

# Contents

## Part I Melanoma

<b>1</b>	<b>Melanoma—Introduction, History and Epidemiology</b>	<b>3</b>
1.1	Introduction	4
1.1.1	Basics of Structure and Functions of Skin	4
1.1.2	Melanocytes	4
1.1.3	Melanoma—Definition	5
1.1.4	Prominent People Who Were Diagnosed with Melanoma	5
1.2	History	7
1.2.1	Initial Descriptions of Melanoma	7
1.2.2	Hereditary Nature of Melanoma	9
1.2.3	Descriptions of Uveal Melanoma	9
1.2.4	Introduction of Term ‘Melanoma’	9
1.2.5	Descriptions of Association Between Melanoma and Skin Color	10
1.2.6	Introduction of Clark’s Level and Breslow Thickness	10
1.2.7	Descriptions of Associations Between Sunlight, MC1R Mutations and Melanoma	11
1.2.8	Description of Familial Atypical Multiple Mole Melanoma and CDKN2A Mutations	11
1.2.9	Discovery of Ras Oncogenes and Their Relationship with Melanoma	12
	References	17
<b>2</b>	<b>Melanoma—Diagnosis, Subtypes and AJCC Stages</b>	<b>21</b>
2.1	Introduction	22
2.2	Signs and Symptoms of Melanoma	22
2.3	Diagnosis	22
2.3.1	Dermoscopy	24
2.3.2	Total-Body Photography	25

2.3.3	<i>In Vivo</i> Reflectance Confocal Laser Microscopy . . . . .	26
2.3.4	Histopathology. . . . .	26
2.3.5	Molecular Diagnosis . . . . .	27
2.4	Types of Melanoma . . . . .	28
2.4.1	Superficial Spreading Melanoma . . . . .	29
2.4.2	Lentigo Maligna Melanoma. . . . .	29
2.4.3	Acral Lentiginous Melanoma. . . . .	30
2.4.4	Nodular Melanoma . . . . .	32
2.4.5	Desmoplastic Melanoma . . . . .	33
2.4.6	Nevoid Melanoma . . . . .	35
2.4.7	Verrucous Melanoma. . . . .	36
2.5	Melanoma Stages . . . . .	36
2.5.1	Clark Classification . . . . .	36
2.5.2	Breslow Classification . . . . .	39
2.5.3	TNM (Tumor, Node and Metastasis) Classification . . . . .	39
2.5.4	Melanoma Staging—AJCC System . . . . .	40
	References. . . . .	42
<b>3</b>	<b>Etiology . . . . .</b>	<b>49</b>
3.1	Introduction . . . . .	50
3.2	UV Light and Sun Exposure. . . . .	50
3.2.1	Sunlight Exposure and DNA Damage . . . . .	51
3.2.2	Repair of UV Induced DNA Damage . . . . .	52
3.2.3	Xeroderma Pigmentosum. . . . .	57
3.3	Family History . . . . .	58
3.4	Familial Atypical Multiple Mole Melanoma Syndrome . . . . .	59
3.5	Skin and Hair Color . . . . .	59
3.6	Susceptibility Genes . . . . .	60
3.6.1	Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) . . . . .	60
3.6.2	Cyclin Dependent Kinase 4 (CDK4) . . . . .	62
3.6.3	Melanocortin 1 Receptor ( <i>MC1R</i> ) . . . . .	62
3.6.4	Microphthalmia-associated Transcription Factor (MITF) . . . . .	63
3.7	Aberrant Signaling Pathways . . . . .	65
3.7.1	c-KIT or KIT. . . . .	65
3.7.2	RAS Family of Proteins. . . . .	66
3.7.3	BRAF Activation. . . . .	68
	References. . . . .	70
<b>4</b>	<b>Melanoma—Treatment . . . . .</b>	<b>79</b>
4.1	Evolution of Treatment in 19th and 20th Centuries . . . . .	80
4.2	Surgery . . . . .	80
4.2.1	Primary Melanoma . . . . .	81

4.2.2	Regional Lymph Node Metastasis . . . . .	82
4.2.3	Metastatic Melanoma. . . . .	84
4.3	Adjuvant Therapy . . . . .	85
4.3.1	Adjuvant Immunotherapy . . . . .	85
4.3.2	Adjuvant Radiation Therapy . . . . .	88
4.4	Chemotherapy . . . . .	89
4.4.1	Alkylating Agents (Dacarbazine/Temozolomide) . . . . .	89
4.4.2	Biochemotherapy . . . . .	90
4.5	Targeted Therapy . . . . .	91
4.5.1	BRAFV600E Inhibitors . . . . .	91
4.5.2	MEK Inhibitors . . . . .	93
4.6	Immunotherapy . . . . .	95
4.7	Recommendations from Society of Immunotherapy of Cancer for Stage IV Melanoma . . . . .	96
	References. . . . .	102

