Clinical Immunotherapy Guidelines: An Update

Society for Immunotherapy of Cancer

November 2011

Bethesda, MD

CIG Project Development (to date)

ember 2009	Concept proposed to SITC Board of Director
mer 2010	Concept developed internally with SITC leadership
ber 2010	Plans for CIG project presented to SITC membersh
ary 2011	Discussions with Dr. Arlene Fink (UCLA, RAND)
h 2011	Steering Committee established for Melanoma Task Force
2011	Melanoma Task Force faculty identified and invited
2010	Steering Committee develops meeting agenda/cont

Clinical Immunotherapy uidelines: Melanoma Task Forc

Society for Immunotherapy of Cancer

Thursday June 2, 2011

University Club of Chicago

IOM Standards for Developing Trustworthy Clinical Practice Guideline

andard 1 Establishing transparency

andard 2 Management of COI

andard 3 Guidelines for development of group composition

andard 4 Clinical practice guideline-systematic review intersection

andard 5 Establishing evidence foundations for ar rating strength of recommendations

andard 6 Articulation of recommendations

andard 7 External review

SIC Melanoma Task Force
Steering Committee

Michael T. Atkins, MD

F. Steven Hodi, MD

Howard L. Kaufman, MD

John Kirkwood, MD

Melanoma Task Force

atient Eligibility

oxicity Assessment and Management

esponse Assessment and Stopping

reatment Combinations and Sequencing

Faculty Participants

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ene Gonzalez, MD, University of Colorado

Stephen Hodi, MD, Dana Farber Cancer Center

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aura Jane Hyde, Gilda's Club

oward Kaufman, MD, Rush University

ohn Kirkwood, MD, Univ. of Pittsburgh

avid Lawson, MD, Emory University

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Susan Steel, Skin of Steel

Ahmad Tarhini, MD, University of Pittsburgh

John Thompson, MD, University of Washington

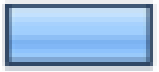
Jill Titze, NP, Rush University

Walter Urba, MD, PhD, Providence Cancer Cente

Richard White, Jr. MD, Carolinas Medical Center

General Track Focus Group Faculty Responses

hat best describes your primary role in melanoma:

		Response Percent	Res C
Medical Oncologist		**80.0%**	
Surgical Oncologist		12.0%	
Nurse		0.0%	
Patient or Patient Advocate		8.0%	
Other (please specify)		0.0%	
		answered question	

Which of the following is the primary focus of your clinical activity:

	Response Percent	Response Count
ocal management of melanoma	0.0%	0
Regional management of melanoma	0.0%	0
Management of advanced melanoma	**56.0%**	**14**
All of the above	40.0%	10
Neither/Not applicable	4.0%	1
Other	0.0%	0
	answered question	**25**

Which of the following do you have clinical experience with (check all that apply):

	Response Percent	Respon Coun
Chemotherapy	84.0%	
Immunotherapy	**96.0%**	
Biochemotherapy	76.0%	
Surgical Resection of Melanoma	24.0%	
Targeted Therapy	88.0%	
Clinical Trials	**96.0%**	
	answered question	
	skipped question	

Which of the following FDA-approved agents have you used or recommended for patients h melanoma:

	Response Percent	Response Count
Dacarbazine	56.0%	14
Interferon-alfa-2b	52.0%	13
Pegylated interferon	8.0%	2
Ipilimumab	**64.0%**	**16**
All of the Above	40.0%	10
Not applicable	4.0%	1
	answered question	**25**
	skipped question	**0**

ich of the following non-FDA-approved agents have you used or recommended for
nts with melanoma:

	Response Percent	Res C
Temozolomide	**87.5%**	
GM-CSF	66.7%	
Biochemotherapy	66.7%	
Carboplatinum/taxol	83.3%	
CVD/CVT chemotherapy	45.8%	
	answered question	
	skipped question	

Status of Immunotherapy for Melanoma

John Kirkwood, MD

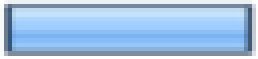
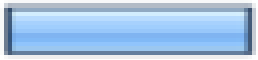
University of Pittsburgh

Patient Eligibility

Mike Atkins, MD

Beth Israel Deaconess Medical Center

What is your first-line adjuvant treatment recommendation for patients with Stage III elanoma with microscopic sentinel node disease:

	Response Percent	Respo Cou
1 year of interferon-alfa	 52.2%	
5 years of pegylated interferon	0.0%	
Short course of interferon-alfa depending on prognostic risk	 21.7%	
Biochemotherapy	 4.3%	
Radiation therapy	0.0%	
No further treatment	 21.7%	
	answered question	

What is your first-line adjuvant treatment recommendation for patients with Stage III elanoma with macroscopic sentinel node disease:

	Response Percent	Response Count
1 year of interferon-alfa	72.7%	16
Pegylated interferon	0.0%	0
Short course of interferon-alfa depending on prognostic risk	9.1%	2
Biochemotherapy	4.5%	1
Radiation therapy	4.5%	1
No further treatment	9.1%	2
answered question		22

What is your first-line treatment recommendation for asymptomatic and good performance status patients with Stage IV melanoma (check only one):

	Response Percent	Respo Cou
Single agent chemotherapy	0.0%	
Combination chemotherapy	0.0%	
High-dose IL-2	**56.5%**	
Ipilimumab	13.0%	
Targeted therapy clinical trial	13.0%	
Other	17.4%	
	answered question	
	skipped question	

1	Clinical trial
2	Individualized therapy based on molecular features of tumor, pt's HLA type age/performance status
3	Depends on all sorts of things. That's what we're meeting about. YOu did provide this option for adjuvant treatments but the same applies: a clinical

Patient Eligibility

- Who should receive adjuvant interferon?
- Who should receive pegylated interferon?
- Who should undergo surgical resection for tage IV disease?
- Who should receive high-dose IL-2?
- Who should receive ipilumimab?
- Who should receive chemotherapy?
- Who should receive a BRAFinhibitor?

Therapy

ge

erformance status

o-morbidities

tage

lceration of primary

entinel Node Status

ite of primary (mucosal, ALM etc)

