The Application of Cytokine Therapy Following TKI Failure

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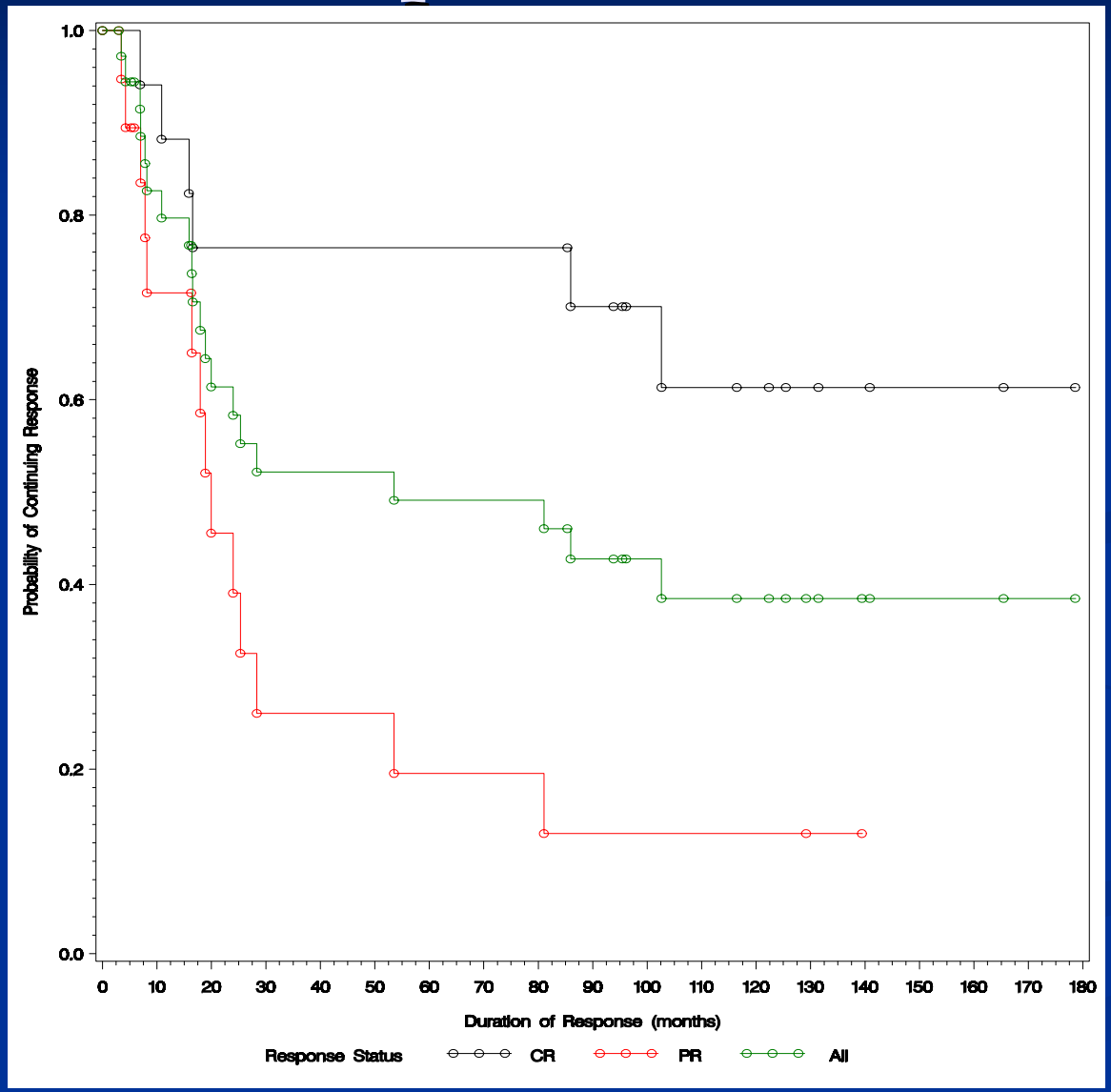
Objectives

