Anti-Angiogenic Tyrosine Kinas Inhibitors in NSCLC

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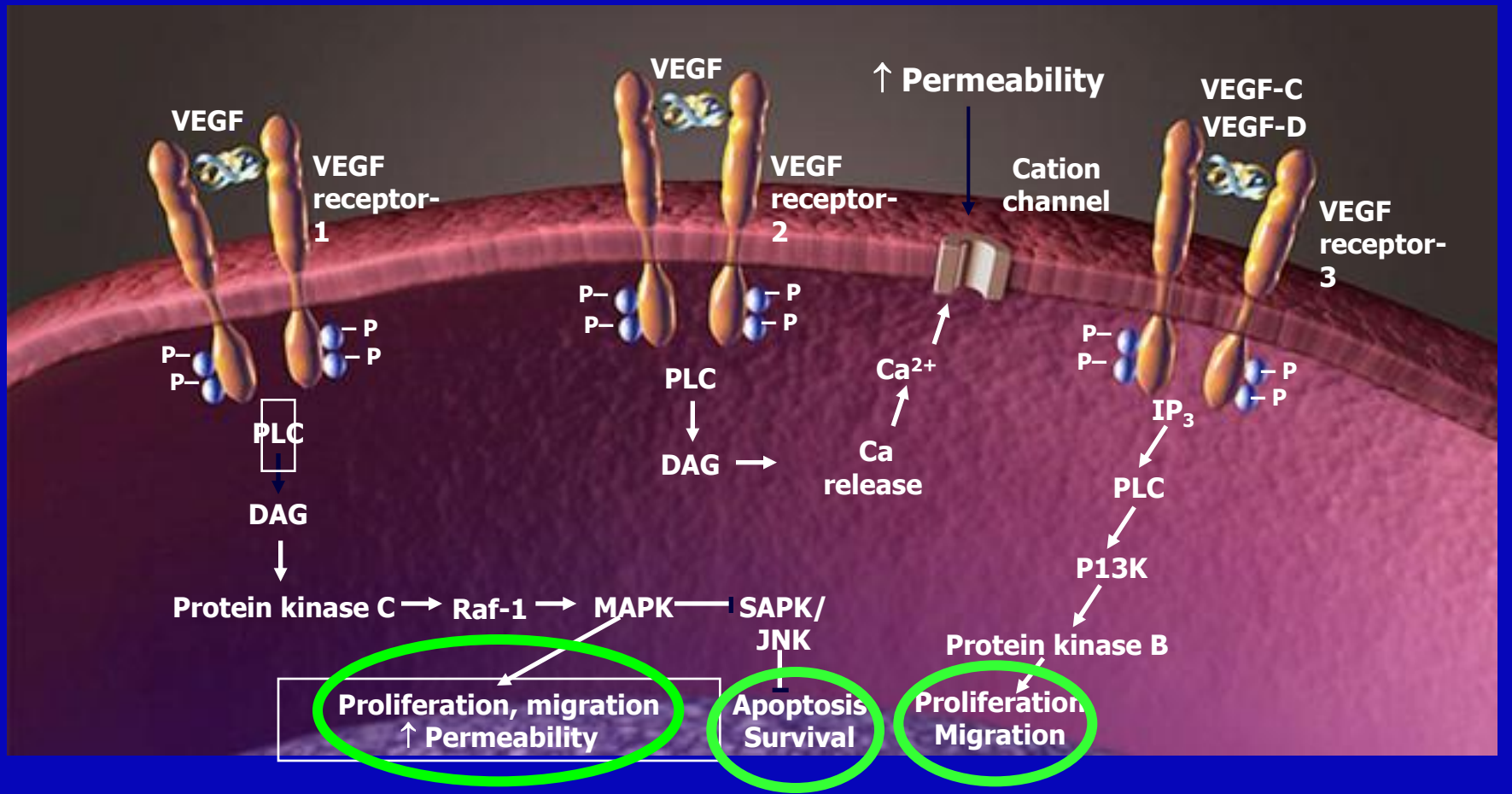
VEGF Receptor on endothelial cells



Shibuya M. Cell Struct Funct 2001;26:25–35

Anti-angiogenesis therapy in the treatment of solid tumors

- Proof of concept established for:
  - Monoclonal antibodies and fusion proteïns
  - Oral Tyrosine Kinase Inhibitors

    - In selected tumor types

Anti-angiogenesis therapy in the treatment of solid tumors

- Proof of concept established for:
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    - In selected tumor types

- In metastatic NSCLC:
  - Bevacizumab is approved
  - Aflibercept failed
  - Anti-angiogenic TKI not convincing so far

Anti-angiogenic TKI in mNSCLC

TKI	VEGFR1-3	PDGFR	c-KIT	BRAF	RAF-1	RET	FLT-3
Apatinib	√						
Axitinib	√	√	√				
BIBF1120*	√	√					
Cediranib	√	√	√				
Motesanib	√	√	√				
Pazopanib	√	√	√				
Sorafenib	√	√	√	√	√		√
Sunitinib	√	√	√			√	√
Vandetanib**	√					√	

