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Information | Research

Oral Presentation Lung Session: 916LBA –2347LBA

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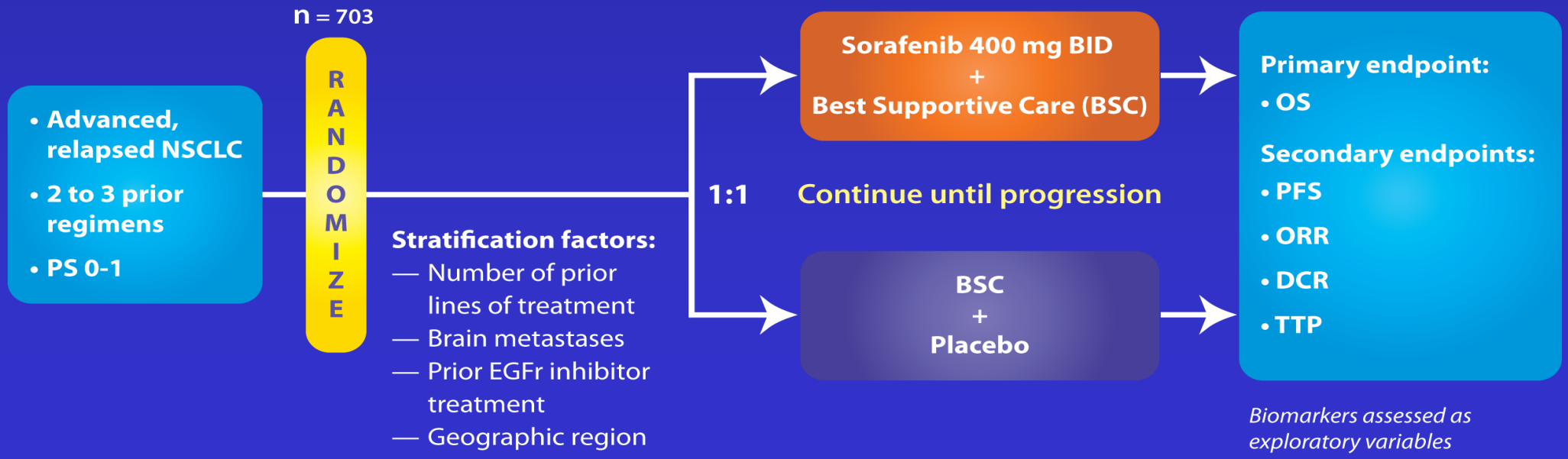
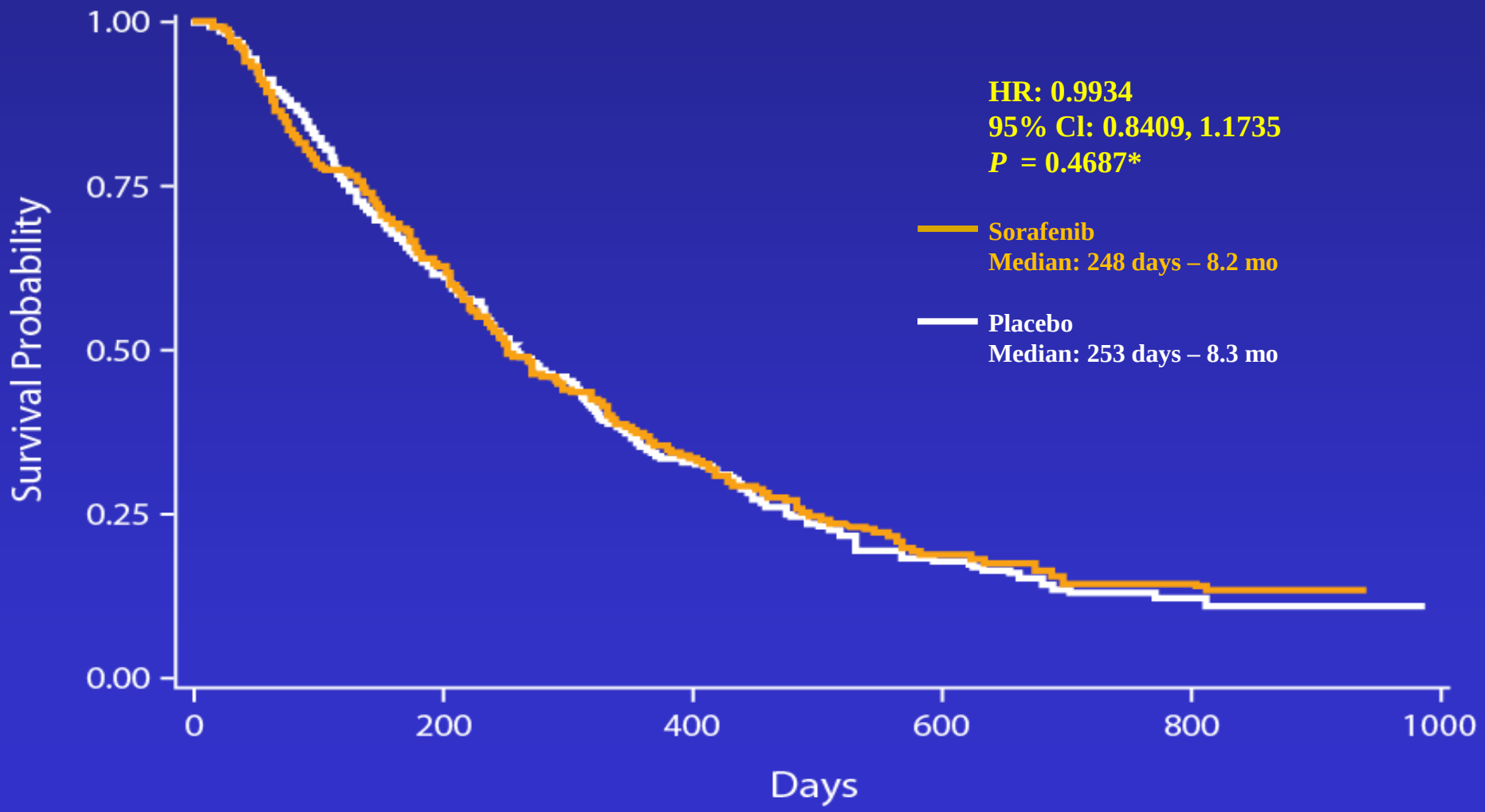
MISSION: Study Objective and Design

- Objective
  - To compare the efficacy and safety of sorafenib plus BSC with BSC alone in patients with relapsed or refractory, advanced, predominantly non-squamous NSCLC with disease progression after two or three prior treatment regimens
- Design
  - Randomized, double-blind, placebo-controlled phase III trial conducted in 31 countries in Europe, North and South America, and Asia Pacific.

