Genitourinary Tumors Renal Cancer Abstracts 791-794

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Disclosures

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793	RJ Motzer	Axitinib vs Sorafenib for advanced renal cell carcinoma: phase III overall survival results and analysis of prognostic factors
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Why CAF's?

CAF	FUNCTIONS
Osteopontin[1] Phosphoglyco-protein	involved in tumor progression by mediating cell adhesion/proliferation, inflammation, complement evasion, metastasis, angiogenesis

1.Bellahcene A et al., Nat Rev Cancer 2008; 2.Yuqi Guo et al., Cancer Treatment reviews 2012;3.Negrier S et al., J Clin Oncol 2004 ; 4.Xie P et al., Cytokine and Growth Factors Reviews 2001;5.Huang D et al., Cancer Res 2012

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IL-6[2]: glycoprotein	produced by various types of cells including cancer cells, wide range of biological activities: cell-proliferation, progression via inhibition of apoptosis, pro-angiogenic, association with poor outcome[3]

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IL-8[4]: member of the CXC chemokine family	Expression in various cancers, mitogenic, pro-angiogenic, motogenic for neutrophils, macrophages, mediates sunitinib-resistance[5]

1.Bellahcene A et al., Nat Rev Cancer 2008; 2.Yuqi Guo et al., Cancer Treatment reviews 2012;3.Negrier S et al., J Clin Oncol 2004 ; 4.Xie P et al., Cytokine and Growth Factors Reviews 2001;5.Huang D et al., Cancer Res 2012

Lancet Oncol. 2012 Aug;13(8):827-37.

Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials

Tran HAT, Liu Y, Zurita AJ, Lin Y, Baker-Neblett KL, Martin AM, Fliglin RA, Hutson TE, Sternberg CN, Amado RG, Pandite LN, Heymach JV

- *3 step approach to investigate the value of candidate plasma signature including CAFs for prediction of PFS and OS benefit in mRCC-patients treated with pazopanib[1]*

  - *High levels of IL-6, IL-8 and Osteopontin=negative prognostic factors*
  - *IL-6 predictive of greater relative benefit from pazopanib*

Multivariate analysis of cytokines and angiogenic factors and established prognostic parameters in mRCC-patients receiving pazopanib or placebo:

Amado J. Zurita et al, Poster 791PD

- **Ongoing work:** are these CAFs are still of prognostic significance relative to established clinical parameters in patients receiving pazopanib?

Progression-Free Survival by CAF and Clinical Classification			
CAF		**PFS, weeks**	***P***
IL-6	Low	24.0	< 0.001
	High	9.9	
OPN	Low	24.0	< 0.0001
	High	8.4	
IL-8	Low	23.9	0.002
	High	8.4	

Multivariate Covariate Model[a]			
Time from diagnosis to treatment < 1 year	0.956	0.618 - 1.477	0.8382
Calcium > ULN	1.136	0.456 - 2.831	0.7844
Hemoglobin < LLN	1.819	1.205 - 2.747	0.0044
Neutrophils > ULN	1.947	1.137 - 3.333	0.0151
Platelets > ULN	0.915	0.564 - 1.484	0.7185

Value of OPN and IL-6 when adjusted for Hemoglobin and Neutrophils

- <u>OPN and IL-6 in the placebo-arm</u>
  - OPN high vs low: 7.9 vs 24 weeks (p=0.034)
  - IL-6 high vs low: 7.9 vs 24.1 weeks (p=0.03)

  and
- <u>OPN alone in the Pazopanib-arm</u>
  - OPN high vs low: 31.3 vs 56.4 weeks, (p=0.0007)

IL-6 becomes a borderline predictive marker (*P* = 0.08)

[a] Adjusted for risk factors of hemoglobin < LLN and neutrophils > ULN as covariates

None of the Three Clinical Classifications was as Strong a Prognostic Marker as the CAFs

Progression-Free Survival by CAF and Clinical Classification

CAF		PFS, weeks	*P*	Clinical Classification		PFS, weeks	*P*
IL-6	Low	24.0	< 0.001	**ECOG**	0	18.4	0.144
	High	9.9			1	13.0	
OPN	Low	24.0	< 0.0001	**MSKCC**	Good	24.0	0.011
	High	8.4			Interm/Poor	12.1	
IL-8	Low	23.9	0.002	**Heng**	Good	24.3	0.139
	High	8.4			Interm/Poor	12.6	

Clinical Implications?

