THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Children's Cancer Hospital

Pediatric Melanoma Treatment Update and Clinical Trial Participation

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Pediatric Melanoma Summit

September 13, 2014

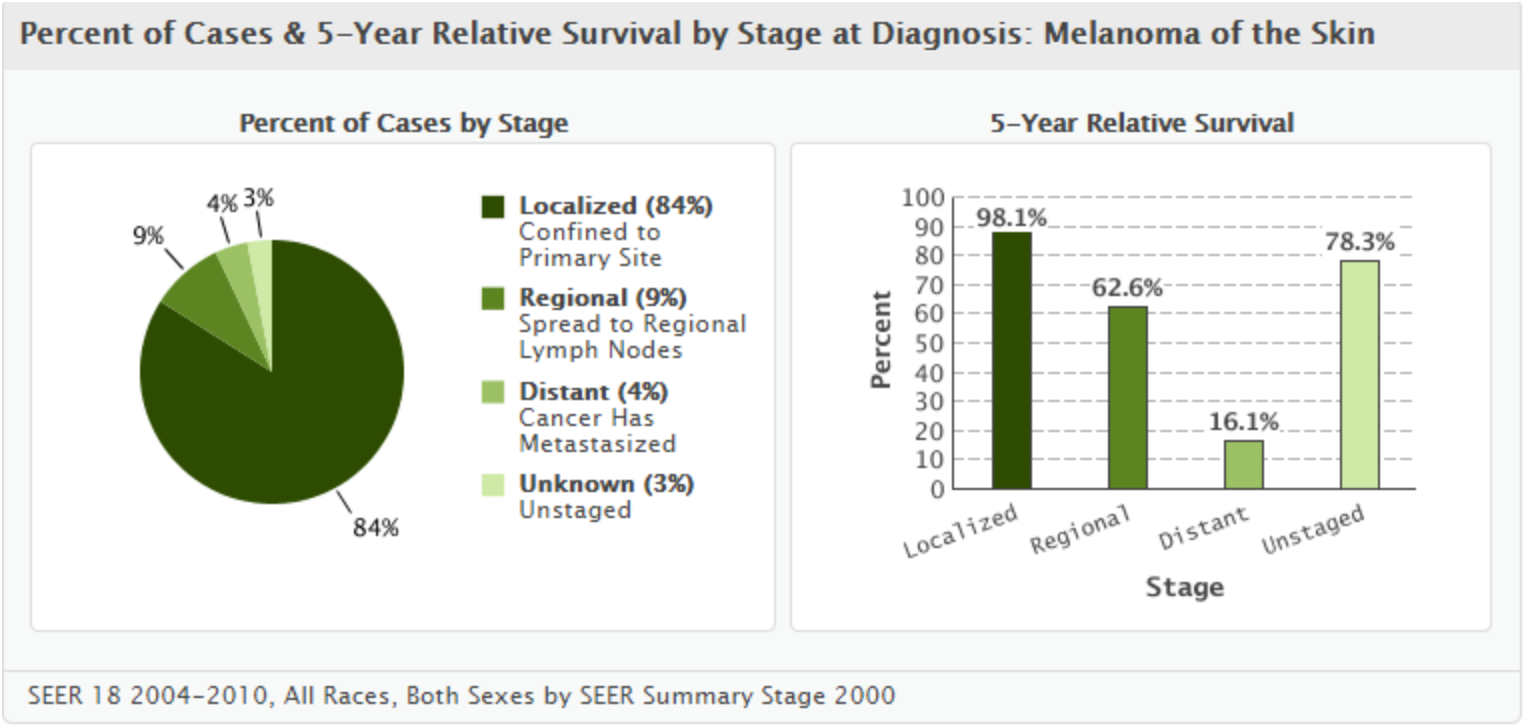
SEER Data

Table 5.1: Incidence of Melanoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000

AGE AT DIAGNOSIS (YEARS)	<5	5-9	10-14	15-19	20-24	25-29
U.S. population, year 2000 census (in millions)	19.176	20.550	20.528	20.220	18.964	19.381
Average incidence per million, 1975-2000, SEER	0.7	0.9	2.8	14.0	38.9	69.4
Average annual % change in incidence, 1975-2000, SEER	na	na	na	0.87	1.23	0.58
Estimated incidence per million, year 2000, U.S.	na	na	4.0	15.5	44.4	73.8
Estimated number of persons diagnosed, year 2000, U.S.	13	19	81	314	841	1431

- Difficult to perform melanoma trials in pediatric patients due to very low patient numbers

SEER Data



- Of the very low number of pediatric patients with melanoma, only about 15% need treatment beyond surgery.

Pediatric Melanoma Treatment

- Based on trials done in adults
- A few trials allow for patients under age 18 (usually to age 16)
- Very few trials in melanoma targeting pediatric patients

2009 AJCC Staging

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration
		b: With ulceration
T3	2.01-4.00	a: Without ulceration
		b: With ulceration
T4	> 4.00	a: Without ulceration
		b: With ulceration

JCO 2009 27(36) 6199-6206

2009 AJCC Staging

N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis*
		b: Macrometastasis†
N2	2-3	a: Micrometastasis*
		b: Macrometastasis†
		c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	

JCO 2009 27(36) 6199-6206

2009 AJCC Staging

M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

JCO 2009 27(36) 6199-6206

Clinical Staging

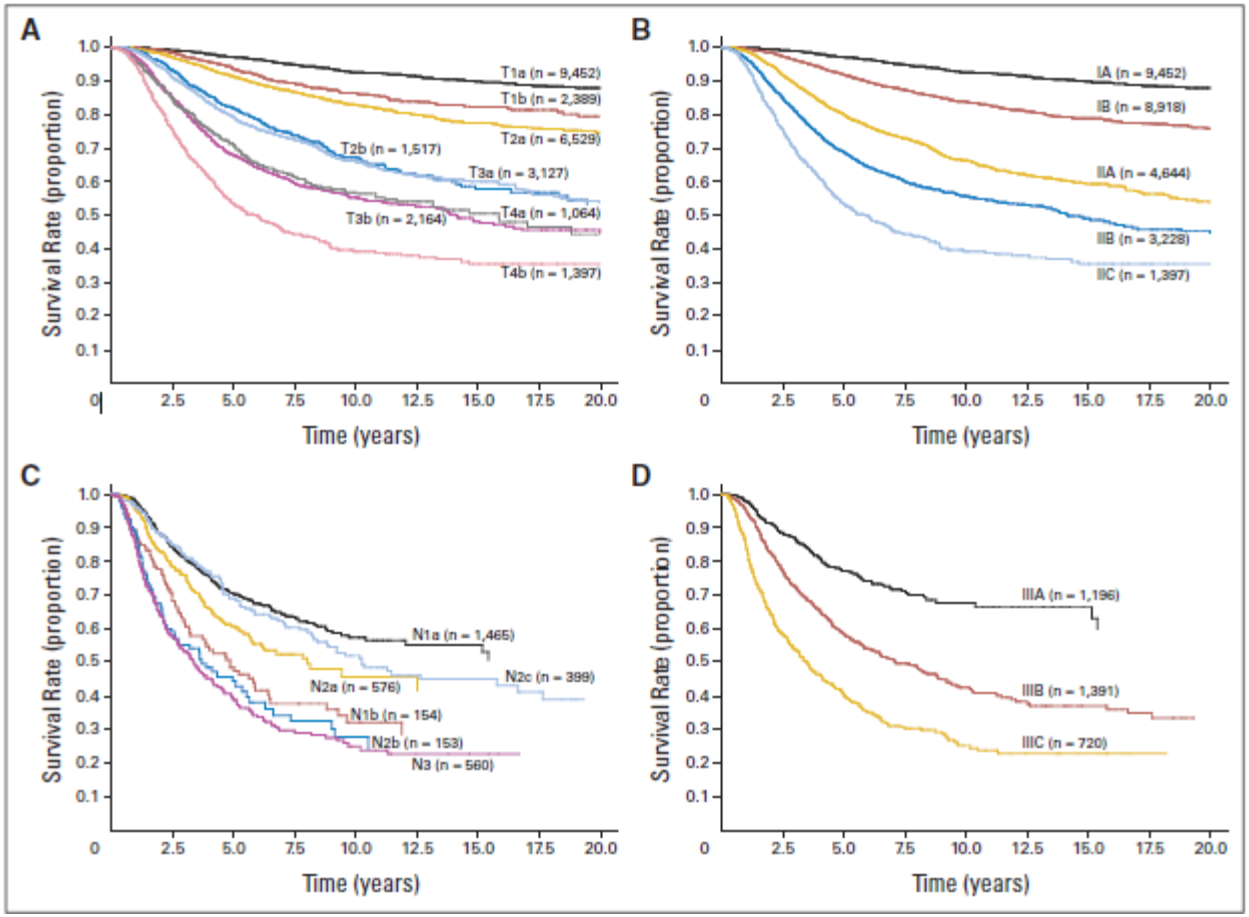
	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N > N0	M0
IV	Any T	Any N	M1

