Melanoma 2020

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I have no financial disclosures to make.

I have no recommendations for “off label usage”.

Today's goals:

1. ...to review features on visual inspection which may suggest melanoma is present.
2. ...to understand risk factors and risk-reduction strategies for high risk patients.
3. ...to understand the available new medical agents and their function in the treatment of melanoma.
4. ...to increase appreciation for current treatment options for patients and the improving outcomes now attainable in the past 9 years.

Epidemiology

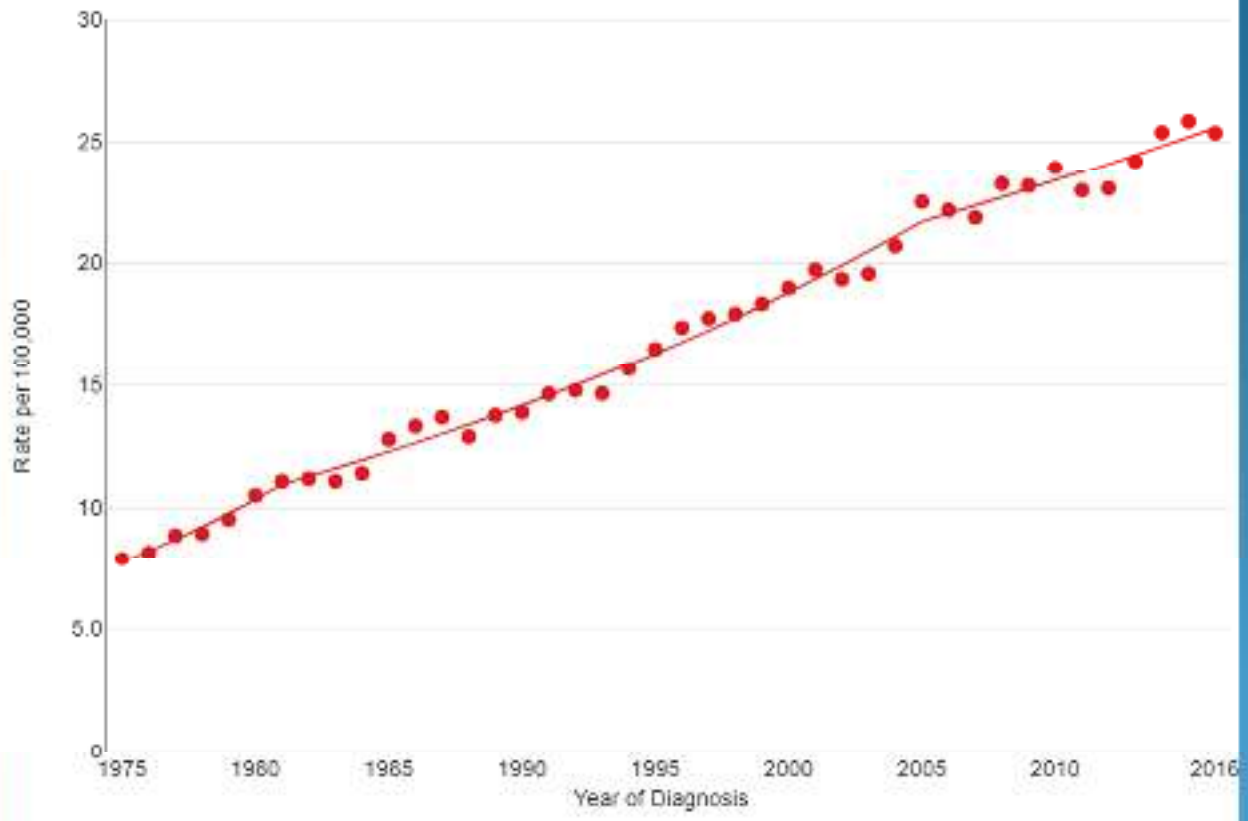
Most cancers are tracked by SEER data.

Melanoma:

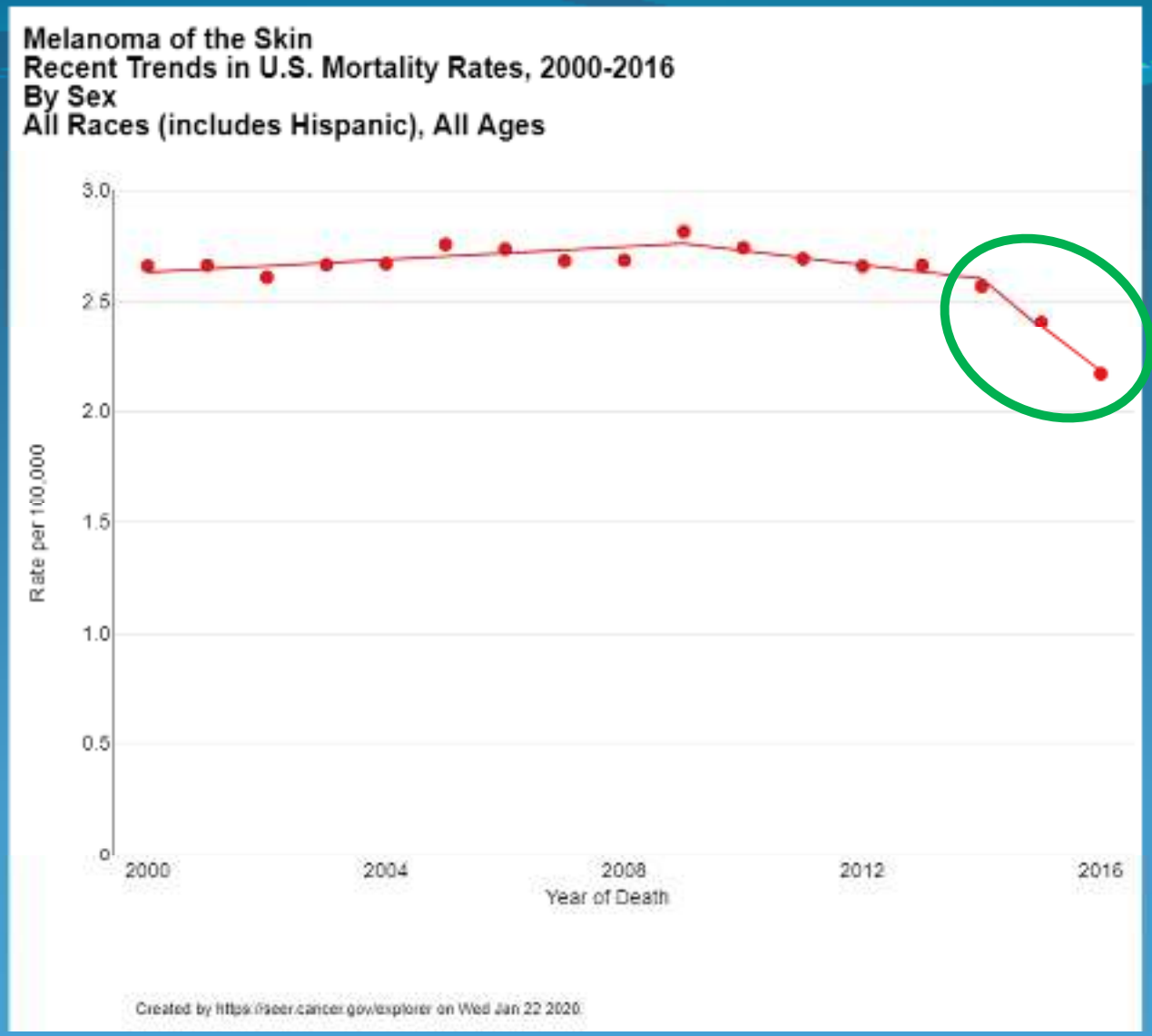
- Incidence has been rising over the past ~40 years.
  - - In 2019 the number of new cases was 96,480 in the U.S.
  - - For 2016, the incidence per population was 25.4/100,000 (up from 7.85 in 1975).
- Mortality rates are beginning to drop.
- 5 year O.S. has increased.

http://seer.cancer.gov

Melanoma of the Skin
Long-Term Trends in SEER Incidence Rates, 1975-2016
By Sex
All Races (includes Hispanic), All Ages, Observed Rates

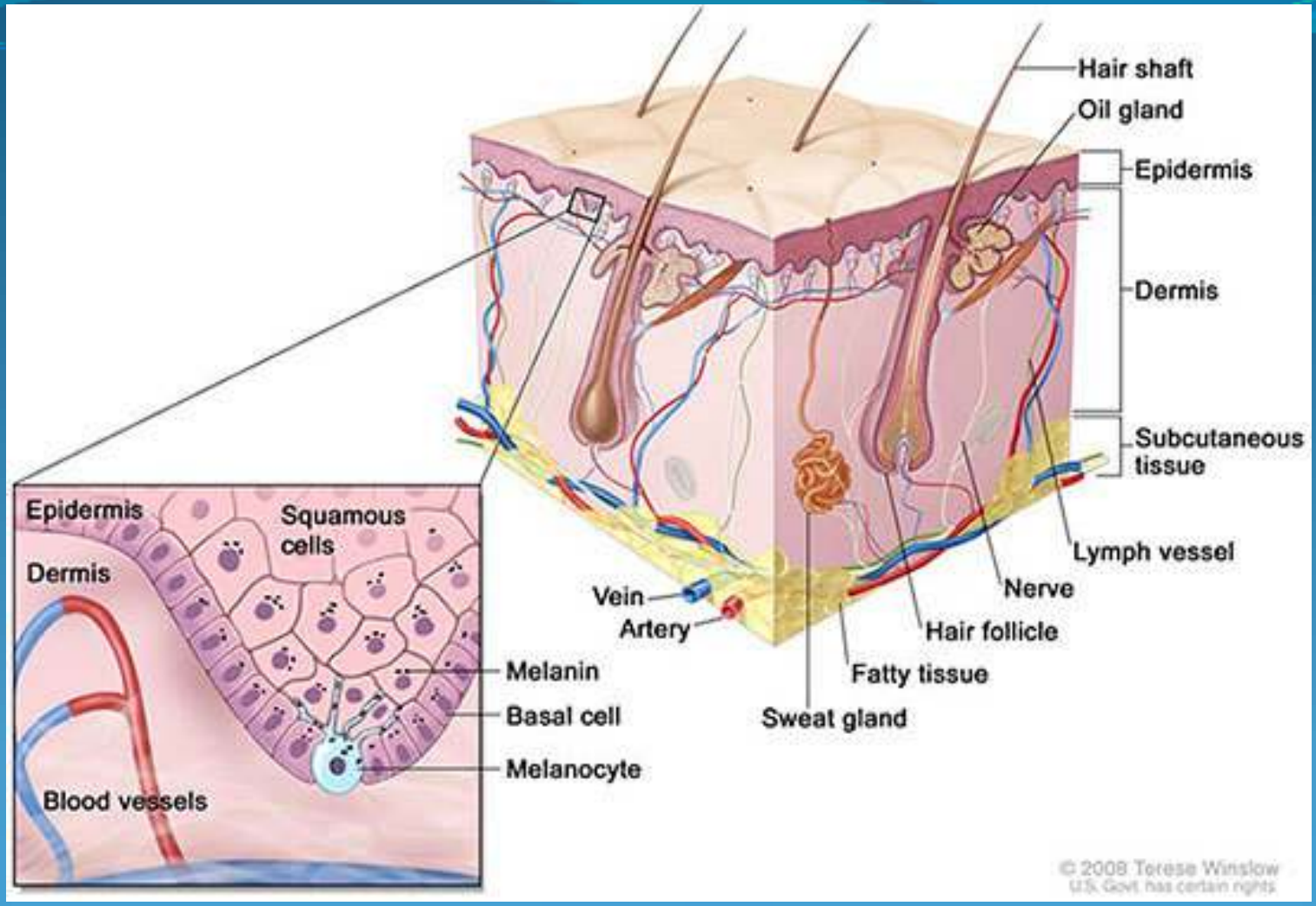


Created by https://seer.cancer.gov/explorer on Wed Jan 22 2020


Melanoma of the Skin
Recent Trends in U.S. Mortality Rates, 2000-2016
By Sex
All Races (includes Hispanic), All Ages
Rate per 100,000
3.0
2.5
2.0
1.5
1.0
0.5
0
2000
2004
2008
2012
2016
Year of Death
Created by https://seer.cancer.gov/explorer on Wed Jan 22 2020

	Common Types of Cancer	Estimated New Cases 2019	Estimated Deaths 2019
1.	Breast Cancer (Female)	268,600	41,760
2.	Lung and Bronchus Cancer	228,150	142,670
3.	Prostate Cancer	174,650	31,620
4.	Colorectal Cancer	145,600	51,020
5.	Melanoma of the Skin	96,480	7,230
6.	Bladder Cancer	80,470	17,670
7.	Non-Hodgkin Lymphoma	74,200	19,970
8.	Kidney and Renal Pelvis Cancer	73,820	14,770
9.	Uterine Cancer	61,880	12,160
10.	Leukemia	61,780	22,840

http://seer.cancer.gov



http://seer.cancer.gov

Types of Melanoma

Superficial spreading – lateral spread often from dysplastic nevus.

Nodular melanoma - appears as stated, more aggressive. Has vertical growth phase.

Acral lentiginous - can appear on palms, soles, and subungual. Comprises 5% of all melanomas. Seen more often in Asian ethnicity.

Desmoplastic - melanoma surrounded by fibrous tissue amidst UV damaged skin.

Mucosal - seen on mucosal surfaces.

Choroidal - within ocular globe.

"ABCD"s of Melanotic Lesions

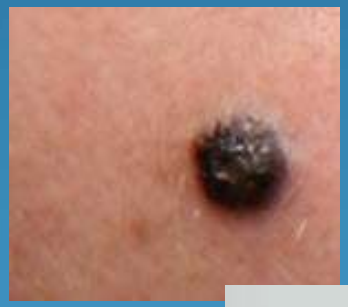
A - Asymmetry

B - Border (irregular)

C - Color (pigmentation)

D - Diameter (>6 mm or enlarging)


15



Risk Factors

- UV light exposure. – usually chronic exposure. A blistering sunburn can increase later melanoma development by ~2x over avg. however.
- "fair" skin complexion. – In comparison African ethnicity lends a risk 1/10th of Caucasians
- Multiple nevi syndromes. - >100 nevi will increase the risk. A history of dysplastic nevi, or numerous atypical nevi also increases melanoma risk.
- Familial syndromes. – a number of genes are suspect.

