarction	1	0	0	0	0	1	0	0	0	0
Oedema	1	1	0	0	0	1	0	0	0	0
Fatigue	34	2	0	1 (1·0%)	1·0%	17	5	2	0	2·0%
Fever	18	4	0	0	0	20	3	0	0	0
Dermatitis	52	2	0	0	0	48	6	0	0	0
Anorexia	35	7	1	1 (1·0%)	2·1%	26	3	3	0	3·1%
Oesophagitis	45	15	1	0	1·0%	45	12	0	0	0
Nausea	18	2	0	..	0	14	1	1	..	1·0%
Vomiting	3	1	0	0	0	5	1	0	0	0
Haemorrhage	3	0	3	0	3·1%	1	0	0	0	0
Febrile neutropenia	..	..	2	0	2·1%	..	..	0	0	0
Infection	1	6	12	0	12·5%	3	6	4	0	4·1%
Pain	5	1	0	0	0	7	0	0	0	0
Cough	30	8	0	..	0	33	10	1	..	1·0%
Dyspnoea	..	12	3	1 (1·0%)	4·2%	..	13	3	2 (2·0%)	5·1%
Pneumonitis	13	6	1	0	1·0%	24	11	2	1 (1·0%)	3·1%
Late radiotherapy morbidity†										
Oesophagus	6	1	1	0	1·1%	3	0	0	0	0
Heart	2	1	0	0	0	1	1	2	0	2·1%
Lung	36	18	3	3 (3·2%)	6·5%	40	21	5	0	5·3%
Skin	4	0	0	0	0	9	0	0	0	0

Atagi S et al, Lancet Oncol 2012

CBNPC localement avancé

	Chemoradiotherapy (n=96)					Radiotherapy (n=98)*				
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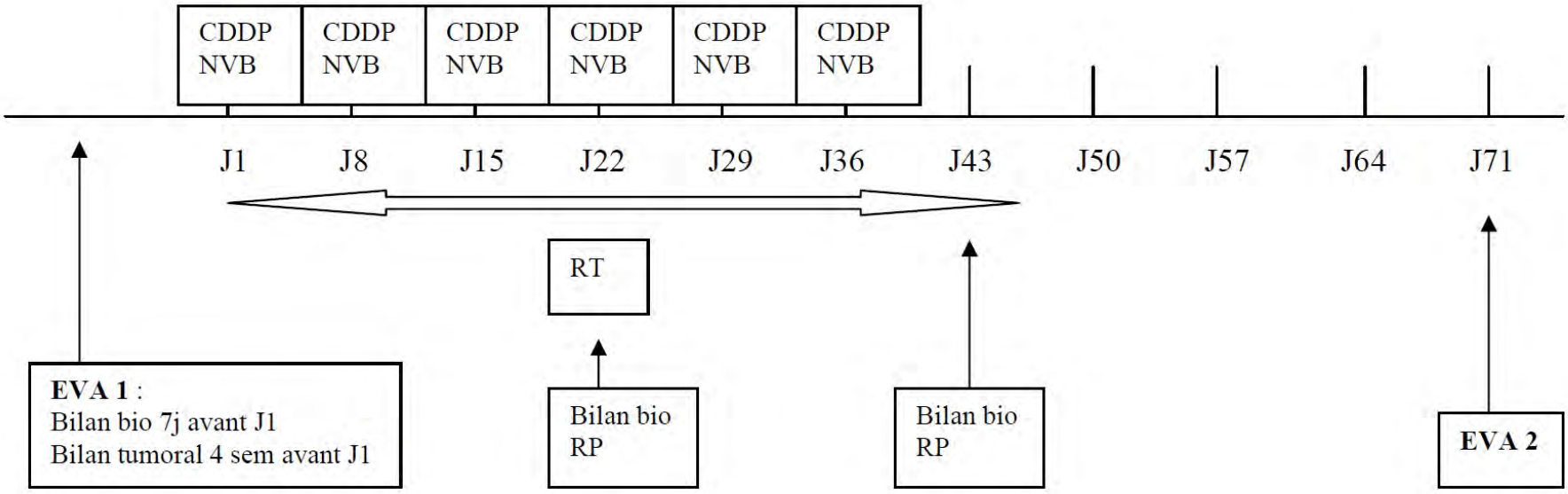
Anaemia	26	33	4	1 (1·0%)	5·2%	22	15	0	0	0
Thrombocytopenia	18	23	28	0	29·2%	3	0	2	0	2·0%
Cardiac ischaemia or infarction	1	0	0	0	0	1	0	0	0	0
Oedema	1	1	0	0	0	1	0	0	0	0
Fatigue	34	2	0	1 (1·0%)	1·0%	17	5	2	0	2·0%
Fever	18	4	0	0	0	20	3	0	0	0
Dermatitis	52	2	0	0	0	48	6	0	0	0
Anorexia	35	7	1	1 (1·0%)	2·1%	26	3	3	0	3·1%
Oesophagitis	45	15	1	0	1·0%	45	12	0	0	0
Nausea	18	2	0	..	0	14	1	1	..	1·0%
Vomiting	3	1	0	0	0	5	1	0	0	0
Haemorrhage	3	0	3	0	3·1%	1	0	0	0	0
Infection	1	6	12	0	12·5%	3	6	4	0	4·1%
Pain	5	1	0	0	0	7	0	0	0	0
Cough	30	8	0	..	0	33	10	1	..	1·0%
Dyspnoea	..	12	3	1 (1·0%)	4·2%	..	13	3	2 (2·0%)	5·1%
Pneumonitis	13	6	1	0	1·0%	24	11	2	1 (1·0%)	3·1%
Late radiotherapy morbidity†										
Oesophagus	6	1	1	0	1·1%	3	0	0	0	0
Heart	2	1	0	0	0	1	1	2	0	2·1%
Lung	36	18	3	3 (3·2%)	6·5%	40	21	5	0	5·3%
Skin	4	0	0	0	0	9	0	0	0	0

Atagi S et al, Lancet Oncol 2012

CBNPC localement avancé

- Patients ≥ 70 ans, indépendants sur le plan gériatrique
- CBNPC stade III, non résécable



GFPC 08-06, RACCOSA, EudraCT: 2009-01241321; WCLC 2013

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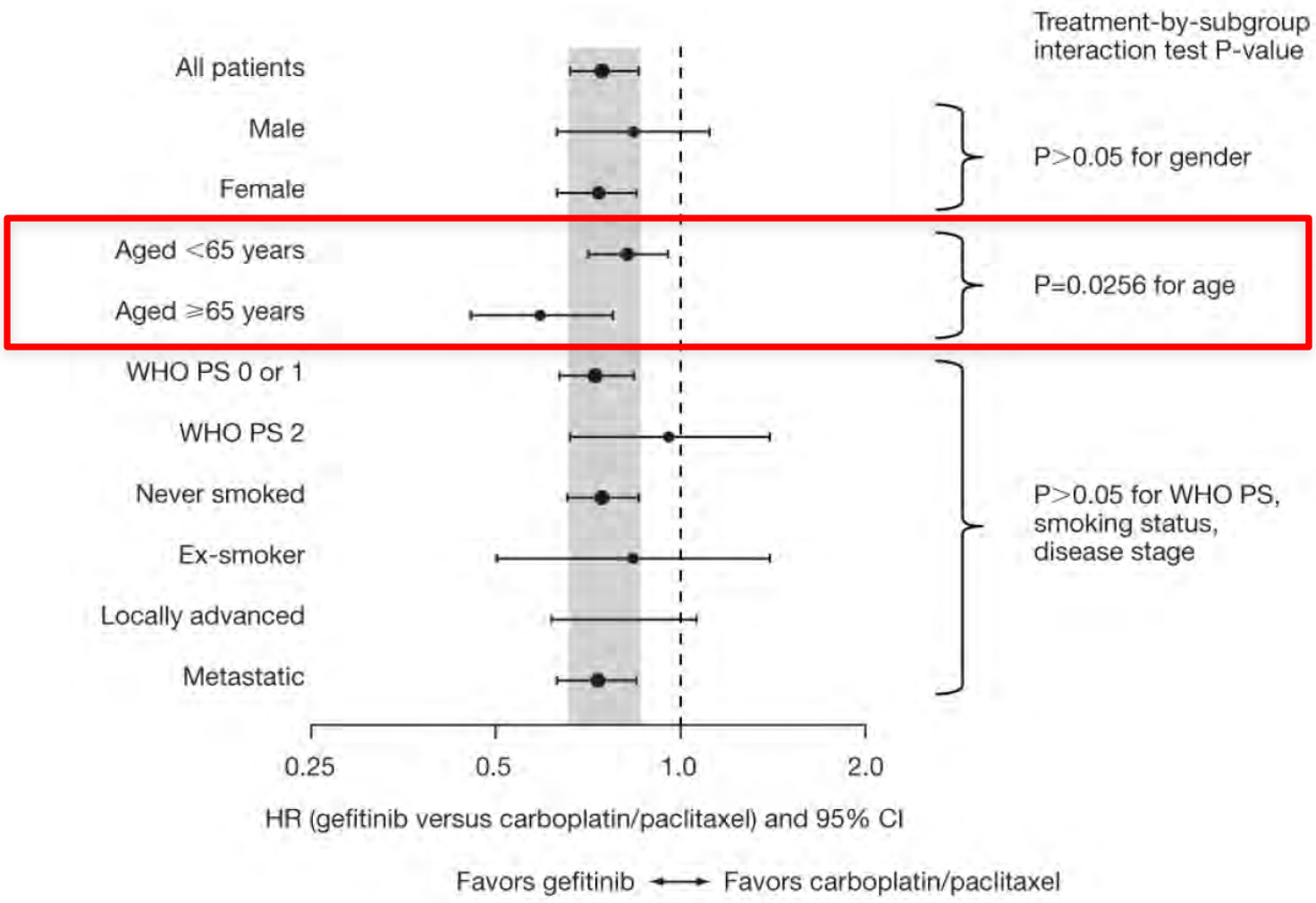
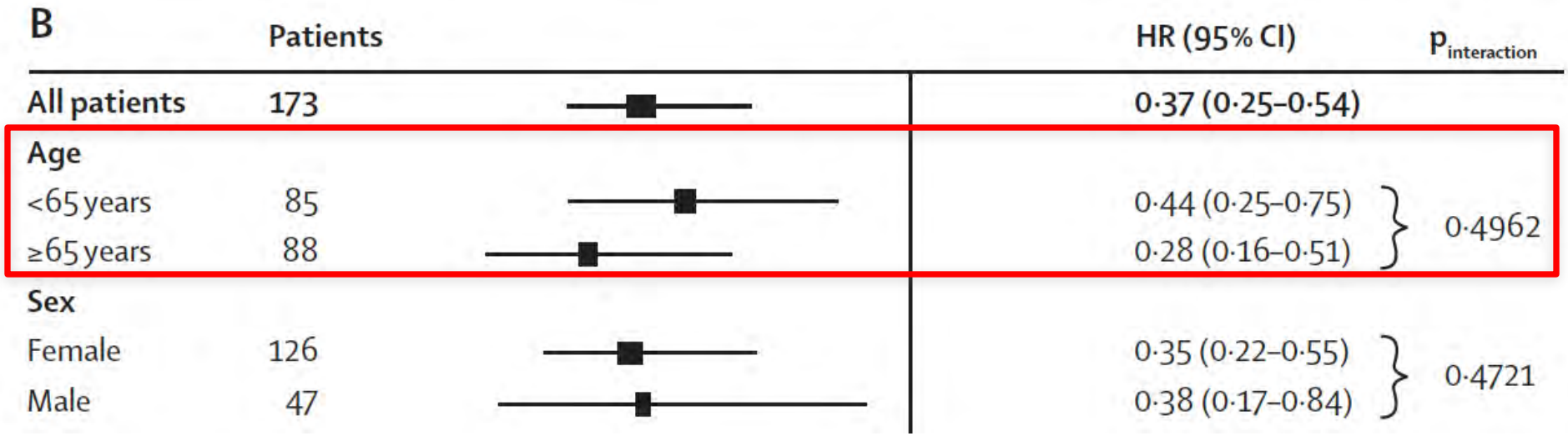
Gefitinib & EGFRm