Pathologic Staging

	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a	N2c	M0
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

JCO 2009 27(36) 6199-6206

2009 AJCC Staging



JCO 2009 27(36) 6199-6206

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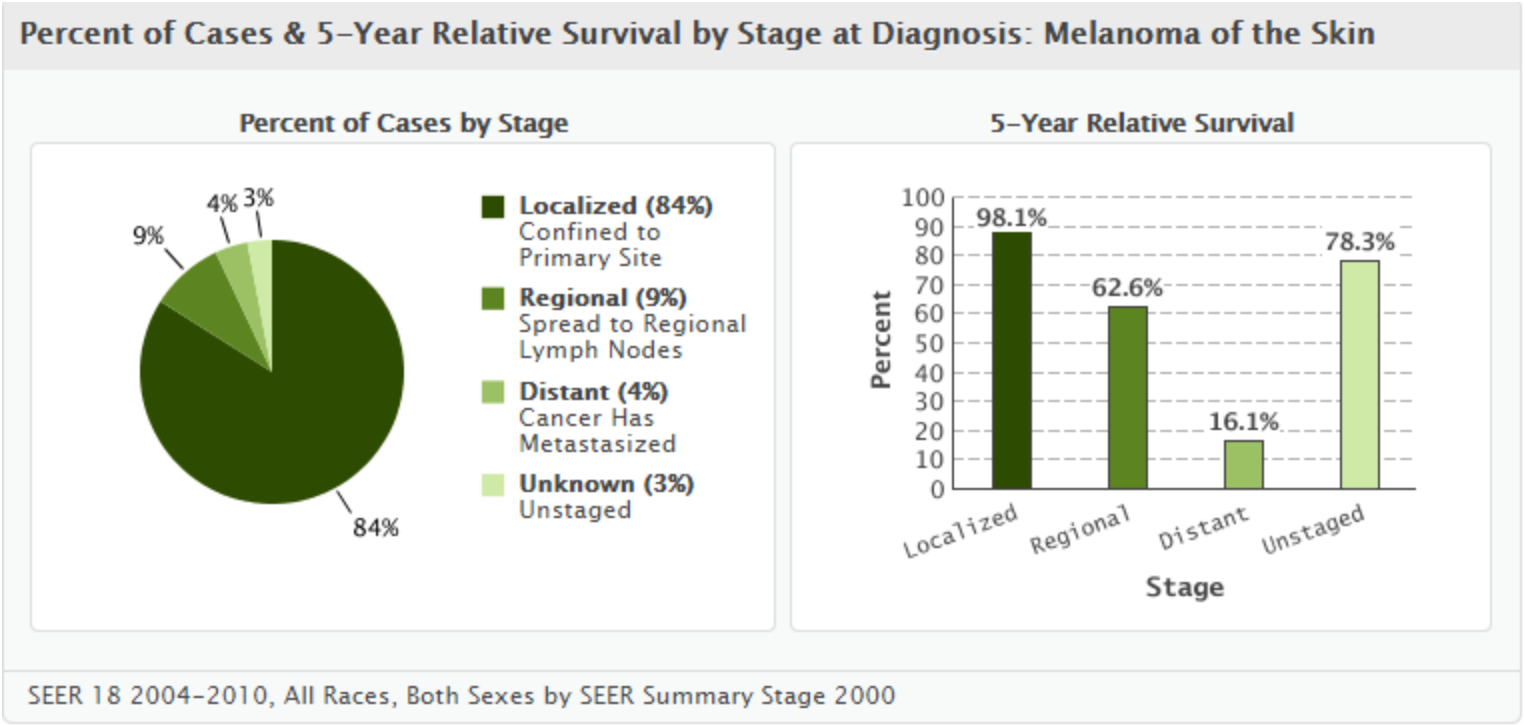


- Of the very low number of pediatric patients with melanoma, only about 15% need treatment beyond surgery.

Adult Trial – ECOG1684

- Established the use of interferon in treating melanoma
- Study done prior to lymph node mapping being used to stage melanoma

JCO 1996 14(1) 7-17

Adult Trial – ECOG1684

- CS1PS1 - >4 mm
- CS1PS2 – N1 regional lymph node metastasis detected at elective lymph node dissection with clinically inapparent regional lymph node metastasis
- CS2 PS2 - clinically apparent N1 regional lymph node involvement synchronous
- CS2R - regional lymph node recurrence