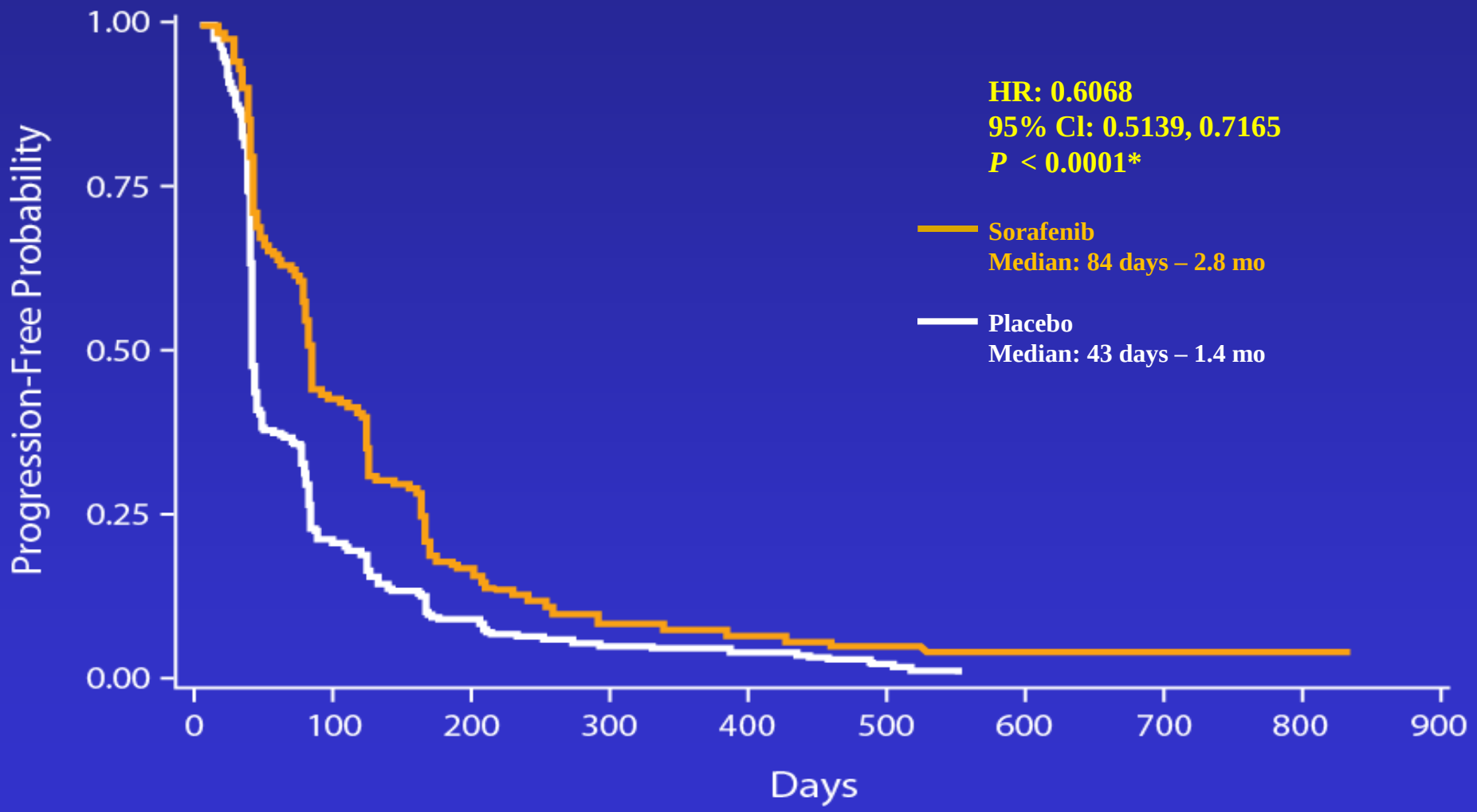


MISSION: Overall Survival



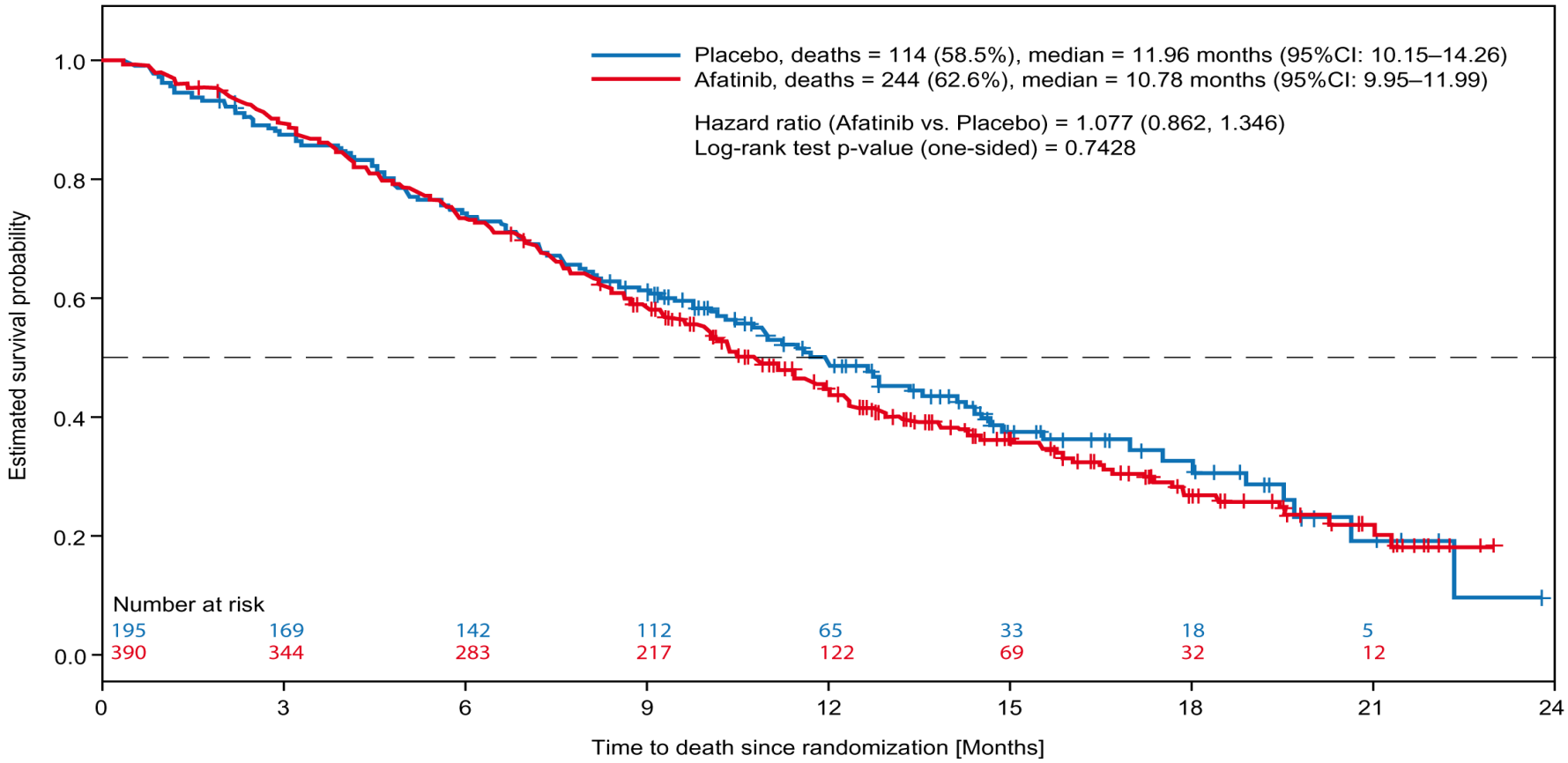
*one-sided stratified log-rank test

MISSION:Progression-Free Survival



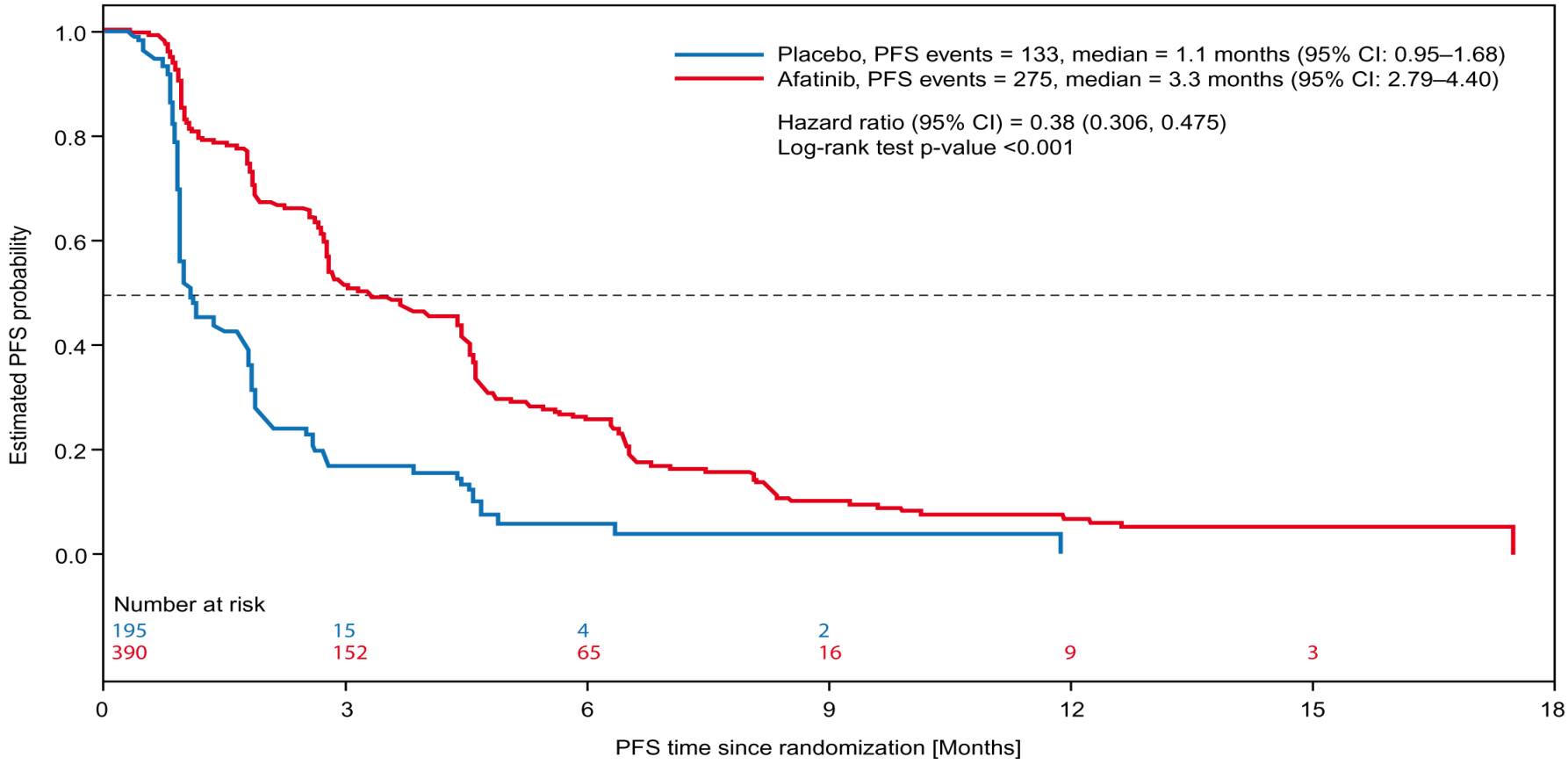
*one-sided stratified log-rank test

LUX LUNG 1 (3- 4-line) : overall survival



Miller VA et al, Lancet Oncology 2012

LUX LUNG 1 (3- 4-line) : PFS



Miller VA et al, Lancet Oncology 2012

3 AND 4-LINES THERAPIES IN ADVANCED NSCLC

IN THE MISSION AND LUX-1 TRIALS PFS BENEFIT BUT NO SURVIVAL BENEFIT:

- Effect on survival of subsequent lines therapies even after 3 or 4 treatment line?
(very selected patients receiving multiple treatment lines)

- In this subset of patients considering the palliative setting can be PFS a reliable study endpoint ?

IS THERE A ROLE FOR 3- AND 4-LINE TREATMENTS IN ADVANCED NSCLC ?

3- AND 4-LINE THERAPIES IN ADVANCED NSCLC: ISSUES

- Large tumor burden

- Drugs resistance

- Often included in clinical trial patients with poor clinical condition (“the last opportunity”)

- Reduced tolerability to drugs

- Primary study endpoint? (OS,PFS,QoL, symptoms relief)

- To date no positive trial without a molecular marker

IS THERE A POTENTIAL ROLE FOR MULTITARGETED ANTIANGIOGENETIC AGENTS IN ADVANCED NSCLC ?