*Binds also to FGFR
**Binds also to EGFR

Anti-angiogenic TKI in mNSCLC
APATINIB (pure anti VEGFR TKI)

- **Early development**
  - Randomized (2:1) phase II, 3rd line vs placebo
  - 92 vs. 46 patients (median age 52-55 y)
  - Non-squamous

- **PFS (1st End-Point):**

  4.7 vs. 1.9 m HR 0.27 p<0.0001

  - RR 20 vs. 2%
  - DCR 69 vs. 24%
  - No OS data

Li Zhang ASCO 2012 Poster Abstract 7548

Anti-angiogenic TKI in mNSCLC

AXITINIB (anti VEGFR 1, 2, 3, PDGFR c-KIT)

- **Early development* : single arm/single agent, phase II n=32**
  - **All histologies, 72% 2nd line**
  - **RR 9% DCR 41% PFS 4.9m OS 14.8m**

- **Randomized phase II PEM-Cis +/- Axitinib****
  - **Non-squamous, 1st line**

	Arm I (55) Axi Cont. 5mg PEM Cis D1-21		Arm II (58) Axi 5mg D2-19 PEM Cis D1-21		Arm III (57) PEM Cis (500/75) D1-21
PFS m	8	ns	7.9	ns	7.1
OS m	16.6	ns	14.7	ns	15.9
ORR %	45	0.013	40	0.07	26

*J Schiller JCO 2009 3836

** C Belani ASCO 2012 Poster abstract 7551

Anti-angiogenic TKI in mNSCLC

BIBF 1120 Vargatef (anti VEGFR 1, 2, 3, PDGFR, FGFR)

- **Early development* : double blind, single agent phase II n=73**
  - All histologies, 2-3rd line, 2 doses (2x250 or 2x 150mg)
  - PFS m = 1.6 (ECOG 0-1 2.9m)
  - No difference between doses

- **Randomized 2nd line studies**

LUM Lung 1 (Doc vs. Doc-BIBF)
n= 1300
Closed to accrual
All histo types
1st EP: PFS

LUM Lung 2 (Pem vs. Pem-BIBF)
n= 717
Closed to accrual
Non-squamous
1st EP: PFS

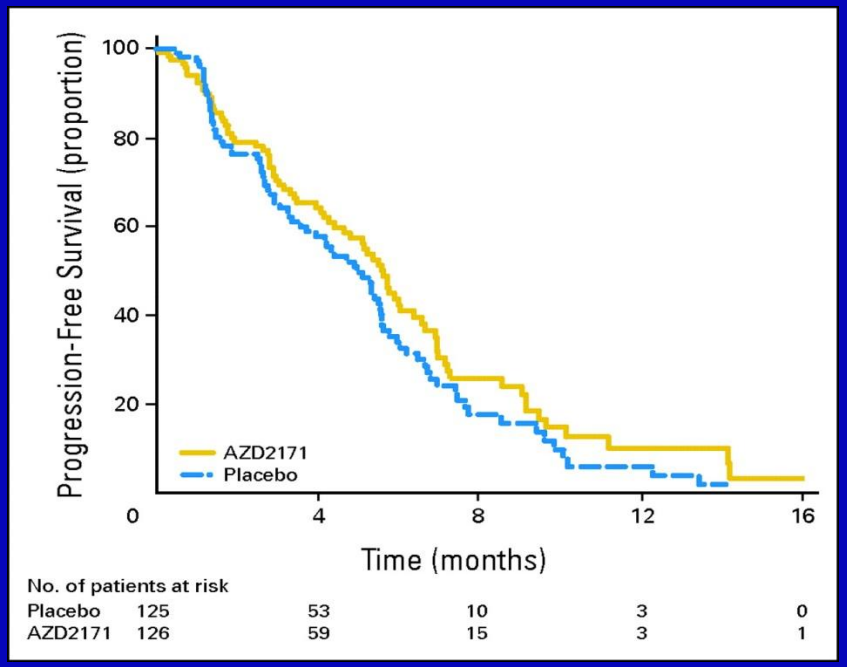
*Reck M JTP 2007 2 (8) S333

Anti-angiogenic TKI in mNSCLC

Cediranib Recentin (anti VEGFR 1, 2, 3, PDGFR, c-KIT)

- **BR 24: Randomized phase II/III CP +/- Cediranib (45 ⟹ 30 mg)**
  - 1st line, all histologies

	CP + Cediranib	CP	p
n	126	123	
RR %	38	16	<0.001
PFS m	5.6	5.0	HR 0.77 P=0.13
OS	10.5	10.1	HR 0.78 P=0.11



Toxicity issue: 13% protocol toxicity death

BR 29 on going at 20 mg Cediranib

G Goos et al JCO 2010 49-55

Anti-angiogenic TKI in mNSCLC

Cediranib Recentin (anti VEGFR 1, 2, 3, PDGFR, c-KIT)