- **demonstrates** that CAFs are among the most reliable markers to estimate the course of the disease
  - **confirms** that CAFs are strongly involved in the biological behaviour[1-5]
- However**: data still prognostic rather than predictive:**
- **In clinical practice**, levels of IL-6, IL-8 and OPN…:
  - may not influence the treatment decision (yes vs no): less benefit ≠ no benefit
  - may not influence the treatment choice (paz or sun): MoA quite similar, role of CAF‘s may be similar in sunitinib and pazopanib-patients
  - would rather influence the expectations regarding individual outcome

1.Bellahcene A et al., Nat Rev Cancer 2008; 2.Yuqi Guo et al., Cancer Treatment reviews 2012;3.Negrier S et al., J Clin Oncol 2004 ; 4.Xie P et al., Cytokine and Growth Factors Reviews 2001;5.Huang D et al., Cancer Res 2012

Clinical Implications Beyond Prognosis and Prediction?

The present work…

- suggests that these interactions between cytokines and tumor should no longer be therapeutically neglected
- It may be essential to endorse current treatment strategies …
  - adding IL-8 inhibitors to TKIs upon occurrence of resistance?[1]
  - using IL-6 antibodies[2] or corticoids?[3-5] ?

1.Huang D et al., Cancer Res 2010; 2. Rossi RF et al., British J Cancer 2010
3. Arai Y et al., Cancer Invest 2008; 4.Iwai A et al., Mol Cell Endocrinol 2004, 5.Schöffski P et al., Cancer Invest 2009

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Background, Methods

- Previous studies of sunitinib in metastatic RCC have shown potential correlations with circulating proteins[1,2], HIF-1α expression[3-5] , VHL gene inactivation[5-7], and germline SNPs in the promotor region of VEGF genes[6,7]

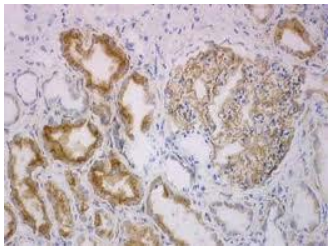
→Investigations performed in patients from the randomized phase II trial on first-line sunitinib intermittent vs continuous dosing

1. Rini BI, Michaelson MD, Rosenberg JE, et al. *J Clin Oncol 2008;26:3743–3748.*
2. Harmon CS, Figlin RA, Hutson, TE, et al. *J Clin Oncol 2011;29(Suppl.) (Abstract 10525).*
3.Muriel López C, Esteban E, Astudillo A, et al. *Invest New Drugs 2012; May 27*
4. Pena C, Lathia C, Shan M, et al. *Clin Cancer Res 2010;16:4853–4863.*
5. Figlin RA, de Souza P, McDermott D, et al. *Cancer 2009;115:3651–3660.*
6.Escudier B, Loomis AK, Kaprin A, et al. *Eur J Cancer 2011;47:S505 (Abstract 7103).*
7. Garcia-Donas J, Esteban E, Leandro-García LJ, et al. *Lancet Oncol 2011;12:1143–1150.*

Results

low Ang-2 and high MMP-2 levels correlated significantly with CR/PR when compared to SD/PD-patients in 4/2-schedule (p=0.018 and 0.02)

40 proteins investigated,
2 different platforms, only 2 proteins showed correlations with response on BOTH platforms



ICH-HIF-1α expression low vs high

Patients both schedules:
Low expression= longer PFS (p=0.034)
(ns for TTP and OS)
Schedule 4/2 alone:
low HIF-1α = longer TTP and PFS
(p=0.03 and 0.02)

- No correlation between any of the VEGF-A or VEGFR3 SNPs and outcome;
- marginal differences in TTP, PFS and OS favoring genotyped patients
- No associations with response or survival by inactivation mechanisms

Conclusions

- Based on the present data, Ang-2, MMP-2 and HIF-1α identified as potential biomarkers for further research based on their prognostic value in patients receiving sunitinib

- Unknown as to whether these biomarkers can be of predictive value, because all patients had sunitinib (no inactive comparator)

Clinical Implications: Ang2

Data suggest

- Low baseline Angiopoietin-levels may indicate that tumor angiogenesis relies primarily on VEGF rather than on the Ang2/Tie-2 axis, which is regarded as an alternative mechanism for promoting angiogenesis

➢ Low-Ang2-level-patients may therefore benefit from a VEGF-TKI

Potential for the future: could serve as a predictive marker to decide whether a patient should receive a VEGF-inhibitor or an Ang2-Inhibitor