Antiangiogenic tyrosine kinase receptor inhibitors and their targets

Agent	VEGFR-1	VEGFR-2	VEGFR-3	PDGFR	EGFR	Other targets
Vandetanib		•			•	RET
Sunitinib	•	•	•	•		KIT, FLT3, RET
Axitinib	•	•	•			
Sorafenib	•	•	•	•		KIT, RAF, FLT3
Vatalanib	•	•	•	•		KIT
Cediranib	•	•	•	•		KIT
Motesanib	•	•	•	•		KIT, RET
Pazopanib	•	•	•	•		KIT
BIBF 1120		•		•		FGFR

Scagliotti GV et al, Oncologist 2012

Published Ahead of Print on July 30, 2012 as 10.1200/JCO.2011.39.7646
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2011.39.7646

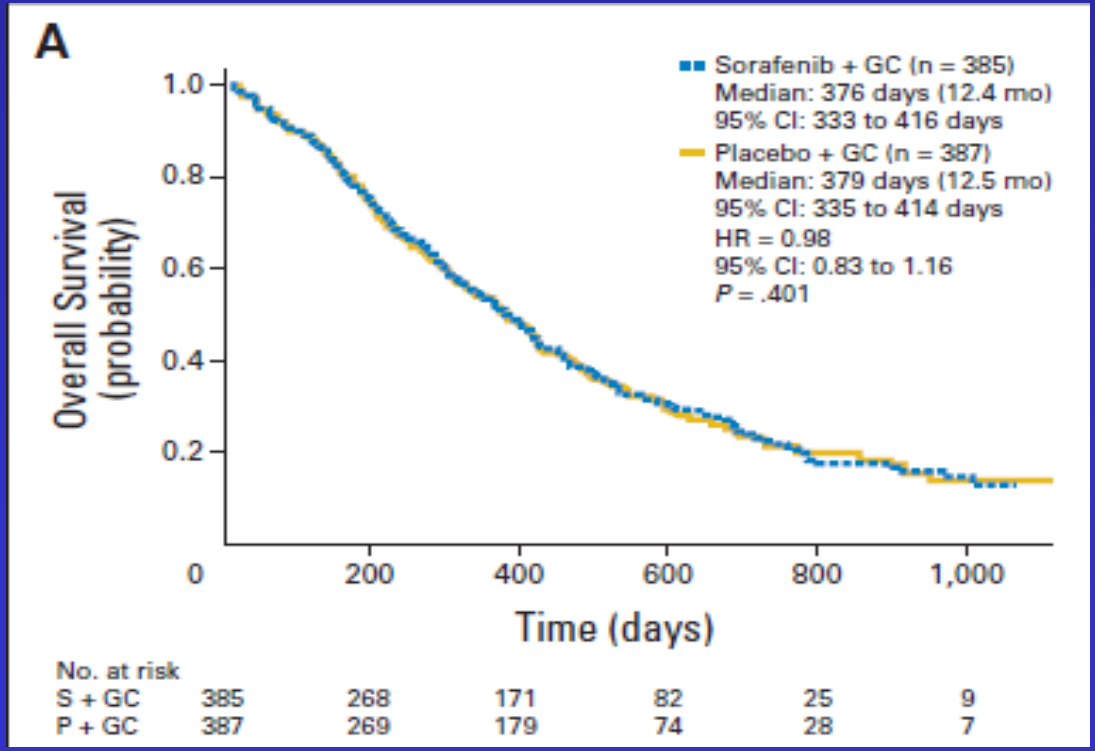
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

NEXUS trial

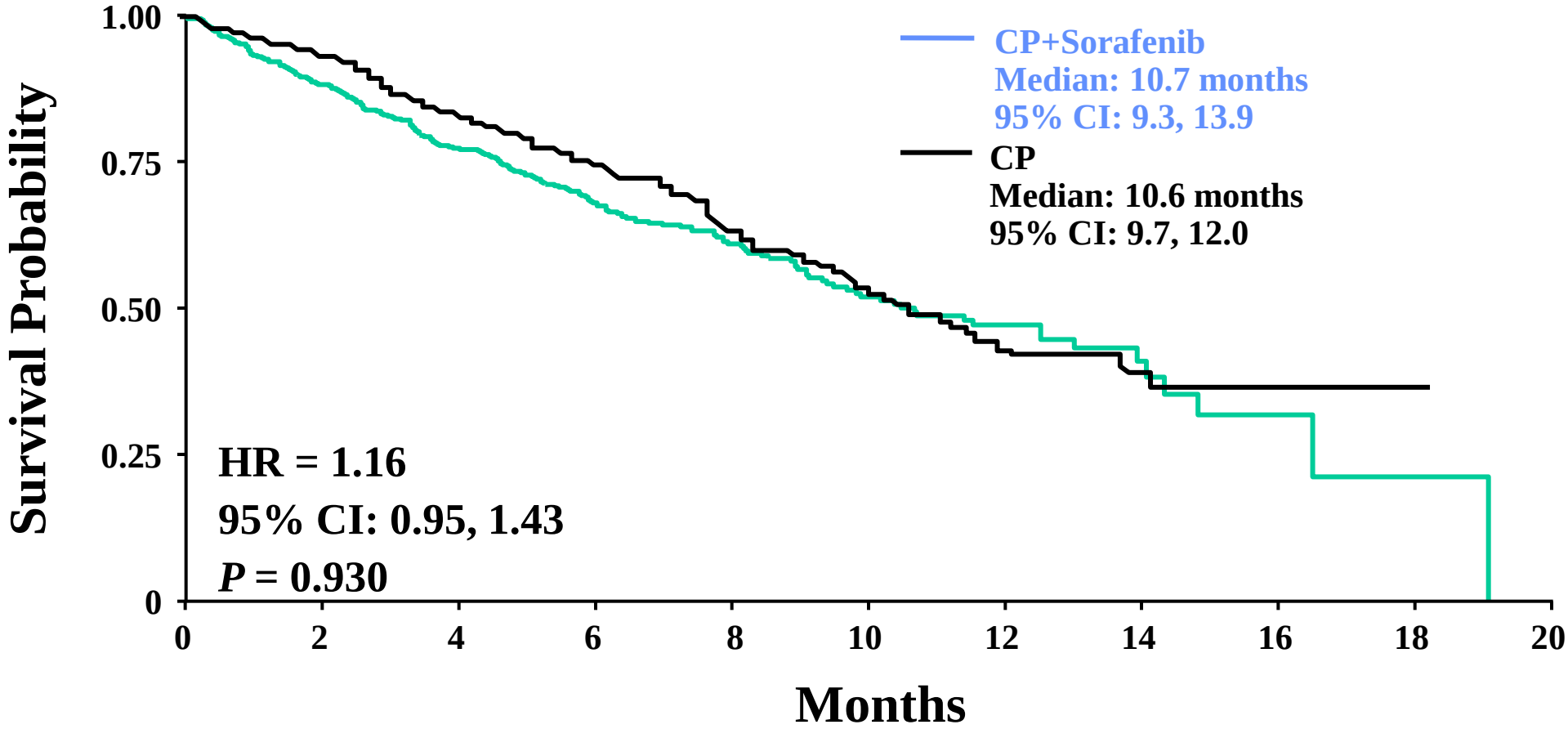
Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Gemcitabine/Cisplatin Alone or With Sorafenib for the First-Line Treatment of Advanced, Nonsquamous Non–Small-Cell Lung Cancer

Luis G. Paz-Ares, Bonne Biesma, David Heigener, Joachim von Pawel, Timothy Eisen, Jaafar Bennouna, Li Zhang, Meilin Liao, Yan Sun, Steven Gans, Kostas Syrigos, Etienne Le Marie, Maya Gottfried, Johan Vansteenkiste, Vincente Alberola, Uwe Phillip Strauss, Elaine Montegriffo, Teng Jin Ong, and Armando Santoro