Genetic, Molecular Risks

A mutation in the CDKN2A gene has been implicated.

Function of CDKN2A: coding of p16 which limits cell cycling at the G1/S transition.

In absence of proper p16 the RB gene product is phosphorylated and likewise a TF E2F activates S-phase and relevant transcription of division and growth occurs.

Familial melanoma has been studied for CDKN2A mutations.

An increased incidence is correlated from 20-57%.

(CDKN2A has also been linked to pancreatic, lung and breast cancers as well… in standard clinical practice this is not checked for).

J. Med. Genet. 2007;44(2):99.

Surgical Concepts of Local Control

- Surgical excision is paramount.
- Margin size is established (depends on depth).
- Lymphadenectomy of clinically positive regional LN basins is important.
- Sentinel lymph node mapping can accurately predict the status of clinically occult nodes (and potentially save complications and morbidity of lymphadenectomy if negative).
- A completion lymph node dissection after +SLN mapping is no longer requisite.

Melanoma Staging

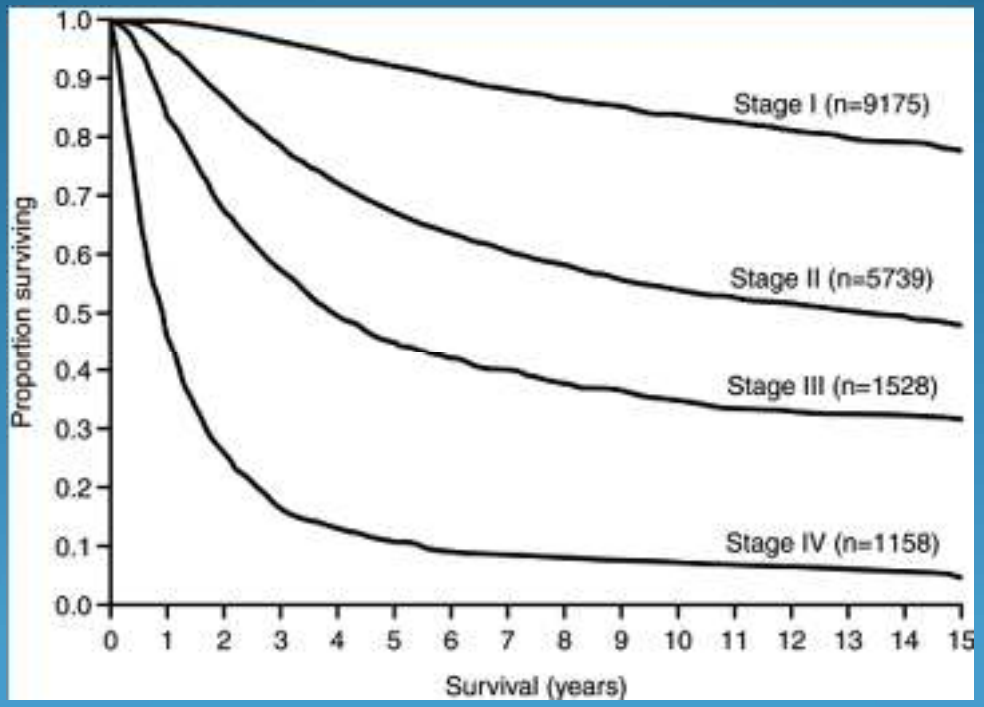
Table. TNM Pathological Staging Overview

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
IA	T1a or T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b or T3a	N0	M0
IIB	T3b or T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1a/b or T2a	N1a or N2a	M0
IIIB	T0 T1a/b or T2a T2b or T3a	N1b or N1c N1b/c or N2b N1a/b/c or N2a/b	M0
IIIC	T0 T1a/b, T2a/b, or T3a T3b or T4a T4b	N2b/c or N3b/c N2c or N3a/b/c Any N ≥N1 N1a/b/c or N2a/b/c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

N, number of tumor-involved regional lymph nodes; M, number of metastases at distant site; T, primary tumor thickness.

Melanoma Research Alliance

Historical Survival by Stage:



(now out-of-date!)

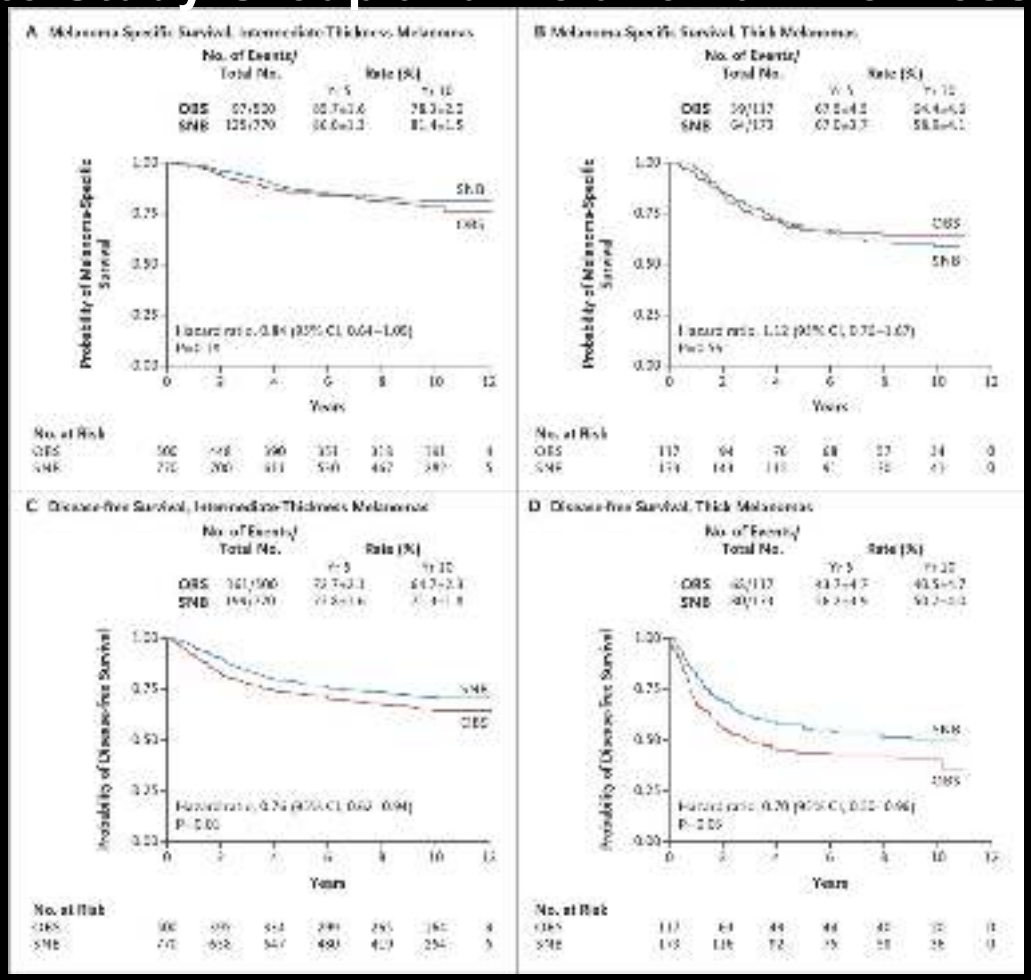
J Clin Oncol 2001;19(16):3635-3648.

MSLT Trial

- Designed to test: reliability/efficacy of SLN mapping, usefulness of SLN to predict nodal basin, DFS and O.S. with regard to intervention.
- Intermediate and thick melanomas were investigated: >1 mm depth (occult LN involvement more likely in advanced stages).
- 2001 patients randomized to:
  - SLN mapping vs. clinical observation of clinically negative nodal basins.
- Completion lymphadenectomy if SLN+ (or at time of clinical relapse for observation group).

NEJM 2014;370:599-609.

Melanoma-Specific and Disease-free Survival, According to Study Group and Melanoma Thickness.



Morton DL et al. N Engl J Med 2014;370:599-609.

MSLT Conclusions

- A positive SLN yielded poorer outcomes (shorter O.S.) regardless of tumor thickness .
- The frequency of nodal metastases was about 20% in intermediate thickness and ~40% in adv. thickness.
- A SLN is identified at least 99.4% of the time.
- DFS is improved with –SLN results vs. +SLN.
- The accuracy of a +SLN to predict nodal basin status was 96%.
- At least in int. thickness, DFS results improved with SLN mapping over clinical observation.
- <u>No difference in O.S.</u>

NEJM 2014;370:599-609.

MSLT Criticism/Questions

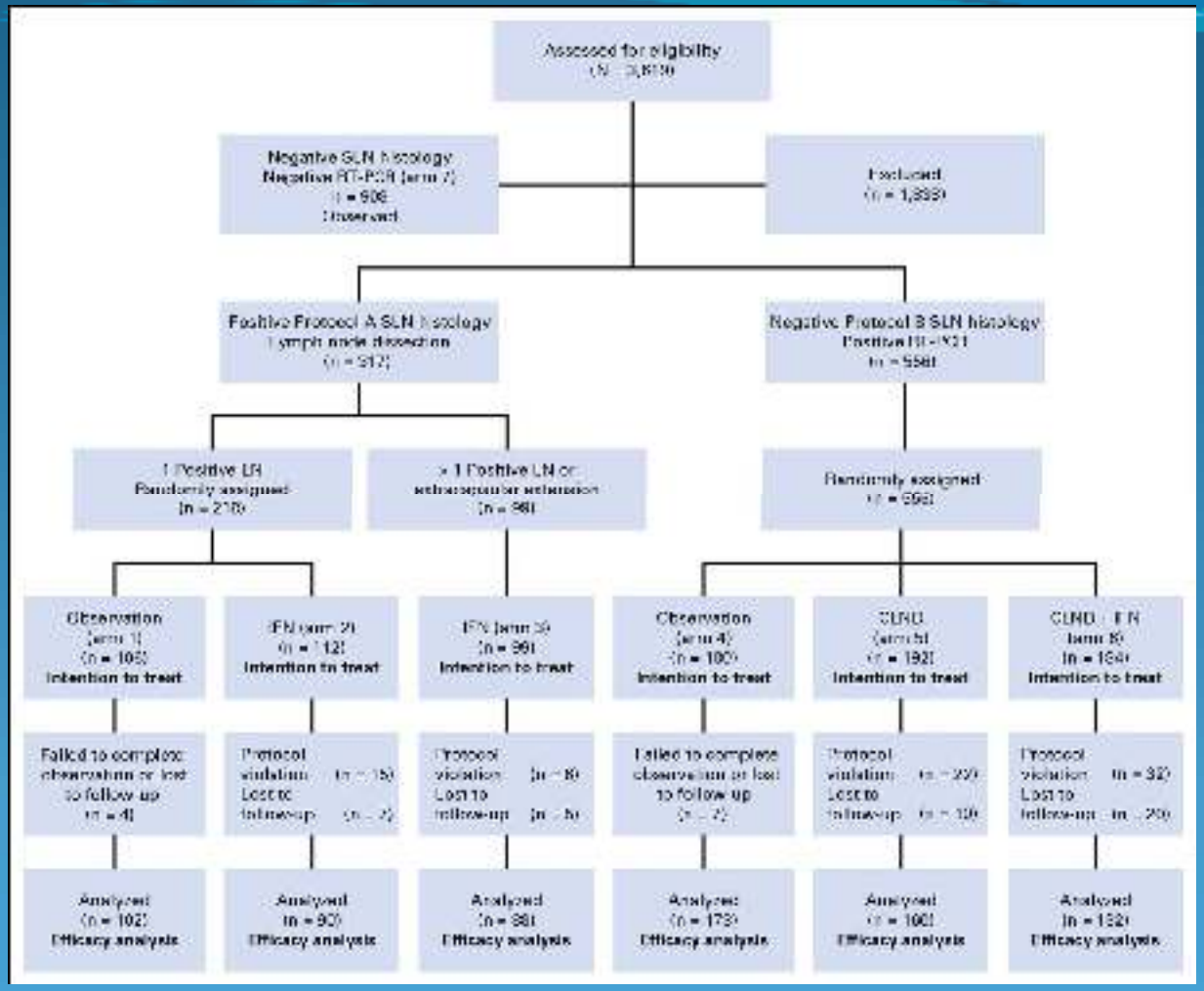
- O.S. seemingly not supported by SLN technique, Why?
- Is improved DFS (which was seen) important?
- Subset analyses published/promoted without original trial designed for such statistical backing.
- Data has been continuously revised (updated stats) over the prolonged follow-up.
- Are there other (non-surgical) strategies which improve outcomes?