Clinical Implications for low HIF1α-expression less clear

- The relationship between **HIF-1α expression and outcome has been discussed controversially:**

➢ *while the majority found an association between low HIF-1α-expression and outcome[1,2] some found a statistically significant association of high HIF-levels in sunitinib-responders[3]*

- Potential limitation in routine clinical practice: HIFα-antigenicity deteriorates with age of the paraffin block ($p<0.0001$)[4]
- →*important implication for biomarkers studies and real world setting*

1. Muriel Lopez C et al., Clin Genitourin Cancer 2012; 2. Dorevic G et al., J Exp Clin Cancer Res 2009;
3. Patel PH et al., ASCO 2008, abstr. 5008; 4.Biswas S et al., Carcinogenesis 2012;

Findings on HIF also create many questions

- **Difficult to understand the role of low HIF-1α-expression because HIF-1 appeared to be the „good guy“**
  - *HIF-1α: inhibitor of cell cycle progression by inhibiting c-myc-oncoprotein[1]*
  - *In VHL disease, HIF-1α expression gradually decreases whereas HIF2 expression increases upon occurrence of RCCs[2,3]*
- **What is the role of HIF-2 expression in this context?**
  - *HIF-1α and HIF-2α: overlapping effects on angiogenesis, however with distinct effects on cell metabolism and proliferation[4]*
  - *pVHL-deficient cc-RCCs expressing „only“ HIF-2α were shown to display ↑activity of c-Myc-oncoprotein → enhanced proliferation[5]*

1.Koshiji M et al., Embo J 2004; 2.Mandriota SJ et al., Cancer Cell 2002; 3.Raval RR et al., Mol Cell;
4.Shinojima T et al., Carcinogenesis 2007; 5.Gordan JD et al., Cancer Cell 2008

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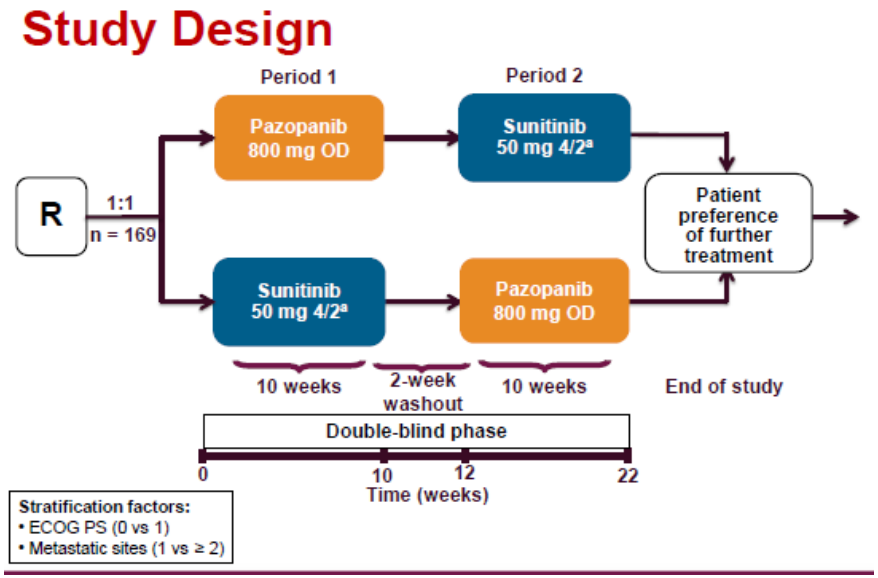
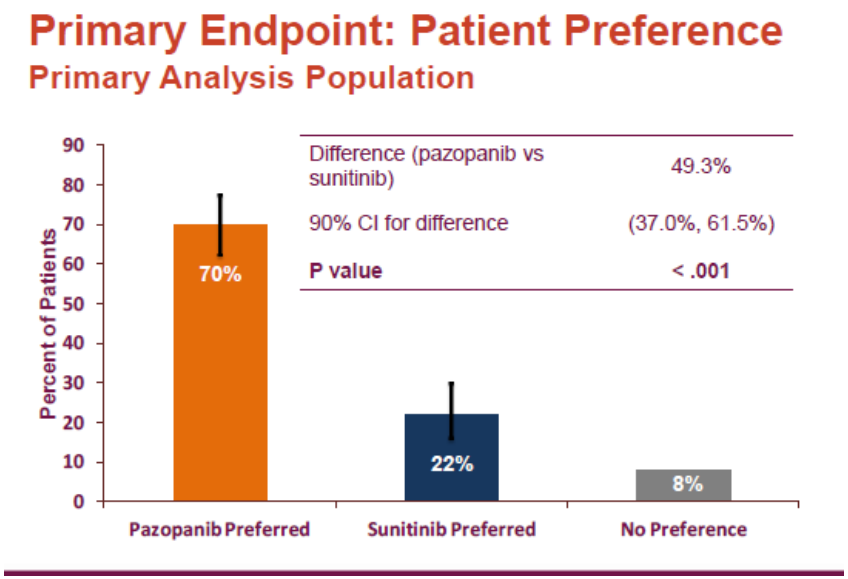
Quality of life among renal cell carcinoma patients in a randomized double-blind cross-over study of pazopanib versus sunitinib