## Part II Tumor Immunology

<b>5</b>	<b>Overview of Immune System . . . . .</b>	<b>113</b>
5.1	Introduction . . . . .	113
5.2	Innate Immune System . . . . .	114
5.2.1	Neutrophils . . . . .	115
5.2.2	Complement System . . . . .	116
5.2.3	Eosinophils . . . . .	119
5.2.4	Mast Cells . . . . .	120
5.2.5	Natural Killer Cells . . . . .	122
5.2.6	Antigen Presenting Cells . . . . .	125
5.3	Adaptive Immune System . . . . .	130
5.3.1	B-Lymphocytes (B-Cells) . . . . .	130
	References. . . . .	137
<b>6</b>	<b>Dendritic Cells . . . . .</b>	<b>143</b>
6.1	Introduction . . . . .	143
6.2	Subtypes . . . . .	144
6.3	Functions . . . . .	146
6.3.1	Antigen Presentation and Activation of T-Cells. . . . .	146
6.3.2	Connect Innate and Adaptive Immunity . . . . .	153
6.3.3	T-Cell Differentiation. . . . .	154
6.3.4	T-Cell Memory . . . . .	156
6.3.5	Antigen Presentation and Activation of B-Cells. . . . .	158
6.3.6	Immune Tolerance. . . . .	159
6.4	DCs in Tumor Microenvironment. . . . .	160
	References. . . . .	162
<b>7</b>	<b>T-Lymphocytes . . . . .</b>	<b>167</b>
7.1	Introduction . . . . .	167

7.2	T-Cell Receptor . . . . .	169
7.3	Development of T-Cells in Thymus . . . . .	170
7.4	T-Cell Subsets . . . . .	172
7.5	Activation of T-Cells . . . . .	174
7.6	Markers of T-Cells . . . . .	175
7.7	CD4 <sup>+</sup> and CD8 <sup>+</sup> T-Cell Differentiation . . . . .	177
7.7.1	Th1 Cells . . . . .	178
7.7.2	Th2 Cells . . . . .	180
7.7.3	Th17 Cells . . . . .	182
7.7.4	Tregs . . . . .	183
7.8	Cytotoxic T-Lymphocytes . . . . .	185
7.9	NK T-Cells . . . . .	188
7.10	$\gamma\delta$ T-Cells . . . . .	189
	References . . . . .	191
<b>8</b>	<b>Mechanisms of Immune Evasion by Cancer . . . . .</b>	<b>199</b>
8.1	Introduction to Immune Evasion . . . . .	199
8.2	Immunosurveillance . . . . .	200
8.3	Immunoediting . . . . .	202
8.4	Defective T-Cell Recognition . . . . .	203
8.4.1	Major Histocompatibility Complex (MHC) or Human Leukocyte Antigen (HLA) Class I . . . . .	203
8.4.2	Antigen Presenting Machinery . . . . .	204
8.5	Inhibition of T-Cell Recruitment . . . . .	204
8.6	Intrinsic Resistance to Apoptosis . . . . .	205
8.6.1	Death Receptor Pathway . . . . .	205
8.6.2	Granule Exocytosis Pathway . . . . .	206
8.6.3	Counter Attack by Tumor Cells . . . . .	207
8.7	Accumulation of Immunosuppressive Cells . . . . .	210
8.7.1	Regulatory T-Cells (Tregs) . . . . .	210
8.7.2	Myeloid Derived Suppressor Cells (MDSCs) . . . . .	211
8.7.3	Tumor Associated Macrophages (TAMs) . . . . .	211
8.8	Amino Acid Depletion . . . . .	213
8.8.1	Indoleamine 2,3-Dioxygenase (IDO) . . . . .	214
8.8.2	Arginase . . . . .	214
8.9	Tumor Derived Immuno-Inhibitory Cytokines . . . . .	217
8.9.1	TGF- $\beta$ . . . . .	218
8.9.2	Macrophage Migration Inhibitory Factor (MIF or MMIF) . . . . .	218
8.9.3	PGE2 . . . . .	219
8.10	Expression of Ligands for Negative Regulatory Receptors on T-Cells . . . . .	219
8.11	Protein-Glycan Interactions . . . . .	220
	References . . . . .	223

## Part III Immune Based Drugs Approved for Treatment of Melanoma

<b>9</b>	<b>Interferon-<math>\alpha</math>2b</b>	235
9.1	Introduction	236
9.2	Structure and Biology	237
9.3	Signal Transduction	238
9.4	Use in Melanoma	240
9.5	Intron A (IFN- $\alpha$ 2b)	243
9.6	Sylatron (Pegylated IFN- $\alpha$ 2b)	244
9.7	Clinical Pharmacology	244
9.8	Mechanism of Action	245
9.9	Adverse Effects	247
9.10	Drug Interactions	250
9.11	Contraindications	251
9.12	Limitations	251
	References	252
<b>10</b>	<b>Interleukin-2</b>	257
10.1	Introduction	257
10.2	Structure and Biology	258
10.3	Signal Transduction	260
10.4	Use in Melanoma	262
10.5	Proleukin	263
10.6	Clinical Pharmacology	264
10.7	Mechanism of Action	264
10.8	Adverse Reactions	266
10.9	Drug Interactions	267
10.10	Contraindications	268
10.11	Limitations	268
	References	271
<b>11</b>	<b>Ipilimumab</b>	275
11.1	Introduction	275
11.2	Structure and Expression of CTLA-4 Receptor	277
11.3	Signal Transduction	277
11.4	Yervoy	279
11.5	Clinical Pharmacology	279
11.6	Mechanism of Action	280
11.7	Use in Melanoma	281
11.8	Adverse Effects	288
11.9	Drug Interactions	290
11.10	Contraindications	290
11.11	Limitations	290
	References	292

