Interleukin-2 and Related Cytokines: Indications and Clinical Management

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SITC: Advances in Cancer Immunotherapy Meeting

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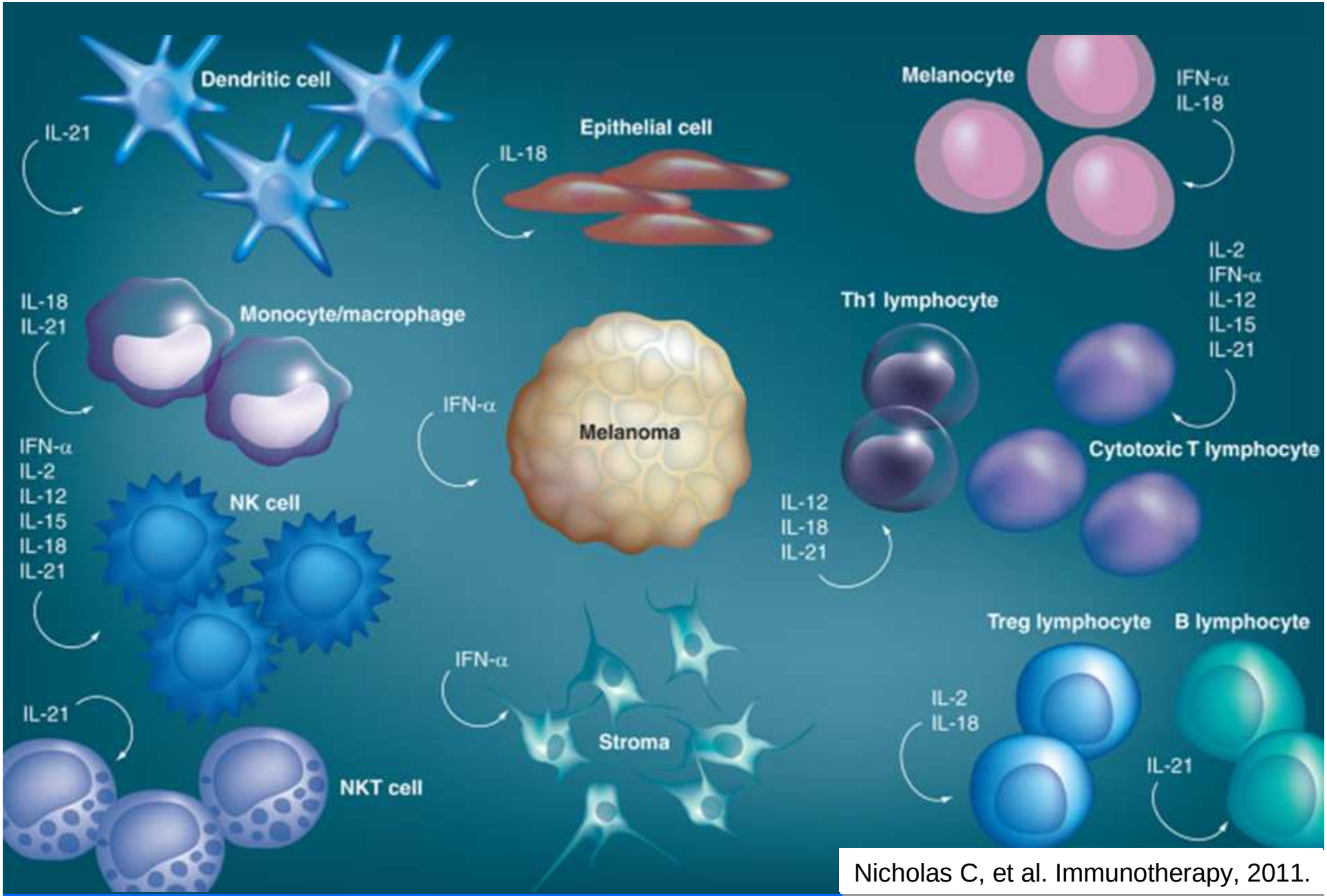
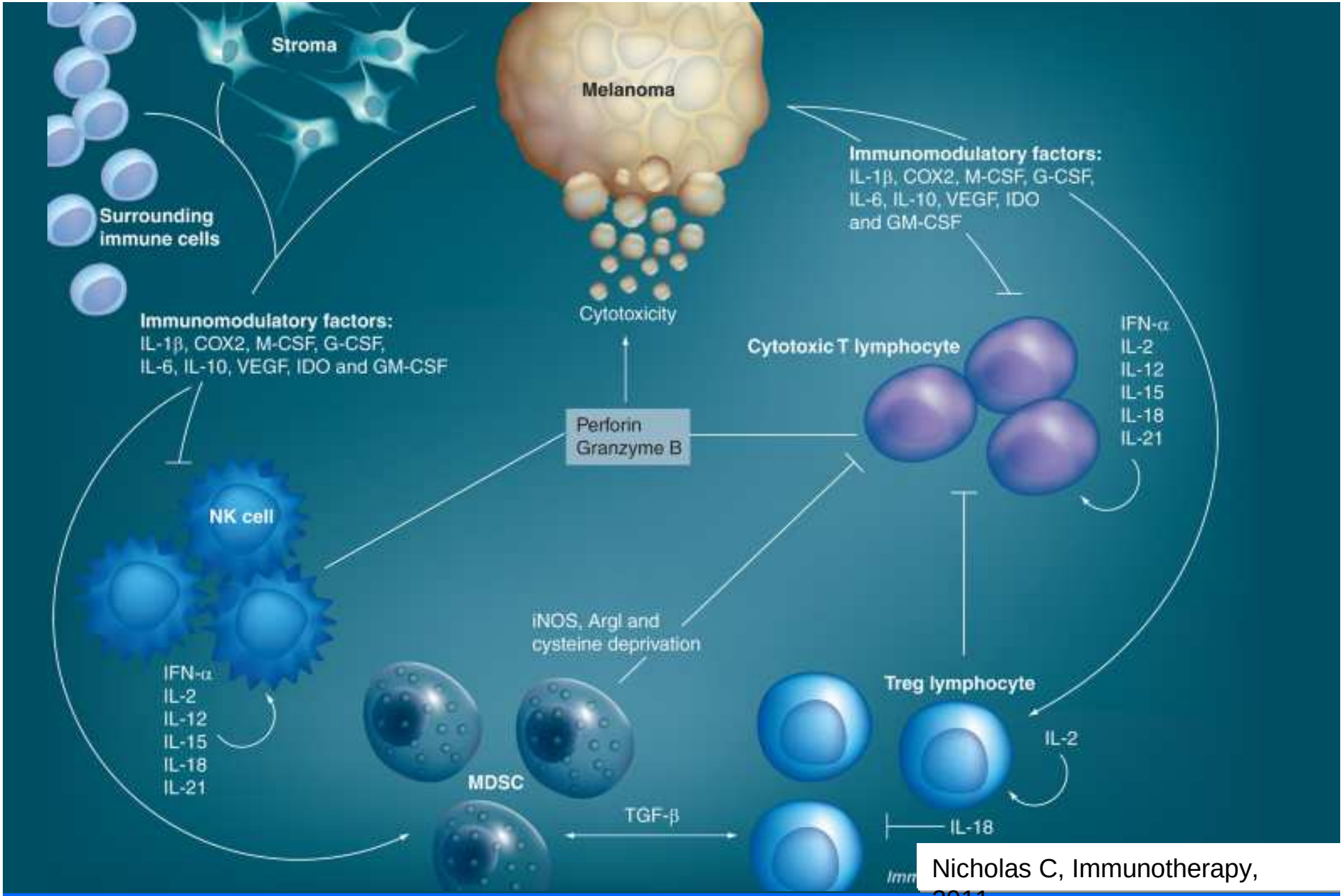