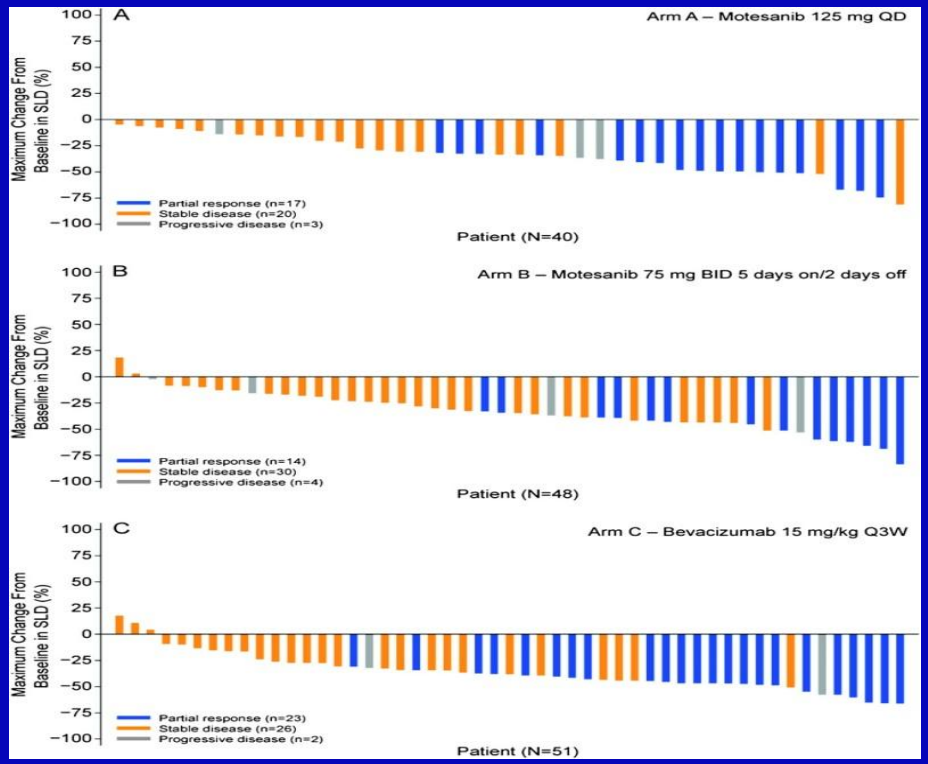
- **BR 29: Randomized phase II/III CP +/- Cediranib 20 mg/d**
  - 1st line, all histologies
  - 1st End-Point: OS
  - Planned interim analysis (260 patients, 170 PFS events)
    - HR for PFS 0.89: study terminated

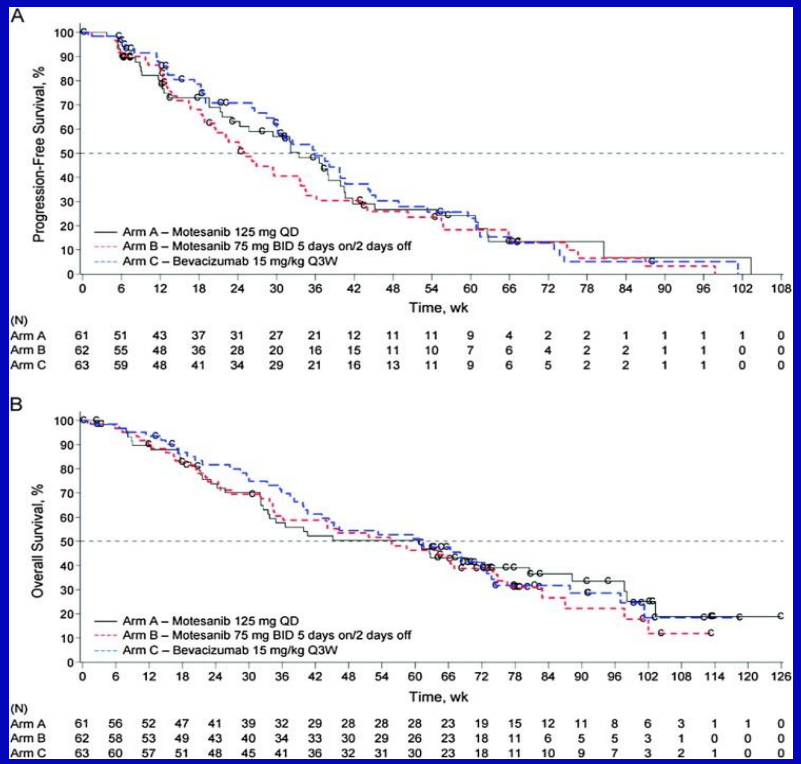
	CED	PLA	
• RR %	51	34	p<0.009
• PFS	5.5	5.5	HR 0.91
• OS	12.2	12.1	HR 0.94

Anti-angiogenic TKI in mNSCLC

Motesanib (anti VEGFR 1, 2, 3, PDGFR, c-KIT)

- **Randomized phase II, non-squamous, 1st line**
  - Motesanib 125 mg daily, 15 mg Bid or Bev 15mg/kg + CP Q 3 weeks
  - Outcome comparable to Bev CP, more toxicity





