Maintenance Chemotherapy for advanced NSCLC

Dr.M.V.Nagarjuna

Objectives of this seminar

1. Definitions
2. Switch maintenance
3. Continuation Maintenance
4. Immunotherapy as maintenance
5. Conclusions

DEFINITIONS - (BEYOND FIRST LINE THERAPY)

- Continuation Chemotherapy :
  - Continuation of the same drugs used in the first line regimen beyond the stipulated 4-6 cycles.

- Continuation Maintenance Therapy:
  - Continuation of one or more drugs (at a lower intensity) used in the first line regimen beyond 4-6 cycles in a patient who has a stable or responsive disease

- Switch Maintenance Therapy :
  - Initiation of a new agent not included in the first line regimen to a patient who has undergone 4-6 cycles of first line therapy and has a stable or responsive disease.

- Second line Therapy:
  - Initiation of alternative therapy in patients who have progressed either during or after their first line regimen.

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

RESPONSE DEFINITIONS (RECIST 1.1)

RECIST : Response Evaluation Criteria In Solid Tumors.
Updated in 2009.

1. COMPLETE RESPONSE (CR) : Disappearance of all lesions (both target and non target).

2. PARTIAL RESPONSE (PR) : 30% decrease in the sum of diameters of the target lesions with a non progressive disease in the non target lesions.

3. PROGRESSIVE DISEASE (PD) : 20% increase in the sum of diameters of the target lesions, the appearance of a new lesion or unequivocal progression of non target lesions.

4. STABLE DISEASE : Tumor which does not qualify for either a PR or a PD.

SURVIVAL MEASURES

1. Overall Survival (OS) :
   - Defined as the time from randomization to death
   - Gold standard for demonstrating clinical benefit
   - Drawbacks :
     - Requires a large sample size and requires a long follow up.
     - Confounded because of the subsequent therapies administered after the discontinuation of the study drug.
2. Progression Free Survival (PFS)
   - Defined as the time from randomization to disease progression or death.
   - May or may not translate to clinical benefit.
   - Does not directly measure how a patient feels, functions, or survives, it just measures the effect of the drug on the tumor.

- Benefits of PFS :
  - Needs shorter follow up as compared to OS
  - Not diluted by the effect of subsequent treatments given.
- Drawbacks :
  - May not translate to clinical benefit if no difference in OS.

Survival Measures

- Time to Tumor Progression (TTP)
  - Time from Randomization to Tumor Progression (Deaths are censored)
- Time to treatment Failure (TTF)
  - Time from Randomization to the end of treatment (either because of progression, toxicity, patient of physician preference or death)
- Overall Response Rate (ORR)
  - Percentage of patients achieving a CR or a PR at a prespecified time interval

What to look at when interpreting a clinical trial?

- PFS / OS benefit (p value) – Statistical Significance
- Absolute benefit of PFS/OS – Clinical Significance
- Adverse effects of the drugs
- Quality of life scores when on treatment

Switch Maintenance Regimes

The drugs which have been evaluated are

		No of RCTs	Name	Year	Pt number
1.	Docetaxel :	1		2009	309
2.	Pemetrexed :	1	JMEN	2009	663
3.	Erlotinib :	3	SATURN	2010	889
			ATLAS	2009 A	743
			IFCT-GFPC	2010 A	464
4.	Geftinib :	2	WJTOG203	2010	604
			INFORM	2012	296

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of Immediate Compared With Delayed Docetaxel After Front-Line Therapy With Gemcitabine Plus Carboplatin in Advanced Non–Small-Cell Lung Cancer

- 309 patients randomized to the two treatment arms.
  - Immediate docetaxel : Docetaxel 75 mg/m2 every 21 days for a maximum of 6 cycles immediately after completing First line regimen.
  - Delayed Docetaxel : Docetaxel received only at tumor progression

- Results :
  - PFS – Improved (5.7 months vs 2.7 months) p=0.0001
  - OS – Better (12.3 months vs 9.7 months) p=0.0853
  - QOL – Similar between the 2 groups

- Results :

  - Only 63 % of the patients in the delayed treatment arm actually received docetaxel.

  - The OS was not different between the 2 arms when only those patients who received treatment compared.

  - The trend towards better OS is mainly because a larger number of patients received docetaxel when treatment started early.

Lancet 2009; 374: 1432–40

Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study

A total of 663 patients randomized (2:1) to receive three weekly pemetrexed (500 mg/m2) after completing 4 cycles of platinum based duplet chemotherapy with a SD/PR/CR.

- Results:
  - PFS : Better (4.3 vs 2.6 months) $p<0.0001$
  - OS :Better (13.4 vs 10.6 months) $p=0.012$
  - ADR : More in the pemetrexed group (Fatigue and Neutropenia)
  - QOL : Similar to placebo but with delayed onset of pain and hemoptysis and slight increase in anorexia

- Results :
  - PFS and OS benefit seen only in non squamous histology
  - Subgroup of East Asian patients (n=128) also showed better PFS but OS was not significantly improved.

J Thorac Oncol. 2012;7: 567–573

  - OS benefit more in patients with SD as compared to those with CR/PR

Drugs 2012; 72 Suppl. 1: 20-27

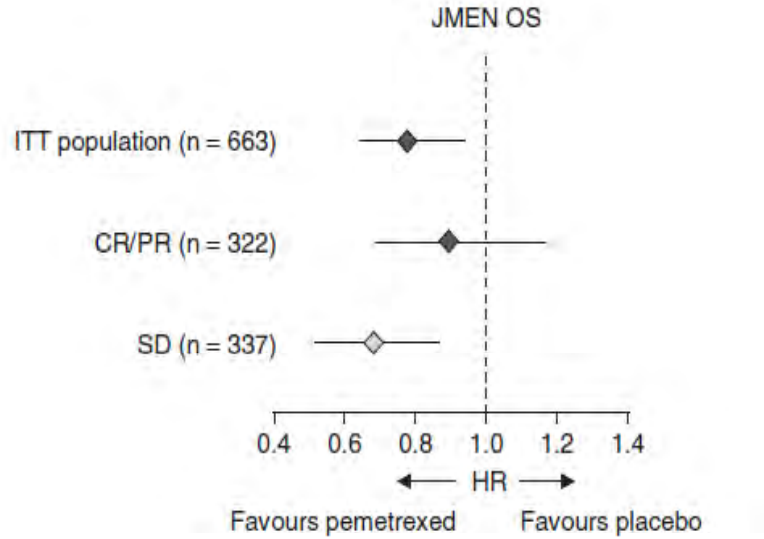


TABLE 2. Phase III Trials of "Switch" Maintenance Chemotherapy

First Author	No. of Patients Enrolled	Chemotherapy Comparison[a]	Median PFS	Median OS
Westeel[15]	573	Vinorelbine ($N = 91$)	5 mo	12.3 mo
		Observation ($N = 90$)	3 mo	12.3 mo
			HR = 0.77, $p = 0.11$	HR = 1.08, $p = 0.65$
Fidias[16]	566	Immediate Docetaxel ($N = 153$)	5.7 mo	12.3 mo
		Delayed Docetaxel ($N = 156$)	2.7 mo	9.7 mo
			$p = 0.0001$	$p = 0.0853$
Ciuleanu[17]	NA	Pemetrexed ($N = 441$)	4.0 mo[b]	13.4 mo
		Placebo ($N = 222$)	2.0 mo	10.6 mo
			HR = 0.60, $p < 0.0001$	HR = 0.79, $p = 0.012$
Nonsquamous ($N = 481$)		Pemetrexed	4.4 mo[b]	15.5 mo
		Placebo	1.8 mo	10.3 mo
			HR = 0.47, $p < 0.0001$	HR = 0.70, $p = 0.002$
Squamous ($N = 182$)		Pemetrexed	2.4 mo[b]	9.9 mo
		Placebo	2.5 mo	10.8 mo
			HR = 1.03, $p = 0.896$	HR = 1.07, $p = 0.678$

[a] *N* values represent number of patients randomized.
[b] PFS represents values from independent review.
PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NA, not available.