Nicholas C, et al. Immunotherapy, 2011.



Nicholas C, Immunotherapy, 2011.

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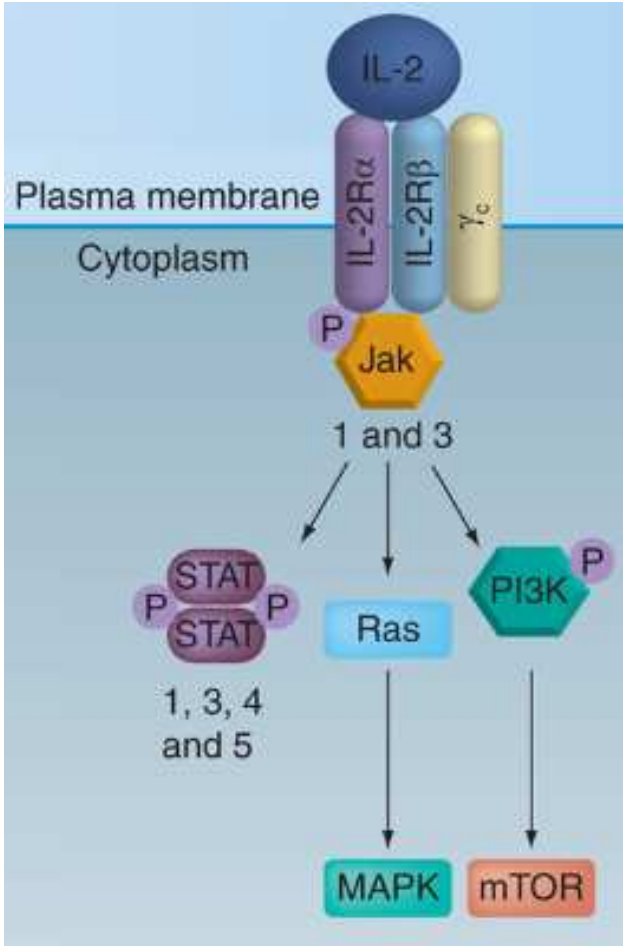
Interleukin-2

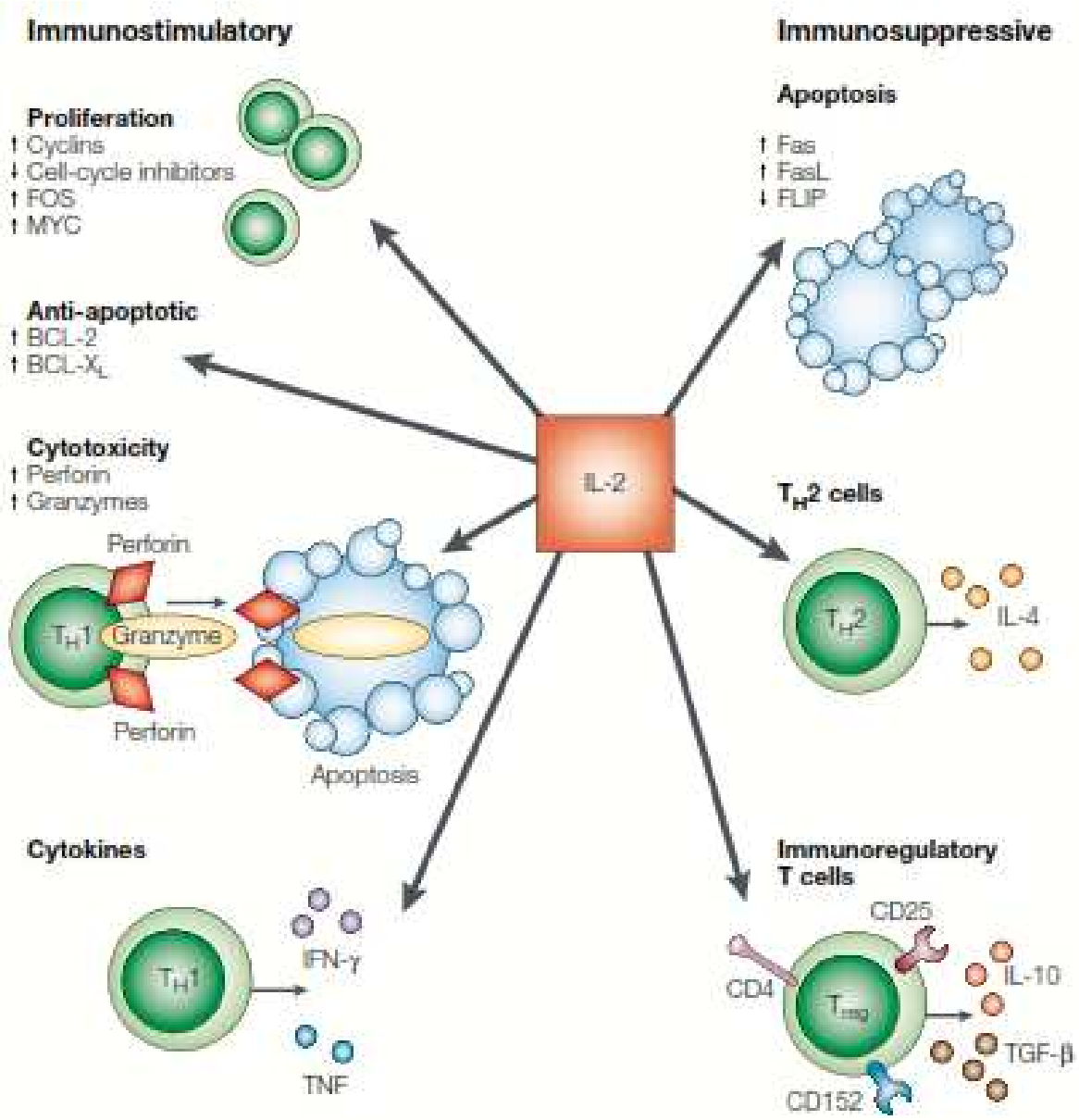
- Immunomodulatory agent
  - T-cell proliferation/activity,
  - T-cell secretion of cytokines
  - NK/LAK cell activation
- Activity in multiple cancer models
  - RCC
  - Melanoma
- FDA-Approved in 1992 (RCC) and 1998 (melanoma)