NEXUS trial



ESCAPE TRIAL: Overall Survival



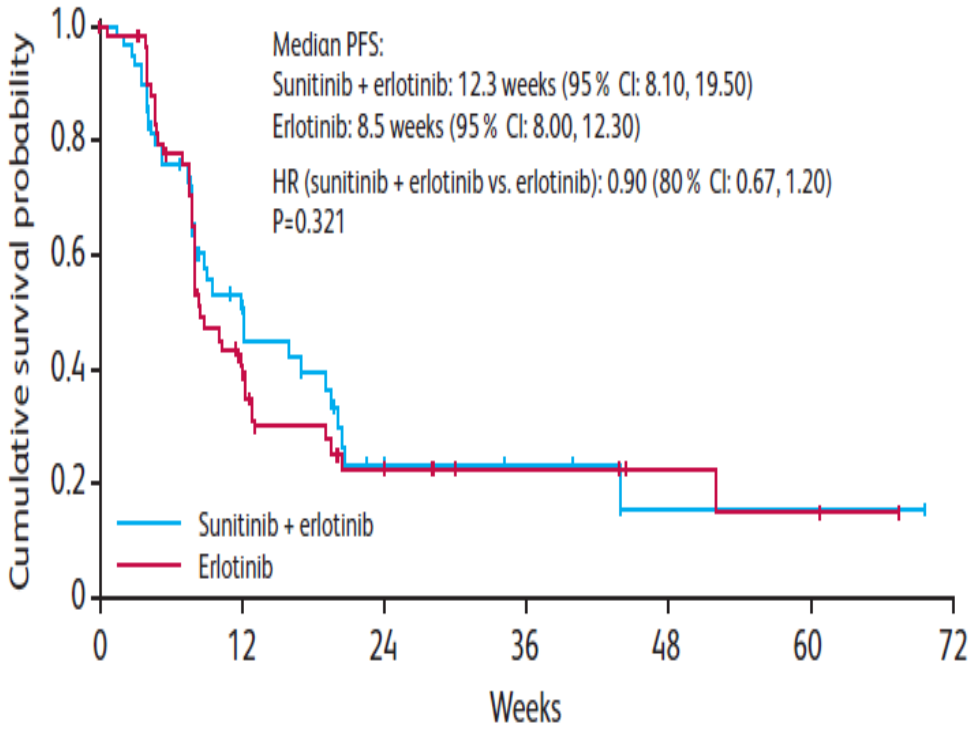
CPS	464	406	354	268	155	86	47	16	7	1

Scagliotti G et al, J Clin Oncol 2010

SUNITINIB ± ERLOTINIB IN 2nd-LINE NSCLC TREATMENT

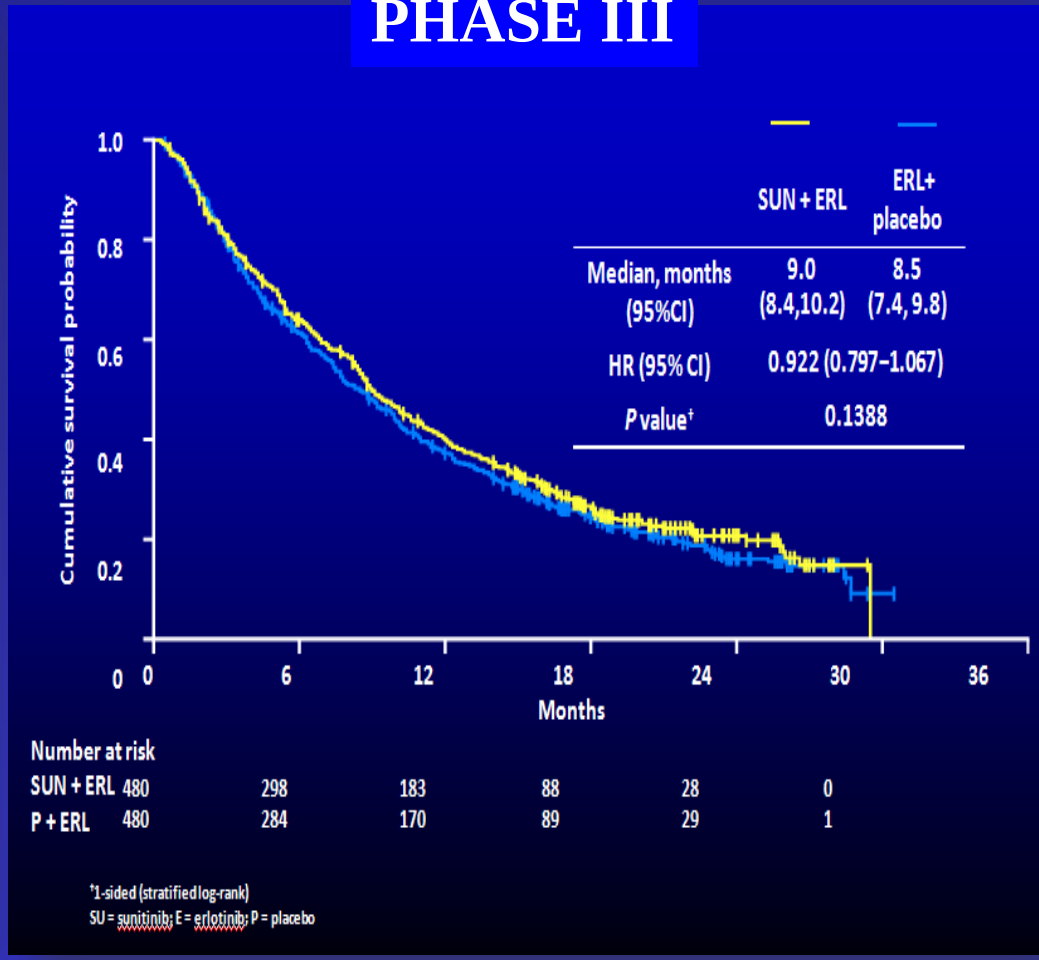
Survival from Randomized Trials

PHASE II



HJ Groen et al, P ESMO 2010

PHASE III



GV Scagliotti et al, J Clin Oncol 2012

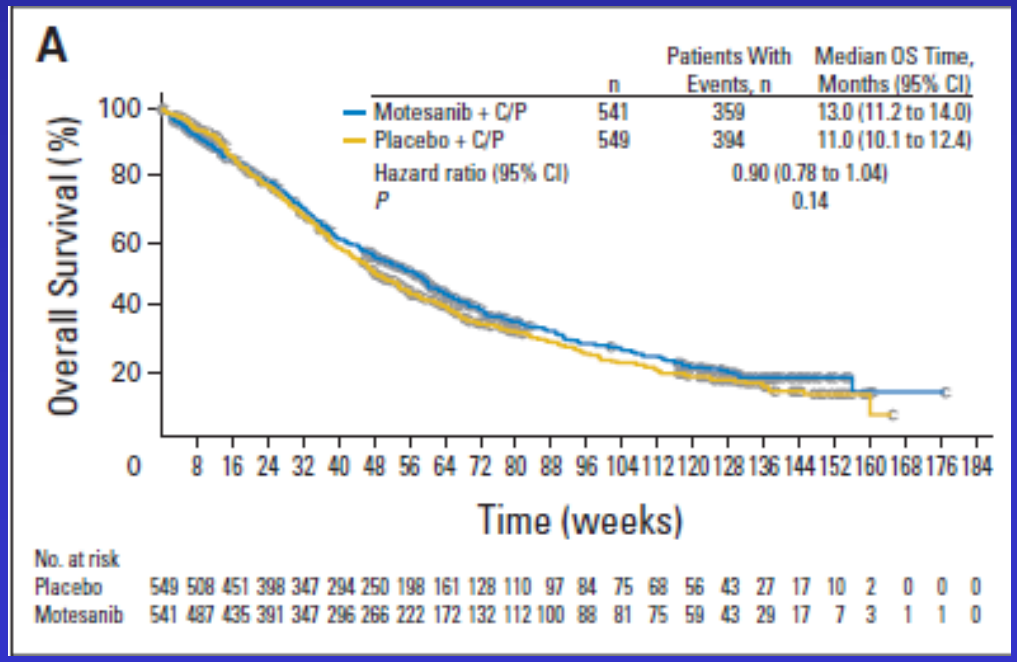
VOLUME 30 · NUMBER 23 · AUGUST 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

International, Randomized, Placebo-Controlled, Double-Blind Phase III Study of Motesanib Plus Carboplatin/Paclitaxel in Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancer: MONET1

Giorgio V. Scagliotti, Ihor Vynnychenko, Keunchil Park, Yukito Ichinose, Kaoru Kubota, Fiona Blackhall, Robert Pirker, Rinat Galiulin, Tudor-Eliade Ciuleanu, Oleksandr Sydorenko, Mircea Dediu, Zsolt Papai-Szekely, Natividad Martinez Banaclocha, Sheryl McCoy, Bin Yao, Yong-jiang Hei, Francesco Galimi, and David R. Spigel



Conclusion
Motesanib plus carboplatin/paclitaxel did not significantly improve OS over carboplatin/paclitaxel alone in patients with advanced nonsquamous NSCLC or in the adenocarcinoma subset.

Phase II/III clinical studies with multi-angiokinase inhibitors in NSCLC.[a]

Agent	Phase	Patient characteristics	Treatment arm(s)	Clinical trial identifier
Dual target				
Sorafenib	II	1 prior EGFR TKI and ≤ 1 prior chemotherapy regimen	Sorafenib monotherapy	NCT00922584
	II	First-line	Sorafenib + metronomic docetaxel	NCT00801801
	II	≤2 prior lines of therapy; latest therapy single-agent erlotinib	Sorafenib + erlotinib versus sorafenib alone	NCT00609804
	II	Non-smokers or former light smokers, 1 prior chemotherapy regimen	Sorafenib monotherapy	NCT00754923
	III	2 or 3 prior chemotherapy regimens	Sorafenib monotherapy	NCT00863746
Sunitinib	II	1 prior chemotherapy regimen	Sunitinib versus pemetrexed versus sunitinib + pemetrexed	NCT00698815 (CALGB 30704)
	II	First-line	Sunitinib + docetaxel + cisplatin	NCT01019798
	II		Maintenance following first-line, platinum-based chemotherapy	NCT01210053
	III		Maintenance following first-line, platinum-based doublet chemotherapy	NCT00693992 (CALGB 30607)
	III	≤ 2 prior chemotherapy regimens, including a platinum-based regimen	Sunitinib + erlotinib versus placebo + erlotinib	NCT00457392
Cediranib	III	First-line	Cediranib + carboplatin/paclitaxel	NCT00795340 (BR29)
Axitinib	I/II	First-line, nonsquamous histology	Cisplatin/pemetrexed ± axitinib	NCT00768755
	II	First-line, squamous histology	Cisplatin/gemcitabine + axitinib	NCT00735904
Motesanib	III	First-line, nonsquamous histology	Carboplatin/paclitaxel ± motesanib	NCT00460317
Linifinib	II	First-line, nonsquamous histology	Carboplatin/paclitaxel ± linifinib	NCT00716534
Brivanib	II	NSCLC and other tumor types	Brivanib monotherapy	NCT00633789
Triple target				
Nintedanib (BIBF 1120)	III	Second-line (prior bevacizumab permitted), all histologies	Nintedanib BIBF 1120 + docetaxel versus placebo + docetaxel	NCT00805194 (LUME-Lung 1)
	III	Second-line (prior bevacizumab permitted), nonsquamous histology	Nintedanib BIBF 1120 + pemetrexed versus placebo + pemetrexed	NCT00806819 (LUME-Lung 2)
Pazopanib	II	≥2 prior therapies, stage IV	Pazopanib monotherapy	NCT01049776
	II	First-line, stage IIIB/IV	Pazopanib + paclitaxel versus carboplatin + paclitaxel	NCT00866528
	II	1–2 prior chemotherapy regimens for advanced disease, stage IIIB/IV	Pazopanib + erlotinib versus placebo + erlotinib	NCT01027598
	II	First-line, stage IIIB/IV, predominantly nonsquamous histology	Pazopanib + pemetrexed versus cisplatin + pemetrexed	NCT00871403
	II	Progression on first-line bevacizumab, stage IIIB/IV	Pazopanib monotherapy	NCT01262820
	II	Progression on first-line bevacizumab, stage IIIB/IV	Pazopanib + pemetrexed versus pazopanib alone	NCT01107652
	II	Stage IVA/IVB	Pazopanib versus pemetrexed maintenance after carboplatin/cisplatin + pemetrexed induction	NCT01313663
	II/III	Stage IIIB/IV	Pazopanib versus placebo maintenance	NCT01208064
	II/III	Stage I, adjuvant therapy	Pazopanib monotherapy versus placebo	NCT00775307

