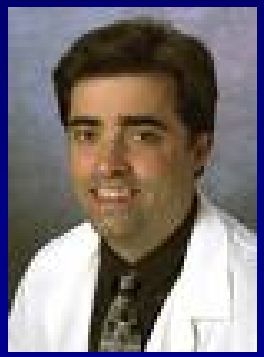
The High-Dose Aldesleukin (IL-2) "Select" Trial in Patients with Metastatic RCC



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Disclosures

- Advisory Role:
  - Genentech, Glaxo Smith Kline, Novartis, Roche, Onyx, Wyeth
- Honoraria:
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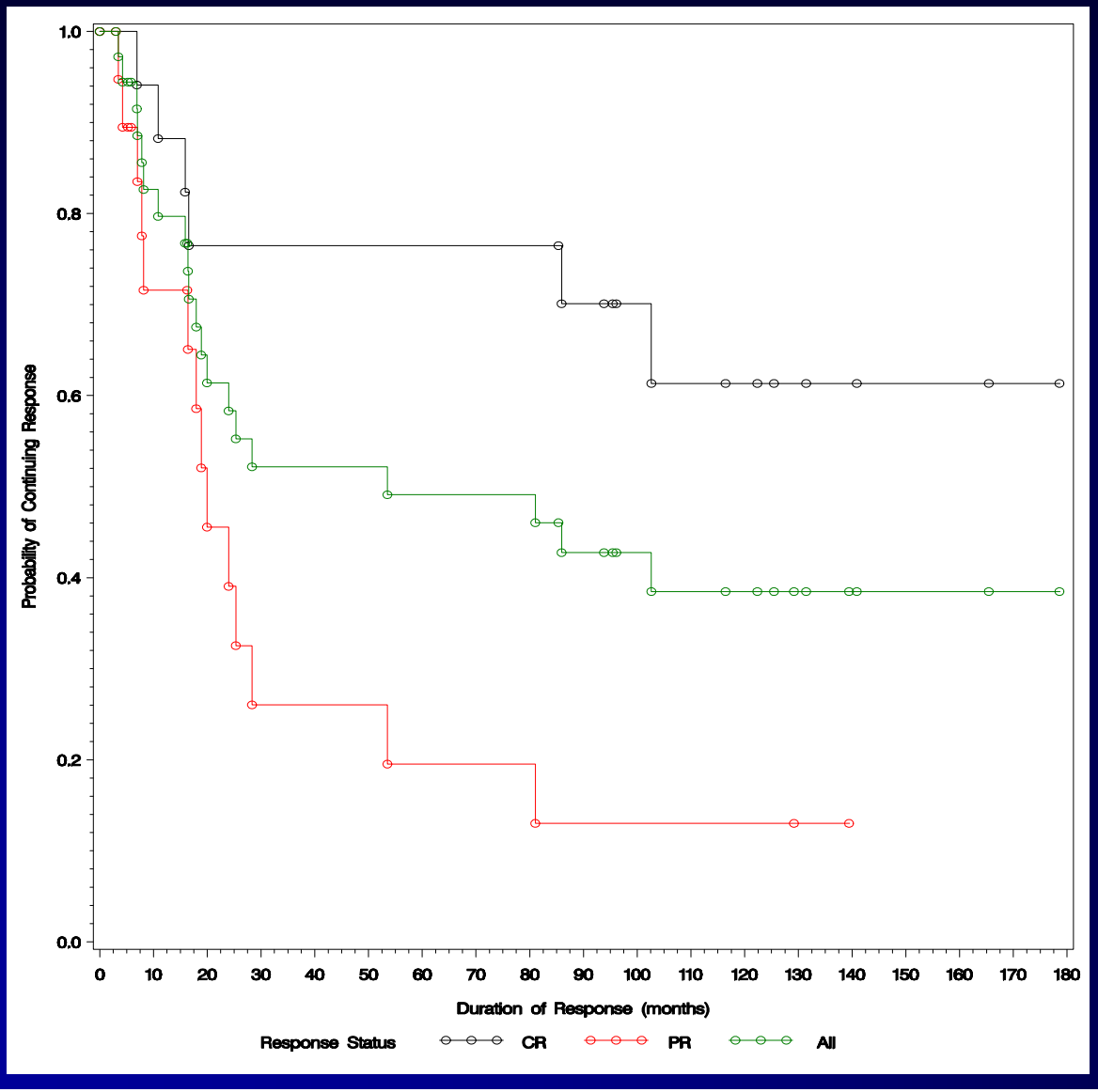
High-Dose IL-2 for mRCC