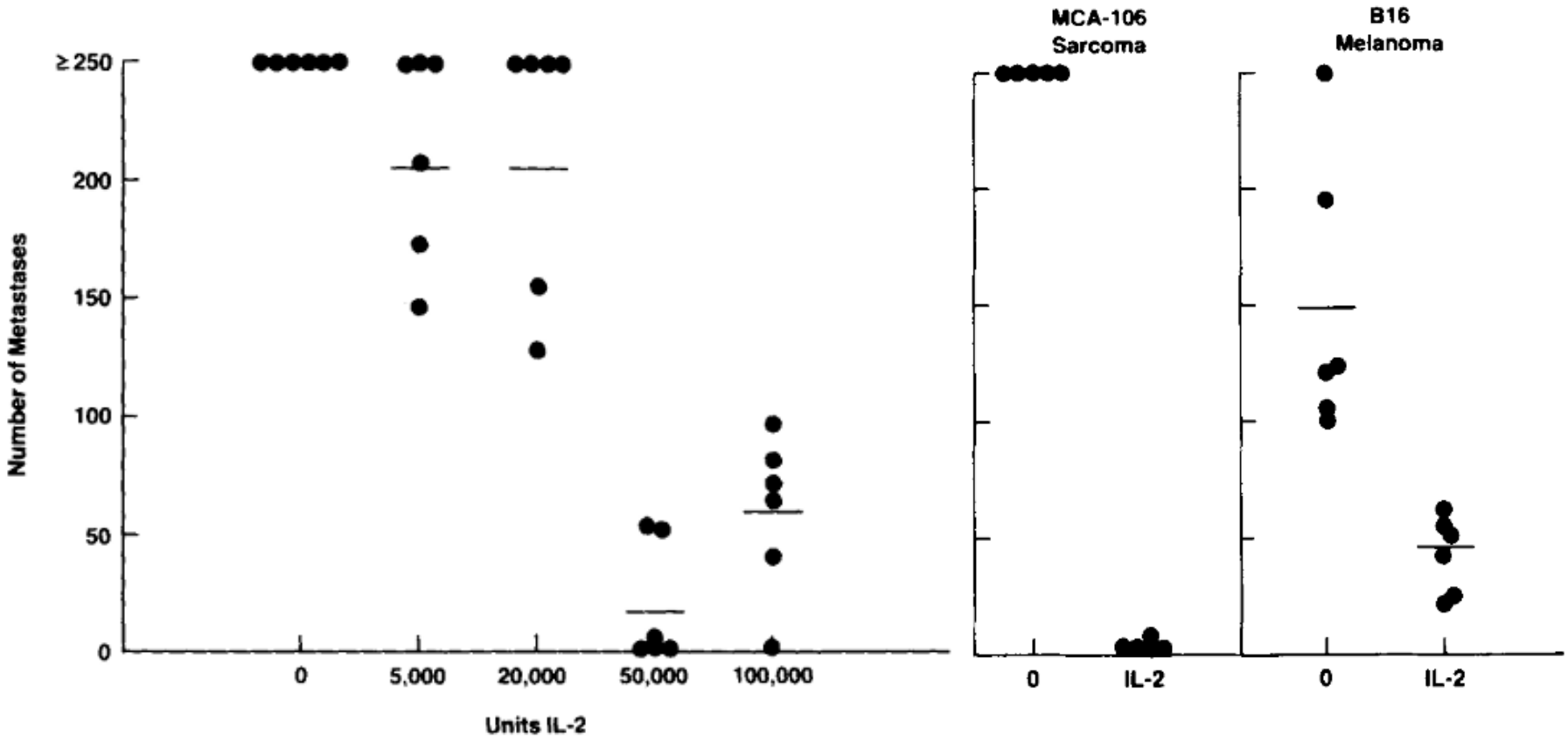
Nicholas C, Immunotherapy, 2011.