GR Blumenschein et al Ann Oncol 2011 2057

Anti-angiogenic TKI in mNSCLC

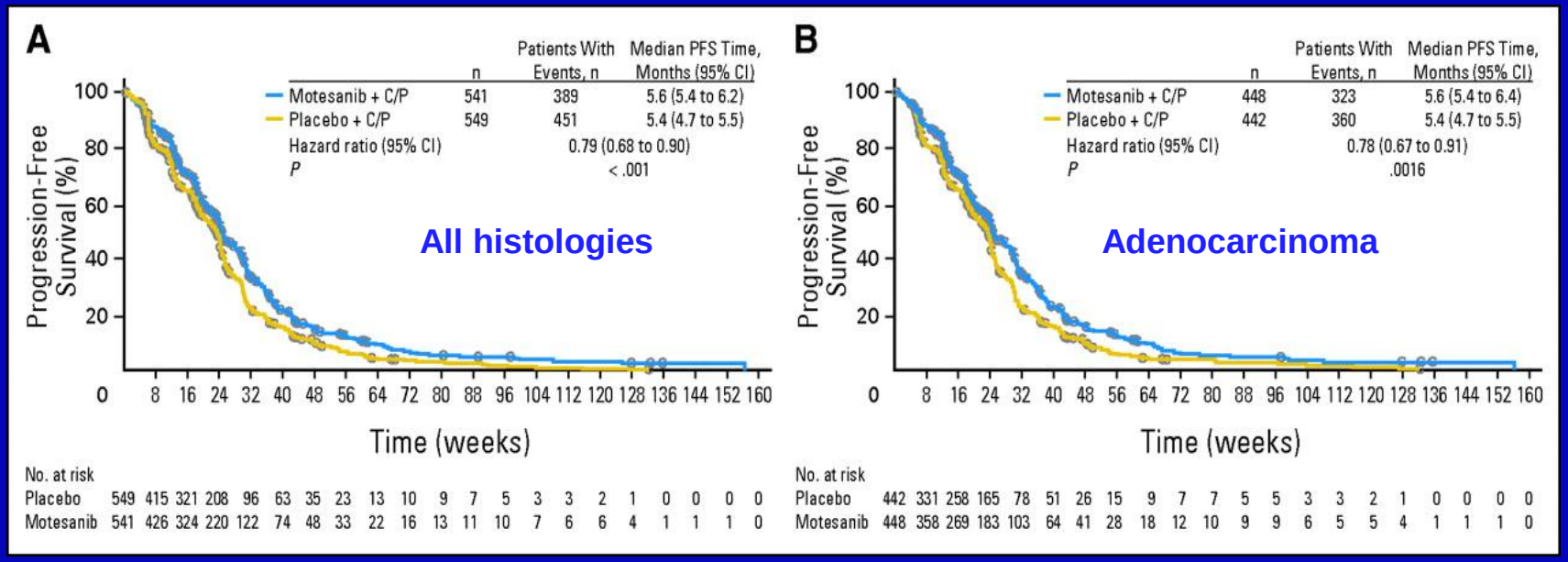
Motesanib (anti VEGFR 1, 2, 3, PDGFR, c-KIT)

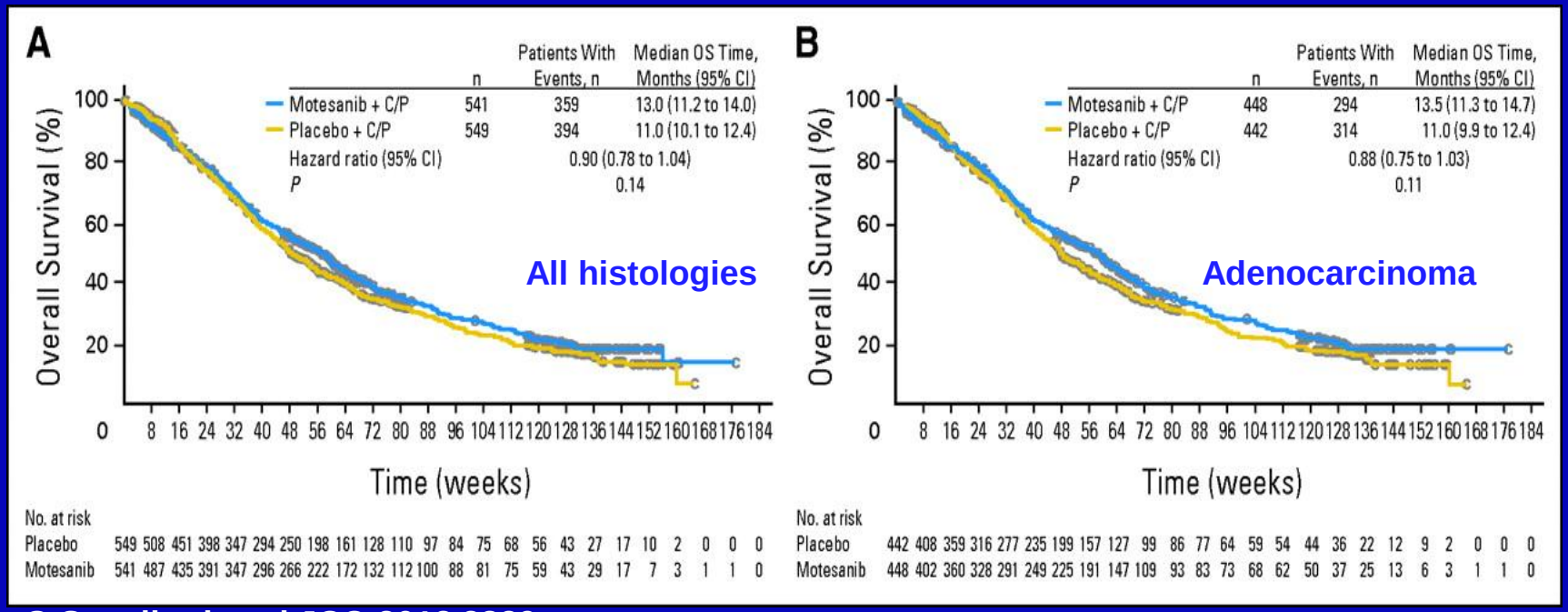
- **MONET1: Randomized phase III, 1st line,**
  - CP +/- Motesanid 125 mg daily
  - 1090 pts with non-squamous NSCLC (82% Adenocarcinoma
  - Primary end-point: OS
  - Secondary end-points: RR, PFS, safety