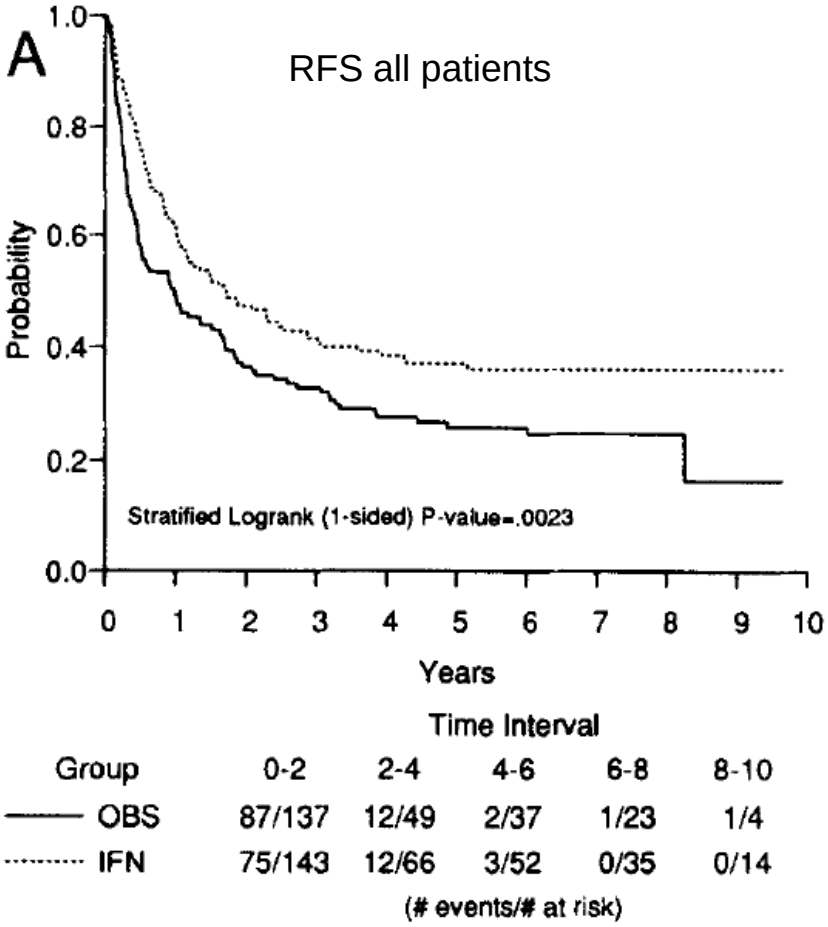
JCO 1996 14(1) 7-17

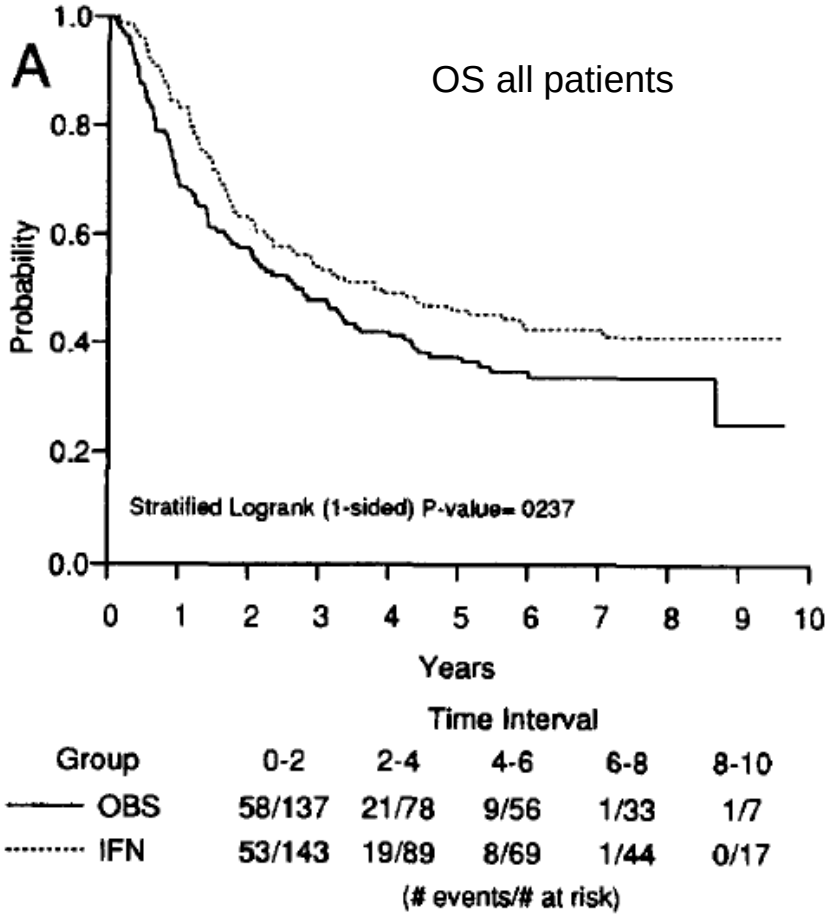
Adult Trial – ECOG1684

- Randomized to observation or interferon a-2b
- IFN treatment
  - 20 MU/m2/d IV 5 days per week for 4 weeks, then
  - 10 MU/m2/d SC three times weekly for 48 weeks

JCO 1996 14(1) 7-17

Adult Trial – ECOG1684





JCO 1996 14(1) 7-17

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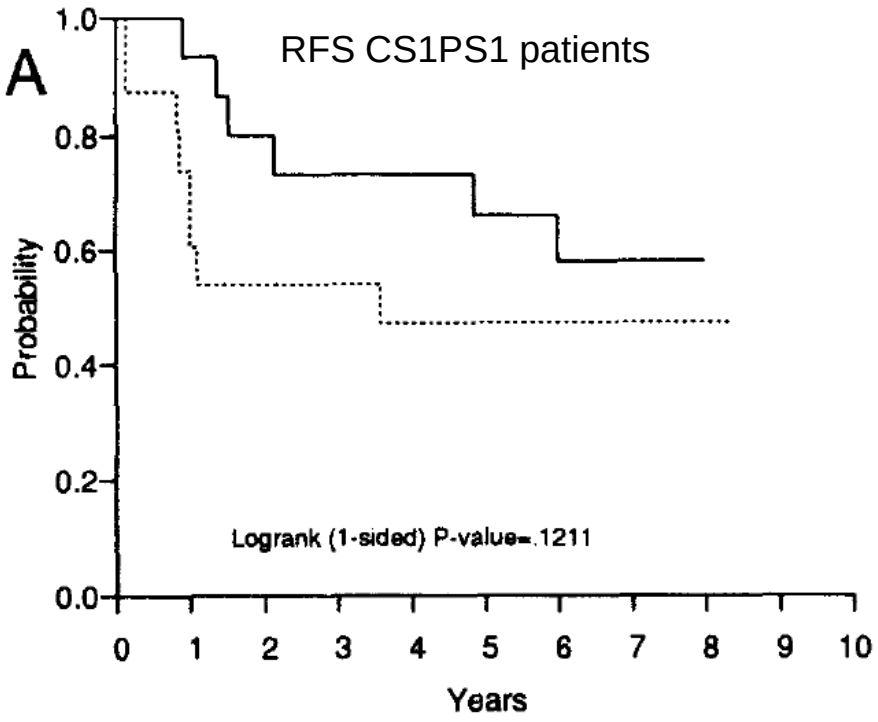
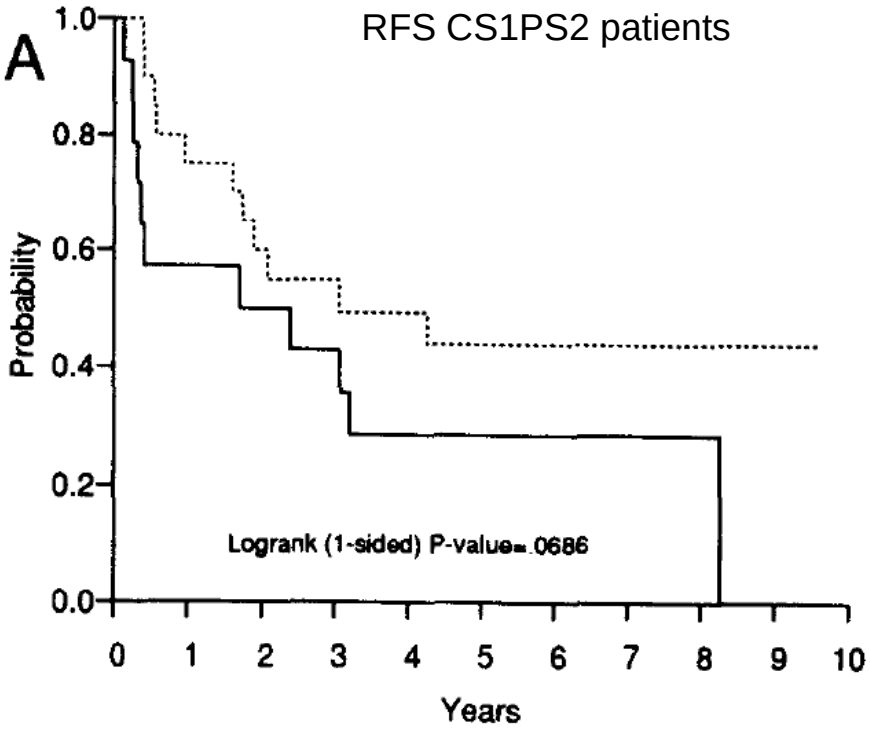
Adult Trial – ECOG1684