Immune effects of Interleukin-2

O'Shea J, et al Nature Reviews, 2001

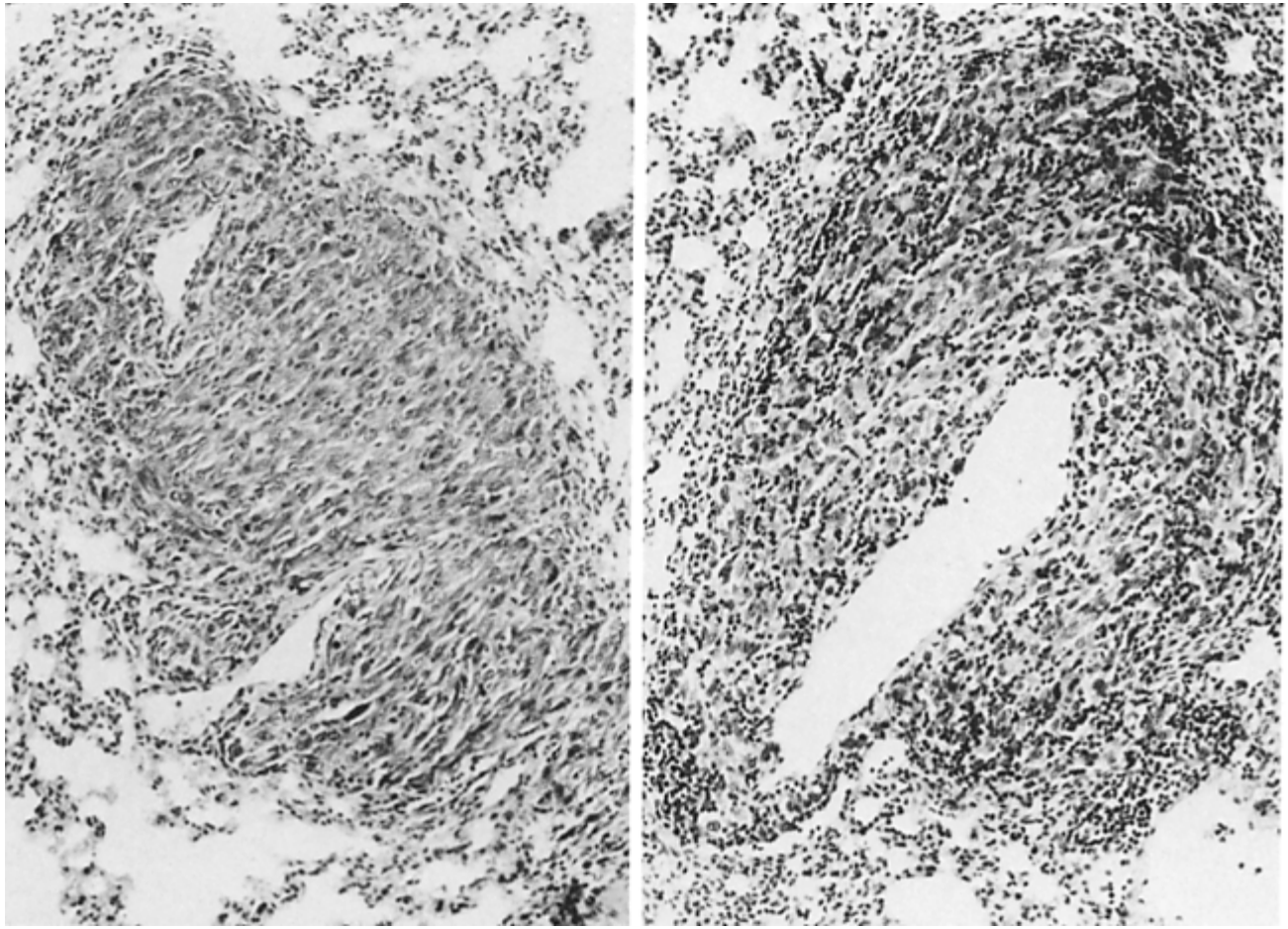


Initial Preclinical Activity of IL-2



Rosenberg SA, J Exp Med, 1985

Initial Preclinical Activity of IL-2



Rosenberg SA, J Exp Med, 1985

IL-2 Clinical Studies

- Many retrospective and prospective studies of high dose recombinant IL-2
  - focus on RCC and melanoma
- Dose range: 600,000 to 720,000 IU/kg

  as a 15 minute intravenous infusion
- Treatment schedule:
  - Q8hrs over five consecutive days
  - One course = two cycles, begin days 1 and 15.
  - Responding/stable patients are retreated for up to three courses total (repeat every 12 wks)

NCI Experience with IL-2 Rosenberg SA, JAMA, 1994

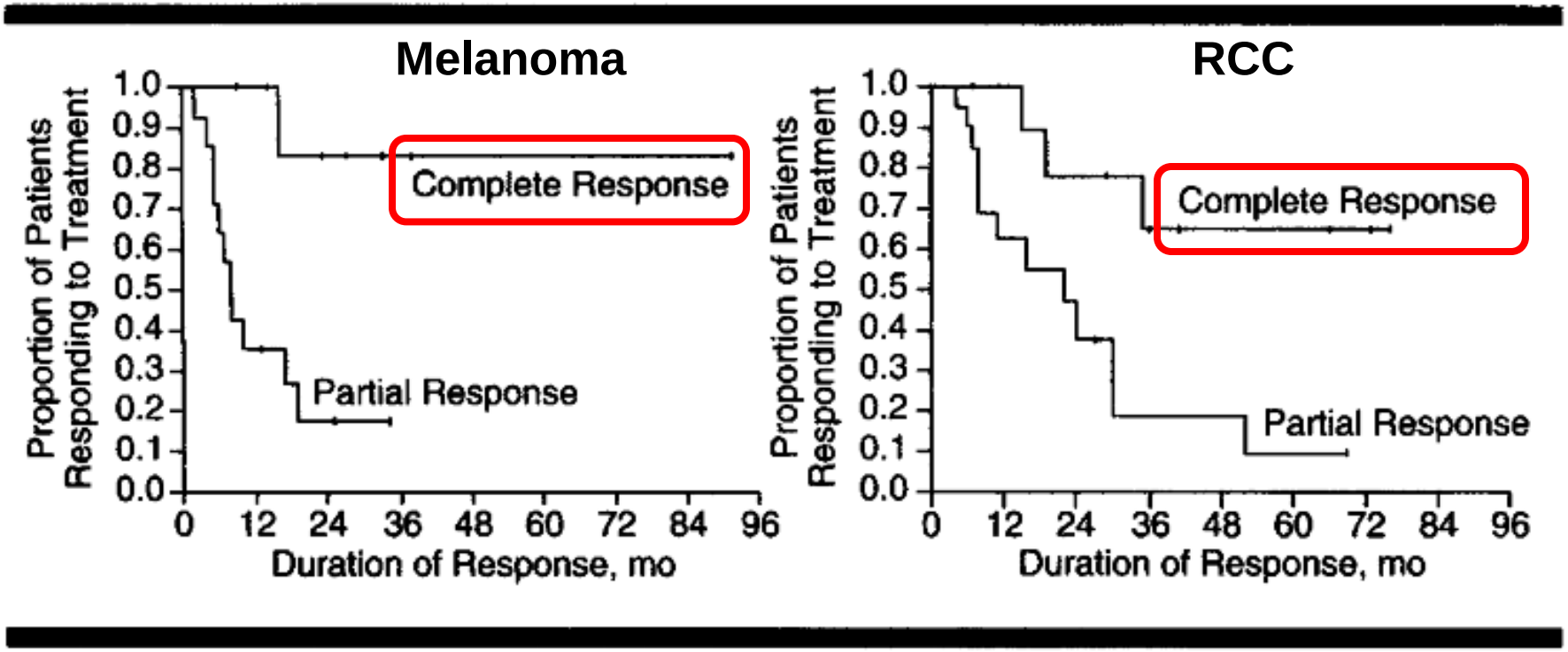
- 283 consecutive pts with RCC or Melanoma pts
- 14% prior chemotherapy
- 25% prior immunotherapy
- 75% ECOG PS of 0
- Age range 11- 70 yrs old