Sunbelt Melanoma Trial

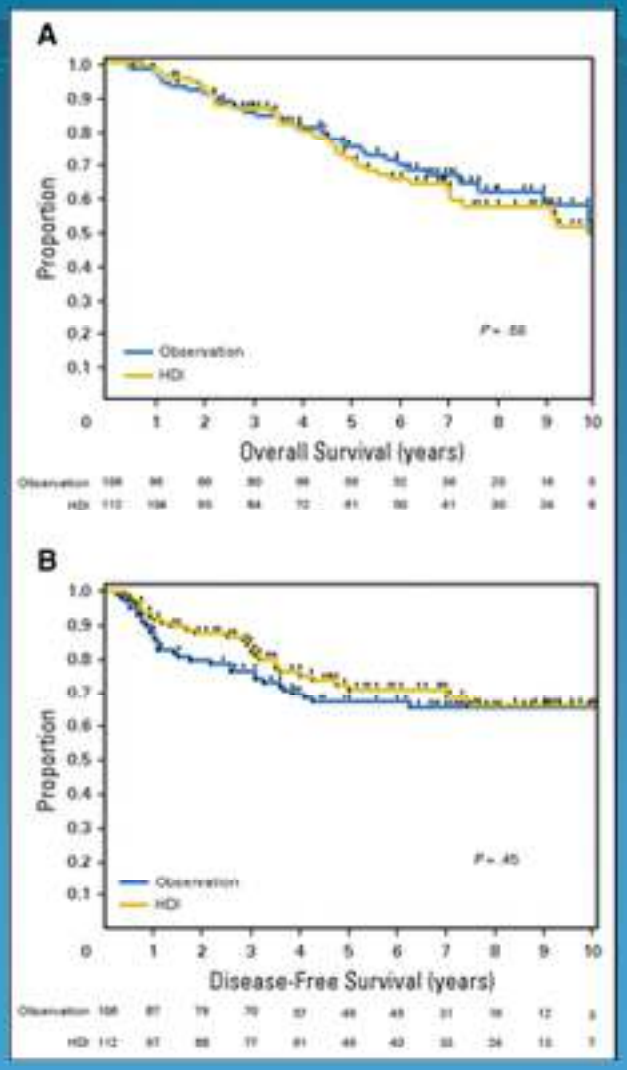
Devised in 1996 to test hypotheses:

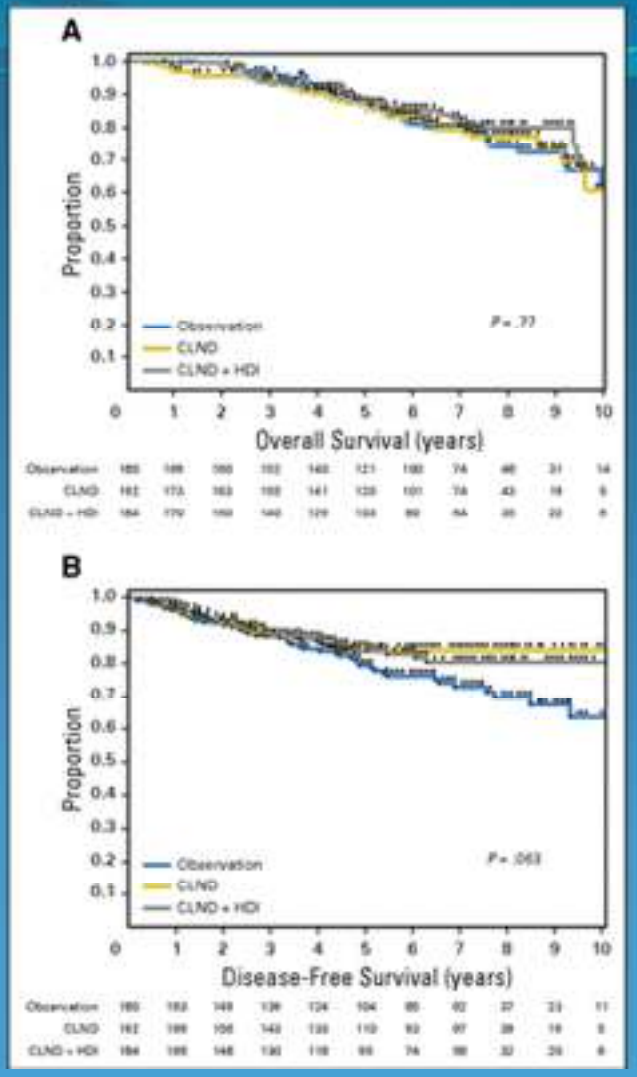
1. Adjuvant high-dose interferon improves DFS and OS with single +SLN (by H&E staining).
2. Completion LN dissection improves DFS and OS when SLN is negative by H&E staining but positive by RT-PCR.
3. Adjuvant high-dose interferon improves DFS and OS when SLN is negative by H&E staining but positive by RT-PCR.

JCO 2016;34:1079-86.

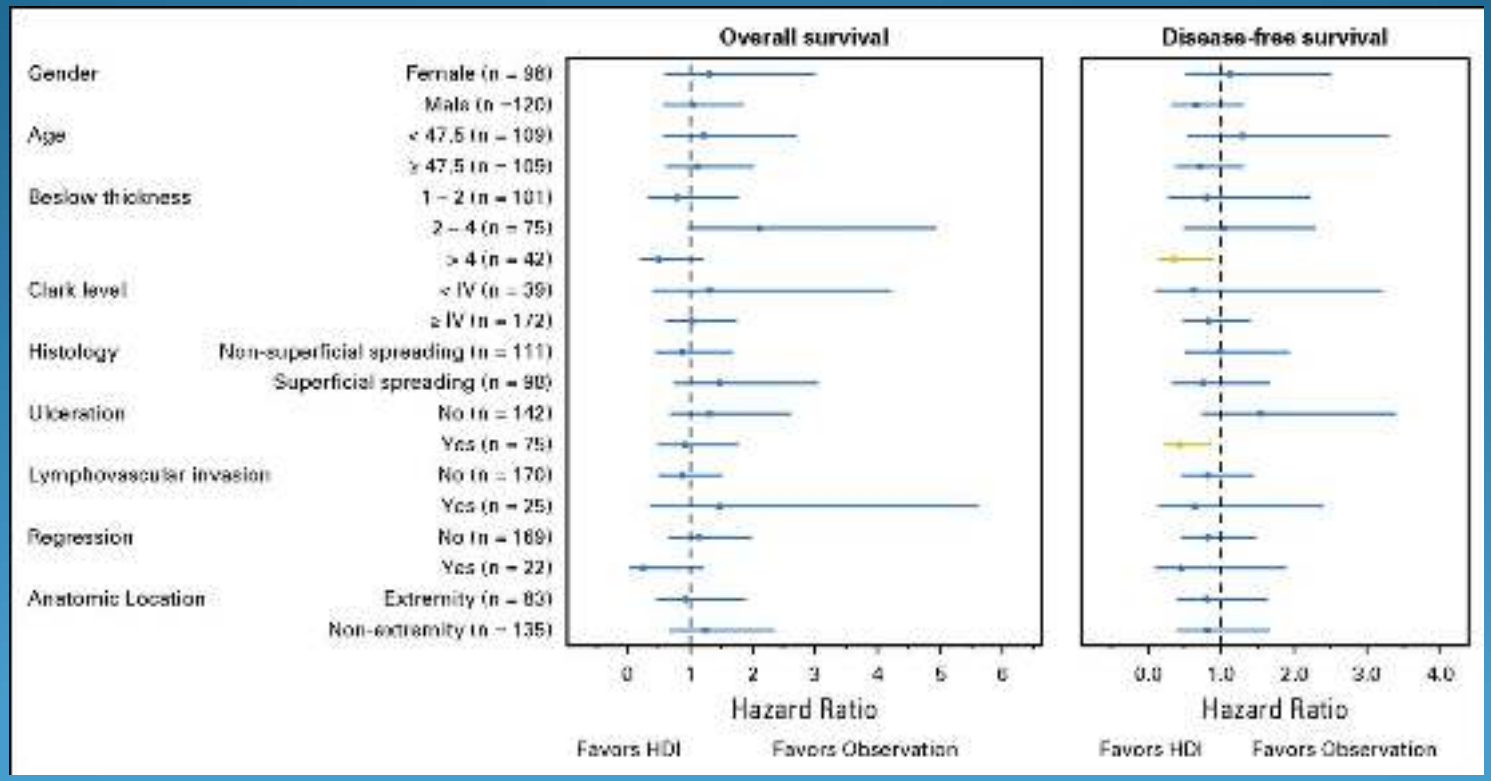


JCO 2016;34:1079-86.





JCO 2016;34:1079-86.



JCO 2016;34:1079-86.

Conclusions of Sunbelt

(The trial failed to meet accrual goals.)

- No DFS or O.S. advantage to HD Int.-α with +SLN.
- No O.S. advantage for HD Int.-α or CLND for (H&E) -SLN even if + by RT-PCR.

(The f/u MSLT-II study further investigated the usefulness of CLND vs. observation for +SLN).

MSLT-II

Goal: To f/u MSLT-I which showed a melanoma-specific O.S. (DFS) with the use of SLN mapping in intermediate thick melanomas. What contribution to survival stems from completion lymphadenectomy?

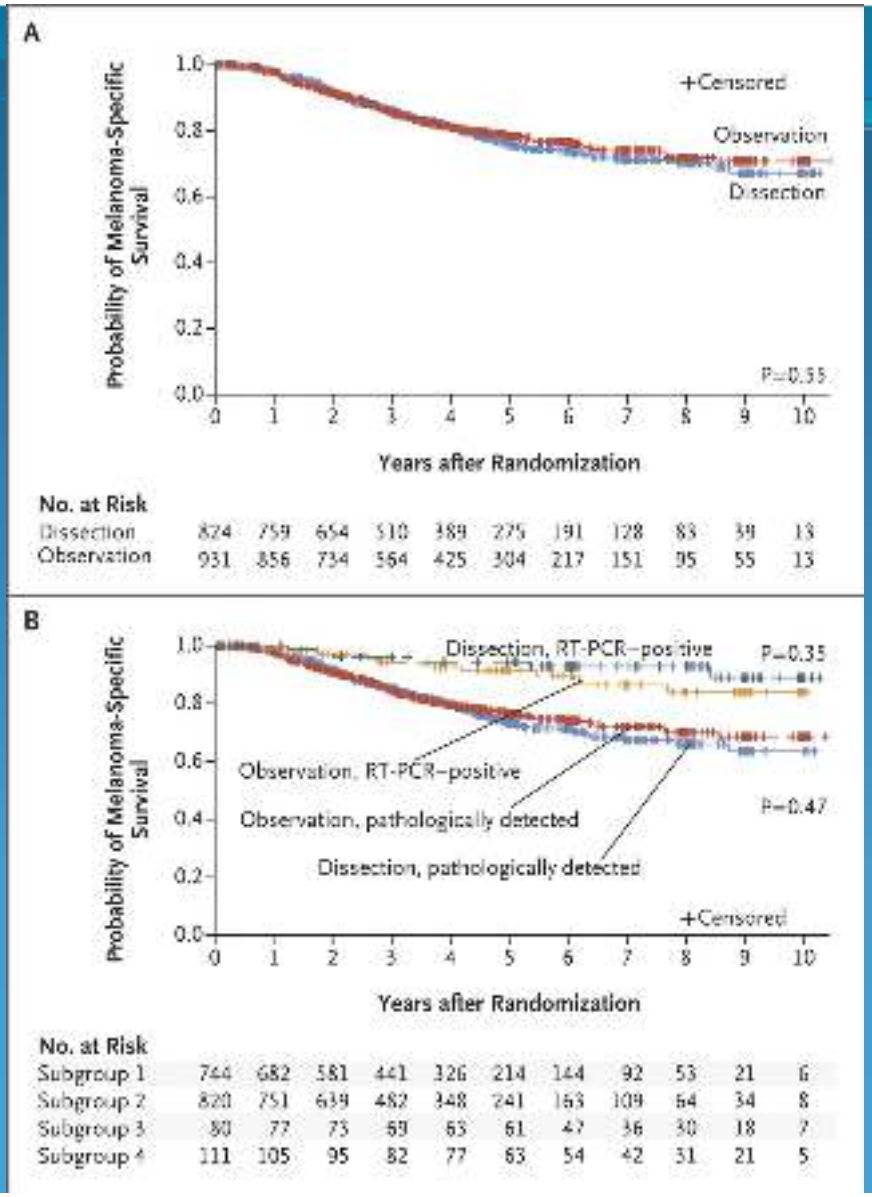
MSLT-II was a multi-centered international trial enrolling from 2004-2014.

1934 patients were enrolled:

If SLN mapping was positive, randomization to:

Completion LAD (N=967) vs Observation including U/S (N=967).

NEJM 2017;376:2211-22.


A
Probability of Melanoma-Specific Survival
1.0
0.8
0.6
0.4
0.2
0.0
+Censored
Observation
Dissection
P=0.35
0 1 2 3 4 5 6 7 8 9 10
Years after Randomization
No. at Risk
Dissection 824 759 654 510 389 275 191 128 83 39 13
Observation 931 856 734 564 425 304 217 151 95 55 13
B
Probability of Melanoma-Specific Survival
1.0
0.8
0.6
0.4
0.2
0.0
Dissection, RT-PCR–positive
P=0.35
Observation, RT-PCR–positive
Observation, pathologically detected
P=0.47
Dissection, pathologically detected
+Censored
0 1 2 3 4 5 6 7 8 9 10
Years after Randomization
No. at Risk
Subgroup 1 744 682 581 441 326 214 144 92 53 21 6
Subgroup 2 820 751 639 482 348 241 163 109 64 34 8
Subgroup 3 80 77 73 59 63 61 47 36 30 18 7
Subgroup 4 111 105 95 82 77 63 54 42 31 21 5

MSLT-II Conclusions

- DFS was not statistically different with CLND versus observation and delayed surgical clearance at relapse (if it occurred) later.
- Optimal timing of delayed surgery is not known.
- Implications of patients who could not return/comply with surgical nodal observation was not addressed.
- Adverse events (e.g. lymphedema) were more common with the CLND group: 24.1% versus 6.3% in obs. group.
- Reaffirming prior understanding, Breslow thickness and presence of a positive LN (>0) were significant factors which predict melanoma-related death.

NEJM 2017;376:2211-22.

Current Surgical Standards (early stage disease)

1. Biopsy.
2. Attain full surgical excision of disease (WLE).
3. Perform SLN mapping if >/= 0.8 mm depth; Order CT or PET staging to r/o distant metastases.
4. If SLN +, CLND not mandatory and nodal basin surveillance with U/S and exam q4 mos for 5 years; Adjuvant therapy discussed – otherwise if SLN -, proceed to #6.
5. Refer to Oncology if adjuvant therapy needed or if metastases seen (high risk stage II-IV).
6. Refer to Dermatology to continue surveillance life-long.

Systemic Therapies

- Chemotherapy
- Interferon
- Interleukin-2
- Immunotherapy
- Targeted, cell cycling inhibitors

Chemotherapy

- Few agents effective (e.g. taxanes, alkylating agents, platinum).
- Side-effects known, generally predictable.
- Response rates and duration of responses are low.
- Curing metastatic disease is unlikely.
- Thus traditional O.S. ~ 6 months has been seen in stage IV disease.
- Presently not a first line manouver.

Interferon

- This incorporates cytokines of the inflammatory response which causes antiangiogenic, anti proliferative, immunomodulatory, antiviral and antitumoral signals.
- Dose and schedule has varied.
- Response rates also variable but potentially better in combination with another systemic agent
- Side-effects abound (debilitating and low QOL at high doses).
- Now eclipsed as a single-agent modality by new drugs.