Group	Time Interval 0-2	2-4	4-6	6-8	8-10
OBS	3/15	1/12	1/11	1/8	0/0
IFN	7/16	1/8	0/7	0/3	0/1

(# events/# at risk)



Group	Time Interval 0-2	2-4	4-6	6-8	8-10
OBS	7/14	3/7	0/4	0/1	1/1
IFN	8/20	2/12	1/9	0/7	0/3

(# events/# at risk)

JCO 1996 14(1) 7-17

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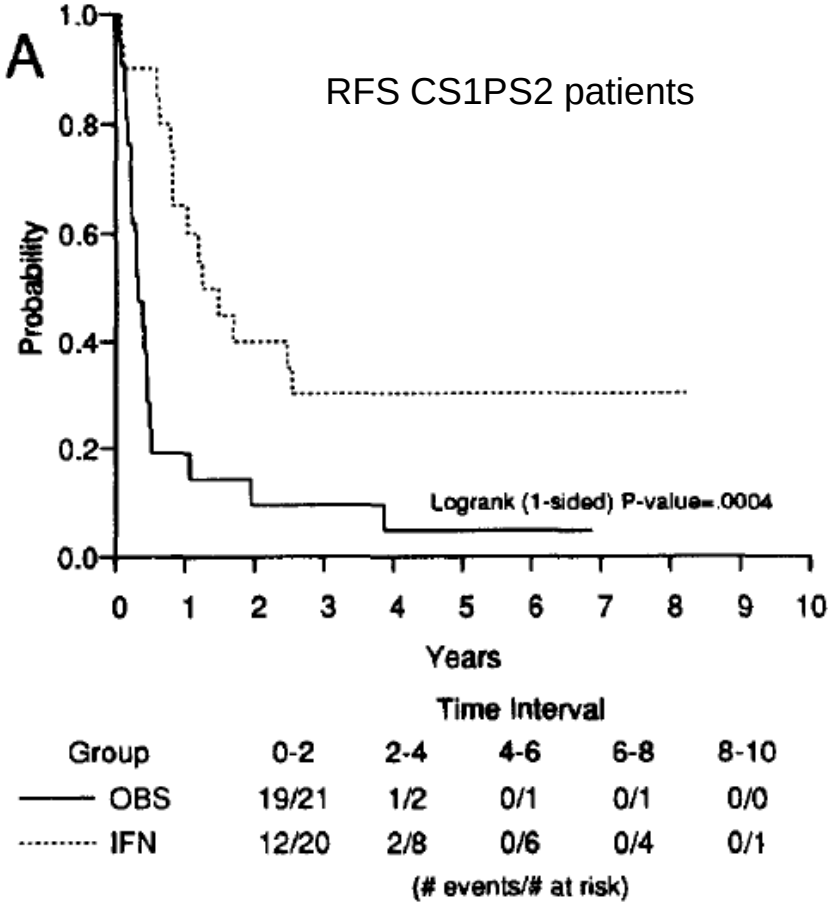
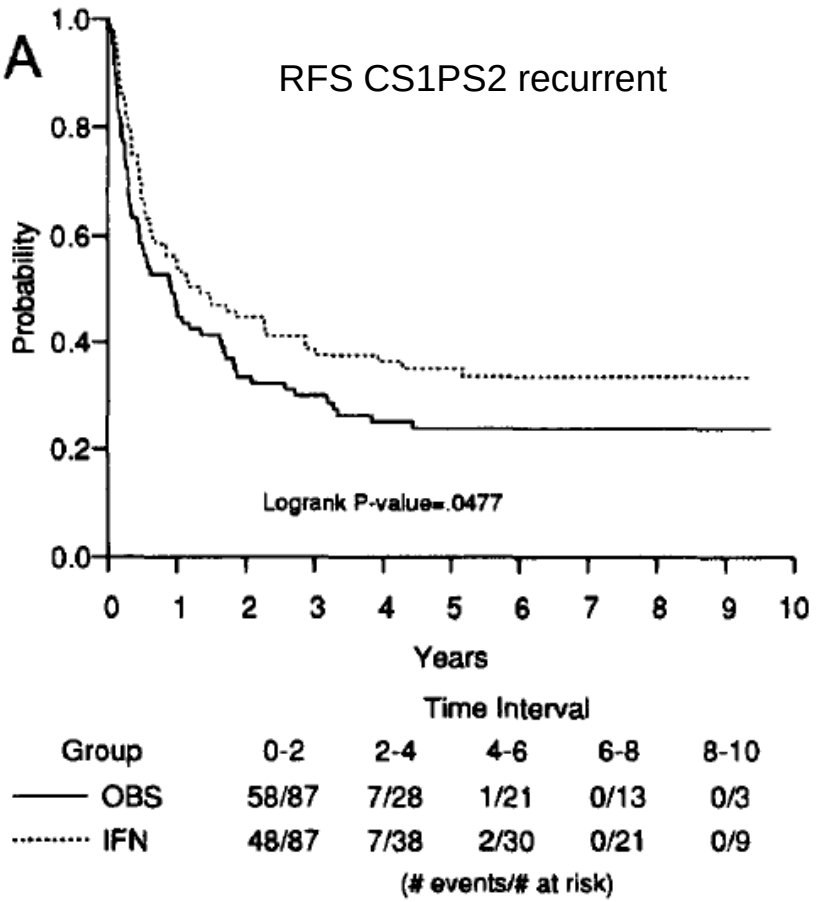
Adult Trial – ECOG1684





JCO 1996 14(1) 7-17

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Adult Trial – ECOG1684

Table 6. Toxic Events by Type and Degree

Type	Grade (N = 143)				
	1	2	3	4	5
Constitutional*	18	53	64	5	0
Myelosuppression	37	57	34	0	0
Hepatotoxicity	30	39	20	0	2
Neurologic	31	47	33	7	0
Worst grade/patient	2	30	96	13	2

*Worst grade of any constitutional toxicity, including fever, chill, and flu-like symptoms: fatigue, malaise, diaphoresis.

