The Changing Landscape of Melanoma Treatment

BY

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Objectives

- Understand different histologic types of cutaneous melanoma
- Know stages of Melanoma
- Know advances in melanoma treatment

Types of Melanoma

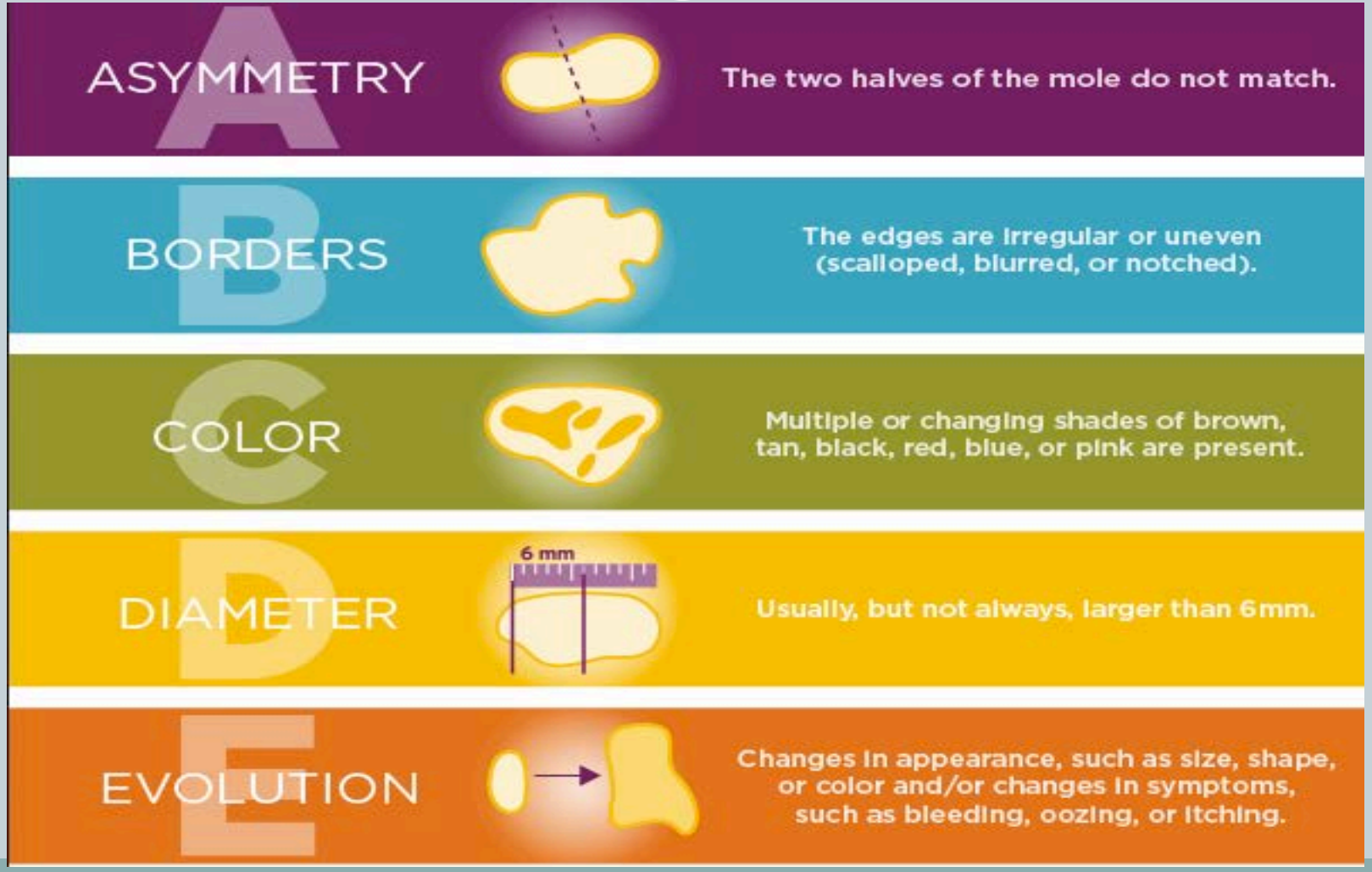
- Cutaneous melanoma
- Mucosal melanoma
- Uveal melanoma

Incidence, Risk factors

- Incidence- 21.6/100000

- Risk Factors:
  - Sun exposure (intense intermittent exposure), Ultraviolet exposure
  - Atypical Nevi (>5 count)
  - High nevi count (>100)
  - Skin pigmentation, hair color, freckles
  - Familial (10%)
  - Immunosuppression