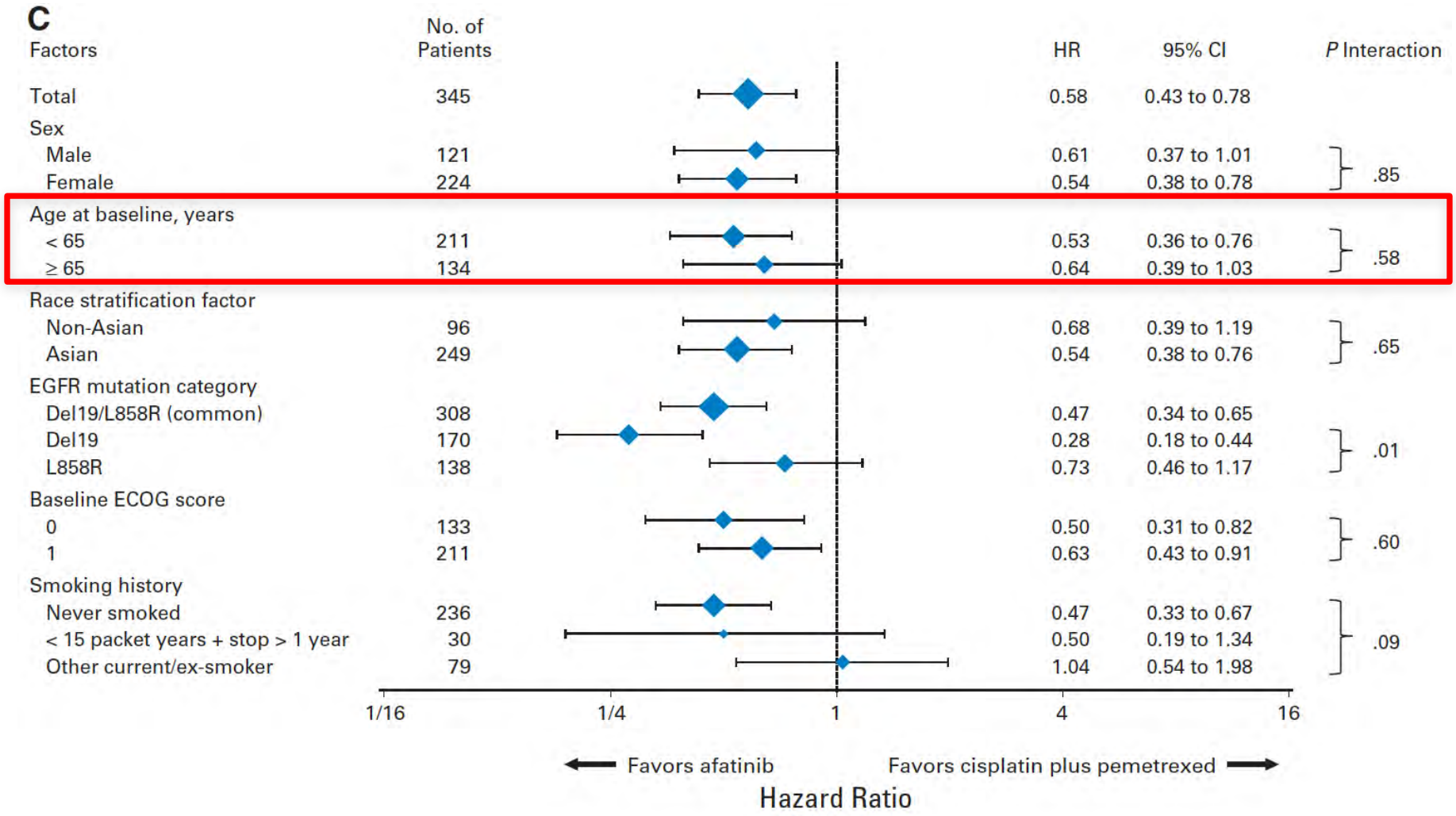
Mok et al, N J Engl Med 2009

Erlotinib & EGFRm



Rosell et al, Lancet Oncol 2012

Afatinib & EGFRm



Sequist LV et al, J Clin Oncol 2013

Gefitinib & EGFRm

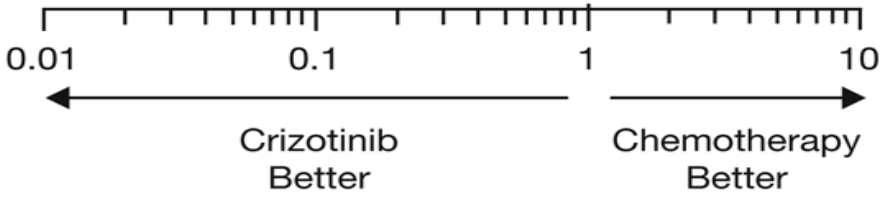
Author, year	N (median age)	ORR (%) IC95%	Median PFS (months)	Median OS (months)
Takahashi, 2014	20 (79.5)	70 45.7-88.1	10.0	26.4
Maemondo, 2012	31 (80)	74 58-91	12.3	NR
Asami, 2011	17 (81)	59 33-81	12.9 2.2-23.6	NR

Takahashi et al, Cancer Chemother Pharmacol 2014;

Maemondo et al. J Thor Oncol 2012; Asami et al, Clin Lung Cancer 2011

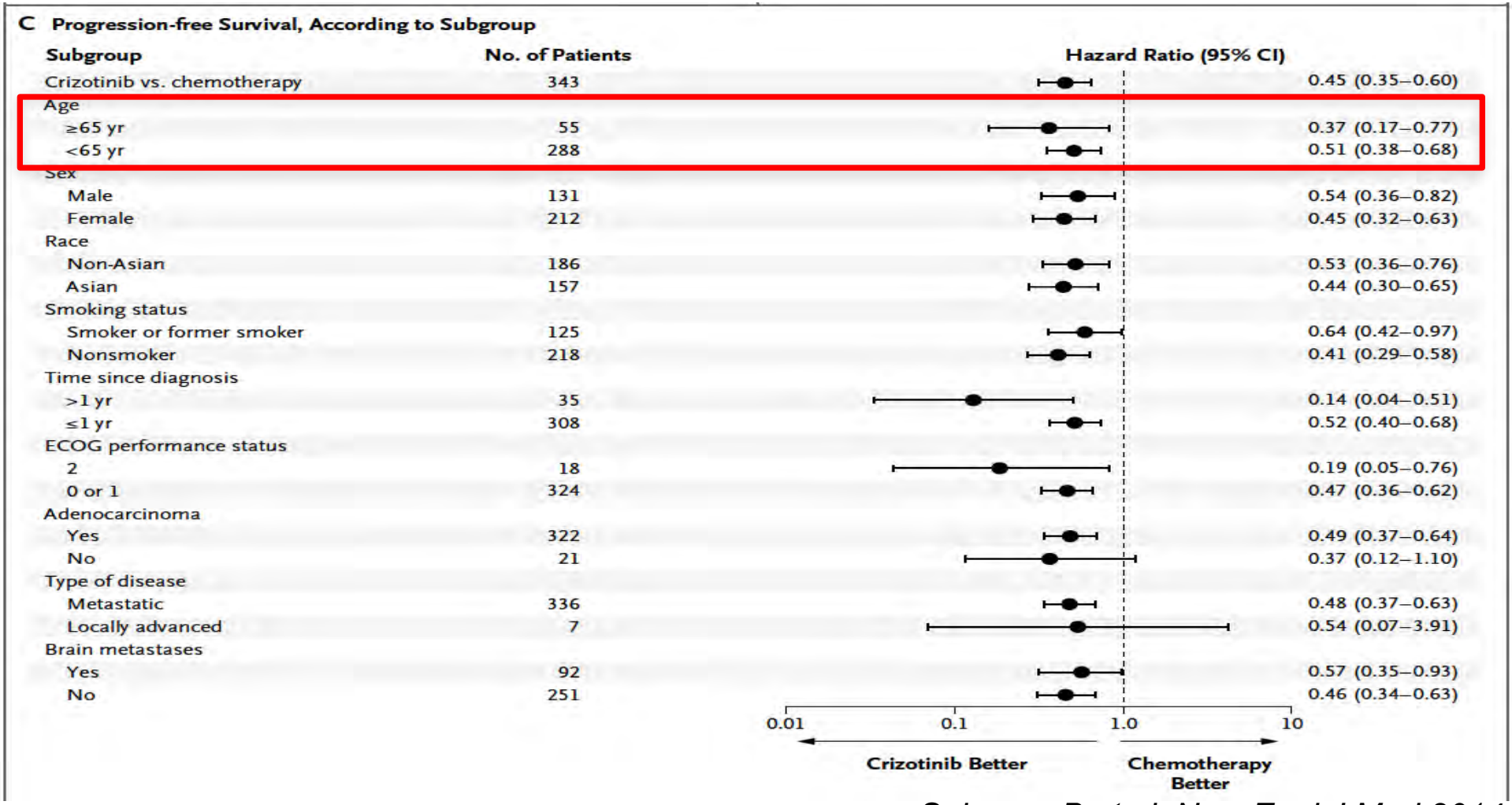
Crizotinib & ALK (2nd line)

Subgroup	No.*	Hazard Ratio (95% CI)
All patients	347	0.49 (0.37–0.64)
Age ≥65 years	50	0.54 (0.27–1.08)
Age <65 years	297	0.49 (0.37–0.65)
Male	153	0.52 (0.35–0.77)
Female	194	0.48 (0.34–0.68)
Non-Asian	190	0.45 (0.30–0.66)
Asian	157	0.53 (0.36–0.76)
Non-smoker	219	0.45 (0.32–0.63)
Smoker or ex-smoker	127	0.53 (0.34–0.83)
Adenocarcinoma	328	0.50 (0.38–0.66)
Non-adenocarcinoma	12	0.12 (0.01–1.02)
ECOG PS 0/1	313	0.48 (0.36–0.63)
ECOG PS 2	34	0.31 (0.12–0.86)
Brain metastases present	120	0.67 (0.44–1.03)
Brain metastases absent	227	0.43 (0.30–0.60)
Prior EGFR TKI	41	0.48 (0.22–1.03)
No prior EGFR TKI	306	0.49 (0.37–0.66)



Shaw A et al, New Engl J Med 2013

Crizotinib & ALK (1st line)