	Diagnosis		
	Melanoma	Renal Cell	Total
	No. (Mean±1 SD) of Doses		
No. of IL-2 doses per cycle			
Course 1			
Cycle 1	9.7±2.4	8.8±2.5	9.2±2.5
Cycle 2	7.4±2.4	6.0±2.6	6.7±2.6
Course 2			
Cycle 1	8.3±2.6	7.6±2.3	7.9±2.4
Cycle 2	5.8±2.3	4.7±2.3	5.2±2.4
Course 3			
Cycle 1	8.5±2.8	7.4±2.0	7.8±2.4
Cycle 2	6.3±2.3	4.4±1.6	5.2±2.1

Table 3.—Results of Immunotherapy With High-Dose Bolus Interleukin 2 in Patients With Advanced Cancer

	No. (%) of Patients			
Diagnosis	Total	Complete Regression	Partial Regression	Complete or Partial Regression
Melanoma	134	9 (7)	14 (10)	23 (17)
Renal cell cancer	149	10 (7)	20 (13)	30 (20)
Total	**283**	**19** (7)	**34** (12)	**53** (19)

NCI Experience with IL-2



High rate of Toxicities with IL-2

Gr3-4 or Serious Event	% of patients
Chills/Rigors	18%
Nausea/Vomiting	38%
Diarrhea	30%
Fatigue	15%
Anemia/Thrombocytopenia	Most patients
Oliguria / Cr > 2.0 mg/dL	22% / 69%
Weight gain (>10%)	28%
Hypotension	52%
Angina / Arrhythmias	1% / 6%
Respiratory failure requiring intubation	3%
Infection	4%
Death	1%

Rosenberg SA, JAMA, 1994

Toxicity Management

- Etiology:
  - Direct injury to organ systems
  - Release of secondary cytokines
  - Vasogenic dilation and leak

Event	Management
Rigors	premedicate (indomethacin, acetaminophen, diphenhydramine), opiates (hydromorphone, meperidine)
Hypotension	hold antihypertensives; IVF, dopamine infusion, ICU transfer
Renal failure	IVF, diuretics, dopamine infusion, hemodialysis
Infection	prophylactic antibiotics, line care
Arrhythmias	continuous cardiac monitoring, anti-arrhythmics

Patient Selection (Favorable Predictive Biomarkers)

Melanoma

- Subcutaneous mets
- Normal serum LDH
- Low pretreatment serum markers:
  - CRP
  - IL-6
  - VEGF
  - Fibronectin
- Development of vitiligo or auto-immune thyroid disorder
- Genotype (NRAS mutation)

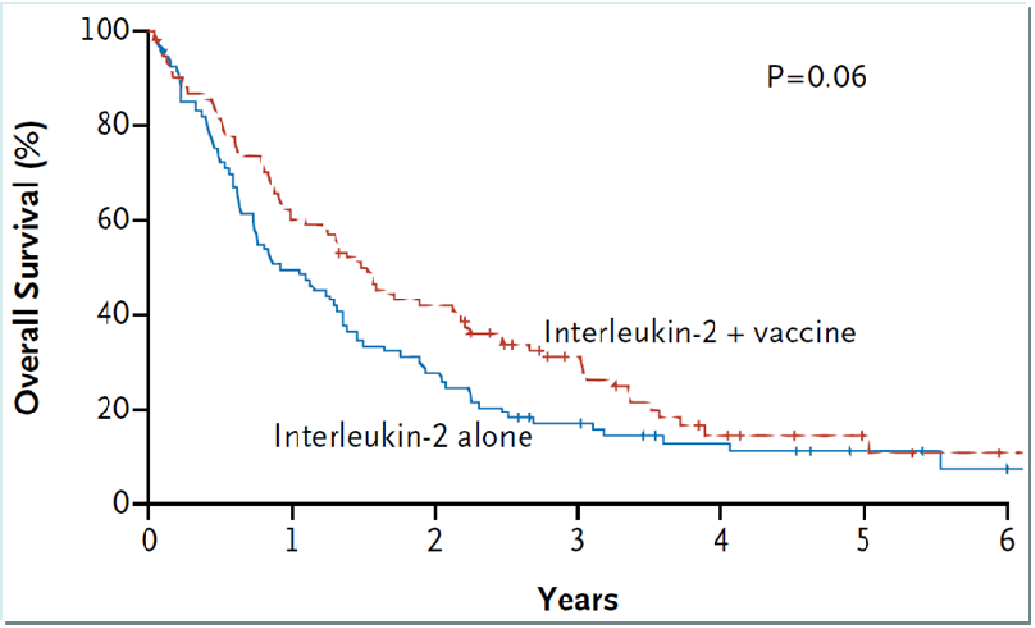
RCC

- Less aggressive disease (only 1 met site, PFS > 1yr, no liver/mediastinal LN disease)
- Prior nephrectomy
- Development of thrombocytopenia and hypothyroidism
- Clear cell histology, especially with alveolar features
- High carbonic anhydrase IX (CAIX) expression