Watch the Mole



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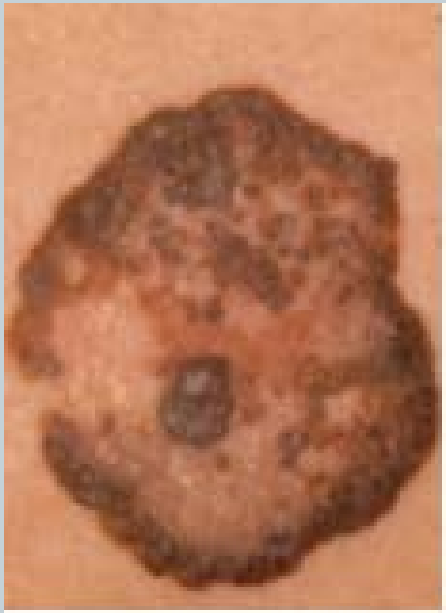
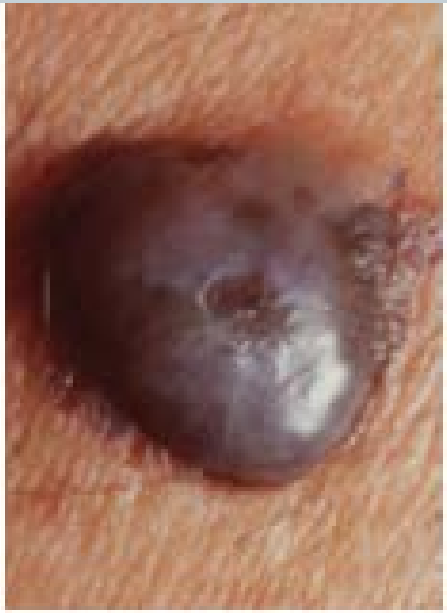
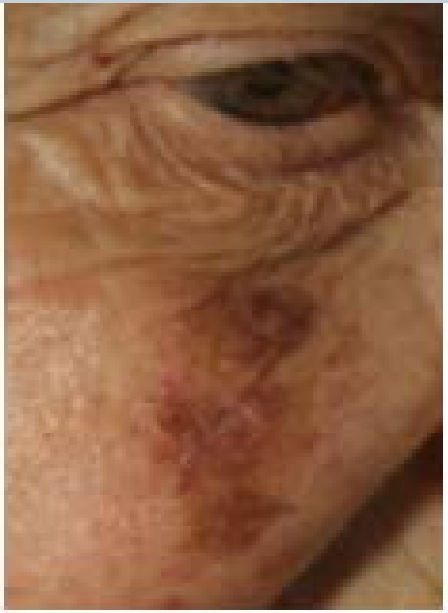
Cutaneous Melanoma Subtypes



