

Treatment of Advanced Melanoma: Myths, Facts and Clinical Trials

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Adjuvant Therapy:

What to do after surgery?

- Careful observation- CT scans, physical exams, blood tests
- Clinical trials- mainly of investigational immunotherapies (vaccines and antibodies)
- High dose interferon alfa (Intron A)

Interferon- α

- Approved in 1995 based on results of ECOG-1684 (9 % survival benefit)
- 20 MU/m² IV, 5 days/week x 4 weeks, then 10 MU/m² SC, TIW x 11 months
- Hepatic, cardiac, constitutional and psychiatric toxicities necessitating dose reduction in 2/3 of patients
- ECOG-1690: a confirmatory trial?

ECOG-1690

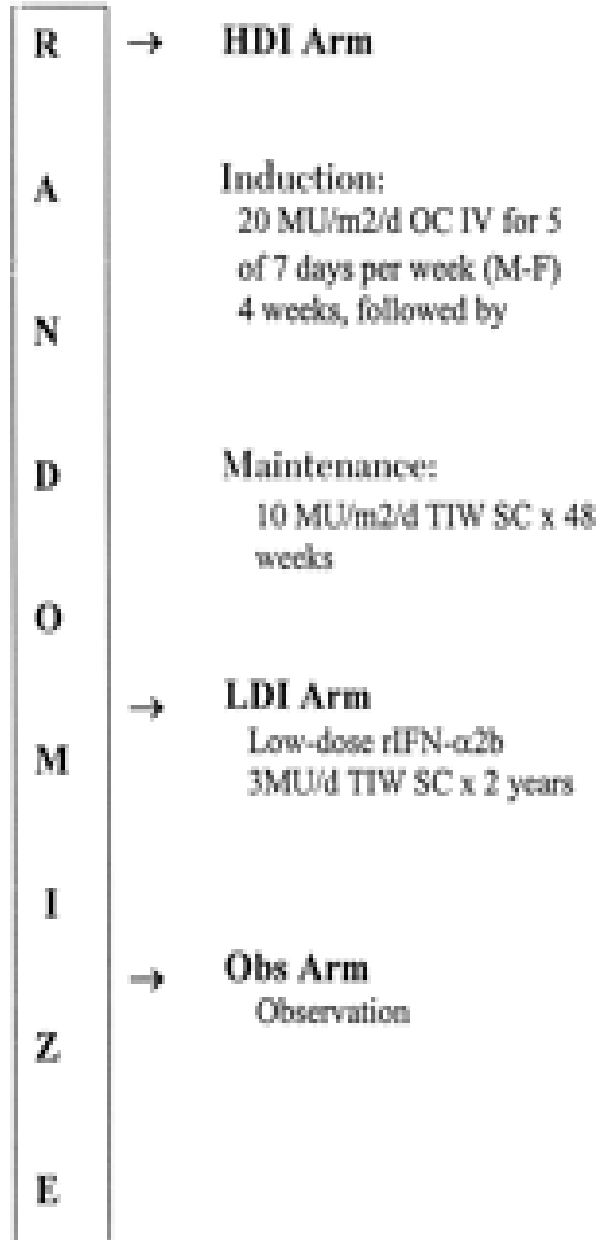
Stratification Groups

I. Stage at Randomization

T4 N0 M0	(AJCC stage IIB) deep primary melanoma without lymph node involvement (either clinical or pathologic)
T1-4 N1 M0	Resected stage IIIA except local recurrence and in-transit metastases) Synchronous presentation of primary melanoma with clinically undetectable (occult) regional lymph node metastases found at lymphadenectomy
T1-4 N1-2 M0	(Lymph node recurrence metachronous regional lymph node metastases

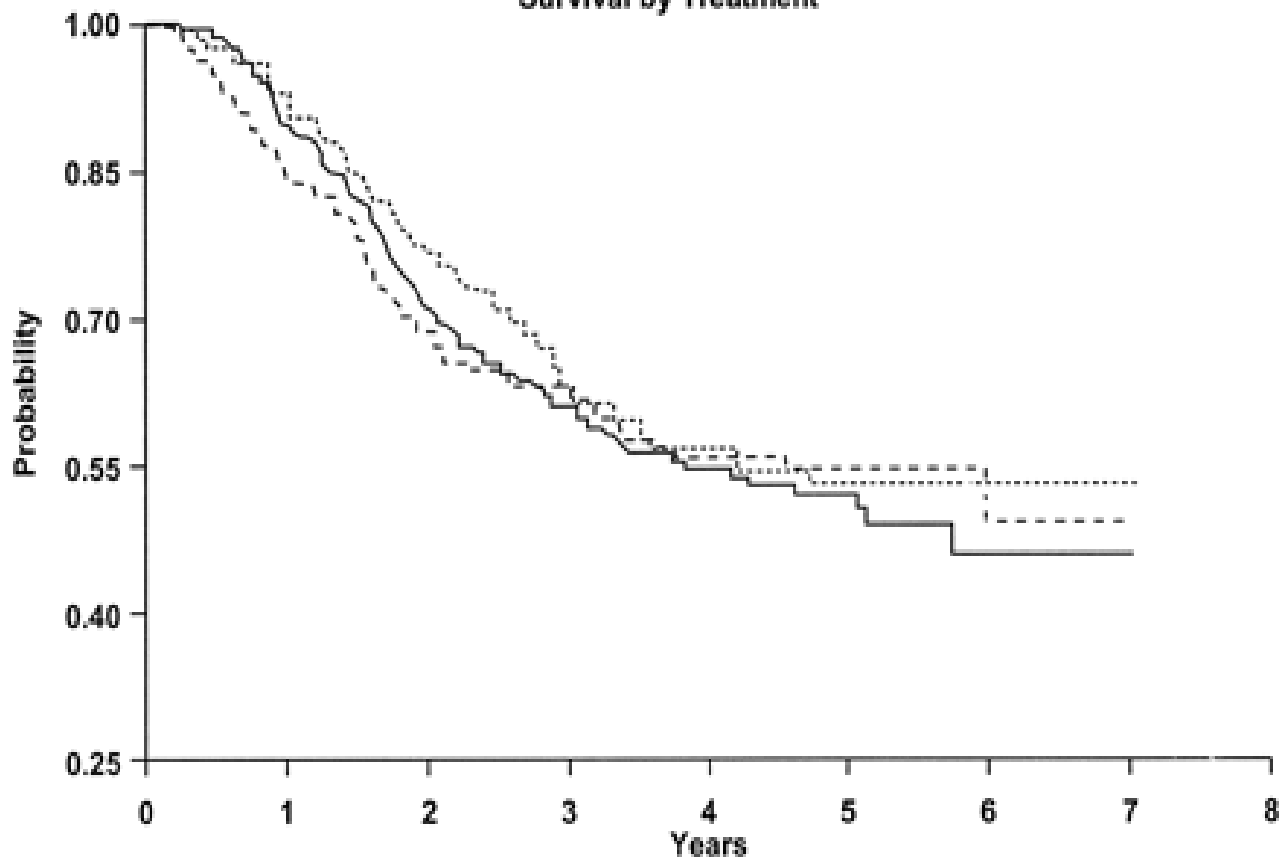
II. Number of Nodes Positive at Lymphadenectomy