- High Dose IL2 for RCC
- Anti- VEGF Therapy
  - Bevacizumab
  - Sunitinib malate
  - Sorafenib
- Retrospective analysis of IL-2 therapy as second line treatment after anti- VEGF resistance

High-Dose IL-2 Therapy: Response Durations - 255 pts



FDA Approval 1992

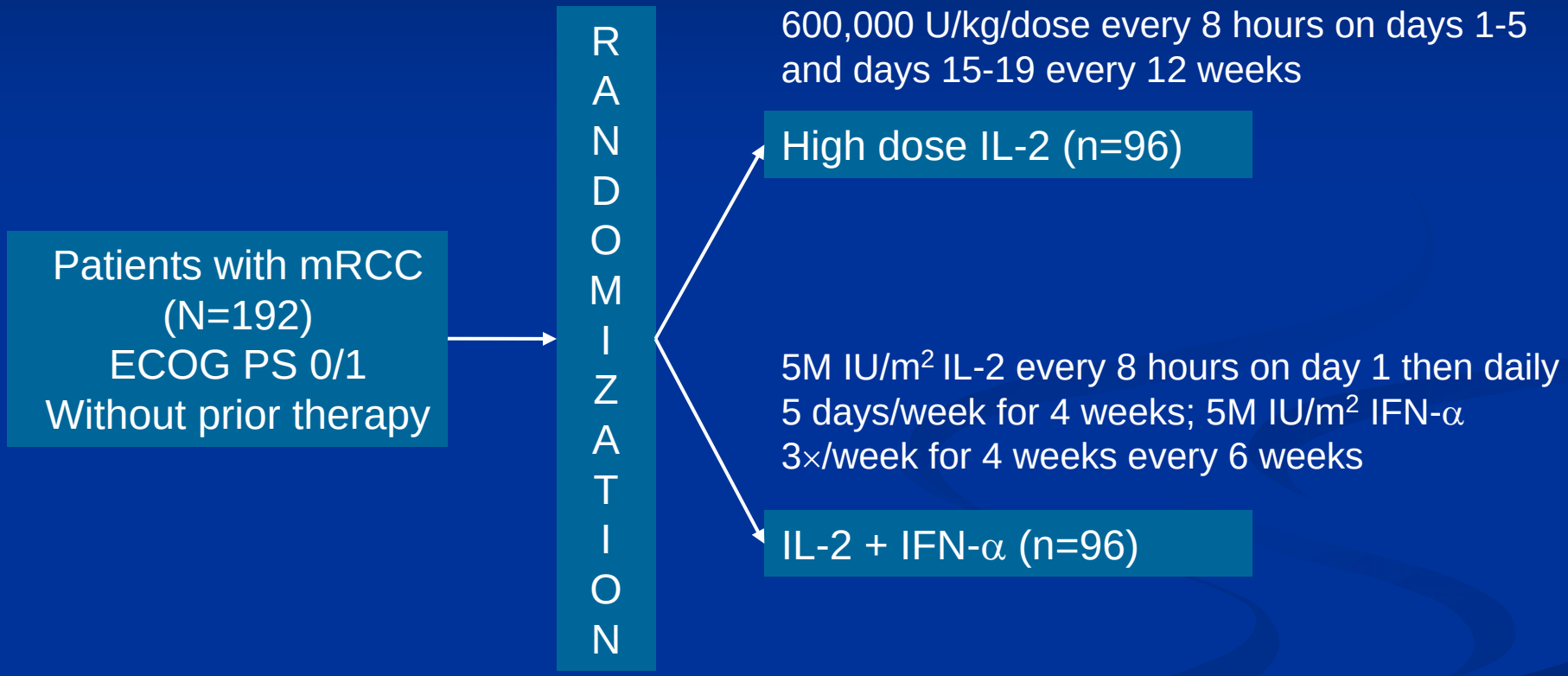
15% response rate with durable responses in a small percentage of patients

Median Response Duration – 50 months

But:

Significant toxicity and cost*

High-Dose IL-2 vs IL-2 Plus IFN-α in mRCC: Phase 3 Study Design



- Primary end point: 3-year PFS

McDermott DF et al. *J Clin Oncol.* 2005;23:133-141.