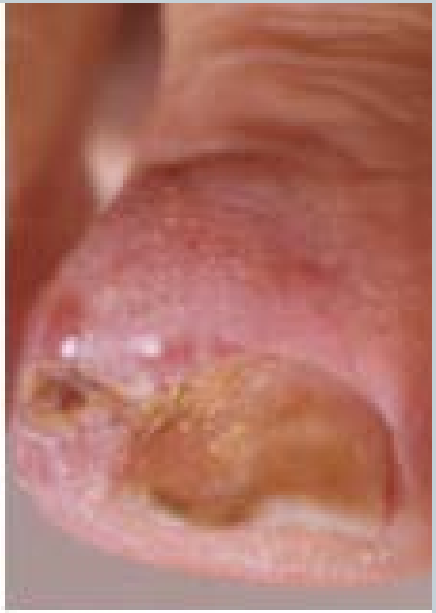
Surface Spreading Melanoma



Nodular Melanoma



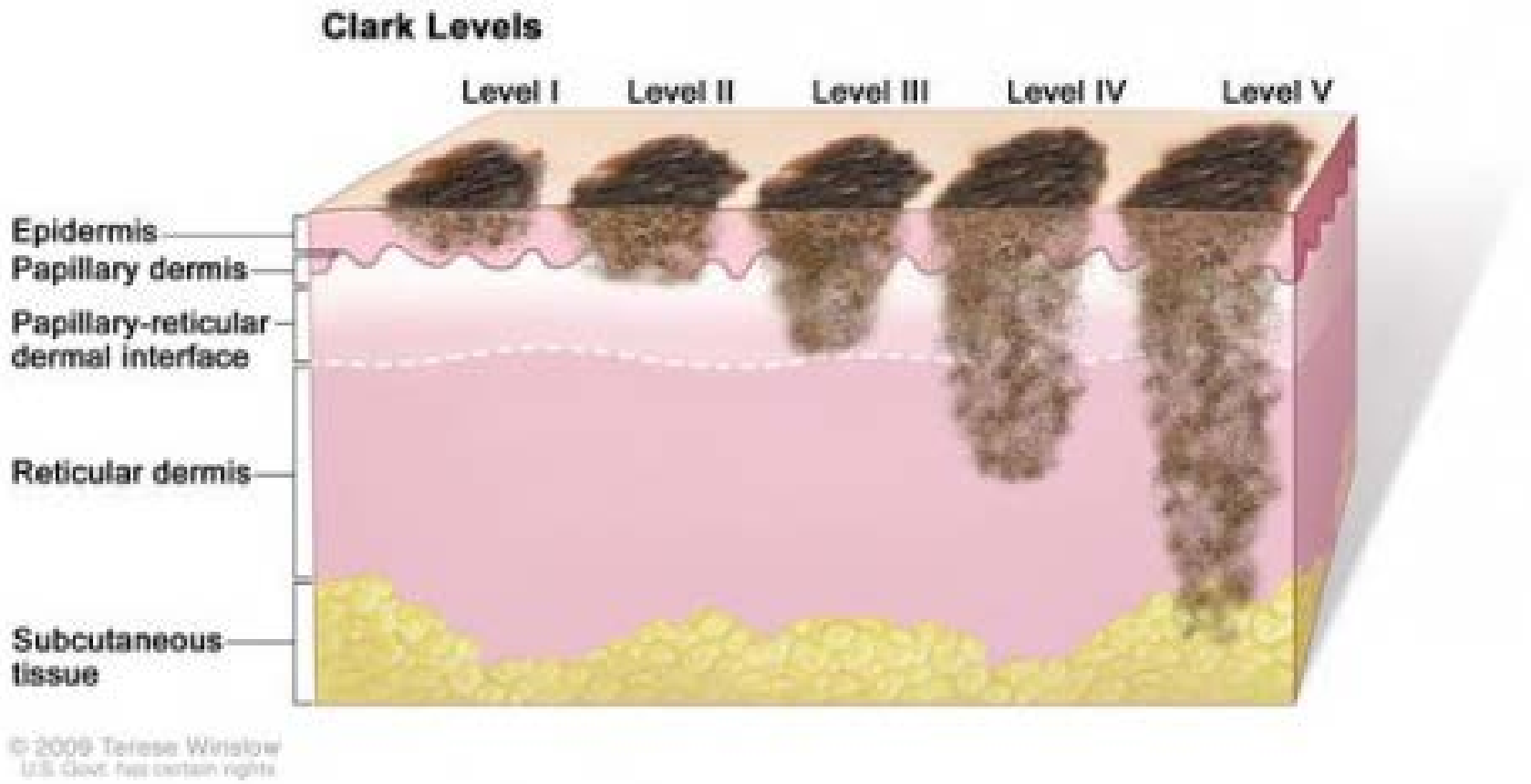
Lentigo Maligna Melanoma



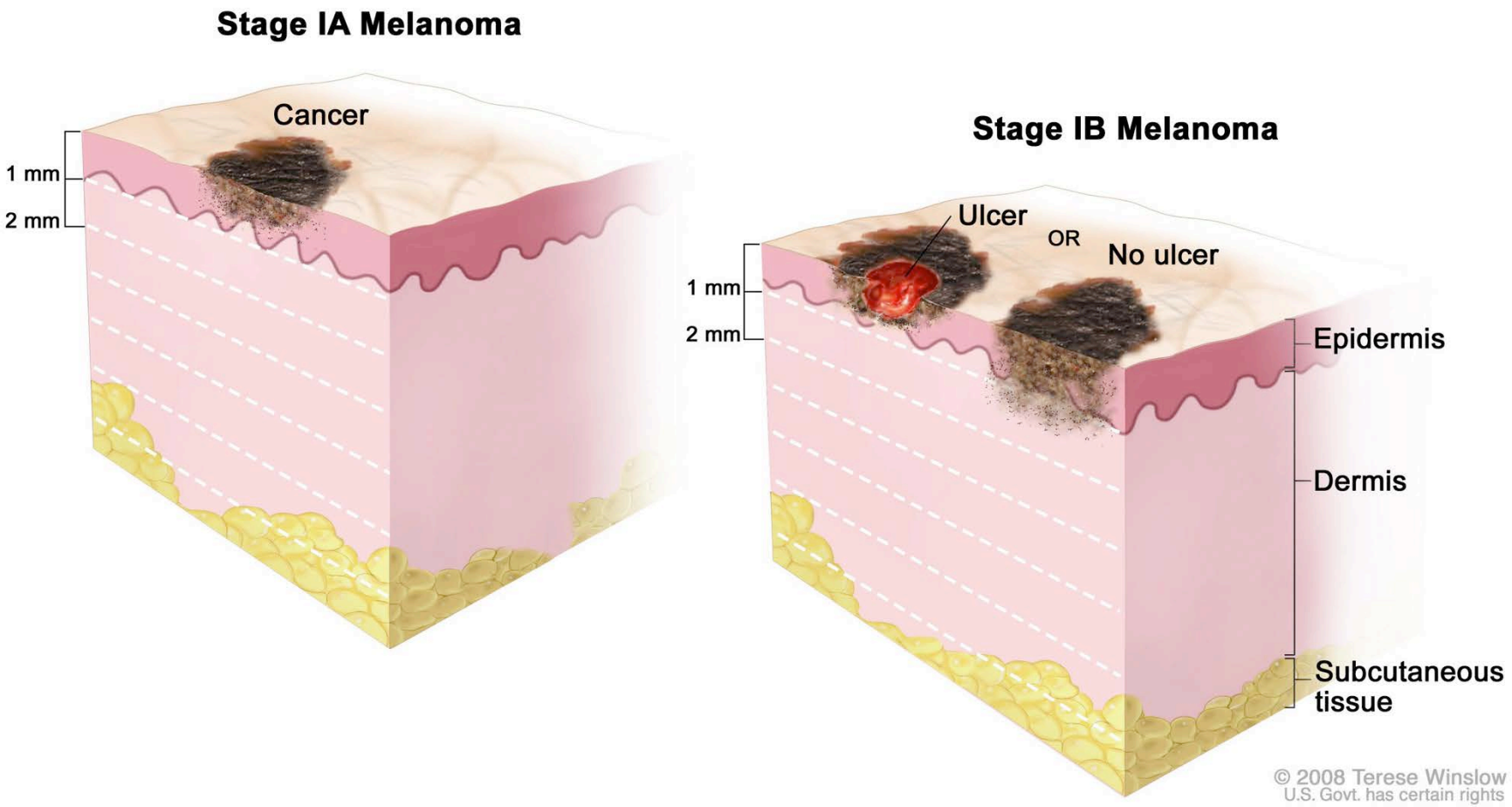
Acral Lentiginous Melanoma

Hoek etal.

