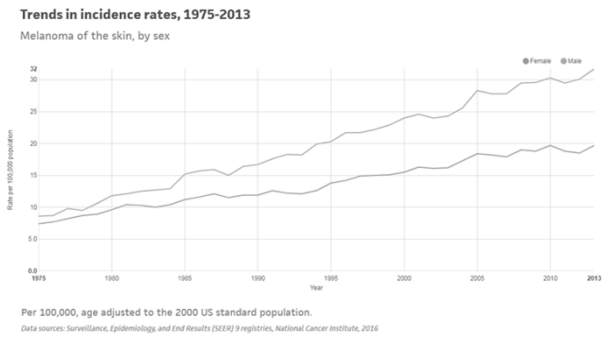
Malignant Melanoma

Alicia M. Terando, MD
Assistant Professor of Surgery
Department of Surgery
Division of Surgical Oncology
The Ohio State University Wexner Medical Center

Background

- **Melanoma** is a malignancy of pigment-producing cells located predominantly in the skin, but also eyes, ears, GI tract, mucous membranes
- Accounts for 4% of all skin cancers
- Causes the greatest number of skin cancer-related deaths worldwide
- Early detection is the best means of reducing mortality

Incidence Continues to Rise



American Cancer Society Statistics - 2017

87,110 estimated new cases (52,170 men and 34,940 women)

9,730 melanoma deaths estimated

Incidence Rates by Race

- Whites: 1:50
- Hispanic: 1:200
- Black: 1:1000

Risk Factors

Table 1. Risk factors for developing cutaneous melanoma

Risk factor	Estimated relative risk
High-risk traits	
Xeroderma pigmentosum	1000
Dysplastic nevi, prior melanoma, and familial melanoma	500
Dysplastic nevi, no prior melanoma, and familial melanoma	148
Dysplastic nevi, no PH*, or FH† of melanoma	7–27
Many nevi (≥ 50)	7–54
Caucasian (versus African American)	15–20
Congenital melanocytic nevi (especially large nevi)	17–21
Personal history of melanoma	9
Cutaneous melanoma in first-degree blood relative	8
Low-risk traits	
Dense sun-induced freckles	3–20
Prior history of NMSC	3–17
Immunosuppression	2–8
Other phenotypic traits: red hair, blond hair, blue eyes	1–6
History of severe and painful sunburns	1–6
Sun sensitivity, relative inability to tan	1–5

*PH, personal history; †FH, familial history.

Benvenuto-Andrade, C., Oseitutu, A., Agero, A. L. and Marghoob, A. A. (2005), Cutaneous melanoma: surveillance of patients for recurrence and new primary melanomas. Dermatologic Therapy, 18: 423–435. doi:10.1111/j.1529-8019.2005.00049.x

Sun Exposure

UVA radiation (320-400 nm) - penetrates deeper into the dermis. Responsible for sun-induced changes in dermal connective tissue and loss of elasticity (wrinkles, signs of aging)

UVB (290-320 nm) - causes sunburn, induction of increased melanin production in skin

UVA and UVB carcinogenic

Also found in tanning beds

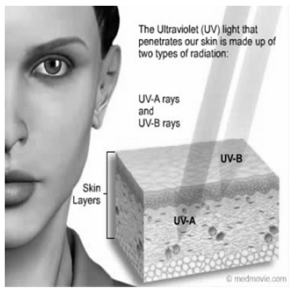


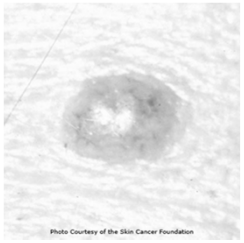
Image source: FDA, Radiation-emitting Products, Ultraviolet Radiation (February 2010). https://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/Tanning/ucm116425.htm

Melanoma: Diagnosis

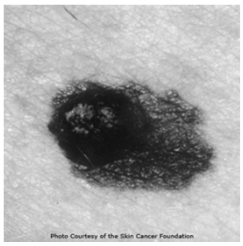
- **Early diagnosis is key to improved outcomes**
- **ABCDE**
  - **Asymmetry**
  - **Border irregularity**
  - **Color**
  - **Diameter**
  - **Evolution**

Asymmetry

- If you could fold the lesion in half, the 2 halves would not match.



Benign



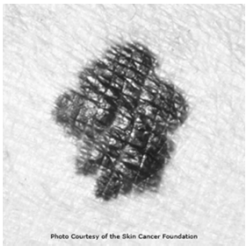
Malignant

Photos Courtesy of the Skin Cancer Foundation

Border

Melanoma often has uneven or blurred borders

Benign

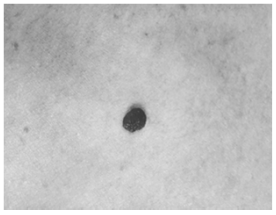


Malignant

Photos Courtesy of the Skin Cancer Foundation

Color

- Melanoma contains mixed shades of tan, brown and black; it can show traces of red, blue or white



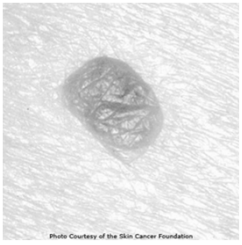
Benign

Malignant

Photos Courtesy of the Skin Cancer Foundation

Diameter

- Melanoma is usually greater than 6 mm (the size of a pencil eraser)



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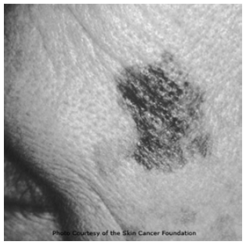


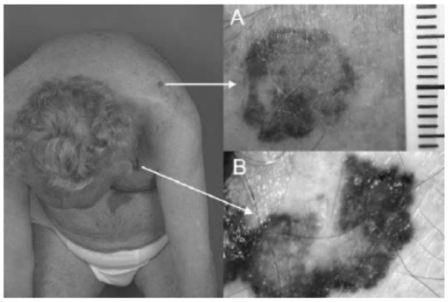
Malignant

Photos Courtesy of the Skin Cancer Foundation

Evolution and other suspicious signs

- Changes in appearance, such as spreading of pigment into surrounding skin
- A mole that looks scaly, oozes or bleeds
- Itching, tenderness or pain in a mole
- Brown or black streak under a nail
- Bruise on the foot that does not heal

ABCD: asymmetry, borders, color, diameter > 6mm



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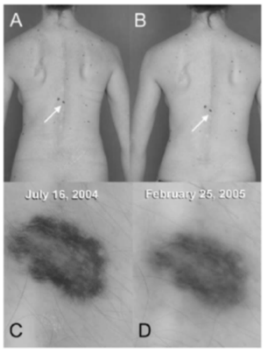
E is for Evolution:



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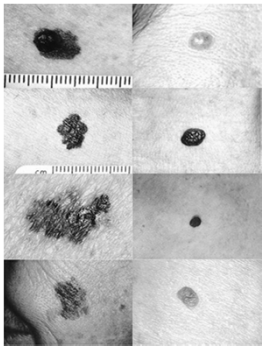
Benign or Malignant??