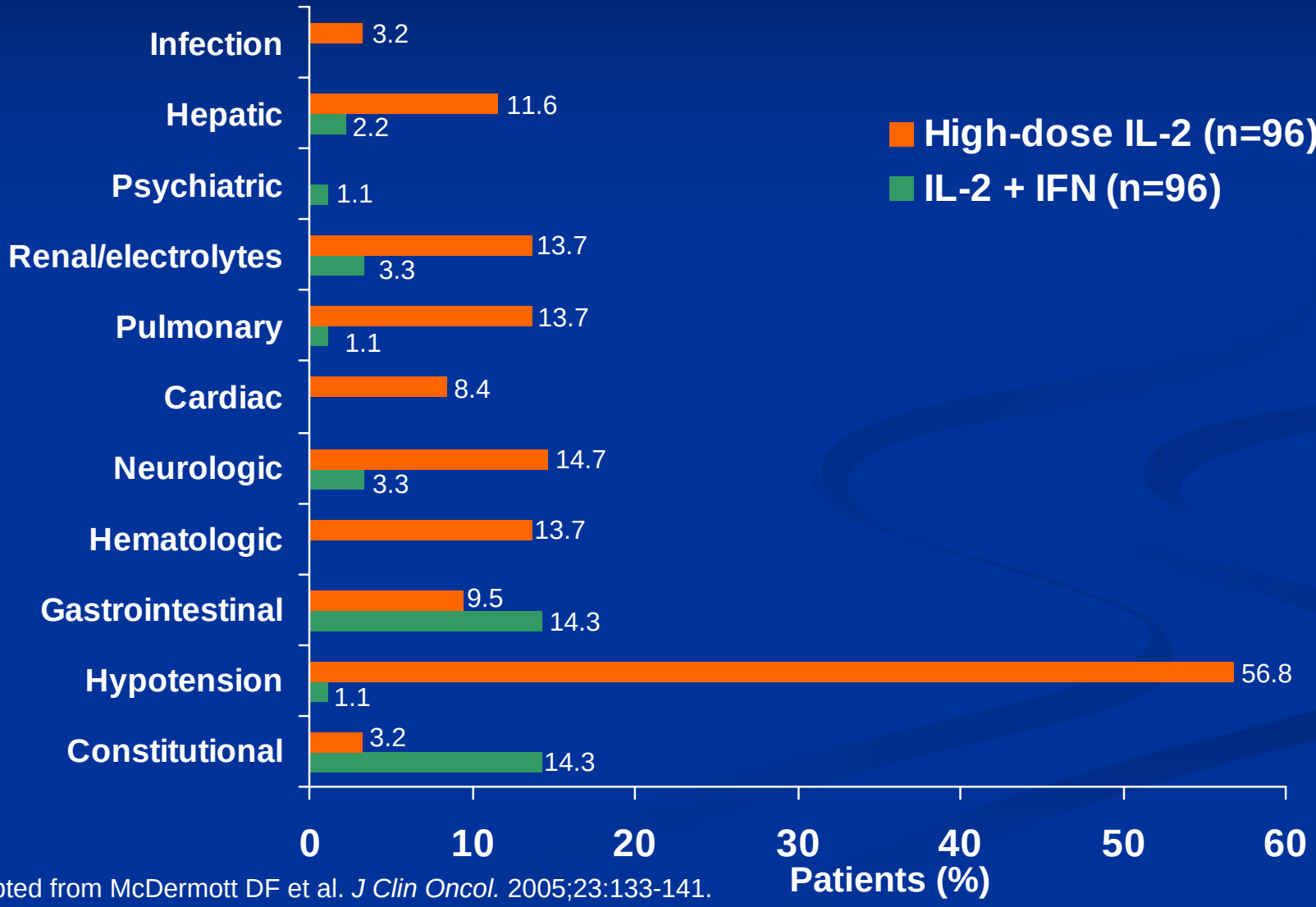
Phase III Trials in Metastatic RCC

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

More durable responses, especially CRs, with HD IL-2
No significant difference in OS or quality of life