<b>12</b>	<b>Nivolumab</b>	297
12.1	Introduction	297
12.2	Structure and Biology of PD-1 Receptor	299
12.3	Signal Transduction	299
12.4	Opdivo	300
12.5	Clinical Pharmacology	301
12.6	Mechanism of Action	302
12.7	Use in Melanoma	303
12.8	Adverse Effects	309
12.9	Drug Interactions	310
12.10	Contraindications	310
12.11	Limitations	312
	References	312
<b>13</b>	<b>Pembrolizumab</b>	319
13.1	Keytruda	319
13.2	Clinical Pharmacology	320
13.3	Mechanism of Action	320
13.4	Use in Melanoma	320
13.5	Adverse Effects	326
13.6	Drug Interactions	329
13.7	Contraindications	329
13.8	Limitations	329
	References	331
<b>14</b>	<b>Talimogene Laherparepvec</b>	333
14.1	Introduction	333
14.2	T-VEC	334
14.3	Use in Melanoma	335
14.4	Imlygic	340
14.5	Clinical Pharmacology	340
14.6	Mechanism of Action	341
14.7	Adverse Effects	341
14.8	Drug Interactions	344
14.9	Contraindications	344
14.10	Limitations	344
	References	345

## Part IV Ongoing Research

<b>15</b>	<b>Promising Immunotherapeutic Approaches in Clinical Trials</b>	351
15.1	Introduction	352
15.2	Monoclonal Antibodies	352
15.2.1	Programmed Cell Death Receptor (PD-1) and Its Ligands	352
15.2.2	CD27 and CD27 Agonistic Antibodies	358

15.2.3	Antibodies Targeting B7-H3 Receptors . . . . .	360
15.2.4	Anti Phosphatidylserine Antibodies . . . . .	361
15.3	Cytokines . . . . .	362
15.3.1	Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) . . . . .	362
15.3.2	Interleukin-12 (IL-12) . . . . .	369
15.3.3	Interleukin-15 (IL-15) . . . . .	372
15.3.4	Interleukin-18 (IL-18) . . . . .	373
15.3.5	Interleukin-21 (IL-21) . . . . .	374
15.4	Cancer Vaccines . . . . .	377
15.4.1	Peptides of TAAs . . . . .	380
15.4.2	Cancer Cell Lysates . . . . .	383
15.4.3	Gene Delivery Systems to Deliver Target TAAs . . . . .	384
15.5	Dendritic Cells . . . . .	385
15.5.1	Rationale for DC-Based Therapy . . . . .	388
15.5.2	Animal Studies Showing DC-Mediated Tumor Rejection . . . . .	389
15.5.3	Clinical Studies . . . . .	390
15.5.4	Ongoing Clinical Trials . . . . .	391
15.6	Adoptive T Cell Therapy . . . . .	394
15.6.1	Early Animal Studies . . . . .	394
15.6.2	Use of IL-2 . . . . .	395
15.6.3	Tumor-Infiltrating Lymphocytes and Lymphodepletion . . . . .	395
15.6.4	T-Cell Receptor (TCR) Engineering . . . . .	396
15.6.5	Clinical Studies . . . . .	397
15.6.6	Ongoing Clinical Trials . . . . .	398
	References . . . . .	400

## Part V Challenges

<b>16</b>	<b>Challenges of Immunotherapy . . . . .</b>	<b>419</b>
16.1	Defining Efficacy and Response Rates . . . . .	420
16.1.1	Pseudoprogression . . . . .	420
16.1.2	Immune-Related Response Patterns . . . . .	421
16.2	Low Response Rates . . . . .	422
16.2.1	Intrinsic Resistance . . . . .	423
16.2.2	Acquired Resistance . . . . .	424
16.2.3	Immunoediting and Tumor Antigen Load . . . . .	424
16.2.4	Tumor Microenvironment Based on Lymphocyte Infiltration (TILs) and PD-L1 Expression . . . . .	425
16.3	Immune-Related Adverse Events . . . . .	427
16.4	High Cost of the Therapy . . . . .	428
	References . . . . .	431

Immunotherapy of Melanoma

Rotte, A.; Bhandaru, M.

2016, XI, 434 p. 59 illus., 52 illus. in color., Hardcover

ISBN: 978-3-319-48065-7