ESMO Briefing

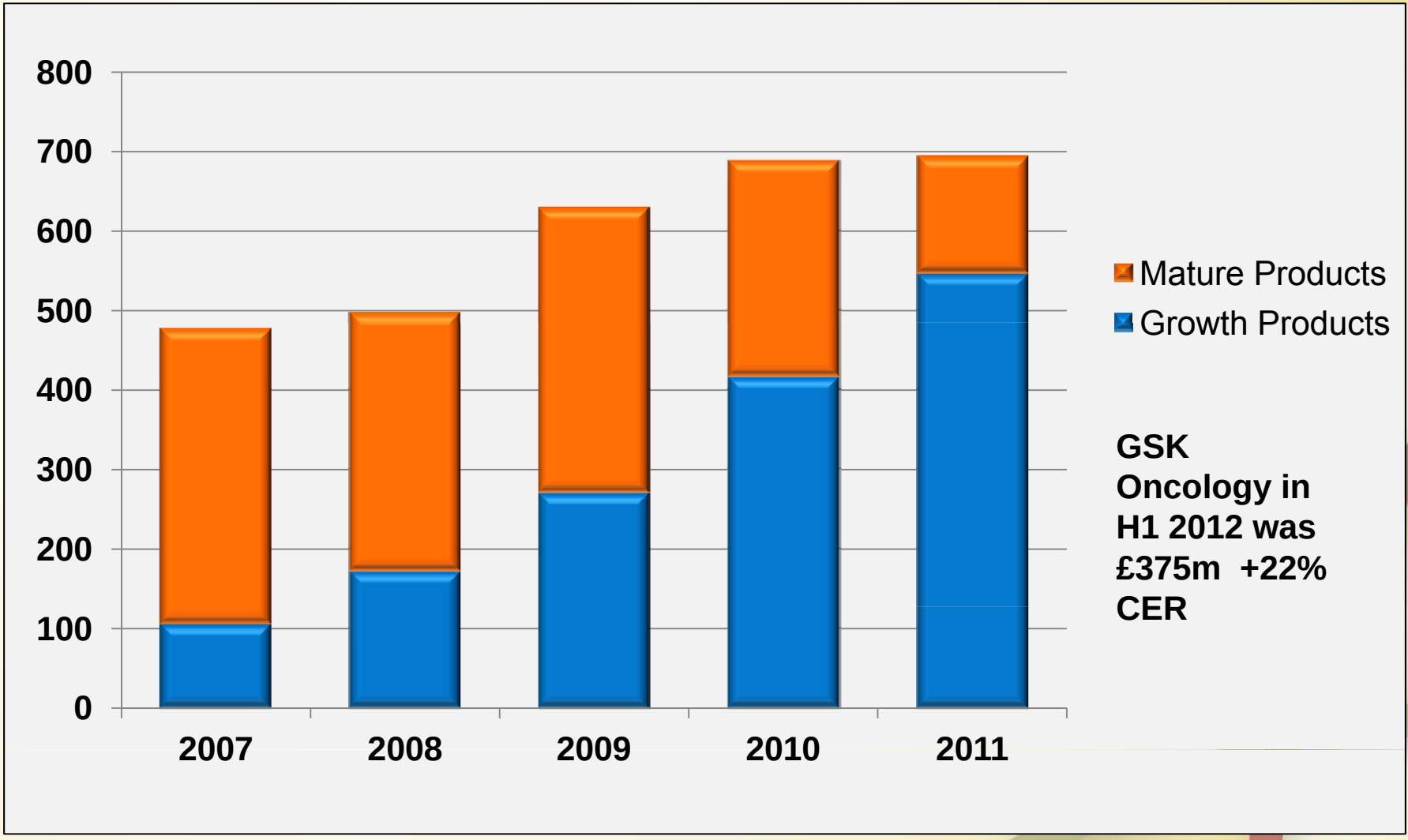
Paolo Paoletti, MD
President, GSK Oncology

Since ASCO

- Promacta/Revolade ® study in aplastic anaemia published in New England Journal of Medicine
- Withdrawal of Tykerb/Tyverb ® FDA application for dual blockade
- EU approval for Votrient ® in advanced soft tissue sarcoma
- Dabrafenib monotherapy submissions in US and EU
- Trametinib monotherapy submission in US
- Submission of PMA for companion diagnostic by bioMerieux

gsk GlaxoSmithKline Oncology

Our Growth


800
700
600
500
400
300
200
100
0
2007
2008
2009
2010
2011
Mature Products
Growth Products
GSK Oncology in H1 2012 was £375m +22% CER