Phase III Melanoma Study of IL-2 vs IL-2 plus GP100 vaccine

	IL-2 = 94	IL-2+GP = 91
CR	1%	9%
PR	5%	7%
mPFS	1.6 mos	2.2 mos
mOS	11.1 mos	17.8 mos
AE (Gr3-5)	80%	86%

Common AEs (Gr3-5)
- BM suppression (35%/48%)
- Cardiovascular (27%/36%)
- GI (18%/21%)
- Hepatic (39%/40%)
- Metabolic (21%/42%)
- Neurologic (12%/26%)
- Pulmonary (21%/22%)
- Renal/GU (15%/19%)

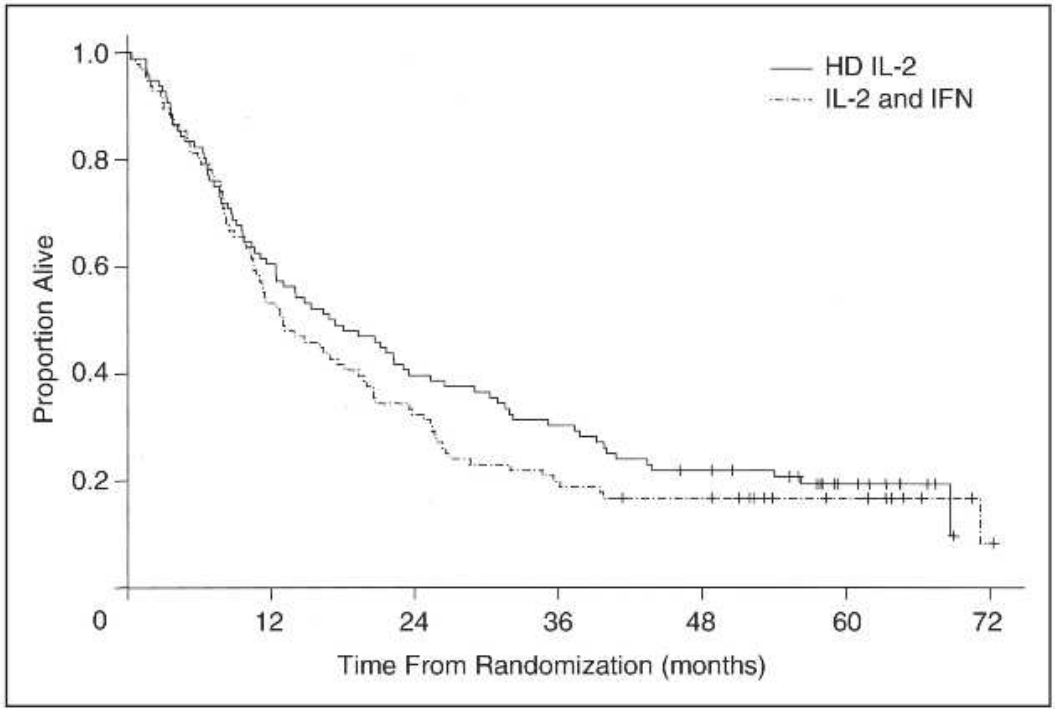


Schwartzentruber DJ, N Eng J Med, 2011

Phase III RCC Study of Standard IL-2 vs Subcutaneous IL-2 + IFNa

	HD IL-2 = 95	SC IL-2 + IFN = 91
CR	8.4%	3.3%
PR	14.7%	6.6%
mPFS	similar	
mOS	17 mos	13 mos

Common AEs (Gr3-4)
- Constitutional (3% / 14%)
- Hypotension (57% / 1%)
- Cardiac (8% / 0%)
- GI (9% / 10%)
- Hepatic (12% / 2%)
- Renal/electrolytes (14% / 3%)
- Neurologic (15% / 3%)
- Pulmonary (14% / 1%)