Yang et al JCO 2003; McDermott et al JCO 2005

Grade 3 and 4 Toxicities



Adapted from McDermott DF et al. *J Clin Oncol.* 2005;23:133-141.

Immunotherapy Summary

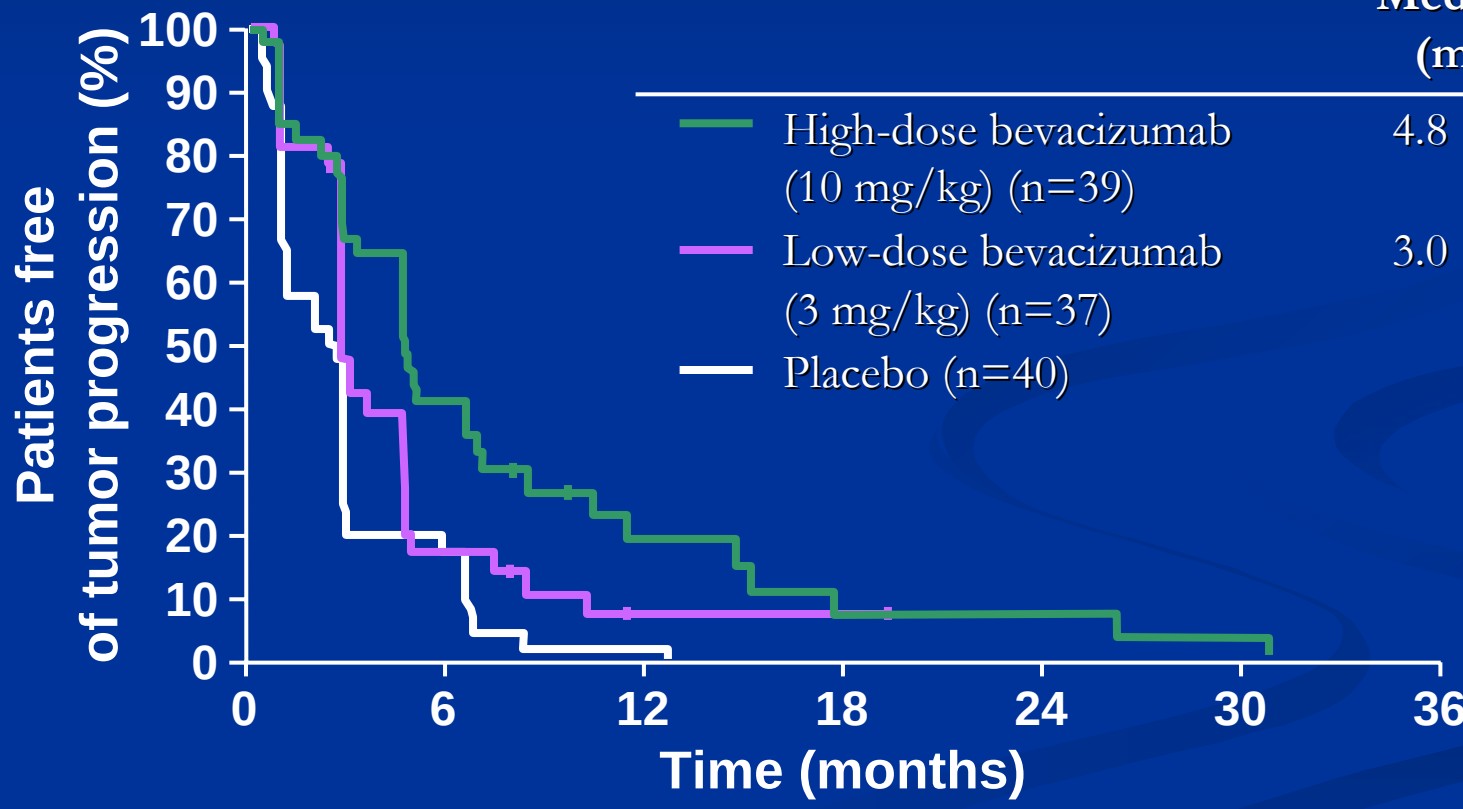
- Bottom line:
  - Median survival ~13 months
  - HD-IL-2 RR 15-23% with 5% sustained response
  - Significant toxicity
  - Patient selection is important
    - No CNS metastases
    - Clear Cell histology
    - Good PS
    - ? No prior TKI therapy ?