JCO 1996 14(1) 7-17

Pediatric Trials – MEL06

- Phase II in melanoma
- Objectives
  - Response of temozolomide/PEG-IFN in unresected stage III, metastatic or recurrent
  - Safety of temozolomide/PEG-IFN in resected IIIC, unresected III, metastatic or recurrent
  - Safety/feasibility of 48 wks PEG-IFN in IIC and resected IIIA and IIIB

Pediatric Trials – MEL06

- Secondary Objectives
  - Pharmacokinetics of IFN (+/- PEG) in pedi patients
  - Pharmacokinetics of temozolomide with PEG-IFN
  - Quality of Life
  - Utility of FDG PET/CT in high risk melanoma
  - Tissue/serum banking

Pediatric Trials – MEL06

Eligibility

- ≤21 years of age
- Melanoma IIC (T4b), III (LN mets) or IV (mets)
- Performance Status ≥50%
- Hematologic Function: ANC ≥ 1.0 x 10^9/L, Platelet ≥ 75 x 10^9/L, Hgb >8.0 (transfusion permitted)
- Hepatic: Bili ≤1.5xULN, SGPT ≤3xULN, Albumin ≥2g/dl
- Renal: Creatine appropriate for age
- Pancreatic: Amylase & lipase ≤1.5xULN

Pediatric Trials – MEL06

Eligibility

- Echo: SF≥28%
- Prior Therapy Statum A – None
- Prior Therapy Stratum B – fully recovered
  - Myelosuppresive – at least 2 weeks
  - Biologics – prior biologics ok, including IFN
  - XRT at least 3 weeks
  - Growth factors – at least 1 week

Pediatric Trials – MEL06

Treatment

- Statum A (resected IIC, IIIA and IIIB)
  - IFNα-2b 20MU/m2 IV 5d/wk x 4wk
  - PEGIFNα-2b 1mcg/kg subq weekly x 48wk
- Statum B (IIIC, IV, unresected III, recurrent)
  - Up to 7 courses
  - PEGIFNα-2b 0.5mcg/kg subq weekly x 8wk
  - Temozolomide 75 mg/m2/d PO for 6 weeks
  - B1 (measurable disease) – reasses for resectability after each course, postop treatment to complete 7 courses

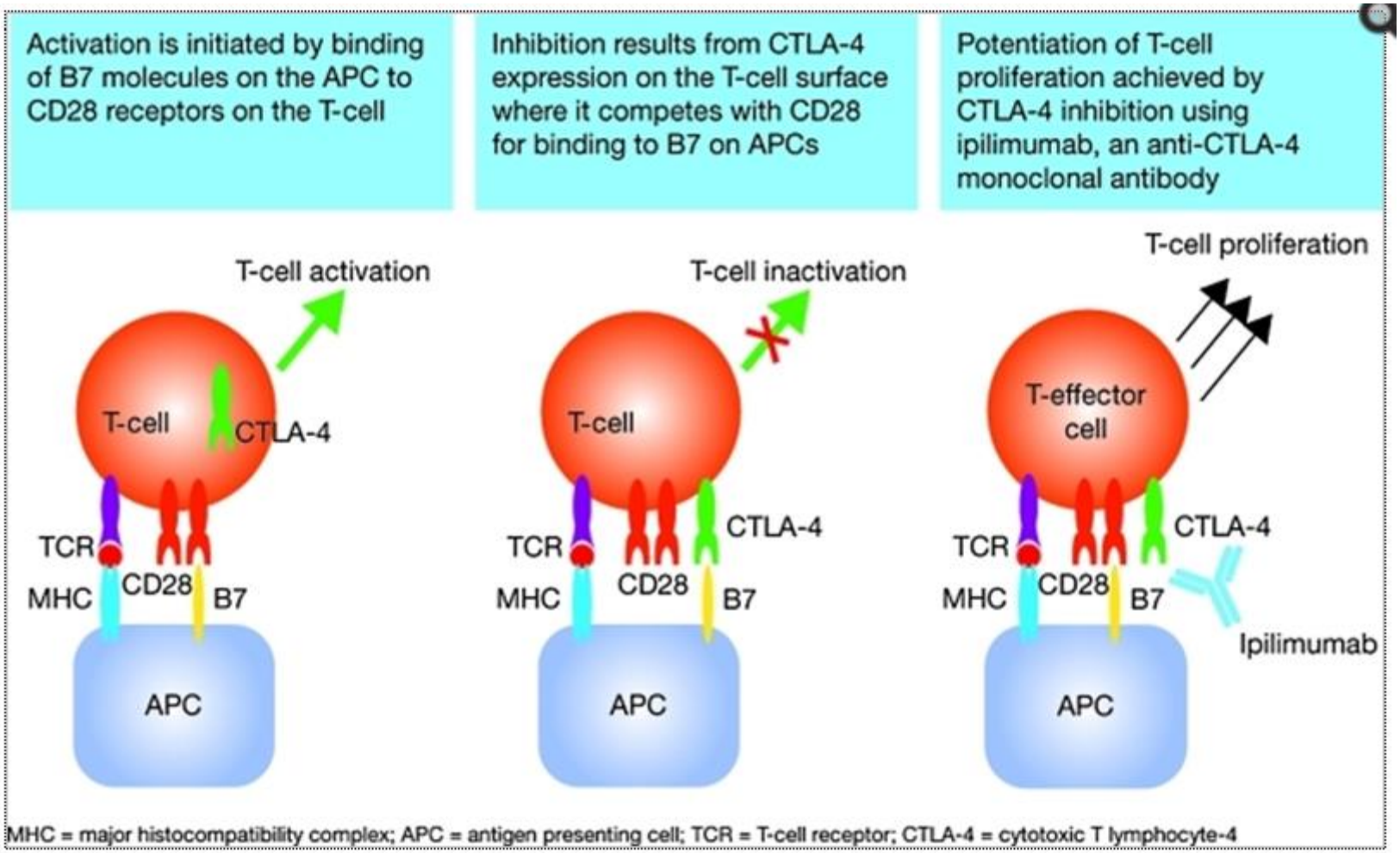
Pediatric Trials – MEL06

- Activation date
  - St Jude 10/2007
  - MD Anderson 3/2009
- Study closed 12/2012
- Enrollment at time of closure – 29 patients
  - St. Jude:
    - Stratum A -17 patients
    - Stratum B1- 2 patients
    - Stratum B2- 3 Patient
  - MD Anderson:
    - Stratum A- 6 patients
    - Statum B2- 1 Patient

Ipilimumab

- Ipilimumab is a medicine that helps stimulate the immune system to fight against cancer cells.
- Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4).
- CTLA-4 is a down-regulator of T-cell activation pathways. Blocking CTLA-4 allows for enhanced T-cell activation and proliferation.
- In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors.