- Recently presented results from the PISCES study reported that 70% of patients who had received both pazopanib and sunitinib treatment preferred pazopanib, whereas only 22% stated a preference for sunitinib.





Cella D et al.,
Reasons for this Patient Preference as Measured by:

- **Determination** of the
  - **primary reasons** for patient preference
  - **most common most important reason** for patient preference

- **Assessment of Quality of Life**, using the Functional Assessment of Cancer Therapy-Fatigue **(FACIT-F)**, Supplementary Quality of Life Questionnaire (assessment of worst soreness in mouth/throat/hands/fett) **(SQLQ)** and the EuroQoL Group standardized measure of health status **(EQ-5D)**

Reasons for Patient Preference

- Most common reasons
  - **for sunitinib preference:** *'diarrhoea had less impact on my life' and 'QoL was generally better'.*
  - **for pazopanib preference:** *'QoL was generally better' and 'fatigue had less impact on my life'*.

- Most common most important reason
  - for **sunitinib preference:** *'less impact of diarrhoea',*
  - for **pazopanib preference:** *'fatigue had less impact on my life'.*

Patient-Reported QoL Crossover Analyses

Favored pazopanib over sunitinib on:

- Fatigue
- Foot soreness
- Hand soreness
- Mouth/throat soreness

Interpretation of Findings, Clinical Implications and Consequences (1)

- **Data need to be interpreted in the context of efficacy data (COMPARZ: LBA 8, Presidential Symposium II, 17.15 Hall A)**
- ↓Timing of assessment of patient‘s preference clearly unfavoured sunitinib: end of week 22=day 28 in a sunitinib cycle!
  - Were the patients informed that side effects (including HFS/ fatigue) are regarded as predictive of efficacy? How would preference then look like?*
- ↑Assessment of QoL (baseline and then every 2 weeks) well balanced for timing
  - The fact that HRQoL favored pazopanib for fatigue, foot/hand soreness and mouth/throat soreness is consistent with most real world observations that pazopanib has less „off-target“-side effects

*Poster 7850 by Donskov F et al, proffered paper session 14.00 Hall D

Interpretation of Findings, Clinical Implications and Consequences (2)

- →Data should not lead to the general perception that one drug is safe, the other not…! Individualized toxicity management remains a critical factor for occurrence and severity of AE‘s
- → Results underline that some side effects are still difficult to manage: e.g. fatigue, stomatitis
- ↓ In contrast: the relevance of HFS in this study appears surprising: HFS should not be an issue anymore after 6 years experience with TA
- → Interesting observation: among the various AE‘s of TKIs, only few are relevant for QoL