Clark Staging



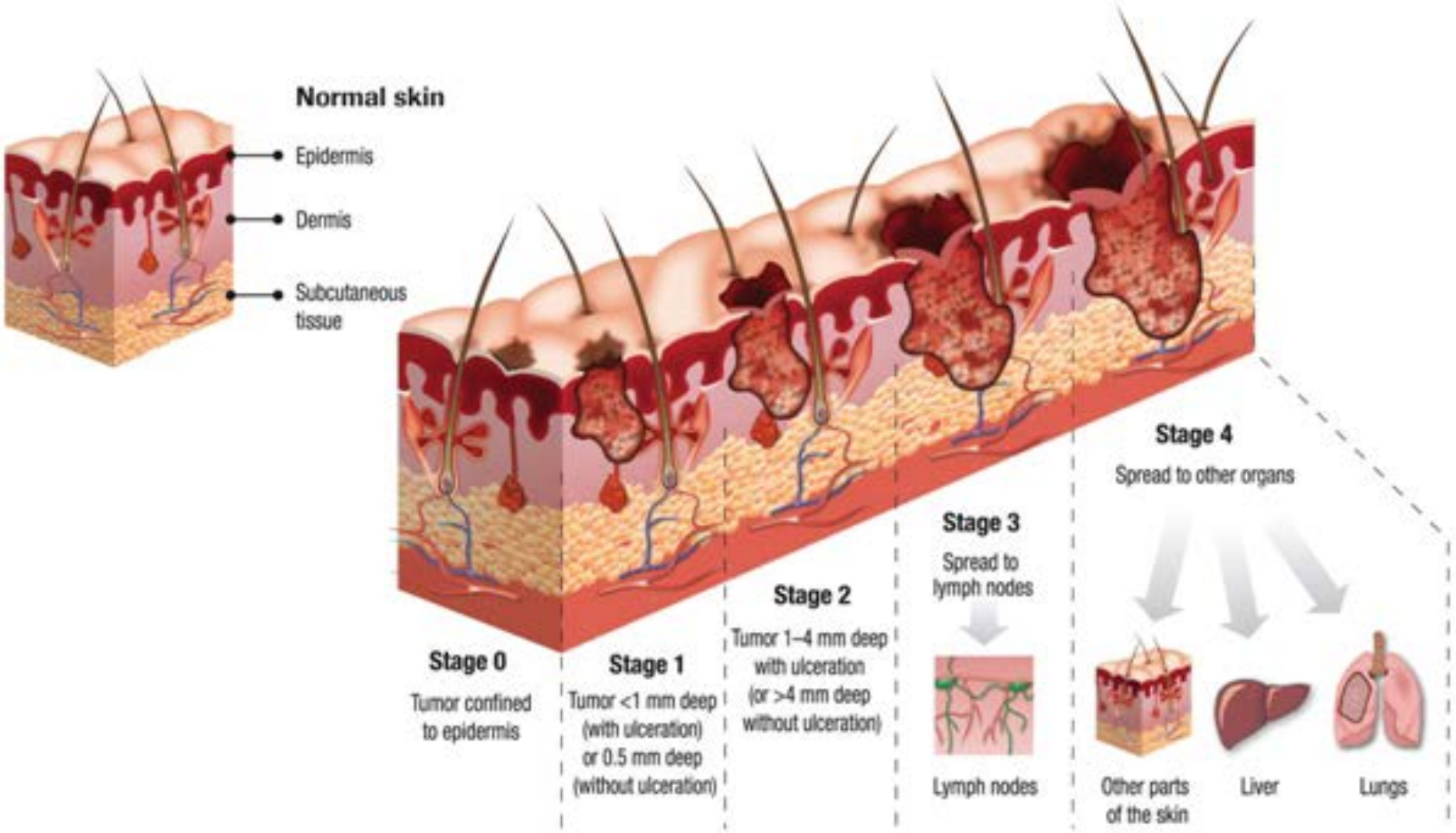
Melanoma Ulceration



Primary tumor (T)	
TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed primary)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1.0 mm
	a: without ulceration and mitoses <1/mm^2
	b: with ulceration or mitoses ≥1/mm^2
T2	1.01-2.0 mm
	a: without ulceration
	b: with ulceration
T3	2.01-4.0 mm
	a: without ulceration
	b: with ulceration
T4	>4.0 mm
	a: without ulceration
	b: with ulceration
Regional lymph nodes (N)	
NX	Patients in whom the regional nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1	One lymph node
	a: micrometastases*
	b: macrometastases¶
N2	Two or three lymph nodes
	a: micrometastases*
	b: macrometastases¶
	c: in-transit met(s)/satellite(s) without metastatic lymph nodes
N3	Four or more metastatic lymph nodes, or matted lymph nodes, or in-transit met(s)/satellite(s) with metastatic lymph node(s)
Distant metastasis (M)	
M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH
M1b	Lung metastases, normal LDH
M1c	Metastasis to other visceral metastases with a normal LDH, or any distant metastases and an elevated LDH

STAGE	TNM Classification	Breslow Depth	Ulceration	Mitotic Rate	Nodal status, Intransit or distant metastases
IA	T1a N0 M0	≤ 1.0 mm	NO	<1/mm²	------
IB	T1b N0 M0	≤ 1.0 mm	Yes	≥1/mm²	------
	T2a N0 M0	1.01-2.0 mm	No		------
IIA	T2b N0 M0	1.01-2.0 mm	Yes		------
	T3a N0 M0	2.01-4.0 mm	No		------
IIB	T3b N0 M0	2.01-4.0 mm	Yes		------
	T4a N0 M0	> 4.0 mm	No		------
IIC	T4b N0 M0	> 4.0 mm	Yes		------
IIIA	T1a-4a N1a M0	Any	No		one node with micro. Metastasis
	T1a-4a N2a M0	Any	No		2-3 nodes, micro metastasis
IIIB	T1-4b N1a M0	Any	Yes		One node with micro metastasis
	T1-4b N2a M0	Any	Yes		2-3 nodes with micro metastasis
	T1-4a N1b M0	Any	No		one node with Macro. Metastasis
	T1-4a N2b M0	Any	No		2-3 nodes with Macro. Metastasis
	T1-4a N2c M0	Any	Any		Intransit/satellite without nodes
IIIC	T1b-4b N1b M0	Any	Yes		One node with Macro. Metastasis
	T1b-4b N2b M0	Any	Yes		2-3 nodes with macro. Metastasis
	T1-4a N2c M0	Any	Any		Intransit/satellite without nodes
	Any T N3 M0	Any	Any		≥ 4 metast/matted Nodes/ In-transit/ satellitosis
Stage IV	Any**T** Any**N** Any**M**	Any	Any		
	M1a – distant skin, subcutaneous or nodal metastases				
	M1b – Lung metastases				
	M1c – other viscera and distant metastases				