Ellis M et al, Crit Rev Oncol Hematol 2012

MULTITARGETED ANTIANGIOGENETIC AGENTS: THE REAL PROBLEM

Drugs with a leading target (VEGF) with no predictive factors for efficacy and no opportunity for patients selection

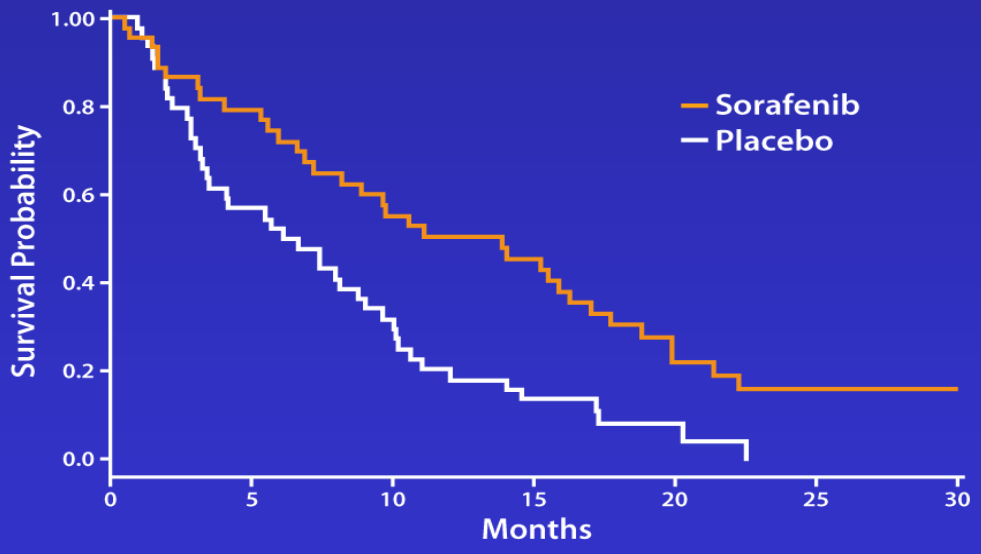
ANGIANGIOGENETIC AGENTS: PREDICTIVE FACTORS ?

- **There are no firmly established markers to measure antiangiogenic efficacy in vivo and select patients**
- **Potential markers currently being evaluated, include**
  - **serum, plasma and urine soluble proteins/receptors**
  - **imaging**
    - ***in vivo* blood flow and/or capillary permeability measurement (CT, MRI, ultrasound)**
    - ***in vivo* metabolic/proliferative imaging techniques (PET)**
  - **microvessel density**

Exploratory analysis: OS and PFS in Patients with EGFR Mutation in Tumor or Plasma

OS

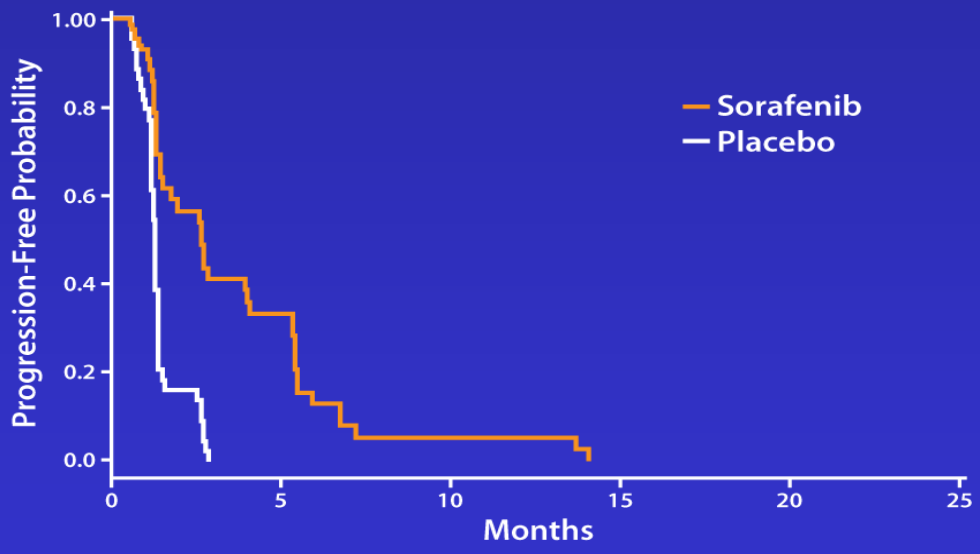
- Sorafenib N=44; Placebo N=45
- HR=0.48 (95% CI 0.3,0.76)
- P-value=0.002
- Sorafenib median OS= 13.9 mo (423d)
- Placebo median OS= 6.5 mo (197d)



Biomarker*treatment interaction analysis: p-value=0.023

PFS

- Sorafenib N=44; Placebo N=45
- HR=0.27 (95% CI 0.16,0.46)
- P-value<0.001
- Sorafenib median PFS= 2.7 mo (83d)
- Placebo median PFS= 1.4 mo (42d)

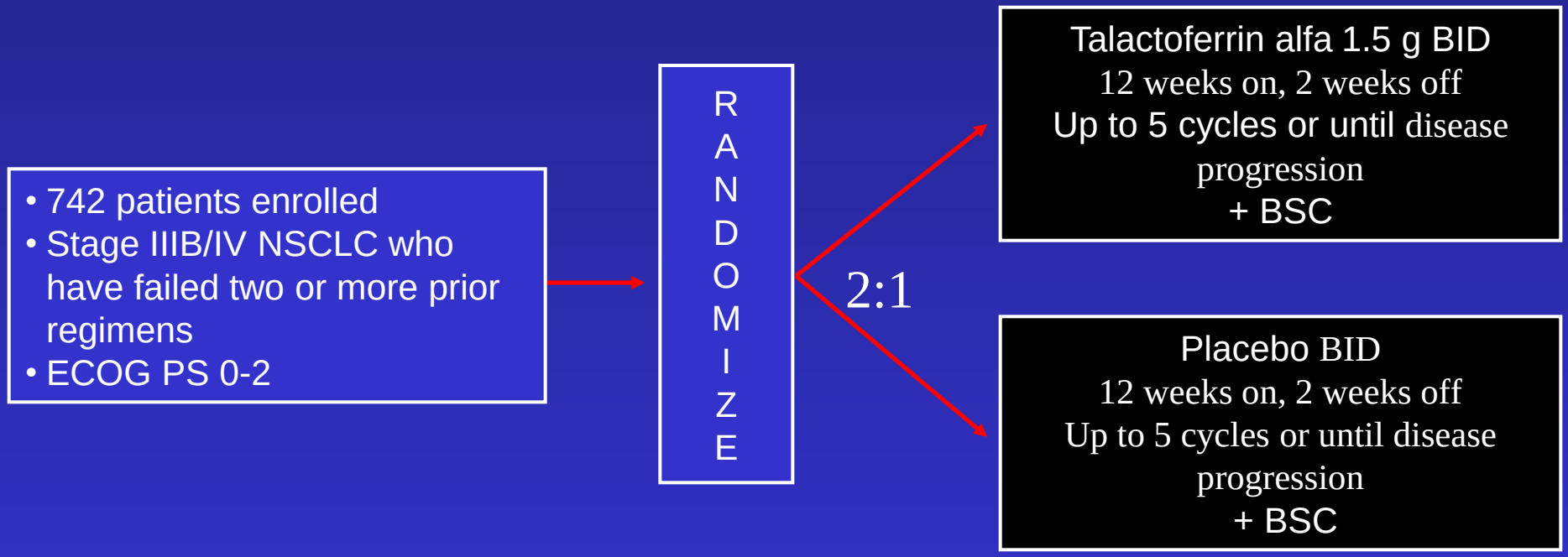


Biomarker*treatment interaction analysis: p-value=0.015

Mok TS, et al. *ESMO* 2012, Abstract LBA 9.