Malignant Benign



Asymmetry

Border

Color

Diameter

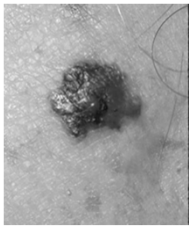
Photos Courtesy of the Skin Cancer Foundation

Histologic Subtypes of Melanoma

Superfical spreading melanoma
Nodular melanoma
Lentigo maligna melanoma
Acral lentiginous

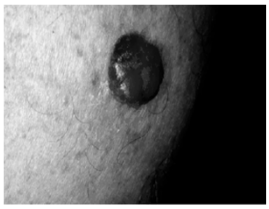
Superficial spreading melanoma

- **Most common subtype (~70%)**
- **Occurs anywhere on the body (non-chronic sun damaged skin)**
- **Derives its name from histologic evidence of lateral growth for a period of time before vertical growth**



Nodular melanoma

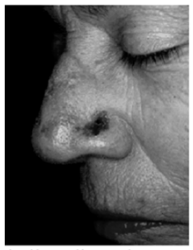
- **Comprise 15-30% of all melanomas**
- **Discrete nodule with dark black pigmentation is typical clinically**
- **Present with clinical and histologic evidence of vertical growth only**



Nodular melanoma Nodular melanomas present as discrete nodules, usually with dark pigmentation. Courtesy of James C Shaw, MD.

Lentigo maligna melanoma

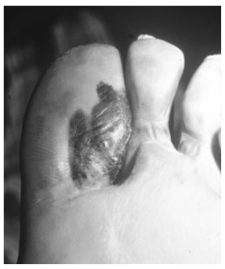
- **~ 5% of melanomas**
- **Arises from *in situ* melanoma on sun-damaged skin**
- **Usually head or neck**



Lentigo maligna melanoma Lentigo maligna melanoma usually arises in areas of sun-damaged skin, particularly on the head and neck. Courtesy of James C Shaw, MD.

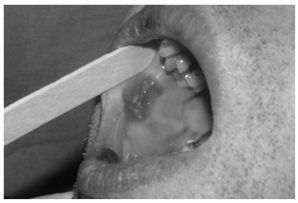
Acral Lentiginous Melanoma

- **~ 2-10% of melanomas**
- **Most common subtype in dark-skinned individuals**
- **Involves palms, soles, and nail beds**
- **More aggressive than other types – ? due to depth at diagnosis**



Mucosal Melanoma- where the "sun don't shine"

- **Rare, but can occur on almost any mucosal surface**
- **2x higher in whites vs blacks**
- **Head/neck (ie nasal, sinus, mouth), female genital tract, anorectal region, urinary tract**



Melanoma: Diagnosis

Excisional biopsy (elliptical, punch, or saucerization): 1-3 mm margin, avoid larger margin to permit accurate lymphatic mapping

Full thickness incisional or punch: attempt to perform in clinically thickest portion of lesion

Evaluation of Patients with Newly Diagnosed Melanoma

•Pathology

- •Breslow depth
- •Ulceration
- •Mitotic rate
- •Satellites?
- •Status of the deep margin – important for thin melanoma

•Physical Exam

- •Size and location of the lesion?
- •Residual pigment?
- •Satellites?
- •Palpable or suspicious nodes?

Melanoma: surgical care

Wide excision of the primary lesion

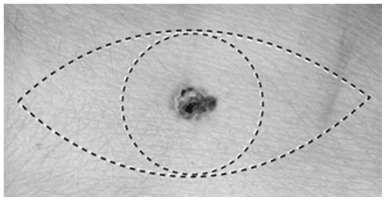
Nodal assessment

Surgical Margins

Tumor Thickness	Recommended margin
– In situ	– 0.5 cm
– ≤ 1 mm	– 1 cm
– 1.01 – 2 mm	– 1 – 2 cm
– 2.01 – 4 mm	– 2 cm
– > 4 mm	– 2 cm

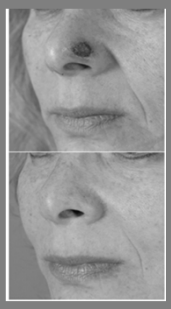
Margins of >2cm do not improve rate of local recurrence, disease-free survival, or overall survival, but they do increase the risk of requiring a skin graft or flap closure of the defect

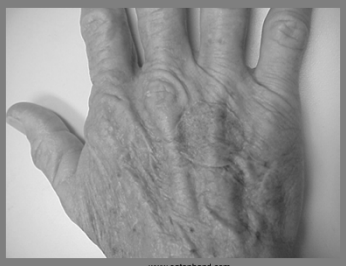
Wide excision with Primary Closure



Length = 3-4 x Width

Skin graft

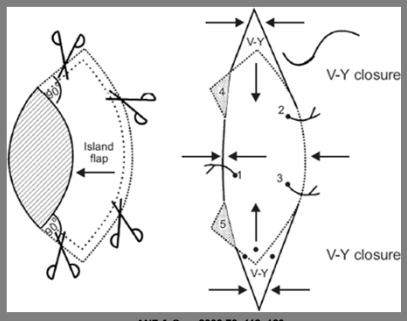




www.eatonhand.com

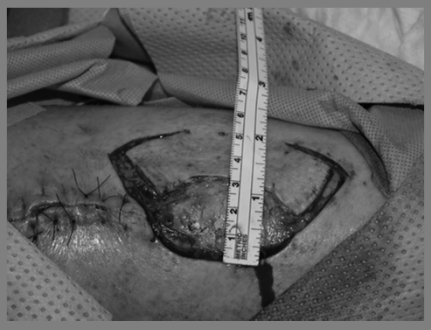
Spear M, ed. Skin Grafts – Indications, Applications and Current Research. August 29, 2011

Local Tissue Rearrangement

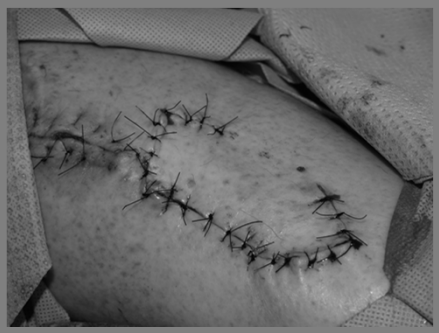


*ANZ J. Surg.*2003;73: 112–120;