Solomon B et al, New Engl J Med 2014

Agenda

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  - **Hors addiction oncogénique**
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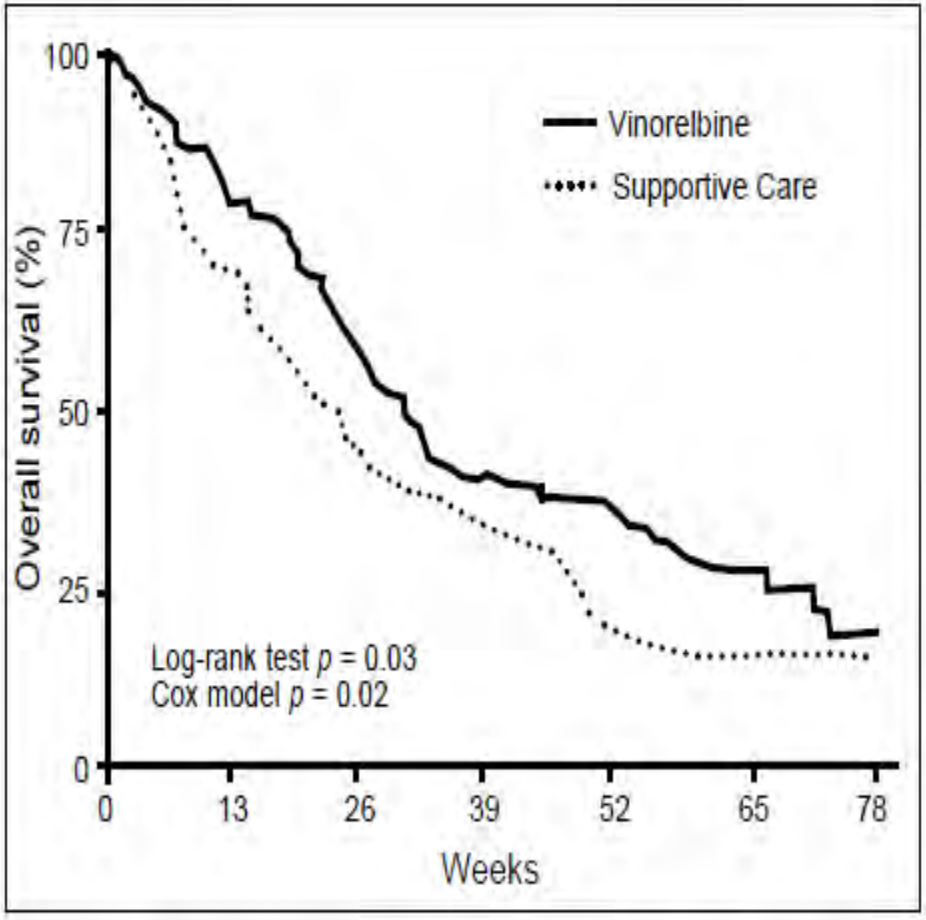
ELVIS trial: l'essai princeps

Table 2. Characteristics of patients randomized to BSC or BSC plus vinorelbine [14]

	BSC ($n = 78$)	BSC + Vinorelbine ($n = 76$)
Median age	74 years	74 years
(range)	(70 – 86)	(70 – 85)
Male	89%	86%
Stage IIIB/IV	28%/72%	27%/73%
ECOG PS: 0	19%	18%
1	56%	58%
2	24%	24%



J Natl Cancer Instit 1999; Gridelli C, Oncologist 2001

Doublets sans platine

Table 3. Phase III trials of non-platinum combination chemotherapy regimens in or predominantly including patients aged >70 years with advanced non-small-cell lung cancer

References	Patients (*N*)	Regimen	Patient age, median (range), years	Performance status	ORR (%)	OS	1-year survival (%)
Frasci et al. [102]	120	GMB/VNR	75 (71–83)	0–2	22	29 weeks*	30*
		VNR	74 (71–81)		15	18 weeks	13
Gridelli et al. [103]	707	GMB/VNR	74 (69–84)	0–2	21†	30 weeks†	30
		VNR	74 (63–83)		18	30 weeks	38
		GMB	74 (70–86)		16	28 weeks	28
Comella et al. [104]	264[a]	GMB/PCL	73 (53–83)	0–2	32	9.2 months[b]	44
		GMB/VNR	72 (42–82)		23	9.7 months	32
		PCL	72 (50–81)		13	6.4 months	25
		GMB	75 (49–86)		18	5.1 months	29
Hainsworth et al. [105]	345	TXT/GMB	74 (47–91)	0–2	25†	5.5 months†	26†
		TXT	74 (45–90)		17	5.1 months	24

[a]220 were >70 years.
[b]Pooled comparison of survival significantly favoured combination therapy over single-agent therapy.
*$P < 0.01$.
†Non-significant difference versus single-agent therapy.
ORR, overall response rate; OS, overall survival; GMB, gemcitabine; VNR, vinorelbine; PCL, paclitaxel; TXT, docetaxel.

Blanco et al, Ann Oncol 2015

Doublets sans platine

Table 3. Phase III trials of non-platinum combination chemotherapy regimens in or predominantly including patients aged >70 years with advanced non-small-cell lung cancer

References	Patients (*N*)	Regimen	Patient age, median (range), years	Performance status	ORR (%)	OS	1-year survival (%)
Frasci et al. [102]	120	GMB/VNR	75 (71–83)	0–2	22	29 weeks*	30*
		VNR	74 (71–81)		15	18 weeks	13
Gridelli et al. [103]	707	GMB/VNR	74 (69–84)	0–2	21†	30 weeks†	30
		VNR	74 (63–83)		18	30 weeks	38
		GMB	74 (70–86)		16	28 weeks	28
Comella et al. [104]	264[a]	GMB/PCL	73 (53–83)	0–2	32	9.2 months[b]	44
		GMB/VNR	72 (42–82)		23	9.7 months	32
		PCL	72 (50–81)		13	6.4 months	25
		GMB	75 (49–86)		18	5.1 months	29
Hainsworth et al. [105]	345	TXT/GMB	74 (47–91)	0–2	25†	5.5 months†	26†
		TXT	74 (45–90)		17	5.1 months	24

[a]220 were >70 years.
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*$P < 0.01$.
†Non-significant difference versus single-agent therapy.
ORR, overall response rate; OS, overall survival; GMB, gemcitabine; VNR, vinorelbine; PCL, paclitaxel; TXT, docetaxel.

Blanco et al, Ann Oncol 2015

Place des sels de platine ?

Table 4. Cisplatin- and carboplatin-based chemotherapy trials in patients with advanced non-small-cell lung cancer: treatment outcomes according to age

References	Patients (*N*)	Regimen	Age group (years)	ORR (%)	*P* value	TTP (months)	*P* value	OS (months)	*P* value
Kelly et al. [109]	491	CDDP/VNR or Carbo/PCL	<70			4.2	0.62	8.6	0.06
	117		≥70			3.9		6.9	
Langer et al. [110]	488	CDDP/PCL or VP/CDDP	<70	21.5	0.66	4.37	0.29	9.05	0.29
	86		≥70	23.3		4.30		8.53	
Langer et al. [111]	912	CCDP/PCL or CDDP/GMB or	<70	22.1	0.76	3.71		8.15	
	227	CDDP/TXT or Carbo/VNR	≥70	24.5		3.75		8.25	
Hensing et al. [112]	163	Carbo/PCL	<70	20	NS	3.0	0.049	7.8	NS
	67		≥70	27		4.8		7.1	
Belani and Fossella [113]	817	CCDP/TXT or Carbo/TXT or	<65	NR	NR	NR	NR	11.0 versus 12.6[a]	NS
	401	CDDP/VNR	≥65	NR		NR		9.7 versus 9.0[a]	NS
								10.1 versus 9.9[a]	NS
Sederholm et al. [114]	213	Carbo/GMB or GMB	<70	18.6	NR	NR	0.004[b]	NR	NS
	121		≥70	22.1		NR		NR	
Lilenbaum et al. [115]	406	PCL or Carbo/PCL	<70	15 versus 28[c]	NR	NR	NR	6.8 versus 9.0[c]	NS
	155		≥70	21 versus 36[c]		NR		5.8 versus 8.0[c]	
Goto et al. [116]	497	CDDP/CPT or Carbo/PCL or	<70	NR	NS[d]	NR	NR	NR	NS[d]
	105	CDDP/GMB or CDDP/VNR	≥70	NR		NR		NR	
Ansari et al. [117]	797	Carbo/GMB or PCL/GMB or	<70	30	NS	4.5	NS	8.6	NS
	338	Carbo/PCL	≥70	27		7.9		7.9	
Blanchard et al. [118]	494	CDDP/VNR or Carbo/PCL	<70	27	NS	4.0[e]	NS	9.0	0.04
	122		≥70	30		4.0[e]		7.0	

[a]<65 versus ≥65 years for the respective regimen.
[b]TTP values not reported but favoured patients aged ≥70 years.
[c]PCL versus Carbo/PCL (there were no statistically significant differences between treatments in each patient age group).
[d]No significant differences between age groups for each treatment regimen for response rates and 1-year survival.
[e]Progression-free survival.
ORR, overall response rate; TTP, time-to-tumour progression; OS, overall survival; CDDP, cisplatin; VNR, vinorelbine; Carbo, carboplatin; PCL, paclitaxel; VP, etoposide; GMB, gemcitabine; TXT, docetaxel; NS, non-significant; NR, not reported; CPT, irinotecan.

Blanco et al, Ann Oncol 2015

Place des sels de platine ?

Table 4. Cisplatin- and carboplatin-based chemotherapy trials in patients with advanced non-small-cell lung cancer: treatment outcomes according to age

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Kelly et al. [109]	491	CDDP/VNR or Carbo/PCL	<70			4.2	0.62	8.6	0.06
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	86		≥70	23.3		4.30		8.53	
Langer et al. [111]	912	CCDP/PCL or CDDP/GMB or	<70	22.1	0.76	3.71		8.15	
	227	CDDP/TXT or Carbo/VNR	≥70	24.5		3.75		8.25	
Hensing et al. [112]	163	Carbo/PCL	<70	20	NS	3.0	0.049	7.8	NS
	67		≥70	27		4.8		7.1	
Belani and Fossella [113]	817	CCDP/TXT or Carbo/TXT or	<65	NR	NR	NR	NR	11.0 versus 12.6[a]	NS
	401	CDDP/VNR	≥65	NR		NR		9.7 versus 9.0[a]	NS
								10.1 versus 9.9[a]	NS
Sederholm et al. [114]	213	Carbo/GMB or GMB	<70	18.6	NR	NR	0.004[b]	NR	NS
	121		≥70	22.1		NR		NR	
Lilenbaum et al. [115]	406	PCL or Carbo/PCL	<70	15 versus 28[c]	NR	NR	NR	6.8 versus 9.0[c]	NS
	155		≥70	21 versus 36[c]		NR		5.8 versus 8.0[c]	
Goto et al. [116]	497	CDDP/CPT or Carbo/PCL or	<70	NR	NS[d]	NR	NR	NR	NS[d]
	105	CDDP/GMB or CDDP/VNR	≥70	NR		NR		NR	
Ansari et al. [117]	797	Carbo/GMB or PCL/GMB or	<70	30	NS	4.5	NS	8.6	NS
	338	Carbo/PCL	≥70	27		7.9		7.9	
Blanchard et al. [118]	494	CDDP/VNR or Carbo/PCL	<70	27	NS	4.0[e]	NS	9.0	0.04
	122		≥70	30		4.0[e]		7.0	

[a]<65 versus ≥65 years for the respective regimen.
[b]TTP values not reported but favoured patients aged ≥70 years.
[c]PCL versus Carbo/PCL (there were no statistically significant differences between treatments in each patient age group).
[d]No significant differences between age groups for each treatment regimen for response rates and 1-year survival.
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ORR, overall response rate; TTP, time-to-tumour progression; OS, overall survival; CDDP, cisplatin; VNR, vinorelbine; Carbo, carboplatin; PCL, paclitaxel; VP, etoposide; GMB, gemcitabine; TXT, docetaxel; NS, non-significant; NR, not reported; CPT, irinotecan.