ERLOTINIB FOR SWITCH MAINTENANCE

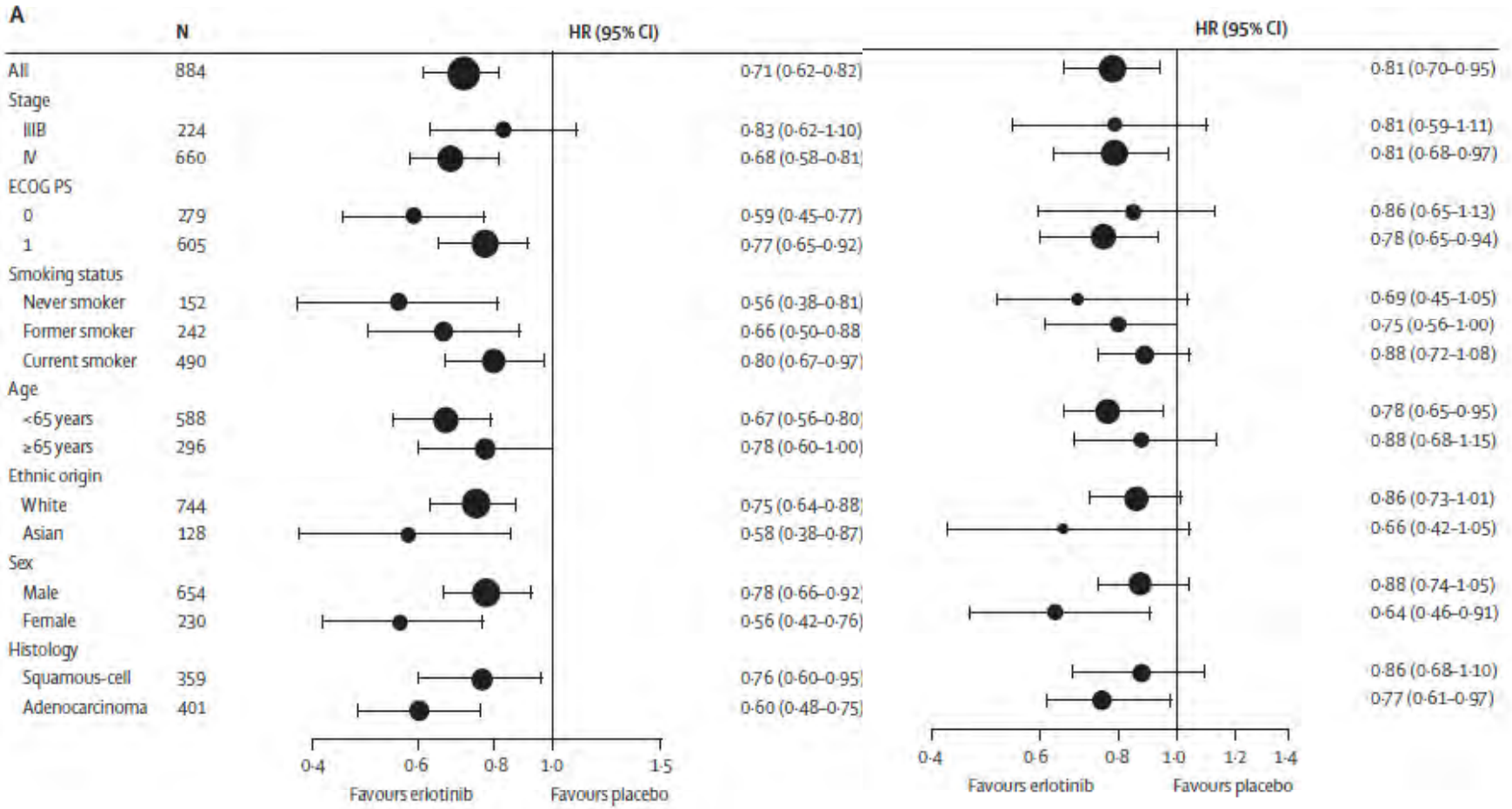
Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study *Lancet Oncol* 2010; 11: 521–29

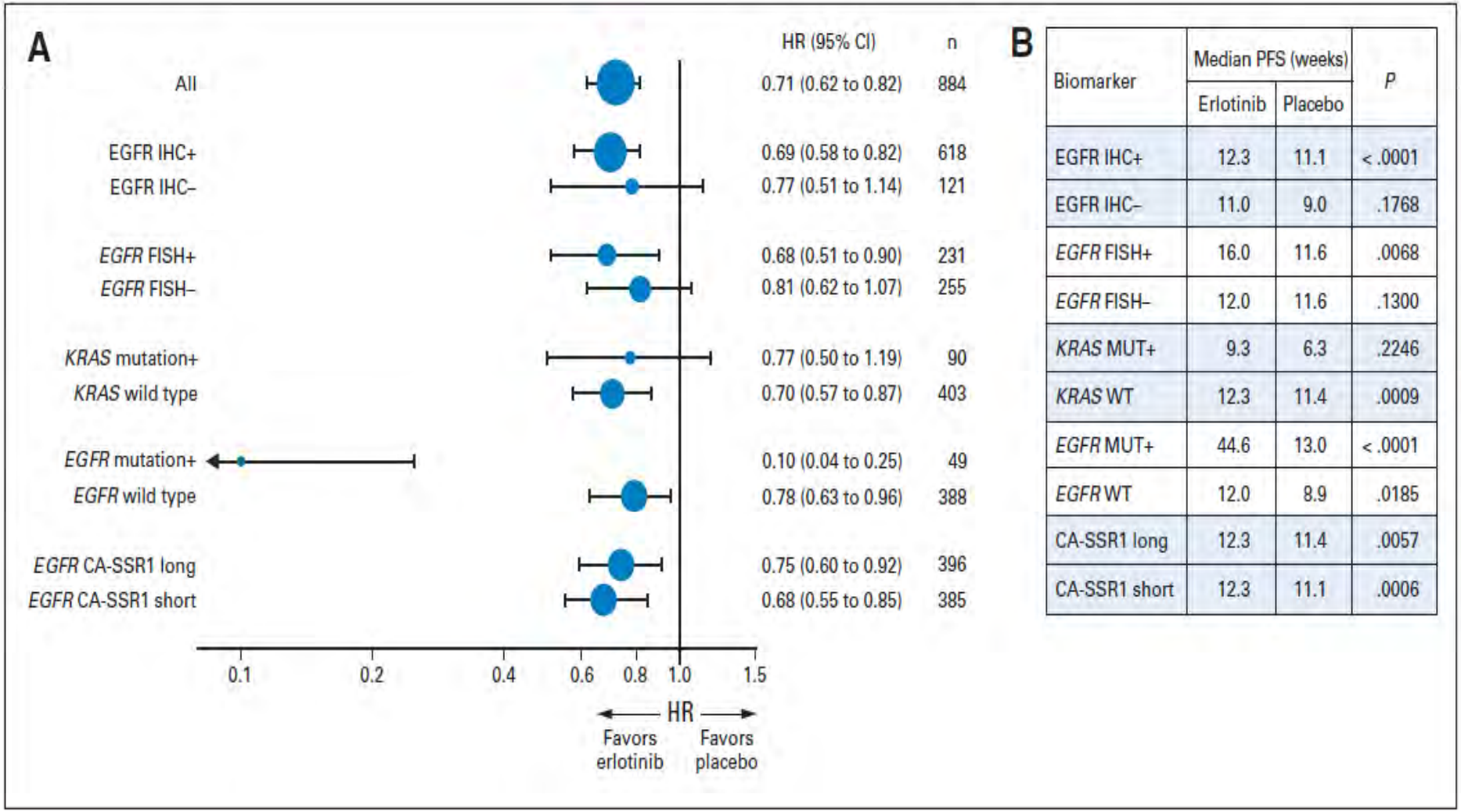
- SATURN trial : Sequential Tarceva in Unresectable NSCLC

- 884 patients were randomized (1:1) to receive either Erlotinib (150 mg/day) or placebo after 4 cycles of platinum based duplet chemotherapy.

- Results :
  - PFS better (12.3 vs 11.1 weeks) $p<0.001$
  - OS better (12 vs 11 months) $p=0.0088$
  - ADR : More in Erlotinib (60% - Rash, 20% - Diarrhea)