Key ESMO Highlights

- Combination Dabrafenib+Trametinib
  - Randomised, open-label data for dabrafenib alone vs combination in pts with BRAF V600 mutation-positive metastatic melanoma
- Votrient®
  - Results of the COMPARZ trial
  - Results of HRQoL data from PALETTE
  - Quality of life (QoL) in renal cell carcinoma patients in a randomised double blind cross-over patient preference study of pazopanib versus sunitinib
- Tykerb/Tyverb ®
  - Results from CEREBEL (Tykerb/Tyverb plus capecitabine vs. Trastuzumab plus capecitabine)
- PRAME
  - Immunogenicity and safety of the PRAME cancer immunotherapeutic in metastatic melanoma : phase I/II dose escalation study

gsk GlaxoSmithKline Oncology

Dabrafenib+Trametinib Phase II Randomised Data: Study 113220

Dr. Georgina Long, BSc, PhD, MBBS, FRACP

Westmead Hospital and the Melanoma Institute Australia

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

Keith T. Flaherty, M.D., Jeffery R. Infante, M.D., Adil Daud, M.D., Rene Gonzalez, M.D., Richard F. Kefford, M.D., Ph.D., Jeffrey Sosman, M.D., Omid Hamid, M.D., Lynn Schuchter, M.D., Jonathan Cebon, M.D., Ph.D., Nageatte Ibrahim, M.D., Ragini Kudchadkar, M.D., Howard A. Burris, >III, M.D., Gerald Falchook, M.D., Alain Algazi, M.D., Karl Lewis, M.D., Georgina V. Long, M.D., Ph.D., Igor Puzanov, M.D., M.S.C.I., Peter Lebowitz, M.D., Ph.D., Ajay Singh, M.D., Shonda Little, M.P.H., Peng Sun, Ph.D., Alicia Allred, Ph.D., Daniele Ouellet, Ph.D., Kevin B. Kim, M.D., Kiran Patel, M.D., M.B.A., and Jeffrey Weber, M.D., Ph.D.

September 29, 2012 | DOI: 10.1056/NEJMoa1210093

gsk GlaxoSmithKline Oncology

Randomised Phase II study of BRAF inhibitor dabrafenib vs combination with MEK inhibitor trametinib in BRAF V600 mutant metastatic melanoma

G.V. Long, J. Sosman, A. Daud, J. Weber, K. Flaherty, J. Infante, O. Hamid, L. Schuchter, J. Cebon, I. Puzanov, A. Algazi, R. Kudchadkar, K. Lewis, W. Hwu, R. F. Kefford, P. Sun, S. Little, R. Gonzalez, K. Patel, K.B. Kim

VIENNA 2012 ESMO congress

www.esmo2012.org

Rationale for Combination

BRAFi (dabrafenib)
PFS 5.1 mo; RR 53%[1]

MEKi (trametinib)
OS HR 0.54 v chemo
PFS 4.8 mo; RR 22%[2]

Preclinical BRAFi +MEKi
Delays BRAFi resistance
↓ Hyperproliferative skin AE

1. Hauschild A, *Lancet* 2012; 2. Flaherty K, *NEJM* 2012

Part C Randomised Phase II Study Design

- BRAF $V600^{E/K}$ metastatic melanoma
- No prior BRAFi or MEKi
- Up to 1 prior treatment
- Treated and stable brain mets