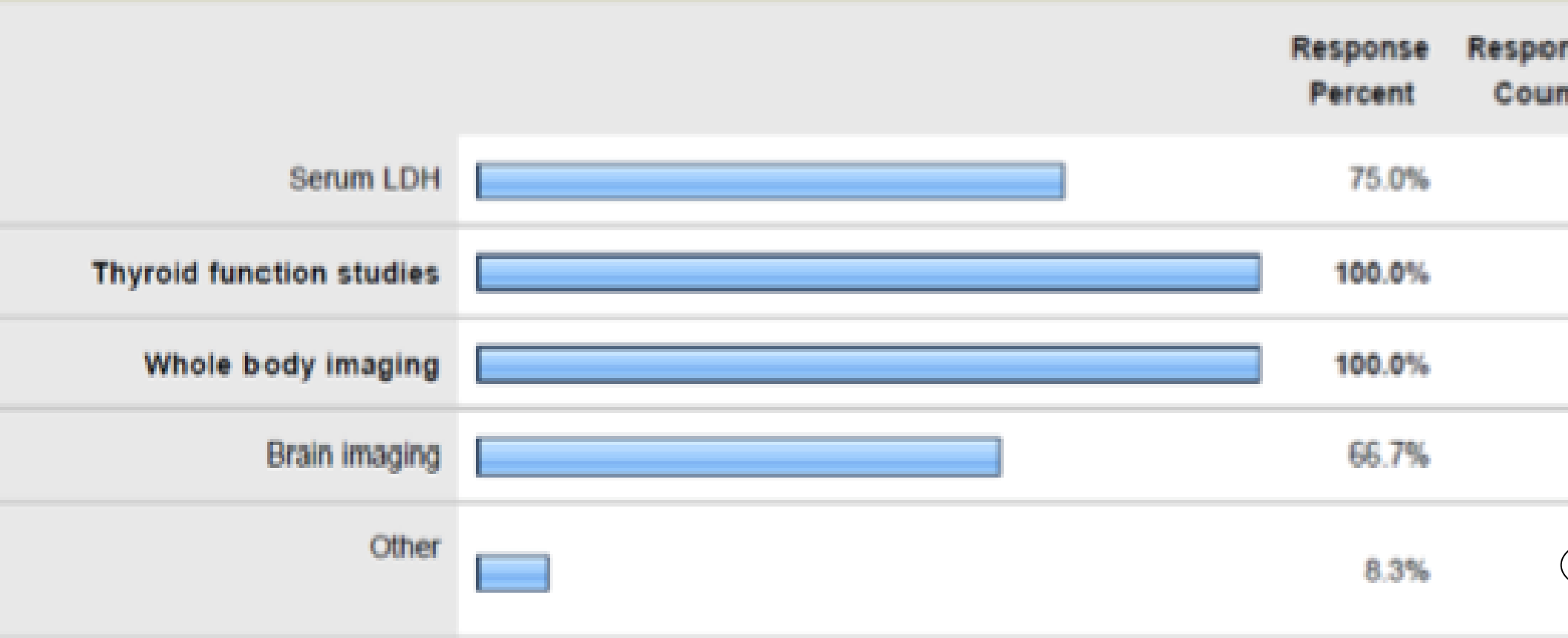
Stage IV Therapy

tes of metastases
Soft tissue
Lung
CNS
umber of metastatic sites
DH status
RAF mutation status
RAS mutational status
Kit mutational status
mune infiltration
DL1 expression

Toxicity Assessment and Management

John Kirkwood, MD
University of Pittsburgh

13. Which of the following do you routinely monitor in patients treated with immunotherapy
check all that apply):



1 CBC, metabolic profile

14. What techniques do you use to monitor patients with Stage III melanoma being treated with interferon-alfa or pegylated interferon (check all that apply):

	Response Percent	Respon Coun
CT scan of the chest, abdomen and pelvis	52.2%	
MRI of the brain	13.0%	
PET scan	17.4%	
Whole body PET-CT scan	21.7%	
Ultrasound	0.0%	
Liver function studies, LDH	**65.2%**	
Chest X-ray	39.1%	
Other (please specify)	13.0%	
	answered question	
	skipped question	

1 combination of above, depending on clinical context and how long after surge

ow do you manage interferon-related depression:

	Response Percent	Resp Co
Place ALL patients on anti-depressants at the start of treatment	31.8%	
cribe anti-depressants for CTED patients when signs of depression develop	**45.5%**	
atients to a psychologist or hiatrist prior to treatment if e is a history of depression	13.6%	
atients to a psychologist or atrist only when symptoms develop	13.6%	
I do not use interferon	18.2%	
Other	9.1%	
	answered question	
	skipped question	

Prescribe anti-depressants for SELECTED patients when signs of depressio
develop AND refer patients to a psychologist or psychiatrist prior to treatmne

oxicity Assessment and Manageme

terferon

- Hepatic toxicity
- Hematologic toxicity
- Neuropsychiatric toxicity
- Endocrine and other autoimmune effects

terleukin-2

- Capillary leak syndrome
- Management of autoimmune hypothyroidism

ilimumab

- Autoimmune toxicity

acarbazine

Considerations for Toxicity

- ime course of anticipated toxicity
- ndications for dose reduction/holding
- ndications for supportive interventions
- ndications for stopping treatment ermanently
- iomarker functions of autoimmune and ther ‘toxicity’ events

Response Assessment and Treatment Cessation

F. Stephen Hodi, MD

Dana Farber Cancer Center

21. A patient with Stage IV melanoma completes four cycles of Ipilimumab and has stable disease and one new lung nodule. How would you manage this patient:

	Response Percent	Response Count
Continue maintenance Ipilimumab	**39.1%**	**9**
Stop Ipilimumab treatment	21.7%	5
Obtain a biopsy of the lung nodule	8.7%	2
Surgically resect the new lung nodule and then continue Ipilimumab	8.7%	2
Other	34.8%	8
	answered question	**23**
	skipped question	**2**

A patient with Stage IV melanoma completes four cycles of Ipilimumab and has stable disease and one nodule. How would you manage this patient:

- Obtain short interval (approx 6 weeks) follow up imaging to assess disease progression
- monitor
- surgically resect nodule. should I continue Ipi?
- resect lung nodule. FDA did not approve maintenance
- ipi has no maintenance indication. you stop the drug and watch. if all other disappear, consider resect nodule if growing later
- repeat scan in 4-6 weeks
- since approval there is no maintenance therapy allowed

Response Assessment

- What is the best measure of clinical response?
- In the presence of partial response, when do you continue current treatment?
- In the presence of stable disease, when do you continue current treatment?
- In the presence of progressive disease, when do you continue current treatment?
- What imaging modalities should be used to define responses with immunotherapy?