A Paradigm Shift: Anti-Angiogenic Therapy

Targeted Therapy
VHL Pathway in RCC

- Von Hippel Lindau (VHL) gene product: oxygen sensor in renal tubular cells
- Majority of clear cell RCC characterized by biallelic VHL loss (60% of cases)
- Loss of function leads to upregulation of downstream targets due to increased levels of HIF
- Tumor suppressor gene

Bevacizumab in mRCC: Progression-Free Survival



	Median TTP (months)
High-dose bevacizumab (10 mg/kg) (n=39)	4.8 ($P<.001$)
Low-dose bevacizumab (3 mg/kg) (n=37)	3.0 ($P<.041$)
Placebo (n=40)	2.5

Adapted from Yang JC et al. *N Engl J Med*. 2003;349:427-434.

Results

	Placebo	Low dose	High Dose
OR	0	0	4 (10%)
(All were PR)			
Stable Disease			
at 4 mo	20%	39%	64%
at 8 mo	5%	14%	30%
Side Effects			
HTN	2	1	14 (36%)
Malaise	6	6	13 (33%)
Proteinuria	15	15	25 (64%)
Hematuria	0	1	5 (13%)

Yang, J. C. et al. N Engl J Med 2003;349:427-434

Sunitinib in mRCC

- Phase III RCT of Sunitinib v IFN demonstrated RR=37% by RECIST criteria with stable disease in 47% of pts.
- Most frequent adverse events included fatigue, diarrhea, nausea, stomatitis, HTN, and hand-foot syndrome.
- Improved PFS (11 vs 5 mo) compared with IFN
  - Survival data not mature

Motzer et al, *NEJM* 2007;356:115-124.

Treatment-Related Adverse Events

Event	Sunitinib (%)		IFN-α (%)	
	All grade	Grade 3/4	All grade	Grade 3/4
Fatigue	51	7	51	11/<1*
Diarrhea	53	5*	13	0
Nausea	44	3	33	1
Stomatitis	25	1	2	<1
Hypertension	24	8*	1	<1
Hand-foot syndrome	20	5*	1	0
Ejection fraction decline	10	2	3	1
Pyrexia	7	1	34	0
Chills	6	1	29	0
Myalgia	5	<1	16	<1
Flu-like symptoms	1	0	8	<1

Sorafenib in mRCC

- Phase III RCT of Sorafenib v placebo demonstrated RR=10% by RECIST criteria with stable disease in 74% of pts.
- Most frequent adverse events leading to discontinuation were hand-foot syndrome and hypertension
- Improved PFS (5.5 vs 2.8 mo) compared with placebo
  - Preliminary data suggest a trend towards increased overall survival

Escudier et al, *NEJM* 2007;356:125-134.