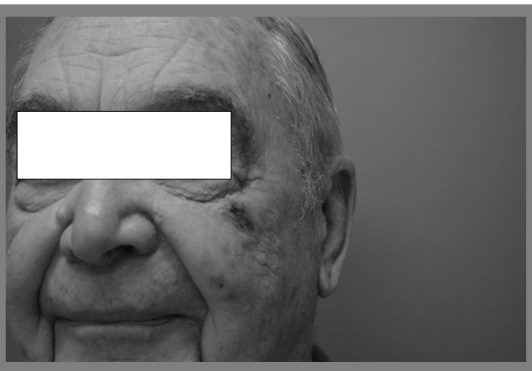
Local Tissue Rearrangement



Local Tissue Rearrangement



Facial Reconstruction



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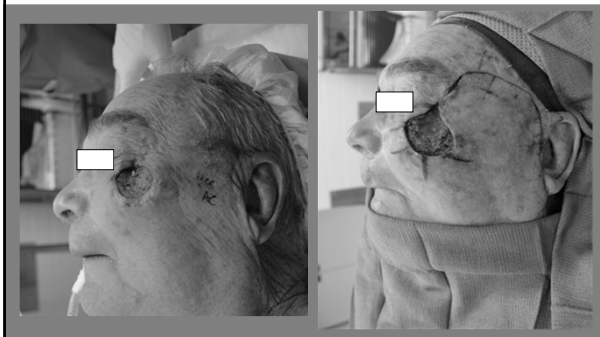

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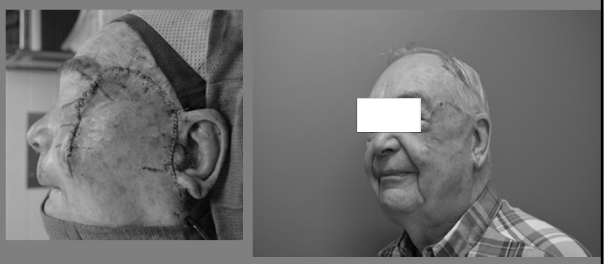

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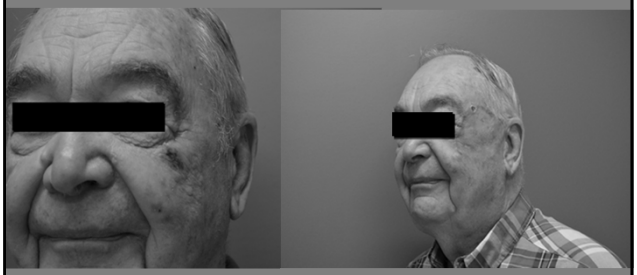
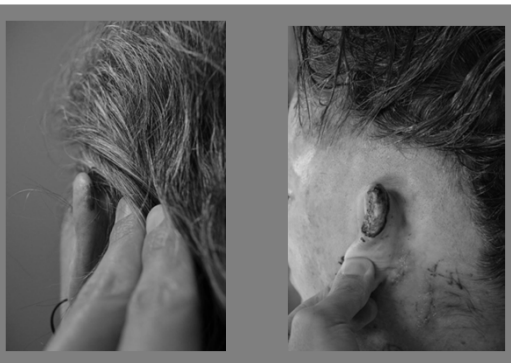


Ear Reconstruction



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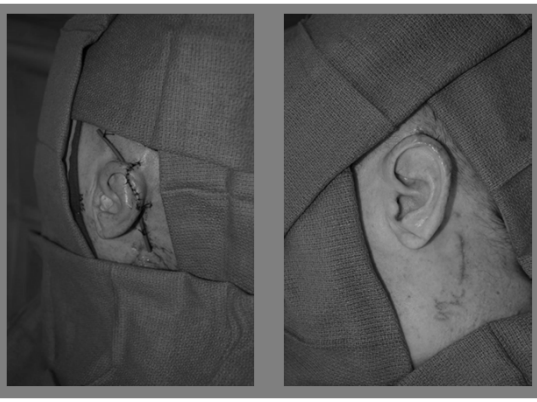

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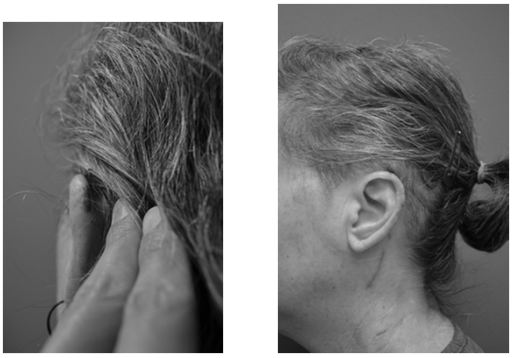


How and When to Manage the Draining Lymph Node Basin

Elective Versus Therapeutic Lymph Node Dissection

Therapeutic lymph node dissection

"watch and wait"

- **Delayed until the time of nodal recurrence**
- **Avoided LND complications in node-negative patients.**
- **Strategy assumes there will be no evidence of distant metastatic disease at the time of nodal recurrence – not necessarily**

Elective Versus Therapeutic Lymph Node Dissection

Elective lymph node dissection

"search and destroy"

- **Performed at the time of WLE.**
- **80% of patients were node-negative.**
- **Survival advantage in retrospective studies.**

Therapeutic vs. Elective Lymph Node Dissection

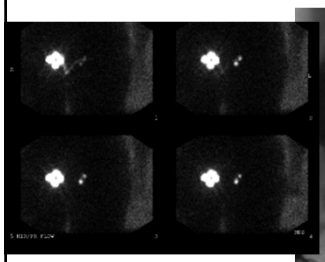
Therapeutic	Elective
•Avoid complications from node dissection in node negative patients •Risk of local failure •Potentially allowing greater opportunity for metastatic spread	•Subjecting node negative patients to surgical morbidity •Decrease risk of local failure •Some patients will develop metastatic disease without nodal disease

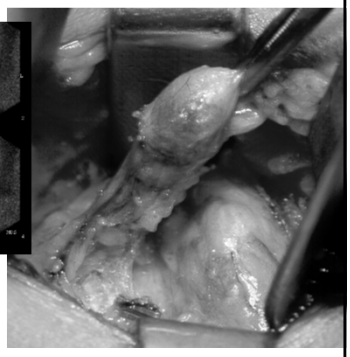
Revolution circa 1994: Sentinel lymph node biopsy

- Developed by Dr. Donald Morton at the John Wayne Cancer Center in Los Angeles
- Identify the first draining lymph node
- If the sentinel node is negative – extremely unlikely that there is any disease in the nodal basin
- If the sentinel node is positive – completion lymph node dissection
- Reserve lymphadenectomy for the patients who really need it

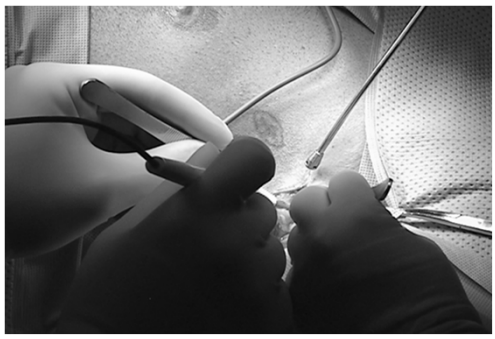
Video: Injection and Lymphoscintigraphy

Lymphoscintigraphy; Blue dye





Video: Surgical Sentinel Lymph Node Biopsy



When do we do Sentinel Lymph Node Biopsy?