LBA2347

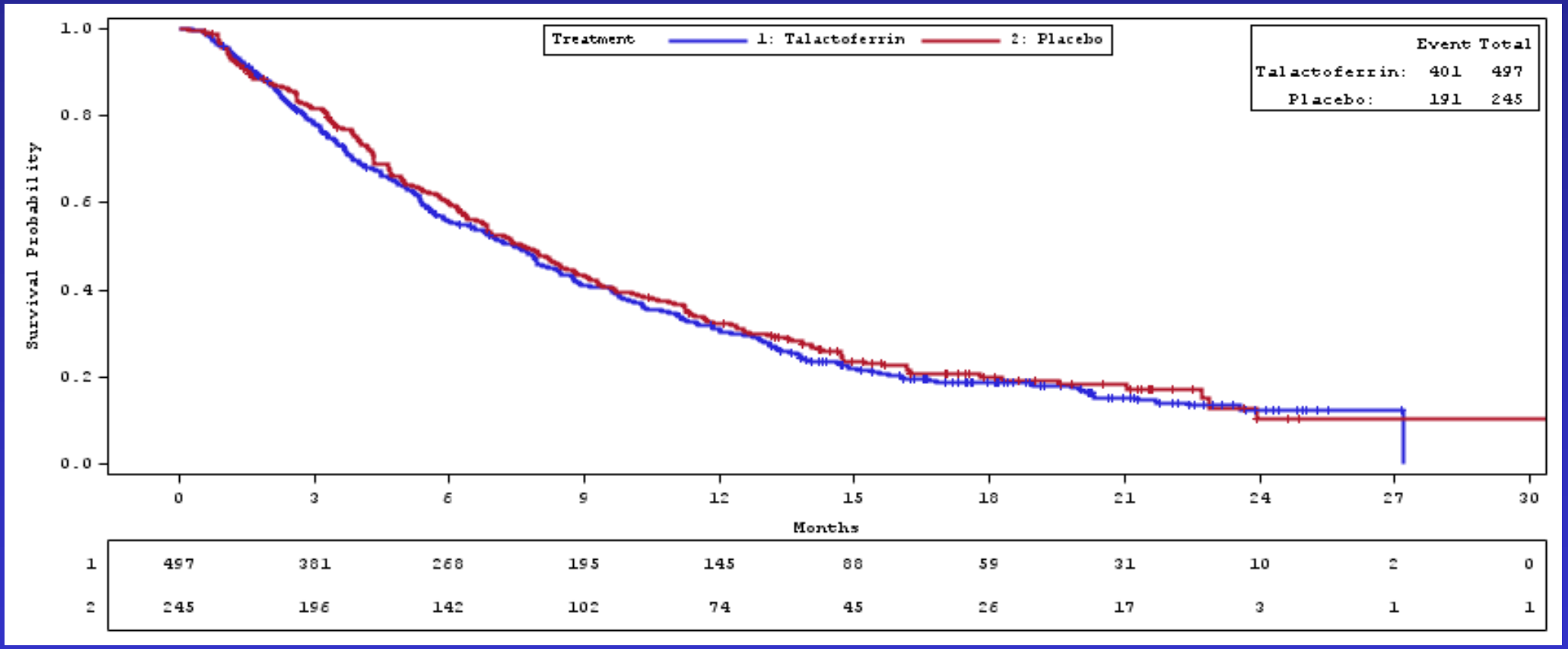
FORTIS-M: Randomized, Double-Blind, Placebo-Controlled Study of Oral Talactoferrin Alfa in Relapsed Advanced NSCLC



Primary endpoint: Overall survival

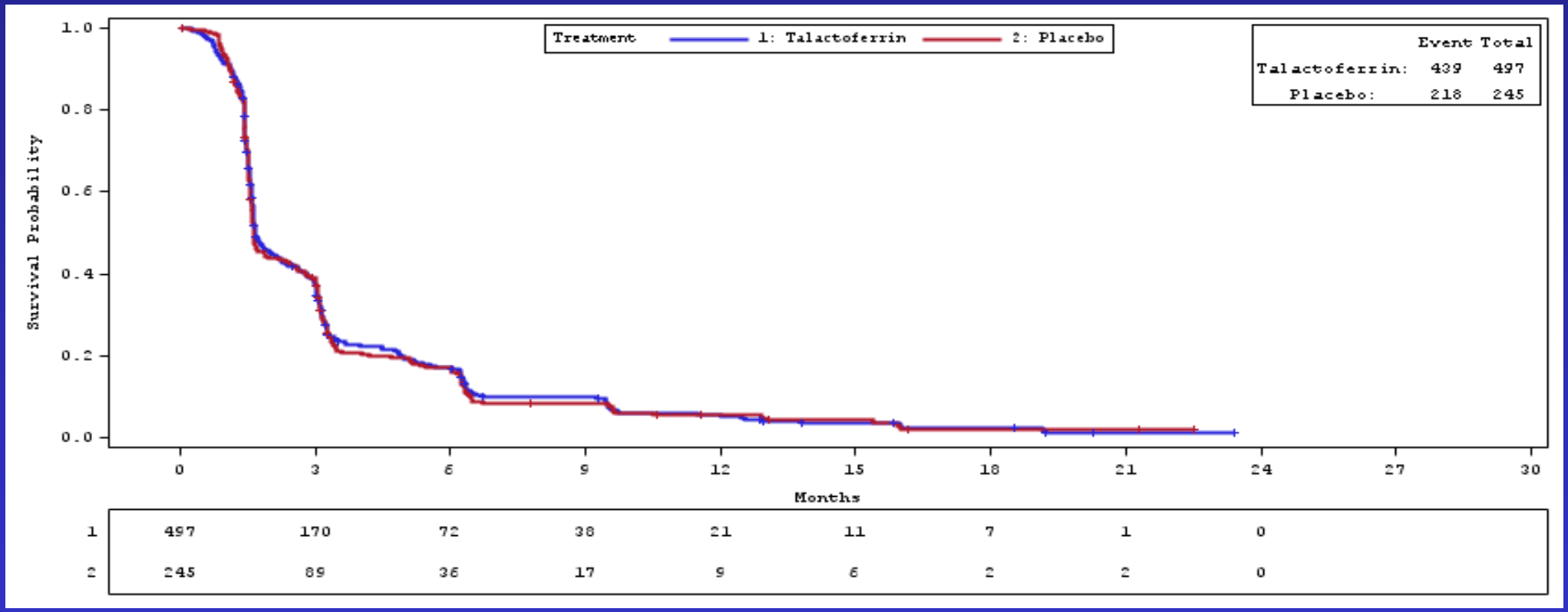
Secondary endpoints: 6-month and 1-year survival rate, PFS, ORR, DSR, safety and tolerability

FORTIS-M: Primary Endpoint – Overall Survival (ITT Population)



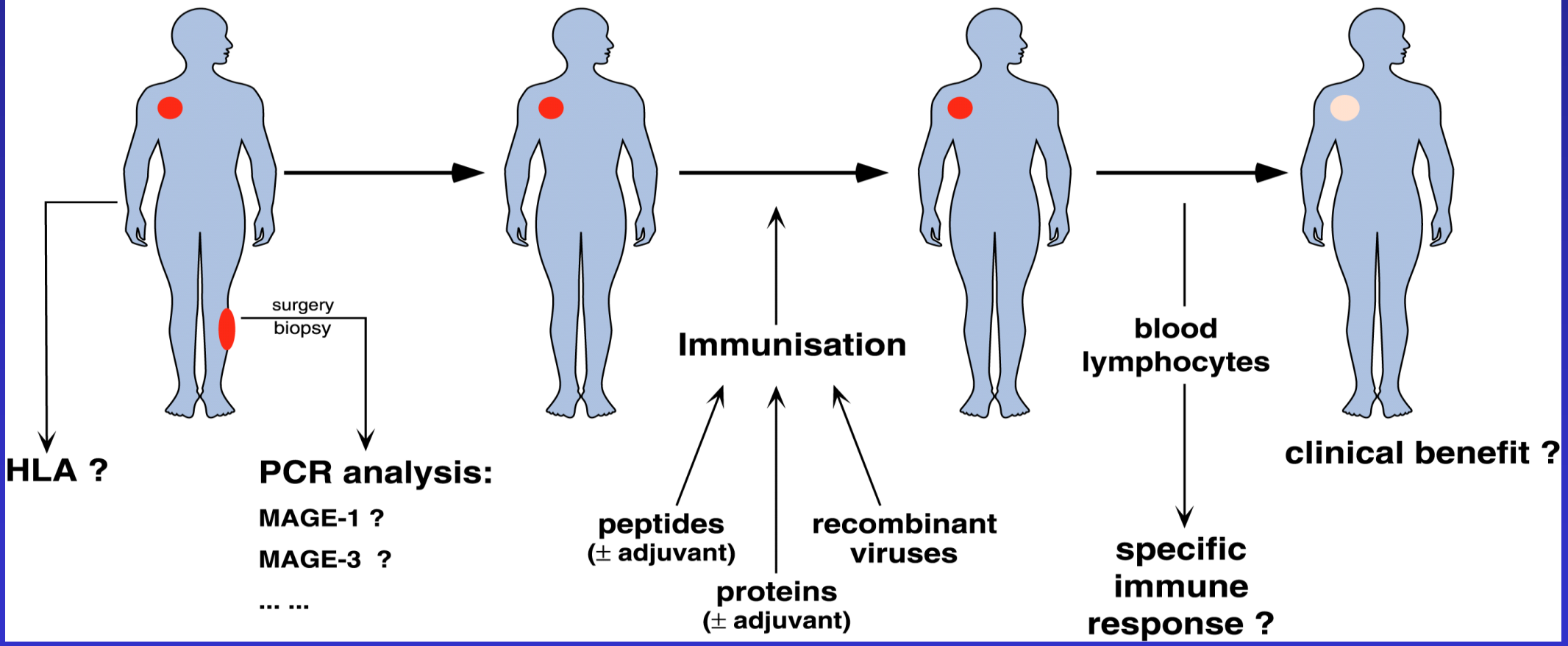
Median OS of 7.66 Months in the placebo arm, 7.49 Months in the talactoferrin arm
HR = 1.04 (0.873, 1.24)
P=0.6602 (two-sided)

FORTIS-M: Secondary Endpoint – PFS



Median PFS in the talactoferrin arm was 1.68 months compared to 1.64 months for placebo.
HR = 0.99 (0.835, 1.16),
P=0.8073 (two-sided)

immunotherapy of cancer



1972

choice for infection due to anaerobes from the abdomen or pelvis.[4]

For these reasons the evidence for the clinical effectiveness of clindamycin in the treatment of anaerobic infections presented by Bartlett, Sutter and Finegold in this issue of the *Journal* is timely. It seems clear that clindamycin and lincomycin are useful alternatives to penicillin in the treatment of infections due to anaerobes from the respiratory tract in penicillin-allergic patients. More importantly, clindamycin, which is now approved for parenteral administration, may be a useful alternative to chloramphenicol for infections due to anaerobes from the bowel or genital tract, particularly when the treatment is empirical and antibiotic susceptibilities are unknown. This very early experience, however, must be interpreted cautiously. Patients often present a complex clinical picture and occasionally improve solely as a consequence of draining of the focus of infection. Only two such patients with *B. fragilis* infection in the current report were treated with clindamycin; clearly, more published data are needed on the use of clindamycin in seriously ill patients with these infections. If such data confirm its clinical effectiveness, it will become increasingly important to avoid unrestrained use of clindamycin in view of the remarkable emergence of *B. fragilis* isolates resistant to another antibiotic, tetracycline, over the past 15 years.[5] Finally, for patients with anaerobic infections, who often have foul, gassy discharges, perforated visci, and hidden abscesses, it should be remembered that the critical therapeutic act is often to find and drain the focus of infection. Medicine and surgery must synergize lest once again all the world become anaerobic.

