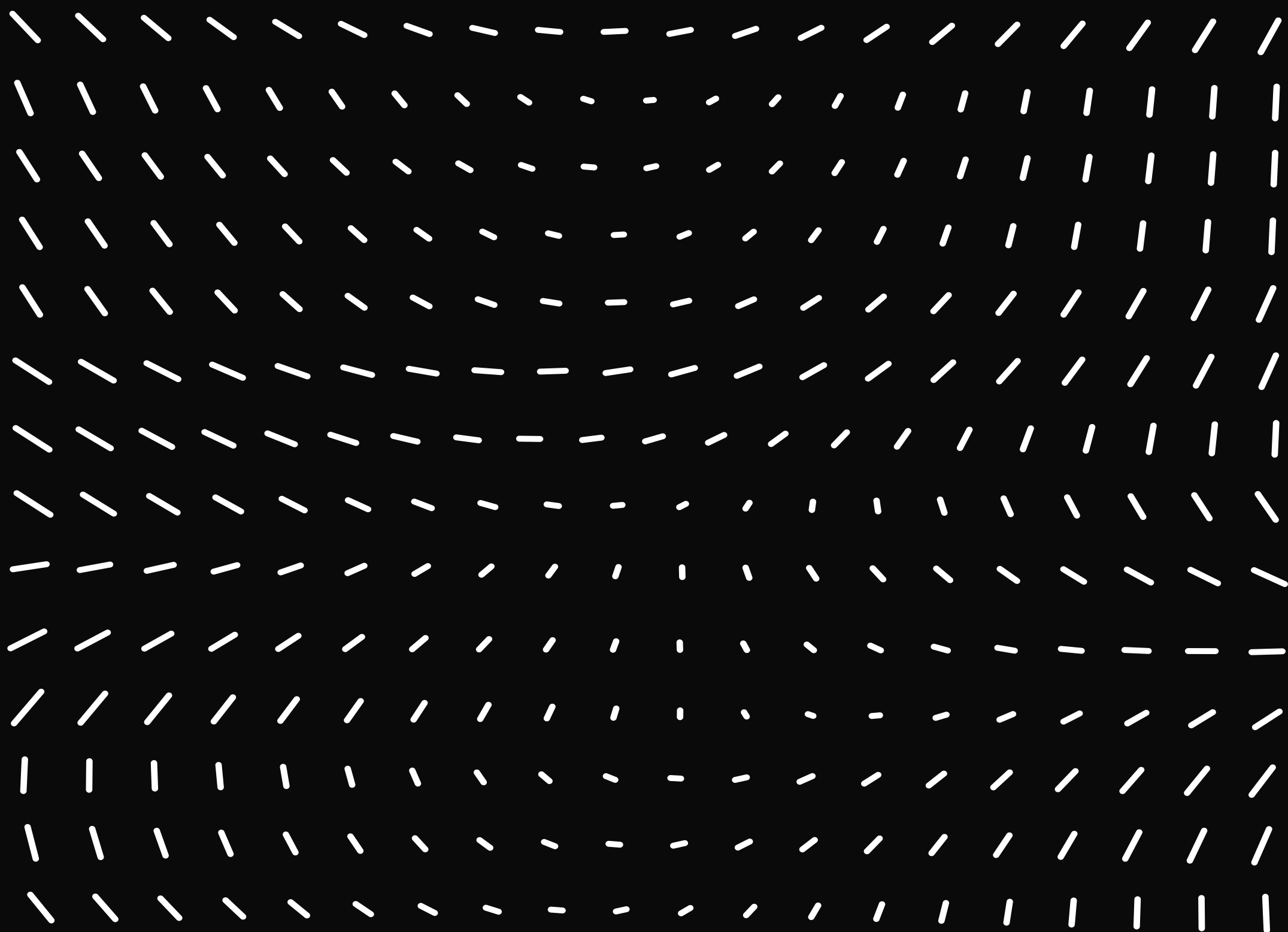


Malignant

Melanoma



→ Clinical subtypes of malignant melanoma.

WHO classification 2018 - 9 subtypes according to cumulative sun damage (CSD)

I) Low CSD - superficial spreading melanoma (SSM)

- intermittent sun exposure in early life, tanning beds
- BRAF V600E mutated.

II) High CSD - lentigo maligna melanoma (LMM)

- skin = severe solar elastosis
- poorly circumscribed
- BRAF & Non BRAF - NRAS, NF1 mutations

III) High CSD - desmoplastic melanoma.

- Amelanotic, dense fibrous tissue.
- S100, Sox-10 positive.
- NF1 mutated.

melanoma not consistently associated to cumulative sun damage (SAM & triple N)

IV) Spitz melanoma

- malignant counterpart of Spitz nevi.
- Reason for malignant transformation not known
- HRAS mutated.

V) Acral melanoma.

- occurring in glabrous, non hair bearing skin.
- CCND1, NRAS mutated.

VI) mucosal melanoma.

- Genital, anal, sinonasal, conjunctival.
- NRAS mutated.

VII) melanoma from Congenital Nevus.

- Giant nevus - 51 times higher risk of developing melanoma.
- NRAS mutation.

VIII) melanoma from Blue Nevus

- uncommon.
- GNAQ, GNA11 mutation.

IX) Nodular melanoma

- amelanotic
- pink papulonodular lesion
- BRAF, NRAS mutation.

Cutaneous Melanoma—Tumor, Node, Metastasis Classification

T Classification		Thickness	Ulceration Status, Thickness Detail
TX		Thickness cannot be assessed	
T0		No evidence of primary tumor (e.g., unknown or regressed primary)	
Tis		Melanoma in situ	
T1		≤ 1.0 mm	a: < 0.8 mm ^a without ulceration
			b: ulcerated or 0.8 ^a to 1.0 mm
T2		1.1 mm to 2.0 mm	a: without ulceration
			b: with ulceration
T3		2.1 mm to 4.0 mm	a: without ulceration
			b: with ulceration
T4		> 4.0 mm	a: without ulceration
			b: with ulceration
N Classification		#/Size of Metastatic Nodes	In-transit/Satellite Metastases
NX		Regional nodes not assessed: Except for T1, use cN.	
N0		None	none
N1	a	1 clinically occult node	none
	b	1 clinically detected node	none
	c	None	Yes
N2	a	2–3 clinically occult nodes	none
	b	2–3 nodes, with ≥1 clinically detected	none
	c	1 node (clinically occult or clinically detected)	Yes
N3	a	four or more clinically occult nodes	none
	b	4 nodes, with ≥1 clinically detected; or any matted nodes	none
	c	2 or more nodes (clinically occult or clinically detected) and/or matted nodes	Yes
M Classification		Site	Serum Lactate Dehydrogenase
M0		No evidence of distant metastasis	
M1a		Distant skin, SQ, soft tissue (incl muscle), or nodal mets	(0) Not elevated
			(1) Elevated
M1b		Lung metastases	(0) Not elevated
			(1) Elevated
M1c		Other non-CNS visceral metastases	(0) Not elevated
			(1) Elevated
M1d		CNS metastasis	(0) Not elevated
			(1) Elevated

Thickness based on Breslow thickness

Clark's levels:

I - Epidermis (in situ)

II - invasion into papillary dermis

III - junction of papillary & Reticular dermis

IV - Reticular dermis.