Treatment Combinations and Sequencing

Howard L. Kaufman, MD
Rush University

reatment Combination and Sequencin

ocus on Stage IV melanoma

onsider agents in clinical development

eatment options for Stage IV Melanon

acarbazine

terleukin-2

ilimumab

RAF inhibitors (CKIT, MEK, etc.)

EGF inhibitors

nti-PD1 antibody

VD/CVT chemotherapy

arboplatin/Taxol chemotherapy

A BRAF wild type Stage IV melanoma patient with good performance status presents f
atment. Your recommendation is:

	Response Percent	Respo Cou
igh-dose IL-2 first, and if no response, then Ipilimumab	**56.5%**	
Ipilimumab first, and if not response, then high-dose IL-2	17.4%	
motherapy first, then consider immunotherapy	4.3%	
Clinical trial	13.0%	
Other	8.7%	
	answered question	
	skipped question	

eatment Combinations and Sequenci

re there any combination immunotherapy regimens that c
e recommended?

hat are the priorities for clinical testing of combination
mmunotherapy?

hen should IL-2 be first-line treatment?

hen should ipilimumab be first-line treatment?

hen should dacarbazine/temozolomide be first-line
eatment?

hen should a clinical trial be first-line treatment?

hen should metastasectomy be considered?

hat parameters should be considered in sequencing of

Consideration in Treatment Combinations and Sequencing

atient-specific factors

performance status

age

LDH

umor-specific factors

BRAF status (or others)