SATURN – SUBGROUP ANALYSIS





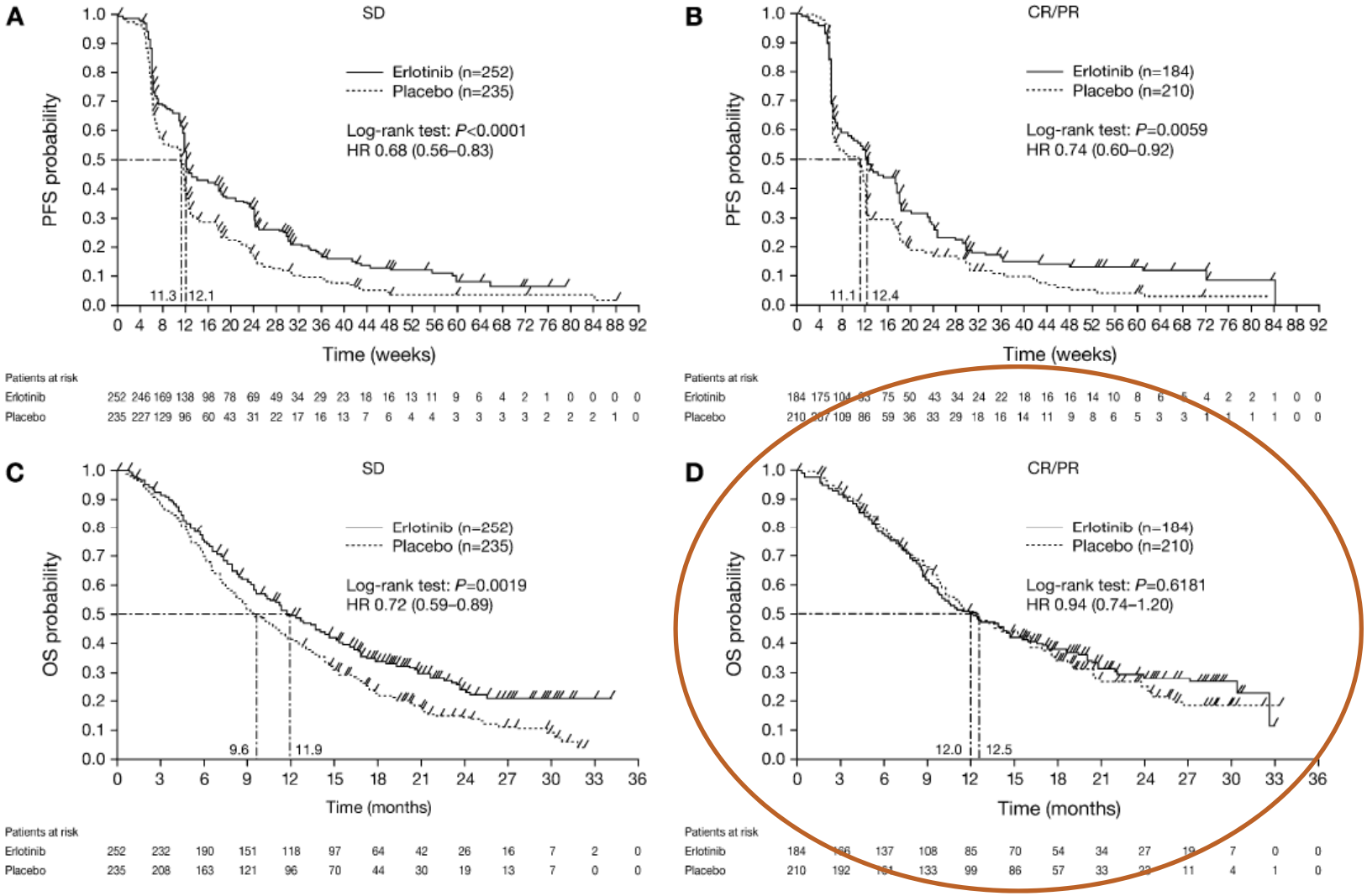
B

Biomarker	Median PFS (weeks)		P
	Erlotinib	Placebo	
EGFR IHC+	12.3	11.1	< .0001
EGFR IHC–	11.0	9.0	.1768
EGFR FISH+	16.0	11.6	.0068
EGFR FISH–	12.0	11.6	.1300
KRAS MUT+	9.3	6.3	.2246
KRAS WT	12.3	11.4	.0009
EGFR MUT+	44.6	13.0	< .0001
EGFR WT	12.0	8.9	.0185
CA-SSR1 long	12.3	11.4	.0057
CA-SSR1 short	12.3	11.1	.0006

- Maximum benefit of PFS seen in patients who are EGFR mutation positive (exon 19 deletion or exon 21 point mutation L858R).

J Clin Oncol 29:4113-4120.

Annals of Oncology 23: 388–394, 2012



Patients with SD are likely to have cancers which are atleast partially resistant to the chemotherapy drugs and hence may benefit more from a change in the therapeutic mechanism of action.

Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study

Lung Cancer 77 (2012) 339–345

Table 2
Comparison of survival outcomes in the Asian subpopulation and the overall population of SATURN.

	SATURN Asian population		Overall SATURN population	
	HR (95% CI)	Log-rank *p* value	HR (95% CI)	Log-rank *p* value
PFS				
All patients	0.57 (0.37–0.86)	0.0067	0.71 (0.62–0.82)	<0.0001
EGFR IHC-positive	0.50 (0.30–0.83)	0.0057	0.69 (0.58–0.82)	<0.0001
OS				
All patients	0.67 (0.42–1.07)	0.0931	0.81 (0.70–0.95)	0.0088
EGFR IHC-positive	0.53 (0.30–0.93)	0.0233	0.77 (0.64–0.93)	0.0063

Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials

Fausto Petrelli, Karen Borgonovo, Mary Cabiddu and Sandro Barni

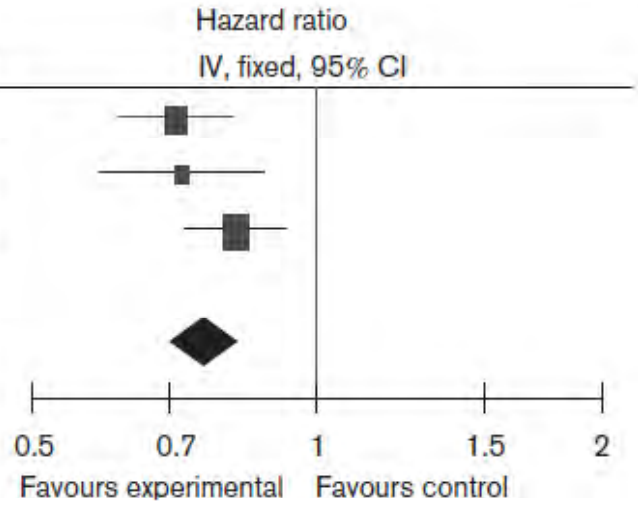
Anti-Cancer Drugs 2011, **22**:1010–1019

- The OS was superior in the 963 patients treated with erlotinib than in the 979 non treated patients [HR= 0.87 (P= 0.003), [13% reduction in the risk of death].
- The pooled HR for the PFS is 0.76 (P <.00001), corresponding to a 24% lower risk of being progression free.
- On subgroup analysis, maximum benefit seen in
  - Women
  - Non smokers
  - Non squamous histology
  - PS 0
- Both SD and PR/CR have equal PFS benefit

Study or subgroup	Log(hazard ratio)	SE	Weight	Hazard ratio IV, fixed, 95% CI
Cappuzzo SATURN	−0.342	0.071	35.8%	0.71 (0.62, 0.82)
Miller ATLAS	−0.329	0.102	17.3%	0.72 (0.59, 0.88)
Perol IFCT-GFPC 0502	−0.198	0.062	46.9%	0.82 (0.73, 0.93)
Total (95% CI)			100.0%	0.76 (0.70, 0.83)

Heterogeneity: $\chi^2 = 2.71$, d.f. = 2 ($P = 0.26$); $I^2 = 26\%$

Test for overall effect: $Z = 6.41$ ($P < 0.00001$)

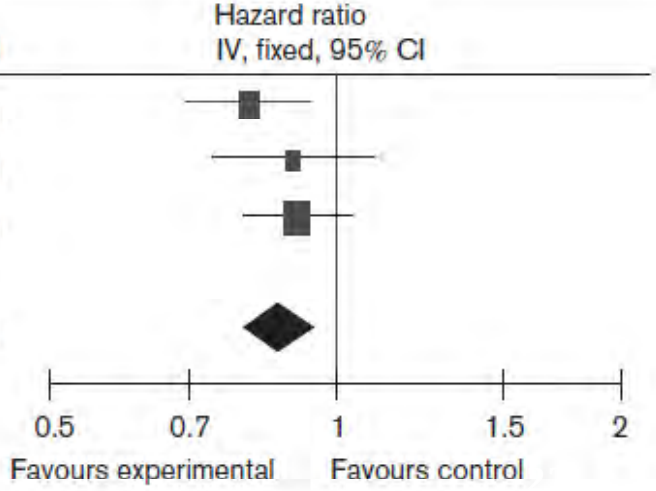


Meta-analysis of (hazard ratio) HR for (progression-free survival) PFS; fixed-effect model.

Study or subgroup	Log(hazard ratio)	SE	Weight	Hazard ratio IV, fixed, 95% CI
Cappuzzo SATURN	−0.211	0.078	33.6%	0.81 (0.69, 0.94)
Miller ATLAS	−0.105	0.099	20.9%	0.90 (0.74, 1.09)
Perol IFCT-GFPC 0502	−0.094	0.067	45.5%	0.91 (0.80, 1.04)
Total (95% CI)			100.0%	0.87 (0.80, 0.95)

Heterogeneity: $\chi^2 = 1.42$, d.f. = 2 ($P = 0.49$); $I^2 = 0\%$

Test for overall effect: $Z = 3.00$ ($P = 0.003$)



Meta-analysis of hazard ratio (HR) for overall survival (OS); fixed-effect model.

Phase III Trial of Maintenance Gefitinib or Placebo After Concurrent Chemoradiotherapy and Docetaxel Consolidation in Inoperable Stage III Non–Small-Cell Lung Cancer: SWOG S0023

J Clin Oncol 26:2450-2456.

Karen Kelly, Kari Chansky, Laurie E. Gaspar, Kathy S. Albain, James Jett, Yee C. Ung, Derick H.M. Lau, John J. Crowley, and David R. Gandara

- First line chemotherapy with 2 cycles of cisplatin/etoposide based concurrent chemoradiotherapy followed by 3 cycles of consolidation docetaxel.
- 243 patients randomized to maintenance with Geftinib or placebo.
- Terminated early after an unplanned interim analysis showed negative results.

- Results:
  - PFS : 8.3 vs 11.7 months (p=0.13)
  - OS : 23 vs 35 months (p=0.013)
  - ADR : More common in the Geftinib arm

- Reasons for Negative Results:
  - EGFR and Kras status unknown- may be confounding

J Clin Oncol 28:753-760.

Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203)

Koji Takeda, Toyoaki Hida, Tosiya Sato, Masahiko Ando, Takashi Seto, Miyako Satouchi, Yukito Ichinose, Nobuyuki Katakami, Nobuyuki Yamamoto, Shinzoh Kudoh, Jiichiro Sasaki, Kaoru Matsui, Koichi Takayama, Tatsuhiko Kashii, Yasuo Iwamoto, Toshiyuki Sawa, Isamu Okamoto, Takayasu Kurata, Kazuhiko Nakagawa, and Masahiro Fukuoka

- 604 patients randomly assigned to receive 3 cycles of chemotherapy followed by either maintenance with Geftinib vs Continuation chemotherapy for 3 more cycles.