ANTONE A. MEDEIROS, M.D.

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2. Moore WEC, Cato EP, Holdeman LV: Anaerobic bacteria of the gastrointestinal flora and their occurrence in clinical infections. J Infect Dis 119:641-649, 1969
3. Washington JA: Evaluation of two commercially available media for detection of bacteremia. Appl Microbiol 23:956-959, 1972
4. Bodner SJ, Koenig MG, Goodman JS: Bacteremic bacteroides infection. Ann Intern Med 73:537-544, 1970
5. Martin WJ, Gardner M, Washington JA: In vitro antimicrobial susceptibility of anaerobic bacteria isolated from clinical specimens. Antimicrob Agents Chemother 1:148-158, 1972
6. Nastro LJ, Finegold SM: Bactericidal activity of five antimicrobial agents against *Bacteroides fragilis*. J Infect Dis 126:104-107, 1972

IATROGENIC IMMUNOTHERAPY OF LUNG CANCER

In attempts to rid himself of cancerous growths, man has used fire and cryogenics, laser and x-ray beams, caustics and excision, and an infinite spectrum of diets, drugs and suggestion. Every few years one or another method is rediscovered when one or several physicians record unusual responses of patients with cancer to one or another circumstance. A report in this issue provides evidence that empyema in the postoperative period may improve survival in some patients with lung cancer.

The American literature concerned with the anticancer activity of micro-organisms traces its historical roots to the reports of Coley, who in 1891 (during his first year in practice) induced erysipelas-like infections in tumor masses. Later he and others tried a series of mixed infections and filtrates of several organisms and reported sporadic encouragement; these and subsequent studies have been summarized by Nauts.[1]

A predominant ingredient of most mixed toxins was extracts of *Serratia marcescens*. Vigorous attempts have been made to confirm the carcinolytic properties of *S. marcescens* and to isolate the active molecule (or molecules). O'Malley and his co-workers[2] reported that a polysaccharide from *S. marcescens* damaged newly formed blood vessels of experimental tumors. Algire, Legallais and Park[3] directly observed the effect of the *S. marcescens* on tumor vessels and concluded that the damage, in the form of stasis, thrombi and hemorrhage, was proportional to the degree and duration of hypotension associated with the agent. The antitumor effectiveness of this and related compounds was brief and limited by severe toxicity and the loss of effectiveness after an initial infection. Approximately 20 patients are known to have been given the purified polysaccharide of *S. marcescens*, but severe toxicity discouraged further trials.

Another interesting endotoxin that has had intensive study was prepared from *Trypanosoma cruzi* (K-R factor). The Russians reported remarkable tumor damage with K-R. Hauschka[4] reported that K-R from several species did damage tumors in mice but did not prolong their survival.

Christensen[5] treated rabbits that were implanted with the Brown-Pearse carcinoma with living and dead hemolytic streptococci. Repeated massive infections reduced the number of metastases but failed to affect the primary tumor implant. Various lysates and endotoxins were impotent.

There are few malignant tumors in man that have been exposed to infection in a manner that permits valid study. Actually, most large tumor masses are infected, and infections of superficial ulcerating cancers of the skin do not seem to inhibit progress of the disease.

A unique clinical experiment that may be pertinent involves the implantation of tumor cells at colon anastomoses. Comparative studies of suture-line recurrences have been made in patients prepared for surgery of the colon by mechanical cleansing or antibiotics. Claims that the implantation of cancer cells in the suture line is more frequent in patients given antibiotics have been made by a number of surgeons. Herter and Slanetz[6] reported that of 16 patients with cancerous recurrence at the suture line after anterior resections of the colon, all but one had been "prepared" with antibiotics. Unfortunately, no adequate prospective clinical assessment of the problem has been made.

Vink[7] noted a striking increase in tumor implants at

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doi:10.1093/annonc/mds260

What future opportunities may immuno-oncology provide for improving the treatment of patients with lung cancer?

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Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany

2012

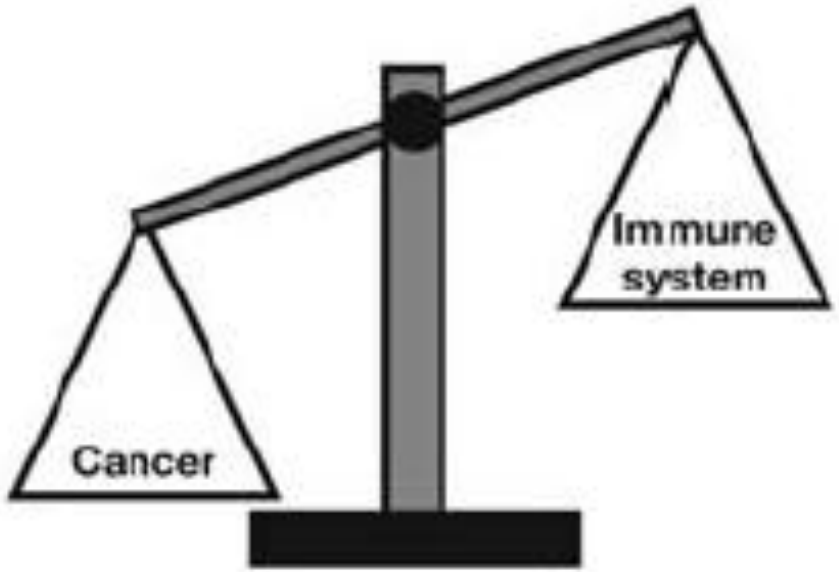
Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of all cases. Most patients with NSCLC are diagnosed at an advanced stage and have a poor prognosis, with a 5-year survival rate of <5%. Despite the introduction of new chemotherapeutic agents and molecularly targeted drugs, outcomes remain poor, emphasising the need for new treatment approaches. Inducing or potentiating immune responses via immunotherapeutic manipulation is a viable treatment approach for lung cancer. Antigen-specific, tumour-cell, and dendritic cell-based vaccines have all been evaluated in lung cancer, and some have shown promising clinical activity in phase II trials. These include liposomal BLP25 vaccine (L-BLP25), which targets mucin 1, and melanoma-associated antigen 3 (MAGE-A3) antigen-specific cancer immunotherapeutic (ASCI), which targets MAGE-A3, a peptide expressed almost exclusively on tumour cells. MAGE-A3 ASCI is being evaluated in the adjuvant setting in a phase III trial of patients with early-stage NSCLC, while a phase III trial of L-BLP25 is enrolling patients with unresectable stage III NSCLC. T-cell modulating agents (e.g. antibodies against programmed death 1 and cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4]) are also being investigated. For example, in patients with NSCLC treated with paclitaxel and carboplatin, the phased administration of ipilimumab (an antibody against CTLA-4) resulted in substantial improvements in immune-related progression-free survival compared with chemotherapy alone (5.7 versus 4.6 months; $P = 0.05$). Immunotherapy in lung cancer is starting to deliver promising results in clinical trials. However, further research will be required to establish the optimal timing of therapy (i.e. in the adjuvant or metastatic settings). In addition, it will be important to determine if immunotherapies are most effective when used alone or in combination with other agents.

Key words: antibody, antigen-specific vaccines, extensive disease-small-cell lung cancer (ED-SCLC), immunotherapy, non-small-cell lung cancer (NSCLC), T-cell modulation

