John Haanen, MD PhD

High dose interleukin-2

- Approved in 1992 for metastatic RCC
  - Based on multiple phase II studies
  - Large unmet medical need
- Bolus infusions (15 min) of 600,000 IU/kg
- Responding patients may receive more than 1 cycle

Results from RCT

	Regimen	N	RR	p-value	Dur CR
NCI SB	HD IV IL-2	156	21%	0.05	8
	vs				
	LD IV IL-2	150	13%		3
CWG	HD IV IL-2	95	23%	0.02	7
	vs				
	LD SC IL-2/IFN	91	10%		0

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Yang et al JCO 2003; McDermott et al JCO 2005

Patient Selection Criteria?

- Clinical criteria:
  - MSKCC criteria (int med risk pts 18% alive at 5 years
- Histological features
  - >50% alveolar, no papillar, no granular: RR of 25-39%
- CAIX expression:
  - >85% expression

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Refined Pathology Risk Group		Non-Responder (n=39)	Responder (n=27)
Good risk path or intermediate path with high CAIX	Good*	18 (46%)	26 (96%)
Poor risk path or intermediate path with low CAIX	Poor	21 (54%)	1 (4%)

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Atkins et al., Clin Can Res 2005

The High-Dose Interleukin-2 “Select” Trial in Patients with Metastatic RCC

D McDermott, M Ghebremichael, S Signoretti, K Margolin, J Clark, J Sosman, J Dutcher, T Logan, R Figlin and M Atkins on behalf of the Cytokine Working Group

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Study Summary

- All patients met eligibility criteria
  - Measurable mRCC of all histologic subtypes
  - No prior systemic rx
  - Candidates for HD IL-2
- Accrual: Nov 2006 to July 2009
- Patients Registered: 123
- Withdrew Consent: 3
- Toxicities were as anticipated for this regimen
- Treatment related deaths: 2
- Tumor (98%) and blood (94%) collected on most pts

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Primary Endpoint

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

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Patient Characteristics

Characteristics	*n=120*
Median age, yrs (range)	58 (28-70)
ECOG PS 0/1 (%)	72/24
Prior nephrectomy (%)	99
MSKCC risk factors[1] (%)	
0 (favorable)	26
1-2 (intermediate)	69
≥3 (poor)	5
UCLA SANI Score[2] (%)	
Low	8
Intermediate	85
High	7

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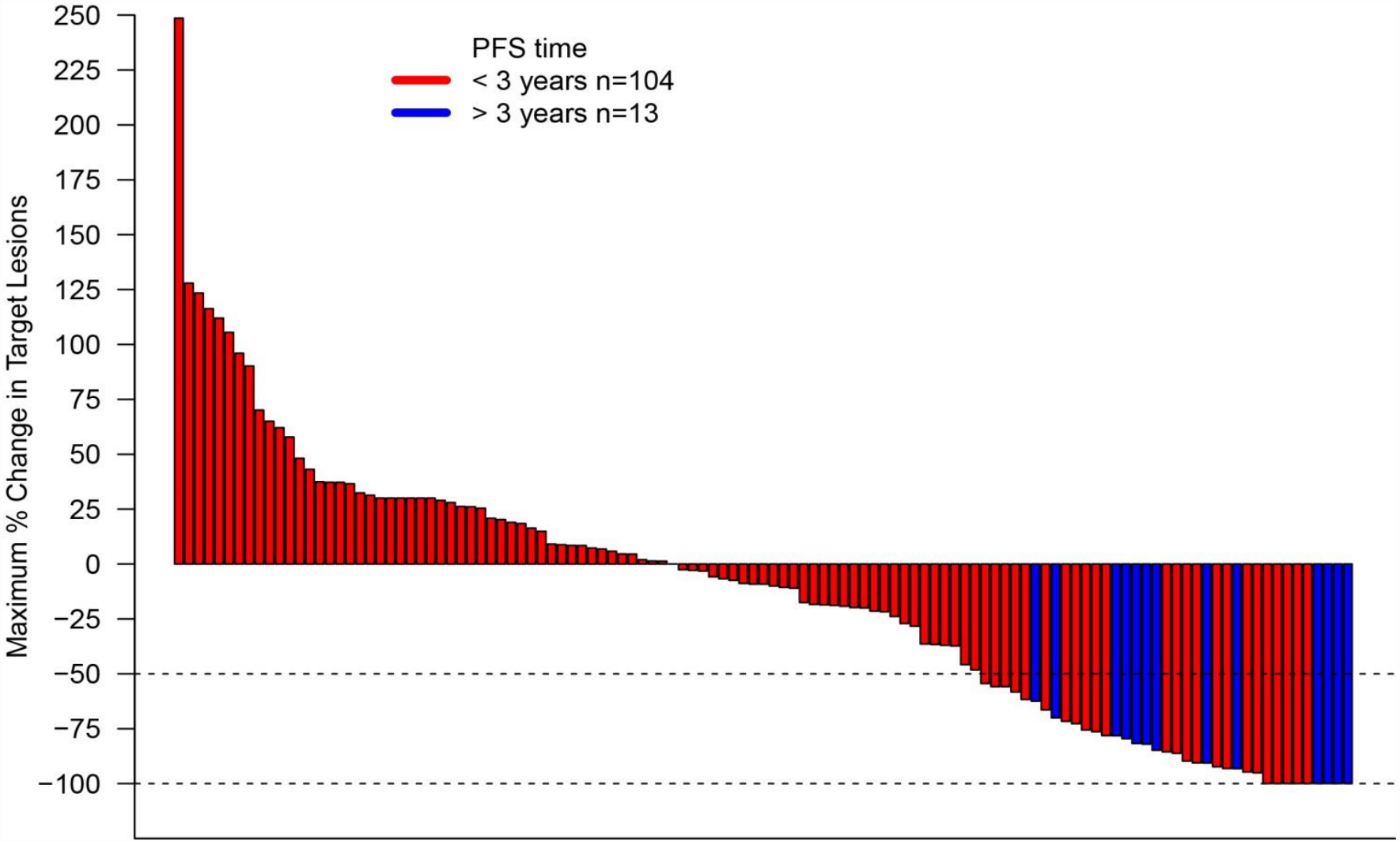
[1]Motzer et al. JCO 2002; [2]Leibovich et al, Cancer 2003