Blanco et al, Ann Oncol 2015

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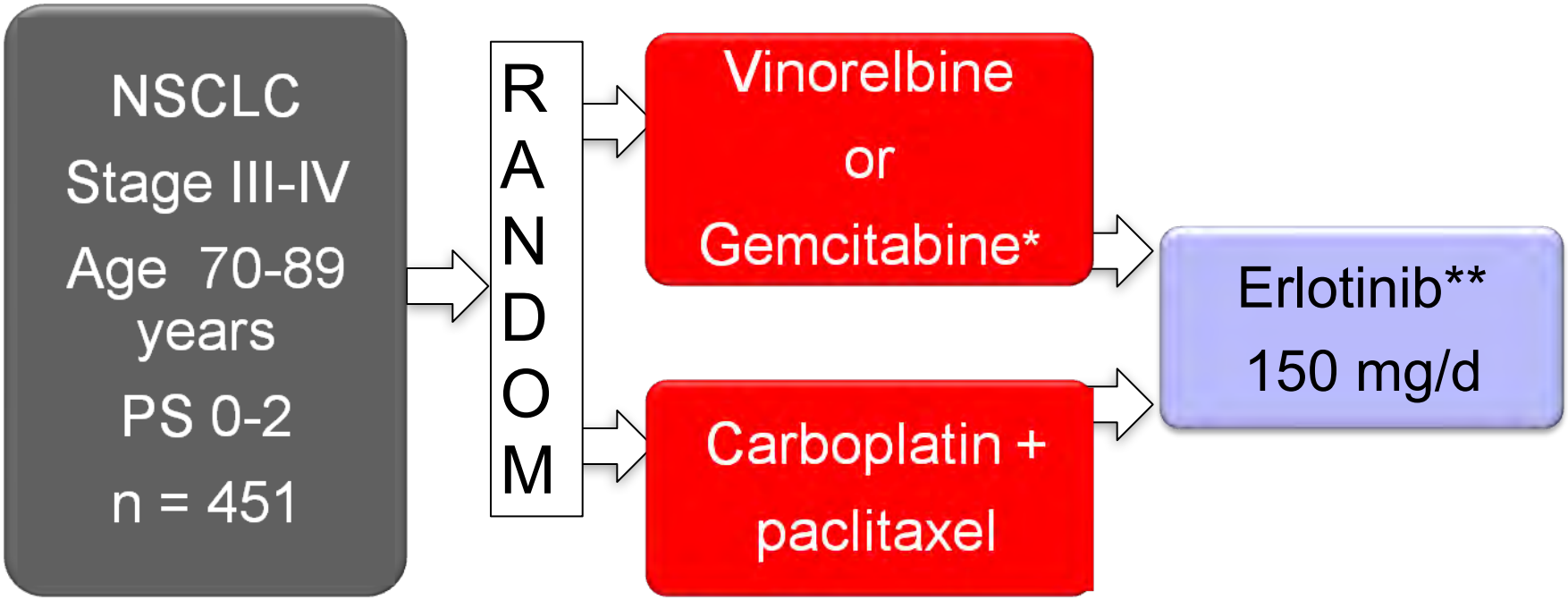


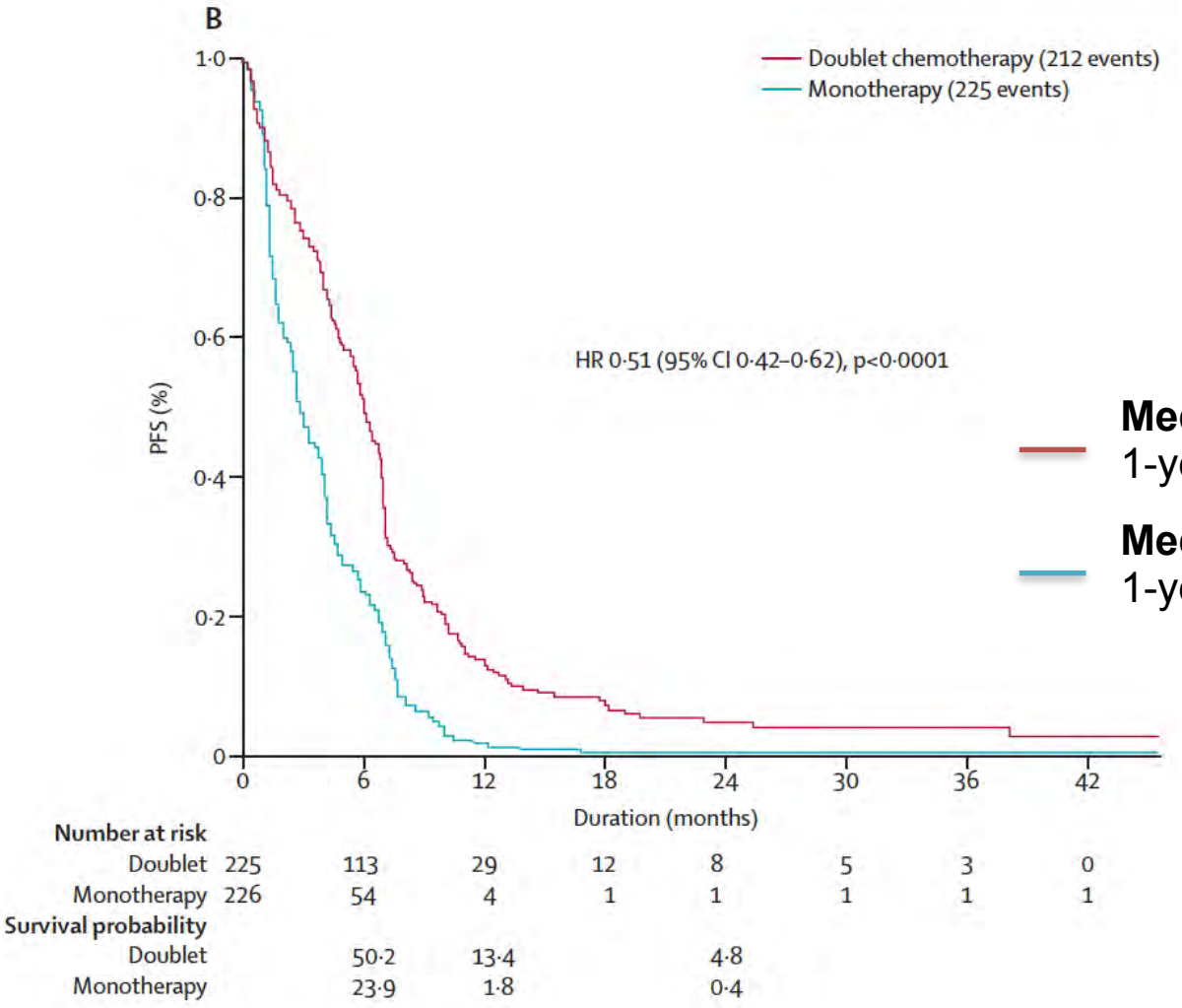
Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study

** In case of PD or excessive toxicity

Quoix E et al, Lancet 2011

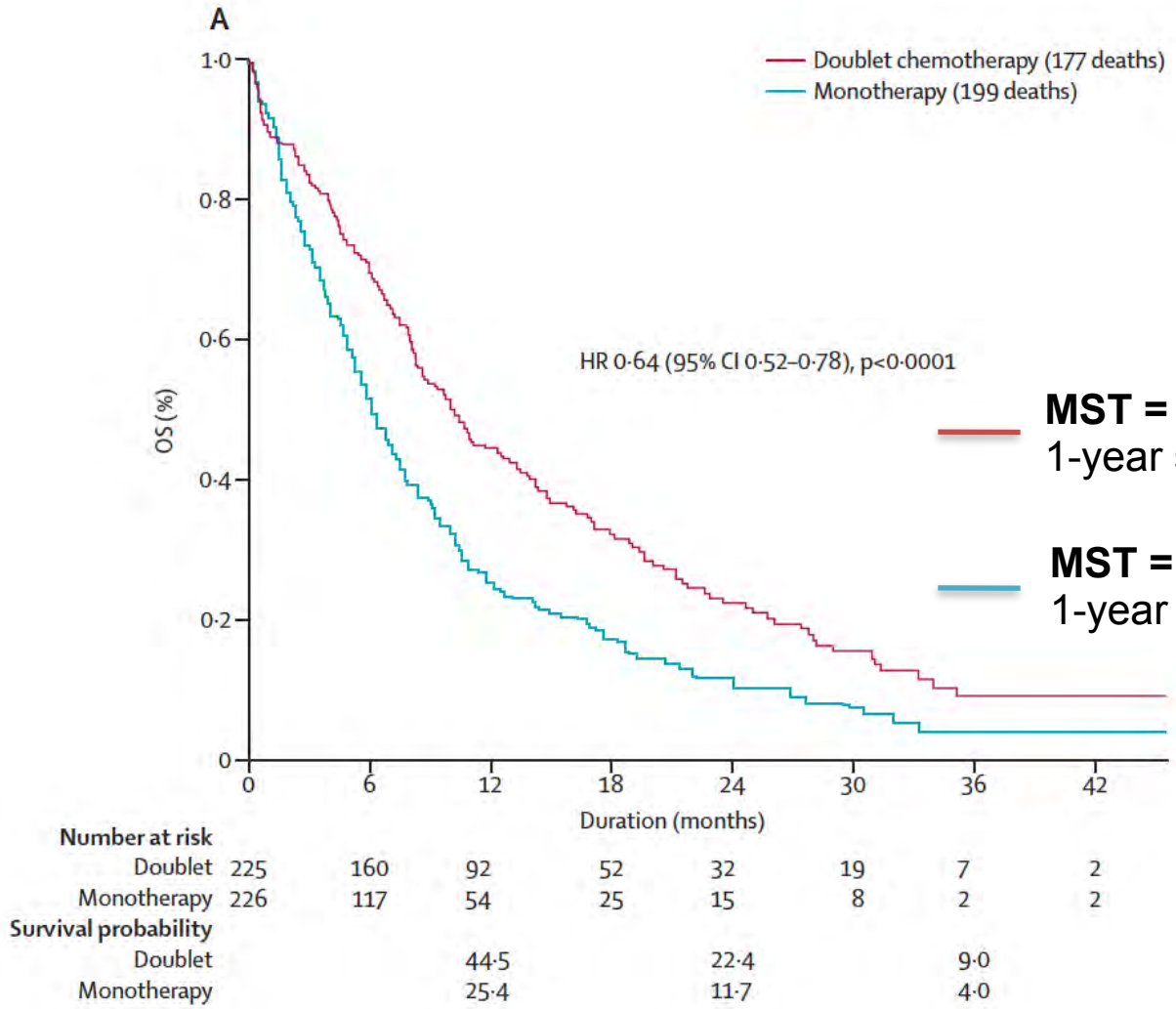
Survie sans progression



Median : 6.0 months (95% CI 5.5-6.8)
1-year PFS : 13.4% (95% CI 9.3-18.3)