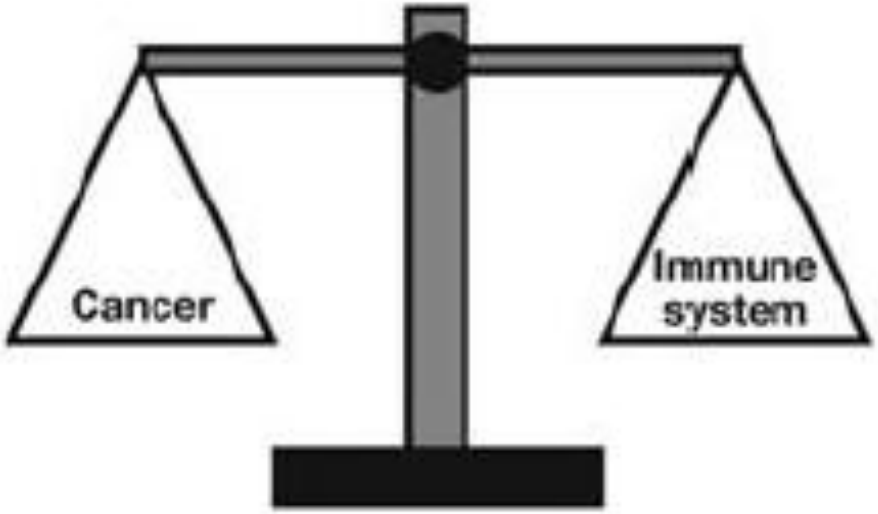
IMMUNOTHERAPY OF LUNG CANCER

- ABOUT 40 YEARS OF INVESTIGATION
- NO POSITIVE LARGE PHASE III STUDY
- NO REGISTERED DRUG IN LUNG CANCER

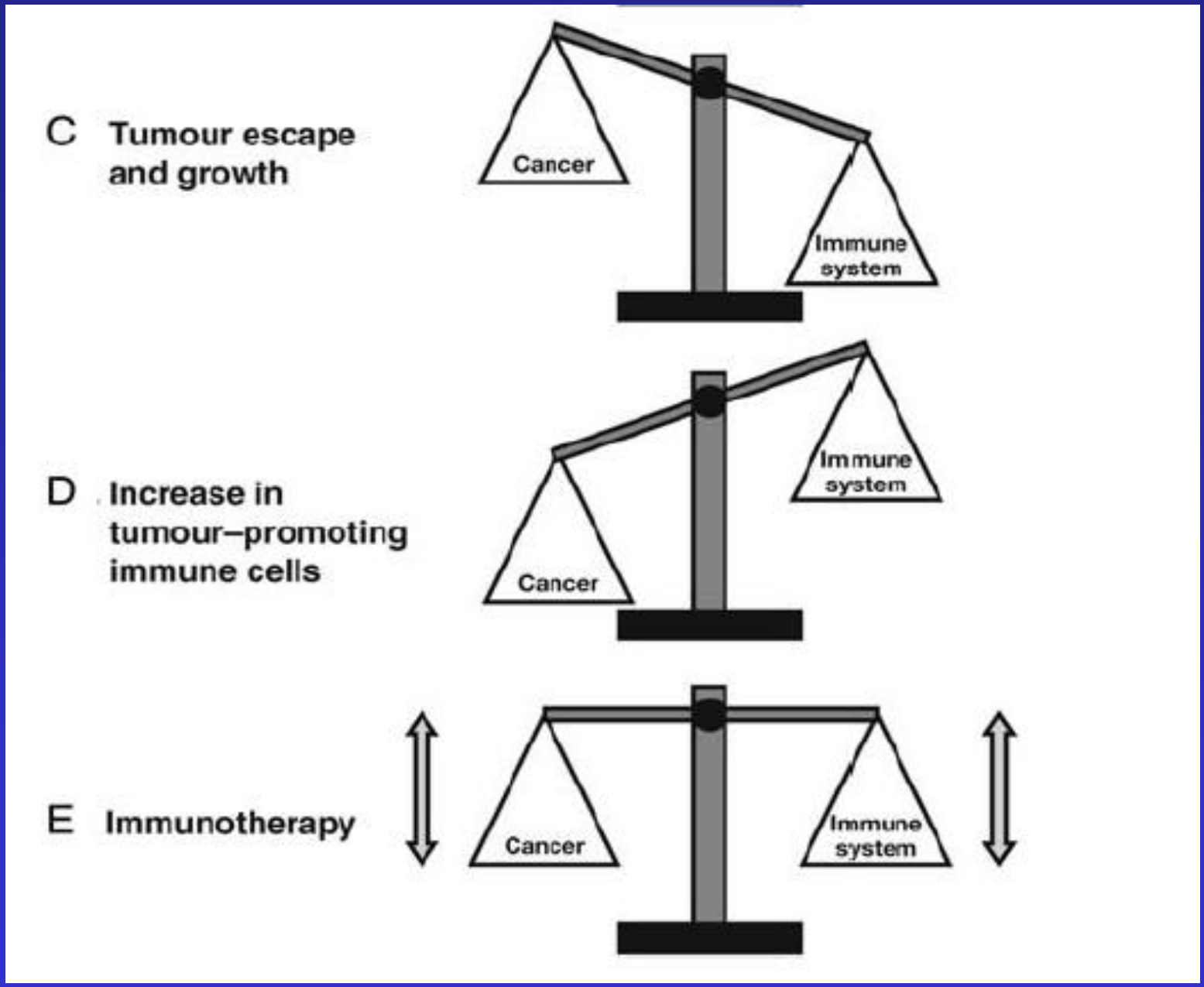
A Elimination



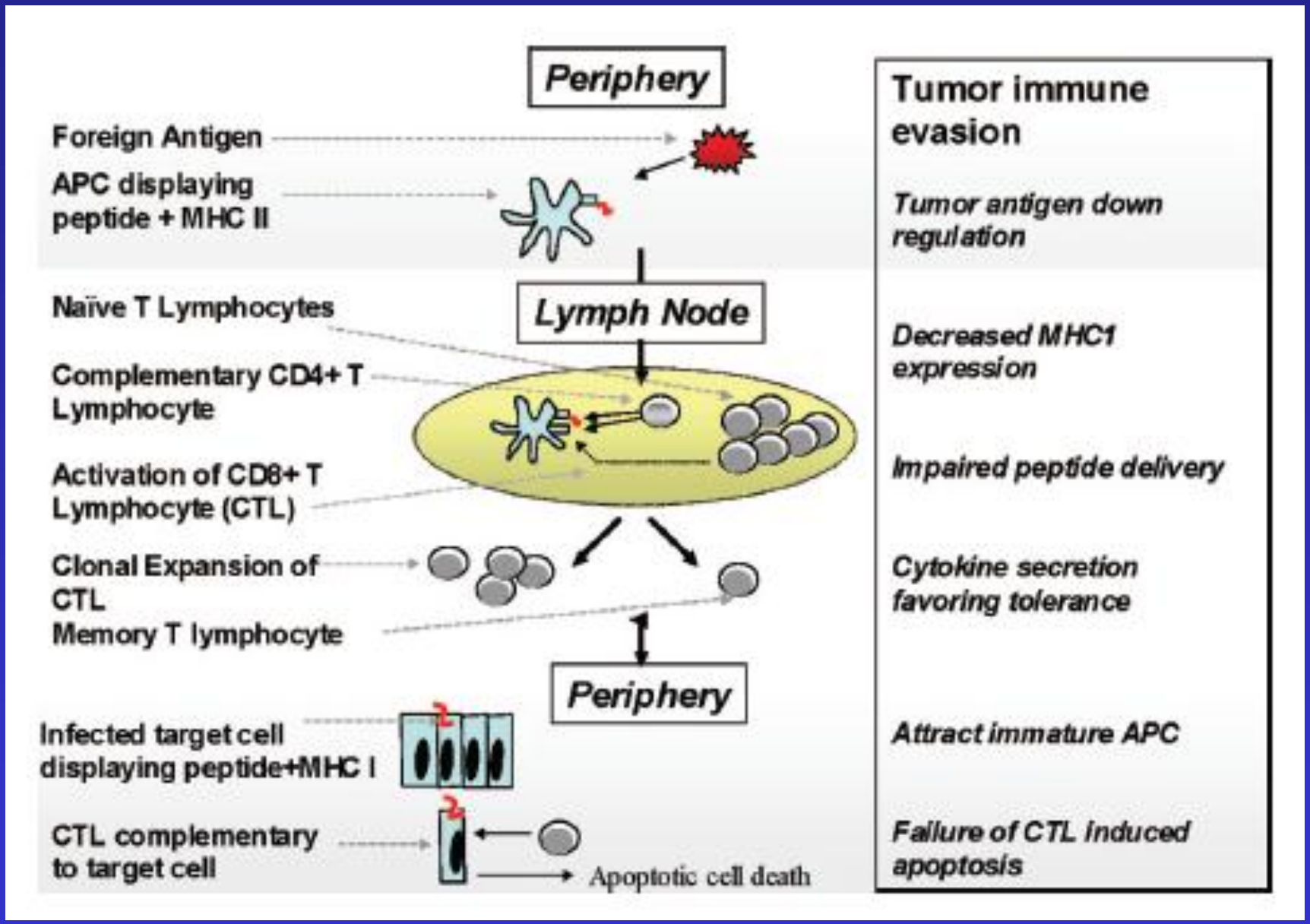
B Equilibrium



Finn OJ, Ann Oncol 2012.



Finn OJ, Ann Oncol 2012.



Bradbury P et al, J Thorac Oncol, 2008.

IMMUNOTHERAPY OF LUNG CANCER

- Unfortunately, such as in the FORTIS M trial, usually immunotherapy used in pretreated patients and in very advanced disease (high cancer immune evasion)

- No biomarkers to select patients that can experience the greatest benefit

Table 1: Ongoing clinical trials of immunotherapies for non-small-cell lung cancer

	Intervention	Study design	Estimated enrolment (n)	Stage	Main eligibility requirements	Endpoints
FORTIS-M	Talactoferrin or placebo	Phase 3 randomised, double-blind placebo-controlled	720	Stage IIIB or IV	Progressive disease after two or more previous systemic therapies	Primary: OS. Secondary: PFS, objective response, disease stabilisation rate, safety

Unfortunately trial stopped due to company problems

MAGE=melanoma-associated antigen. PFS=progression-free survival. OS=overall survival.

Thomas A et al, Lancet Oncology 2012

Table 1: Ongoing clinical trials of immunotherapies for non-small-cell lung cancer

	Intervention	Study design	Estimated enrolment (n)	Stage	Main eligibility requirements	Endpoints
START	Liposomal BLP25 or placebo	Phase 3 randomised, double-blind placebo-controlled	1476	Unresectable stage III	Stable disease or objective response after primary chemoradiotherapy. Two or more cycles of platinum-based chemotherapy, ≥50 Gy radiation	Primary: OS. Secondary: time to symptom progression, time to disease progression, 1, 2, and 3 year survival, safety
INSPIRE	Liposomal BLP25 or placebo	Phase 3 randomised, double-blind placebo-controlled	420	Unresectable stage III	Stable disease or objective response after primary chemoradiotherapy. Two or more cycles of platinum-based chemotherapy, ≥50 Gy radiation	Primary: OS. Secondary: time to symptom progression, time to disease progression, PFS, time to treatment failure, safety
STOP	Belagenpumatucel-L or placebo	Phase 3 randomised, double-blind placebo-controlled	506	Unresectable stage III or IV	Stable disease or objective response after primary platinum-based chemoradiotherapy	Primary: OS. Secondary: PFS, quality of life, time to progression, objective response, response duration, rate of CNS metastases development, safety
MAGRIT	MAGE-A3 vaccine or placebo	Phase 3 randomised, double-blind placebo-controlled	2270	Completely resected, stage IB, II, or IIIA	Tumour expresses MAGE-A3 gene.	Primary: disease-free survival. Secondary: lung-cancer-specific survival, OS, anti-MAGE-A3 and anti-protein D seropositivity rate, adverse events

MAGE=melanoma-associated antigen. PFS=progression-free survival. OS=overall survival.

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