Ipilimumab Mechanism



Cancer Biother Radiopharm. Dec 2010; 25(6): 601–613

Trials - Ipilimumab

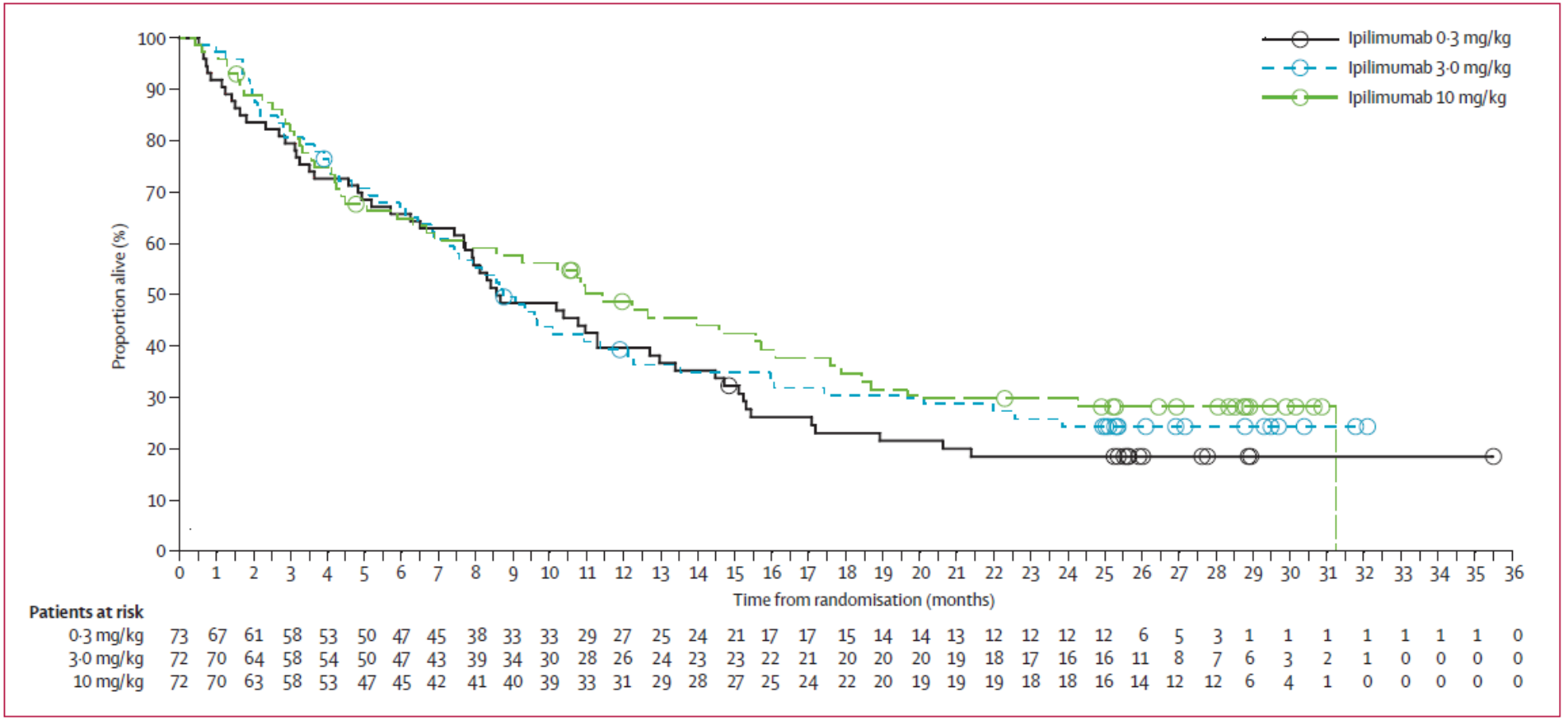


Figure 2: **Kaplan-Meier estimate for overall survival, by treatment arm**

Lancet Oncol 2010 11(1) 155-64

Trials - Ipilimumab

	Ipilimumab 0·3 mg/kg (n=72)	Ipilimumab 3 mg/kg (n=71)	Ipilimumab 10 mg/kg (n=71)
Overall serious adverse events			
Total	26	35	38
Grade 5	15	14	15
Drug-related	6	13	19
Drug-related (grade 5)	0	0*	0
Adverse events leading to discontinuation			
Total	9	7	19
Drug-related (any grade)	2	5	11
Drug-related (grade 3–4)	2	4	9

Lancet Oncol 2010 11(1) 155-64

Pediatric Trials - Ipilimumab

- A phase II trial looking ipilimumab in children
- Advanced melanoma that cannot be removed with surgery.
- Ipilimumab is already FDA approved for use in treating adults with melanoma.
- Open at multiple sites in the United States and throughout the world.

Pediatric Trials - Ipilimumab

- Primary Outcome Measures:
  - Overall Survival Rate at 1-Year
  - Severe Immune-mediated Adverse Events (imARs) rate 1-Year
- Secondary Outcome Measures:
  - Disease Control Rate (DCR) at 1-Year
    - DC is defined as a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD
  - Progression-Free Survival (PFS) at 1-Year
  - Best Overall Response Rate (BORR)) at 1-Year

Pediatric Trials - Ipilimumab

- Inclusion Criteria:
  - 12 < 18 years of age
  - Previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma
  - Karnofsky Performance Status (KPS) or Lansky Score ≥ 50
- Exclusion Criteria:
  - Primary Ocular Melanoma
  - Prior therapy with a Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) or Programmed death- 1 (PD-1) antagonist, or Programmed cell death- ligand 1 (PD-L1) or CD137 agonists
  - Symptomatic brain metastases
  - History of autoimmune diseases

Pediatric Trials - Ipilimumab

- Ipilimumab
  - 3 mg/Kg solution by Intravenous (IV) once every 3 weeks for 4 doses, then
  - every 12 weeks until progression of disease or unacceptable toxicity

Pediatric Trials - Ipilimumab

- Diarrhea
- Nausea and vomiting
- Itching and/or rash
- Fatigue
- Colitis
- Immune related
  - GI/liver
  - Endocrine
  - Skin