N=162

RANDOMISE

Monotherapy D 150mg BID*
N= 54

Combination D+T 150/1
N= 54

Combination D+T 150/2
N= 54

*cross over to Combination D+T 150/2 after progression allowed

Objectives

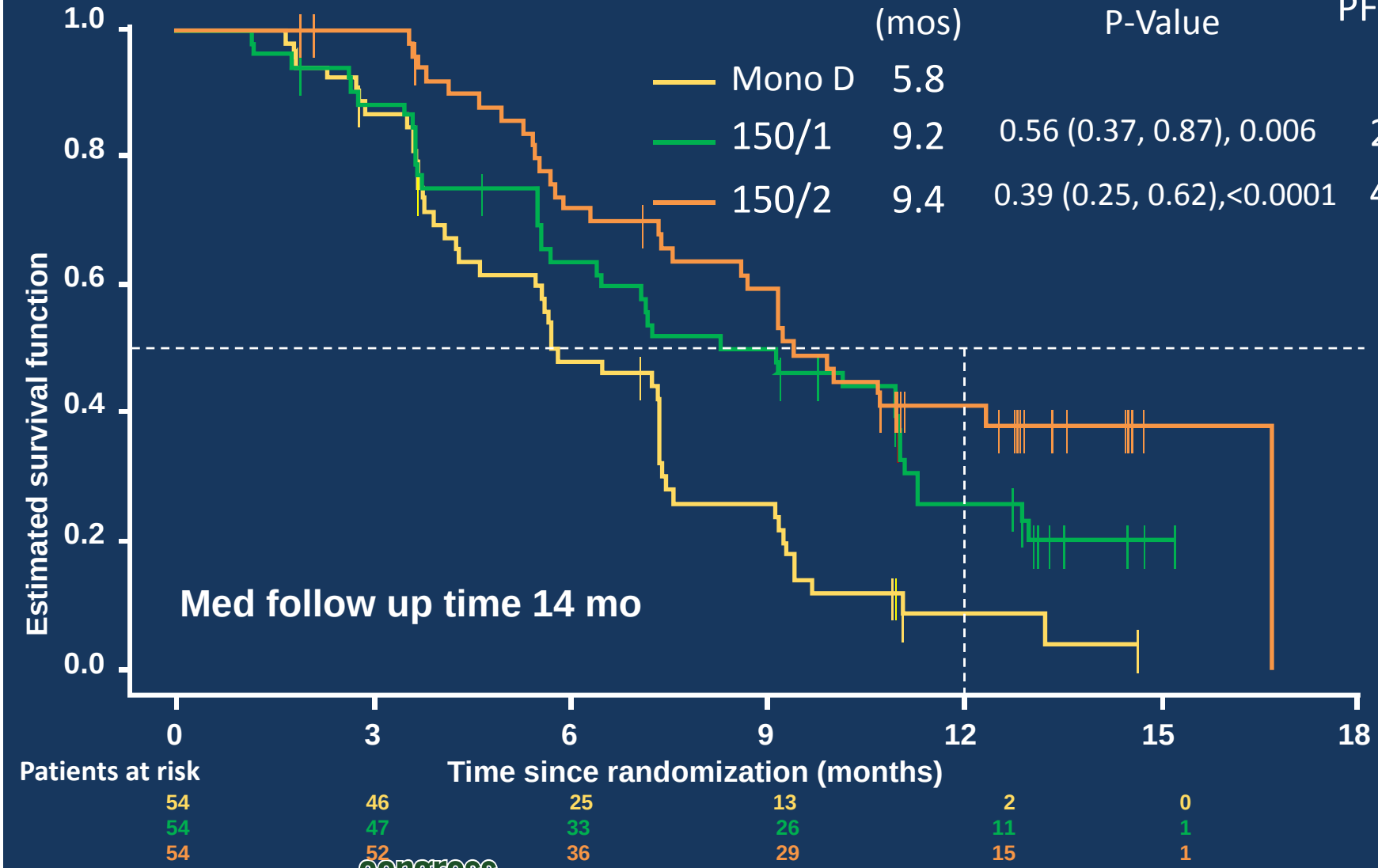
- PFS, ORR, duration of response, incidence rate of cuSCC and safety
- OS

Confirmed Response Rate

	Mono D (N=54)	Combination D+T 150/1 (N=54)*	Combination D+T 150/2 (N=54)
CR	2 (4)	3 (6)	5 (9)
PR	27 (50)	24 (44)	36 (67)
SD	22 (41)	24 (44)	13 (24)
PD	3 (6)	2 (4)	0
Response Rate†	29 (54%)	27 (50%) p=0.77	41 (76%) p=0.026
Duration of Response Months (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, NA)	10.5 (7.4, 14.9)