McDermott DF, J Clin Oncol, 2005

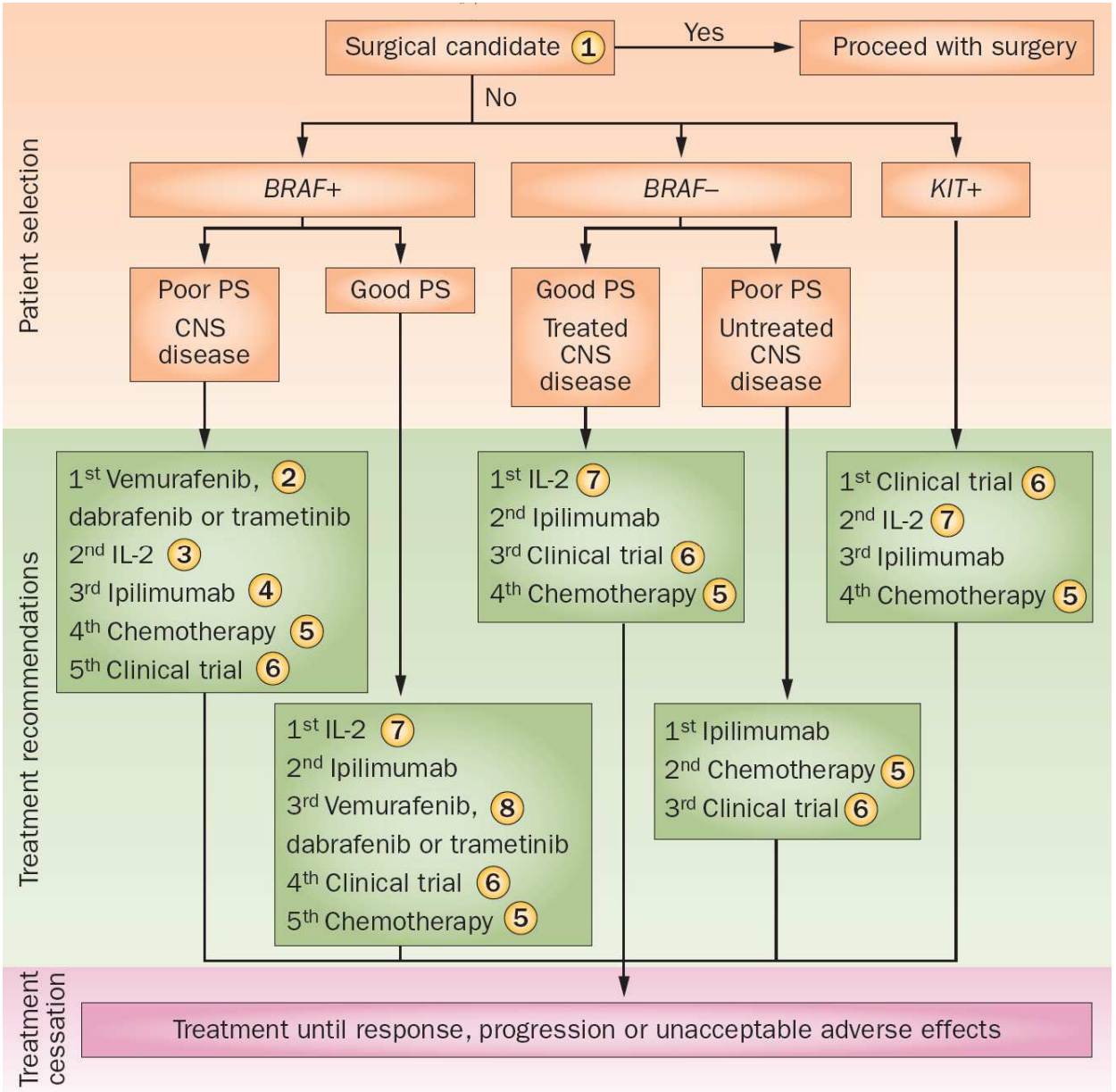
Melanoma Therapies 2013

Chemotherapy	Immunotherapy	Targeted Therapy
Dacarbazine (FDA approved 1975)	**Interleukin-2 (FDA approved 1998)**	Vemurafenib (FDA approved 2011)
Temozolomide*	High-dose Interferon adjuvant tx (FDA approved 1995)	Dabrafenib (FDA approved 2013)
Carboplatin/Paclitaxel*	Adoptive Cell Therapy (TIL)*	Trametinib (FDA approved 2013)
	PEG-Interferon Adjuvant tx (FDA approved 2011)	Imatinib*
	Ipilimumab (FDA approved 2011)	
Biochemotherapy* (Cisplatin, Dacarbazine, Vinblastine, IL2, IFN)		

*Not FDA–approved indication, but used off-label

Melanoma Treatment Algorithm recommended by SITC

Kaufman HL,
Nat Rev Clin Oncol
2013



RCC Therapies 2013

Chemotherapy	Immunotherapy	Targeted Therapy
Capecitabine*	**Interleukin-2 (FDA approved 1992)**	Sorafenib (FDA approved 2005)
Gemcitabine*	Interferon-alpha* (single agent)	Sunitinib (FDA approved 2006)
Doxorubicin/ifosfamide*		Temsirolimus (FDA approved 2007)
	IFN-alpha plus bevacizumab (FDA approved 2009)	
		Pazopanib (FDA approved 2009)
		Everolimus (FDA approved 2009)
		Axitinib (FDA approved 2012)

*Not FDA–approved indication, but used off-label

RCC Treatment Options

Adapted from:

NCCN guidelines
Escudier B, Nat Rev Clin Oncol, 2012

	Therapies
First tier options	HD IL-2* Sunitinib Temsirolimus** Bevacizumab + IFNa
Second tier options	Axitinib Sorafenib Pazopanib Everolimus
Further options	Chemotherapy Clinical trial

* Good PS; NL LDH, calcium, and Hb levels; prior nephrectomy; clear cell histology
** Generally first line for poor prognosis and non-clear cell patients

Interferon alpha

Melanoma

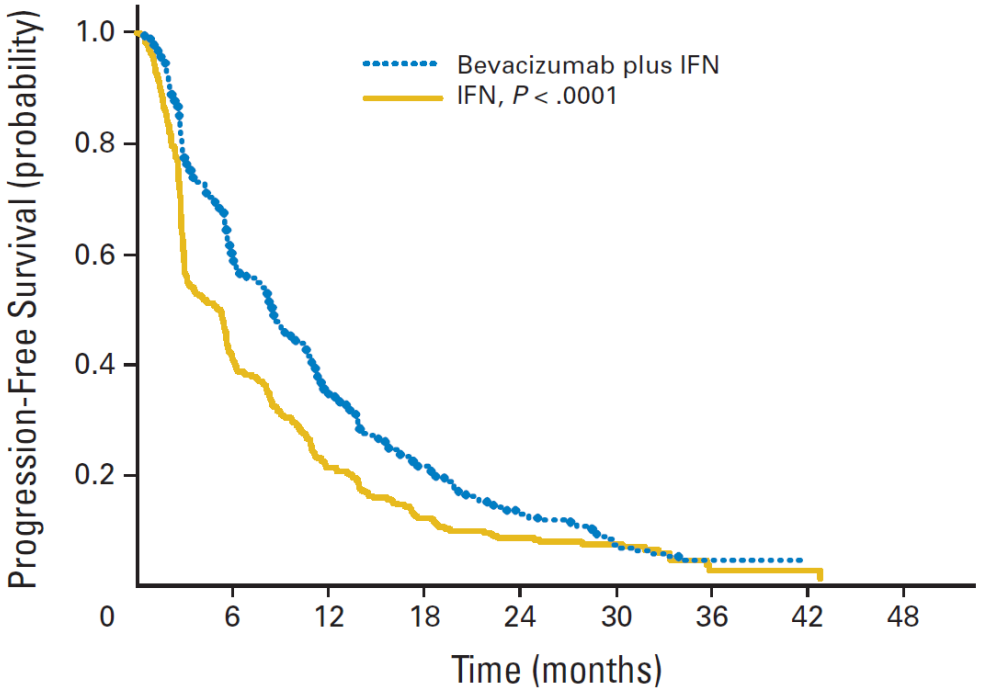
- FDA approved for adjuvant tx; clinical benefit remains controversial
- Objective responses seen in metastatic melanoma, but current use limited to clinical trials