V - Subcutaneous fat.

- Management of primary lesion

* metastatic work up for thin melanoma without ulceration
(clinical stage I A | II)

- No imaging recommended.

- CXR -- false positive rate -- 50-100%.

No evidence for metastatic work up in thin melanoma.

Thicker melanoma

↓
upto 2mm thickness

- FDG PET/CT

- MRI - Brain

- LDH - elevated LDH is a poor prognostic factor.

- Management based on thickness:

Tis - WLE $\pm$ 0.5-1cm margin

- SNB not indicated

- No adjuvant therapy.

T1a - < 0.75mm

- WLE $\pm$ primary closure / SSC

- No SNB / adjuvant

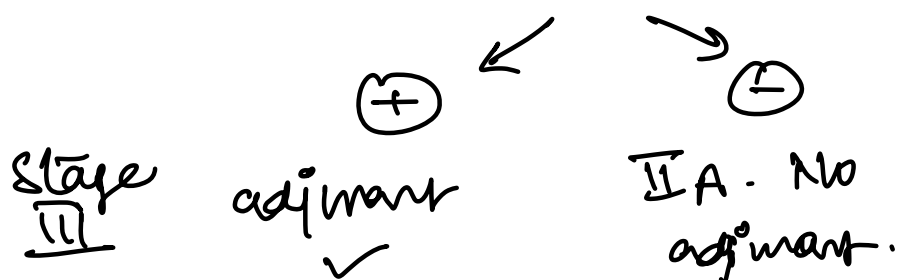
T1b - 0.8-1mm

- WLE $\pm$ SNB (No strong recommendation)

- No adjuvant if No.

T2a, 2b - 1-2mm with / without ulceration

- WLE $\pm$ SNB



T3a - 2-4mm $\nexists$ ulceration

- WLE $\pm$ 2cm margin + SNB.

- LDH $\pm$ imaging.

T3b - 2-4mm $\exists$ ulceration

- imaging + LDH.

- WLE $\pm$ 2cm margin + SNB.

T4a / 4b - $\geq$ 4mm $\nexists$ / $\exists$ ulceration

- CT thorax + A+P + MRI Brain + LDH.

- WLE $\pm$ 2cm margin + SNB

→ Trials for margin in melanoma:

TABLE 63.4

Prospective Randomized Clinical Trials of Melanoma Excision Margins

Clinical Trial	N	Thickness Ranges (mm)	Margins-Study Groups (cm)	Local Recurrence	Disease-Free Survival	Overall Survival
World Health Organization Melanoma Program Trial No. 10	612	0-2	1 vs 3-5	None for 0-1 mm with 1 cm margins; for 1-2 mm, more local recurrences with 1 cm margins (NS)	—	No difference
French Cooperative Surgical trial	337	0-2	2 vs 5		No difference; 10-y DFS 85% and 83%, respectively	No difference; 10-y survival 87% and 86%, respectively
Swedish Cooperative Surgical Trial	989	0.8-2	2 vs 5	<1% overall	No difference; relative hazard rate for 2 cm margin 1.02 (0.8, 1.3)	No difference; relative hazard rate for 2 cm margin 0.96 (0.75, 1.24)
Intergroup Melanoma trial	740	1-4	2 vs 4	0.4% (first, recurrence) 0.9% (first recurrence), 2.1% ever for 2 cm margins; 2.6% ever for 4 cm margins	—	10-y disease-specific survival 70% for 2 cm margins; 77% for 4 cm margins (P= 0.074, NS)
British Cooperative Group trial	900	≥2	1 vs 3	(Locoregional = local + in-transit + nodal) Increase with 1 cm margin (hazard ratio 1.26, P= 0.05)	—	Similar; trend to better survival with 3 cm margins, P> 0.1 (NS)

DFS, disease-free survival; NS, not significant.

Source: DeVita 12th Edition

↓
Trial did not include SNAs.
So, locoregional recurrence is true recurrence/
affected node - not known.

NCCN margin Recommendations :

Tumor thickness	Recommended peripheral margin
Tis in situ	0.5 - 1 cm
T1 ≤ 1 mm	1 cm
T2 1-2 mm	1-2 cm
T3 2-4 mm	2 cm
T4 > 4 mm	2 cm

- Alternatives to WLE in mm

1) Primary RT:

- Lentigo maligna | lentigo malignant melanoma:
 - * usually in elderly patient
 - * Broad. distribution
 - * cosmetically difficult areas
- Superficial skin radiation

2) Hemostatic RT. for bleeding primary

3) Subungual melanoma - Amputation at interphalangeal joint of toe

→ Management of Nodes in Malignant melanoma:

Role of SLNB:

Initial studies by Morton et al by injecting
Trosulphan blue in the peritumoral region.

Patient selection for SLNB in mm:

- mm at least 1mm thick.
- thinner melanoma $\Rightarrow$ ulceration
- clinically non palpable LN.
- Post WLE of primary - 99% success rate by multicenter study

* pure desmoplastic melanoma - decreased risk of nodal mets. SLN may be avoided.

* SLNB of head & neck melanoma - intra parotid nodal spread
technically challenging.