*1 patient in 150/1 group was not evaluable

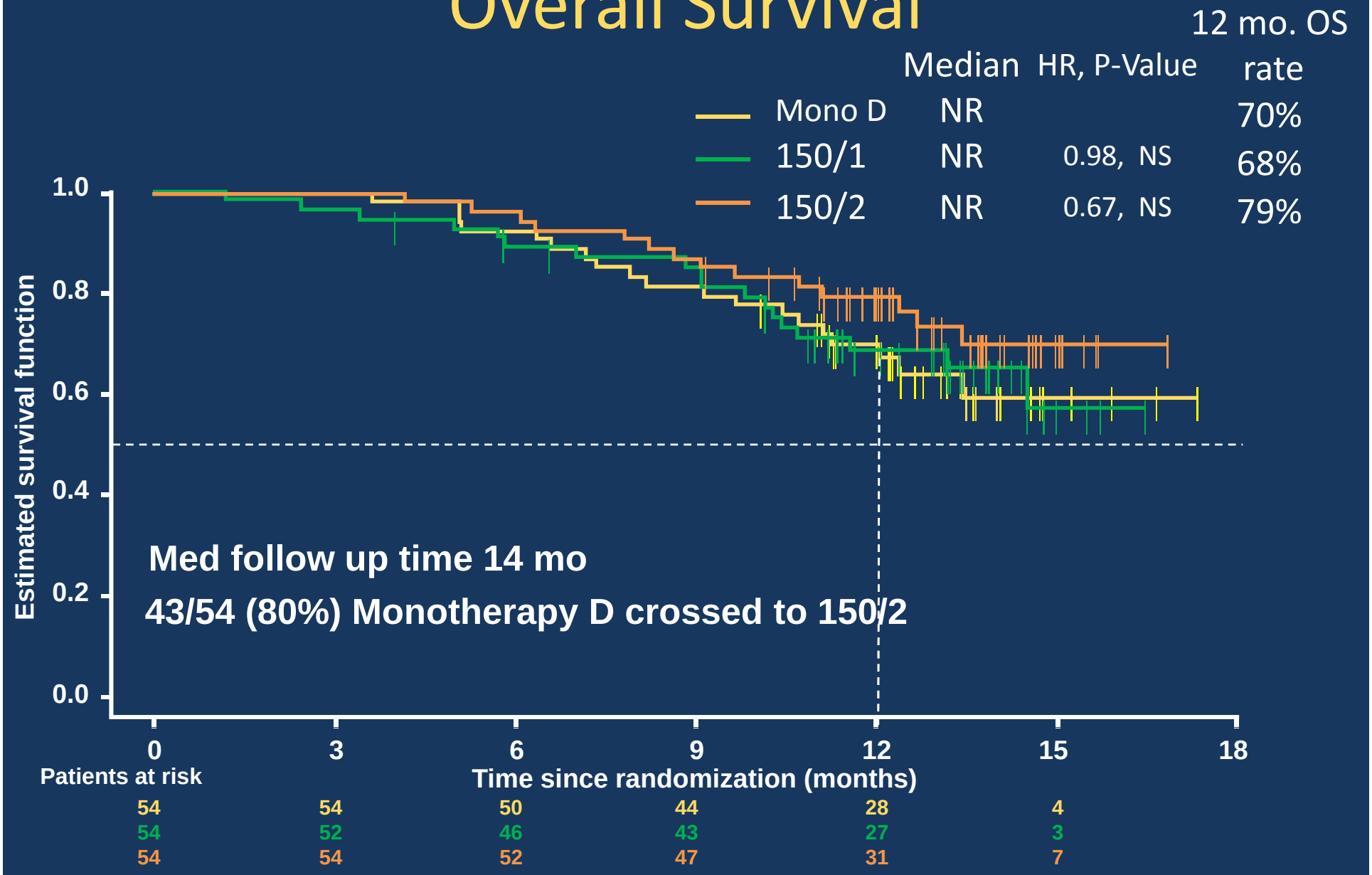
Progression-Free Survival



VIENNA 2012 ESMO congress

www.esmo2012.org

Overall Survival



VIENNA 2012 ESMO congress

www.esmo2012.org

MEKi and BRAFi Associated Adverse Events

	Monotherapy D (n=53)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=55)
Alopecia	16 (30)	2 (4)	3 (5)
Skin papilloma	8 (15)	4 (7)	2 (4)
Hyperkeratosis	16 (30)	3 (6)	5 (9)
Squamous cell carcinoma/ keratoacanthoma P-value	10 (19)	1 (2) 0.004	4 (7) 0.09
Actinic keratosis	5 (9)	4 (7)	8 (15)
Rash/Skin toxicities*	36 (68)	31 (57)	36 (65)
Acneiform rash	2 (4)	6 (11)	9 (16)
Peripheral Oedema	4 (8)	9 (17)	11 (20)
↓ Ejection Fraction	0	2 (4)	5 (9)
Chorioretinopathy	0	0	1 (2)

*Skin toxicities include multiple terms
No cases of RVO

Treatment-Related AEs ≥ 20% (All Grades)

	Monotherapy D (n=53*)	Combination D+T 150/1 (n=54)	Combination D+T 150/2 (n=55*)
Pyrexia†	12 (23)	34 (63)	37 (67)
Chills	9 (17)	22 (41)	28 (51)
Night Sweats	3 (6)	8 (15)	12 (22)
Fatigue	18 (34)	25 (46)	25 (45)
Arthralgia	14 (26)	22 (41)	14 (25)
Myalgia	9 (17)	11 (20)	11 (20)
Vomiting	6 (11)	15 (28)	19 (35)
Nausea	9 (17)	18 (33)	18 (33)
Diarrhoea	12 (23)	8 (15)	17 (31)

† pyrexia = temperature ≥ 38.5 degrees Celsius
*Mono D (n=53) - 1 patient in this arm received Combination D+T 150/2 (n=55) due to a dispensing error

Conclusions

- This is the 1st kinase-kinase combination to:
  - Show enhanced anti-tumour activity over the single agent
  - Reduce specific oncogenic toxicities, with biological rationale
- Combined dabrafenib and trametinib prolongs PFS and ORR over dabrafenib alone in $BRAF^{V600}$ metastatic melanoma:
  - Med PFS 9.4 mo vs 5.8 mo; HR 0.39; p<0.0001
  - ORR 76% vs 54%; p=0.026
- Combined dabrafenib and trametinib safety profile was tolerable and manageable:
  - ↓cuSCC events
  - ↑ pyrexia, neutropenia and GI toxicities
- Two phase III studies (COMBI-d and COMBI-v) are ongoing

COMPARZ

Dr. Paul Nathan MBBS, PhD, FRCP
Consultant Medical Oncologist
Director R&D
Mount Vernon Cancer Centre, UK

Study Objectives

Primary

- To evaluate and compare PFS in patients treated with pazopanib to those treated with sunitinib

Secondary

- Overall survival (OS)
- Objective response rate (ORR)
- Safety
- Patient-reported outcomes