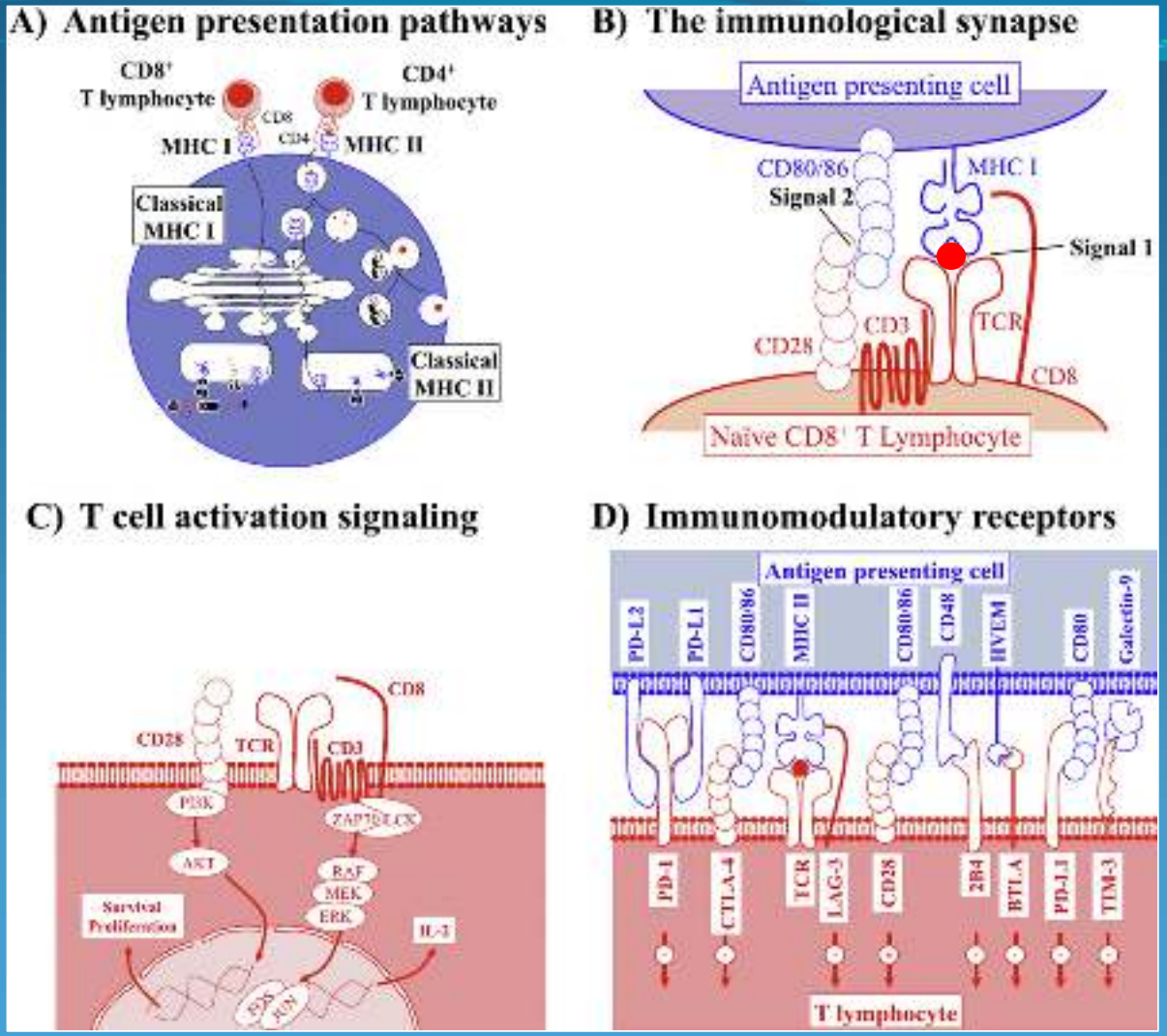
Interleukin-2

- Effects the immune system and increases T-reg and T-effector cells. Tumors generally don't express IL-2 ligands.
- Treatment required inpatient at specialized center.
- Many side-effects/toxicities (capillary leak, effusions, seizures, coma, hypoxia, cardiac ischemia, hypotension, Gram + infections, death)
- Yet, complete responses seen ~5% and many durable.
- Thus, a first demonstration of immune system stimulation which could treat cancer.
- Side-effects/risks and lack of expertise limit its use.

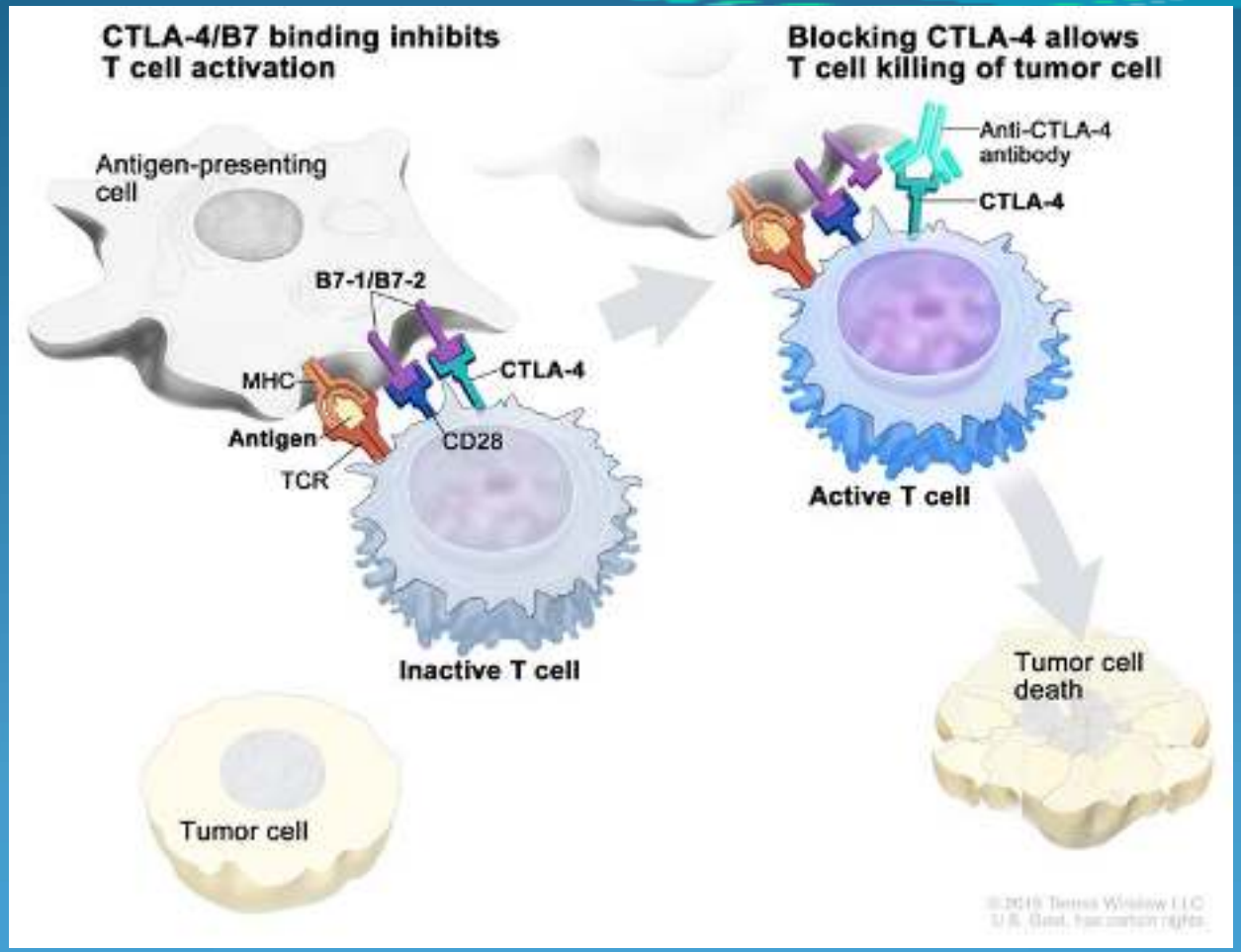
Immunotherapy

- Investigators have found that the immune system is down-regulated in the presence of cancer.
- The CTLA-4 receptor (CD152) has been investigated: this is expressed by cytotoxic T-cells in conjunction with antigen presentation. It interacts with CD80 and CD86.
- The effect is to cause a signal cascade and down-regulate cytotoxic T-cells -> they become anergic.
- Cancer is therefore allowed to proliferate.
- Blocking CTLA-4 can down-regulate the down-regulation and thus stimulate cytotoxic killing.
- Higher RR, DFS and O.S. rates are now seen with this.
- A new success strategy as elaborated next.

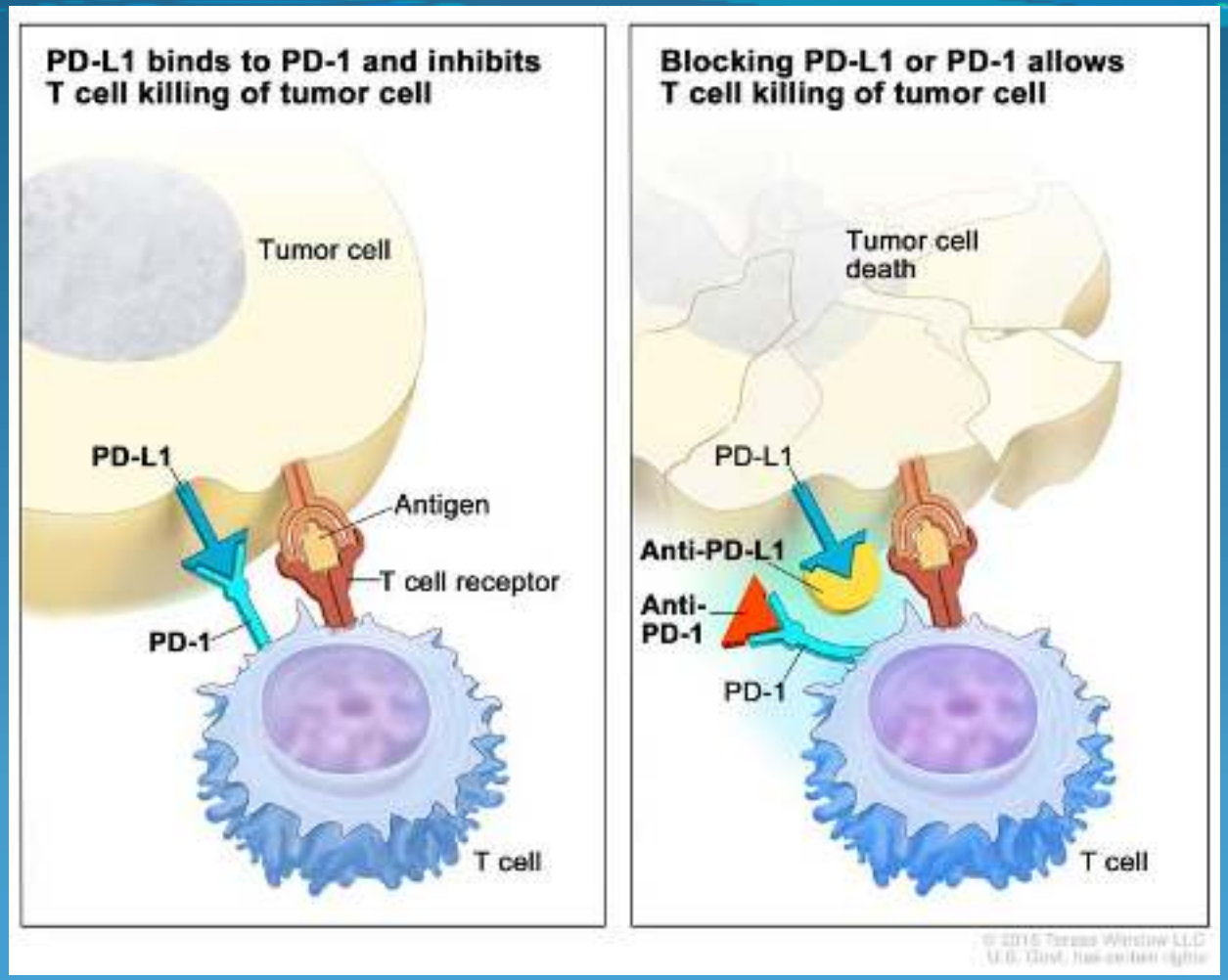
Dermatol. Res. Pract. 2012;2012 182157.



Semin Oncol 2015; 42(4):601-16.


CTLA-4/B7 binding inhibits
T cell activation
Antigen-presenting
cell
B7-1/B7-2
MHC
CTLA-4
Antigen
CD28
TCR
Inactive T cell
Tumor cell
Blocking CTLA-4 allows
T cell killing of tumor cell
Anti-CTLA-4
antibody
CTLA-4
Active T cell
Tumor cell
death

Cancer.gov


PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti-PD-L1
Anti-PD-1
PD-1
T cell

Cancer.gov

Ipilimumab

An anti-CTLA-4 Ab. On basis mentioned it entered clinical trials for metastatic patients.

Phase I and II studies showed activity in metastatic patients, even after heavy pre-treatment. One year O.S. was reached in over half of patients initially.

A recent dose escalation trial was conducted investigating 0.3 mg/kg, 3 mg/kg and 10 mg/kg and reported in 2010. This was a multicenter trial in 66 countries involving 217 patients.