Median : 2.8 months (95% CI 2.6-3.7)
1-year PFS : 1.8% (95% CI 0.6-4.2)

Survie globale

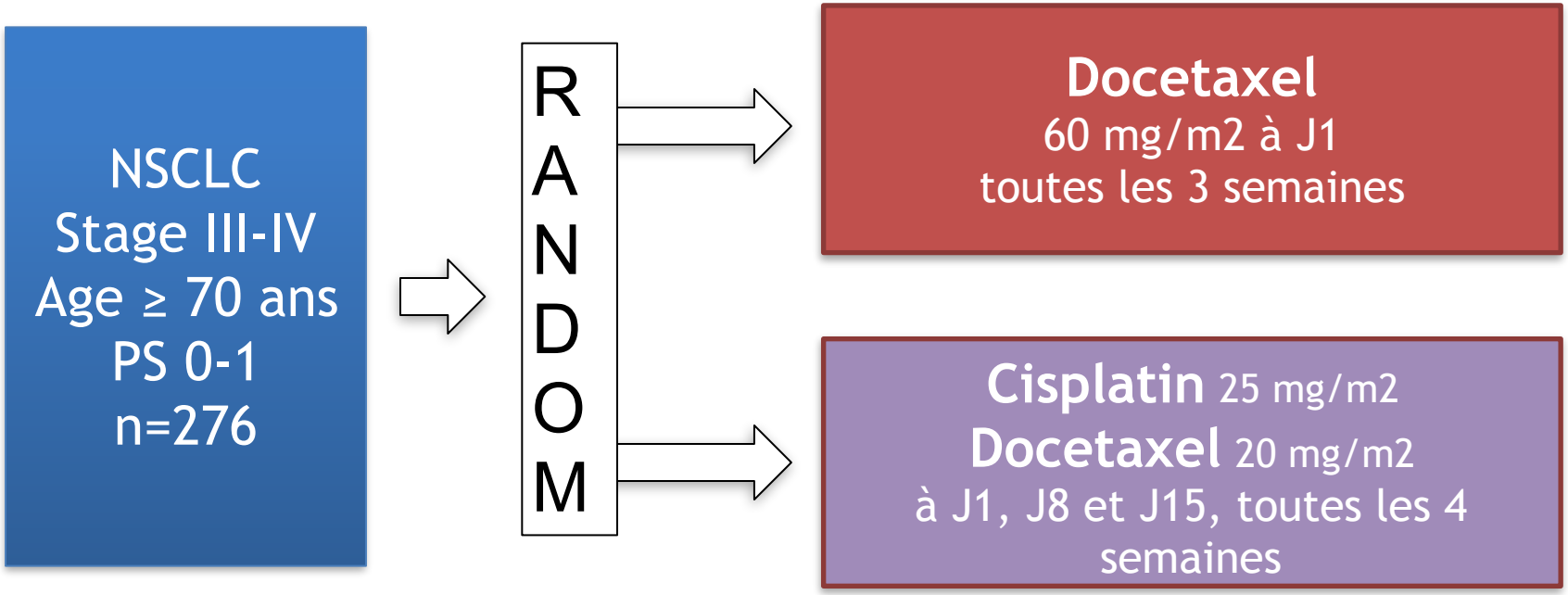


MST = 10.3 months (95% CI 8.3-12.6)
1-year survival 44.5% (95% CI 37.9-50.9)

MST = 6.2 months (95% CI 5.3-7.3)
1-year survival 25.4% (95% CI 19.9-31.3)

Quoix E et al, Lancet 2011

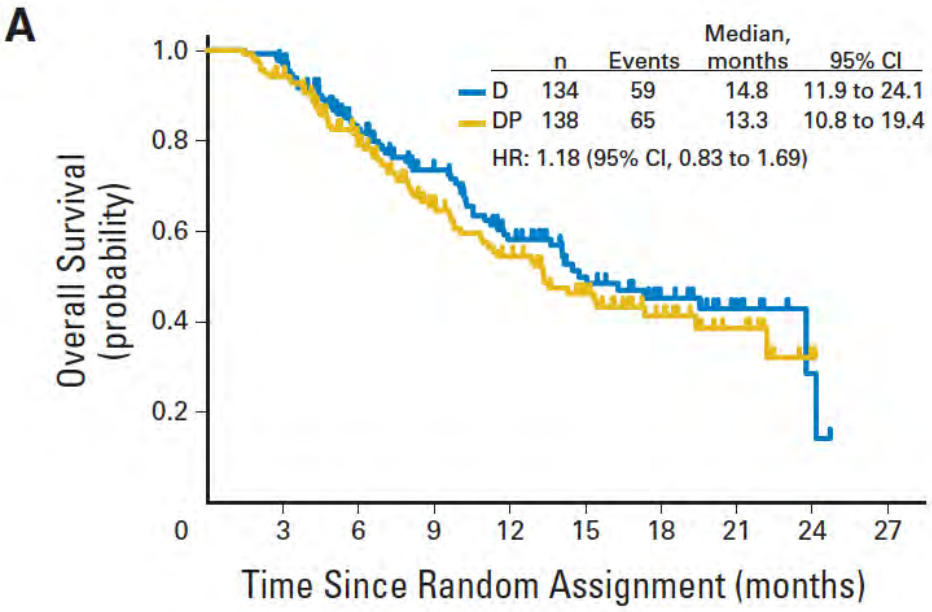
JCOG0803-WJOG4307L

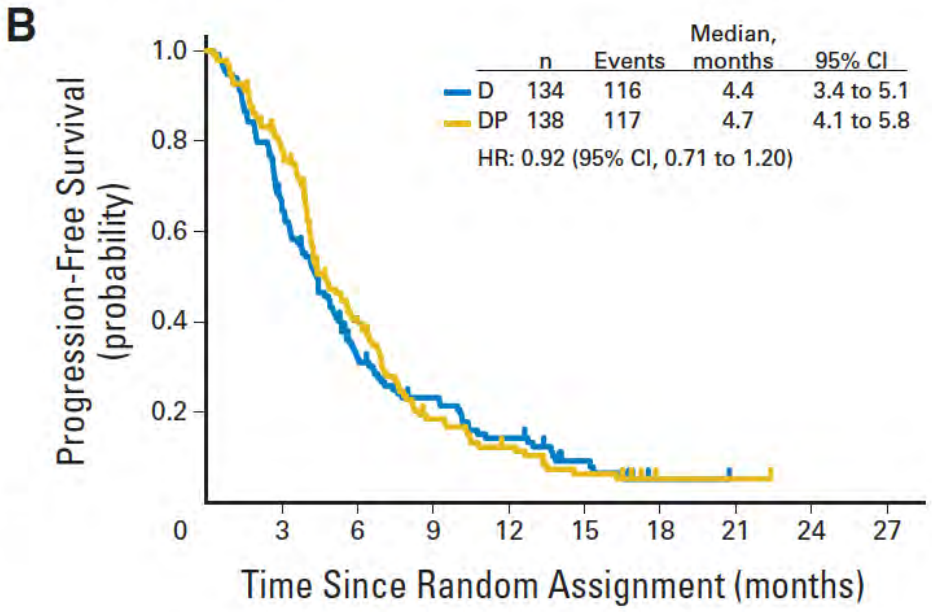


Stratification by centre, age ≥ 75 vs. <75, and stage III vs. IV

Abe T et al, J Clin Oncol 2015

JCOG0803-WJOG4307L

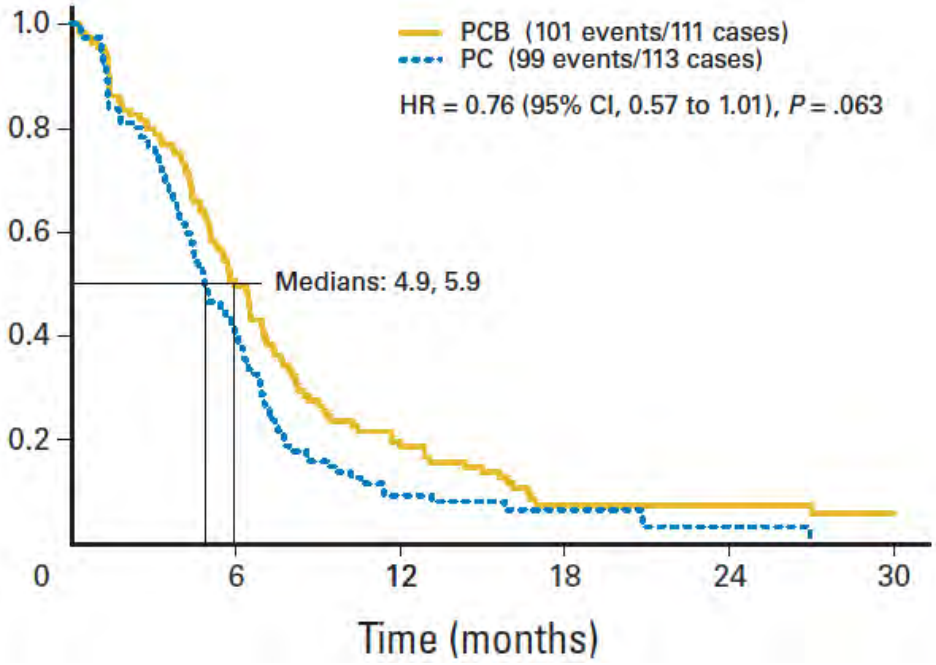


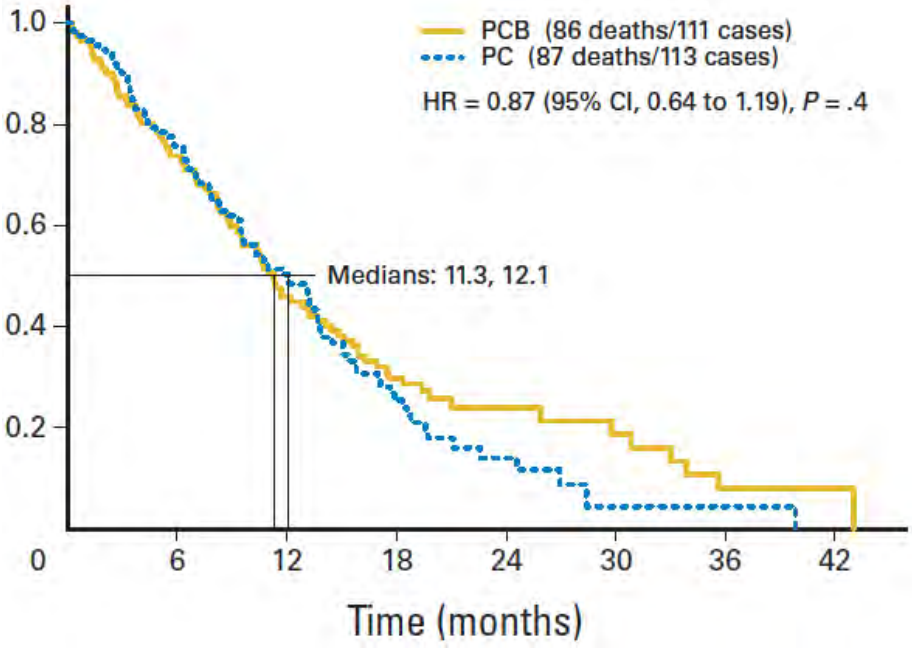


Abe T et al, J Clin Oncol 2015

Bevacizumab (E4599 sous groupe)