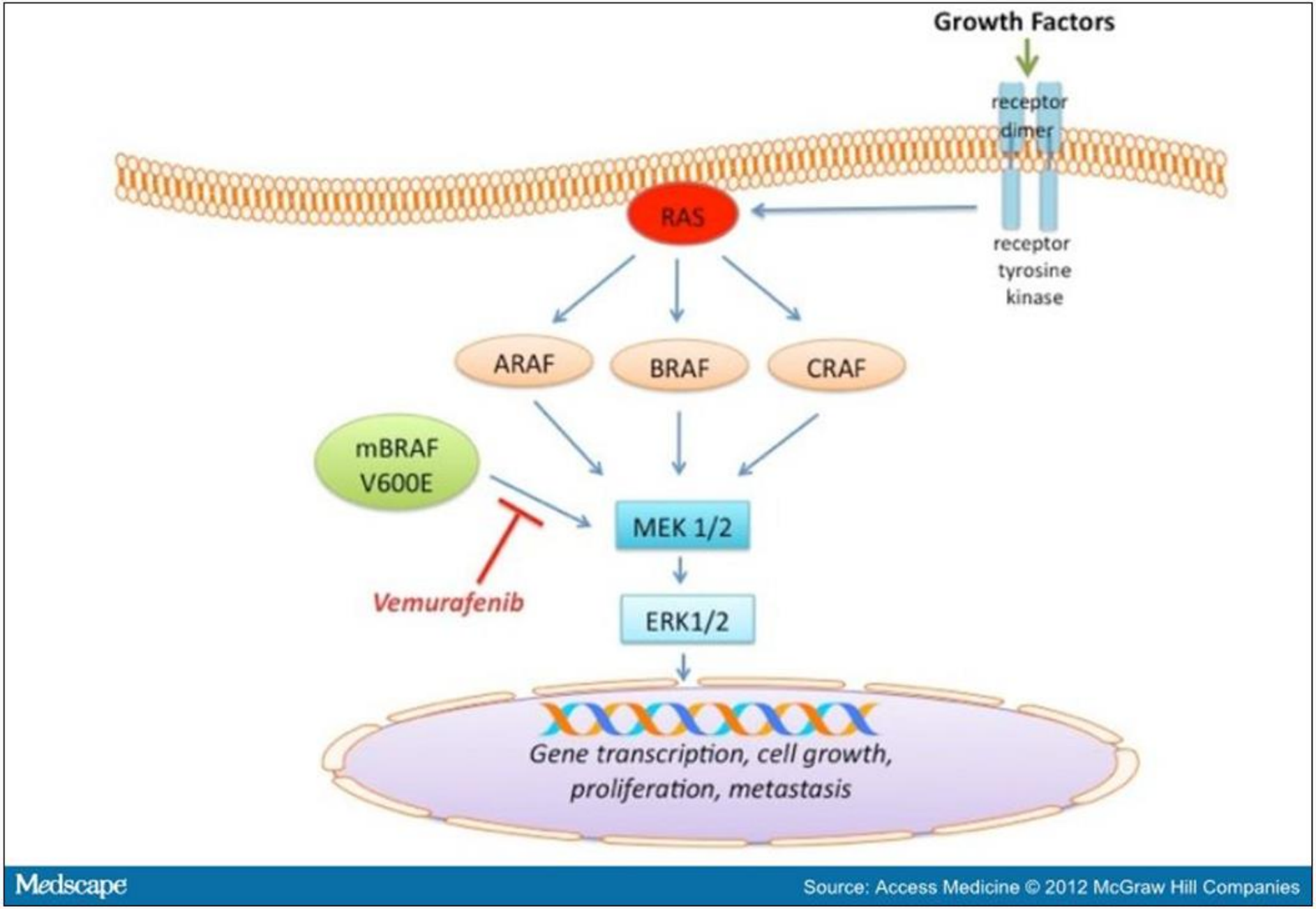
Pediatric Trials - Ipilimumab

Recruitment – estimated 30 patients

- Started - November, 2012
- Planned End – July, 2017

Vemurafenib

- Vemurafenib is a type of biologic therapy called a BRAF inhibitor.
- BRAF is a protein that sends signals to cells telling them to divide and grow.
- Blocking BRAF may stop cancer cells growing.
- Certain changes in the BRAF gene cause a change in the BRAF protein that can increase the growth and spread of cancer cells.



Trials - Vemurafenib

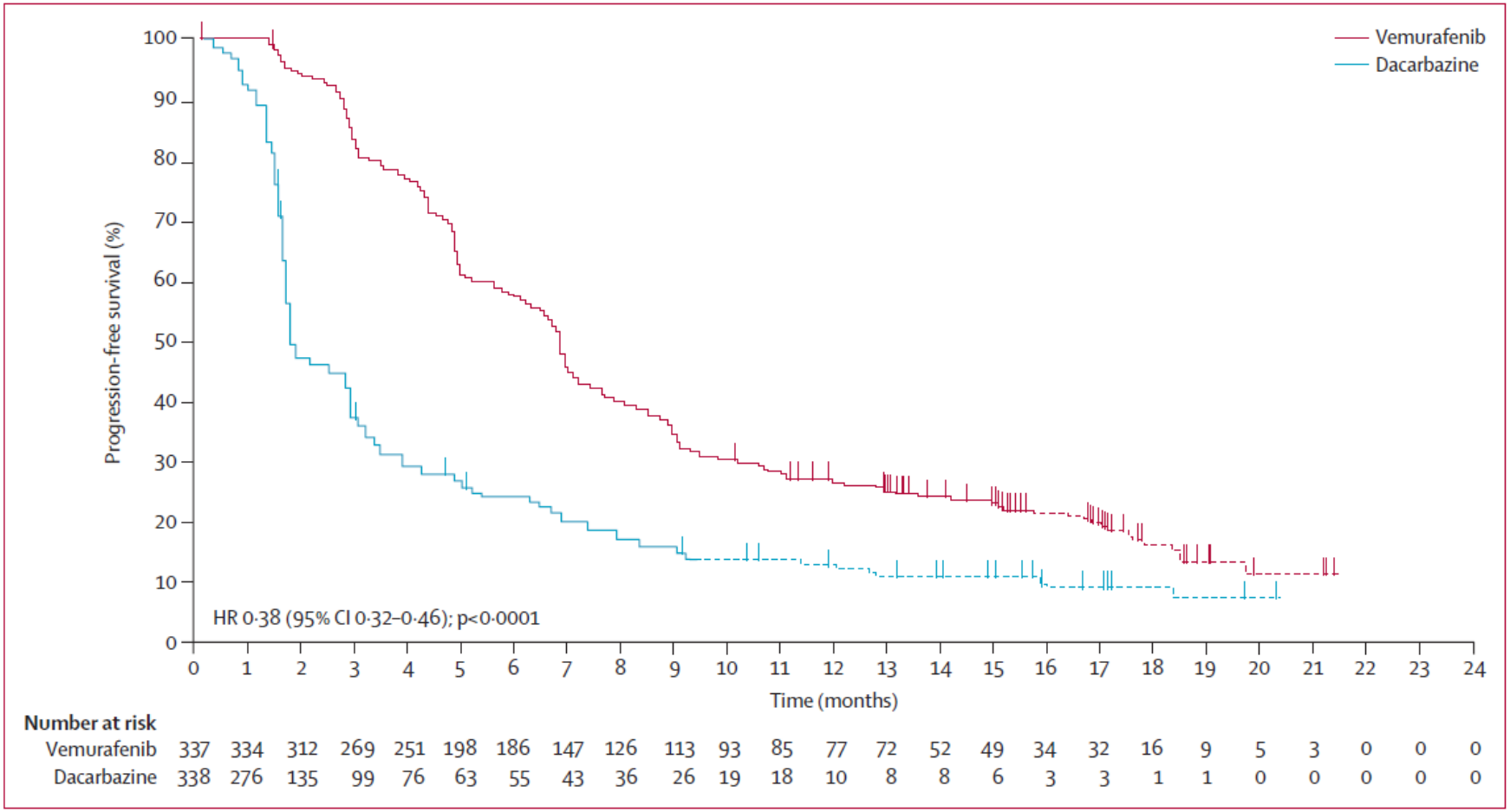


Figure 3: Progression-free survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