- 0
- 1
- 2-3
- ≥4



ECOG-1690: OS

Survival by Treatment



Group	Time interval							
	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
—— HDI	21/203	37/182	20/143	10/109	3/71	3/36	0/11	0/1
..... LDI	15/203	32/188	26/155	11/118	4/77	0/30	0/9	0/1
- - - - Obs	31/202	31/170	12/137	11/115	1/75	1/37	0/8	0/0

(# events/# at risk)

(MMAIT) – Multicenter Phase III Trial of Canvaxin™ vs Placebo as Post Surgical Adjuvant

AJCC Stage III Melanoma

Surgical Resection Rendering Pt NED

Stratification Factors

- #tumor-involved lymph nodes: 1, 2-4, 5+
- Clinical status: palpable/nonpalpable nodes

Randomize

**Canvaxin™
+ BCG***

**Placebo
+ BCG***

*Both Arms received BCG with first two doses

*M1b: visceral mets

AJCC Stage IV Melanoma

Surgical Resection Rendering Pt NED

Stratification Factors

- Site of Mets: M1a: soft tissue & nodal mets
M1b/c: visceral mets*
- # individual metastatic lesions: 1, 2-3, 4-5

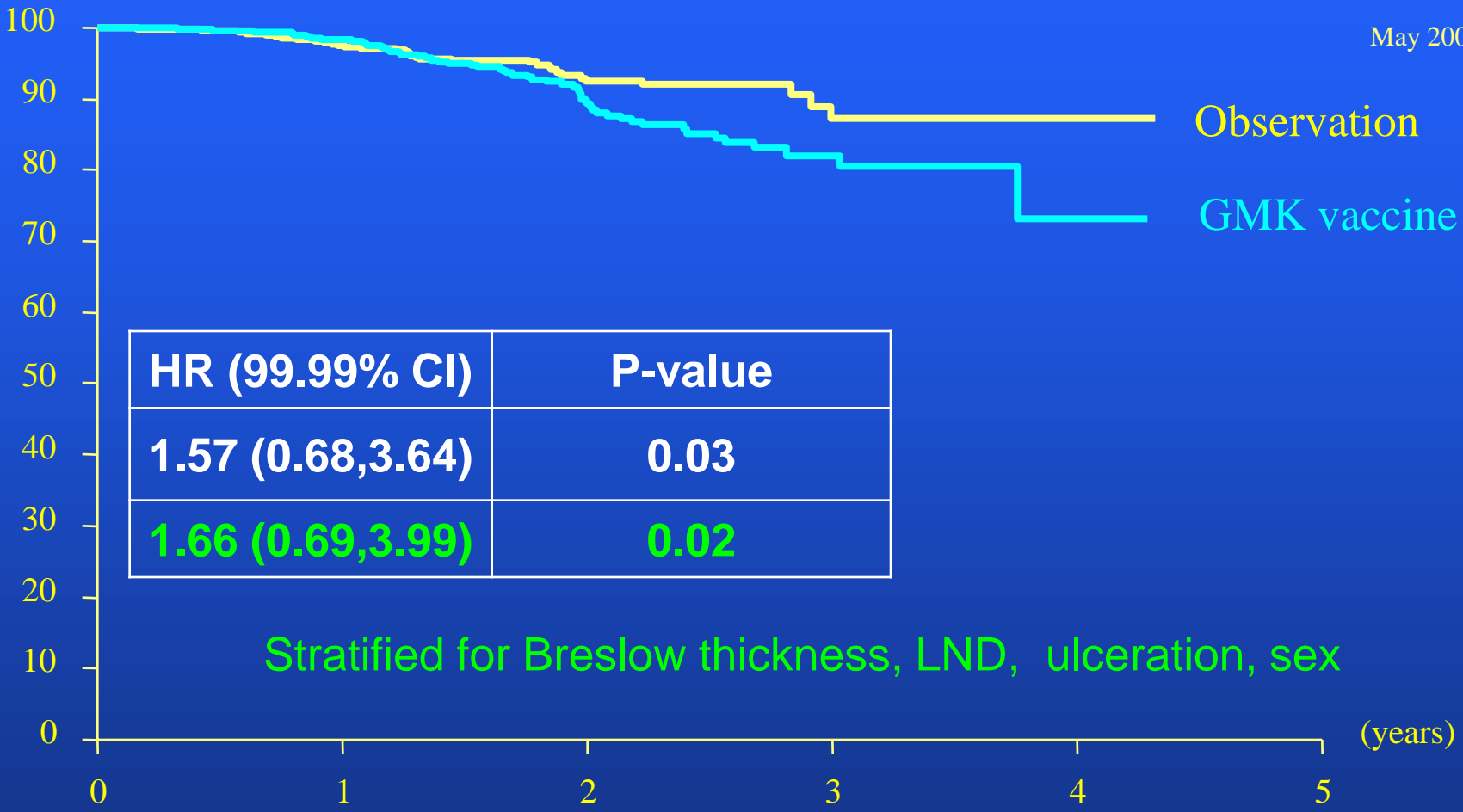
Randomize

**Canvaxin™
+ BCG***

**Placebo
+ BCG***

M1b + M1c = AJCC 2000

May 2007

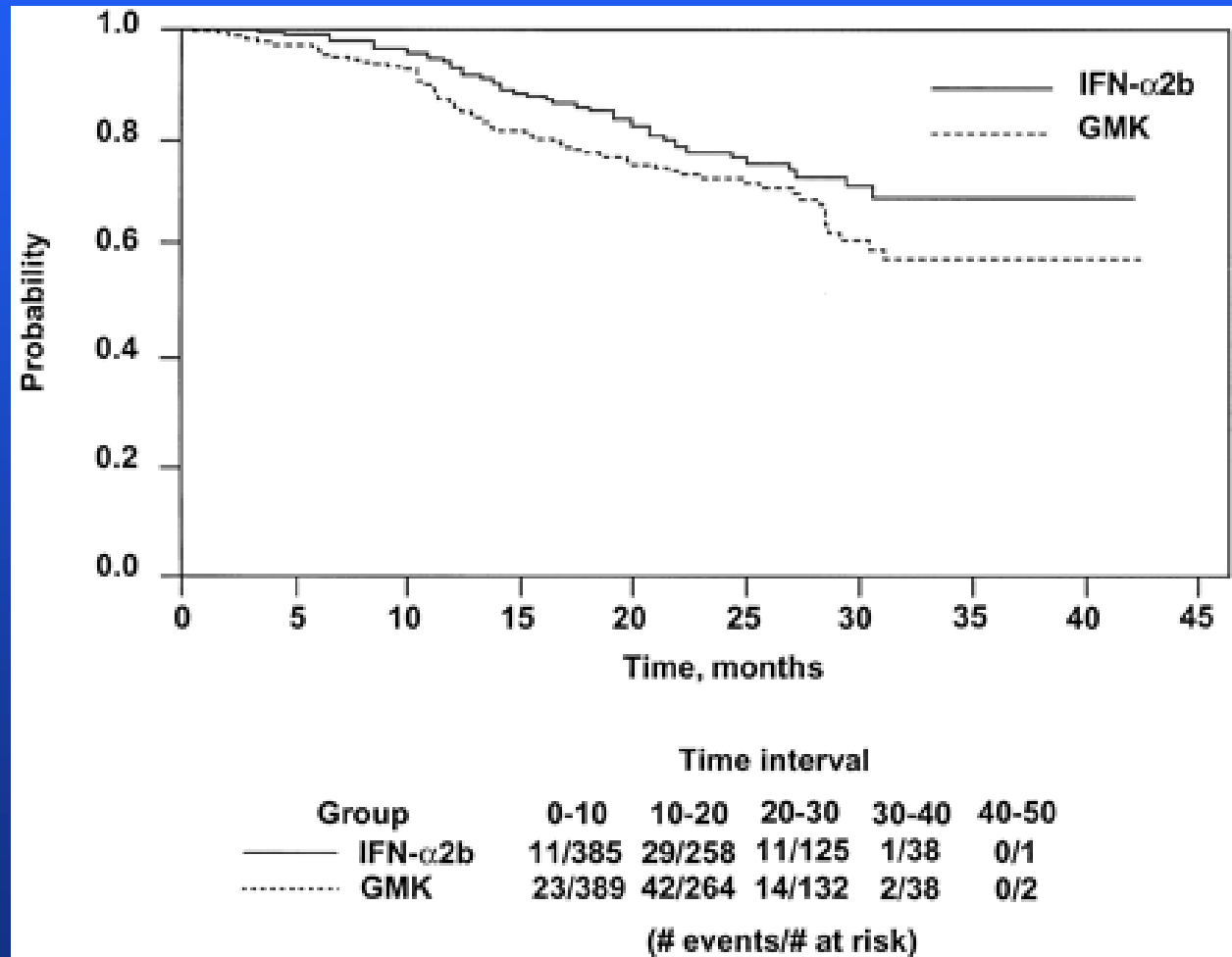


O	N	Number of patients at risk :					Treatment
35	657	477	214	51	3	— Observation	
56	657	478	221	57	4	— GMK vaccine	

High Dose IFN versus GMK (ECOG 1694)

- OS
- HR 1.38
- P = 0.023

- 18961
- HR 1.66
- P = 0.02



What to do if recurrence happens?