Sorafenib in mRCC: Safety

	Sorafenib	Placebo (n=384)
	Grades 3/4	Grades 3/4
Cardiac general		
Hypertension	4 (1%)	–
Constitutional symptoms		
Fatigue	7 (2%)	5 (1%)
Gastrointestinal		
Diarrhea	5 (1%)	3 (1%)
Nausea	1 (<1%)	1 (<1%)
Anorexia	2 (1%)	2 (1%)
Vomiting	–	1 (<1%)
Constipation	–	–
Mucositis	2 (1%)	–
Dermatology/skin		
Rash/desquamation	3 (1%)	1 (<1%)
Hand-foot skin reaction	20 (5%)	–

Conclusions

- Standard of care for advanced RCC has changed
- Angiogenesis inhibition: both Sunitinib and Sorafenib are approved for the treatment of advanced RCC
- Other anti-angiogenic agents including Bevacizumab are active as well

What is the Safety and Efficacy of IL2 after Anti-angiogemic Therapy?

Experience with IL-2 in TKI Failures

- Limited
- Referrals for IL-2 are declining at many centers
- TKI failure patients are often not well enough to meet IL-2 eligibility criteria
- Role of IL-2 following resistance to anti-angiogenic therapy remains unexplored

HD IL-2 for Anti-VEGF Failures at BIDMC

- Retrospective analysis
- 16 consecutive patients (7/04-5/07)
- All 16 eligible for IL-2 prior to anti-VEGF therapy, assumed they could get it later
- Treatment tolerability and toxicity compared to High Dose IL-2 arm of CWG Phase III trial (McDermott, et al JCO 2005)

Schwarzberg, et al ISBT abstract, 2007

Patient Characteristics

- Median Age 61 (range 48-70)
- ECOG PS
  - PS 0 - 9 patients
  - PS 1 - 6 patients
  - PS 2 - 1 patient
- Male:Female 12:4
- 15/16 pts met HD IL-2 eligibility
  - 15 received HD IL-2, 1 received LD IL-2

Schwarzberg, et al ISBT abstract, 2007

Prior Therapy

- Prior therapy:
  - Bevacizumab alone = 6
  - Sorafenib alone = 2
  - Sunitunib alone = 2
  - Sorafenib then Sunitinib = 2
  - Bevacizumab then Sunitinib = 3
  - Bevacizumab then Sorafenib = 1
- Duration of prior therapy ranged from 2 months to 28 months
- Interval between TKI and IL-2 ranged from 1-8 months

Results: Doses Received

- Median number of IL-2 doses received in our analysis
  - Course 1, Week 1 = 11 (79%)
  - Course 1, Week 2 = 8 (61%)
  - Median for course 1 was 18/28 (64%)
- Median number of IL-2 doses received in the CWG Trial
  - Course 1, Week 1 = 12
  - Course 1, Week 2 = 8
  - Median for Course 1 was 21 (68%)

Results: Doses Received

- Our Analysis:
  - 6/16 (37.5%) patients (95% CI 15.2% - 64.6%) did not receive C1 W2

- CWG Phase III Trial:
  - 12/89 (13.5%) patients (95% CI 7.2%- 22.4%) did not receive C1 W2 therapy

    (p=.03)

Impact of TKI Therapy

- 6/10 pts (60%) with prior TKI did not receive week 2
- 0/6 pts (0%) with prior Bevacizumab alone did not receive week 2

  p=0.034

Results: Toxicities

- Expected toxicities seen
- Toxicities that prevented further Rx
  - Bullous pemphigoid
  - Irreversible cardiomyopathy
  - Myocarditis
  - Severe angina
  - Atrial fibrillation with associated hypotension and bowel ischemia
  - Sudden fatal cardiac arrest

Results: Toxicities

- Incidence of severe (grade 3-5) cardiac toxicities in pts with prior TKI therapy was 50%
  - (95% CI 18.7% to 82.3%)
- Incidence is 8.5% in CWG Phase III trial
- No responses seen

Conclusions

- Small, retrospective analysis highlights unexpected and severe cardiac toxicity in TKI failures receiving IL-2
- The assumption that IL-2 can be given safely to TKI failures may not be valid
- Further examination of the safety of this approach is necessary and more cautious patient selection appears warranted

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