FDA Approval 1992 for RCC

14% response rate with durable responses in a small percentage of patients

But:

Significant toxicity, cost and limited efficacy

Application narrowed to selected patients treated at a few centers

Fyfe G, et al. *J Clin Oncol*. 1995;13:688-696

Background

- Can we pick likely responders before we begin IL-2 therapy?
- **Retrospective** analyses suggested that clinical characteristics and tumor features could predict for benefit [1,2,3,4]
  - UCLA SANI Score
  - Clear cell histology
  - Carbonic anhydrase 9 (CA-9)
- The current trial was conducted to improve the therapeutic index of HD IL-2

[1]Bui et al. Clin Cancer Res 2003, [2]Leibovich et al. Cancer. 2003, [3]Upton et al J Immunotherapy 2005, [4]Atkins et al Clin Cancer Res 2003

Primary Endpoint

- Response Rate
  - **To prospectively determine if the RR to HD IL-2 in mRCC patients with "good" pathologic predictive features was significantly higher than a historical, unselected population**

Secondary Endpoints

- **To prospectively determine:**
  - **The response rate for patients with "poor" pathologic features**
  - **To determine prospectively if other predictive and prognostic models (MSKCC[1], UCLA SANI Score[2]) can help define further the optimal population to receive HD IL2**
  - **Confirm the predictive value of factors that were associated with response to immunotherapy in other retrospective studies**
    - **(e.g. CAIX SNPs, B7H1, serum VEGF)**

[1]Motzer et al J Clin Oncol 2002, [2]Leibovich et al.Cancer 2003

Study Summary

- All patients met eligibility criteria
  - Measurable mRCC of all histologic subtypes
  - No prior systemic rx
  - Candidates for HD IL-2
- Accrual:
  - 120 pts enrolled from Nov 2006 to July 2009 at 14 sites
- Toxicities were as anticipated for this regimen
- Treatment related deaths: 2
- Tumor (98%) and blood (94%) collected on most patients

Patient Characteristics

Characteristics	*n=120*
Median age, yrs (range)	56 (28-70)
ECOG PS 0/1 (%)	72/24
Prior nephrectomy (%)	99
MSKCC risk factors[1] (%)	
0 (favorable)	18
1-2 (intermediate)	68
≥3 (poor)	15
UCLA SANI Score[2] (%)	
Low	8
Intermediate	85
High	7

[1]Motzer et al. JCO 2002; [2]Leibovich et al, Cancer 2003

UCLA SANI Score

- **S**urvival **A**fter **N**ephrectomy and **I**mmunotherapy[1]
- Scoring algorithm developed at UCLA from 173 pts who had Nx→ IL-2 based Rx
- Factors that predicted survival and response to IL-2
  - Regional LN status
  - Symptoms
  - Location of mets
  - Sarcomatoid histology
  - TSH level
- Low, intermediate and high risk groups