	ALL non-squamous		Adenocarcinoma	
	Motesanib + CP	Placebo + CP	Motesanib + CP	Placebo + CP
RR %	40 p<0.001	26	39 p<0.001	25
DCR%	79	51	81	76

G Scagliotti et al JCO 2012 2829

MONET1: study results





G Scagliotti et al JCO 2012 2829

Anti-angiogenic TKI in mNSCLC

Pazopanib (anti VEGFR 1, 2, 3, PDGFR, c-KIT)

- No trials in stage IV (1 discontinued early for toxicity)
- 1 on going phase II (n=42)
- 1 small neo-adjuvant trial (not contributing)
- 1 adjuvant trial in stage I: closed to accrual
  - (n= 140)

Anti-angiogenic TKI in mNSCLC

Sorafenib (anti VEGFR 1, 2, 3, PDGFR, c-KIT, BRAF, RAF1, Flt-3)

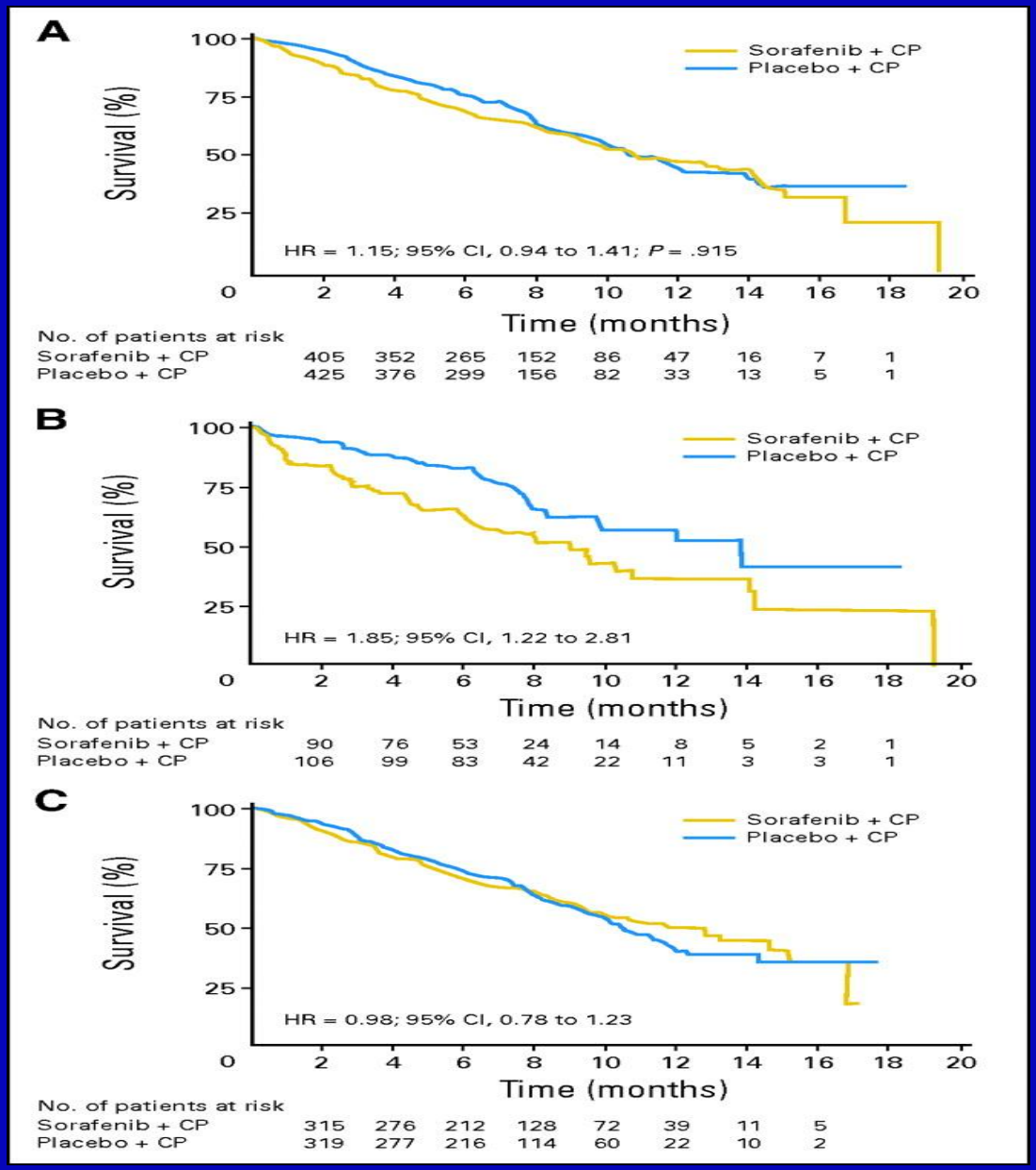
- Promising results and tolerance profile in variety of early development phase
  - As single agents
  - In combination with chemotherapy