Study Design

Key Eligibility Criteria

- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS ≥ 70
- Adequate organ function

Randomized 1:1

Pazopanib
800 mg qd
continuous dosing
Dose reductions to
600 mg or 400 mg

Sunitinib
50 mg qd
4 wk on/2 wk off
Dose reductions to
37.5 mg or 25 mg

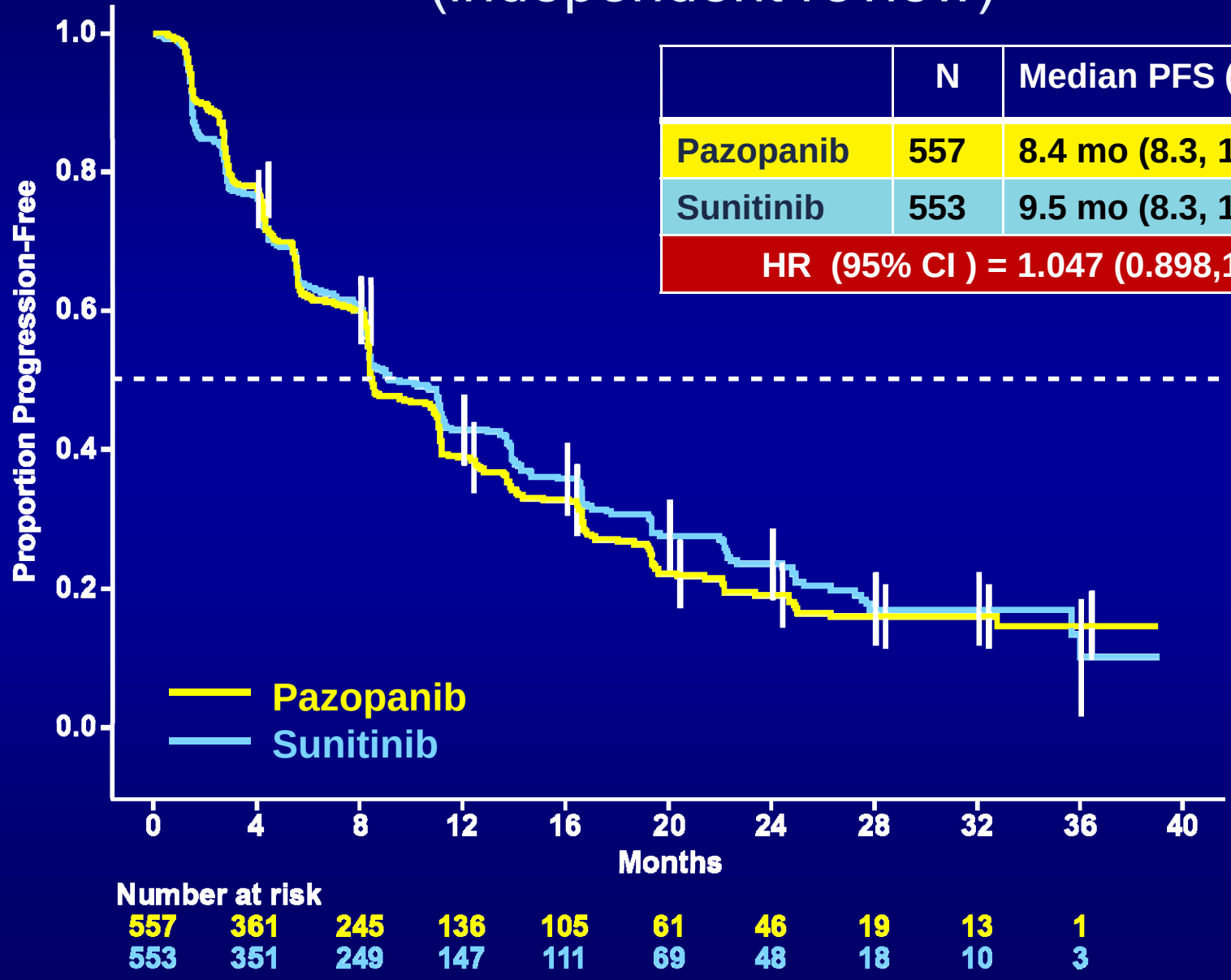
Stratification Factors

- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs ≤1.5×ULN

Statistical Analysis Plan

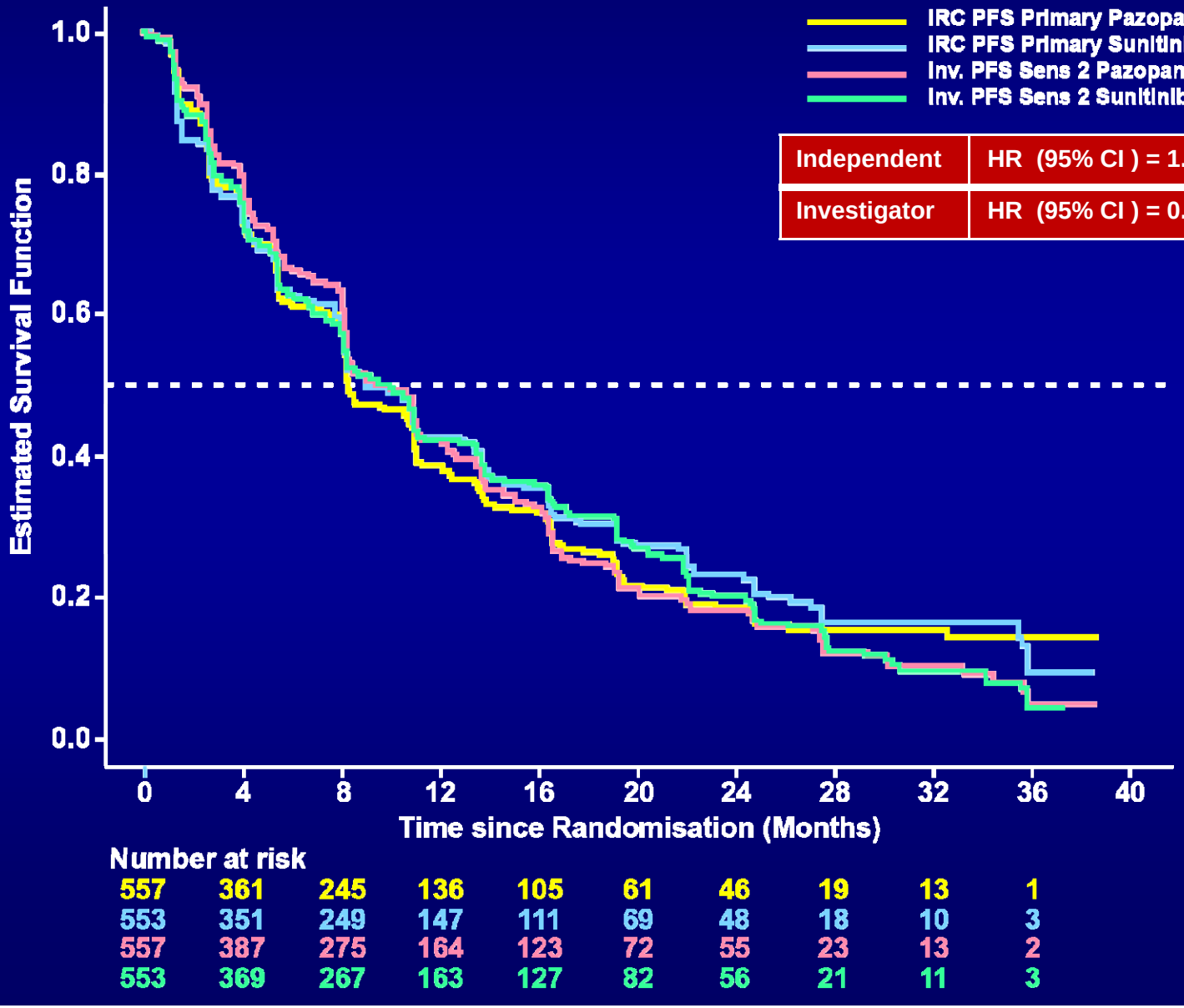
- PFS non-inferiority demonstrated if upper bound of 95% CI for HR<1.25
  - Cox proportional hazard analysis adjusted for stratification factors
  - By independent review
- 631 PFS events needed for 80% power
- Planned enrollment of 1100 patients

Primary Endpoint: Progression-free Survival (independent review)



	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		

Primary Endpoint: Progression-free Survival (independent and investigator review)