N=224 (26%)





Ramalingam SS et al, J Clin Oncol 2008

Bevacizumab (E4599 sous groupe)

N=224 (26%)

Toxicités	≥70 ans	<70 ans	p
Neutropénie grade 4	34 %	22 %	0.02
Saignements digestifs	3.5 %	0 %	0.005
Protéinurie	7.9 %	1.3 %	0.001
Neuropathie	3.5 %	0.6 %	0.05
Grade 3-4	87 %	70 %	< 0.001

Ramalingam SS et al, J Clin Oncol 2008

Bevacizumab (AVAIL sous groupe)

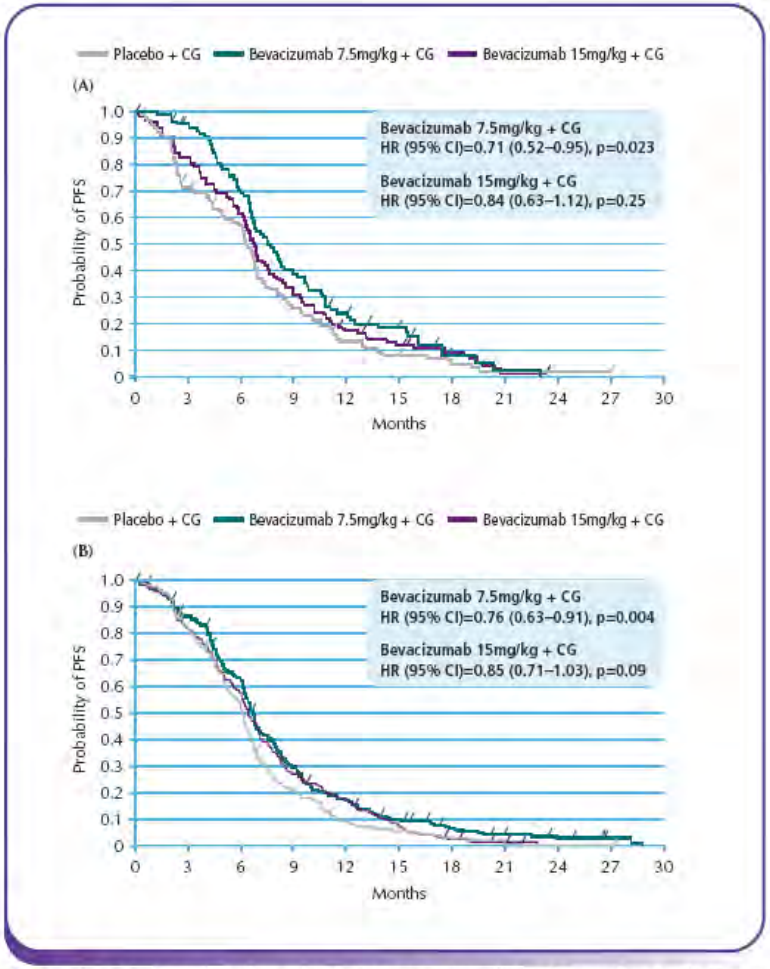


Figure 2. Plots of Kaplan-Meier estimates for PFS (intent to treat population) for (A) patients aged ≥65 years and (B) patients aged <65 years.

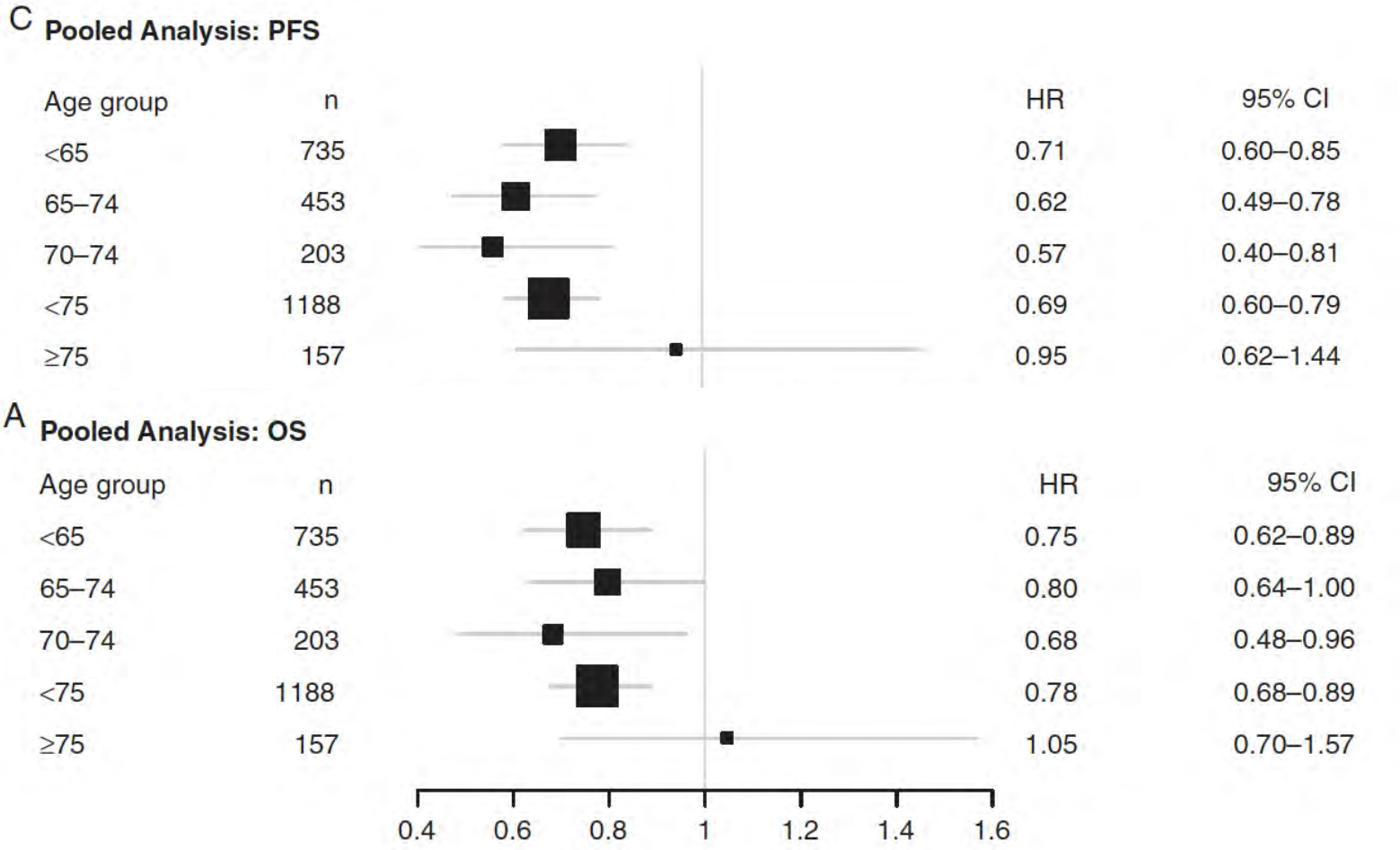
Table 2. Selected AEs grade ≥3 and AEs of special interest for patients aged ≥65 years and <65 years (safety population).

	Patients ≥65 years			Patients <65 years		
	Placebo + CG (n=103)	Bevacizumab 7.5mg/kg + CG (n=86)	Bevacizumab 15mg/kg + CG (n=95)	Placebo + CG (n=223)	Bevacizumab 7.5mg/kg + CG (n=245)	Bevacizumab 15mg/kg + CG (n=234)
All AEs (grade ≥3) (%)	80	84	80	76	78	85
Selected AEs (grade ≥3) with incidence in either bevacizumab arm exceeding the placebo group by ≥2% (%)						
Thrombocytopenia	27	40	38	25	29	24
Asthenia and fatigue	11	13	16	9	14	10
Pulmonary embolism	5	8	4	2	3	3
Other AEs including AEs of special interest (grade ≥3) (%)						
Proteinuria	0	0	4	0	2	2
Gastrointestinal perforation	0	0	0	0.9	0	0.4
Venous thromboembolic events	8	10	6	7	7	7
Haemorrhage	3	7	3	1	3	6
Haemoptysis	0	0	0	0.5	0.8	1
Neutropenia (grade 4/5)	13	15	17	15	18	18
Febrile neutropenia	1	0	1	2	2	3
Hypertension (baseline)	1	8	7	3	7	10
Neuropathy*	0	1	1	1	0.4	0
Congestive heart failure	0	1	0	0	0.4	0
Treatment-related deaths	6	2	4	4	4	5

*Includes polyneuropathy, peripheral neuropathy and peripheral sensory neuropathy

Leighl NB et al, ASCO 2009, J Thorac Oncol 2010

Bevacizumab (E4599 et PointBreak sous groupes)