Results:

- PFS : 4.6 vs 4.3 months ($p < 0.001$)
- OS : 13.7 vs 12.9 months ($p = 0.11$)
- ADR : hematologic ADR more common with continuation chemoRx. ILD Geftinib related occurred in 2 patients
- QOL : Not different

Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial

Lancet Oncol 2012; 13: 466–75

*Li Zhang, Shenglin Ma, Xiangqun Song, Baohui Han, Ying Cheng, Cheng Huang, Shujun Yang, Xiaoqing Liu, Yunpeng Liu, Shun Lu, Jie Wang, Shucai Zhang, Caicun Zhou, Xiangwei Zhang, Nobuya Hayashi, Mengzhao Wang, on behalf of the INFORM investigators**

- 296 East Asian patients randomized (1:1) to receive either Geftinib (250 mg/day) or placebo after 4 cycles of first line platinum based chemotherapy.

- Results :
  - PFS Better (4.6 vs 4.3 months) p <0.001
  - OS (13.7 vs 12,9 months) p=0.11
  - ADR higher in the Geftinib arm (Rash -50%, Diarrhea -25%). 3 deaths due to Geftinib.
  - QOL : Not assessed

GEFTINIB - SUMMARY

Author/ Trial	Year	No.of.patients	PFS	OS	ADR
Kelly et al (SW S0	2008	243 (Prematur	8.3 vs 11.7 mo	23 vs 35 mo	More with gefitinib
Tal (W			(p <0.001	months (p=0.11)	itis
Zhang et al (INFORM)	2012	296	4.6 vs 4.3 months (p <0.001)	13.7 vs 12,9 mon (p=0.11)	Rash, Diarrhea, ILD
Gaafar et al	2010 A	173 (Prematur e closure)	4.1 vs 2.9 mon (p=0.002)	10.9 vs 9.4 mon (p=0.23)	NA

Geftinib – No Clinically meaningful benefit

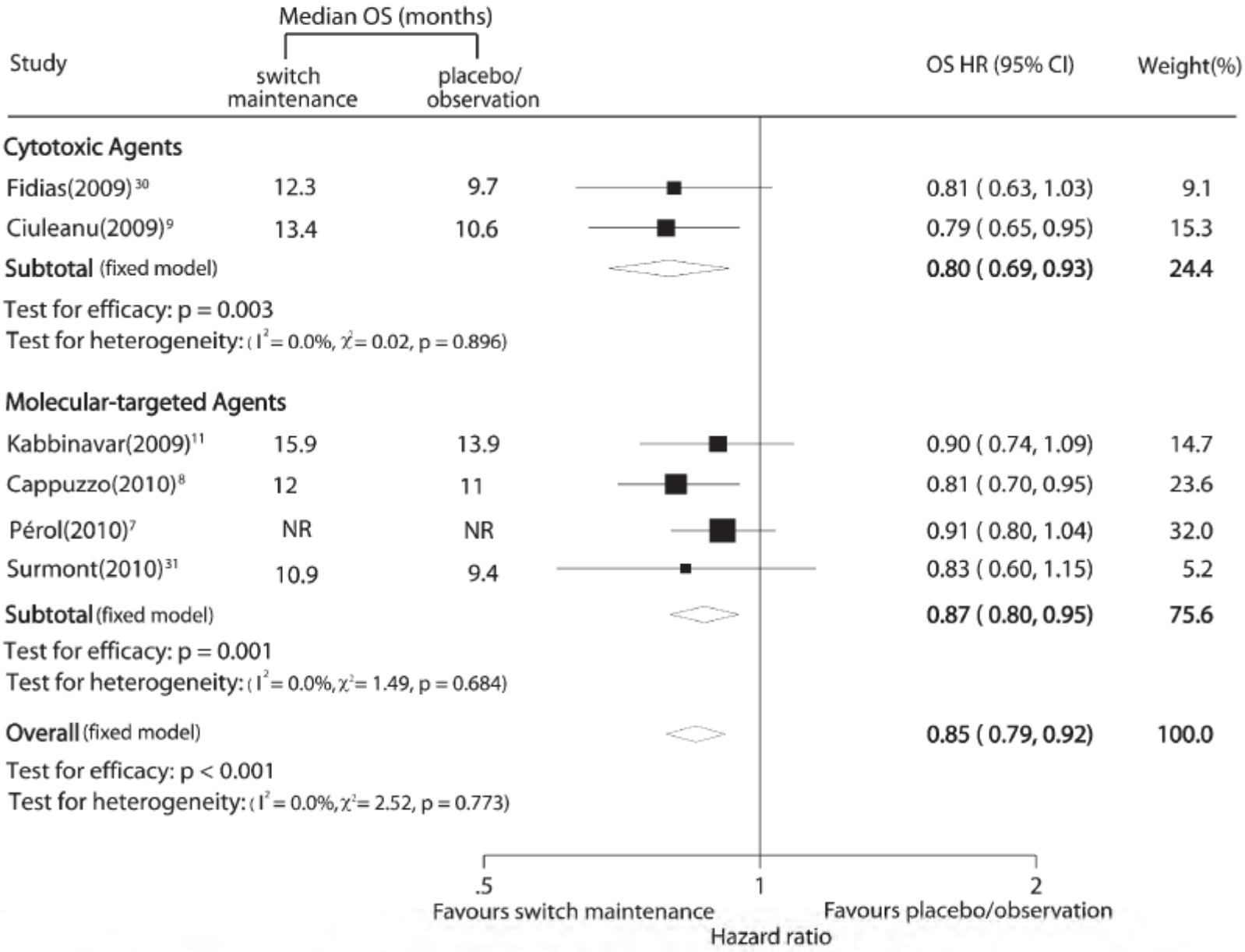
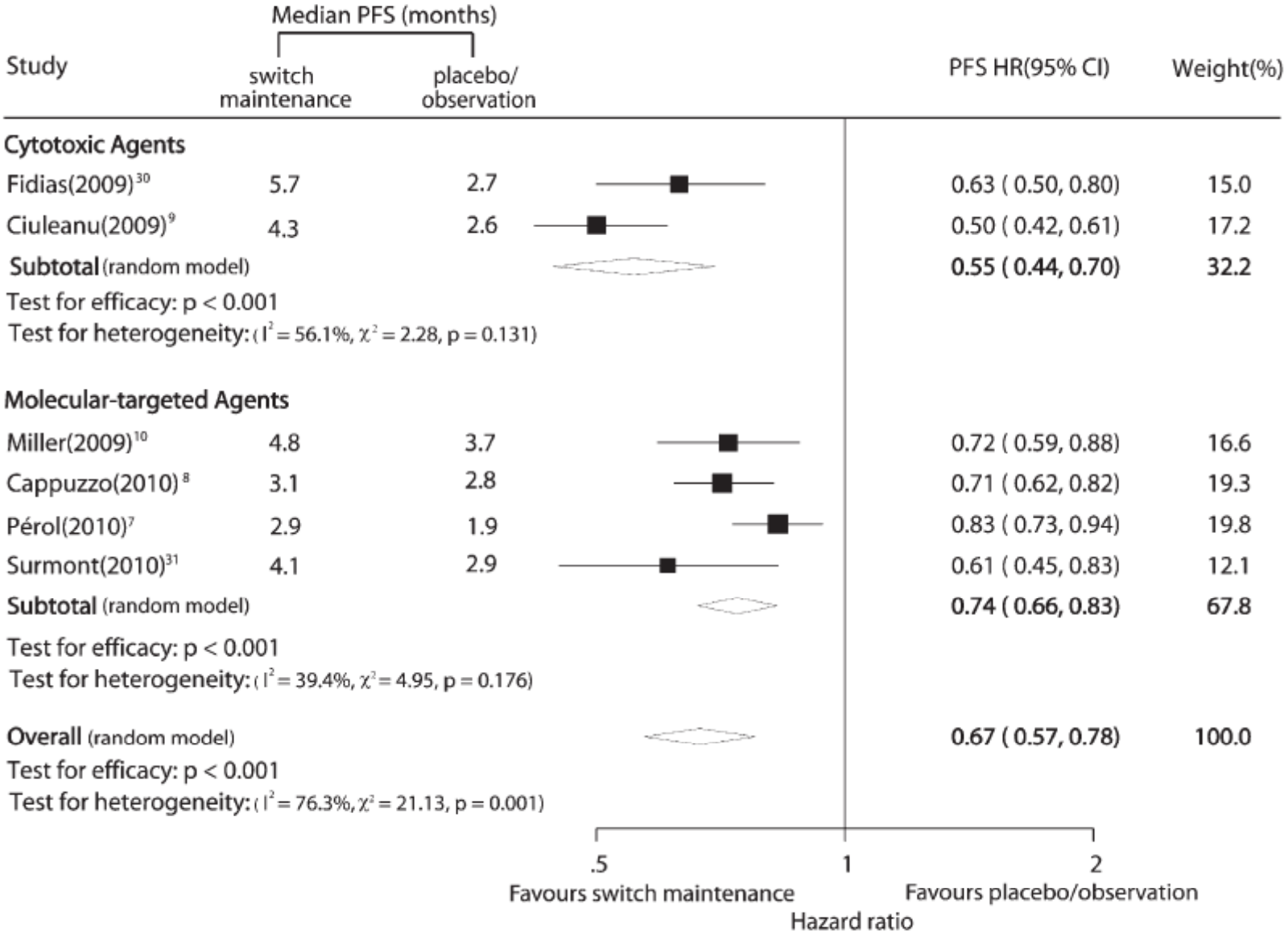