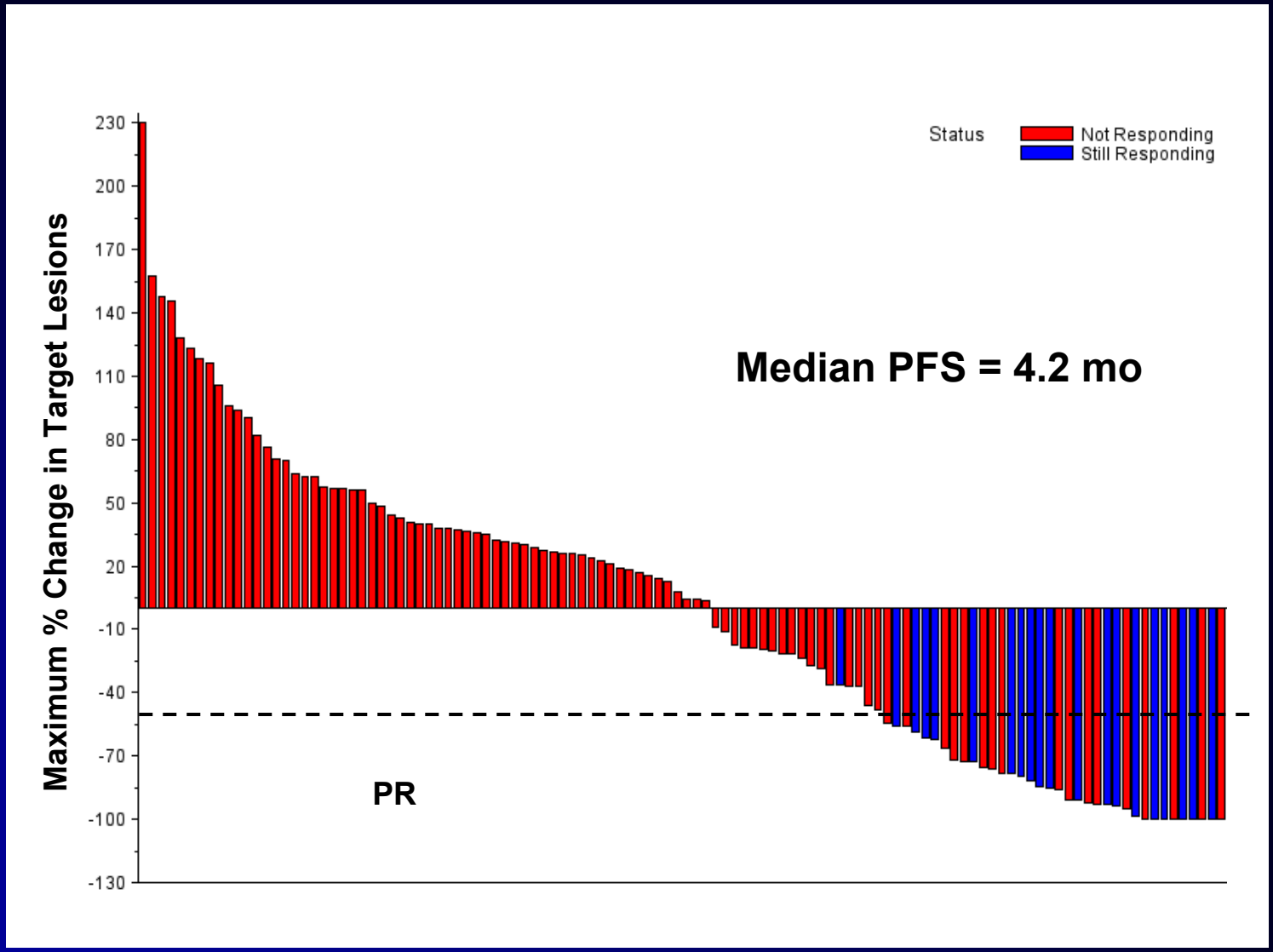
[1]Leibovich et al, Cancer 2003

Efficacy Results

Response*	N (%)
Patients with measurable disease at baseline (n)	120 (100)
Objective response	**30 (25)**
Complete response	4 (3)
Partial response	26 (22)
Stable disease (> 6 months)	16 (13)
Progressive disease/not evaluable	74 (62)

*Independently reviewed using WHO Criteria

Tumor Shrinkage Plot (n=118)

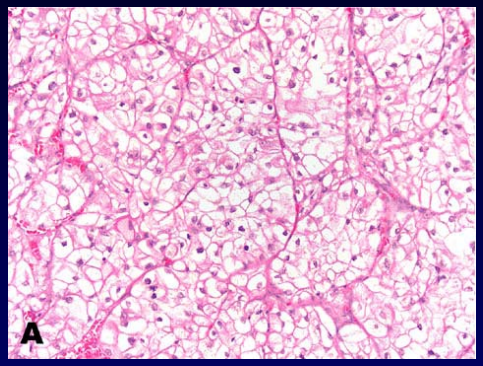


Statistical Considerations

- After enrollment, Pathology Core at DFHCC determined patient's pathologic risk group
- Goal to use selection criteria to double historical control RR (14%)[1]
- Target RR in this "good risk" subset of patients $\geq$ 28%
- Sample size of 110 pts was estimated to be necessary to enroll 66 "good risk" patients
  - 80% power, 2-sided α=0.05

[1]Fyfe G, et al. *J Clin Oncol*. 1995;13:688-696.