Results showed:

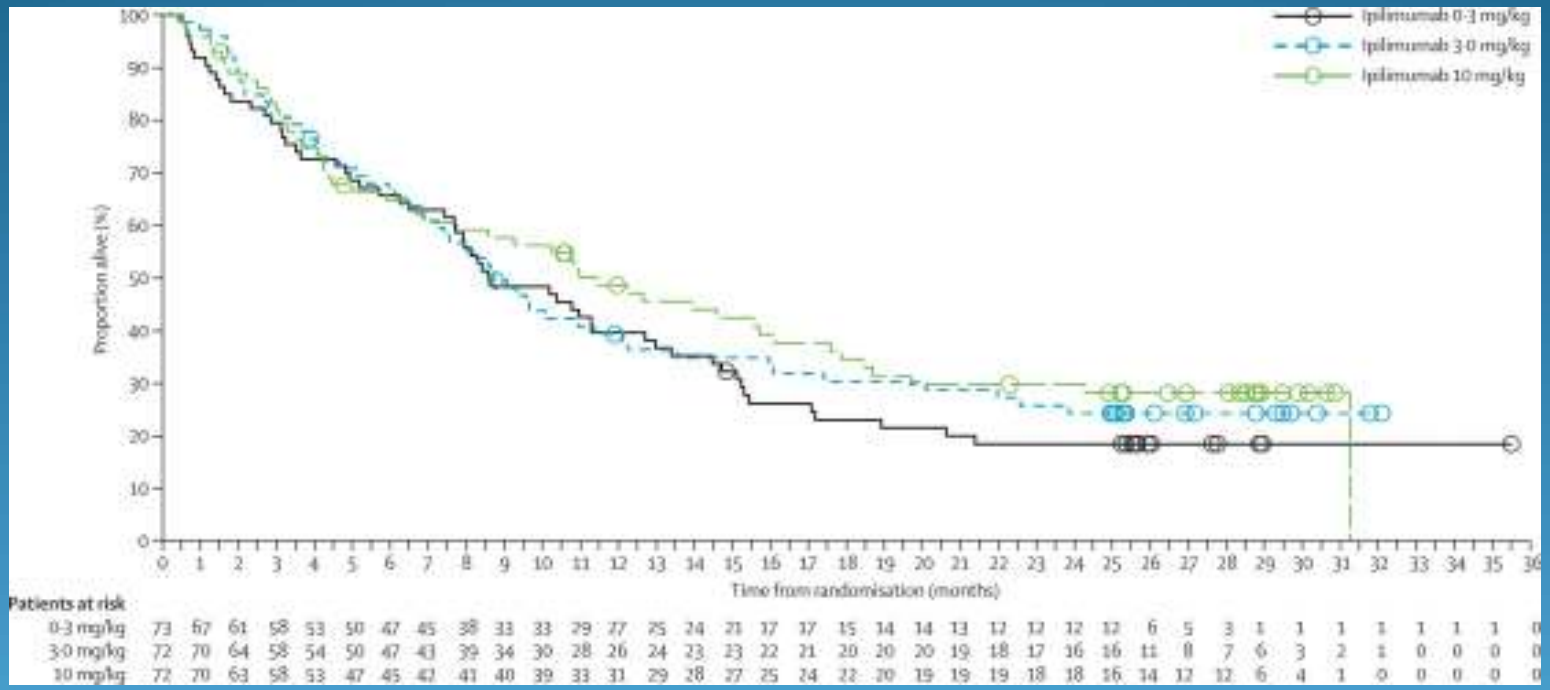
~11% response rate (10mg/kg dose).

Med. O.S. 11.1 months (10mg/kg dose).

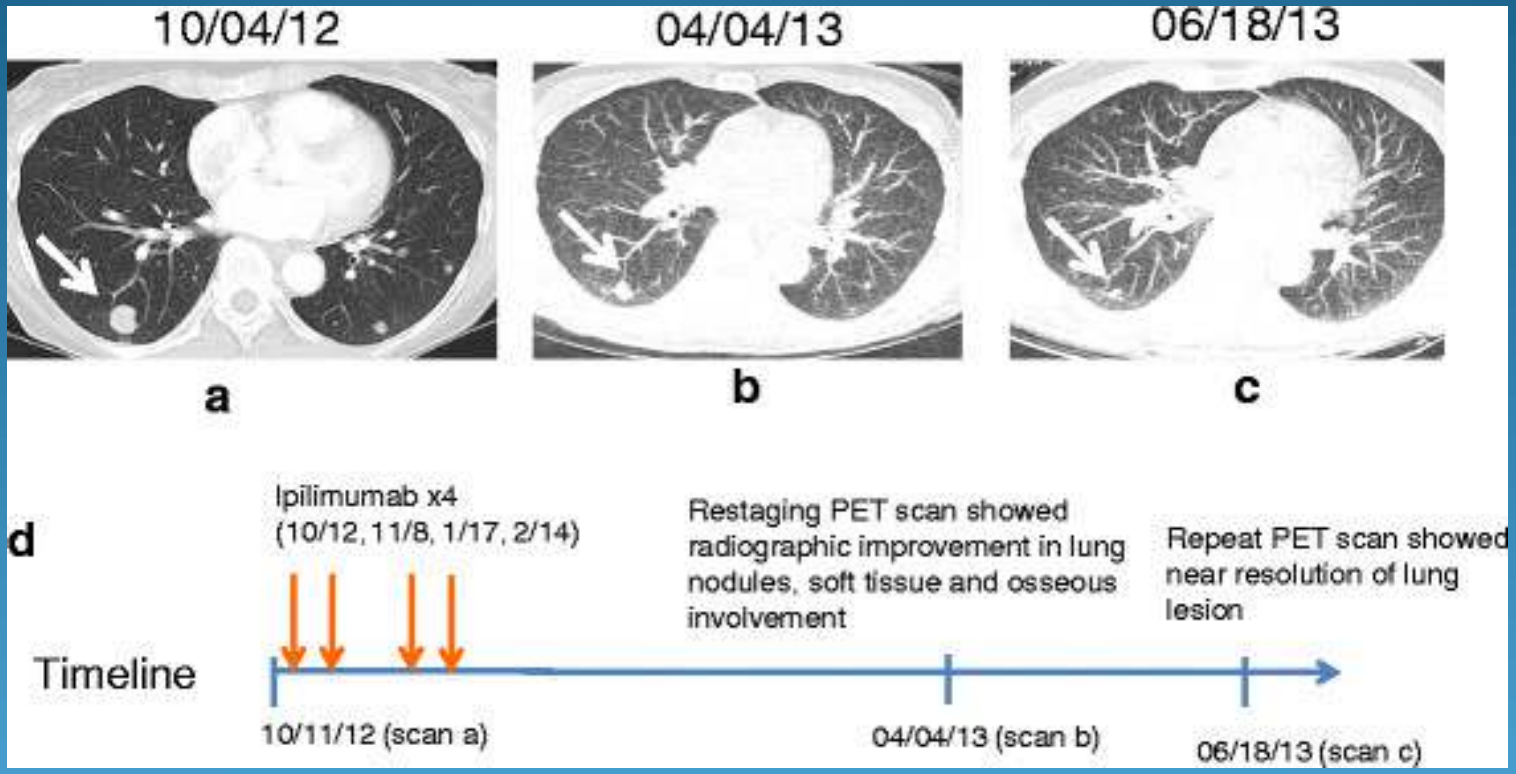
AEs: 50/71 patients.

GI, Endocrine, resp. side-effects seen; often resolution in 3-4 weeks with steroids.

Lancet Oncol. 2010;11:155-64.

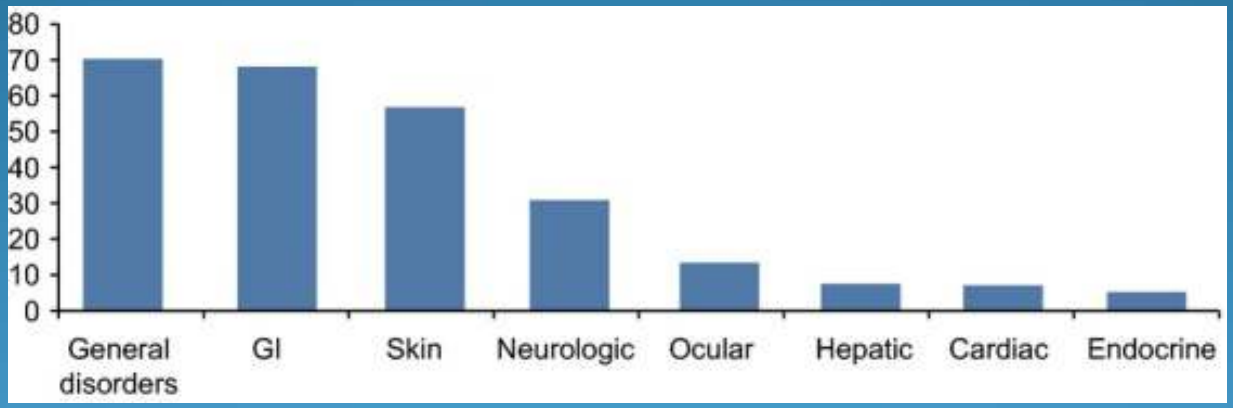


Lancet Oncol. 2010;11:155-64.

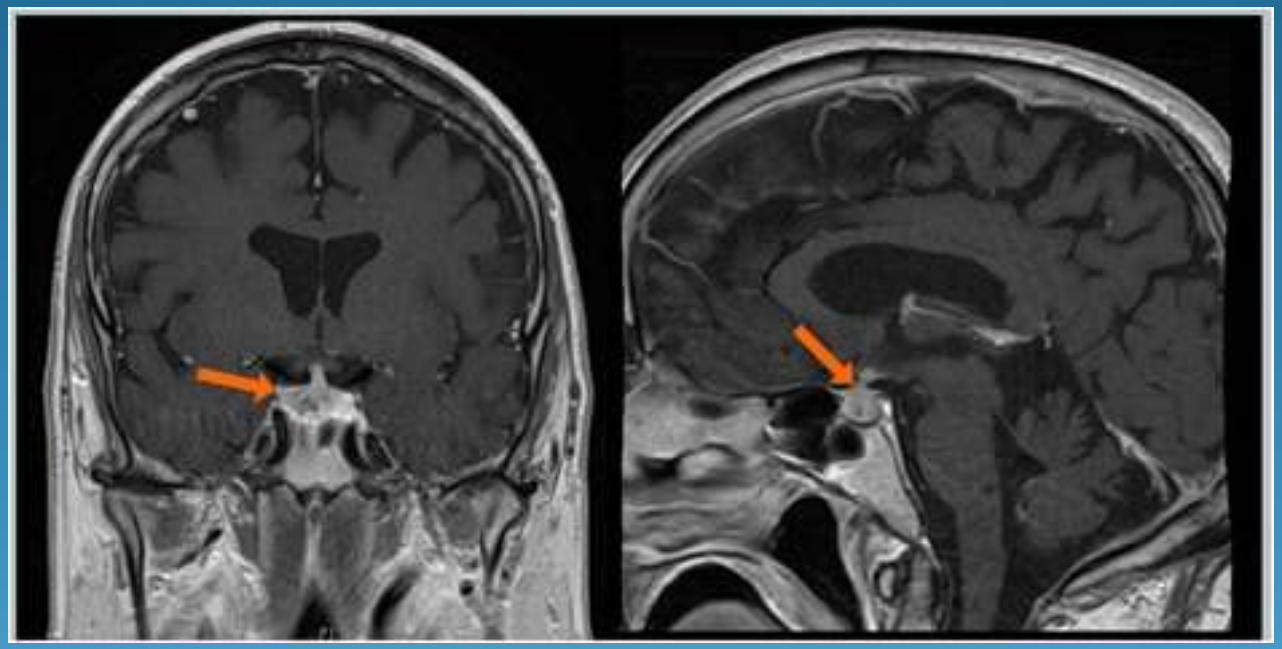


J. for Immunother. Cancer 2014;2:35.

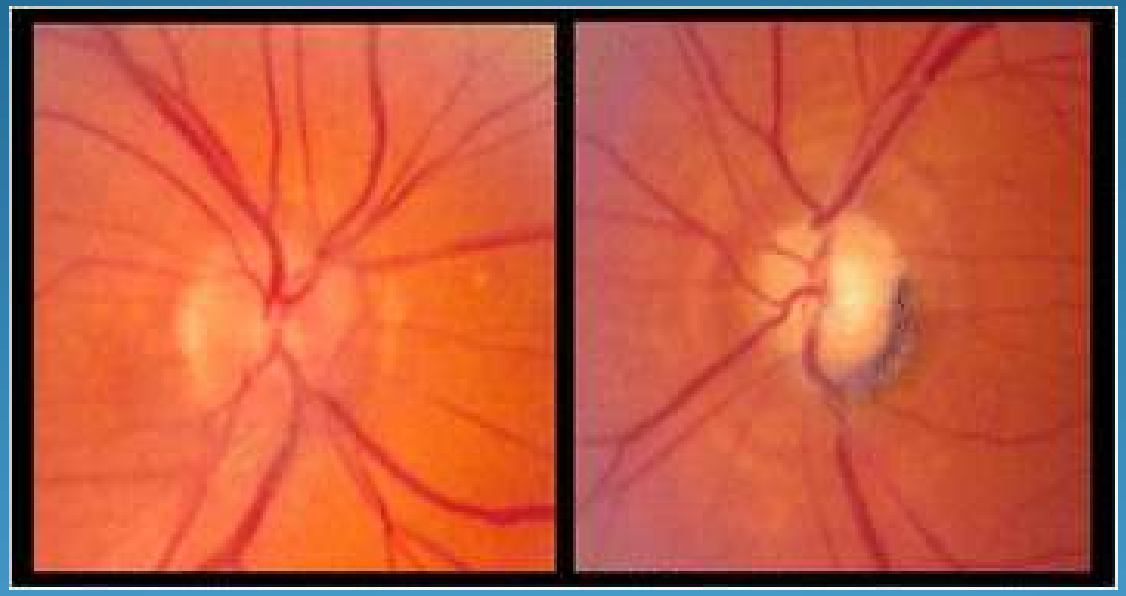
Toxicity of Immunotherapy



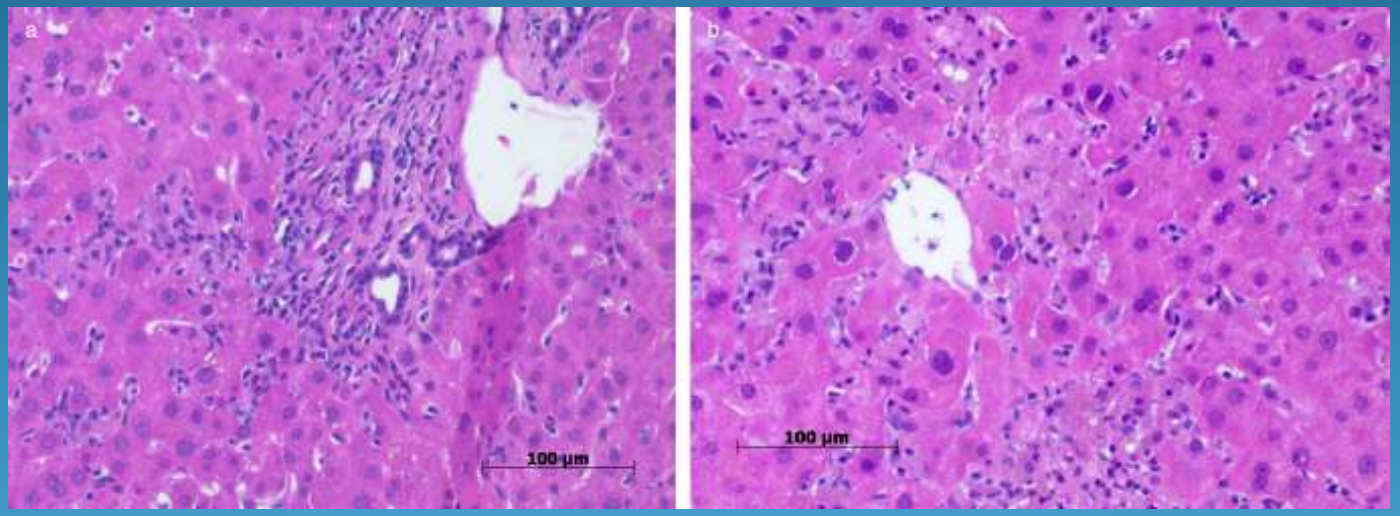
Cancer Med. 2015;5:661-72.