Lancet Oncol 2014 15(3) 323-32

Trials - Vemurafenib

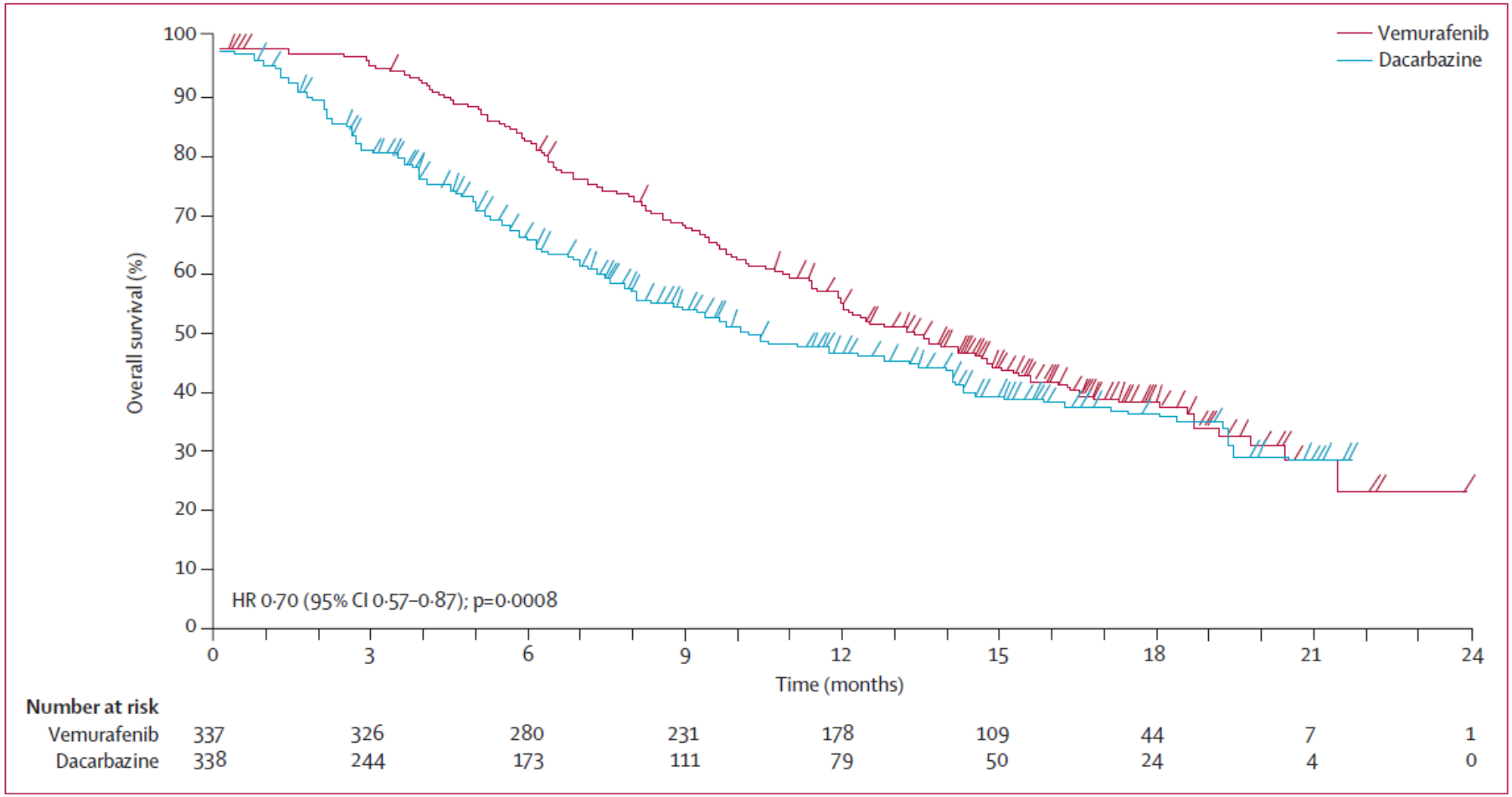


Figure 2: Overall survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

Lancet Oncol 2014 15(3) 323-32

Trials - Vemurafenib

	Dacarbazine (n=287)			Vemurafenib (n=337)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Arthralgia	8 (3%)	3 (1%)	..	169 (50%)	20 (6%)	..
Rash	6 (2%)	..	..	108 (32%)	30 (9%)	..
Fatigue	94 (33%)	6 (2%)	..	146 (43%)	10 (3%)	..
Photosensitivity	13 (5%)	..	..	124 (37%)	13 (4%)	..
Increase in LFTs	16 (6%)	6 (2%)	..	83 (25%)	35 (10%)	3 (1%)
Cutaneous squamous-cell carcinoma	..	2 (<1%)	..	..	65 (19%)	..
Keratoacanthoma	..	2 (<1%)	..	3 (<1%)	34 (10%)	..
Skin papilloma	1 (<1%)	..	..	94 (28%)	2 (<1%)	..
Nausea	123 (43%)	5 (2%)	..	121 (36%)	7 (2%)	..
Neutropenia	8 (3%)	17 (6%)	9 (3%)	1 (<1%)	..	1 (<1%)
New primary melanoma	..	..	..	2 (<1%)	6 (2%)	..

Data are number of patients (%). LFT=liver function test.

Table 4: **Summary of selected adverse events in treated patients (safety population)**

Lancet Oncol 2014 15(3) 323-32

BRIM-P

- A phase I trial looking at vemurafenib (Zelboraf), also known as RO5185426, in children
- Advanced melanoma that cannot be removed with surgery.
- Vemurafenib is already FDA approved for use in treating adults with melanoma.
- Open at multiple sites in the United States and throughout the world.

BRIM-P

The aims of this study are to find out

- The best dose of vemurafenib to give
- How well it works
- About the side effects
- What happens to vemurafenib in the body
- How quickly the body gets rid if it

BRIM-P

Eligibility Criteria

- Between12 and 17 years old
- Stage 3C or 4 melanoma that cannot be removed with surgery
- Melanoma cells with the BRAF gene change
- Melanoma that can be measured by CT or MRI
- Are well enough to be up and about for at least half the day, performance status 60-100%
- Have fully recovered from any surgery
- Able to swallow tablets
- Willing to use reliable contraception during treatment and for 6 months afterwards if sexually active and there is any chance that you or your partner could become pregnant

BRIM-P

Exclusion Criteria

- Chemotherapy, biological therapy, biological therapy, radiotherapy or surgery in the last 2 weeks
- Melanoma that has spread to the brain or spinal cord and is causing you problems
- Still have any side effects from previous treatment
- Radiotherapy to your head, spine or the area between your hips (pelvis) in the last 3 months
- Prior treatment with vemurafenib
- Prior treatment with a BRAF Inhibitor or MEK inhibitor, unless it was sorafenib

BRIM-P

- This study is in two parts. Everyone taking part will take vemurafenib tablets daily.
- People in the 1st part of the study will have the lowest dose of vemurafenib. If they don't have any serious side effects, the next people will have a higher dose, and so on, until they find the best dose to give. This is called a dose escalation study.
- In the 2nd part of the study everyone will have the best dose of vemurafenib found in the first part.
- Vemurafenib tablets can be taken for as long as they are helping.

BRIM-P

Tests before treatment include

- Blood tests
- Physical examination
- Heart trace (ECG)
- Urine tests
- CT or MRI scan
- PET scan
- Skin examination
- Having a sample of tissue taken (biopsy)

BRIM-P

Tests done often while on treatment include

- CT scans or MRI scans every 8 weeks for a year and then every 12 weeks until the cancer gets worse.
- PET scan after 8 weeks of treatment.
- After a participant stops taking vemurafenib they see the trial team 30 days later for a physical examination and blood tests. The trial team will then contact them every 3 months to see how they are.

BRIM-P

The most common side effects of vemurafenib:

- Hair loss
- Feeling or being sick
- Tiredness (fatigue)
- Increased sensitivity to sun light
- Aching joints and muscle pain
- Rash
- Itchy skin
- Diarrhea
- Changes in your skin including skin tags or thickening of the skin
- Non harmful skin cancers, including squamous cell and basal cell cancers happen in about 25%

BRIM-P

Recruitment

- Started - December 22, 2011
- Planned End – April 30, 2015

Enrollment

- Recently enrolled 6th patient