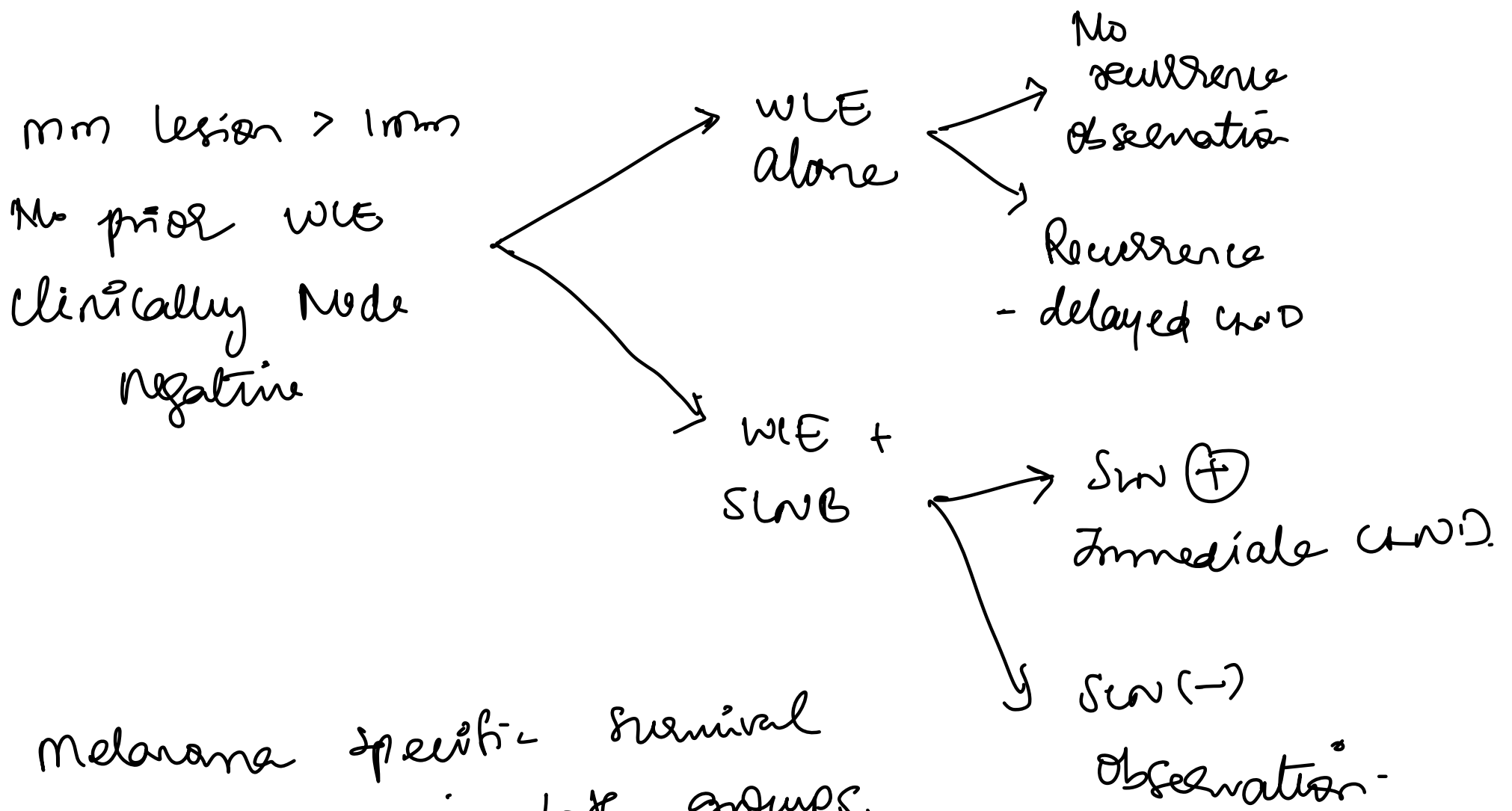
Technique:

- dual dye method - Tc99m labelled colloid + isosulphan / methylene blue
(1 mCi) (1 mL)
- Identification rate - 99% vs 87% for blue dye alone.
 $\downarrow$
Co2 LN Basin may not be predictable.
- FNR - 12%.
- Formal HPE + IHC $\hat{=}$ S100, HMB 45, MART-1, Melan-A
- Frozen section is discouraged.

trials in SLNB-mm:

MSLT-1 (Multicenter Selective Lymphadenectomy trial-1)

* To establish the role of SLNB in mm:



* Melanoma specific survival was similar in both groups.

* But, SLN (+) had worse survival compared to SLN (-)

MSLT-1 established prognostic role of SLNB in mm.

Role of CLND in Sen (+) mm:

1) MSCT-2 trial (observation vs CLND in SenB (+))

- * No significant difference in melanoma specific survival
- * Nodal failure in observation group - only 7%.
- * lymphedema more in CLND group - 24% vs 6%.

2) DeCOG - SLT trial:

- Under powered study
- Distal metastasis free survival similar in CLND & observation group.

Based on these trials:

- Negative Sen is a good prognostic factor
- Positive Sen - No role of immediate CLND. upto 3 nodes positive indicated in ENE (+) patients.
- Positive Sen helps in risk stratification for adjuvant therapy / active surveillance.

→ Role of Completion / therapeutic LND in mm:

Indications:

- clinically evident LN after
 - 1) SWB -ve observation
 - 2) prior LND (Regional nodal recurrence)
 - 3) mets to regional nodes from unknown primary melanoma.

Things to be done differently in mm:

- H&N → modified neck dissection $\pm$ superficial parotidectomy for intracapsular node.
- No role for selective LND.
- Axilla → ALND involving level I, II, III → long thoracic N to pedicle
part of paraxial plexus many need to be sacrificed in bulky nodes.
- groin → superficial + deep inguinal LND → dual LND if bulky inguinal LN.

- Role of adjuvant RT to nodal basin

TROG 02.01 trial

- For high risk patients:

- 1 parotid node
- ≥ 2 cervical / axillary node
- ≥ 3 groin node
- cervical / axillary node > 3 cm
- groin node > 4 cm
- Any node $\geq$ ECE

Adjuvant nodal RT

48 Gy / 20 #

→ Decreased local recurrence risk.

No difference in metastatic survival / OS.

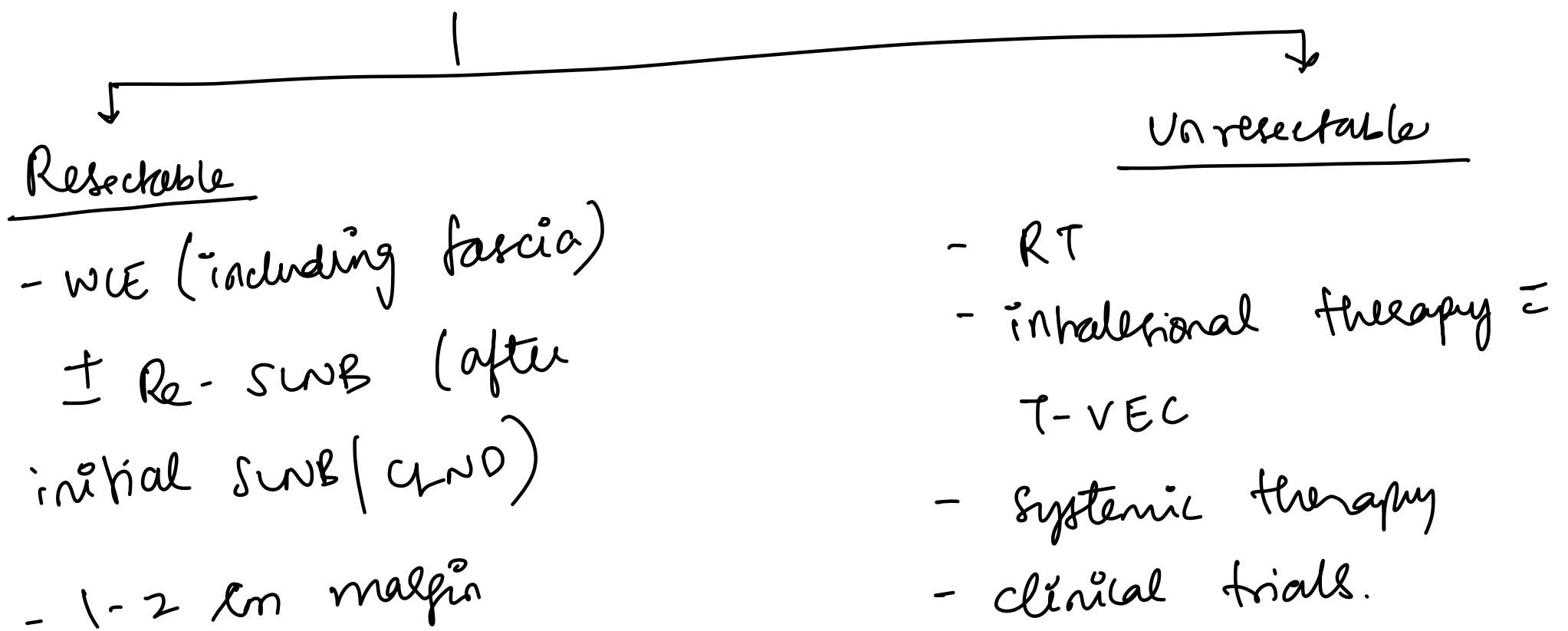
- Management of Regionally metastatic melanoma (stage III)

Definitions:

1. Local Recurrence - in the scar of original excision)
edge of skin graft used for closure.
2. Satellite mets (Synchronous / Metachronous) - Recurrence that is separate from scar but within 5cm of primary.
3. Intransit lesion - lesion > 5 cm away from primary but proximal to regional nodal basin.
4. Regional Nodal recurrence - Nodes at typical regional basin.