J. Immunother. Cancer 2016;4:66.



J. Immunother. Cancer 2016;4:66.



J. Gastroenterol. Hepatol. 2015;30:657-66.

Contraindications to Immunotherapy

- Pre-existing significant auto-immune/Rheumatic Dz.
- Solid organ transplant.
- Inability to tolerate high dose steroids.
- Prior grade IV toxicities from immunotherapy.

Anti-PD1 Immunotherapy.

The checkpoint inhibition with PD1 has been a target of investigation.

Similar to CTLA4 it is felt to downregulate cytotoxic T-cells via the presence of PDL1 expressed on tumor cells.

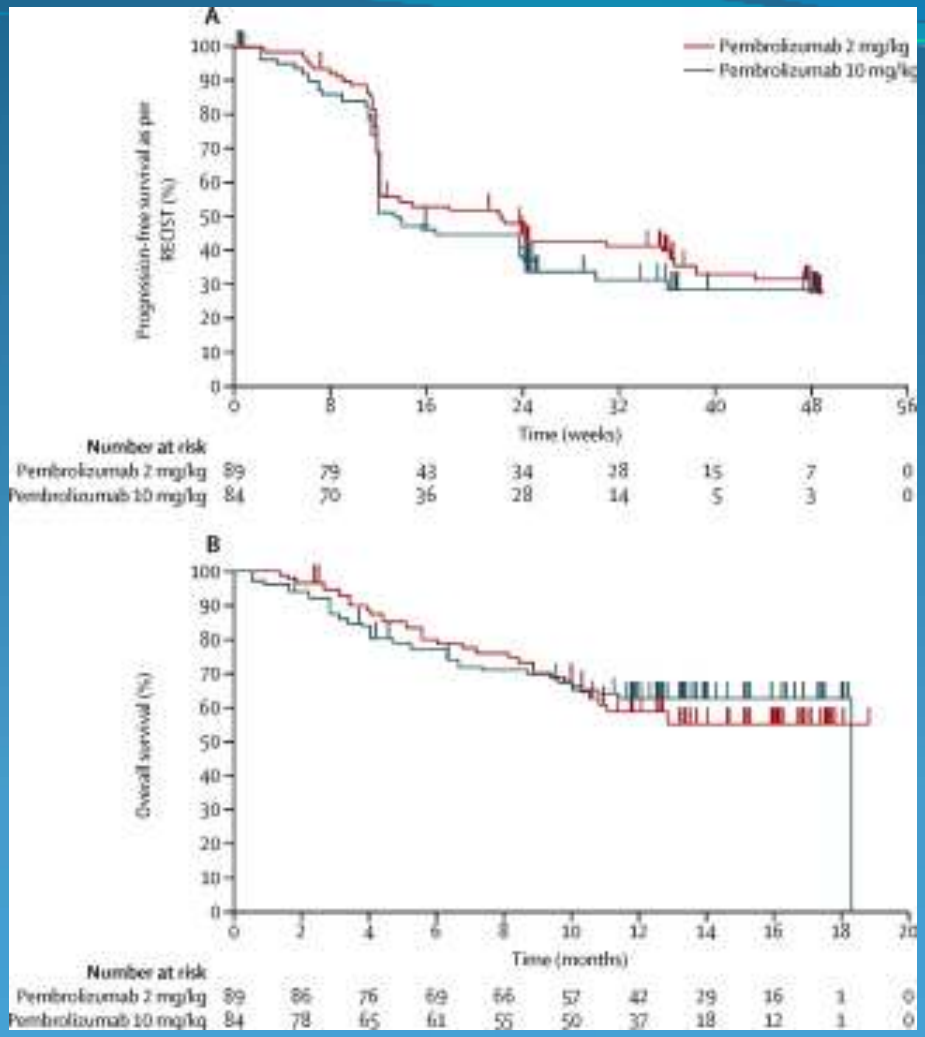
A humanized anti-IgG has been developed: pembrolizumab.

Keynote 001 studied patients with metastatic melanoma with progression after ipilimumab in a large non-randomized trial.

This initially enrolled 135 patients and then expanded.

Various pembrolizumab dosing was investigated.

Lancet 2014;384:1109-17.



Lancet 2014;384:1109-17.

Results:

RR (including SD): 51%

Med PFS: 21 weeks.

1 year O.S.: 58-63% (depending on dosing).

Lancet 2014;384:1109-17.

(Similar results are noted with nivolumab, the other anti-PD1 agent for use in melanoma.)

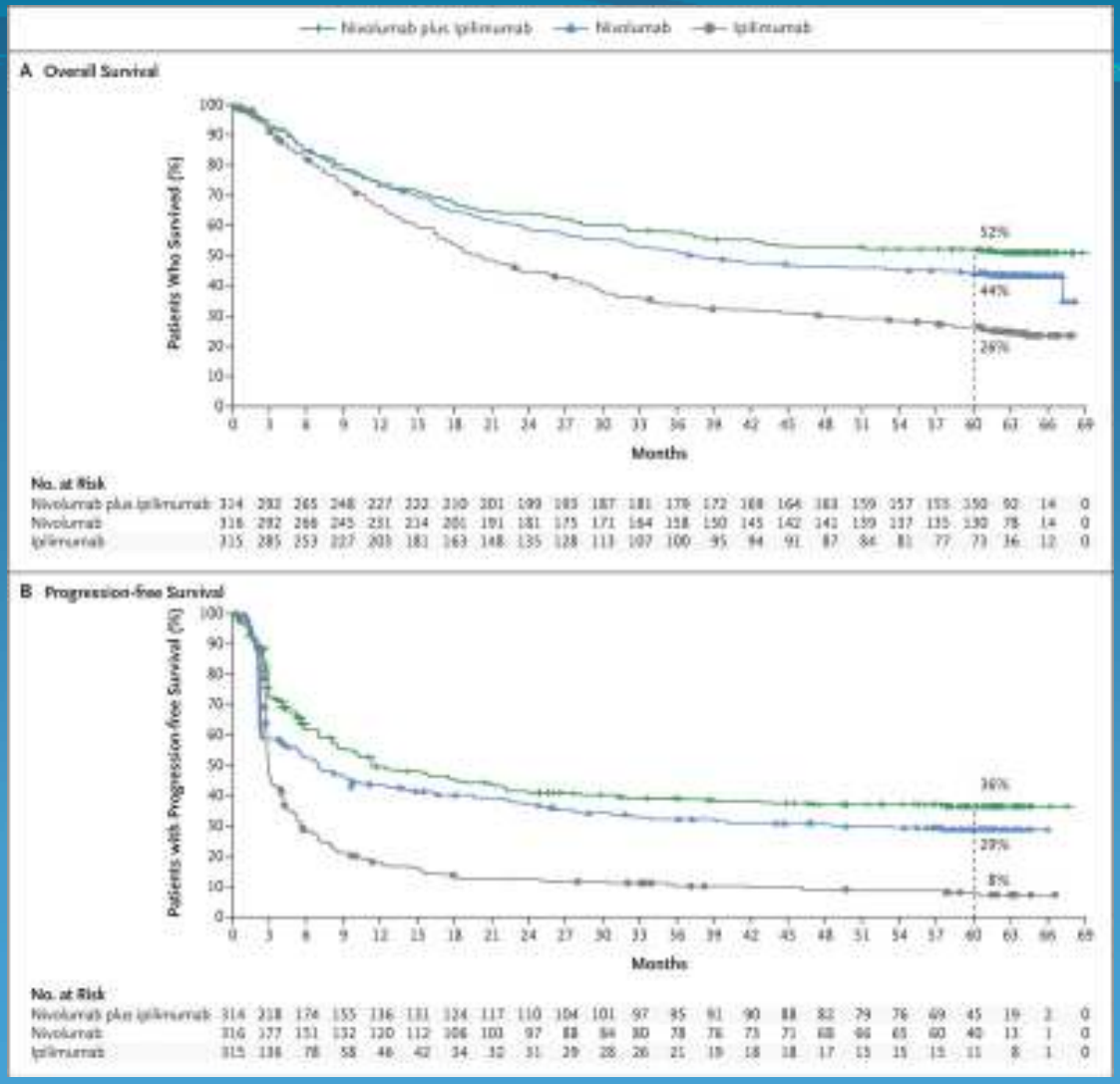
In summary, immunotherapy for stage IV melanoma includes:

- pembrolizumab
- nivolumab
- ipilimumab
- ipilimumab and nivolumab

What is the updated O.S. experience for metastatic patients? (treated with immunotherapy)

- 5 year O.S. is now reported for Checkmate 067

A randomization of:
ipilimumab vs nivolumab vs ipilimumab/nivolumab



NEJM 2019;381:1535-46.

Results show:

med O.S.: >60 mos. ipi/nivo (5 yr O.S. 52%)

36.9 mos. nivolumab (5 yr O.S. 44%)

19.9 mos. ipilimumab (5 yr O.S. 26%)

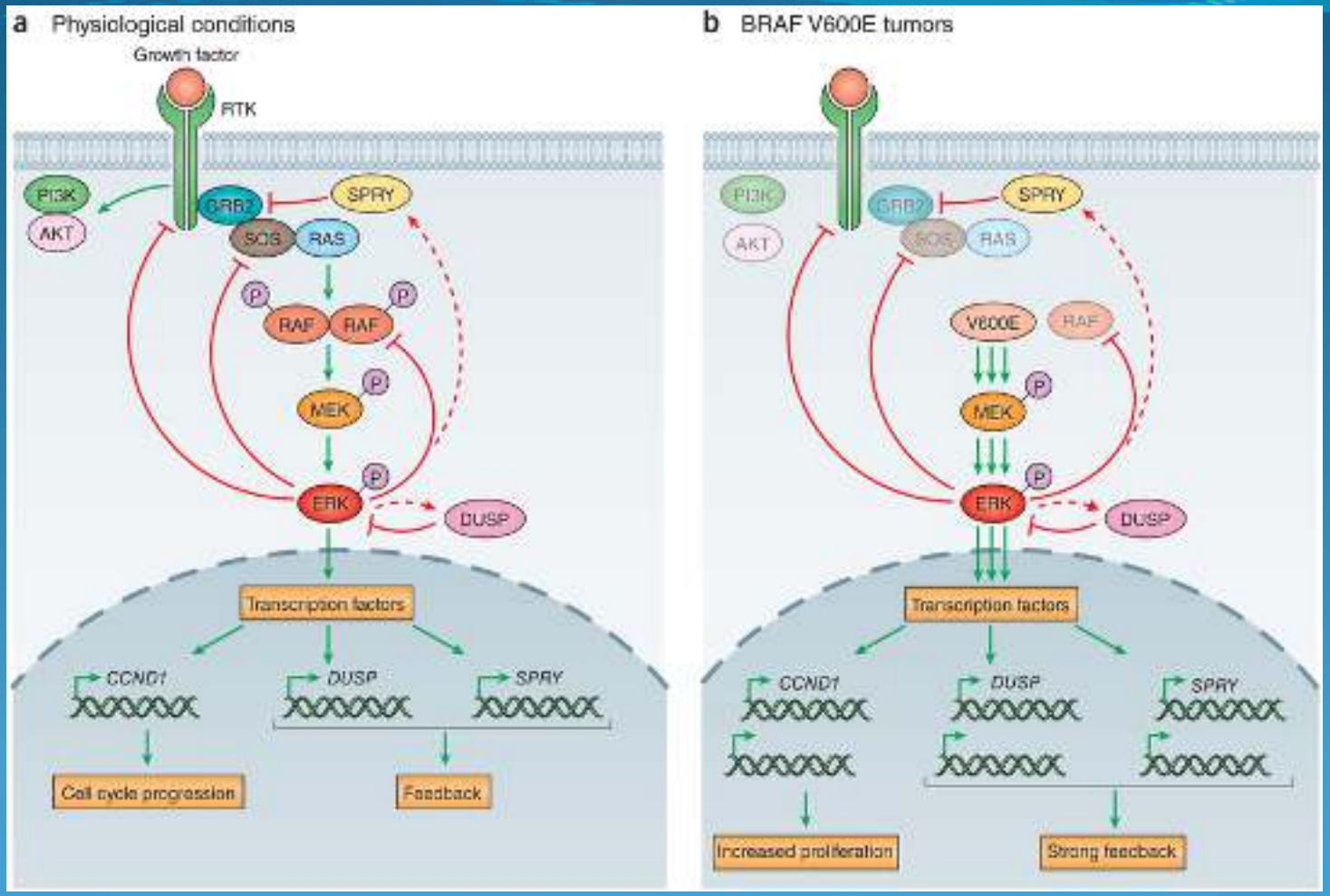
NEJM 2019;381:1535-46

Targeted Therapy: BRAF

Efforts at inhibiting cellular growth have prompted investigation of intra-cellular signaling.