- Surgery
- Radiation Therapy
- Chemotherapy
- Immunologic Therapy

Metastatic Melanoma—2009

<u>Approved Therapies (USA)</u>	<u>Date</u>
• DTIC	1970s
• High-dose interleukin-2	1998

Many patients will receive both agents

Myth:

Chemotherapy doesn't work in
melanoma

Single Agent DTIC Activity*

- Response rate 19%
- Median response duration 4 mos
- Median survival 6–9 mos
- 6-year survival <2%

DTIC has never been compared with observation or best supportive care

Activity of single agents in melanoma

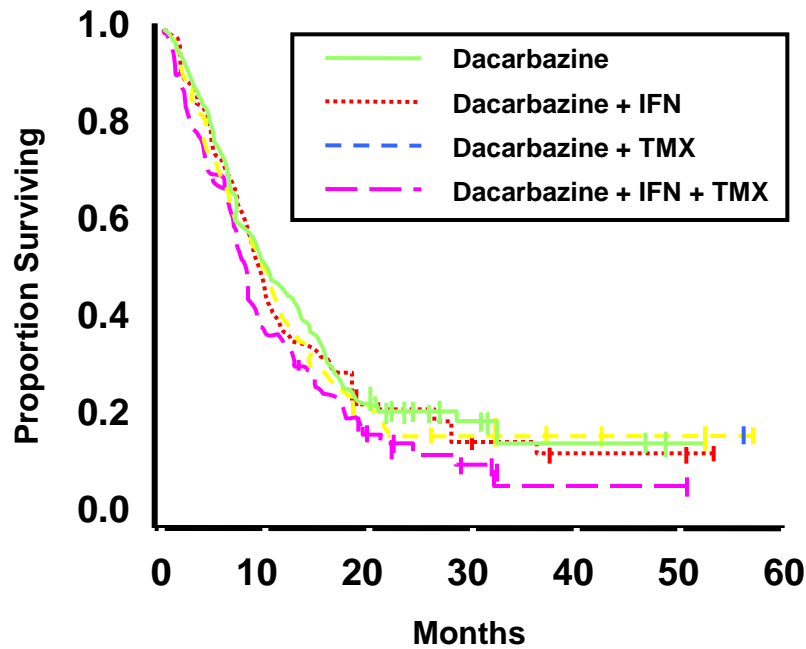
DTIC	10-20%
Nitrosoureas	10-18%
Cisplatin	14-29%
IL-2	18%
Interferon- α	16%
Taxol	14%
Vincristine	12%

Early phase II trials of Dartmouth regimen

	No. of patients	PR	CR	Resp. Rate
Del Prete, et al.	20	7	4	55%
McClay, et al.	45	18	5	51%
Fierro, et al.	32	10	5	47%
Reintgen, et al.	47	11	6	36%
Richards, et al.	20	11	0	55%
Berd, et al.	147	41	17	39%
Total	319	100	40	44%

