

Empowering Ones Own Immune System - the case of metastatic melanoma -

Anitasha Puodziunas
Sr Lead Medical Science Liaison
Bristol-Myers Squibb

September 2010

Incidence of cancer in Canada

Canadian Cancer Society 2010 estimates :

- **173,800 new cases** of cancer (excluding 75,500 non-melanoma skin cancers) and 76,200 deaths
- An estimated **1 out of every 4** Canadians are expected to die from cancer
- **Melanoma:** 5,300 new cases

Melanoma...

• Arises from the melanocytes (pigment cells)

• Primary cause of death due to skin cancer¹

- ◆ melanoma represents approx. 5% skin cancers but accounts for >80% skin cancer deaths²

• Characterized by:

- ◆ tendency to metastasize
- ◆ after diagnosis, >40% of patients' disease recurs or metastasizes within 5 years^{3,4}
- ◆ poor response to existing therapies: high unmet need
- ◆ second most common cancer among those aged 20–39 years,
- ◆ almost a third of cases occurring under the age of 50
- ◆ Among the well-known young figures taken away by this devastating disease is.....



Bob Marley
(melanoma on left toe)

Bristol-Myers Squibb 3

Metastatic melanoma: more than a mole...

The ABCD of (localized) melanoma



Spreading of cancer cells throughout the body (metastasis)

Metastatic melanoma
- On the skin -



- In internal organs -



Liver
Bristol-Myers Squibb 4

5-year Survival of melanoma patients



Adapted from SEER Cancer Statistics Review, 2007

Bristol-Myers Squibb 5

Traditional treatment of melanoma



Simply cut the tree...

But roots may remain...
Burn out the area

But seeds may remain in the ground...

Chemically treat the surroundings

But also kill everything around...

Use specific herbicide

Chemotherapies



Radiation



Induction of
Or... How to get rid of an

SURGERY

Removal
of cancer



Targeted Therapies

Inhibition of
specific molecules



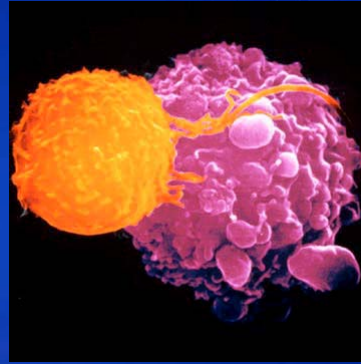
Bristol-Myers Squibb 6

Immunotherapy: directing the immune system to fight cancer

Our immune system constantly eliminates non-self entities (viruses, bacteria, etc.)



COULD IT BE USED TO SPECIFICALLY ELIMINATE CANCER CELLS ???



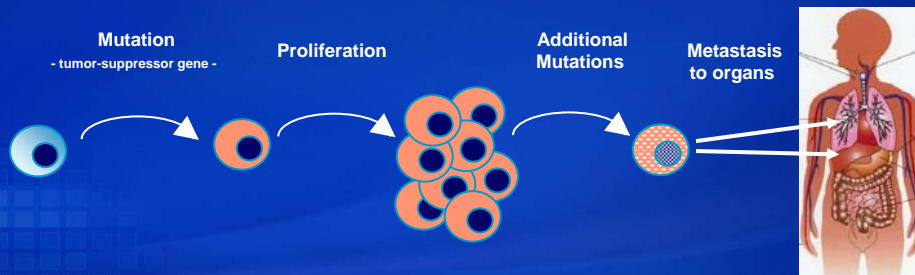
<http://healthinfoispower.files.wordpress.com/2009/05/cellkillcancer.jpg>

Bristol-Myers Squibb 7

But what really are cancer cells ?

Cancer cells are normal cells that have lost their normal properties and usually display increased proliferation rate.

Hence, cancer cells originates from our own body!



CAN WE USE OUR IMMUNE SYSTEM TO FIGHT CANCER ???