Staging


Normal skin
Epidermis
Dermis
Subcutaneous tissue
Stage 0
Tumor confined to epidermis
Stage 1
Tumor <1 mm deep (with ulceration) or 0.5 mm deep (without ulceration)
Stage 2
Tumor 1–4 mm deep with ulceration (or >4 mm deep without ulceration)
Stage 3
Spread to lymph nodes
Lymph nodes
Stage 4
Spread to other organs
Other parts of the skin
Liver
Lungs

Prognosis

STAGE	5 year	10 year
Stage 0	100%	N/A
Stage IA	97%	95%
Stage IB	92%	86%
Stage IIA	81%	67%
Stage IIB	70%	57%
Stage IIC	53%	40%
Stage IIIA	78%	68%
Stage IIIB	59%	43%
Stage IIIC	40%	24%

Prevention Strategies

-  Tanning bed use. ~20-70% increase.
- Sun protection: avoidance of midday sun, protective clothing, shade, sunscreen(SPF.15-30)
- Vitamin D/Calcium – Benefit inconsistent
- Wait time recommended for transplant candidates

Management

- Biopsy
- Wide Local Excision- Margins 1 to 2cm
  - Based on intergroup trial
  - Suggestions of >3cm in few trial but not current practice.
- Sentinel Lymph node biopsy for >1mm thickness
- Complete Lymphadenectomy for SLN positive