Efficacy Results

Response*	N (%)
Patients with measurable disease at baseline (n)	120 (100)
Objective response	**34 (28)**
Complete response	7 (6)
Partial response	27 (22)
Stable disease (> 6 months)	15 (12)
Progressive disease/not evaluable	71 (60)
Durable Responders	**20 (17%)**
Range	6.1 - 34.1 mo
Progression-free Survival (median)	**4.2 mo**

*Using WHO Criteria

Maximum change in summary target lesion measurements compared with baseline (WHO criteria)



Courtesy of D McDermott

IL-2 Select Trial: Response by Baseline Characteristics

	RR (95% CI)	P-value*
All Patients (n=120)	28% (20%-37%)	0.0016
Tumor type		
Clear Cell (n=115)	**30% (21%-39%)**	**0.31**
Non-clear cell (n=5)	**0% (0%-52%)**	
MSKCC Risk Group		
Favorable (n=31)	**32% (17%-51%)**	**0.08**
Intermediate (n=83)	**24% (15%-35%)**	
Poor (n=6)	**67% (22%-96%)**	
UCLA Risk Group		
Low (n=10)	**30% (7%-65%)**	**0.22**
Intermediate (n=101)	**30% (21%-40%)**	
High (n=8)	**0% (0%-37%)**	

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%)	

CAIX 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%)	

Conclusions

- The RR for HD IL-2 maybe significantly better than the historical experience, likely as a result of improved patient selection
- Clinical and pathologic features (e.g. SANI score and histology) may identify patients who are unlikely to respond to HD IL-2 and should not receive it
  - MSKCC criteria may not be predictive of poor response
- This prospective study does not confirm CAIX staining and histologic subtyping to be selective.

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Evaluating the Place of Interleukin-2 in the management of metastatic Renal Cell Cancer in the era of targeted therapy

Manon Evans,
Shien Chow, Victoria Galvis, Rebecca Leach, Elizabeth Keene, Andrea Spencer-Shaw, Alaaeldin Shablak, Jonathon Shanks, Fiona Thistlethwaite, Robert Hawkins

Medical Oncology, The University of Manchester and The Christie Hospital Manchester, UK

MANCHESTER 1824

The Christie NHS Foundation Trust

The Christie Clinic
A private patient partnership between HCA International and The Christie NHS Foundation Trust

Patient selection

- Attempts have been made to select suitable patients pre-treatment
  - MSKCC[1]
  - Upton[2]
  - Histological subtype
- At The Christie - Pathology-based selection criterion[3]

  Suitable patients
  - **'Favourable ' <10% papillary** and at least one of
  - **a) >50% clear cell or b) >50% solid / alveolar architecture**
  - These are preferentially selected for treatment
  - Those with 'other' pathology, if motivated, may also receive treatment

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1. Motzer RJ, Mazumdar M, Bacik J, et al. J Clin Oncol. 1999;17:2530–2540.
2. Upton MP, Parker RA, Youmans A, et al J Immunother. 2005;28:488–495.
3. Shablak A, Sikand K, Shanks JH, et al J Immunother; 2011; 34: 107-112.