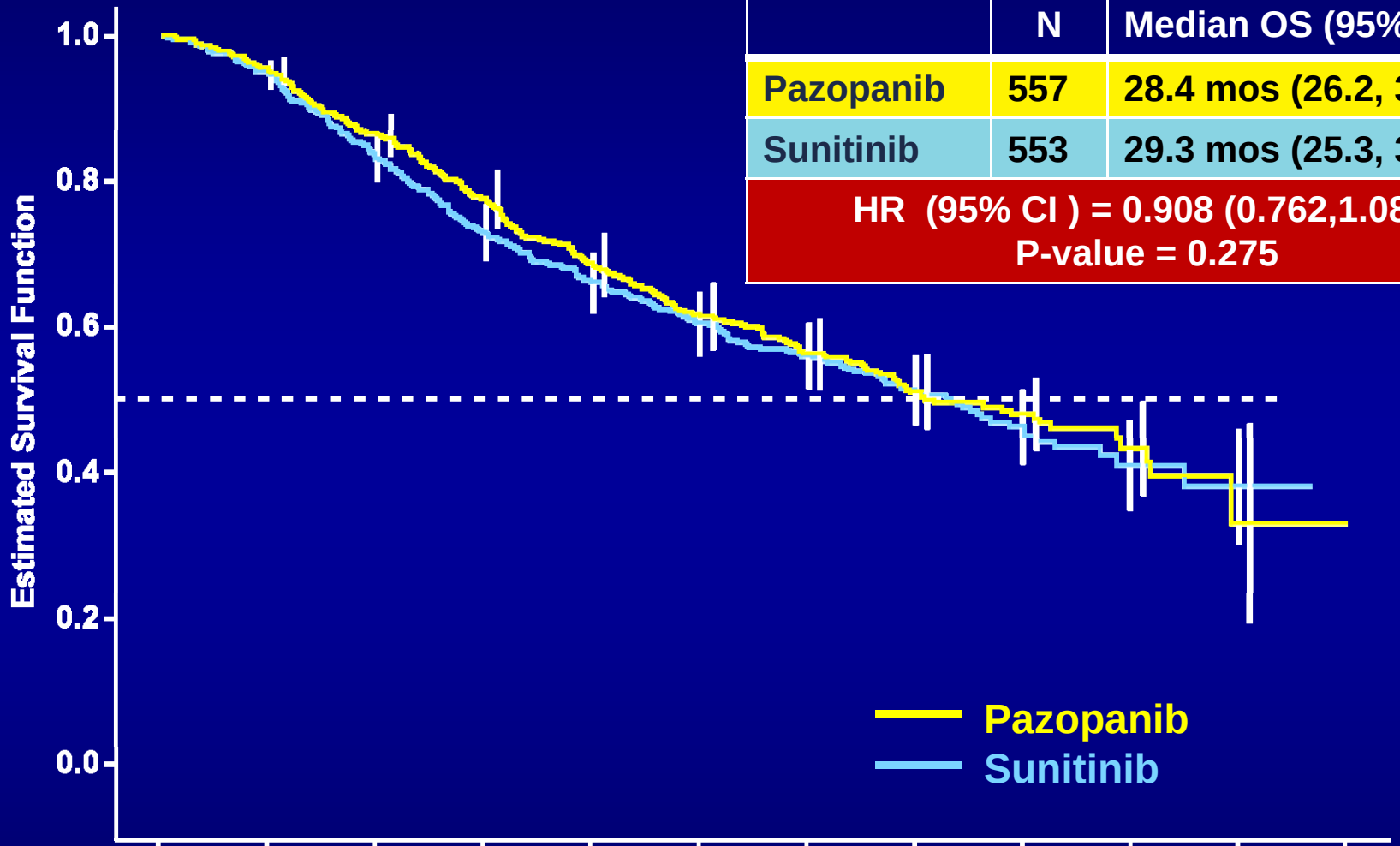
Independent	HR (95% CI) = 1.047 (0.898,1.220)
Investigator	HR (95% CI) = 0.998 (0.863,1.154)

Best Response by RECIST 1.0 (independent review)

	Pazopanib (n = 557)	Sunitinib (n = 553)
Best overall response, %		
Complete response (CR)	<1	<1
Partial response (PR)	31	24
Stable disease	39	44
Progressive disease	17	19
Not evaluable	13	12
Objective Response Rate, %	31	25
95% CI	26.9, 34.5	21.2, 28.4
P value	**0.032**	

Interim Analysis of Overall Survival

	N	Median OS (95% CI)
Pazopanib	557	28.4 mos (26.2, 35.6)
Sunitinib	553	29.3 mos (25.3, 32.5)
HR (95% CI) = 0.908 (0.762,1.082) P-value = 0.275		