- **NCCN recommendations:**
  - **SLN biopsy for patients with melanoma > 1mm regardless of characteristics. Standard of care.**
  - **For lesions 0.75-1.0 mm, consider SLN biopsy if there are aggressive features such as:**
    - **Ulceration**
    - **Clark level IV or V**
    - **(Satellitosis)**
    - **(Regression)**
    - **(Young Age)**
    - **(High Mitotic Rate)**

Some consider SLNbx for these, too

The Case for Sentinel Lymph Node Biopsy

Better pathologic examination

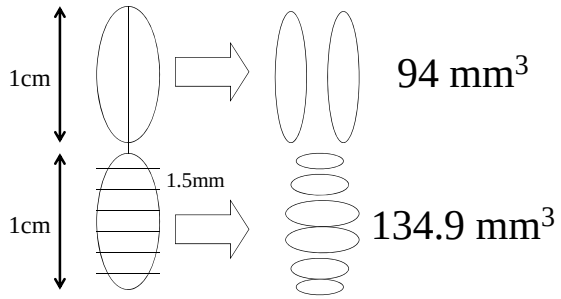
Powerful predictor of survival

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal Recurrence

Avoid complications from ELND for node negative patients

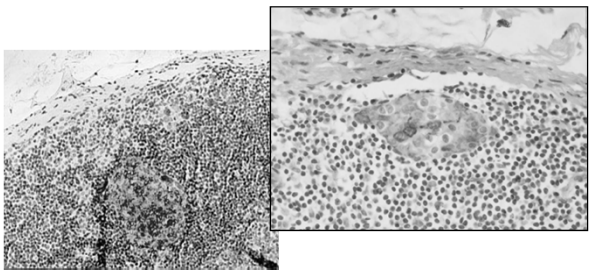
Survival benefit to SLNBx?

Increased cross-sectional area examined with serial sectioning.



Sabel et al. Surgery 2000;128:556-63.

IHC in Sentinel Lymph Node Biopsy

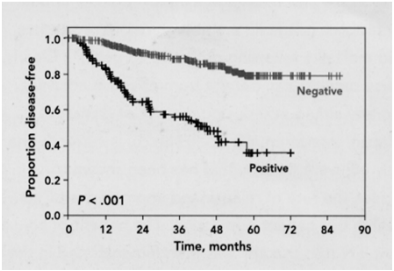


The Case for Sentinel Lymph Node Biopsy

- Better pathologic examination
- Powerful predictor of survival
- Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
- Avoid complications from ELND for node negative patients
- Survival benefit to SLNBx?

Prognosis Associated with Sentinel Node Status

SLN status is the most powerful independent prognostic factor predicting survival, individualizing treatment



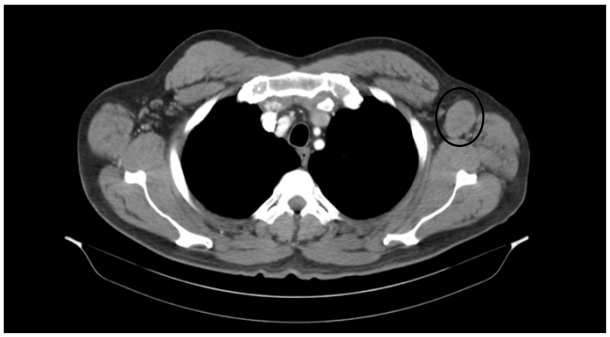
Disease-free survival stratified by SLN status

Gershenwald et al, J Clin Oncol 1999
10.1200/JCO.1999.17.3.976 - *Journal of Clinical Oncology*17, no. 3 (March 1999) 976-976.

The Case for Sentinel Lymph Node Biopsy

- Better pathologic examination
- Powerful predictor of survival
- Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence
- Avoid complications from ELND for node negative patients
- Survival benefit to SLNBx?

Avoid Regional Nodal Failure



The Case for Sentinel Lymph Node Biopsy

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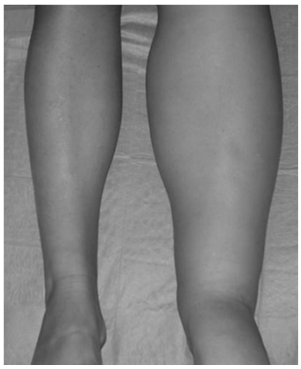
Lymphedema



http://www.medsci.org/v07/p0353/ijmsv07p0353g02.jpg

The Case for Sentinel Lymph Node Biopsy

Better pathologic examination

Powerful predictor of survival

Fewer regional relapses, less morbidity with CLND after + SLNBx vs. TLND after nodal recurrence

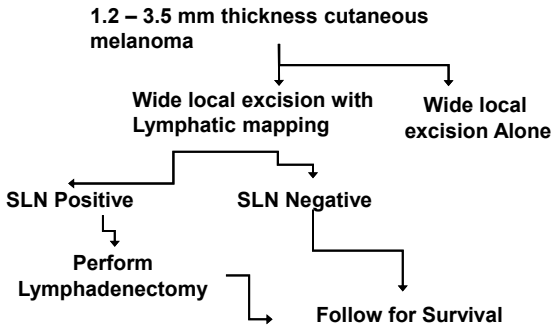
Survival benefit to SLNBx?

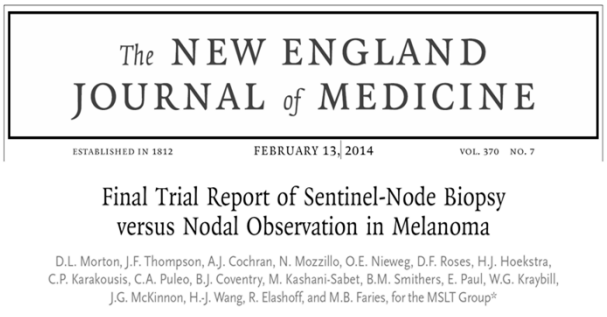
Multicenter Selective Lymphadenectomy Trial -I

Comparing:

- **wide excision alone**
- **wide excision + sentinel lymph node biopsy**

Multicenter Selective Lymphadenectomy Trial -I




The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2014 VOL. 370 NO. 7

Final Trial Report of Sentinel-Node Biopsy versus Nodal Observation in Melanoma

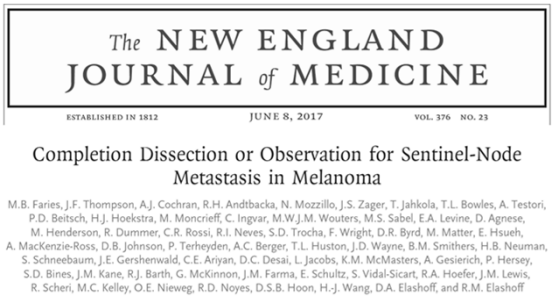
D.L. Morton, J.F. Thompson, A.J. Cochran, N. Mozzillo, O.E. Nieweg, D.F. Roses, H.J. Hoekstra, C.P. Karakousis, C.A. Puleo, B.J. Coventry, M. Kashani-Sabet, B.M. Smithers, E. Paul, W.G. Kraybill, J.G. McKinnon, H.-J. Wang, R. Elashoff, and M.B. Faries, for the MSLT Group*

MSLT-1 Results

- 2001 Patients with primary melanoma
- Wide excision alone vs wide excision + SLN biopsy
- Overall, no difference in 10 year melanoma specific survival
- Among node positive patients (either sentinel node positive or nodal recurrence during observation) 10 year melanoma specific survival:
  - Sentinel node bx: 62.1%
  - Observation (w/e alone) : 41.5%

Multicenter Selective Lymphadenectomy Trial - II

- + SLNbx patients randomized to CLND vs nodal observation (with clinical examinations and ultrasound) to determine if CLND improves relapse rate or survival



MSLT-II Results

- 1934 patients node positive, intermediate thickness melanoma
- Randomized to completion lymph node dissection or nodal observation with ultrasonography
- 3-year Melanoma Specific Survival Similar
- 3-year Disease-Free Survival slightly higher in dissection group (68% vs 63%)
- Lymphedema 24% in dissection group vs 6% in the observation group

Management of Positive Lymph Nodes

Positive Sentinel Node – Observation

Palpable Lymph Node in a patient with a primary melanoma, or a history of melanoma

- **FNA to get a tissue diagnosis**
- **If confirmed to be melanoma, staging work-up indicated to rule out distant metastatic disease**
- **If no distant disease, lymph node dissection**

Melanoma

Kari Kendra, MD, PhD
Associate Professor of Internal Medicine
Department of Internal Medicine
Division of Medical Oncology
The Ohio State University Wexner Medical Center

Metastatic Disease

Case 1

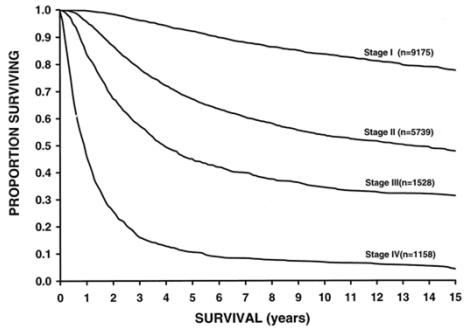
25 y/o male:

- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIb melanoma, left arm, resected
- Biopsy of axillary mass: melanoma

What is his prognosis?

What treatments are available?

Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)



Balch, C. M. et al. J Clin Oncol; 19:3635-3648 2001

JOURNAL OF CLINICAL ONCOLOGY

Recurrent melanoma: Treatment

Localized

- *Surgery* – isolated metastases, limited in size and number, rendered disease free
- *Radiation* – CNS lesions, cord compression, pain control
- *Tvec* (attenuated oncolytic HSV that contains GMCSF)– lesions accessible to injection

T-VEC

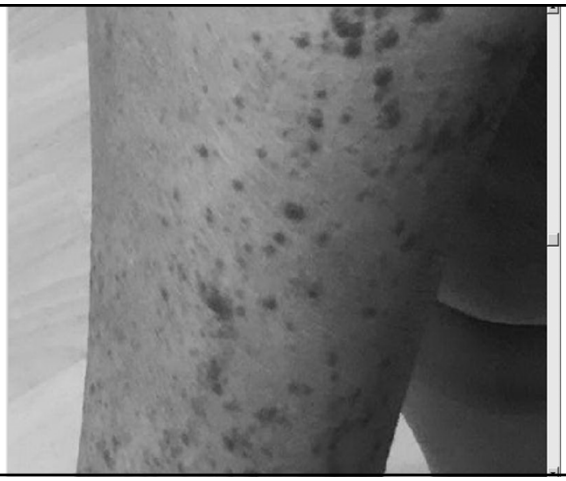
Talimogene laherparepvec

FDA approved as monotherapy for localized treatment of unresectable cutaneous, subcutaneous, and nodal lesions.

- ORR 26%
- Durable response rate 16.3%
- Median overall survival 23.3 mo (Annals of Pharmacotherapy, 2017)

Administration

- Initial injection – 1 x 10(6) PFU/mL, up to 4 mL
- Second injection (3 weeks)– 1 x 10(8) PFU/mL, up to 4 L
- Subsequent injections (q2 weeks) – 1 x 10(8) PFU/mL, up to 4 mL



Case 1

25 y/o male:

- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIb melanoma, left arm, resected
- Biopsy of axillary mass: melanoma (BRAF V600e mutation present)

This patient has widespread disease.

Which systemic treatment to use?

Metastatic melanoma

Systemic therapy:

- *Chemotherapy* –targets rapidly cycling cells
- *Immunotherapy* –activates the immune system to recognize and destroy the cancer
- *Targeted therapy* – for tumors with specific mutations

Other targeted therapies
(under investigation)

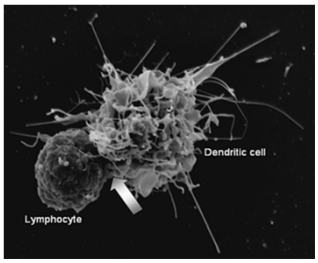
C-kit
Imatinib (Gleevac)

NRAS
Trametinib

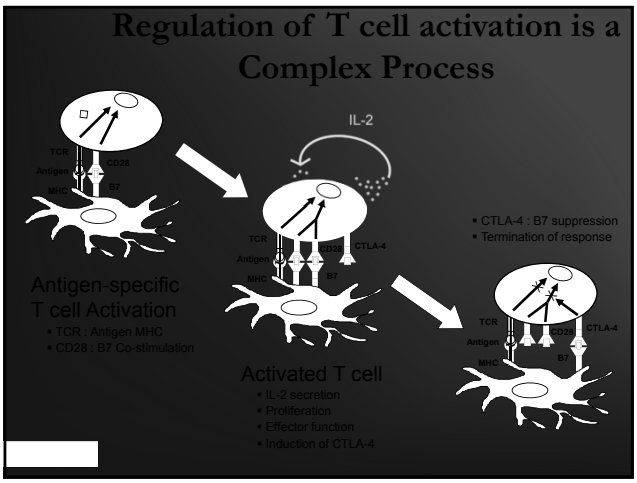
C-Met
crizotinib
cabozantinib

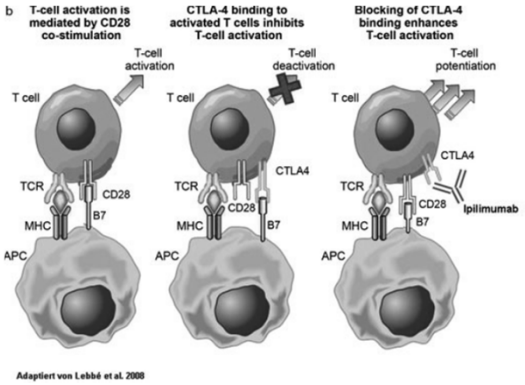
Mechanism of action: immunotherapies

Activated dendritic cells
(Antigen Presenting Cells)