Bristol-Myers Squibb 8

CTLA-4: The Brake on T-Cell Activation

Contact 1

- Ignition -



T-cell receptor : Tumor

Contact 2

- Acceleration -



CD28 : B7

Contact 3

- Brake -



~~CD28 : B7~~
CTLA-4 : B7

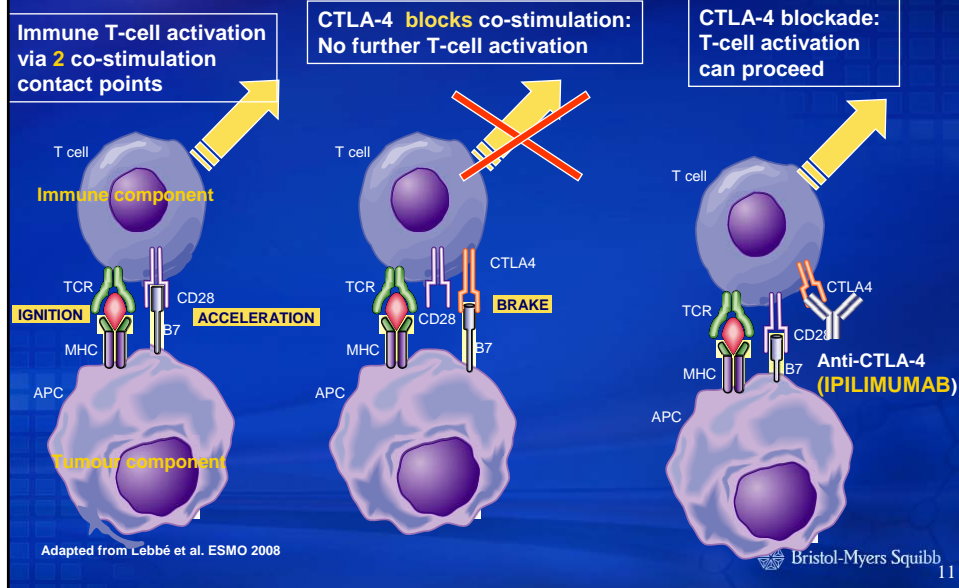
 Bristol-Myers Squibb 9

Ipilimumab: an anti-CTLA-4

- Antibody that binds to the CTLA-4 receptor on activated T cells
 - Blocks signaling from CTLA-4
- Administered through intravenous infusion
- Defined initial course of treatment:
 - 4 infusions (infused every 3 weeks)

 Bristol-Myers Squibb 10

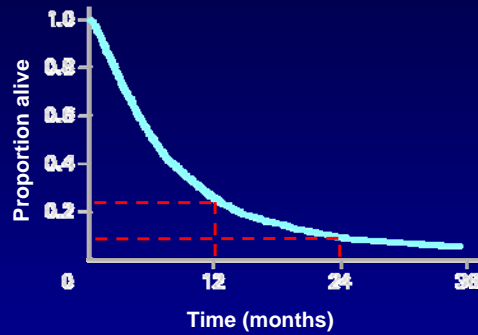
CTLA-4: putting the brakes on T cell activation



Clinical Application of anti-CTLA-4 therapy

- The case for ipilimumab in metastatic melanoma -

Metastatic melanoma: An aggressive cancer without effective treatment



Survival data from 42 Phase II trials with over 2'100 stage IV patients¹:

12 month OS: 25.5 %,
median OS: 6.2 months
(stage IV including patients with brain metastases)

Adapted from Korn 2008

Due to the lack of efficacious therapy, the preferred treatment for metastatic melanoma remains the inclusion in a clinical trial²

¹Korn EL et al. J Clin Oncol 2008;26(4):527-34.

²Dummer R, Hauschild A, Jost L. Cutaneous malignant melanoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008;19 Suppl 2:iii86-8.