Number at risk

557	521	458	384	327	274	223	142	82	28	3
553	501	431	354	313	269	225	148	69	28	3

Most Common Adverse Events

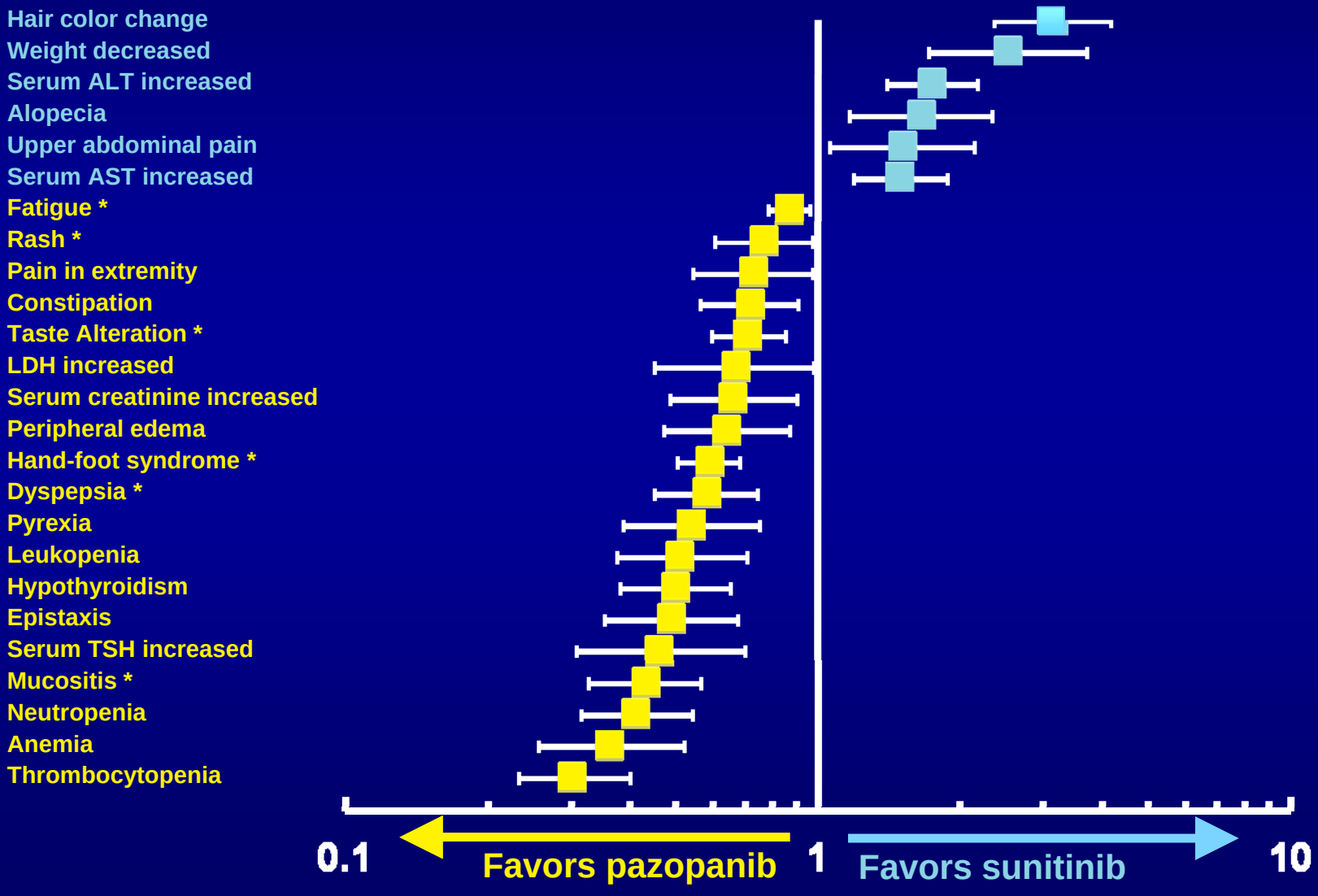
	Pazopanib (n = 554) %	Sunitinib (n = 548) %
Adverse Event [a]	**All Grs**	**All Grs**
Any event [b]	>99	>99
Diarrhea	63	57
Fatigue	55	63
Hypertension	46	41
Nausea	45	46
Decreased appetite	37	37
ALT increased	31	18
Hair color changes	30	10
Hand-foot syndrome	29	50
Taste Alteration	26	36
Thrombocytopenia	10	34

[a] AE ≥30% in either arm

[b] 2% of patients in pazopanib arm and 3% of patients in sunitinib arm had grade 5 adverse events.

Relative Risk in Adverse Events

AE occurrence ≥10% in either arm; 95% CI for RR does not cross 1



Quality of Life Results (first 6 months)

Instrument	Domain Name	Treatment difference in mean change vs sunitinib[1]	P -value
FACIT-F	Fatigue/Total score	**2.32**	**<0.001**
FKSI-19	Kidney Symptom Index/Total score	**1.41**	**0.018**
	Physical	**0.78**	**0.027**
	Emotional	–0.05	0.409
	Treatment Side Effects	**0.31**	**0.033**
	Functional Well Being	**0.31**	0.098
Cancer Treatment Satisfaction Questionnaire	Expectations of Therapy	**1.41**	0.284
	Feelings about Side Effects	**8.50**	**<0.001**
	Satisfaction with Therapy	**3.21**	**<0.001**
Supplemental Quality of Life Questionnaire	Three items on Mouth and Throat Soreness (MTS), Hand soreness (H) and Foot soreness (F)	**–0.505**	**<0.0001**
		–0.204	**0.0016**
		–0.267	**0.0008**
	Two items on limitations due to MTS and F	**0.94**	**<0.001**
		0.65	**0.014**

[1] **Yellow Font**: favors pazopanib. Blue Font: favors sunitinib
P-value <0.05 is statistically significant

Conclusions

- This phase III trial demonstrates non-inferiority of pazopanib relative to sunitinib for progression-free survival
- Pazopanib efficacy is further supported by similar response rates and overall survival
- The differentiated safety profile of pazopanib includes:
  - Lower incidence of hand-foot syndrome, fatigue, and mucositis
  - Higher incidence of liver function test abnormalities
- Improved tolerability supported by better QoL scores for patients receiving pazopanib

Questions?