Regulation of T cell activation is a Complex Process





Ipilimumab

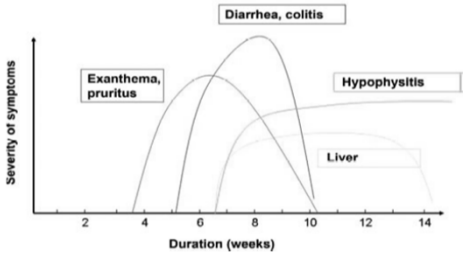
Survival Rate	Ipilimumab + gp100	Ipilimumab alone	Gp100 alone
1-year	44%	46%	25%
2-year	22%	24%	14%

Immune-related Adverse Events associated with ipilimumab

- Rash
- Colitis/enteritis
- Transaminitis
- Thyroiditis
- Adrenal insufficiency
- Hypophysitis

Hodi et al, NEJM, 2010

Ipilimumab toxicities



Weber et al, JCO 2012

Metastatic disease: Ipilimumab

Advantages

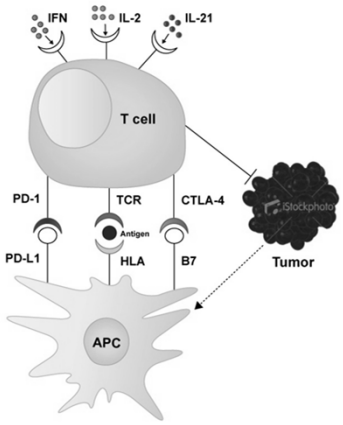
- Response rate improved over chemotherapy
- Durable responses
- Limited treatment duration

Disadvantages

- Delayed onset of response
- Toxicities
- Response rate not high enough

Ipilimumab

Survival Rate	Ipilimumab + gp100	Ipilimumab alone	Gp100 alone
1-year	44%	46%	25%
2-year	22%	24%	14%



CollabRx 2010

Mechanism of action: immunotherapies

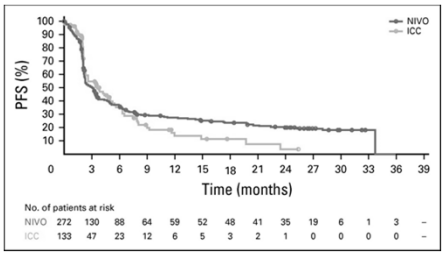
- Anti-CTLA4:
  - Ipilimumab
- Anti PD1
  - Nivolumab
  - Pembrolizumab

Nivolumab

	Nivolumab (n=120)	ICC (n=47)
Objective response	38 (31.7%)	5 (10.6%)
Best overall response		
▪ CR	4 (3.3%)	0
▪ PR	34 (28.3%)	5 (10.6%)
▪ SD	28 (23.2)	16 (34.0%)
▪ PD	42 (35.0%)	15 (31.9%)
▪ unable to establish	12 (12.0%)	11 (23.4%)

Weber et al, Lancet 2015

Nivolumab

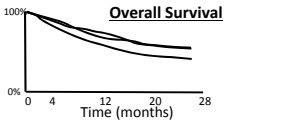


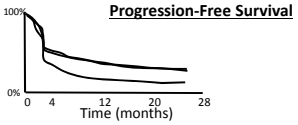
Larkin et al, JCO 2017

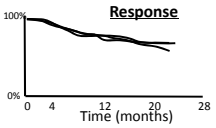
Pembrolizumab vs Ipilimumab

Phase 3 randomized, open-label
N=834

— Pembrolizumab every 2 weeks
— Pembrolizumab every 3 weeks
— Ipilimumab







Schachter et al, Lancet 2017

PD-1 blockade: pembrolizumab, nivolumab

Advantages

- Low toxicity profile
- Increased response rate
- More rapid response
- Durable response

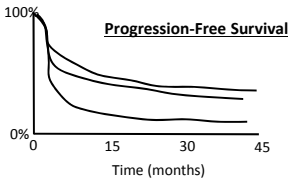
Disadvantages

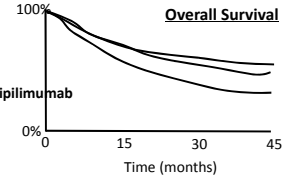
- Duration of treatment is unkown
- Cost
- Unexpected autoimmune toxicities

Phase 3 trial of Nivo + Ipi vs Nivo vs Ipi

Media PFS:
N+I 11.5 mo
I 6.9 mo

PFS at 2 yr:
N+I 43%
N 37%
I 12%





— Nivolumab plus ipilimumab
— Nivolumab
— Ipilimumab

Wolchok et al, NEJM 2017

Systemic therapies for metastatic disease

Immunotherapies

Single agent
- Ipilimumab
- Nivolumab
- Pembrolizumab
- IL2

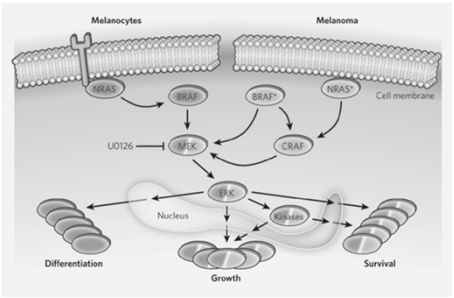
Combination
- Ipi/nivo

Targeted therapies

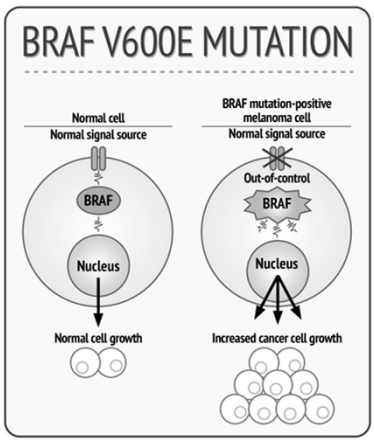
BRAFi
- Dabrafenib
- Vemurafenib

MEKi
- Trametinib
- Cobimetinib

Mechanism of action: targeted therapies



Huang, PH, Marais R. Nature 2009;459;336-337



Objective Responses with vemurafenib

N= 132

- ORR 53%
  - CR 6%
  - PR 47%
- Median duration of response 6.7 mo
- Responses: M1a, M1b, M1c
- The majority with > 30% decrease in change from baseline (RECIST