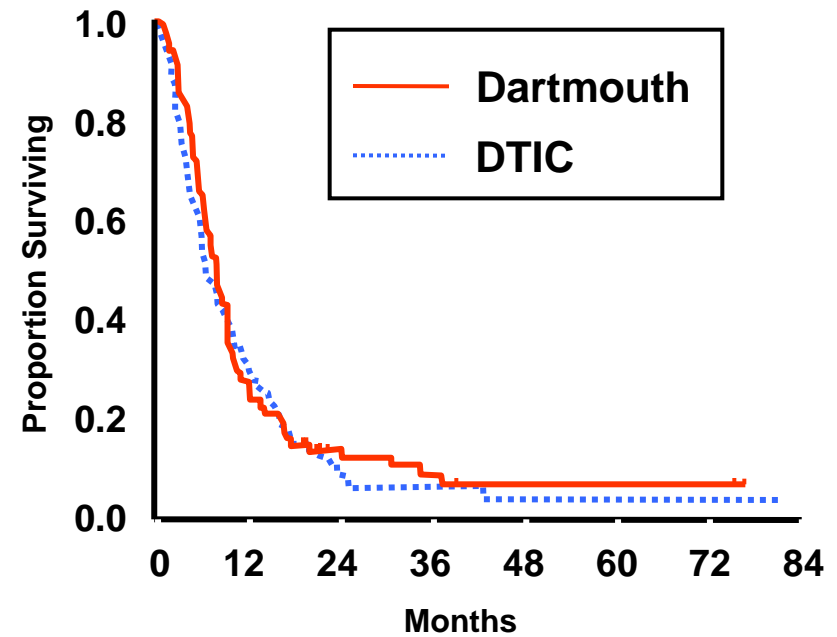
More Recent Phase III Trials

DTIC +/- IFN +/- Tam



Falkson et al. *JCO*, 1997

DTIC vs Dartmouth



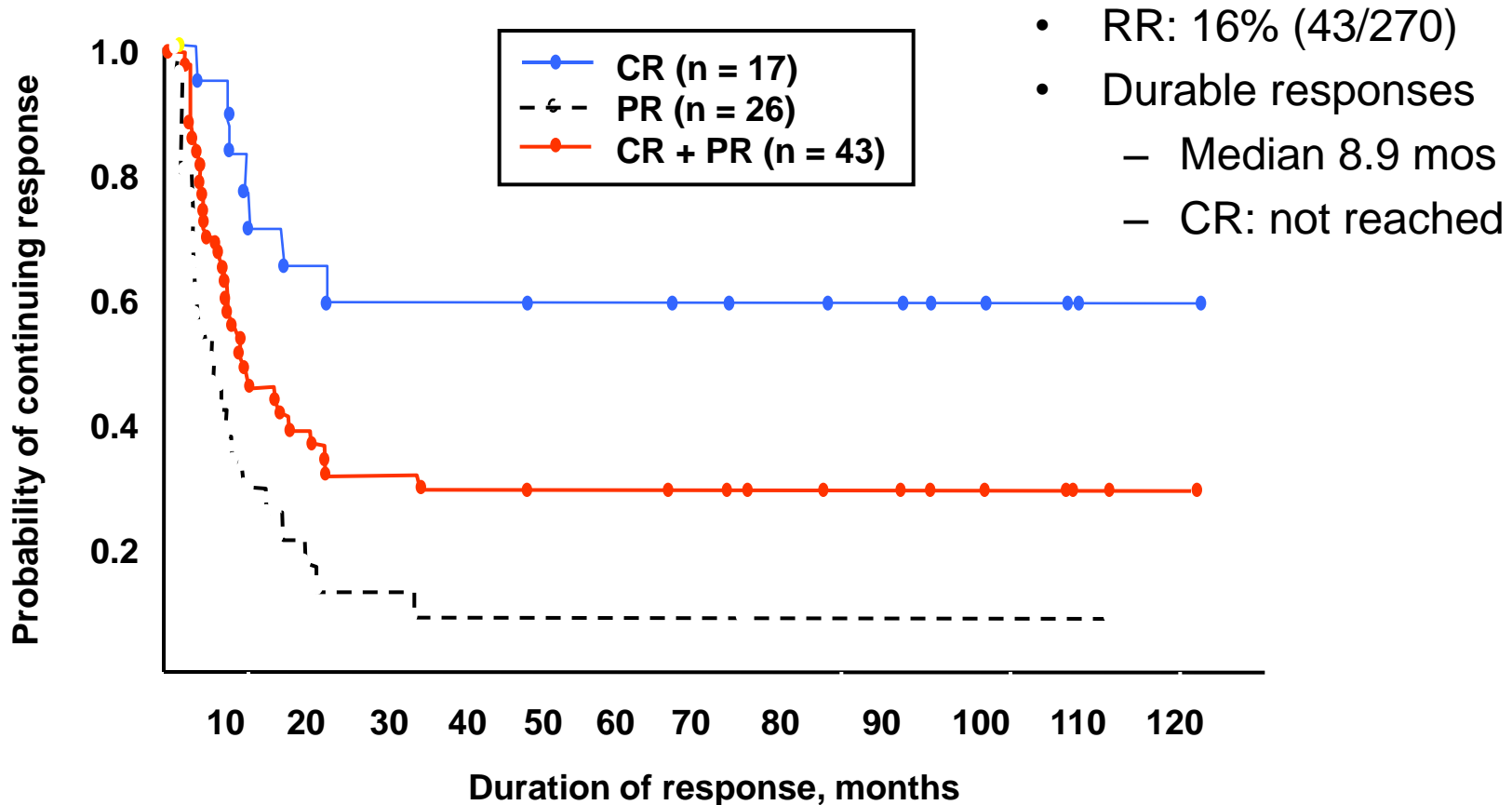
Chapman et al. *JCO*, 1999

Cytotoxic Chemotherapy: Conclusion

There is currently no evidence that combination chemotherapy or the addition of IL-2 or IFN is superior to chemotherapy alone.

Combinations of minimally active drugs yield minimal activity.

High-Dose IL-2 Therapy*



IL-2 Toxicity: Constitutional

- Rigors/fevers
- Myalgias/arthralgias
- Fatigue
- Nausea/vomiting/anorexia
- Diarrhea
- Skin rash/pruritis



T-cell receptor: Antigen-MHC



CD28: B7

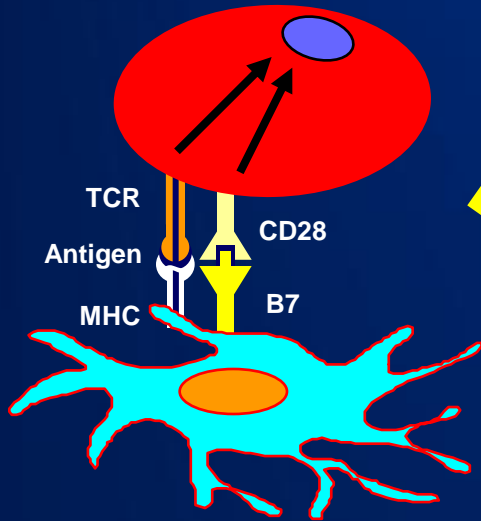


CTLA-4: B7



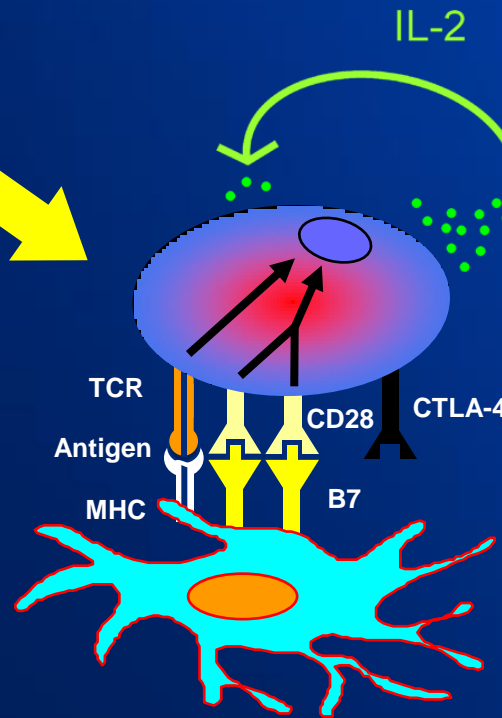
Vaccine?