* Management:

1. Local recurrence & Satellite Nodules - poor prognosis if they occur after margin negative WLE (5y OS - 9-11%)



2. Management of intransit lesions :

Solitary /
localised clusters
which are Resectable

↓
Resection ±
5-10mm margin
↑ repeat SCNB.

Multiple / diffuse
lesions
(mc in lower limb)

Poor prognostic
factor

Intra lesional
therapy

Isolated limb
perfusion / infusion
(ILI / ILI) therapy.

* Limb perfusion therapies :

Isolated limb
perfusion

Complete Response

Rate

58%

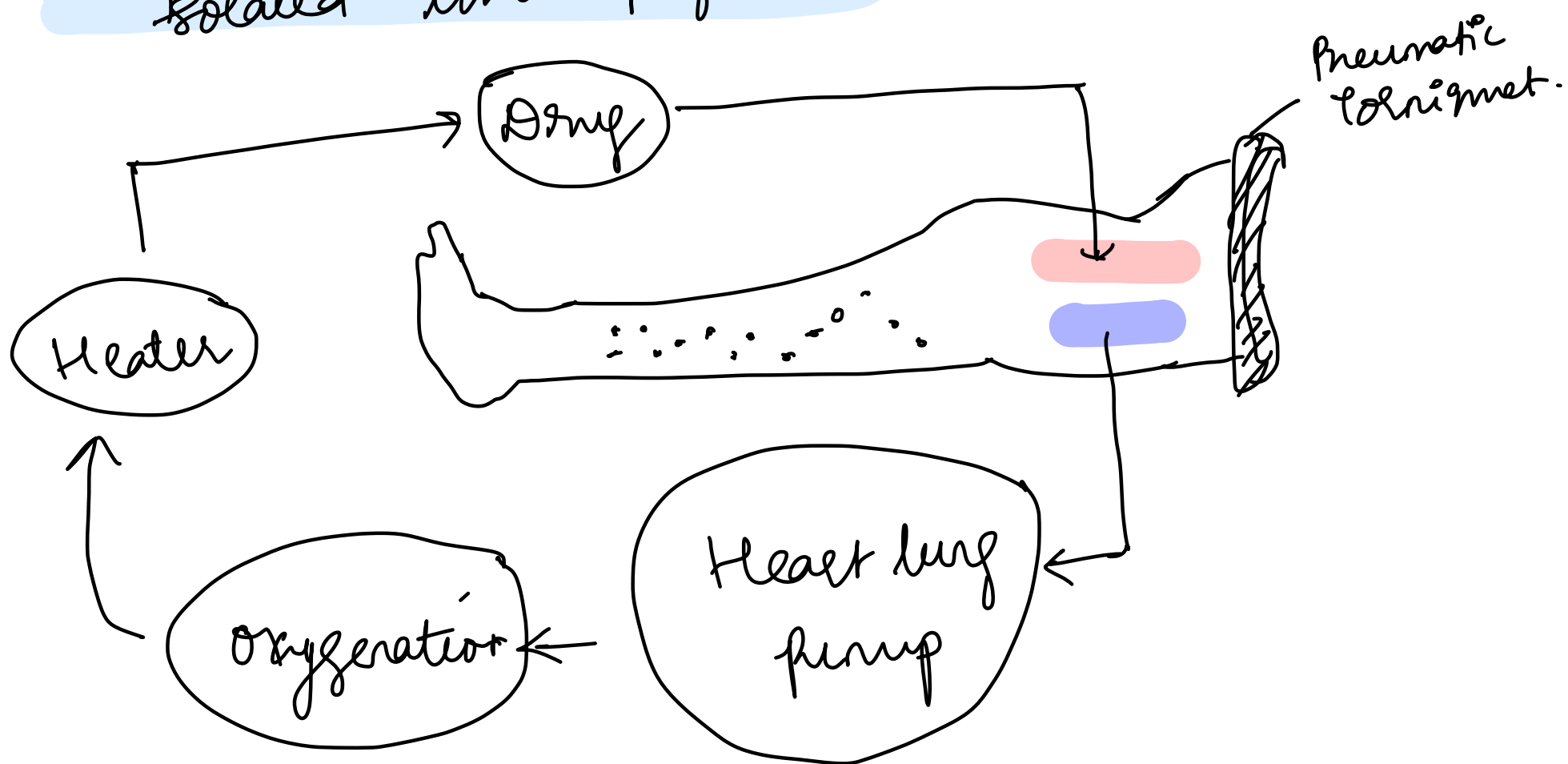
33%

Isolated limb
infusion.

- Surgical access of artery & vein of affected limb
- Catheters connected to a heart-lung machine
↓
oxygenated perfusion
- Catheter insertion via affected groin - difficult.
- Blood needed to prime the circuit.

- Percutaneous access of blood vessel through contralateral limb.
- Hypoxic procedure → marked acidosis of isolated limb.
- Catheter insertion via CL groin - easy.
- No pump → low pressure infusion → risk of systemic toxicity d/t leak is low.

- Isolated limb perfusion:



Drug [melphalan - mc
melphalan + TNF- α
melphalan + Actinomycin

Temperature - 39-40°C

- Hyperthermia increases local drug uptake
- increased sensitivity of tumor cells to heat.

but hyperthermia $\uparrow$ local toxicity.

monitoring systemic toxicity - injecting radioactive tracer along $\bar{c}$ chemo drug which is detected by a precordial tracer.

Combining ILI/ILP $\bar{c}$ systemic therapy

Toxicity [local
systemic d/t
leak of perfusate.