FIGURE 3. Comparison of OS between switch maintenance therapy and placebo or observation. See


Median PFS (months)
Study
switch maintenance
placebo/ observation
PFS HR(95% CI)
Weight(%)
Cytotoxic Agents
Fidias(2009)[30] 5.7 2.7 0.63 (0.50, 0.80) 15.0
Ciuleanu(2009)[9] 4.3 2.6 0.50 (0.42, 0.61) 17.2
Subtotal (random model) 0.55 (0.44, 0.70) 32.2
Test for efficacy: p < 0.001
Test for heterogeneity: (I² = 56.1%, χ² = 2.28, p = 0.131)
Molecular-targeted Agents
Miller(2009)[10] 4.8 3.7 0.72 (0.59, 0.88) 16.6
Cappuzzo(2010)[8] 3.1 2.8 0.71 (0.62, 0.82) 19.3
Pérol(2010)[7] 2.9 1.9 0.83 (0.73, 0.94) 19.8
Surmont(2010)[31] 4.1 2.9 0.61 (0.45, 0.83) 12.1
Subtotal (random model) 0.74 (0.66, 0.83) 67.8
Test for efficacy: p < 0.001
Test for heterogeneity: (I² = 39.4%, χ² = 4.95, p = 0.176)
Overall (random model) 0.67 (0.57, 0.78) 100.0
Test for efficacy: p < 0.001
Test for heterogeneity: (I² = 76.3%, χ² = 21.13, p = 0.001)
.5
1
2
Favours switch maintenance
Favours placebo/observation
Hazard ratio

SUMMARY – ASCO GUIDELINES 2011 UPDATE

- For patients with stable disease or response after 4 cycles of first line chemotherapy, immediate treatment with an alternative agent may be considered.
  - Pemetrexed (Non squamous histology)
  - Docetaxel (Unselected patients)
  - Erlotinib (Unselected patients)

- Break from cytotoxic therapy after fixed course is also acceptable with introduction of second line agent at progression.

Switch Maintenance vs Second line therapy

- Only Docetaxel trial compares the two strategies directly.

- Indirect evidence,
  - Trial — % of patients in the control arm who could receive second line therapy

  1. Docetaxel — 63 %
  2. Pemetrexed — 67% (18% pemetrexed)
  3. Erlotinib (Saturn) — 72% (21% Erlotinib)

- In one third of the patients, disease progresses such that even when closely followed up, poor performance status would make them unfit for any further chemotherapy.

(*J Thorac Oncol.* 2010;5: 540–545)

Who Are Less Likely to Receive Subsequent Chemotherapy Beyond First-Line Therapy for Advanced Non-small Cell Lung Cancer?

Implications for Selection of Patients for Maintenance Therapy

- 271 patients included who had non progressive disease after first line chemotherapy.
- Followed up till progression when second line chemotherapy was given
- 85% received second line chemo whereas 15 % could not receive.

TABLE 2. Multivariate Analysis of Clinical Characteristics Associated with Receiving Only First-Line Therapy

Characteristics	Odds Ratio	95% CI
Poor performance status after first-line therapy: 2 or 3 (vs. 0 or 1)	4.83	1.75–13.36
Less decrease in target lesions after first-line therapy: <20% (vs. ≥20%)	2.47	1.12–5.44
Great sum of long axes of target lesions before first-line: therapy ≥70 mm (vs. <70 mm)	3.83	1.02–14.36
Great sum of long axes of target lesions after first-line therapy: ≥50 mm (vs. <50 mm)	0.72	0.20–2.61

CI, confidence interval.

Continuation Maintenance Regimes

- The drugs which have been evaluated are

1. Paclitaxel
2. Gemcitabine
3. Pemetrexed
4. Bevacizumab
5. Cetuximab
6. Geftinib/ Erlotinib

Multicenter, Randomized Trial for Stage IIIB or IV Non–Small-Cell Lung Cancer Using Weekly Paclitaxel and Carboplatin Followed by Maintenance Weekly Paclitaxel or Observation

- Following first line chemotherapy with paclitaxel/carboplatin regimen, 139 patients were randomized(1:1) to receive weekly paclitaxel (70 mg/m2) vs placebo.

- Results :

Table 7. Disease Progression and Survival in Maintenance Therapy Phase

Maintenance Therapy Phase	Paclitaxel (n = 65)	Observation (n = 65)
Median time to progression, weeks	38	29
Median survival time, weeks	75	60
1-year survival rate, %	72	60
2-year survival rate, %	32	26

- ADR : 86% had ADR on Paclitaxel, 45% had Grade3/4 ADR

J Clin Oncol 21:2933-2939. © *2003*

Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial

- 539 patients randomized (2:1) to receive pemetrexed or placebo.

- Results :
  - PFS : 4.1 vs 2.6 months ($p<0.0001$)
  - OS : 16.9 vs 14 months ($p=0.0195$)
  - Disease control rate (SD/CR/PR) : 72% vs 60%
  - ADR : Increased grade 3 or 4 ADR (9% vs 1%)
  - QOL : Similar in the maintenance phase

Gemcitabine – Continuation Maintenance

TABLE 1. Phase III Trials of Continuation Maintenance Chemotherapy

First Author	No. of Patients Enrolled	Chemotherapy Comparison[a]	Median PFS	Median OS
Brodowicz[20]	352	Gemcitabine ($N = 138$)	3.6 mo[b]	10.2 mo[b]
		BSC ($N = 68$)	2.0 mo	8.1 mo
			$p < 0.001$	$p = 0.172$
Belani[21]	519	Gemcitabine ($N = 128$)	7.4 mo[b]	8.0 mo[b]
		BSC ($N = 127$)	7.7 mo	9.3 mo
			HR = 1.09, $p = 0.575$	HR = 0.97, $p = 0.838$
Perol[22]	834[c]	Gemcitabine ($N = 155$)	3.8 mo	NA
		Observation ($N = 155$)	1.9 mo	NA
			HR = 0.55, $p < 0.0001$	HR = 0.86 (95% CI, 0.66–1.12)
Belani[19]	401	Paclitaxel ($N = 65$)	38 weeks	75 weeks
		Observation ($N = 65$)	29 weeks	60 weeks

[a] N values represent number of patients randomized.
[b] Data reported from time of randomization.
[c] Three-arm trial, of 834 patients enrolled 464 randomized. Results of erlotinib arm included in Table 3.
BSC, best supportive care; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: A phase III trial☆

Lung Cancer (2006) 52, 155–163

- 206 patients randomized (2:1) to Gemcitabine vs BSC following first line chemotherapy.

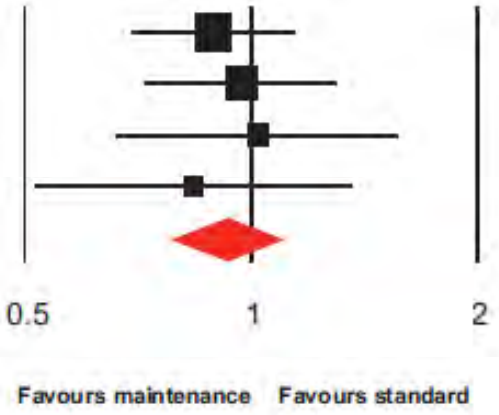
- Results :
  - TTP : 3.6 vs 2 months ($p<0.001$)
  - OS : 13 vs 11 months ($p=0.195$)
  - ADR : More hematologic toxicity in the Gemcitabine arm
  - QOL : Trend towards better QOL in gemcitabine arm

- Belani et al :
  - Trial stopped prematurely due to poor accrual of patients.
  - More number of patients with PS>/= 2 in the maintenance arm.
  - No PFS or OS benefit
  - Summary – Maintenance is not a good option for poor patients with poor PS
- Perol et al :
  - A unique trial because included both continuation maintenance and Switch maintenance in the same study design.
  - PFS benefit seen

Single agent maintenance therapy for advanced stage non-small cell lung cancer: A meta-analysis☆

Lung Cancer 77 (2012) 331–338

Study name	Hazard ratio	Lower limit	Upper limit	Maintenance Therapy	Standard Therapy
Perol-1 2010	0.890	0.689	1.149	154	155
Belani 2010	0.970	0.722	1.303	128	127
Belani 2003	1.020	0.661	1.573	65	65
Brodowicz 2006	0.840	0.516	1.368	138	68
	0.927	0.785	1.094		



Overall Survival- Continuation Maintenance: HR 0.92 (CI 0.78 1.09); P Value 0.33

PARAMOUNT trial not included as OS figures were not yet available

MAINTENANCE CHEMOTHERAPY – TARGETED AGENTS (BEVACIZUMAB)