Regulation of T cell activation is a Complex Process



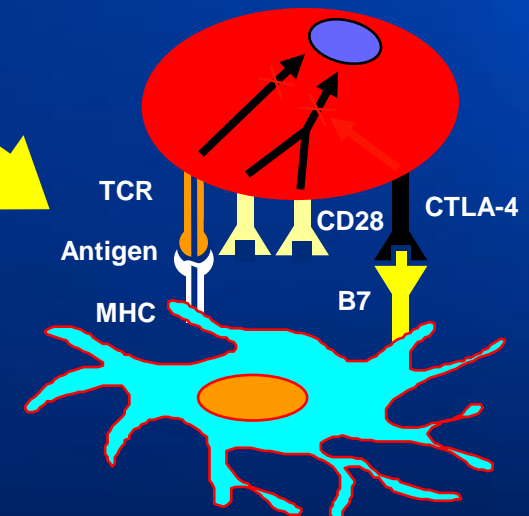
Antigen-specific T cell Activation

- TCR : Antigen MHC
- CD28 : B7 Co-stimulation



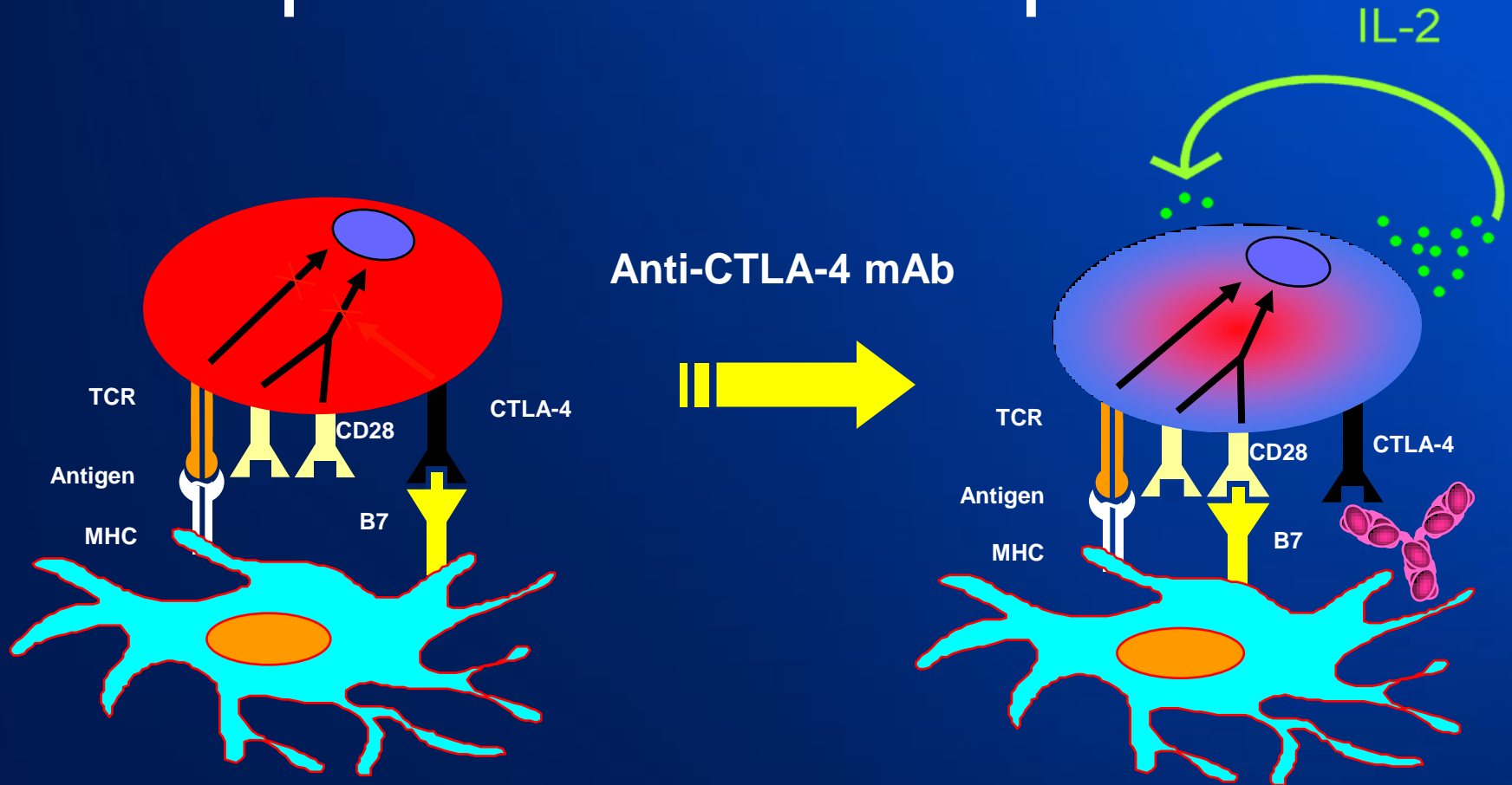
Activated T cell

- IL-2 secretion