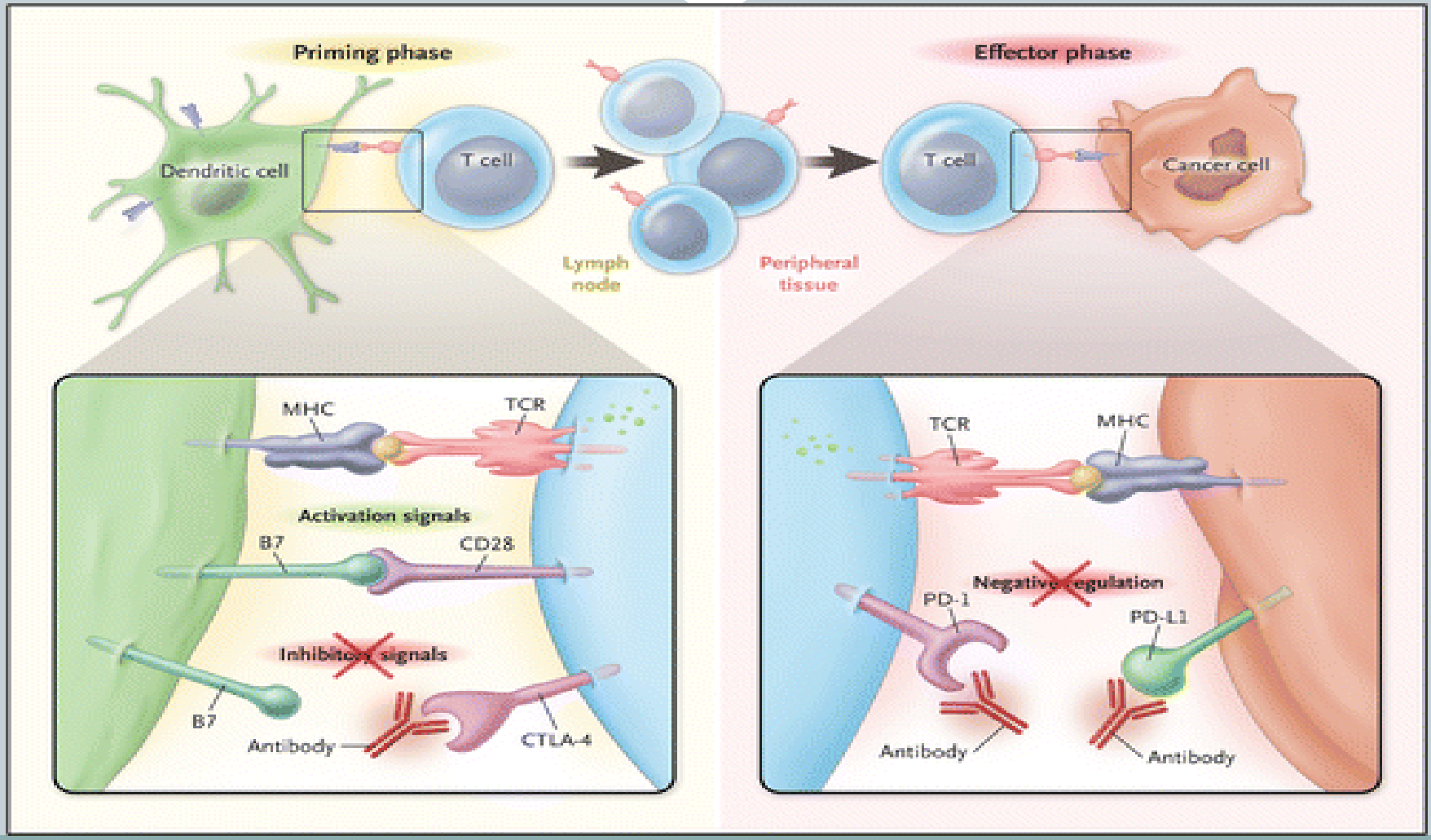
Adjuvant Therapy

- Interferon- ECOG 1684
  - High risk node negative disease (Stage IIB, IIC)
  - Node positive disease (Stage III)
  - Median survival- 3.8yr vs 2.8yr
  - 5 year survival- 46% vs 37%
  - Side effects- cytopenia, fatigue, thyroid dysfunction, depression
- Ipilimumab- EORTC 18071
  - Stage III, Node positive disease
  - 10mg/kg
  - RFS 26mon vs 17mon
  - 5 yr RFS 40.8% vs 30.3%
  - 5 yr OS 65.4% vs 54.4%
  - 5 yr DMFS 48.3% vs 38.9%
  - High toxicity rate. 98% overall. 54% G3/G4, 5 deaths

Advanced Melanoma

- Surgical metastatectomy
- Immunotherapy
- Targeted therapy
- Intralesional therapy
- Chemotherapy
- Radiation

Immunotherapy



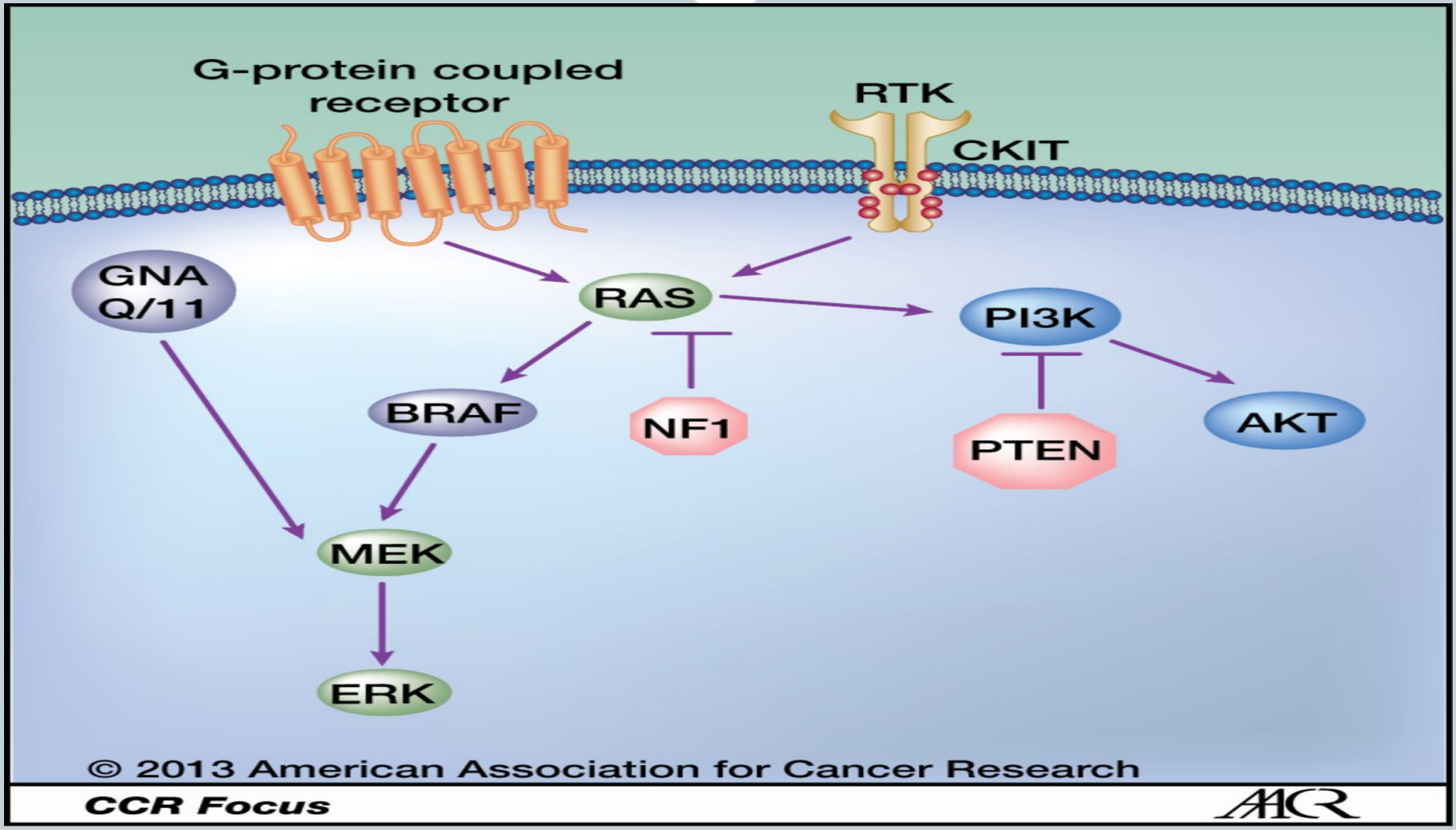
Immunotherapy

- Ipilimumab- anti CTLA-4 antibody
  - 1st line : 11.2mon vs 9.1mon. Compared to chemo
  - 2nd line: 10 mon vs 6.4 mon. Compared to vaccine
  - ~21 percent survival beyond 3 years, 10 year follow-up
  - 10mg vs 3mg. OS – 15.7 m vs 11.5m. 3yr OS- 31% vs 23%
- PD-1 antibodies: Nivolumab, Pembrolizumab (KEYNOTE Trial)
  - Overall better than ipilimumab
  - 2 yr OS: 55% vs 33%
  - OR: 36% vs 13%
  - Grade 3-4 toxicity: 17% vs 20%