Study	Journal/Year/Type	No. of patients	Control arm	Trial arm	Results
ECOG	NEJM 2006 RCT	878	Carbo +Paclitaxel	Carbo+Pacli+Bevacizumab fld by Bevaci till progression/Intolerance	OS- 12.3m vs 10.3 m PFS-6.2 vs 4.5 ADR bleed -4.4% vs 0.7%
AVAIL	JCO 2009 RCT	1043	Cisplatin + Gemcitabine	Cis+ Gem + bevaci (7.5 mg/kg or 15 mg/kg)	PFS- 6.7 vs 6.5 vs 6.1 m ORR-34 vs 30 vs 20% ADR bleed- same OS- not different

Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial

Lancet 2009; 373: 1525–31

- 1125 patients randomized to receive 6 cycles of chemotherapy with cisplatin and vinorelbine +/- Cetuximab
- Cetuximab continued as maintenance till disease progression or intolerance

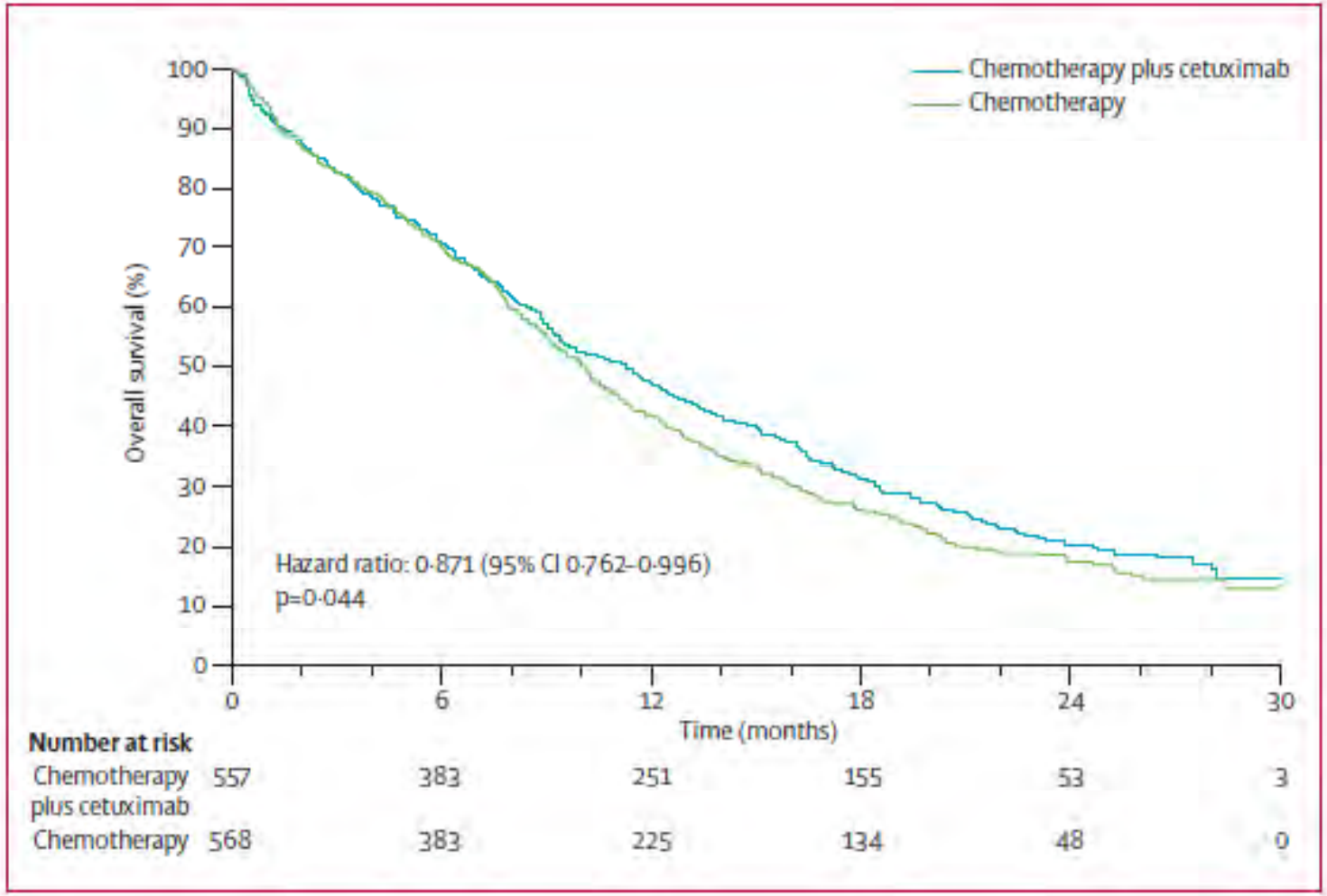
Results:

OS : 11.3 vs 10.1 months (p=0.044)

ORR : 36 % vs 29%

ADR : Grade ¾ Acne like rash, diarrhea and infusion reactions common with cetuximab.

QOL : NA


Chemotherapy plus cetuximab
Chemotherapy
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Hazard ratio: 0·871 (95% CI 0·762–0·996)
p=0·044
0
6
12
18
24
30
Time (months)
Number at risk
Chemotherapy plus cetuximab 557 383 251 155 53 3
Chemotherapy 568 383 225 134 48 0

GEFTINIB/ERLOTINIB

- Geftinib/Erlotinib induce G1 phase cell cycle arrest thereby affecting the response of the chemotherapy when given concurrently.

- FASTACT trial : (phase 2)
  - First line Asian Sequential tarceva and chemotherapy trial
  - Erlotinib given on Day 15-28 of chemotherapy and not concurrently. Followed by Erlotinib maintenance
  - 4-6 cycles of Gemcitabine and cis/carboplatin
  - Results:
    - PFS – 31.3 week vs 23.7 weeks ($p<0.05$)
    - ORR – 36 vs 24 % ($p=0.08$)
    - Disease control rate -80 vs 77%
    - ADR – Equal in both arms

- FASTACT II trial : (phase 3)

  - Abstract published in ASCO 2012 conference
  - 451 patients randomized
  - Intercalated Erlotinib (D15-28)
  - Results:
    - PFS : 7.6 vs 6 months ($p<0.0001$)
    - OS : 18.3 vs 14.9 months ($p=0.069$)
    - ORR : 43% vs 18%
    - ADR : Skin rash more common

CONTINUATION MAINTENANCE

- Not very promising results

- PFS but no OS benefit seen with Gemcitabine
- Both PFS and OS benefit with Pemetrexed.

- Continuation maintenance with Targeted agents – Difficult to separate the effect of concurrent chemo vs that of continuation maintenance.

IMMUNOTHERAPY - MAINTENANCE

- Liposomal BLP25
- Belagempumatecel L
- Melanoma associated antigen A3
- Talactoferrin (Recombinant lactoferrin)
- Ipilimumab / trepilimumab (anti CTLA 4 Ab)
- Mycobacterium vaccae (No benefit in phase 2 study)

BELAGEMPUMATECEL L

- Allogenic tumor cell vaccine cocktail

Basics:

- TGF beta has a tumor associated immunosuppressive role
- Lung cancer secretes high level of TGF beta.
- High levels of TGF beta – Poor prognostic factor in NSCLC
- TGF beta blocks the action of NK cells, T cells and dendritic cells and thus prevents the development of anti tumor immunity.

BELAGEMPUMATECEL L

- Belagenpumatucel-L is a nonviral vaccine derived from extracts of four allogeneic NSCLC cell lines(2 adeno, 1 squamous, 1 large cell).
- Transfected with a plasmid encoding a TGF-2 antisense transgene which suppresses the expression of TGF-2 within the tumor cells comprising the vaccine.
- Increases the immunogenicity of this complex preparation.
- When given intra dermally, this NSCLC extract induces a strong anti tumor immune response to various tumor antigens expressed on the four cell lines as these cell lines have low TGF expression.
- The generated immune cells then attack the patients tumor causing destruction of tumor cells.