- Proliferation
- Effector function
- Induction of CTLA-4

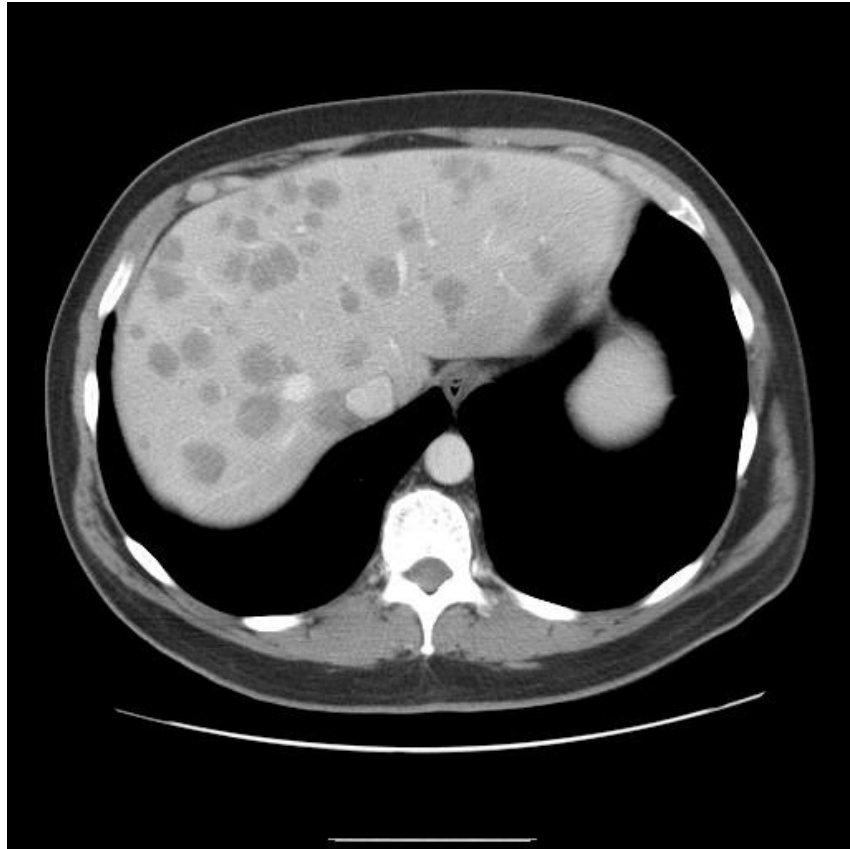


- CTLA-4 : B7 suppression
- Termination of response

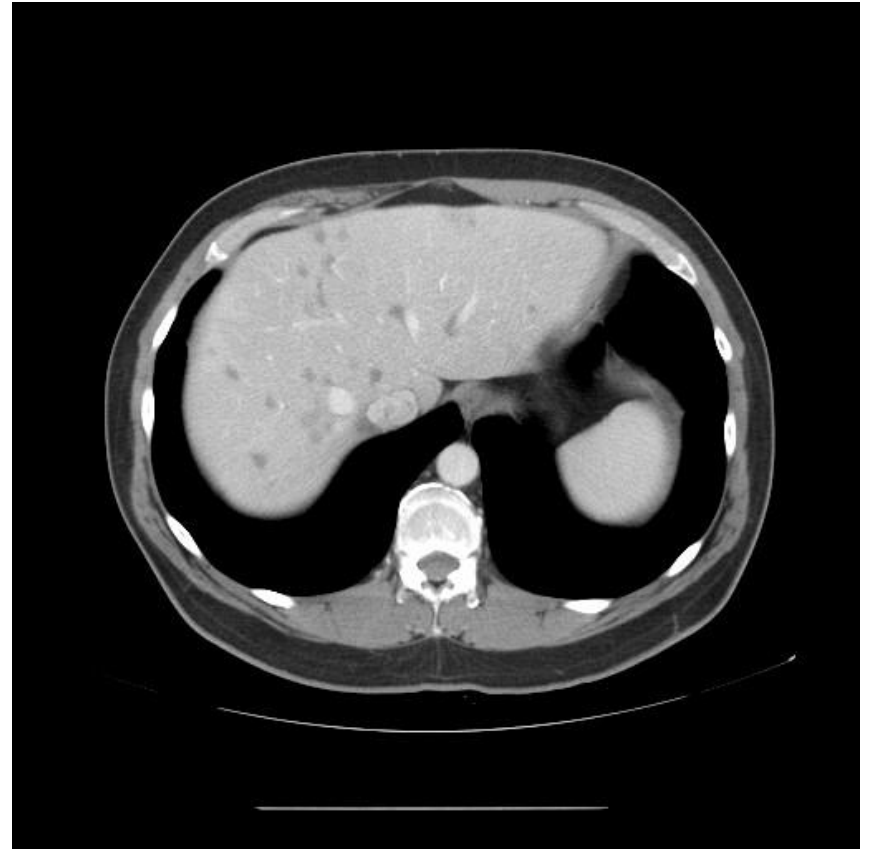
CTLA-4 Blockade Activates Antigen Specific T-cell Responses