Demographics

	Group A: First Line (2003 – 2013)	Group B: After VEGF targeted therapy (2007-2013)
	Total	Total
Total patients	145	35
Median age	56	58
Nephrectomy	141 (97)	34 (97)
MSKCC Good / inter / poor	115 (79) / 26 (18) / 4 (3)	17 (49) / 18 (51) / 0
Pathology-based selection 'Favourable' / 'Other'	127 (88) / 19 (12)	31 (89) / 4 (11)
Prior targeted agents used 1 TKI 2 TKI 1 TKI + mTORi 2 TKI + mTORi	0	 26 (75) 4 (11) 1 (3) 4 (11)

Response

	Group A: First Line (2003 – 2013)			Group B: After VEGF targeted therapy (2007-2013)		
	Total (%)	ORR (%)	CR (%)	Total (%)	ORR (%)	CR (%)
Whole cohort	145	**62 (43)**	**30 (21)**	35	**13 (37)**	**6 (17)**

Response

	Group A: First Line (2003 – 2013)			Group B: After VEGF targeted therapy (2007-2013)		
	Total (%)	ORR (%)	CR (%)	Total (%)	ORR (%)	CR (%)
Whole cohort	145	62 (43)	30 (21)	35	13 (37)	6 (17)
Pathology-based selection	127 (88)	**59 (46)**	**29 (23)**	31 (89)	**13 (42)**	**6 (19)**
'Favourable'						
'Other'	18 (12)	3 (17)	1 (6)	4 (11)	0	0

Response

	Group A: First Line (2003 – 2013)			Group B: After VEGF targeted therapy (2007-2013)		
	Total (%)	ORR (%)	CR (%)	Total (%)	ORR (%)	CR (%)
Whole cohort	145	62 (43)	30 (21)	35	13 (37)	6 (17)
Pathology-based selection ‘Favourable’ ‘Other’	127 (88) 18 (12)	59 (46) 3 (17)	29 (23) 1 (6)	31 (89) 4 (11)	13 (42) 0	6 (19) 0
MSKCC ***Good*** ***Intermediate*** ***Poor***	*115 (79)* *26 (18)* *4 (3)*	***52 (45)*** ***10 (39)*** *0*	***22 (19)*** ***9 (31)***	*17 (49)* *18 (51)* *0*	***20 (41)*** ***17 (33)***	***14 (29)*** ***3 (6)***

Response

	Group A: First Line (2003 – 2013)			Group B: After VEGF targeted therapy (2007-2013)		
	Total (%)	ORR (%)	CR (%)	Total (%)	ORR (%)	CR (%)
Whole cohort	145	62 (43)	30 (21)	35	13 (37)	6 (17)
Pathology-based selection ‘Favourable’ ‘Other’	127 (88) 18 (12)	59 (46) 3 (17)	29 (23) 1 (6)	31 (89) 4 (11)	13 (42) 0	6 (19) 0
MSKCC *Good* *Intermediate* *Poor*	*115 (79)* *26 (18)* *4 (3)*	*52 (45)* *10 (39)* *0*	*22 (19)* *9 (31)*	*17 (49)* *18 (51)* *0*	*20 (41)* *17 (33)*	*14 (29)* *3 (6)*
CAIX **Total** **>80** **>60**	100 (69) 75 (75) 87 (87)	**37 (49)** **42 (48)**	**18 (24)** **23 (27)**	32 (91) 25 (78) 29 (90)	**11 (44)** **12 (41)**	**5 (20)** **6 (21)**

Where do these results differ from the SELECT trial?

- The patient population
  - MSKCC poor risk group did NOT have a response
- CAIX expression
  - Lower expression separated pts responding better than high expression(so CAIX expression is probably not discriminating responders from non-responders
- Pathological features
  - Similar to Select and here selected for responders
- Single institution versus multicenter study

Both studies: RR to IL-2 was much higher than historically observed

Is there still room for high dose IL-2?