Langer CJ et al, Am J Clin Oncol 2015

Agenda

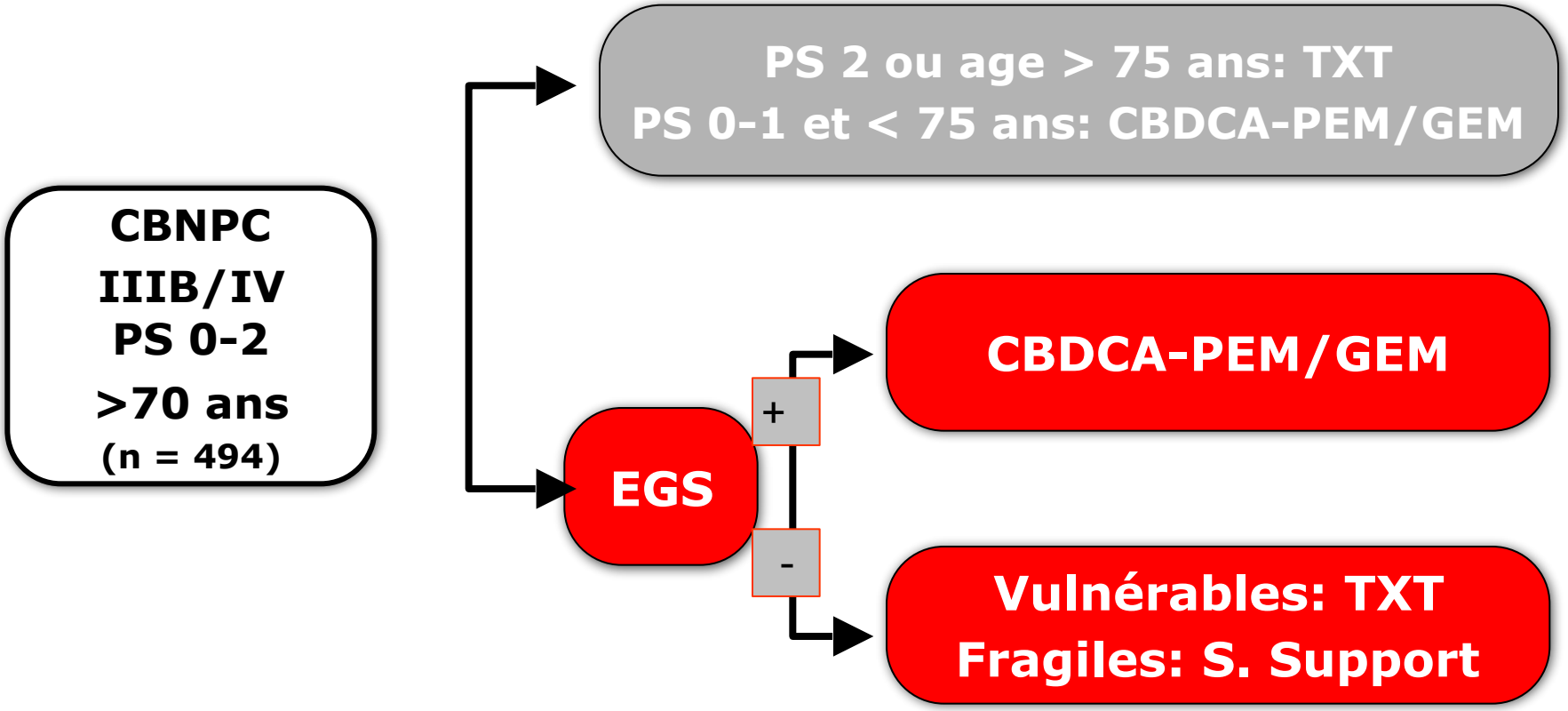
- Une population spéciale…
- CBNPC localisé
- CBNPC localement avancé
- CBNPC métastatique
  - Addiction oncogénique
  - Hors addiction oncogénique
- **Perspectives**

Allouer le bon traitement

	RR (%) / MST (months)	Gr3/4 Hem / Non Hem
GFPC0202a (>65 ans, CCI, PS) BSC ou docetaxel	**10%** **4.3 [1.7-11.1]**	**4** (Anemia) **30** (Fatigue)
GFPC0202b (>65 ans, CCI, PS) Gemcitabine + docetaxel	**34%** **7 [5.6-8.8]**	**12** (Anemia) **30** (Fatigue)
GFPC0504 (>65 ans, EGS: fit pts) Gemcitabine + docetaxel vs erlotinib (CO @ PRG)	**21 vs 17%** **9.4 vs 7.1**	**29** (Neutropenia) **9.8** (Asthenia)
GFPC0505 (>65 ans, EGS:) Gemcitabine vs erlotinib (CO @ PRG)	**18 vs 7%** **4.3 vs 3.9**	**12.5** (Anemia) **28.6** (Fatigue)

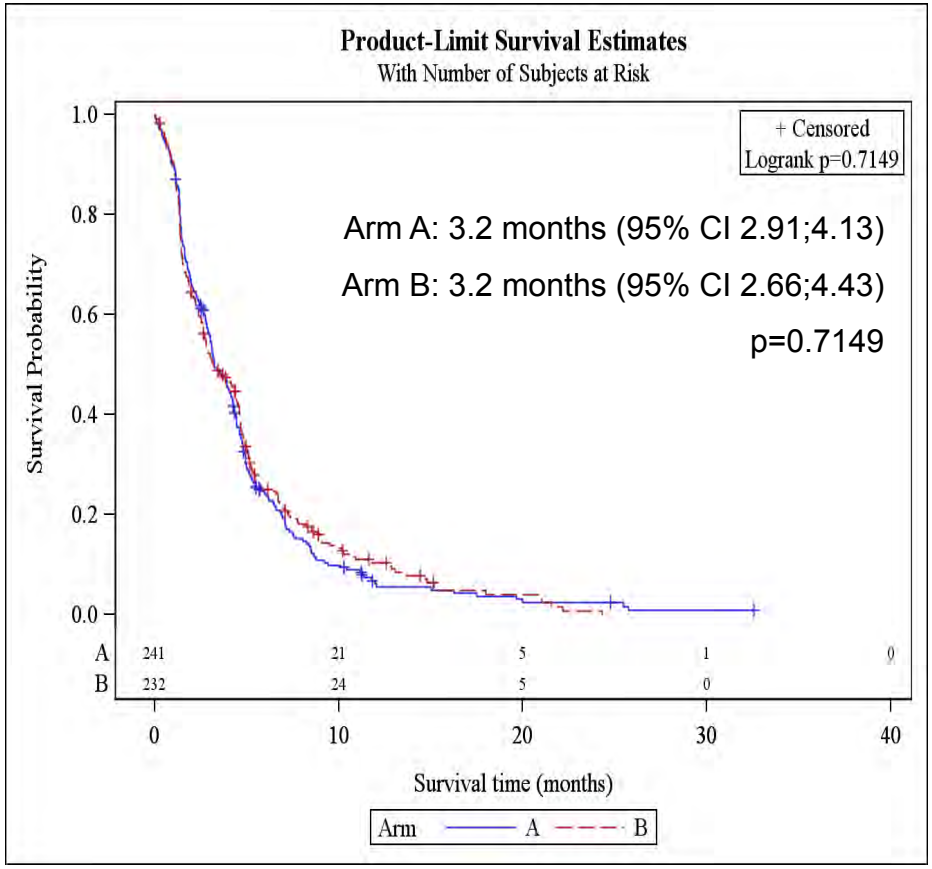
Lecaer, Lung Cancer 2007; Lecaer, Crit Hemat Rev 2007; Lecaer, Br J Cancer 2011; Lecaer, Lung Cancer 2012

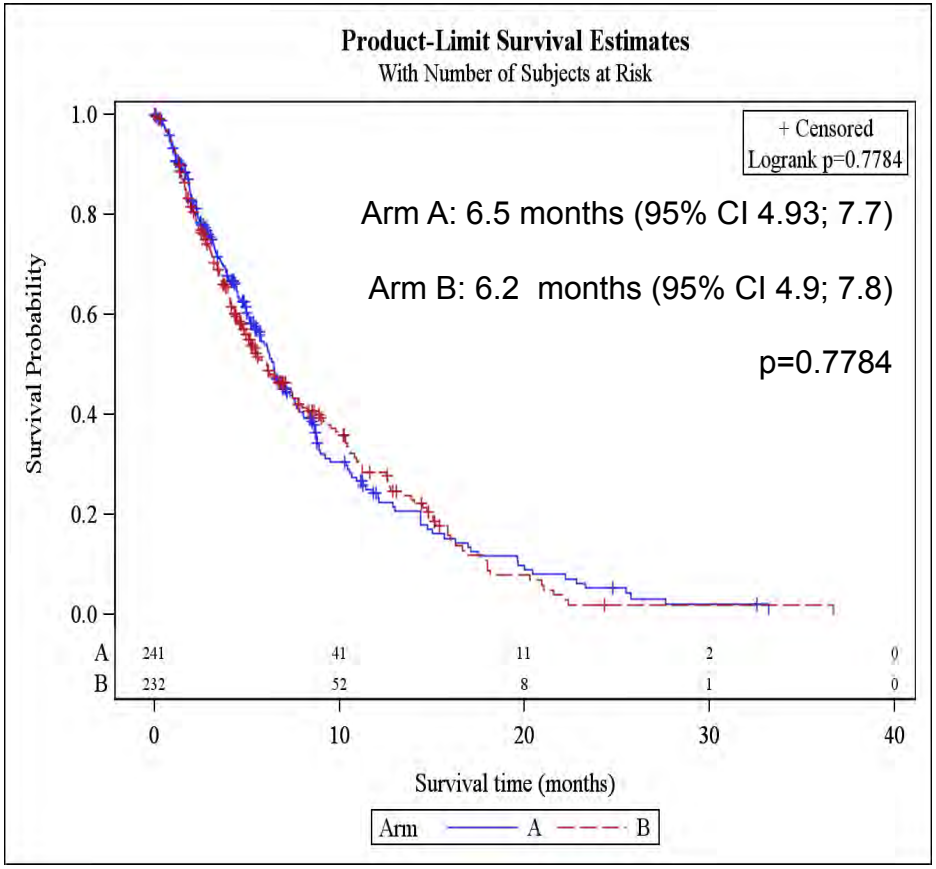
GFPC0802 (ESOGIA)



Corre R et al, WCLC 2013

Résultats





Corre R et al, WCLC 2013

Résultats

	Arm A (PS, age) n=241			Arm B (CGA) n=232			
	C-pem N=62 (25%)	C-Gem N=21 (9%)	Doc N=158 (66%)	C-pem N=84 (36%)	C-Gem N=25 (11%)	Doc N=73 (32%)	BSC N=50 (21%)
mTFF (months)	4.4	4.53	3.1	4.9	4.8	2.7	1.3
mOS (months)	8.9	6.3	5.9	10.2	8.4	4.9	2.9