RCC

- Monotherapy
  - Up to 15% response rate, but generally short lived and few complete responses
  - Daily dosing is between 5 to 10 MU subcutaneous 3x/wk
  - Faired poorly in phase III trials against sunitinib and temsirolimus (similar PFS to sorafenib in phase II evaluation).
- Combination therapy with bevacizumab
  - Rational: clinical benefit already for both IFNa and anti-VEGF tx
  - IFN-a plus bevacizumab has more clinical activity than IFN-a alone

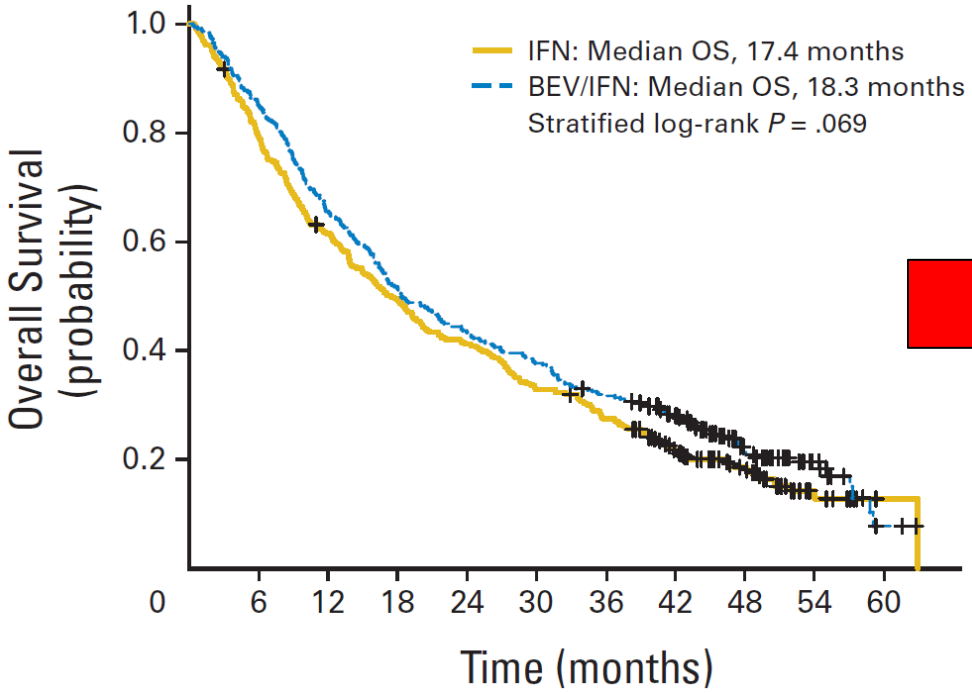
Phase III study of bevacizumab plus IFNa vs IFNa alone in RCC (CALGB 90206)

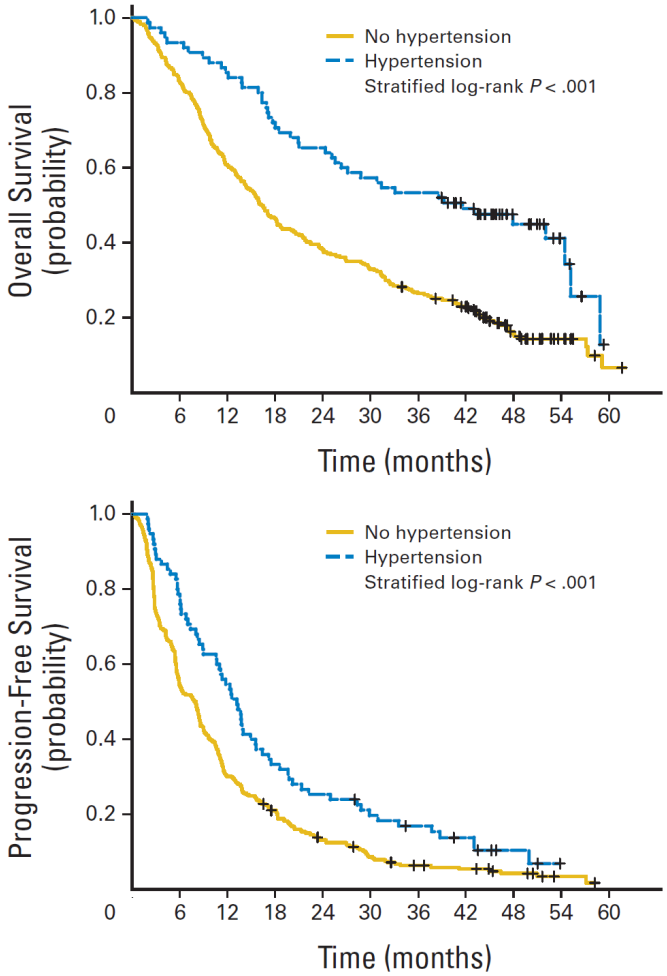
	Bev + IFNa N = 369	IFNa N = 363
ORR	26%	13%
mPFS	8.5 mos	5.2 mos
AE (Gr3)	66%	56%
AE (Gr4)	13%	5%
Common AEs (Gr3-4)		
Hematologic events		
Hypertension		
Fatigue		
Anorexia		
Nausea		
Dyspnea		
Proteinuria		



Rini BI, J Clin Oncol, 2008

Phase III study of bevacizumab plus IFNa vs IFNa alone in RCC (CALGB 90206)





Rini BI, J Clin Oncol, 2010

Other cytokines under investigation as cancer therapeutics

	Mechanism	Cancers
IL-12	Promotes proliferation and activation of NK and cytotoxic T cells; secretion of IFN-γ	RCC, CRC and melanoma, merkel cell carcinoma, prostate cancer, and ovarian cancer
IL-18	Promotes proliferation and activation of NK and cytotoxic T cells; secretion of IFN-proliferation of Tregs	RCC, melanoma, and lymphoma
IL-21	Promotes proliferation of activated B cells, activated NK and NKT cells, and cytotoxic T lymphocytes, and differentiation of plasma cells	Melanoma, RCC, ovarian cancer, and lymphoma