- Late development in phase III trials:

ESCAPE	NEXUS
-n= 926 -1st line randomized phase III -All histologies 58% Adeno -Carbo-Paclitaxel +/-Sorafenib -20% Asian -85% smoker (past or present) -1st End-Point: OS	-n= 902 -1st line randomized phase III -All histologies (squamous excluded based on ESCAPE 04 2008) -Gem-Cis +/- Sorafenib - 1st End-Point: OS

ESCAPE:

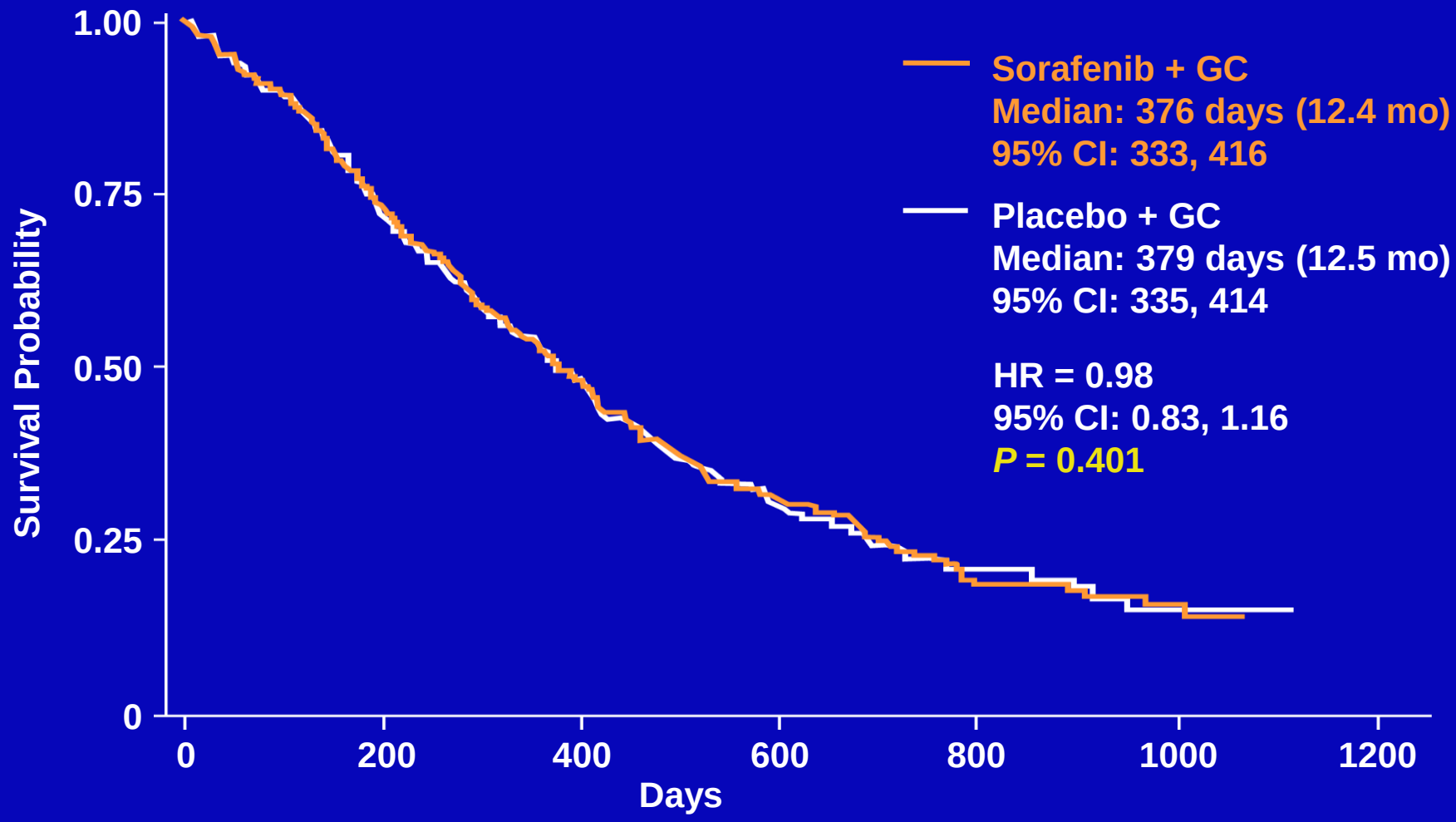
OS (A) overall patient population, (B) squamous cell carcinoma, and (C) other histologies.