Sosman et al, 2012

Inhibition of the BRAF pathway

	Single agent (dabrafenib) (N=211)	Combination (dabrafenib/trametinib) (n=212)
Median OS	■ 18.8 mo	■ 25.1 mo
1 yr OS	■ 68%	■ 74%
2 yr OS	■ 42%	■ 51%
Median PFS	■ 8.8 mo	■ 11.0 mo

Long et al, Lancet 2015

Inhibition of the BRAF pathway

	Single agent (dabrafenib) (N=211)	Combination (dabrafenib/trametinib) (n=212)
3-year PFS	■ 12%	■ 22%
3-year OS	■ 12%	■ 32%
		(58% of those alive at 3 yrs remained on combination therapy)

Long et al, Ann Oncol 2017

Dabrafenib Adverse events

- Peripheral edema (17 – 31%)
- Dermatologic
  - Alopecia (22%)
  - Hand-foot syndrome (20%)
  - Hyperkeratosis (37%)
  - Night sweats (6 – 24%)
  - Papilloma (27%)
  - Rash (17-53%)
- Endocrine
  - Hyperglycemia (50%)
  - Hypokalemia/hypophosph.
- GI
  - Abdominal pain, constipation/diarrhea, N/V
- Hematologic
  - Anemia, leukopenia, neutropenia, thrombocytopenia
- Hepatic
- Musculoskeletal
  - Arthralgia
  - myalgia
- Other
  - Fatigue, fever. rigors

Toxicities

	Dabrafenib	Dabrafenib/trametinib
Squamous cell	9%	2%
Hyperkeratosis	32%	3%
Skin papilloma	21%	14%
Hypertension	14%	22%
Pyrexia	28%	51%
Chills	16%	30%

Flaherty et al NEJM 2012

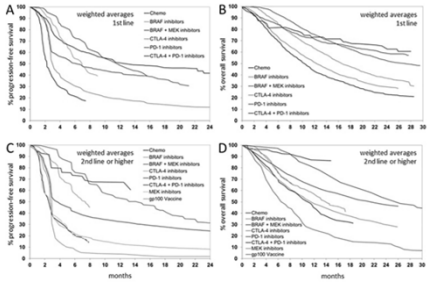
Case 1

25 y/o male:

- Presents with SOB
- Exam: left axillary mass
- CT: bilateral pulmonary nodules, liver nodules, and left axillary mass
- PMH: stage IIb melanoma, left arm, resected
- Biopsy of axillary mass: melanoma (BRAF V600e mutation present)

What is this patients prognosis?.

Which systemic treatment to use?



Ugurel et al, Eur J of Cancer, 2017

Case 1

- Patients prognosis is changing. The recently approved therapies have had significant impact on the duration and quality of life for some.
- Treatment options:
  - Immunotherapies vs targeted therapies, where to start?

	Pros	Cons
Immunotherapy	■ Durable responses ■ RR: 40 – 55% ■ Median OS > 2 years	■ Increased risk of immune mediated events
Targeted therapy	■ Rapid response rate ■ Combination RR 70% ■ Median OS > 2 years	■ 50% of responders develop resistance in 13 months

Clinical trials

Metastatic disease

- EA6134 "A randomized phase II trial of dabrafenib + trametinib followed by ipilimumab and Nivolumab atr progression vs ipilimumab + Nivolumab followed by dabrafenib + trametinb at progression in patients with advanced BRAF V600e mutant melanoma"
- EA131 "Molecular Analysis for Therapy Choice (MATCH)"
- S1320 " A randomized, phase II trial of intermittent vs continuous dosing of dabrafenib and trametinib in BRAFV600e/k mutant melanoma"
- OSU 13124 "a phase 1 expansion cohort evaluating the selective inhibitor of nuclear export (SINE) KPT-330 in patients with unresectable melanoma."
- OSU 17090 "a phase II study of ibrutinib in refractory distant metastatic cutaneous melanoma: correlation of biomarkers with response and resistance

Wexner Medical Center

Case 2

34 y/o female presented with a bleeding mole on her arm.

- *Biopsy*: nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- *Wide excision*: no residual tumor
- *Sentinel Node*: positive for 2/2 LN, with extracapsular extension in 1 LN
- *Axillary LN dissection*: 0/20 LN

Case 2

What is the next step?

Prognostic indicators

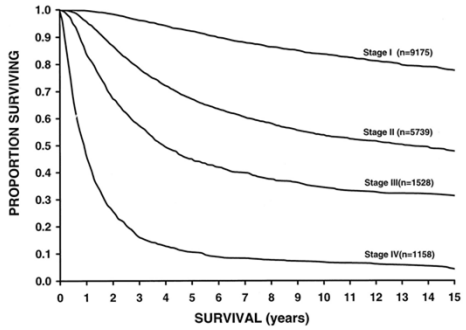
- Thickness (Breslow depth)
- Nodal status
- Ulceration
- Satellite lesions
- In transit lesions

Case 1

Our 34 y/o female has multiple poor prognostic indicators:

- Depth > 1.0 mm
- Lymph nodes positive (macroscopic)
- Ulceration present
- Mitotic rate high

Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)



Balch, C. M. et al. J Clin Oncol; 19:3635-3648 2001

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Adjuvant therapy for high risk patients

What therapies are available?

How do we identify patients for treatment?

Systemic Therapy: Adjuvant

- FDA approved biologic agents
  - IFN (1 year)
  - Pegylated IFN (5 years)
  - Ipilimumab (10 mg/kg, 3 year)
- Data available, not yet FDA approved
  - Nivolumab (1 year)
- Data pending from large clinical trials
  - Ipilimumab (3 mg/kg, 1 year)
  - Pembrolizumab (200 mg, fixed dosing)

Adjuvant radiation

- Adjuvant radiation
  - Dose- 30 Gy in 6 Gy fractions 2 times/week
  - Improvement in local, regional and locoregional disease control
  - No impact on OS or RFS

Adjuvant therapy with Interferon Alfa-2b (E1684)

FDA approved

- IFN-alpha 2b for adjuvant treatment of melanoma patients with thick primary tumors (> 4mm) or resected nodal disease

Kirkwood et al, JCO 1996;14:7

Adjuvant therapy with Interferon Alfa-2b (E1684)

- Patient population
  - Breslows depth >4mm
  - LN+ after ELND
  - clinical LN+ with synchronous primary
  - regional LN recurrence after surgery for primary

Kirkwood et al, JCO 1996;14:7

Adjuvant therapy with Interferon Alfa-2b (E1684)

Treatment

- *high-dose IFNa-2b* : 20 MU/m^2 IV, 5 days per week for 4 weeks (induction phase) followed by 10 MU/m^2 SC TIW for 48 weeks (maintenance)
- *observation*

Adjuvant therapy with Interferon Alfa-2b (E1684)