- overcomes chemotherapy resistance

* Intratumoral Therapies :

TABLE 63.8

Brief Review of Literature on Intratumoral Therapies

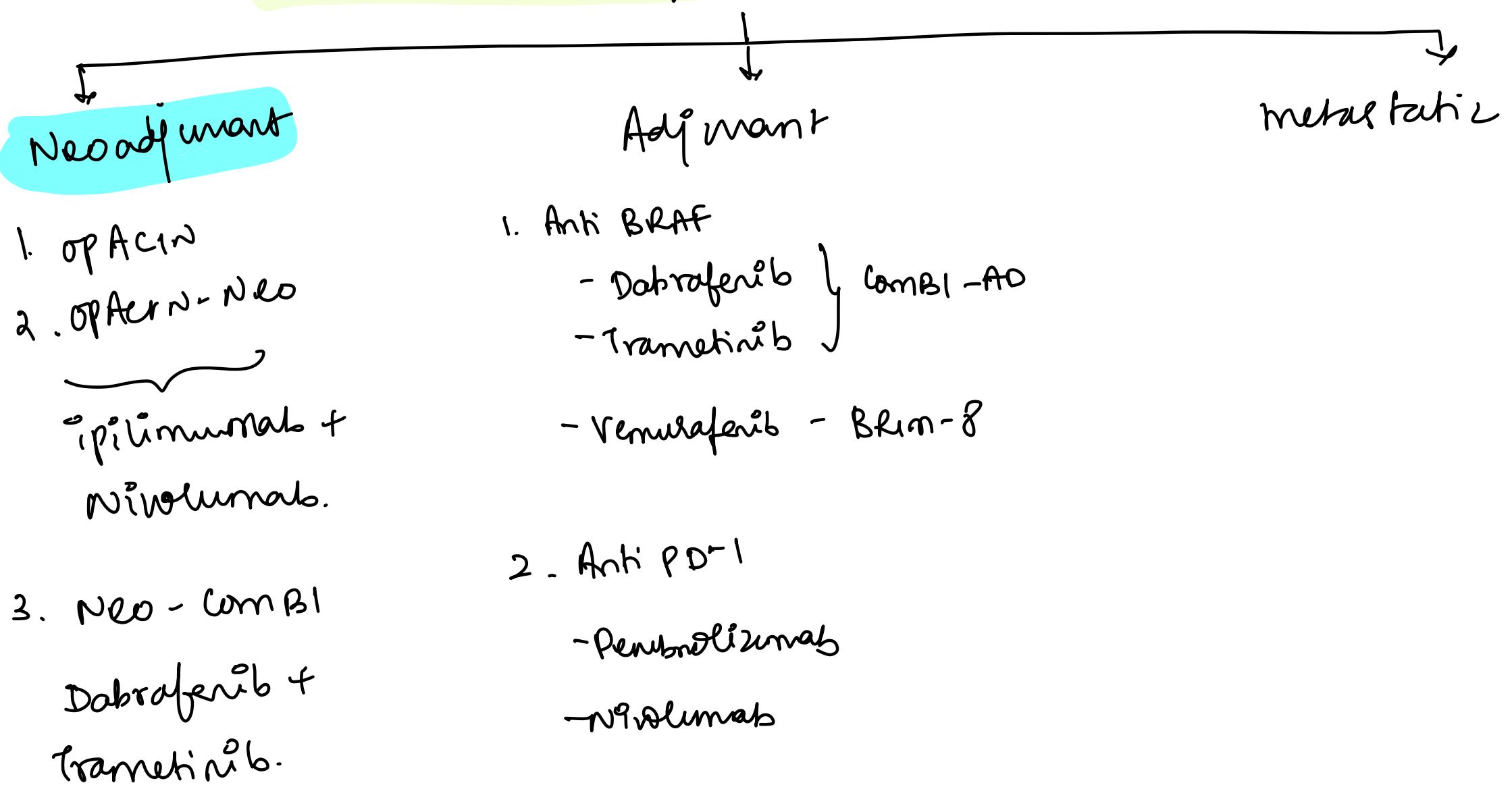
Therapy	Regimen	Response Rate Injection Lesions	Response Rate Distant Lesions
Interferon alpha	10 million IU 3x/wk rec IFNa2b	45% (31% CR, 14% PR)	CR 6%; PR 12% (RR 18%)
Rose Bengal (PV-10)	10% PV-10 w/v in saline, 0.5 ml/cc lesion volume	46%	27%
Interleukin-2	0.3–6 MIU/lesion, based on size 3 x/wk	79% (79% CR)	0%
Electrochemical with bleomycin	Bleomycin (intralesional or IV) plus electrical pulse	96%	New lesions arose soon
Imiquimod	Topical daily or BID	Up to 50%	Low
BCG	Intralesional injection	90%	17%
Talimogene laherparepvec (T-Vec; HSV-1 encoding GM-CSF)	Intralesional injection	26%	26%
		→ High Durable response Rate	
BCG + imiquimod	BCG then, when inflamed, add imiquimod (n = 9)	67% (56% CR, 11% PR)	—
Diphencyprone	Prepared in acetone; administered at increasing doses to cutaneous lesions	100% (57% CR, 43% PR), based on seven patients	Not reported
2,4-Dinitrochlorobenzene	Intralesional	60%	Not reported

CR, complete response; PR, partial response; RR, response rate; IV, intravenously; BID, twice a day; BCG, Bacillus Calmette-Guérin; GM-CSF, granulocyte macrophage-colony-stimulating factor.

Source: DeVita 12th Edition

- * No role for photodynamic therapy in MM.
- * No role for topical 5-FU in MM

Immunotherapy in malignant melanoma



→ Role of Neoadjuvant therapy (for stage III disease)

* Neoadjuvant targeted therapy

① opACIN study

↓

Sx → Adjuvant 4x ipilimumab + nivolumab

2x ipi +
nivolumab

→ Sx →

2x ipi +
nivolumab

neoadjuvant
arm

* pCR 78%

* durable RRs

* high toxicity

② opACIN - neo
study

optimal dose
of NACT ipi/
nivolumab

→ standard dose (3mg/kg ipi
1mg/kg nivo)

→ Reduced dose ipi (1mg/kg ipi
3mg/kg nivo)

→ Sequential dose (3mg/kg ipi
3mg/kg nivo)

* Reduced dose ipi achieved

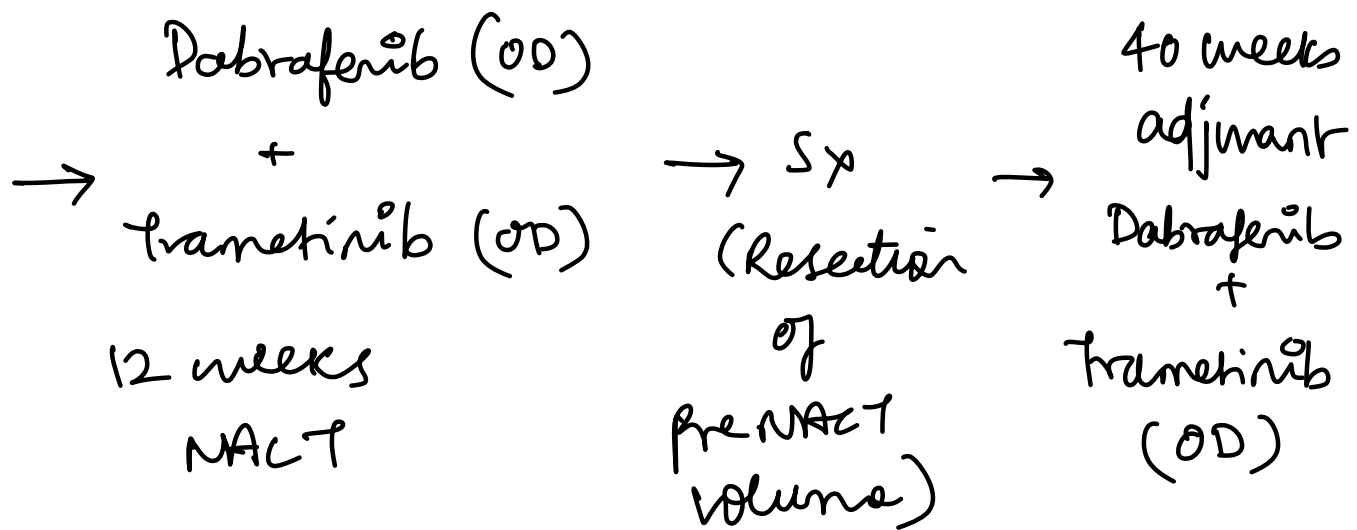
high ORR - 80% (Overall Response Rate)