Immunotherapy

- Ipilimumab+ Nivolumab: CheckMate 067 trial
  - Median PFS- 11.5, 6.9, 2.1 mon
  - PFS 18- 46%, 39%, 14%
  - 2 yr OS: 69% vs 53%
  - Median OS: NR vs 24.8 months (Ipi)
  - OR- 58%, 44%,19%
  - Serious toxicity- 55%, 16%,27%
- Sequential therapy: Phase II trial
  - Nivo- Ipilimumab: 12 month OS 76%
  - Ipilimumab-Nivo: 12 month OS 54%
  - No benefit compared to combination therapy.

RAS Pathway


G-protein coupled receptor
RTK
CKIT
GNA Q/11
RAS
PI3K
BRAF
NF1
PTEN
AKT
MEK
ERK
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CCR Focus
AACR

Targeted Therapy

- RAS pathway mutation: 70% patients
  - BRAF V600E , V600 V-K
  - NRAS
  - C-KIT

- Vemurafenib- BRIM3 trial. OS 13.3 vs 10mon
- Dabrafenib- PFS 5.1 vs 2.7 mon
- Trametenib- Metric trial PFS 4.8 vs 1.5 mon
- Dabrafenib+ Trametinib- Combi-d trial: OS 25.1mon vs 18.7mon
- Vemurafenib+Combimetinib- Combi-v OS 22.3mon vs 17.4mo
- Break-MB trial- For brain mets. 30-39% response.
- Toxicites- Skin toxicity, SCC (9%), fever, fatigue

Metastatic Melanoma therapy

Drug	ORR	CR	Duration of Response	PFS	OS	OS at 1year	Grade 3-4 AE
Dacarbazine	14%	0.8%	6-8 mo	2.2 mo	9-10 mon	36-42%	18
IL-2	16%	6%	5.8, NR	-	11.4	40%	~80%
Ipilumumab	15%	2%	19 mo	2.9 mo	10-11mo	45.6%	30
Anti-PD-1	30-40%	9%	28.2	6 mo	23-31 mo	67-73%	12-16%
Ipi+Nivo	57%	11.5%	NR	11.4 mon	~40 mo	~85%	55%
BRAF	50%	13%	10.6 mo	6-9 mo	13-19 mo	68%	30-58%
MEK	22%	2%	5.5 mo	4.8 mo	-	-	29%
BRAF+MEK	70%	16%	12.9 mo	9.4-11 mo	25.1 mo	74%	32-62%

IMLYGIC therapy

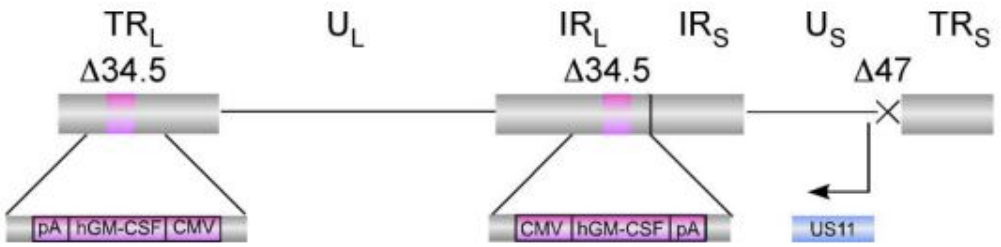
- Recently FDA approved IMLYGIC therapy for Melanoma
- First in class Oncolytic Immunotherapy
- Very well tolerated by patients
- Shown to prolong survival

How Is It Made

- Genetically modified herpes virus

- Deletion of neurovirulence gene- No infection
- Deletion of ICP47- Increases immune response
- Insertion of GM-CSF gene- Increases immune response

Figure 1. Schematic of Talimogene Laherparepvec Genome



The talimogene laherparepvec genome is shown with the positions of the ICP34.5 and ICP47 deletions marked as Δ34.5 and Δ47, respectively; immediate early expression of US11 is driven by the ICP47 promoter. The site of the hGM-CSF cassette insertion is shown in pink and expanded to show the composition of the hGM-CSF expression cassette; the cytomegalovirus (CMV) promoter, hGM-CSF cDNA and a bovine growth hormone polyadenylation signal (pA) signal.