VOLUME 24 · NUMBER 29 · OCTOBER 10 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Belagenpumatucel-L, a Transforming Growth Factor Beta-2 Antisense Gene-Modified Allogeneic Tumor Cell Vaccine in Non–Small-Cell Lung Cancer

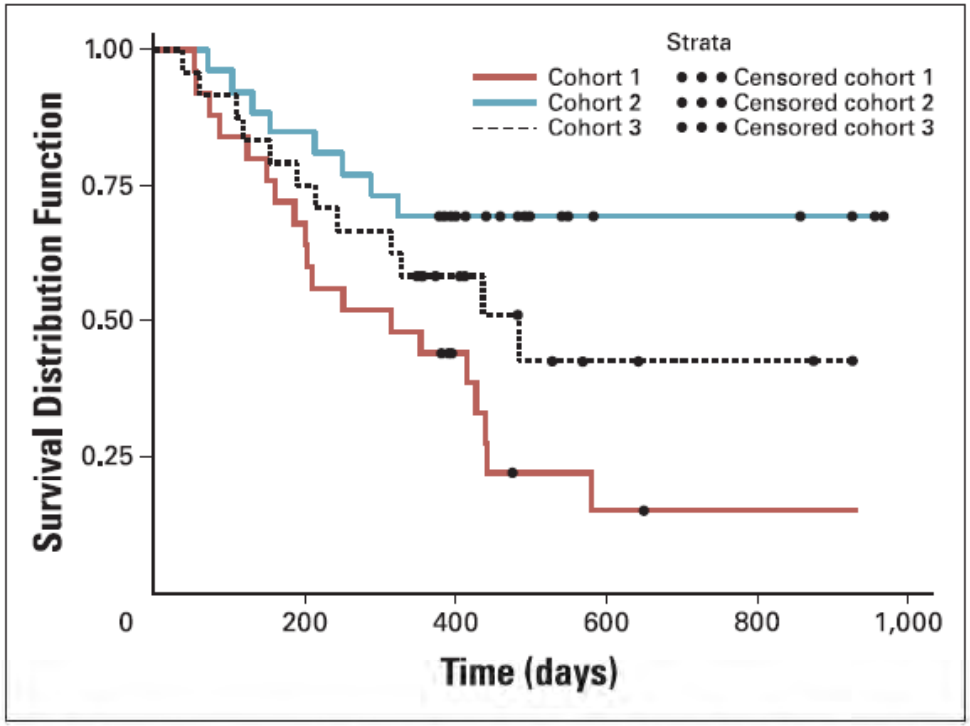


Fig 1. Dose-related survival between cohorts for all patients (N = 75; *P* = .0155).

75 patients who have completed first line chemo. Monthly intradermal vaccine

Cohort 1 : 5 x 10^7 cells/Inj
Cohort 2 : 2.5 x 10^7 cells/Inj
Cohort 3 : 1.25 x 10^7 cells/inj

No significant ADR

1 and 2 yr survival for cohort 1 and 2 together (68 and 52%) vs 39 and 20% for cohort3.

- A response rate of 15% was reported for 61 patients with stage IIIB/IV disease.

- In a subsequent analysis, patients with both a cellular and humoral immune response to this vaccine had improved overall survival compared with those classified as immune response negative (median 32.5 versus 11.6 months, *p .011)*

ORIGINAL ARTICLE

Cancer Gene Therapy (2009) 16, 620–624

Phase II trial of Belagenpumatucel-L, a TGF-β2 antisense gene modified allogeneic tumor vaccine in advanced non small cell lung cancer (NSCLC) patients

- 21 patients of stage 4 NSCLC who have completed first line chemo and have ECOG PS 0f <2.
- Received monthly intra dermal injections of 2.5 x 10^7 cells/Inj.

Results

- Overall survival was 562 days
- Two grade 3 ADRs

LIPOSOMAL L-BLP 25 (EMEPIPIMUT S)

- A specific protein vaccine

Basics

- Mucin 1 (MUC1) , a heavily glycosylated trans membrane protein is widely expressed in apical surface of normal epithelial cells.

- Post-translationally modified in tumor cells to expose a novel antigenic site (the extracellular domain of MUC1 is abnormally glycosylated).

- Exposes a highly immunogenic core peptide of the protein consisting of a 20-amino acid tandem repeating sequence .

- L-BLP25 is a liposome-based vaccine consisting of a synthetic 25-amino acid lipopeptide derived from the tandem repeat region of MUC1, together with the nonspecific adjuvant monophosphoryl lipid A.

LIPOSOMAL L- BLP 25 (EMEPIPIMUT S)

- The level of MUC1 expression in tumors has also been associated with poor prognosis in patients with NSCLC .

- 1-year survival rate was higher in patients with NSCLC who had high compared with low levels of natural MUC1 antibodies.

- L-BLP25 is the first investigational lung cancer vaccine to enter phase III clinical testing in the treatment of unresectable stage III NSCLC

VOLUME 23 · NUMBER 27 · SEPTEMBER 20 2005
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

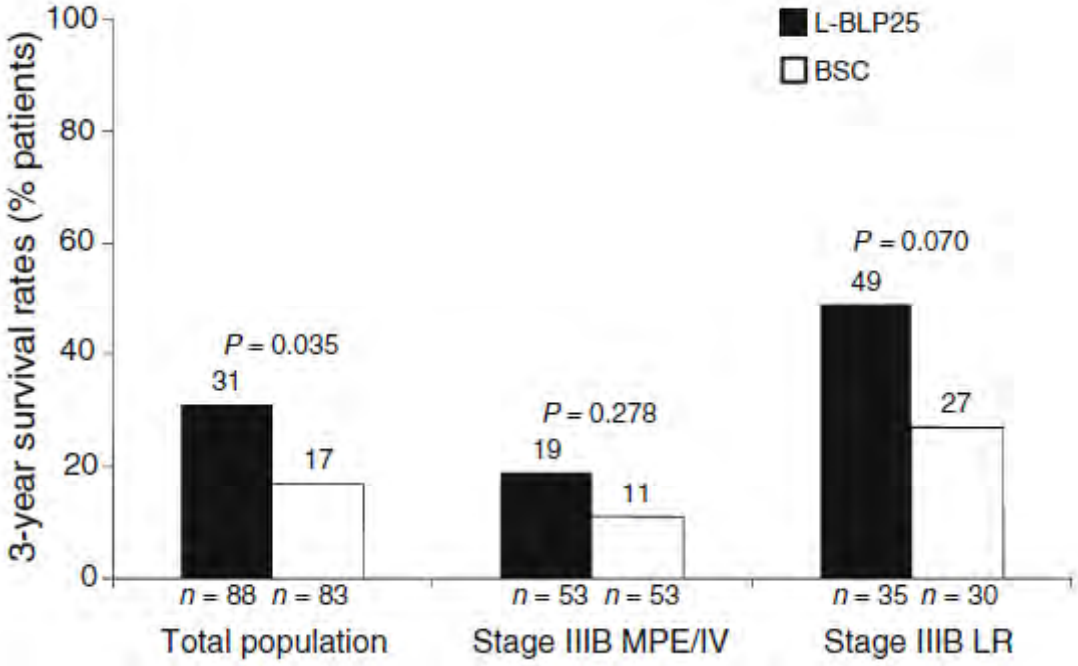
Randomized Phase IIB Trial of BLP25 Liposome Vaccine in Stage IIIB and IV Non–Small-Cell Lung Cancer

- 171 patients with stage 3B/4 NSCLC included who have completed first line chemo and have not progressed.
- 1000 ug 8 weekly injections subcutaneously followed by injections given every 6 weeks.
- Premedication with low dose cyclophosphamide 300 mg/m2

•Survival advantage better in stage 3B cancer
•No significant ADR
•QOL better maintained in the trial arm

Updated survival analysis in patients with stage IIIB or IV non-small-cell lung cancer receiving BLP25 liposome vaccine (L-BLP25): phase IIB randomized, multicenter, open-label trial

J Cancer Res Clin Oncol (2011) 137:1337–1342



Reasons for better survival in stage 3B:

- Pro immunogenic effects of Radiotherapy given earlier
- Short survival time in stage 4 patients may preclude development of an immune response
- Stage 4 patients may be too imunosuppressed to mount an immune response.