- This study shows a high ORR and CR rate!
- Failure to TT did not preclude response to HD IL-2 (if patients were selected well) (although data are conflicting published results)
- TT does not result in cure whereas HD IL-2 can
- Are we better in dealing with toxicity?

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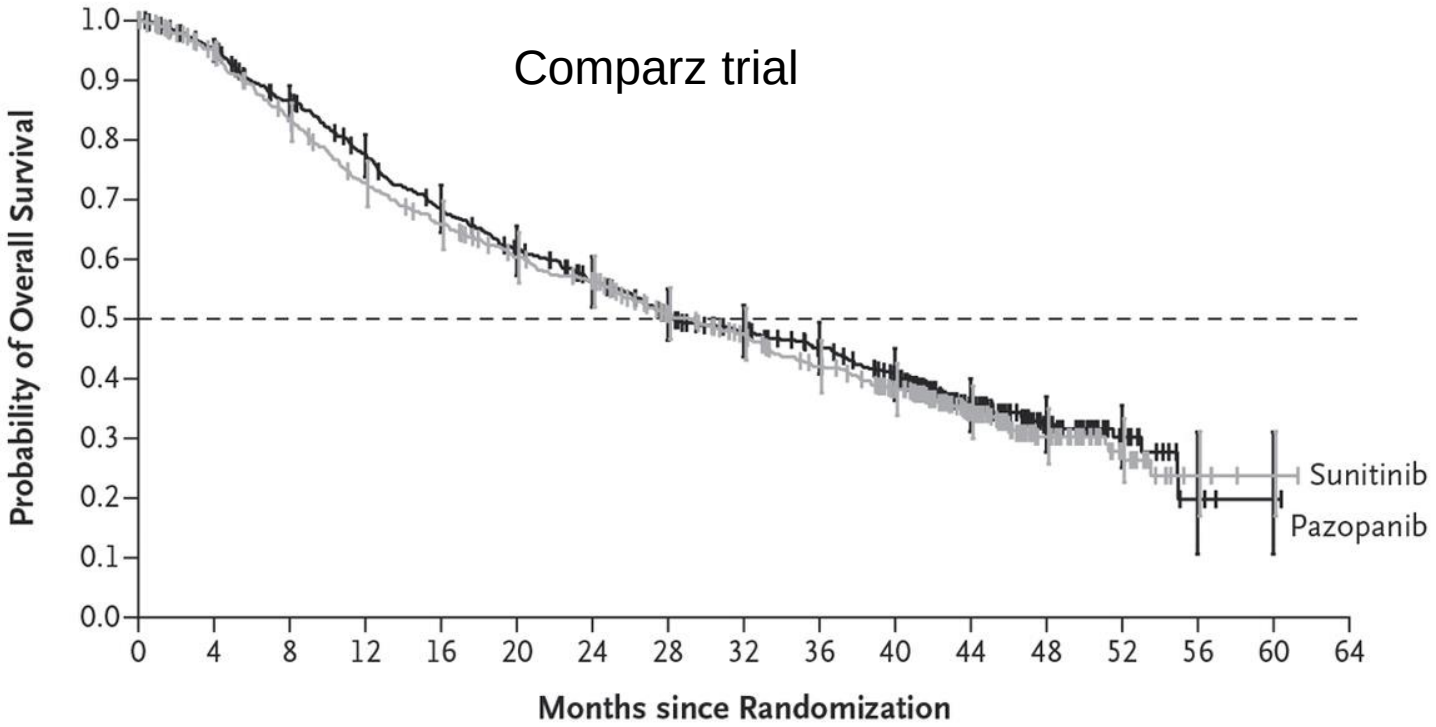
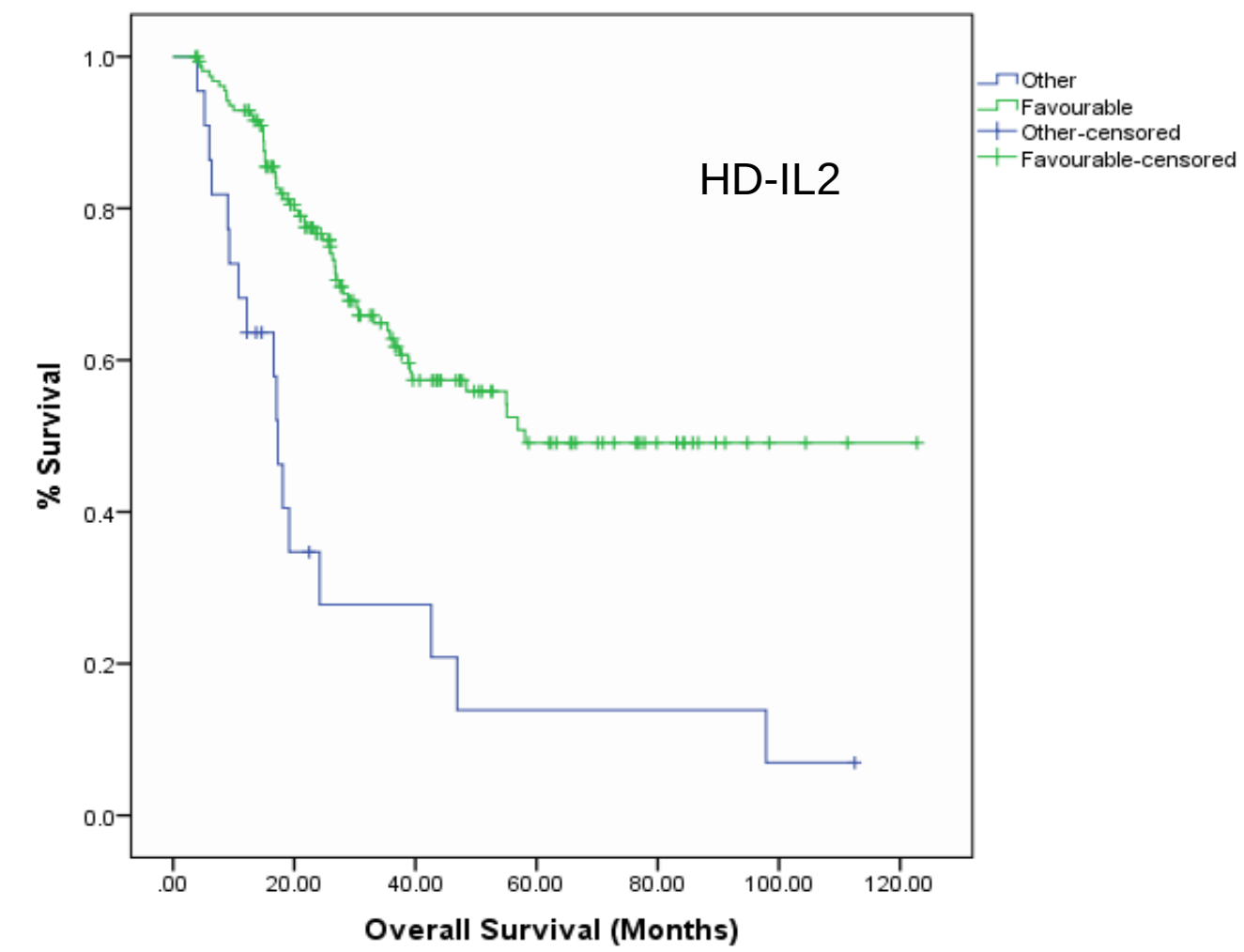
Overall survival



No. at Risk																	
Pazopanib	557	521	462	409	360	320	284	243	221	197	169	99	51	21	4	1	0
Sunitinib	553	501	435	377	339	304	281	237	211	180	153	100	45	20	4	1	0

Overall survival



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Can we select even better?

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Response by tumor expression of B7-H1 (PD-L1) or B7-H3

	RR	p-value*
B7-H1 Tumor		
Negative (n=95)	19%	0.012
Positive (n=18)	50%	
B7-H3 Tumor		
Negative (n=28)	10.7%	0.075
Positive (n=85)	29.4%	

IHC performed at Mayo Clinic by Kwon, Leibovich, et al.

Courtesy of David McDermott

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Conclusion

- HD IL-2 remains a treatment option for a highly selected patient population with mRCC in experienced centers
- In contrast to targeted therapy, HD IL-2 can induce durable remissions, probably cure in CR patients
- HD IL-2 should be given as 1st line treatment, although Il-2 may have similar activity after prior targeted therapy
- New immunotherapies are on their way and results may impact on the future use of HD IL-2 (and targeted agents)

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