The RAS/RAF/MEK/MAPK signaling cascade is an area of investigation.

Some cancers grow due to constituently active intercellular signaling.



Nature Medicine 2013;19:1401-09.

Three anti-BRAF agents:

- dabrafenib
- vemurafenib
- encorafenib

Three anti-MEK agents:

- trametinib
- combimetinib
- binimetinib

At present this strategy incorporates combining an anti-BRAF and anti-MEK therapy together.

The past few years' have yielded positive clinical results from this strategy (intracellular signalling blockade).

Salient recent clinical trial:

947 patients screened (international study).

Eligible: unresectable stage III or IV melanoma with BRAF mutation.

1:1 randomization to:

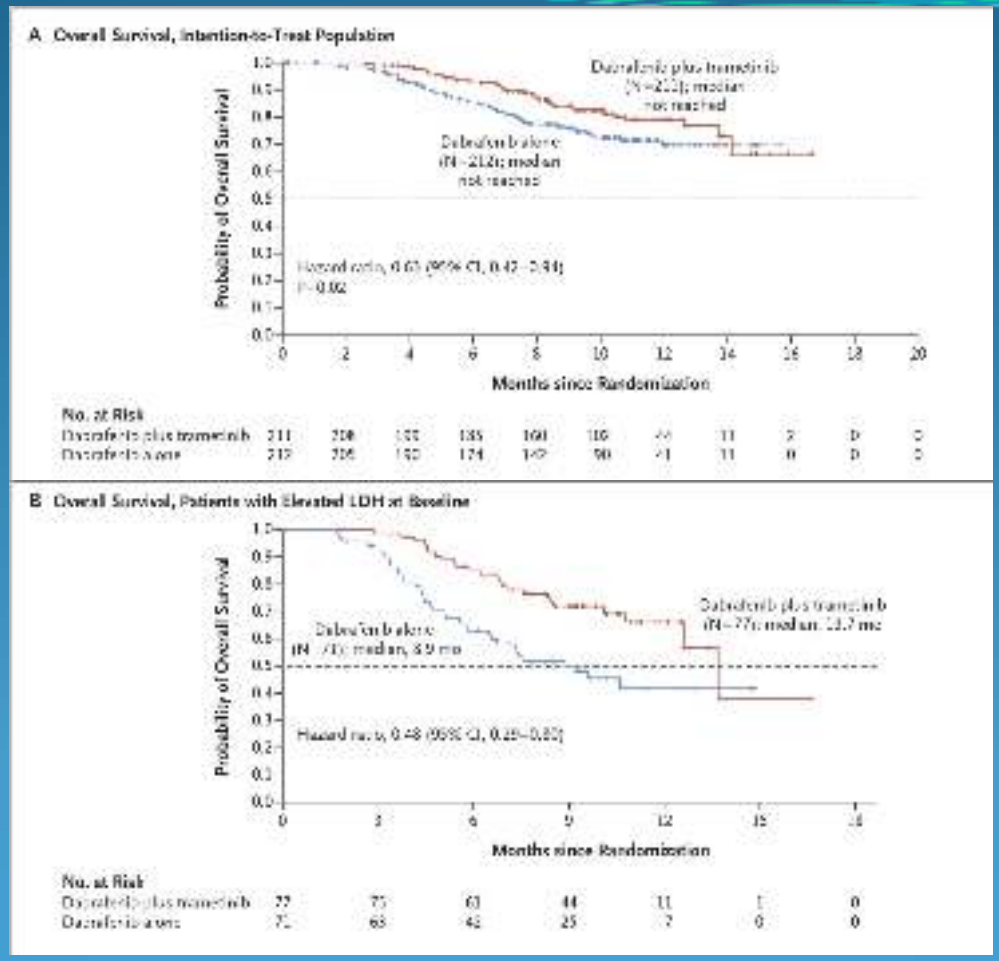
dabrafenib + trametinib vs. dabrafenib

Results:

PFS 7.1 vs. 3.8 mos.

Med. O.S. not reached (but for high LDH 13.7 vs. 8.9 mos).

NEJM 2014:371;1877-88.



NEJM 2014;371:1877-88.

Table 3. Adverse Events.*

Event	Dabrafenib plus Trametinib (N = 209)		Dabrafenib Alone (N = 211)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Any adverse event	199 (95)	66 (32)	203 (96)	72 (34)
Pyrexia‡	107 (51)	12 (6)	59 (28)	4 (2)
Fatigue	74 (35)	4 (2)	74 (35)	2 (1)
Headache	65 (31)	1 (<1)	62 (29)	5 (2)
Nausea	63 (30)	0	54 (26)	3 (1)
Chills	62 (30)	0	33 (16)	0
Arthralgia	51 (24)	1 (<1)	58 (27)	0
Diarrhea	51 (24)	2 (1)	30 (14)	2 (1)
Rash	48 (23)	0	46 (22)	2 (1)
Hypertension	46 (22)	8 (4)	29 (14)	10 (5)
Vomiting	42 (20)	2 (1)	28 (14)	1 (<1)
Cough	34 (16)	0	35 (17)	0
Peripheral edema	31 (14)	1 (<1)	10 (5)	1 (<1)
Pain in a limb	30 (14)	3 (1)	33 (16)	1 (<1)
Decreased appetite	23 (11)	1 (<1)	25 (12)	2 (1)
Abdominal pain	22 (11)	2 (1)	14 (7)	3 (1)
Elevated alanine aminotransferase	22 (11)	4 (2)	10 (5)	1 (<1)
Elevated aspartate aminotransferase	22 (11)	6 (3)	7 (3)	1 (<1)
Constipation	22 (11)	1 (<1)	18 (9)	0
Myalgia	22 (11)	1 (<1)	24 (11)	0
Asthenia	20 (10)	1 (<1)	27 (13)	1 (<1)
Dizziness	20 (10)	0	12 (6)	0
Nasopharyngitis	20 (10)	0	15 (7)	0
Back pain	19 (9)	2 (1)	30 (14)	4 (2)
Dry skin	19 (9)	0	28 (13)	0
Pruritus	17 (8)	0	26 (12)	0
Alopecia	15 (7)	0	55 (26)	0
Hand-foot syndrome§	10 (5)	0	58 (27)	1 (<1)
Hyperkeratosis	7 (3)	0	68 (32)	1 (<1)
Skin papilloma	3 (1)	0	45 (21)	0
Adverse event of interest occurring in <10% of patients				
Cutaneous squamous-cell carcinoma including keratoacanthoma	5 (2)	4 (2)	20 (9)	8 (4)
Decreased ejection fraction	9 (4)	1 (<1)	5 (2)	1 (<1)
Chorioretinopathy	1 (<1)	0	1 (<1)	0
Blurred vision	5 (2)	0	4 (2)	0
Comedo acneiform	15 (7)	0	7 (3)	0

* Listed are adverse events that occurred in at least 10% of patients who received at least one dose of a study drug in any group, except as indicated.

† A total of eight grade 5 events occurred in seven patients (3%) in the dabrafenib–trametinib group (anemia, decreased lymphocyte count, hypoglycemia, pulmonary embolism, brain edema, hepatic hematoma, events related to central nervous system, and pancytopenia) and in seven patients (3%) in the dabrafenib-only group (dyspnea, thrombocytopenia, hypokalemia, cutaneous squamous-cell carcinoma, brain edema, hypercalcemia, febrile neutropenia, and hypovolemic shock). Grade 5 events were reported in four patients (2%) in the dabrafenib–trametinib group (pneumonia and cerebral hemorrhage [in three patients]).

‡ Pyrexia was defined as a body temperature of 38.5°C or higher.

§ The hand-foot syndrome included the terms palmar–plantar erythrodysesthesia, palmar–plantar hyperkeratosis, and palmoplantar keratoderma.

	Toxicity	Early response	Durable response
Immunotherapy			
Anti-PD1	+	++	+++
Anti-CTLA4	++	+	+++
Anti-CTLA4 and anti-PD1	+++	++	++++
Interleukin-2	++++	+	++
Targeted therapy			
Vemurafenib	+	+++++	+
Dabrafenib	+	+++++	+
Dabrafenib and trametinib	+	+++++	+/++
Vemurafenib and cometinib	+	+++++	+/++
Cytotoxic therapy			
Biochemotherapy	++++	+++	++
CVD	++	+++	+

In selecting therapies in each category, the likelihood of toxicity, early response, and durable response should be considered. Grading is based on published results as well as experience. Direct comparison in studies is not available. CVD is cisplatin, vinblastine, and dacarbazine. The number of "+" signs is indicative of the likelihood of developing toxicity, early response, or durable response

Curr. Treat. Options in Oncol. 2016;17:52.

Adjuvant strategies

…if the treatment of metastatic disease is yielding better DFS and O.S. results can we not apply these agents to an adjuvant strategy to prevent disease from recurring after resection?

Adjuvant high dose interferon-α

- Three landmark trials were organized by John Kirkwood, et al. and the Eastern Cooperative Oncology Group. (ECOG 1684, 1690, 1694).
- The goals were to investigate O.S. advantages toward application of adjuvant interferon-α.
- Each trial was a RCT with a different design: (pts. with stage III and high risk stage II disease)

E1684	E1690	E1694
HD int.-α	HD int.-α	HD int.-α
vs.	vs.	vs.
Observation	Interm. dose interferon-α	Ganglioside GM2 vaccine
	vs.	
	Observation	

Results of adj. interferon-α RCTs

ECOG 1684: +5 yr. O.S. advantage.

→ No 10 yr. O.S. difference.

ECOG 1690: No 5 yr. O.S. difference.

ECOG 1694: ~~+5 yr.~~ O.S. advantage.

→ No true O.S. difference.

*(adj. interferon-α appeared better but vaccine arm did worse -> later confirmed with a European study investigating vaccine).

Sunbelt trial: No 5 yr. O.S. difference.

Table 1. IFN Versus Observation In Stage II/III Patients

Trial	Stage	Treatment	DFS	OS
HDI				
NCCTG[16]	II-III	IFNα2a, 3 × 20 MIU/m²/wk, IM, 3 mo	5-yr; HR = 0.77; P = .19	5-yr; HR = 0.88; P = .40
ECOG 1684[17]	IIB, III	IFNα2b, 20 MIU/ m² qd 1–5 IV, + 3 × 10 MIU/ m²/wk SC, 48 wk	6.9 yr; HR = 0.56; P = .0046	6.9 yr; HR = 0.68; P = .046
ECOG 1690[18]	IIB, III	IFNα2b, 20 MIU/ m² qd 1–5 IV, + 3 × 10 MIU/m²/wk SC, 48 wk	4.4 yr; HR = 0.90; P = .054	4.4 yr; HR = 1.07; P = .99
SUNBELT[19]	III SN+	IFNα2b, 20 MIU/ m² qd 1–5 IV, + 3 × 10 MIU/ m²/wk SC, 48 wk	5.3 yr; HR = 0.82; P = .46	5.3 yr; HR = 1.03; P = .90
IDI				
EORTC 18952[20]	IIB-III	IFNα2b, 10 MIU qd 1–5 SC, 4 wk + 3 × 10 MIU/wk SC, 12 mo or 3 × 5 MIU/wk SC, 24 mo	4.65-yr; HR = 0.81; P = .12	4.65-yr; HR = 0.88; P = .40
Nordic[21]	IIB, III	IFNα2b, 10 MIU qd 1–5, SC, 4 wk + 3 × 10 MIU/wk, SC, 12 mo or 3 × 10 MIU/wk, SC, 24 moss	6 yr; HR = 0.83; P = .05	6 yr; HR = 0.88; P = .47
LDI				
French[22]	II	IFNα2a, 3 × 3 MIU/wk for 18 mo	5-yr; HR = 0.75; P = .035	5-yr; HR = 0.72; P = .059
Austrian[23]	II	IFNα2a, 3 MIU qd, 3 wk + 3 × 3 MIU/wk, for 12 mo	3.4 yr; HR = 0.62; P = .02	3.4 yr; HR = 0.83; P = NS
Scottish[24]	IIB, III	IFNα2b, 3 × 3 MIU/wk, for 6 mo	2-yr; HR = 0.72; P = .05	2-year; HR = 0.81; P > .2
ECOG 1690[18]	IIB, III	IFNα2b, 3 × 3 MIU/wk, for 24 mo	5 yr; HR = 0.90; P = .17	5 year; HR = 0.93; P = .81
UKCCR[25]	IIB, III	IFNα2a, 3 × 3 MIU/wk, for 24 mo	5 yr; HR = 0.94; P = .6	5 year; HR = 0.91; P = .3
WHO-16[26]	III	IFNα2a, 3 × 3 MIU/wk, for 36 mo	5 yr; HR = 0.95; P = .5	5 year; HR = 0.96; P > .5
German[27]	III	IFNα2a, 3 × 3 MIU/wk, for 24 mo	4-yr; HR = 0.69; P = .018	4-year; HR = 0.62; P = .0045
EORTC 18871[28]	II-III	IFNα2b, 3 × 1 MIU/wk, for 12 mo	8 yr; HR = 0.96; P > .5	8 yr; HR = 0.96; P > .7

Abbreviations: HDI, high-dose interferon; IDI, intermediate-dose interferon; LDI, low-dose interferon; NCCTG, North Central Cancer Treatment Group; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; UKCCR, United Kingdom Council for Cancer Research; WHO, World Health Organization; SN +, sentinel node–positive; IM, intramuscularly; IV, intravenously; SC, subcutaneously; MIU, million international units; qd: every day; IFNα2a, interferon alpha2a; IFNα2b, interferon alpha2b; DFS, disease-free survival; OS, overall survival; HR, hazard ratio.

Semin. Oncol. 2010;37:455-9

What else in Adjuvant Fashion?

- Chemotherapy (dacarbazine)?
- Immune stimulants (BCG, cornynebacterium, levamisole)?
- Vaccines?
- GM-CSF (ECOG 4697)?