CNS disease

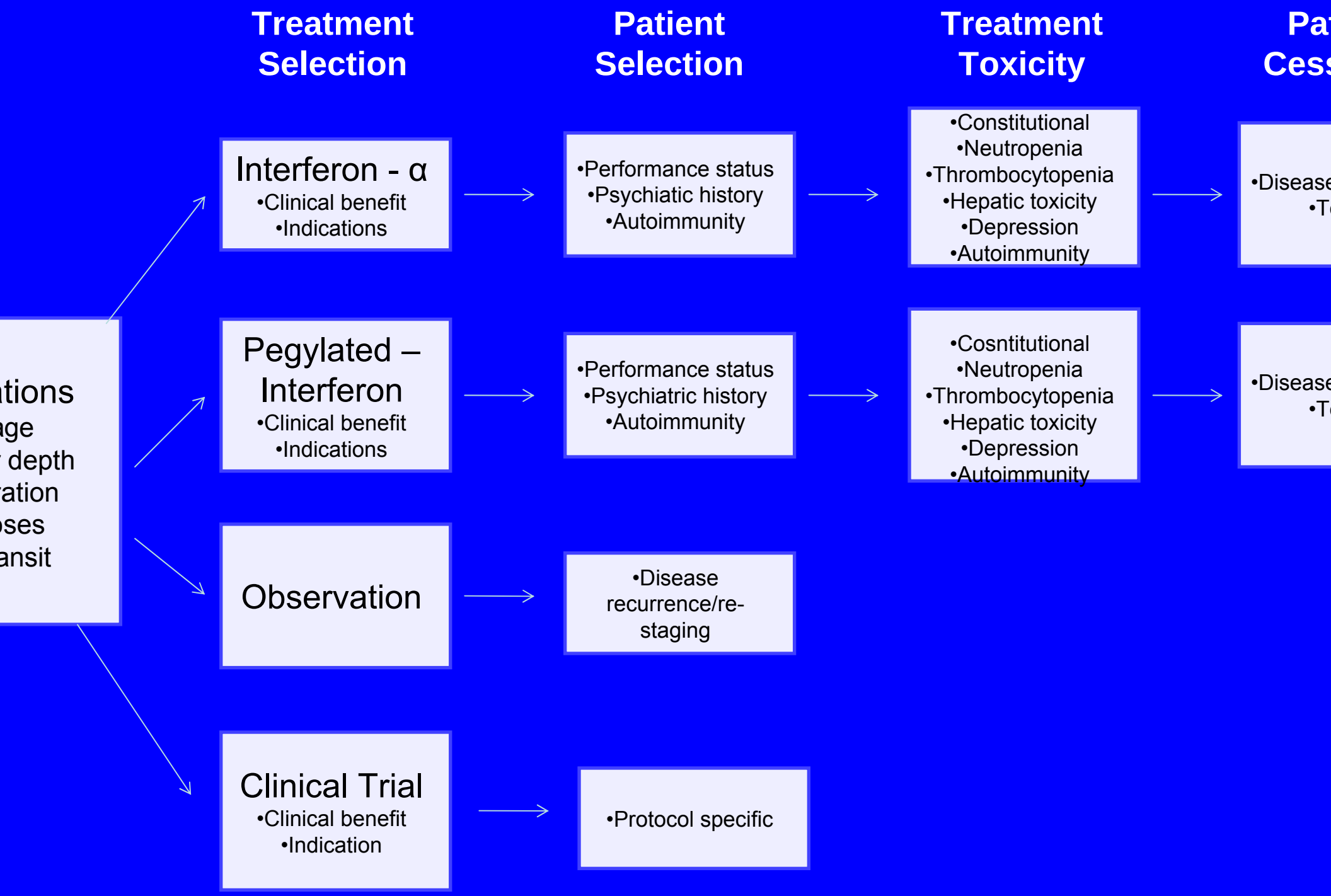
Tumor doubling time

hysician-specific factors

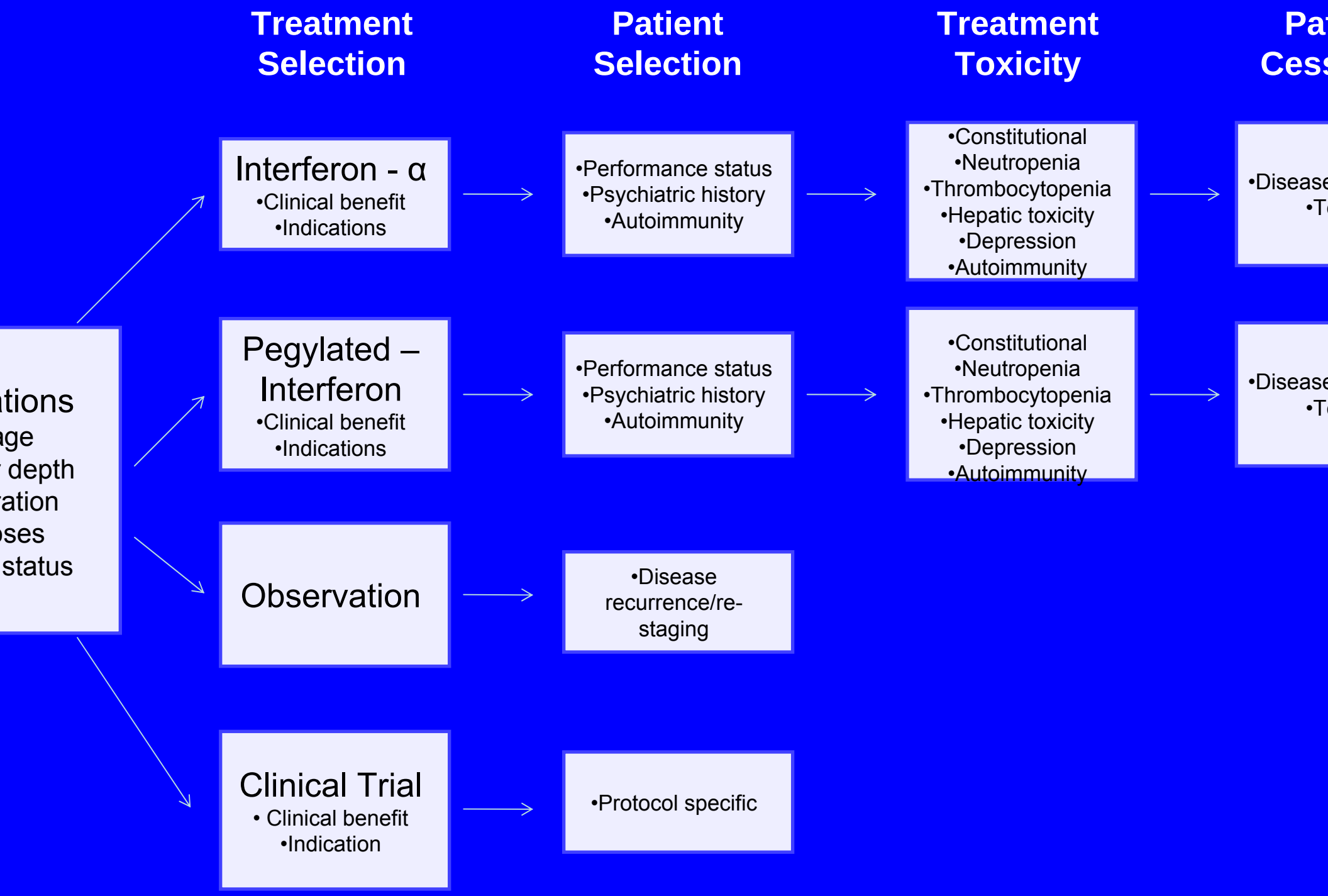
Immunotherapy expertise

DRAFT CLINICAL
MMUNOTHERAPY GUIDELINES
FOR MALIGNANT MELANOMA