pCR - 60%

toxicity - 20%

③ NeoComb 1 trial

- Resectable stage 3B/3C
- BRAF V600 mutation positive
- Phase 2 trial



Pathological response - 100%.

Complete path response - 49%.

Median relapse free survival - 23 months

RECIST response - 86%.

* Rationale of Neoadjuvant therapy:

1. Induce better immune response (T-cell mediated) when tumor & tumor related lymphocytes are in situ.
2. Assess in vivo response of tumor to immunotherapy.
 - PCR rates can tailor adjuvant therapy.
3. Avoid extensive surgery after good response.
4. BRAF targeted therapy may be started in partial responders.

Disadvantage: Toxicity to NACT may delay surgical resection.

→ Adjuvant therapy in mm

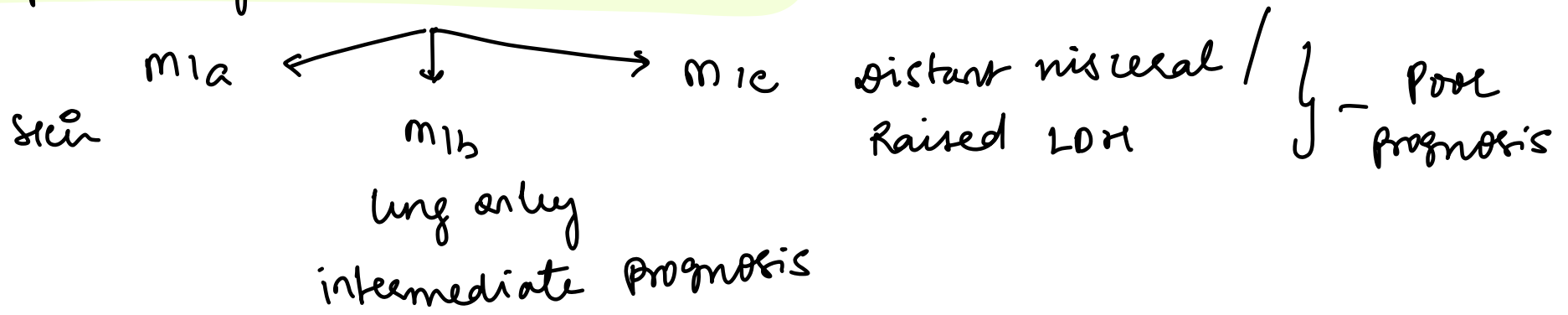
Listing of Major Adjuvant Phase 3 Clinical Trials Enrolling Patients with Surgically Resected Lymph Node Metastases									
Reference	Long et al. NEJM 2017 and Dummer et al. NEJM 2020 ²⁸⁰		Weber et al. NEJM 2017 ²⁷⁷ and Ascierto et al. Lancet 2020		Eggermont et al. NEJM 2018 ²⁷⁵ and Eggermont et al. Lancet Oncol 2021 ²⁷⁶		Grossman et al. Cancer Discovery 2021		
Clinical trial name	COMBI-AD		Checkmate 238		EORTC 1325 or Keynote-054		SWOG S1404		Brim-8
Study arm	Dabrafenib + trametinib <i>BRAF blockade</i>	Placebo	Nivolumab <i>PD-1 blockade</i>	Ipilimumab <i>CTLA-4 blockade</i>	Pembrolizumab <i>PD-1 blockade</i>	Placebo	Pembrolizumab	Ipilimumab or interferon alpha	VEMURAFENIB <i>BRAF blockade</i> Placebo
Stage eligibility	Any T N1a (>1 mm) or higher M0		Any T N2a or higher or M1 resected		Any T N1a (>1 mm) or higher M0		Any T N2a or higher or M1 resected		II C, IIIa, IIIB III C
Number of patients	435	432	453	453	514	505	647	654	
Median RFS	Not Reached	17 months	52 months	24 months					
HR RFS	0.51 (0.42–0.61, <i>P</i> < 0.0001)		0.71 (0.60–0.86, <i>P</i> = 0.0003)		0.60 (0.49–0.73, <i>P</i> < 0.0001)		0.77 (0.59–0.99, <i>P</i> = 0.002)		Not reached.
Landmark RFS	5 year: 52% (48%–58%)	5 year: 36% (32%–41%)	4 year: 52% (47%–53%)	4 year: 41% (36%–46%)					
Median OS	Not Reached	Not Reached	Not Reached	Not Reached	Not Reached	Not Reached	Not Reached	Not Reached	
HR OS	Not mature		Not mature		Not mature		0.82 (0.61–1.09, <i>P</i> = 0.15)		
Median follow up at last reporting	60 months	58 months	51 months	51 months	42 months	42 months	47 months	46 months	

Source: DeVita 12th Edition

Other adjuvant therapy not used any more

- High dose INF α 2b
- pegylated INF α
- Anti CTLA-4 - ipilimumab - inferior to adj Nivolumab - Checkmate 238
|
more toxic
- adj Pembrolizumab - S1404

→ Management of metastatic mm: (Synchronous / metachronous)



Evaluation:

- FDG PET-CT - highly FDG avid except uveal melanoma
- MRI brain
- S. LDH
- Tissue diagnosis from metastatic site [FNAC Bx] IHC can be done [BRAF V600 E/K mutation] done on paraffin blocks / formalin fixed Bx DNA using PCR / Sanger sequencing.

Role of surgery in metastatic mm.

1. metastatectomy after response to immunotherapy (IO)
 - (in oligometastatic patients)
 - SWOG 9430 trial - OS = 21 months
 - MSLT-1 trial
 - poor prognosis in pt. who progressed on IO.

2. Surgery for palliation:

- Intestinal mets causing bleeding
- bowel bowel obstruction
- Cutaneous met = pain / ulceration
- LN mets = neurological symptoms
- symptomatic brain mets → SRS
- life threatening haemorrhage from mets.