Combined Model



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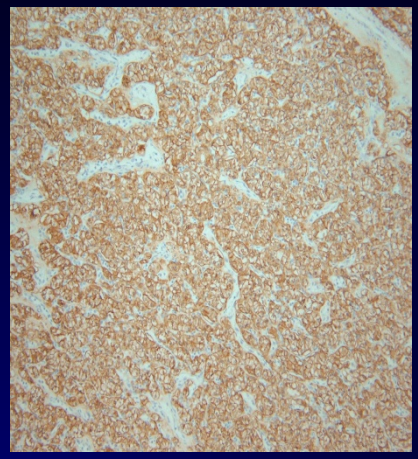


CAIX Staining

Pathology Risk Group	Low	High
Good		
Intermed		
Poor		

Good

Poor

Atkins, et al Clin Can Res, 2005

Pathology Characteristics

Characteristics	*N (%)*
Histologic Risk Group	
Good	**11 (9)**
Intermediate	**83 (70)**
Poor	**25 (21)**
CA-9 Score	
High (>85%)	**78 (67)**
Low (≤ 85%)	**39 (33)**
Combined Score	
Good	**74 (63)**
Poor	**43 (37)**

[1]Upton et al J Immunotherapy 2005, [2]Atkins et al Clin Cancer Res 2003

Response by Pathology Characteristics

Histology risk group	RR (95% CI)	P-value*
Good (n=11)	27% (6%-61%)	0.89
Intermediate (n= 83)	24% (15%-35%)	
Poor (n=25)	28% (12%-49%)	

CA-9 Score		
High (>85% n=77)	22% (13%-33%)	0.19
Low (≤85% n=39)	33% (19%-50%)	

Combined Score		
Good (n=74)	23% (14%-34%)	0.39
Poor (n=42)	30% (17%-46%)	

Response Comparison

Response*	%
Historical rate	14
IL-2 Select Trial (all pts n=120)	**25**
	p=0.0014
	95% CI=17.5-33.7%
Good Risk Patients (n=74)	**23**
	p=0.042
	95% CI=14-34.2%

Likely explanations for improved RR include:

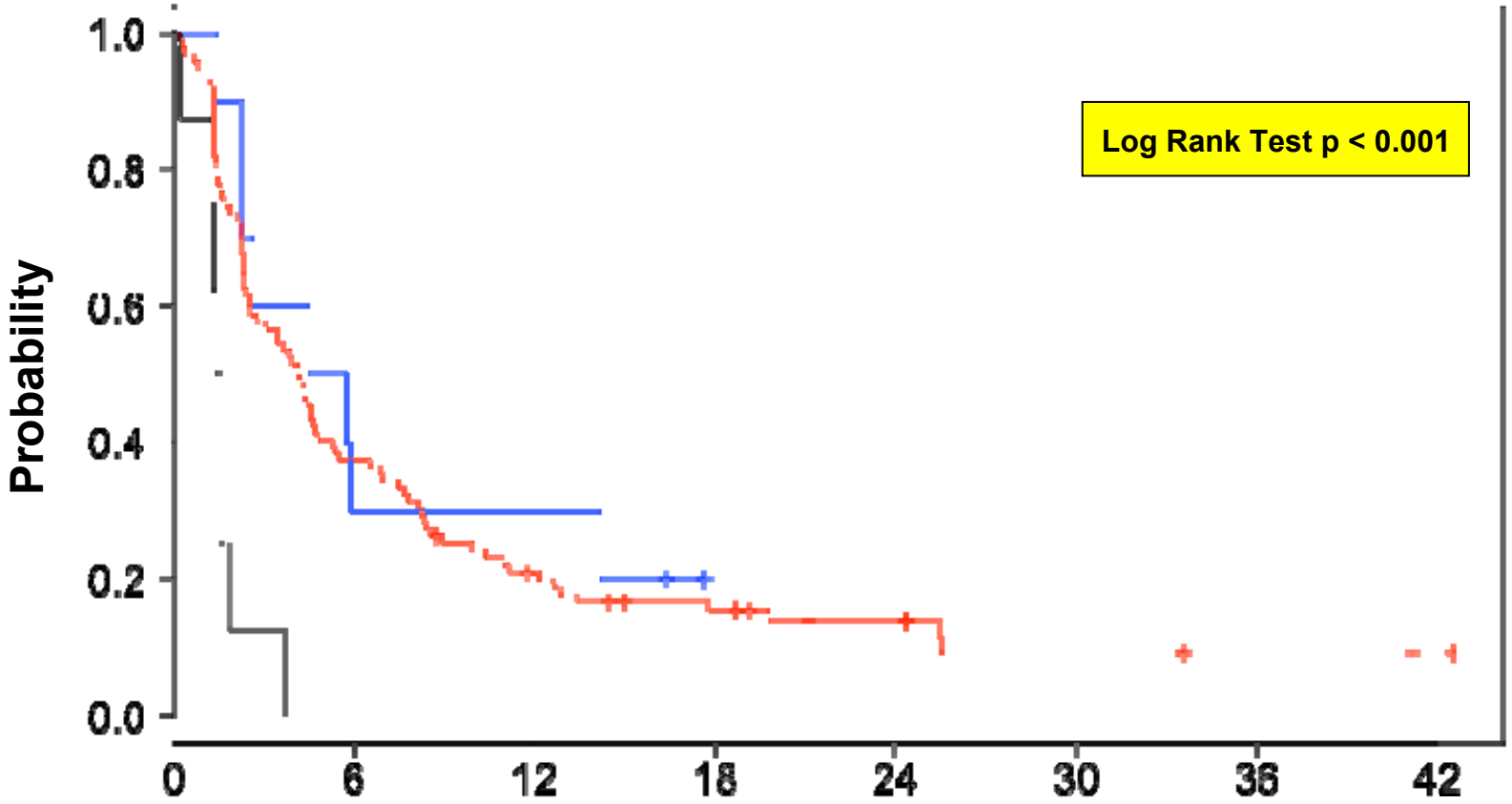
1) Enhanced “pre-screening” including fewer with non-CCRCC histologies
2) Impact of alternative therapies on IL-2 referrals
3) Routine use of cytoreductive nephrectomy
   - Similar medical requirements for candidacy for both
   - Favorable impact on outcome