Corre R et al, WCLC 2013

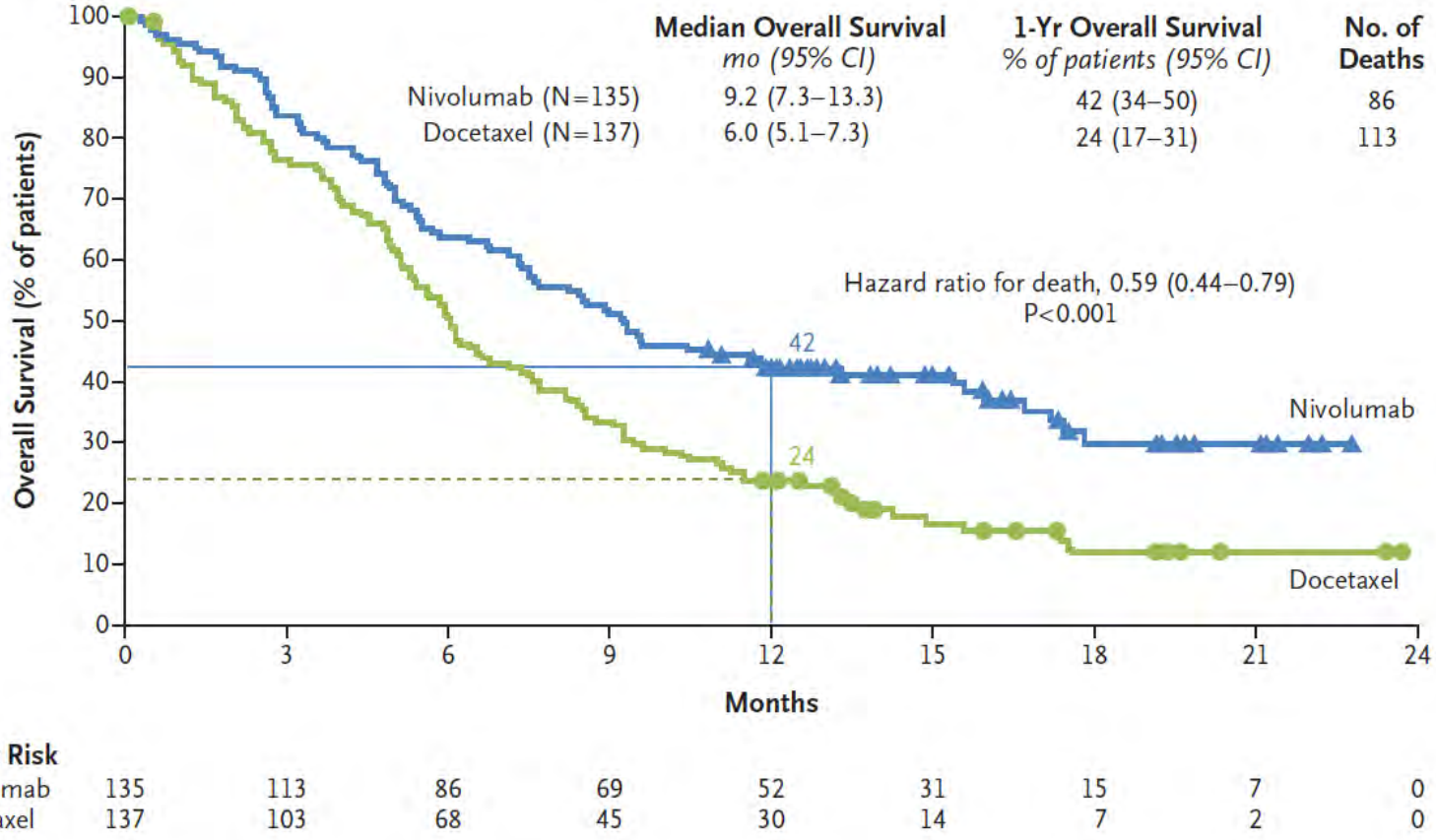
Résultats

	Arm A (PS, Age) N=241			Arm B (CGA) N=232				p
All grades AE	**224 (92.95%)**			**200 (86.21%)**				**0.016**
AE grade≥3	**172 (71.3%)**			**158 (68.1%)**				0.439
Grade 3-4 hematological AE	**All n=241**	Carbo- based doublet n=83	Doc n=158	**All n=232**	Carbo-based doublet n=109	Doc n=73	BSC n=50	
Neutropenia	**25 (10.4%)**	12(14.4%)	13 (8.23%)	**30 (12.9%)**	26 (23.8%)	4 (5.5%)	0	0.386
Febrile neutropenia	**14 (5.8%)**	10 (12.0%)	4 (2.53%)	**7 (3.02%)**	6 (5.5%)	1 (1.4%)	0	0.141
Anemia	**27 (11.2%)**	17(20.5%)	10 (16.1%)	**25 (10.8%)**	18 (16.5%)	4 (.5%)	3 (6%)	0.882
Thrombopenia	**9 (3.7%)**	7(8.4%)	2 (1.27%)	18 **(7.8%)**	18 (16.5%)	0 (0%)	0	0.059

Corre R et al, WCLC 2013

Immunothérapies

Checkmate 017

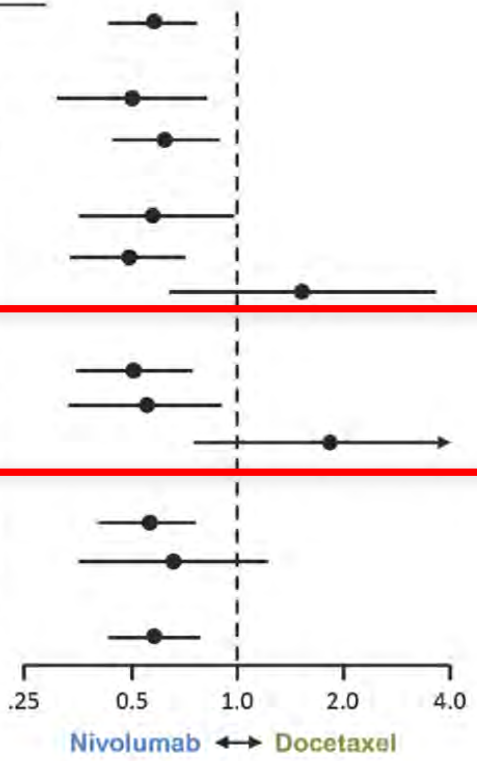


Brahmer J et al, N Engl J Med 2015

Immunothérapies

Checkmate 017

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)



Brahmer J et al, N Engl J Med 2015

Immunothérapies

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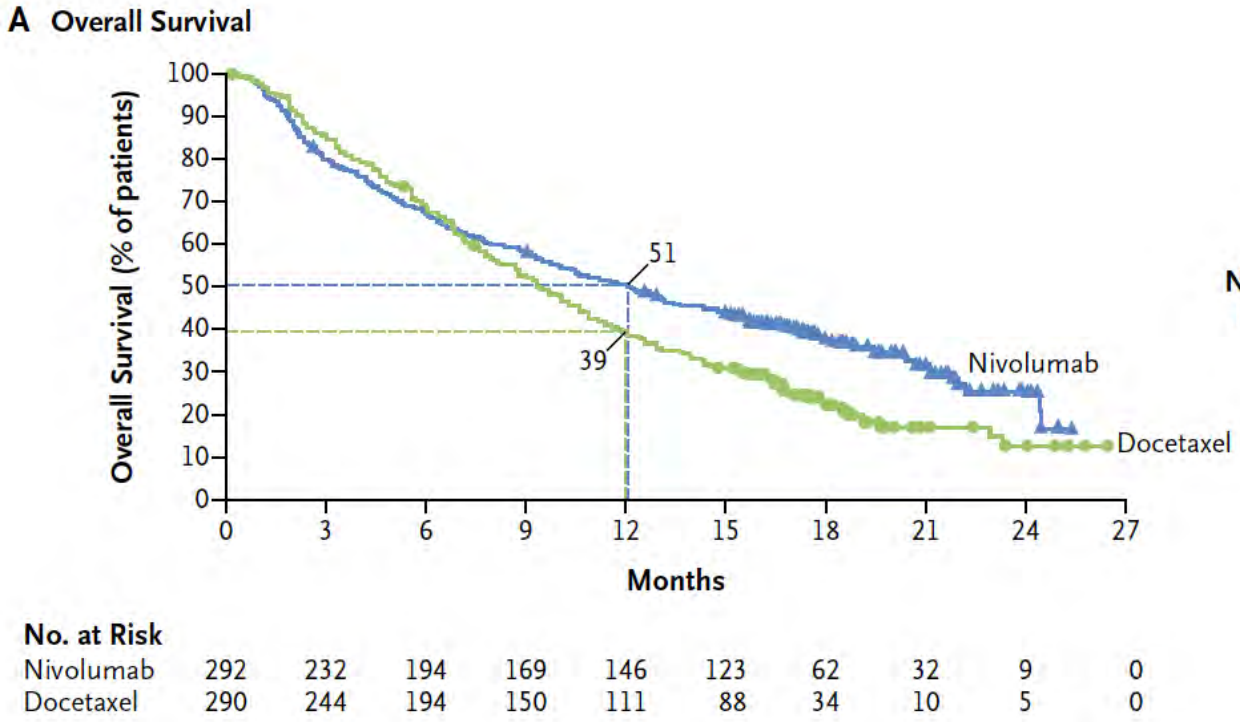
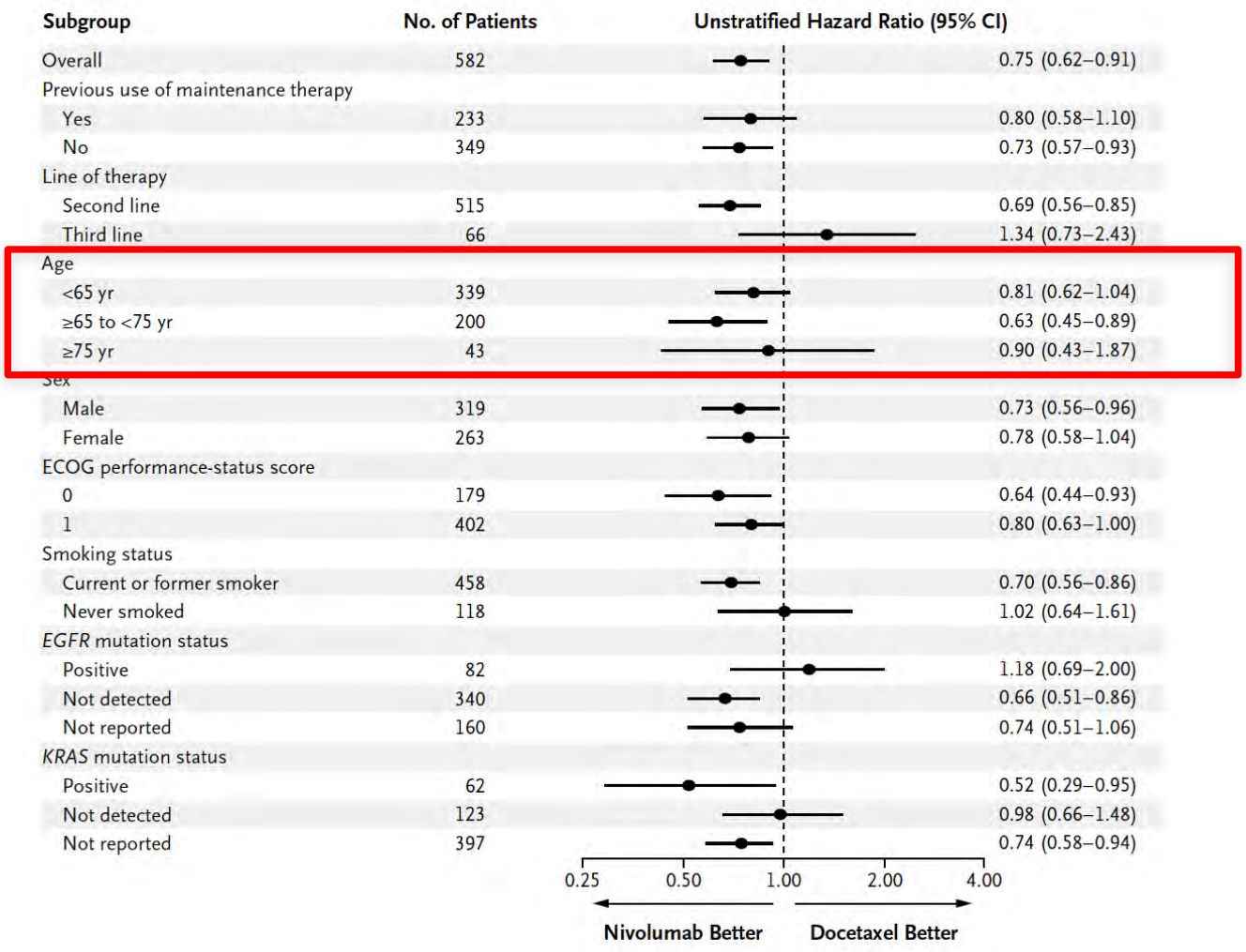


	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

Borghaei H et al, N Engl J Med 2015

Immunothérapies



Borghaei H et al, N Engl J Med 2015

Conclusions