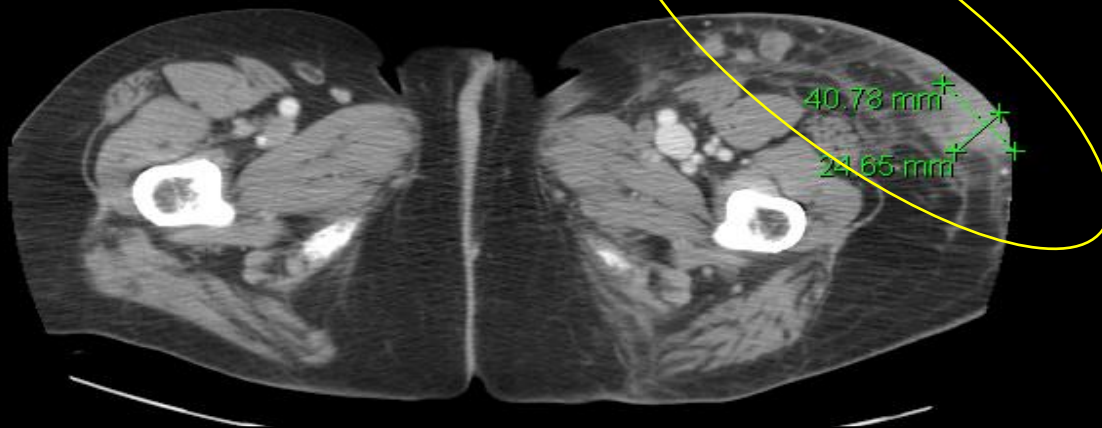
Oct 2006



April 2009

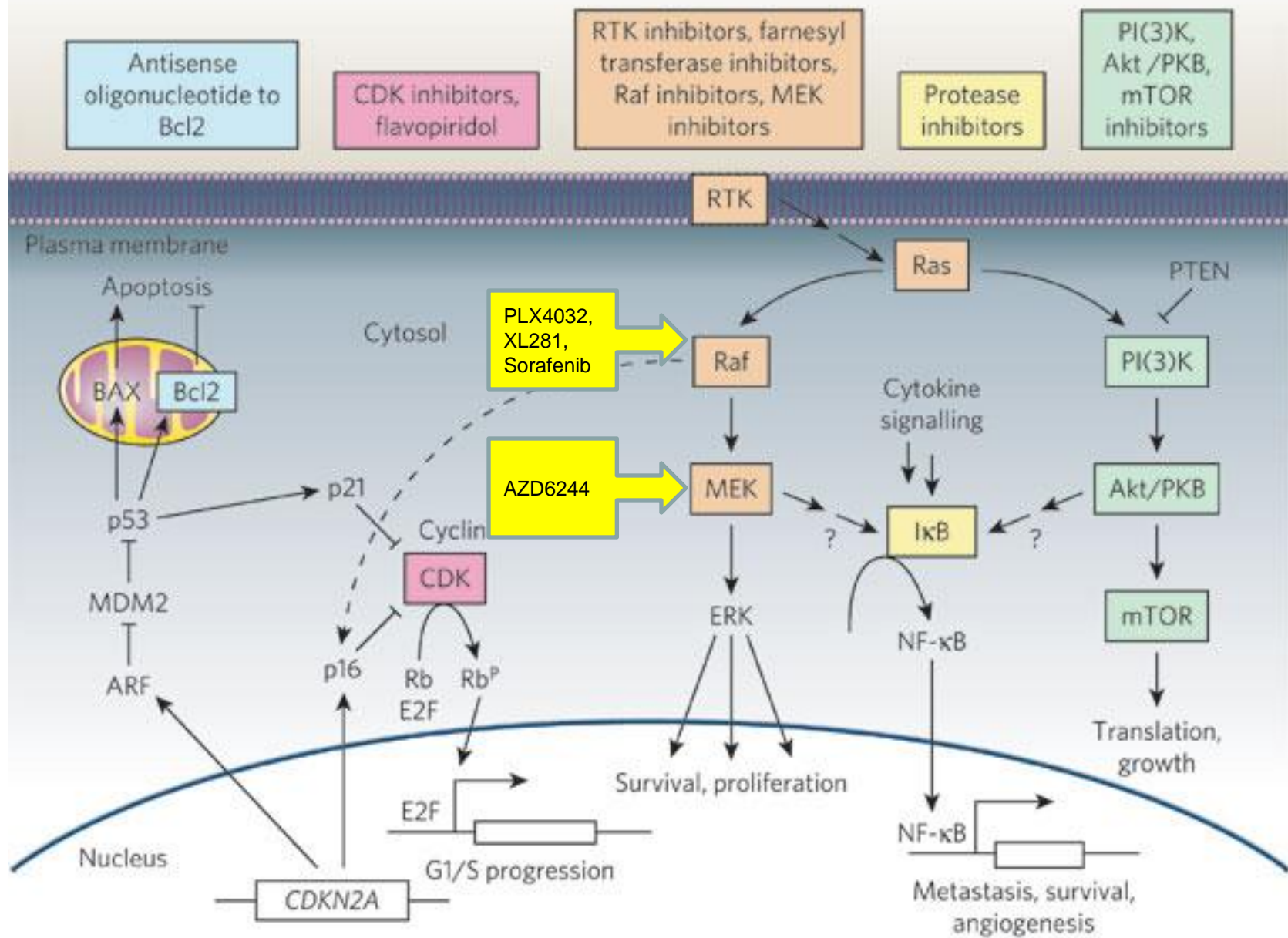


Pre-Treatment



After 4th dose





Important New Findings in Genes Altered in Melanoma- Therapeutic Implications

- B-raf: mutations occur in this gene in 70% of melanomas, mainly those on intermittently sun exposed skin. Several new drugs being tested to inhibit B-raf with responses observed.
- C-kit: mutations in in this gene in a small subset of patients with melanoma on internal surfaces, the face or the bottom of the foot. Imatinib (Gleevec) has shown efficacy in people pre-selected with mutations.