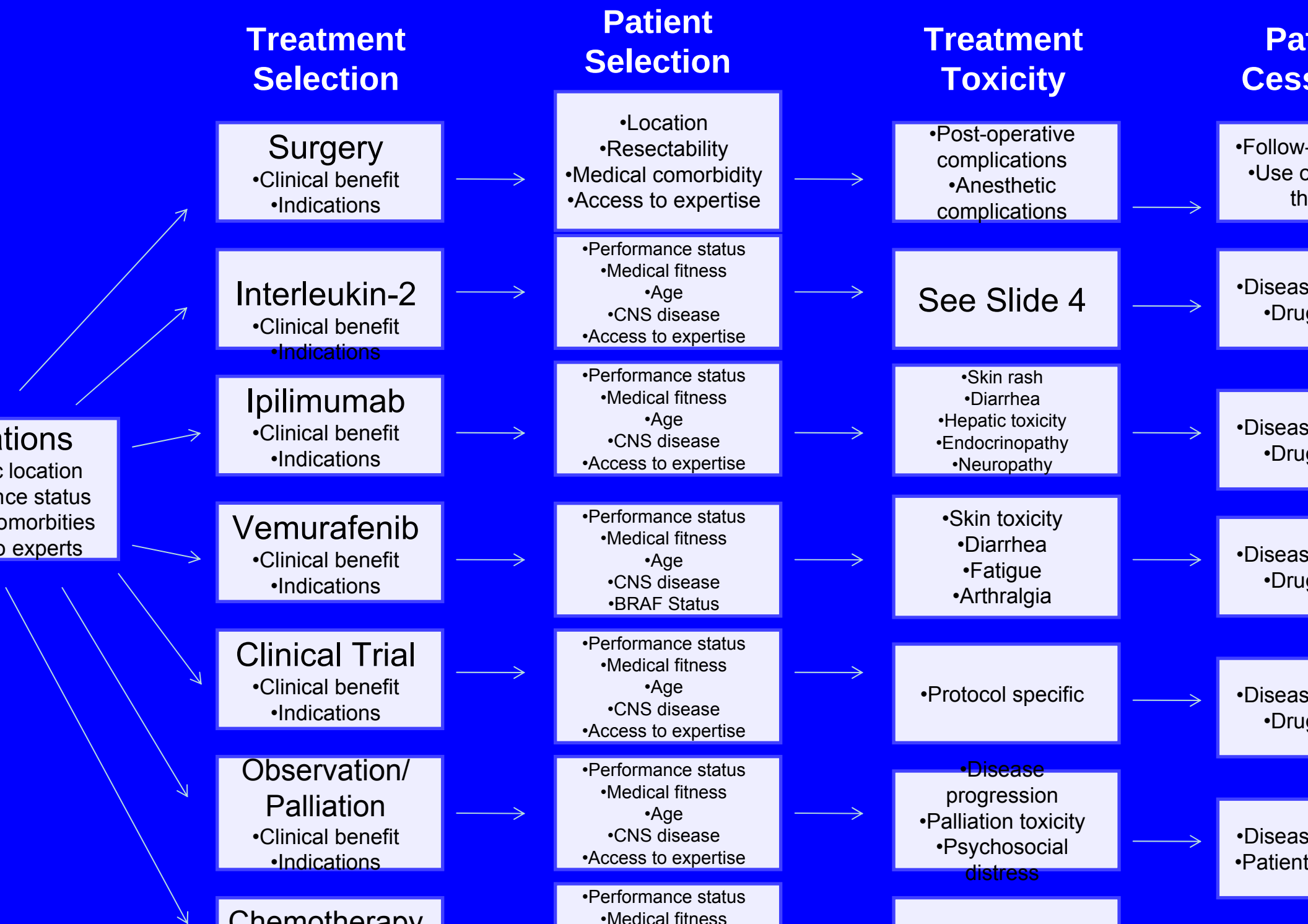
Stage II Melanoma



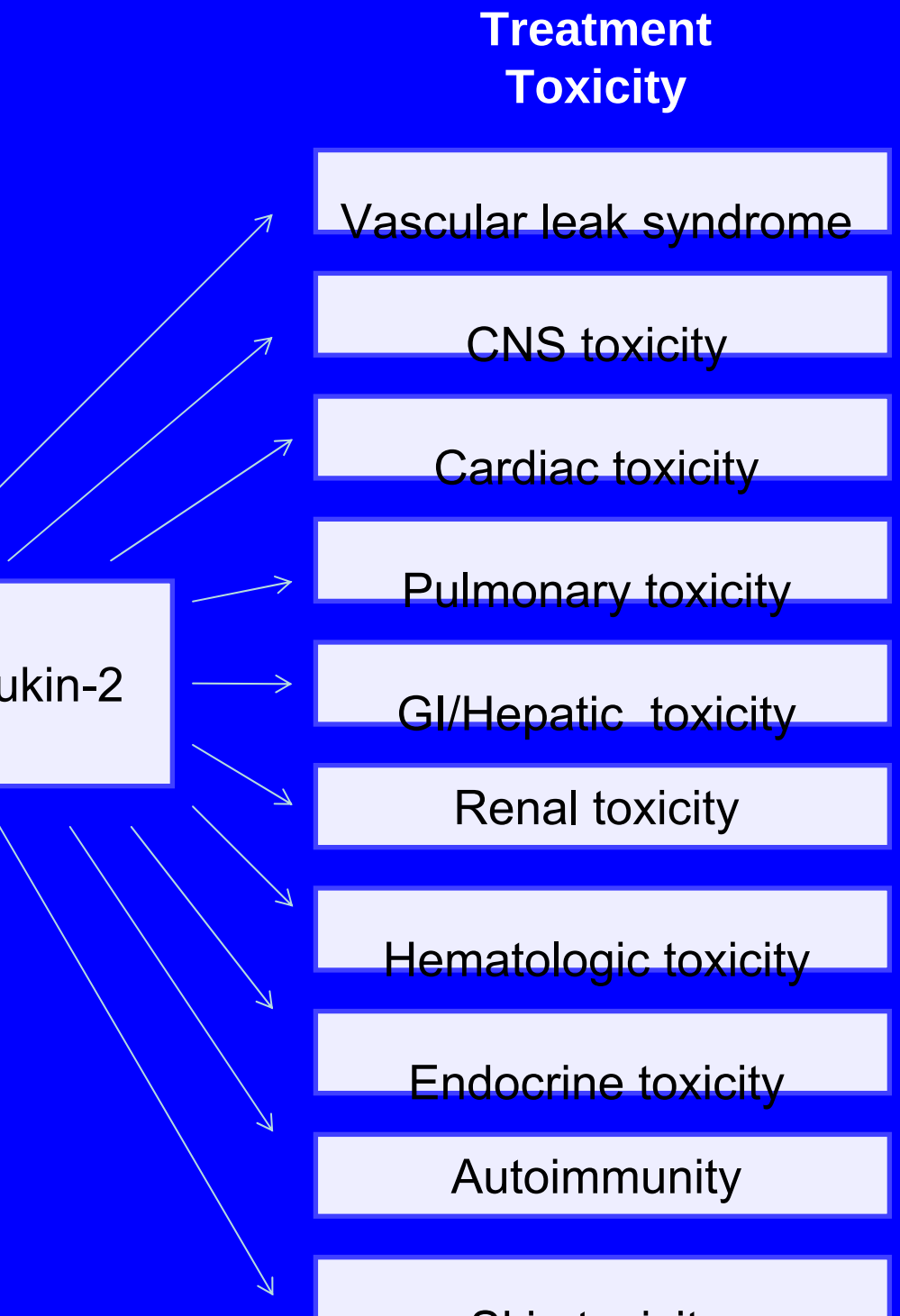
Stage III Melanoma



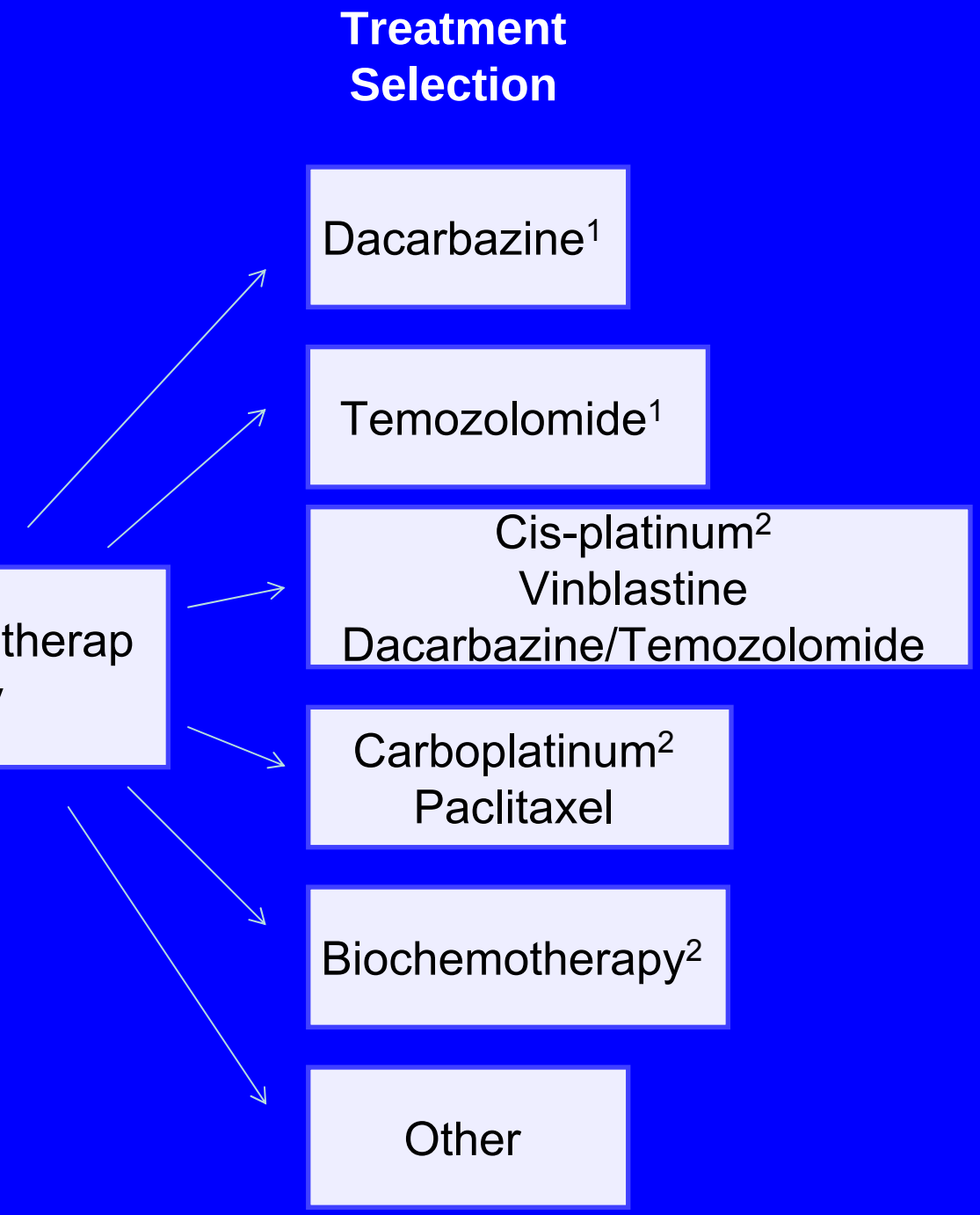
Stage IV Melanoma



Stage IV Melanoma



Stage IV Melanoma



Next Steps

terature review and supporting documentation

ectronic questionnaire to Melanoma Task Force Members

onsensus draft statement prepared

onsensus presented to SITC membership

btain feedback from external peer review

raft manuscript prepared

anuscript submitted for publication

Thank You!

r. Thomas Gajewski and SITC Board

r. Arlene Fink, UCLA/RAND Corporation

ara Withington, CAE and SITC staff

elanoma Steering Committee

elanoma Task Force Faculty Participants