*Independently reviewed using WHO Criteria

Response by Baseline Characteristics

	RR (95% CI)	P-value*
All Patients (n=120)	**25% (18%-34%)**	0.0014
Tumor type		
Clear Cell (n=115)	26% (18%-35%)	0.33
Non-clear cell (n=5)	0% (0%-52%)	
MSKCC Risk Group		
Favorable (n=21)	23% (8%-47%)	0.95
Intermediate (n=81)	25% (16%-36%)	
Poor (n=18)	28% (10%-53%)	
UCLA Risk Group		
Low (n=10)	20% (3%-56%)	0.27
Intermediate (n=101)	27% (19%-37%)	
High (n=8)	0% (0%-37%)	

PFS by UCLA SANI Group



SANI Group	MEDIAN	95% CI	P Value
High-Risk	1.4	0.23 – 1.9	<0.01
Int-Risk	4.2	2.5 – 4.8	
Low-Risk	4.5	1.5 – 14.2	

Conclusions

- The RR for HD IL-2 in this trial was significantly better than the historical experience, probably due to better pts.
- Clinical and pathologic features (e.g. SANI score and histology) may identify patients unlikely to benefit from HD IL-2
- In this trial, central pathology review and staining for CA-9 did not improve pt. selection to benefit from HD IL-2
- Potential explanations
  - Host/not tumor factors may play a larger role
  - Tumor factors important but others better than CA-9
  - Samples are not "representative" due to lack of standards for tumor processing at community centers and lack of adequate representation of primaries and mets