SHOULD WE USE MAINTENANCE THERAPY

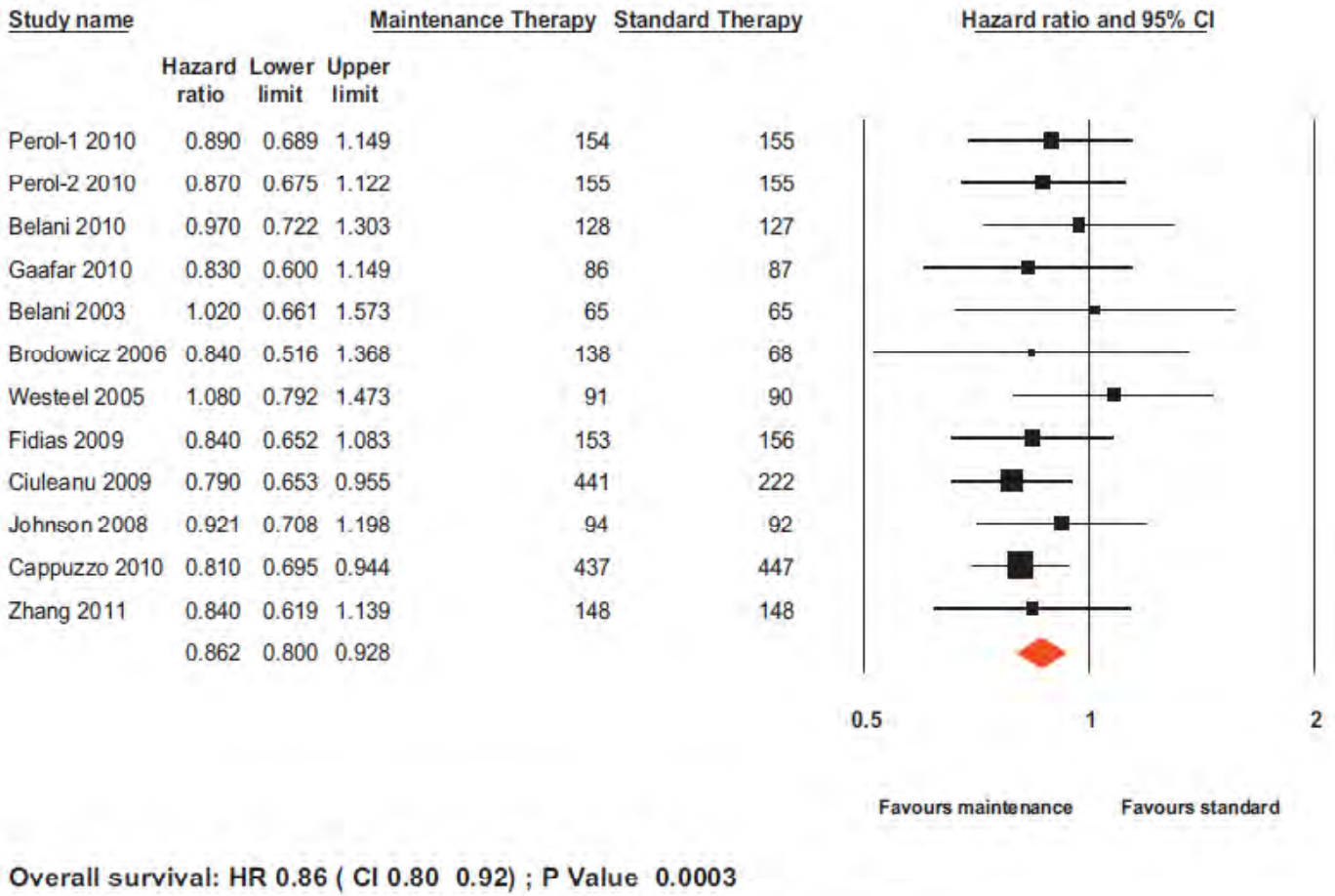


Fig. 2. Forest plot for overall survival with maintenance therapy.

Lung Cancer 77 (2012) 331–338

Maintenance Therapy for Advanced Non–Small-Cell Lung Cancer

A Pilot Study on Patients' Perceptions

(*J Thorac Oncol.* 2012;7: 1291–1295)

Methods: In the absence of data on this topic, we undertook a pilot survey with 10 questions covering the overall patient attitude toward MT, the benefit expected by patients, and the acceptance of side effects or modes of administration. Included patients had stage IV NSCLC and were planned to start first-line platinum-based doublet chemotherapy. The questionnaire was submitted at the start of and after two and four cycles of chemotherapy.

Results: Thirty patients were included. Overall, patients had a positive attitude toward MT. At baseline, it was considered worthwhile by 83%, 67%, and 43% of patients for an OS benefit of 6, 3, or 1 month, respectively, with some decrease over time. Effects on symptom control were crucial for about 90% of the patients. There was a slight preference for oral versus intravenous administration. Side effects were accepted by most patients as long as they were mild to moderate.

Conclusion: Our pilot survey showed that metastatic NSCLC patients in general are in favor of MT. They expect either an OS benefit of at least several months, or better symptom control, in balance with mild-to-moderate side effects.

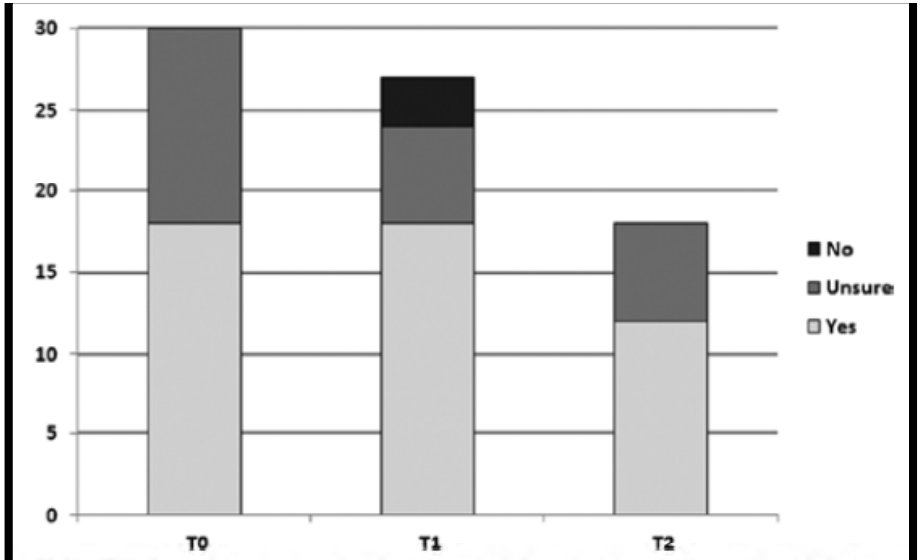


FIGURE 2. Answers to the general question "Do you think maintenance therapy is worthwhile?" T0, time at start of first-line chemotherapy; T1, after two cycles of chemotherapy; T2, after four cycles of chemotherapy.

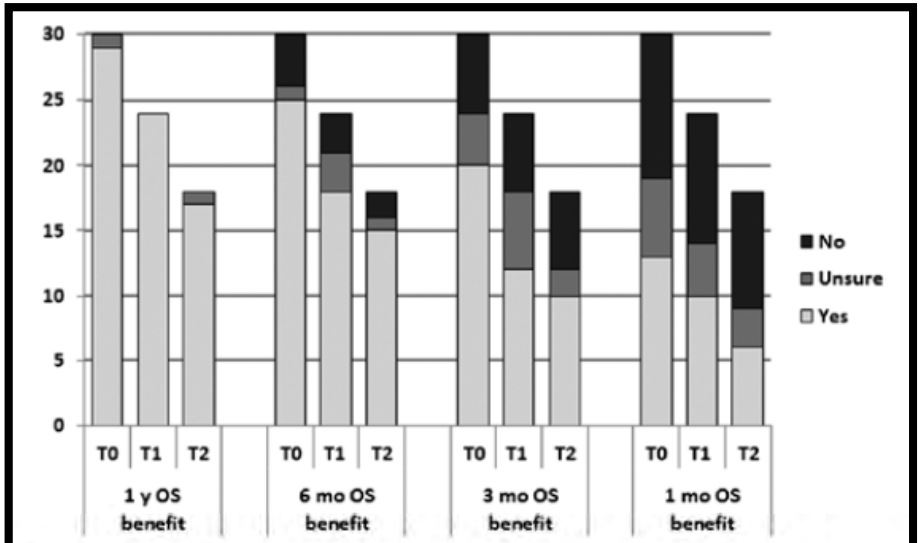


FIGURE 3. Answers to questions regarding whether maintenance therapy would be worthwhile in relation to different predefined expected overall survival benefits. T0, time at start of first-line chemotherapy; T1, after two cycles of chemo-

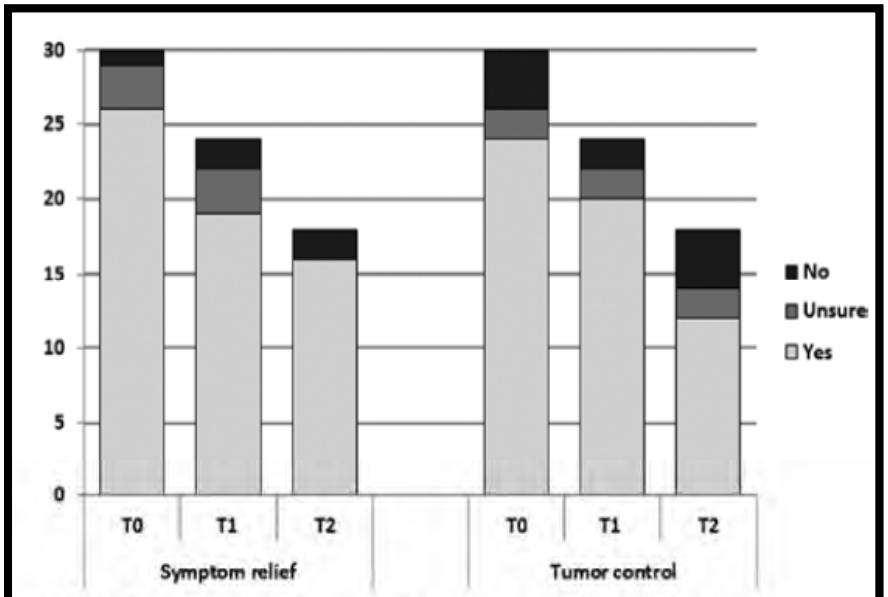


FIGURE 4. Answers to questions regarding whether maintenance therapy would be worthwhile if there would be no survival difference, but benefit in symptom control or imaging findings. T0, time at start of first-line chemotherapy;

CONCLUSIONS

- Maintenance therapy may be used in patients with advanced NSCLC.
- Patients with good performance status 0/1/2 benefit from maintenance therapy.
- Switch maintenance better then continuation maintenance (as a new drug with a different mechanism of action is introduced).
- However, if decided not to use maintenance chemotherapy, a close follow up for disease progression should be done to pick up progression early before it affects the performance status (thereby precluding second line chemo).

Conclusions

- Switch maintenance with Pemetrexed/Erlotinib shown to have overall survival benefit.
- Patients with SD appear to benefit more from switch maintenance as compared to those with CR/PR.
- Continuation Maintenance with Pemetrexed and gemcitabine also may be beneficial.
- Immunotherapy as a maintenance therapy is promising but further large trials are awaited.

Lung Cancer 76 (2012) 269–279