- Adjuvant therapy in metastatic mmo

Source: DeVita 12th Edition

Summary of Best Clinical End Points with Selected Therapies for the Treatment of Advanced Melanoma	
Improved overall survival in randomized trials	Ipilimumab (vs gp100 peptide vaccine) Vemurafenib (vs dacarbazine) Trametinib (vs dacarbazine) Pembrolizumab (vs ipilimumab) Nivolumab (vs ipilimumab) Dabrafenib + trametinib (vs dabrafenib) Dabrafenib + trametinib (vs vemurafenib) Vemurafenib + cobimetinib (vs vemurafenib) Nivolumab + ipilimumab (vs ipilimumab)
Improved progression-free survival in randomized trials	Dabrafenib (vs dacarbazine) Trametinib (vs dacarbazine) Nab-paclitaxel (vs dacarbazine) Encorafenib + binimetinib (vs encorafenib) Encorafenib + binimetinib (vs vemurafenib) Vemurafenib + cobimetinib + atezolizumab (vs vemurafenib + cobimetinib) Nivolumab + relatlimab (vs nivolumab)
Improved response duration in randomized trials	T-Vec (vs granulocyte macrophage-colony-stimulating factor)
Validated antitumor activity in single-arm trials	High dose interleukin-2 TIL ACT Carboplatin-paclitaxel Dacarbazine
Agents and combinations no longer supported by results from advanced clinical trials	Nistosurea combination chemotherapy: CVD, biochemotherapy Dartmouth regimen and tamoxifen-chemotherapy combinations Thalidomide and thalidomide-chemotherapy combinations Sorafenib and sorafenib-chemotherapy combinations Elesclomol-chemotherapy combinations Peptide vaccines TVEC plus pembrolizumab Dabrafenib plus trametinib plus spartalizumab

1. Systemic chemotherapy:

(No longer used as first line treatment)

* Dacarbazine

- Response Rate - 20%.
- myelosuppression, nausea

* Temozolomide

- Active component similar to dacarbazine
- Better CNS penetration.
- Failed to demonstrate improvement over dacarbazine.

* Nab-paclitaxel

- Improved PFS over dacarbazine.

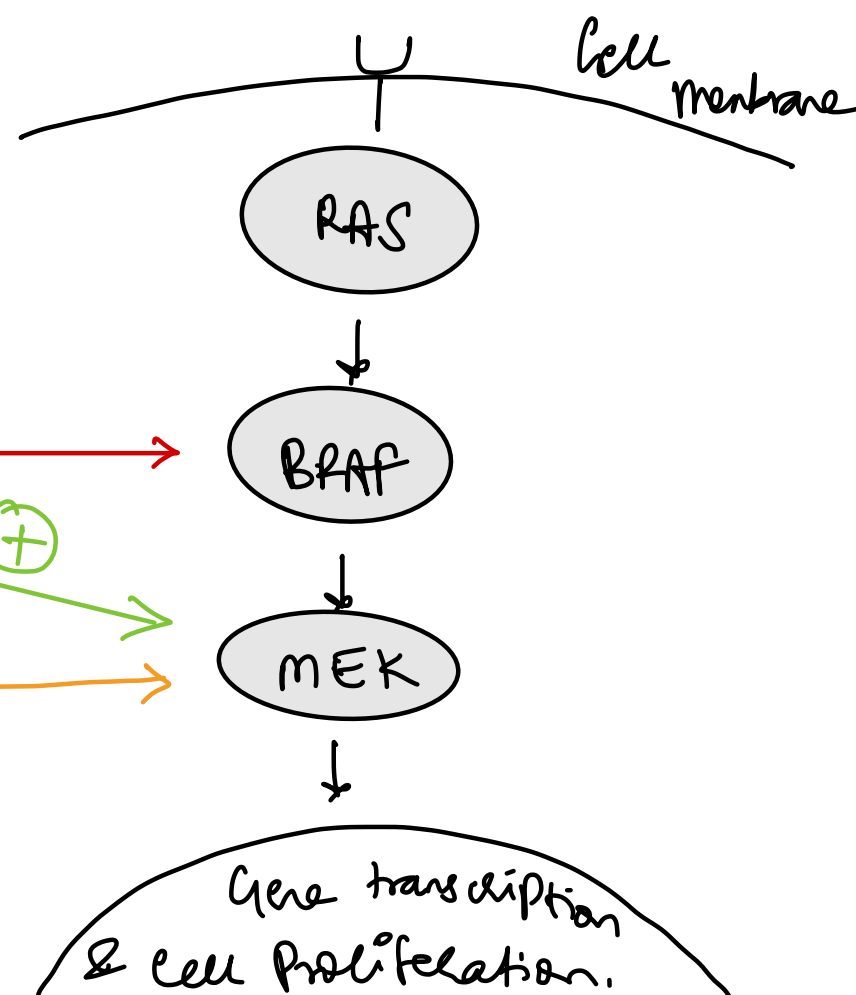
* Combination chemotherapy

Paci - Carbo

2. Targeted therapy:

* Single agent BRAF inhibitors:

* Single agent MEK inhibitors:



BRAF inhibitors
Cause Paradoxical
activation of MEK -
MAPK pathway.

Vemurafenib
Dabrafenib

Trametinib

→

⊕

→

* Single agent BRAF inhibitors

- Response Rate - 48% vs dacarbazine.
- Side effects
 - photoreactivity, rash
 - secondary cutaneous SCC
 - paradoxical activation of MAPK pathway
- Resistance to BRAF inhibitors (2 mechanisms):
 - Reactivation of MAPK pathway
 - MAPK independent cellular proliferation.

Side effects & Resistance overcome by

Combination of BRAF + MEK inhibitors

* RCTs for combination therapy.

- all showed similar efficacy,
similar side effects.
- all combinations decreased incidence of secondary sec.