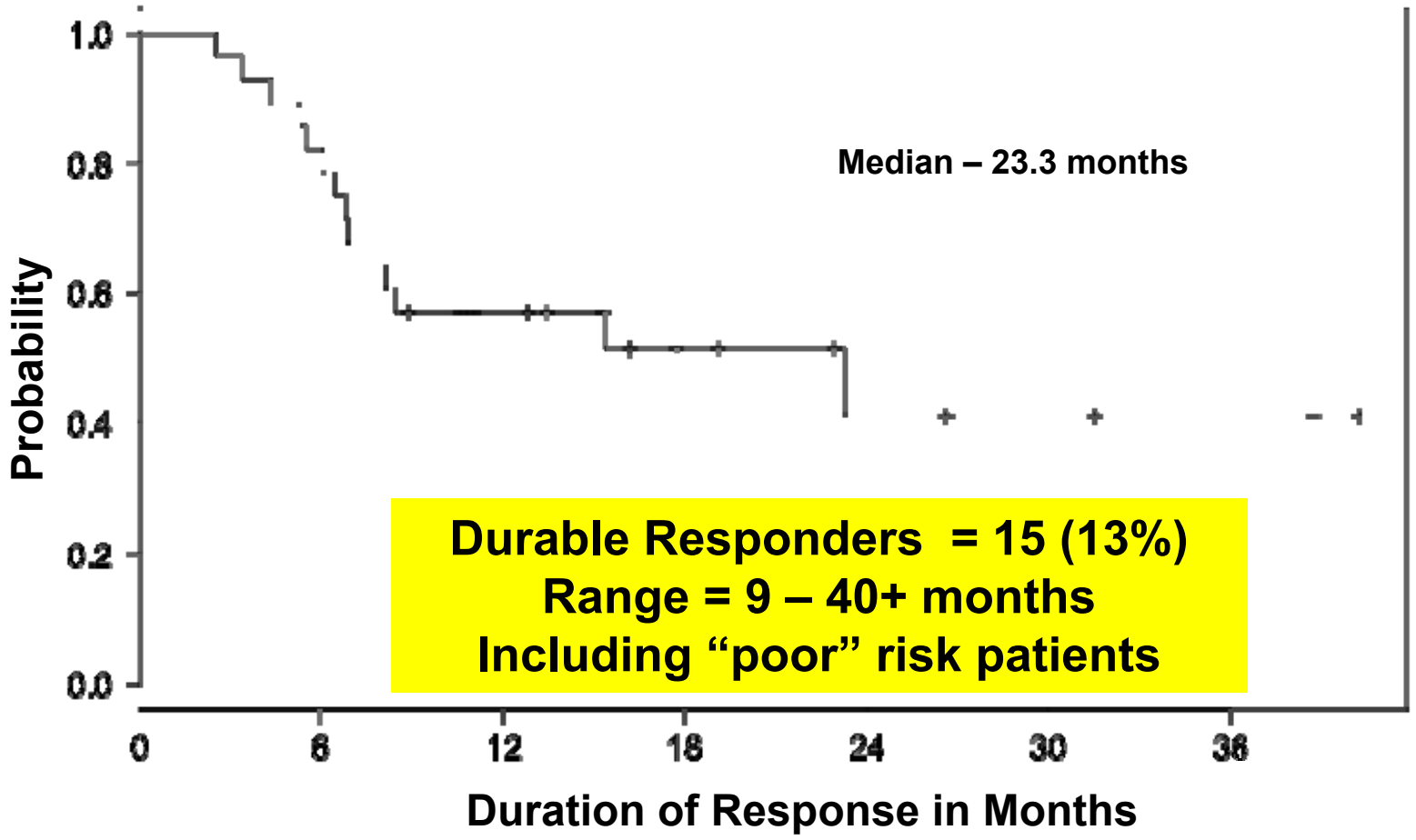
Ongoing Studies

- Efforts to confirm other predictive tumor and host-derived biomarkers are ongoing.
  - CA-9 SNPs, B7H1, B7H3
  - Serum VEGF, others
- Given the high RR and comprehensive tissue collection in this trial, an **improved model** for IL-2 patient selection will likely emerge from these efforts.
- Lessons from this work may guide the development of **"targeted immunotherapies"** (e.g. CTLA-4, PD-1 antibodies) in mRCC.
- Early studies with these agents suggest that they deliver durable benefit with less toxicity.
  - (e.g. MDX-1106 Sznol et al, Abstract #49563 ASCO 2010)

Commentary

- Confirming hypotheses in well designed, prospective trial is essential
  - Until its value as a predictive marker can be confirmed, application of CA-9 IHC staining should be limited.
  - Efforts to standardize RCC tissue collection should be considered in future trials.
- While the longstanding criticisms of HD IL-2 therapy remain valid:
  - Efficacy remains limited
  - Cost remains high
  - Toxicity remains severe
- At the current time, IL-2 based immunotherapy is the only approach that can produce a response duration curve like this:

Response Duration Curve



Acknowledgements

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