Scagliotti G et al. JCO 2010;28:1835-1842

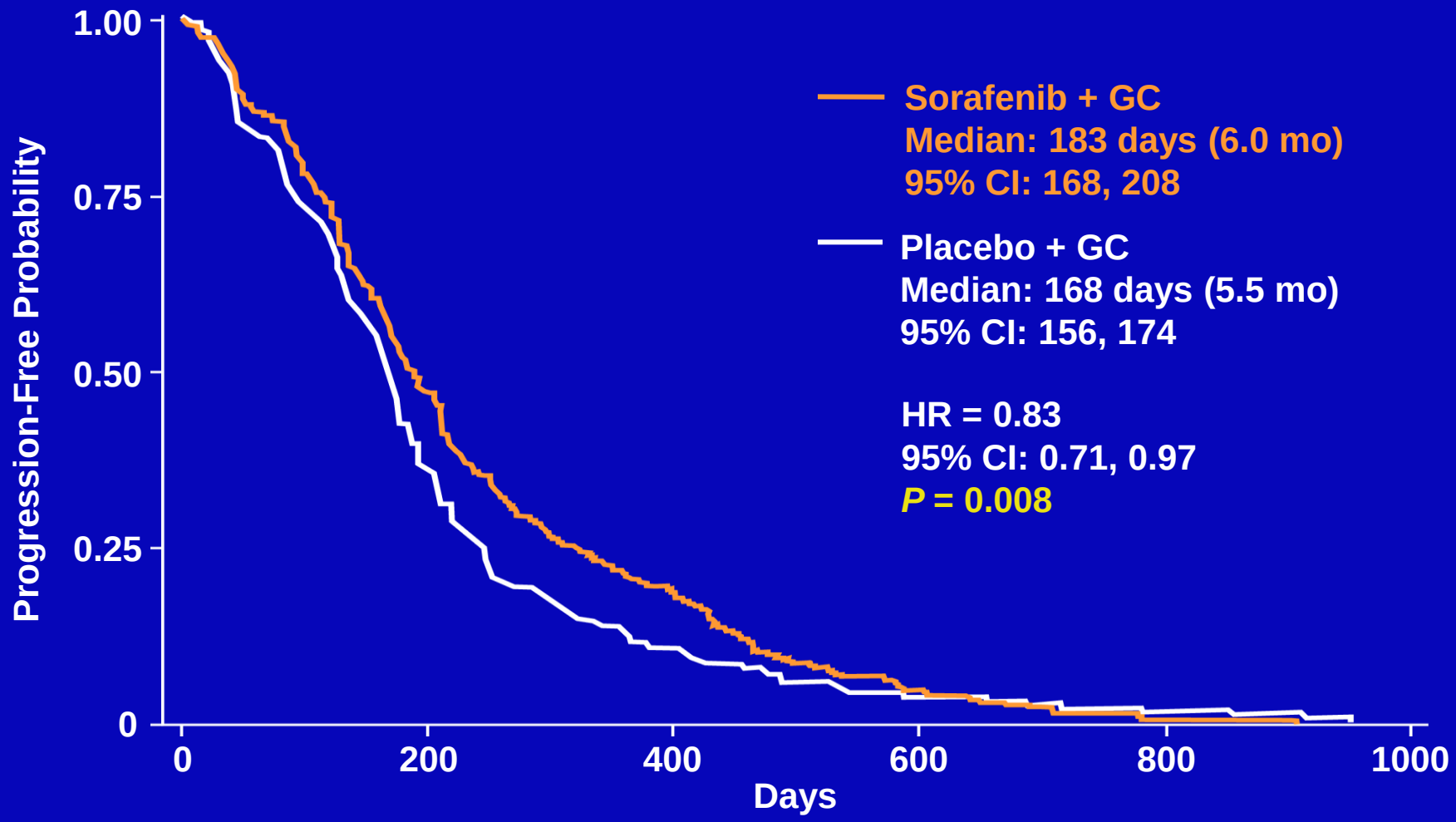
JOURNAL OF CLINICAL ONCOLOGY

NEXUS Overall Survival
Non-Squamous Population (ITT)



Gatzemeier U et al ESMO 2010 Ann Oncol 2010 S8 LBA 16

NEXUS: Progression-Free Survival
Non-Squamous Population (ITT)