COMBI-d - Dabrafenib + Trametinib vs Dabrafenib

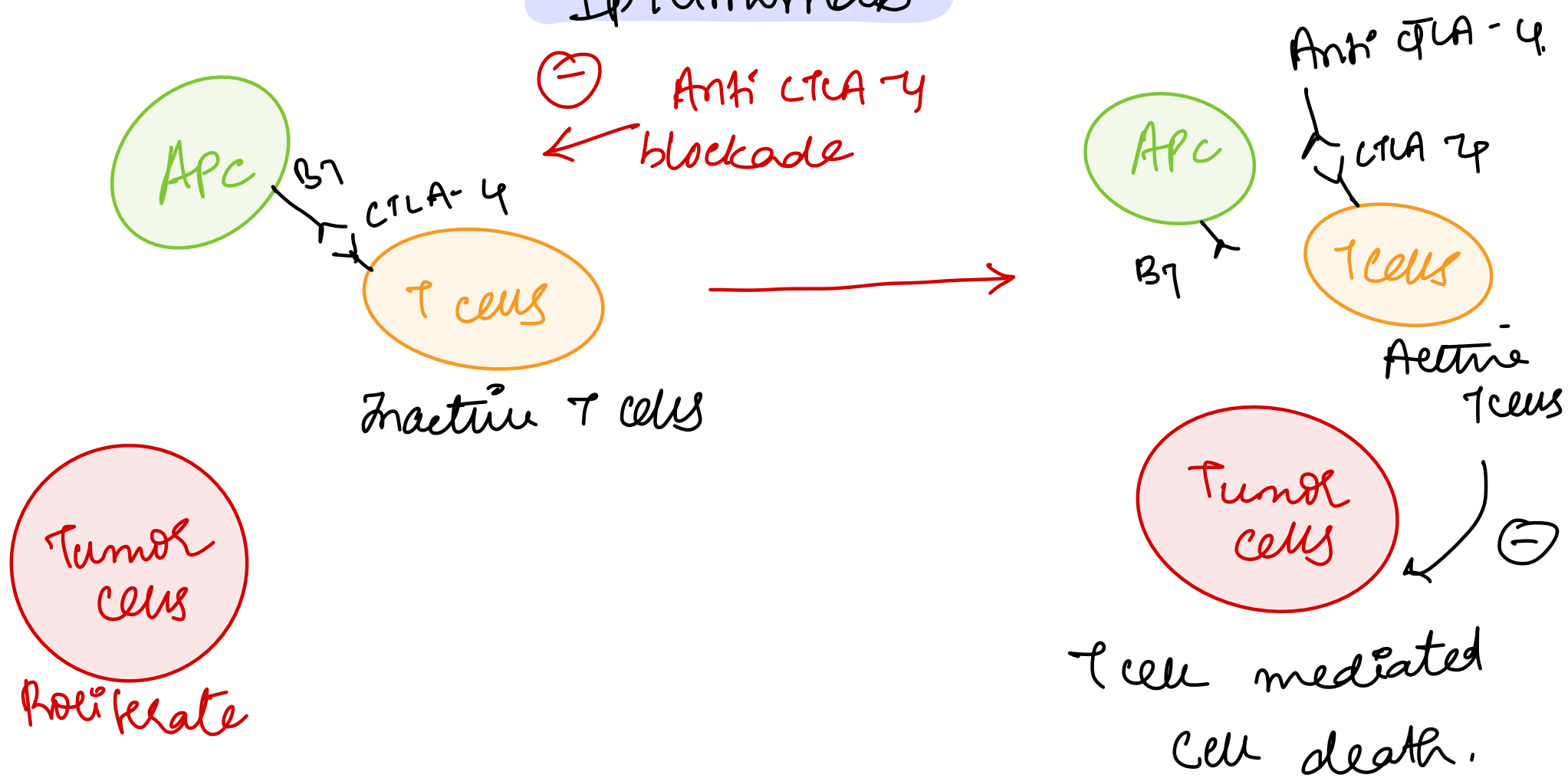
COMBI-v - Dabrafenib + Trametinib vs Vemurafenib

Co-BRim - Vemurafenib + cobimetinib

COLUMBUS - Encorafenib + binimetinib

3. Immunotherapy (Anti CTLA-4 blocking Antibodies) - (immune checkpoint inhibitors)

Ipilimumab



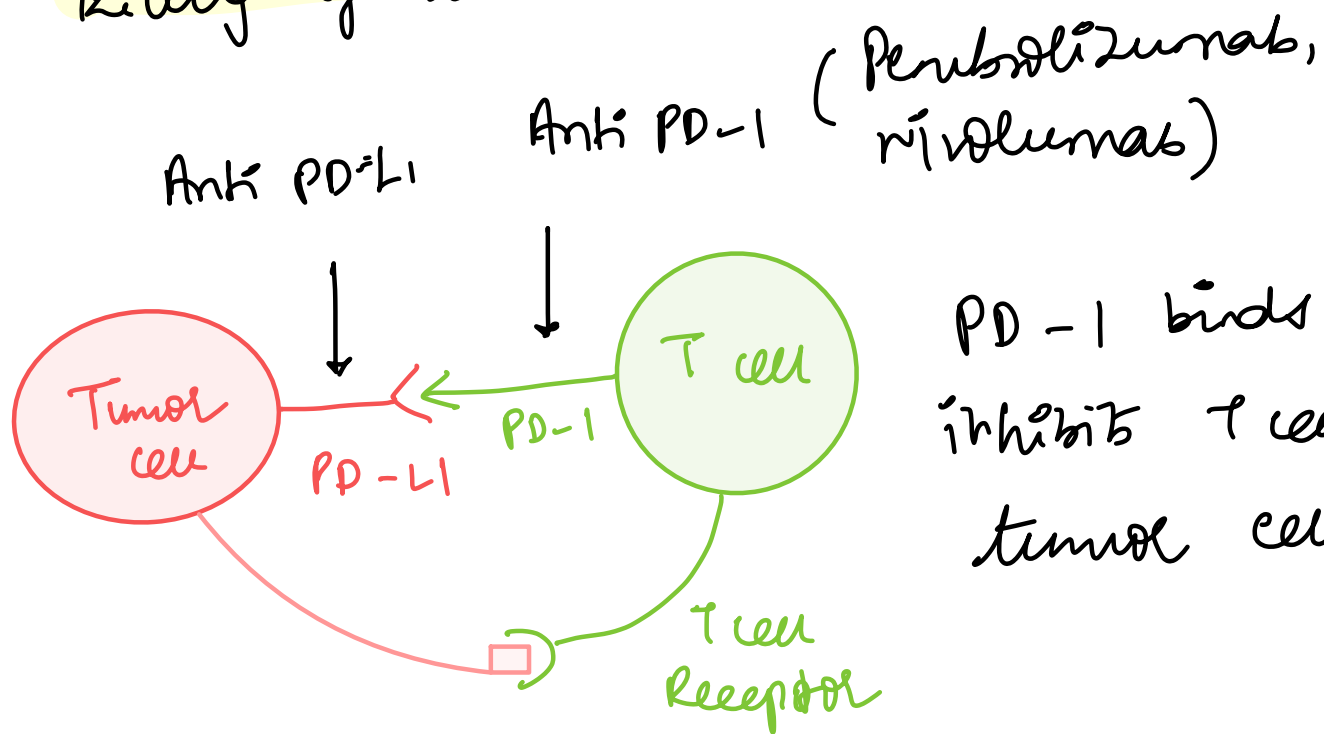
ADR - fatal immune mediated reactions
enterocolitis, Hepatitis,
toxic epidermal necrolysis

Toxicities reduced by combining

Anti PD-1 Antibodies.

4. Immunotherapy (Anti PD-1)

MOA - Blocking PD-L1 or PD-1 allows T-cell killing of tumor cells



* especially effective in desmoplastic melanoma.

Immunotherapy - Anti CTLA-3 - Relatlimab.

5. Combination immunotherapy:

* Keynote 006 - Pembrolizumab vs ipilimumab
PFS 8.4 mo vs 3.4 mo.

* Checkmate 067 - Nivolumab vs Nivo + ipi
median OS (37 mo)

* Relativity 047 - Nivolumab + relatlimab vs nivolumab

6. Combination of Immunotherapy + Targeted therapy

* ImSpire - 150 — Vemurafenib + Cobimetinib +
(concurrent) Atezolizumab

FFS - 15 months.

* DREAMseq trial — Nivolumab + ipilimumab
(sequential) f/b Dabrafenib + Trametinib