Version date: 12-11-09

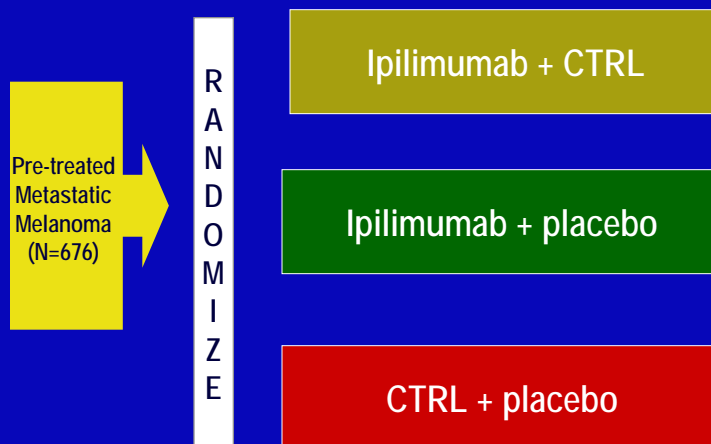
Review Date: 17-11-09

Document Owner: Patrick Garcia

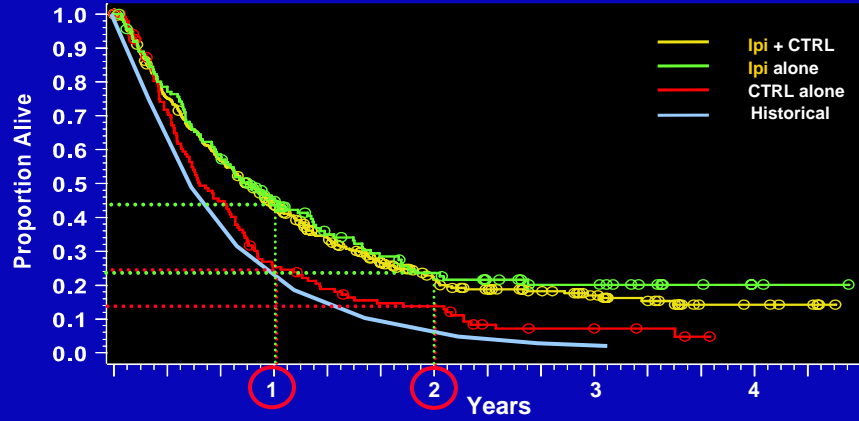
IPI-065-2009

13

Anti-CTLA-4 (Ipilimumab) therapy for pretreated metastatic melanoma patients



Survival Curves according to therapy



Survival Rate	Ipi + CTRL	Ipi	CTRL
1 year	44%	46%	25%
2 year	22%	24%	14%

ASCO 2010

15

Different side effect profile with Immunotherapy

All cancer treatments have various associated detrimental side effects

Chemotherapies:

Hair loss, vomiting, repression of the immune system, neuropathy

Targeted therapies:

Cutaneous Rash, High blood pressure

Radiation:

Repression of the immune system

Immunotherapy: Mainly auto-immune

Dermatologic, GI, Endocrine, Hepatic

- Predictable and tolerable

- Difference in timing

Symptoms of progressive cancer Side-effects of therapy

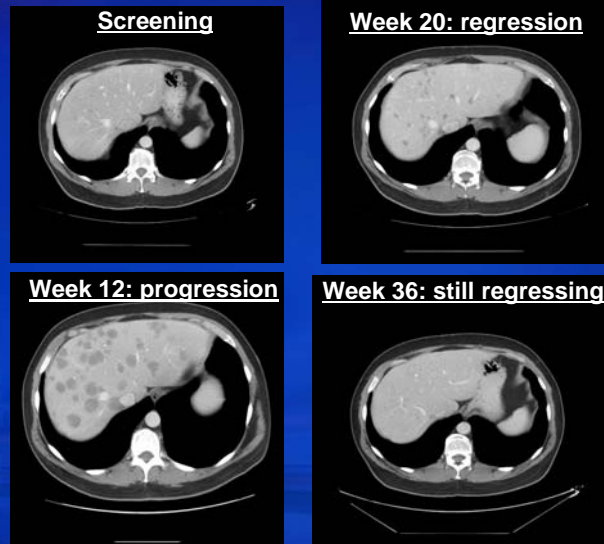


<http://cancergrace.org/lung/files/2010/04/balance.jpg>

Bristol-Myers Squibb 16

Melanoma: Objective Response to ipilimumab after Significant Progression with Tumor Volume Increase

Courtesy of J Wolchok, MSKCC



Bristol-Myers Squibb
17

Summary of Data

- **First** randomized phase III trial to show survival improvement in metastatic melanoma (HR=0.66, 0.68)
- Survival rates in the arms administered ipilimumab were consistent
 - 1 year: Ipi arms 46% (CTRL arm = 25%)
 - 2 years: Ipi arms 24% (CTRL arm = 14%)

Conclusions

Anti-CTLA-4 mediated immunotherapy

(Ipilimumab) represents

- ◆ a novel and
- ◆ effective way to empower ones own immune system to fight cancer

Immunotherapy has the potential to be effective against different tumor types

- ◆ over-all mechanism for augmenting T cell stimulation is not cancer specific.



THANK YOU !

QUESTIONS ?