	IFNα-2b	Observation
median DFS	1.7 yr	1.0 yr
OS	3.8 yr	2.8 yr

* benefit greatest in LN+ patients

Cochrane meta-analysis of IFN alpha adj trials

Outcome measure	RFS	OS
HR	0.83 (0.78 – 0.87) 10,345 subjects (17 trials)	0.91 (0.85-0.97) 9927 subjects (15 trials)
Risk reduction	17%	9%
NNT	16	33

RFS relapse free survival, OS overall survival, HR hazard ration, NNT number needed to treat to prevent one event

Mocellin et al, 2013

Adjuvant therapy with Interferon Alfa-2b (E1684)

TOXICITIES:

constitutional
myelosuppression
hepatotoxocity
neurologic

* 67% of all patients had severe (grade 3) toxicity at some point during treatment
* Supportive care is necessary

Adjuvant Ipilimumab

Ipilimumab (10 mg/kg):

- Stage III melanoma
- Reduced risk of relapse (HR 0.76)
- Improved OS (HR 0.72)
- 5 year recurrence-free survival of 40.8% (placebo 30.3%)

Toxicities

- Immune related toxicities remain high

Eggemont, et al, Lancet Oncol 2016

Adjuvant Ipilimumab (10 mg/kg)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)	0.75 (0.64 – 0.90)	
p value	0.0013	
1 yr RFS	63.5%	56.1%
2 yr RFS	51.5%	43.8%
3 yr RFS	46.5%	34.8%

Eggemont et al, Lancet Oncol 2016

Adjuvant nivolumab

- Randomized, double blinded, phase 3 trial
- N=906
- Stage IIIB, IIIC, or IV – NED from surgical resection
- *Nivolumab* 3 mg/kg every 2 weeks x 1 year vs

Ipilimumab 10 mg/kg every 3 weeks for 4 doses, then every 12 weeks for 1 year

Weber et al, NEJM 2017

Adjuvant nivolumab

Nivolumab vs Ipilimumab

- Relapse free survival: HR 0.65 (97.56% CI, 0.51 – 0.83) p< 0.001
  - PDL1 < 5% HR 0.71 (95% CI, 0.56 – 0.91)
  - PDL1 > 5% HR 0.50 (95% CI, 0.32 – 0.78)

Weber et al, NEJM 2017

Adjuvant Nivolumab

Nivoulmab vs Ipilimumab

Recurrence free survival:

- Stage IIIB or IIIC - Hazard ratio 0.64 (95% CI, 0.52 – 0.82)
- Stage IV – Hazard ratio 0.70 (95% CI, 0.45 – 1.10)

Weber et al, NEJM 2017

Adjuvant ipi vs nivo: treatment related adverse events

Ipilimumab (10 mg/kg)

- Grade 3 or 4 – 45.9%
- Treatment related AE leading to discontinuation – 30%

AE > 2%

- Diarrhea (9.5%)
- Increase ALT (5.7%)
- Increase AST (4.2%)
- Rash (3.1%)
- Hypophysitis (2.4%)
- Maculopapular rash (2.0%)

Nivolumab (3 mg/kg)

- Grade 3 or 4 – 14.4%
- Treatment related AE leading to discontinuation – 4.6%

AE >2% (none)

- Diarrhea (1.5%)
- Increase ALT (1.1%)
- Increase AST (0.4%)
- Rash (1.1%)

Weber et al, NEJM 2017

Adjuvant BRAF inhibitors

Double blind, placebo-controlled, randomized phase 3 trial

- Eligibility:
  - Stage III
  - BRAF V600E or V600K mutations
- 2 arms:
  - Dabrafenib (150 mg po bid) + trametinib (2 mg po qd) (n=438)
  - Placebo (n = 432)

Long et al, NEJM 2017

Dabrafenib + Trametinib vs placebo

- Relapse free survival
  - HR for relapse 0.47 (95% CI, 0.39 – 0.58)
- Overall survival
  - HR for death 0.57 (95% CI, 0.42 – 0.79)

Long et al, NEJM 2017

Dabrafenib + Trametinib vs placebo

- Combination therapy was favored in all subgroups
  - Male/female
  - Age <65/>65
  - Disease stage: IIIa, IIIb, IIIc
  - LN involvement: micrometastasis, macrometastasis
  - Ulceration present/absent
  - Number of nodal mets

Long et al, NEJM 2017

Dabrafenib + Trametinib vs placebo

AE (>20%)

Combination therapy		Placebo	
Any grade	**Grade 3-4**	**Any Grade**	**Grade 3 - 4**
Pyrexia	none	Fatigue	nne
Fatigue		Nausea	
Nausea		Headache	
Headache			
Diarrhea			
Vomiting			
Rash			

Long et al, NEJM 2017

Case 2

34 y/0 female presented with a bleeding mole on her arm.

- *Biopsy*: nodular melanoma, 4.1 mm deep, with ulceration, mitotic rate 15/10 HPF
- *Wide excision*: no residual tumor
- *Sentinel Node*: positive for 2/2 LN
- *Axillary LN dissection*: 0/20 LN

What adjuvant therapy options are available?

Adjuvant systemic therapy

FDA approved

- Interferon
- Pegylated interferon
- Ipilimumab

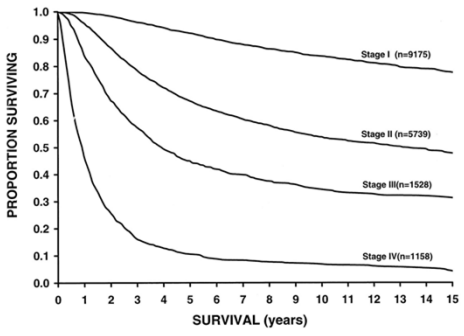
Data just released

- Nivolumab
- Dabrafenib/Trametinib

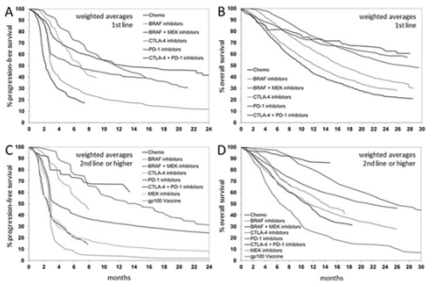
Data pending

- IFN vs LD Ipi vs HD Ipi for 1 year
- Physician choice vs pembrolizumab for 2 yr

Fifteen-year survival curves comparing localized melanoma (stages I and II), regional metastases (stage III), and distant metastases (stage IV)



Balch, C. M. et al. J Clin Oncol; 19:3635-3648 2001



Ugurel et al, Eur J of Cancer, 2017

Improvements in outcomes have been significant:
- but there are many who still do not respond
- many develop resistance
- costs to the health care system are high

Further research needs to continue.

Thank you!

- to all the patients who participated in the clinical trials
- to all the researchers who contributed their ideas
- to all the funding agencies that made these advancements possible