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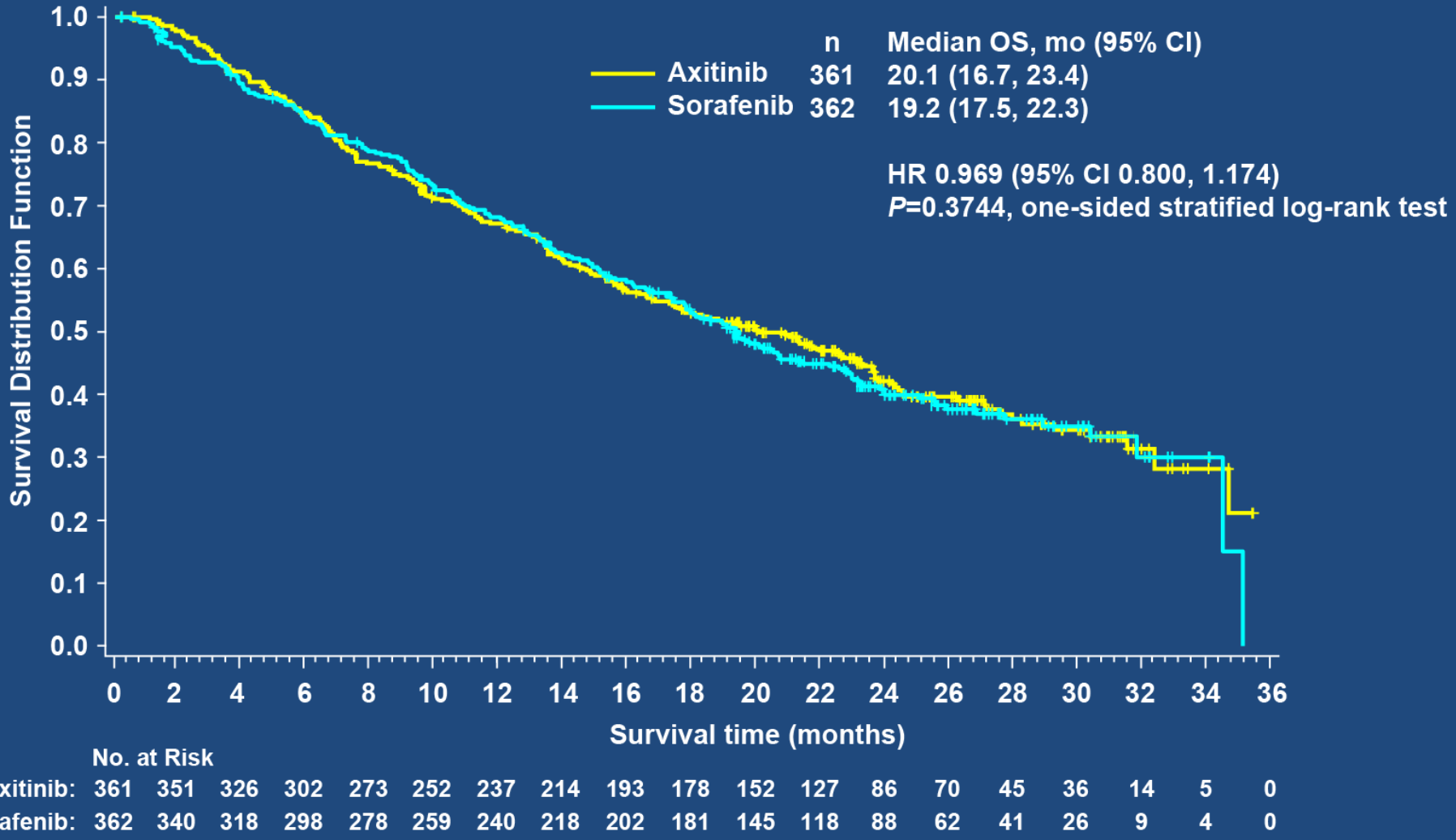
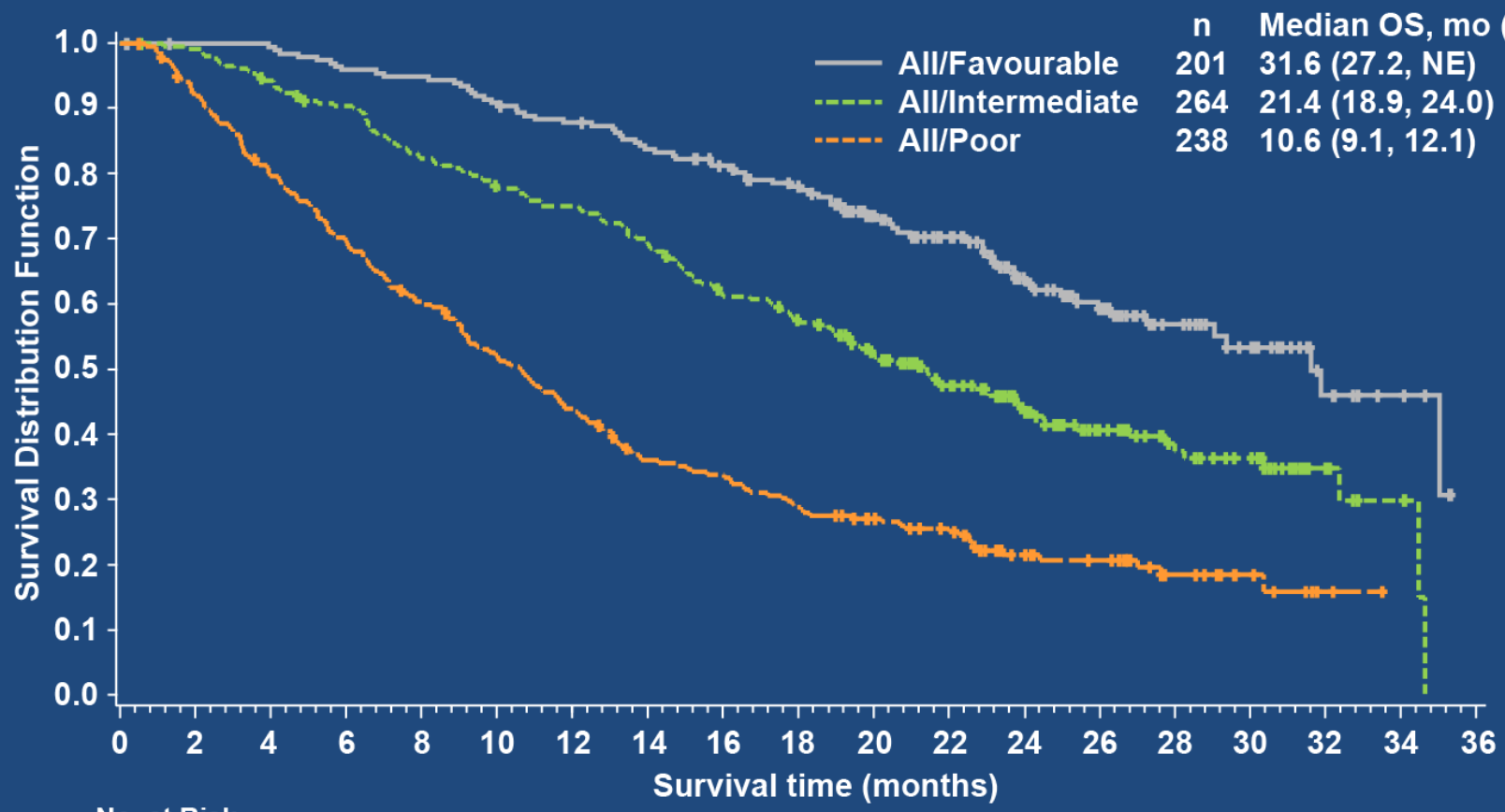
In terms of PFS, 2nd-line axitinib superior to 2nd-line sorafenib →overall survival ?