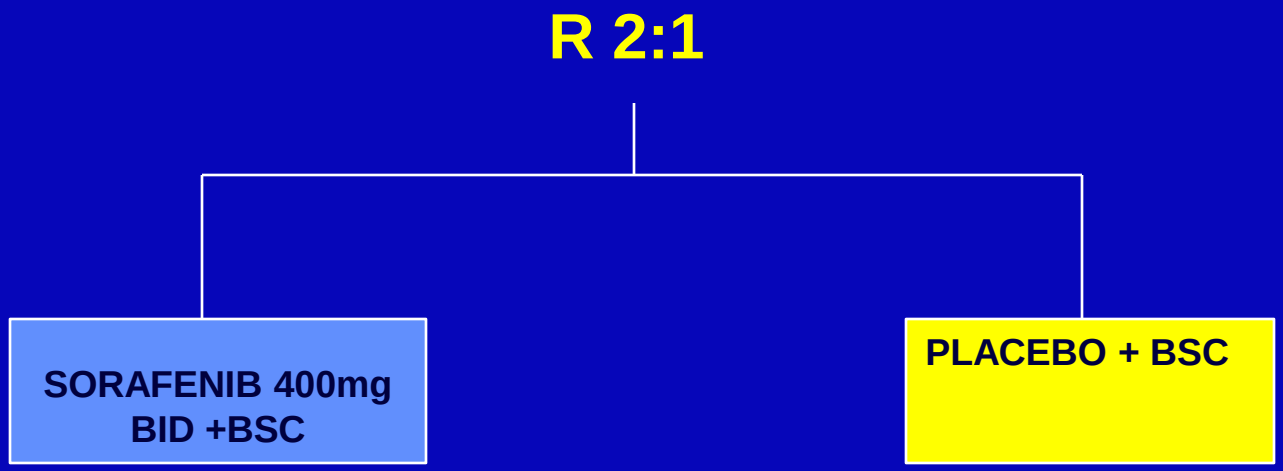


Gatzemeier U et al ESMO 2010 Ann Oncol 2010 S8 LBA 16

Anti-angiogenic TKI in mNSCLC

Sorafenib (anti VEGFR 1, 2, 3, PDGFR, c-KIT, BRAF, RAF1, Flt-3)

- **MISSION:**
  - On going randomized (2:1) phase III
  - 3rd-4th line non-squamous NSCLC
  - 703 patients, closed to accrual
  - 1st End-Point: OS



Anti-angiogenic TKI in mNSCLC

Sunitinib (anti VEGFR 1, 2, 3, PDGFR, c-KIT, RET, Flt-3)

- **Early phase trials**
  - Phase II single agent (4/6w), all histologies, n=63*
  - > 2 lines 41%
  - 1st EP: ORR 11%, DCR 40%
  - 2nd EP: PFS 12w, OS: 23w

  - Phase II single agent cont'd dosing, all histologiesn= 47**
  - > 2 lines 53%
  - 1st EP: ORR 2%, DCR 25%
  - 2nd EP: PFS 12w, OS 37w

* Socinski M et al JCO 2008 650

** Novello S et al BJC 2009 1543

Anti-angiogenic TKI in mNSCLC
Vandetanib (Zactima) (anti VEGFR 1, 2, 3, RET)

The VANDETANIB SAGA

- 4 randomized trials
- A total of > 4000 patients
  - ZODIAC
  - ZEAL
  - ZEST
  - ZEPHYR

Anti-angiogenic TKI in mNSCLC

Vandetanib (Zactima) (anti VEGFR 1, 2, 3, RET)

2nd line trials with chemotherapy

	ZODIAC*		ZEAL**	
	Vandetanib + Docetaxel N=694	Placebo + Docetaxel N=697	Vandetanib + Pem N=256	Placebo + Pem N=278
PFS	4.0 m	3.2 m	17.6 w	11.9 w
HR (p value)	0.79 (0.001)		0.86 (0.108)	
OS m	10.6	10	10.0	9.2
HR p value	0.91 (0.196)		0.86 (0.219)	

* Herbst R et al. The Lancet Oncol 2010 619

**de Boer R et al. JCO 2011 1067

Anti-angiogenic TKI in mNSCLC

Vandetanib (Zactima) (anti VEGFR 1, 2, 3, RET)

	ZEST* 2nd line and more		ZEPHYR** post EGFR	
	Vandetanib N=623	Erlotinib N=617	Vandetanib N=617	Placebo N=307
PFS	2.6 m	2.0 m	1.9 m	1.8 m
HR (p value)	0.98 (0.721)		0.63 (0.001)	
OS m	6.9	7.8	8.5	7.8
HR p value	1.01 (0.830)		0.95 (0.527)	

* Natale R et al. JCO 2011 1059

**Lee JS et al. JCO 2012 1114

Anti-angiogenic TKI in the treatment NSCLC

- Long list of drugs with similar targets, most often multi-TKI
- All trials in phase III have failed to meet their primary end-point
- Totalizing 8927 patients!

Anti-angiogenic TKI in the treatment NSCLC

- Long list of drugs with similar targets, most often multi-TKI
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- Totalizing 8927 patients!

- In most of the cases:
  - Patients were unselected
  - Early single agent in late line provided a weak signal
  - No predictive biomarker identified

Anti-angiogenesis therapy in the treatment NSCLC: Questions

- Is angiogenesis an appropriate target in NSCLC?
  - Bevacizumab approved
  - Aflibercept failed
  - All anti-angiogenicTKI failed so far in NSCLC
    - But work in other solid tumors!

- Should they be used sequentially after CT rather than concurrently with chemotherapy?
- What is the role of VEGFR gene polymorphism or mutation?