HOW WE ADMINISTER

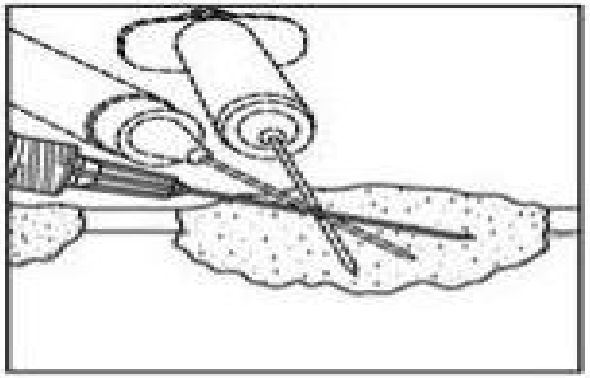


Figure 1: Injection administration for cutaneous lesions

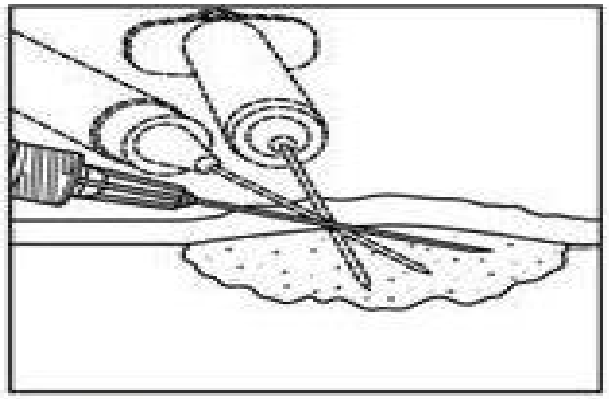


Figure 2: Injection administration for subcutaneous lesions

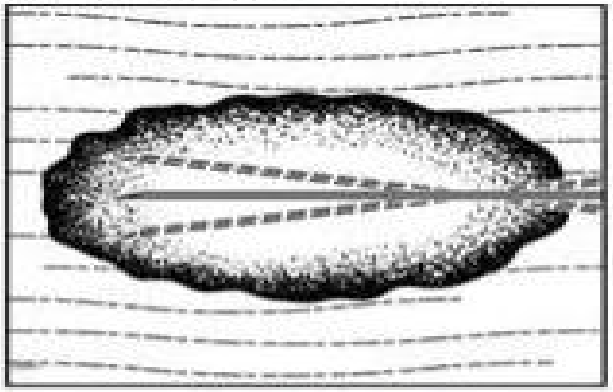
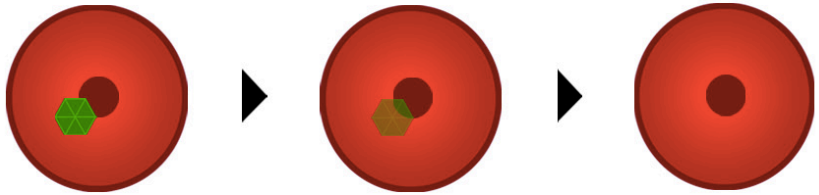


Figure 3: Injection administration for nodal lesions

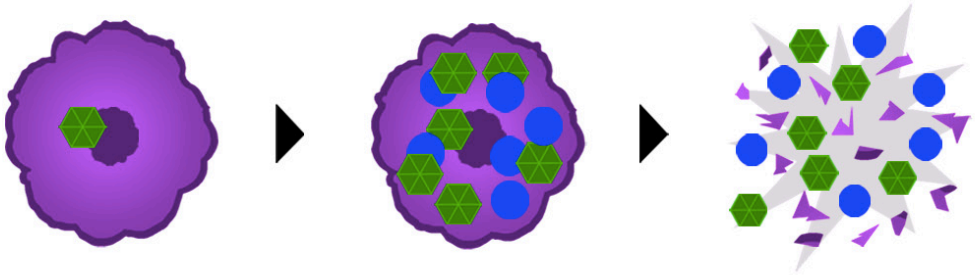
HOW IT WORKS

Talimogene laherparepvec:
proposed mechanism of action
for systemic immunological effect

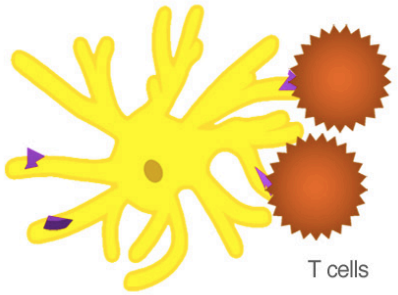
1 Inside a healthy cell, the virus ( ) is unable to replicate, leaving the cell unharmed.



2 Inside a cancer cell, the virus replicates and secretes GM-CSF ( ) until the cell lyses, releasing more viruses, GM-CSF, and antigens ( ).



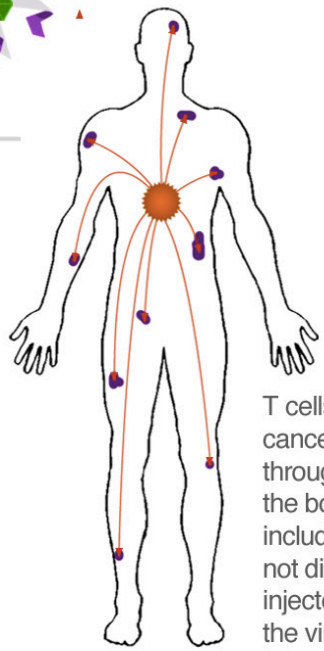
3 GM-CSF attracts dendritic cells to the site, which process and present the antigens to T cells. The T cells are now "programmed" to identify and destroy cancer cells throughout the body.



Dendritic cell

T cells

T cells destroy
noninjected cancer cells



T cells destroy cancer cells throughout the body, including those not directly injected with the virus.

Outcome report

	T-VEC	GM-CSF
Median Duration of Treatment	23 weeks	10 weeks
DRR	16.3%	2.1
ORR	26.4%	5.7%
CR	10.8%	≤1%
TTF	8.2 mon	2.9 mon
OS	23.3 mon	18.9 mon

IMLYGIC therapy

- Median time to response 4.1months
- 10.8% CR- decent for a immunotherapy
- Significantly better response in Stage IIIB, IIIC, IVM1a
- 15% response rate in visceral disease
- Improvement in OS by 4.4months, TTF by 5.3 months
- Very well tolerated

Conclusion

- Overall incidence of melanoma incidence increasing
- Recently multiple Novel therapies are approved and many more in pipeline
- Much better prognosis than a decade ago
- Brain metastasis still with very poor prognosis
- Hoping to attain cure for stage IV melanoma in near future!

THANK YOU

QUESTIONS?