All of the above have failed to show convincing O.S. advantages.

New Adjuvant Techniques

On basis of responses to anti-CTLA4 (ipilimumab) in stage IV disease, investigators have attempted clinical trials for adjuvant therapy.

951 patients with resected stage III disease underwent randomization, double placebo-blinded, to:

ipilimumab 10 mg/kg IV (3 year course) vs. placebo.

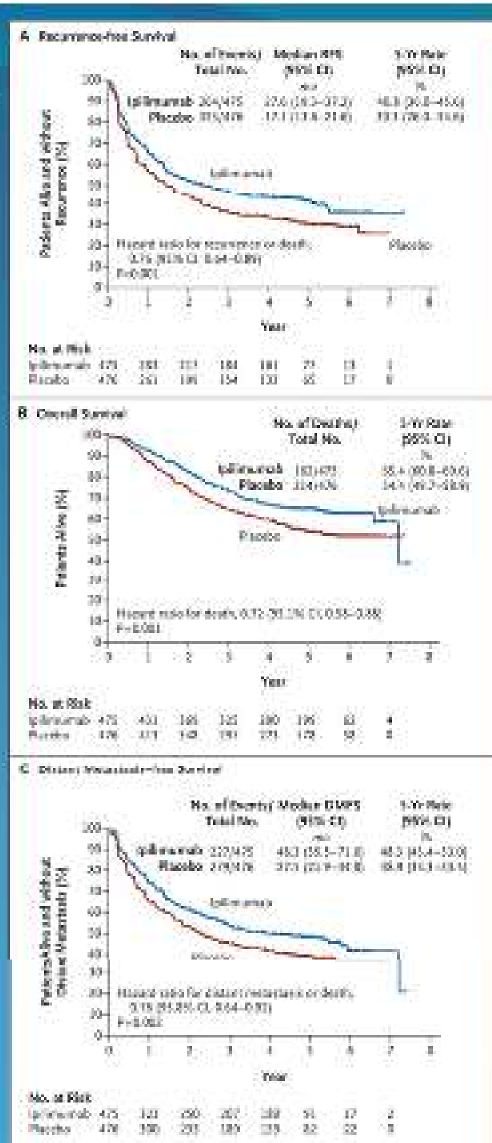
Results:

5 year DFS: 40.8% vs. 30.3%

5 year O.S.: 65.4% vs. 54.4% (HR 0.76, p<0.001).

AEs 54.1% vs. 26.2% -> 40% dropped out by 4 initial doses.

NEJM 2016;375:1845-55.


A Recurrence-free Survival
Ipilimumab
Placebo
Year
No. at Risk
Ipilimumab
Placebo
B Overall Survival
Total No.
Ipilimumab
Placebo
Year
No. at Risk
Ipilimumab
Placebo
C
Total No.
Ipilimumab
Placebo
Year
No. at Risk
Ipilimumab
Placebo

Adjuvant ipilimumab, critique:

Side-effects/risks high – many patients could not tolerate and complete the three year course.

Is dosing to blame?

Is prolonged tx time to blame?

Are side-effects higher in adjuvant tx?

Some side-effects may be permanent if not prolonged.

What about anti-PD1 in adjuvant fashion?

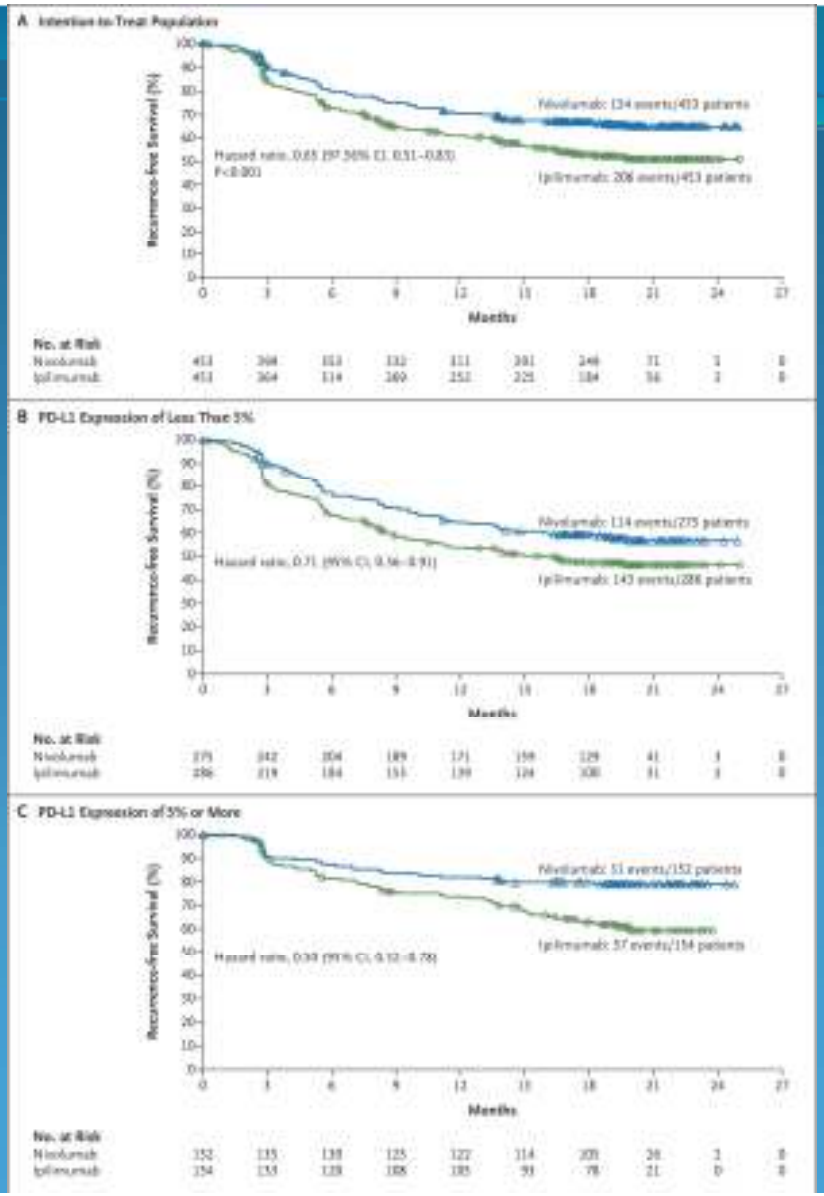
NEJM 2016;375:1845-55.

Adjuvant Nivolumab / Checkmate 238

- A phase 3, double blinded RCT, enrolling patients with resected stage IIIB, IIIC, IV melanoma. 906 patients randomized:
  - Nivolumab 3 mg/kg IV q14 days vs. ipilimumab 10 mg/kg
  - x one year q21 days x 4 then, q3mos x 3 yr.

- Primary endpoint: recurrence-free survival.

NEJM 2017;377:1824-35.


A Intention-to-Treat Population
Recurrence-free Survival (%)
Nivolumab: 134 events/453 patients
Hazard ratio, 0.65 (97.56% CI, 0.51–0.83)
P<0.001
Ipilimumab: 206 events/453 patients
Months
No. at Risk
Nivolumab 453 368 313 332 311 301 246 71 1 0
Ipilimumab 453 364 314 269 252 225 184 56 1 0
B PD-L1 Expression of Less Than 5%
Recurrence-free Survival (%)
Nivolumab: 114 events/275 patients
Hazard ratio, 0.71 (95% CI, 0.56–0.91)
Ipilimumab: 143 events/286 patients
Months
No. at Risk
Nivolumab 275 242 204 189 171 159 129 41 1 0
Ipilimumab 286 219 184 153 139 124 100 31 1 0
C PD-L1 Expression of 5% or More
Recurrence-free Survival (%)
Nivolumab: 51 events/152 patients
Hazard ratio, 0.39 (95% CI, 0.32–0.78)
Ipilimumab: 97 events/154 patients
Months
No. at Risk
Nivolumab 152 135 118 125 122 114 105 26 1 0
Ipilimumab 154 135 128 108 105 91 78 21 0 0

Checkmate 238 Conclusions

- Adjuvant anti-PD1 therapy is superior to anti CTLA-4 therapy (ipilimumab) with regards to DFS.
- The above infers that since adjuvant anti CTLA-4 now conveys a O.S. advantage that this should also be seen with nivolumab and perhaps be greater.
- Benefits were seen in all subgroups.
- All stage III patients had CLND (prior to MSLT-II results).
- Safety profile improved compared with ipilimumab.

NEJM 2017;377:1824-35.

(Similar benefit to adjuvant pembrolizumab is now noted with the randomized Keynote-054 trial in all stage III patients). Only DFS data available.

Combi-AD Trial

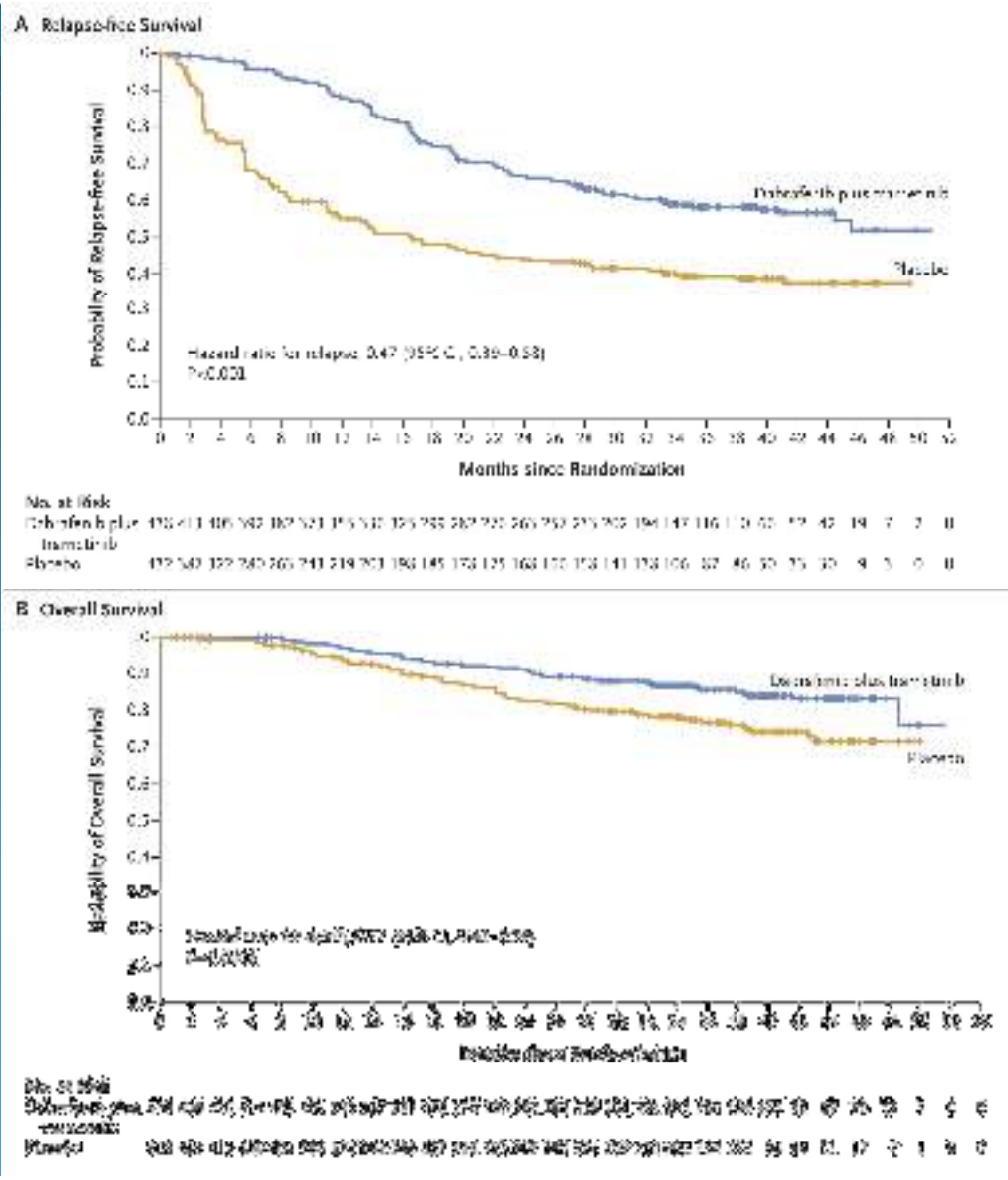
Assessed patients with stage IIIa, IIIb, IIIc and BRAF mutation, after resection to adjuvant dabrafenib/trametinib versus placebo.

Double blinded, RCT, multi-centered. The trial enrolled 169 patients in 26 countries.

Primary endpoint: relapse free survival.

Secondary endpoint: O.S., distant DFS.

NEJM 2017;377:1813-23.


A Relapse-free Survival
Probability of Relapse-free Survival
Months since Randomization
Placebo
B Overall Survival
Probability of Overall Survival

Combi-AD Conclusions

- Results were statistically significant.

- 3 Yr relapse-free survival (mean 2.8 years): 58% vs. 39% (placebo).
- 3 Yr. O.S. 86% vs 77% (placebo). – but didn't meet pre-specified interim analysis.
- 26% of patients discontinued drug. Most common sxs was pyrexia and fatigue.

NEJM 2017;377:1813-23.

Summary of Adjuvant Options

- Adjuvant nivolumab.
- Adjuvant pembrolizumab.
- Adjuvant ipilimumab (but probably not wise to choose and perhaps not long to remain listed).
- Adjuvant dabrafenib/trametinib for BRAF mutated dz.

- Adjuvant vemurafenib did not provide a convincing O.S. advantage.
- Adjuvant XRT can provide local control but no O.S. advantage.
- Adjuvant interferon has been debunked.

Future Directions/Needs

Research is ongoing to:

- Determine biomarkers predictive of immune response.
- Evaluate duration and completeness of immunotherapy.
- Evaluate combinational strategies: immunotherapy, cell-cycling inhibition, adopted t-cell transfer/vaccines, radiation, chemotherapy.
- Improve effectiveness/safety of adjuvant therapy.
- Reduce toxicity.
- Investigate ideal radiology imaging strategies.

Thank you!