Kaplan-Meier estimates of OS by MSKCC risk score in overall trial population



No. at Risk

Favourable:	201	198	197	190	188	180	173	164	155	144	116	99	73	58	39	28	12	5	0
Intermediate:	264	261	247	235	214	202	194	179	157	145	121	94	69	48	33	26	9	4	0
Poor:	238	217	186	163	139	120	101	80	75	64	55	48	30	25	14	8	2	0	0

Multivariate Analysis: Identified Baseline Prognostic Factors for OS (AX and SOR)

1. **Type of prior therapy (cytokine vs non-cytokine)**
2. ECOG 0 vs 1
3. Time from diagnosis to treatment on AXIS 1 vs ≥1 year
4. Number of metastatic sites 1 vs >1
5. Liver metastases yes/no
6. Bone metastases yes/no
7. Corrected calcium > vs ≤ 10 mg/dl
8. Alkaline Phosphatase >ULN vs ≤ ULN
9. LDH > 1.5 x ULN vs ≤ 1.5 x ULN
10. Hemoglobin < LLN vs ≥ LLN
11. Neutrophils >ULN vs ≤ ULN

Clinical Implications and Conclusions (1)

- Similar overall survival of 2 active agents is NOT disappointing: median overall survival beyond 20 months in **second-line** mRCC-treatment demonstrates the progress that has been made with TA in the last years
- PFS is an accepted endpoint in first-line mRCC treatment, correlations of PFS and OS were found[1,2], it remains unclear whether this applies to second-line
- Data of patients without subsequent treatment may be of interest

1.Delea TE et al., J Clin Oncol 2009;27; 2.Heng DY et al., Cancer 2011

Clinical Implications and Conclusions

- Data demonstrate that
  - prior treatment and tumor/disease related factors are more relevant for survival than the type of TKI
  - **During treatment: development of hypertension is critical for successful outcome (both agents)→Treat to hypertension?**

- Sorafenib better than expected
  - (SOR+intermediate risk: 23.9 mo, AX+intermediate risk 18.8 mo)

Similar to wine, Sorafenib is getting better with age: you better watch out which comparator you choose in future trials