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## **The safety of anti PD-1 therapeutics for the treatment of melanoma**

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Journal Article

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	Pembrolizumab (2mg/kg every 3w)		Pembrolizumab (10mg/kg every 3w)		Nivolumab (3mg/kg every 2w)	
	All AEs	Grade 3-4 AEs	All AEs	Grade 3-4 AEs	All AEs	Grade 3-4 AEs
<b>Phase I</b>	82% <sup>61</sup>	15% <sup>61</sup>	82% <sup>61</sup>	8% <sup>76</sup>	68% <sup>18</sup>	16% <sup>18</sup>
<b>Phase II</b>	68% <sup>62</sup>	11% <sup>62</sup>	74% <sup>62</sup>	14% <sup>62</sup>		
<b>Phase III</b>			72.9% <sup>20</sup>	10.1% <sup>13</sup> (G 3-5)	82.1% <sup>22</sup>	43.5% <sup>22</sup>

Severe or life-threatening AE	Pembrolizumab (2mg/kg every 3w) <sup>61-63, 69</sup>	Pembrolizumab (10mg/kg every 3w) <sup>61-63</sup>	Nivolumab (3mg/kg every 2w) <sup>18, 22</sup>
Diarrhea	1%	1%	>1%
Stomatitis	1%	-	1%
Colitis	1%	1%	0.3%
Neutropenia	1%	-	-
Decrease in platelet count	-	0.4%	1%
Decrease in hemoglobin	1%	-	-
Thyroiditis	1%	0.4%	0.3%
		0.4-1%	0.3%
	-	-	0.3%
Orbitis	-	1%	
Generalized motor seizures	1%	-	-
Alopecia	1%	-	-
Musculoskeletal toxicity or pain	1%	1%	-

	Established management	Proposed management	
		Published in literature <sup>97-99</sup>	By authors
	Systemic steroids 1-2 mg/kg/d + consider prophylactic antibiotics, if no improvement within 72-120h ->  Add infliximab 5 mg/kg (if perforation ruled out)	Systemic steroids 0.5-2 mg/kg/d + consider prophylactic antibiotics; if no improvement after 48-72h ->  Infliximab 5mg/kg (if perforation ruled out); if no improvement ->  tacrolimus/MMF 500-1000 mg/d	Infliximab 5 mg/kg single infusion, if no improvement or recurrence – 2nd infusion
	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	Systemic steroids 1-2 mg/kg/d + prophylactic antibiotics; if no improvement within 72-120h->  Add MMF 1000 mg b.d.	Systemic steroids 1-2 mg/kg/d; if no improvement ->  MMF 500-1000 mg/d b.d.	MMF 500-1000 mg/d b.d. until 6 weeks of normalization
	Permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
		Systemic steroids 10 – 20 mg/d, if no improvement ->  systemic steroids 1 mg/kg/d	MTX 15-30 mg/weekly, if no improvement ->  Infliximab 5 mg/kg
	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
is	Systemic steroids 2-4 mg/kg/d +/- empiric antibiotics; if no improvement within 48h->  Add additional immunosuppression	Systemic steroids 1-4 mg/kg/d +/- empiric antibiotics; if no improvement ->  additionally infliximab 500 mg/kg/d / MMF 500-1000 mg/d b.d.	Infliximab 5 mg/kg + Mycophenolat mofetil 500-1000 mg/d b.d.
	Permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	Systemic steroids 1-2 mg/kg/d	Topical steroids; if no improvement ->  Systemic steroids 0.5-1 mg/kg/d	Topical steroids (class IV) for 2 weeks, then switch to topical calcineurin inhibitors
	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	If symptomatic:  systemic steroids 1-2 mg/kg/d + hormone replacement therapy	Symptomatic hyperthyroidism: systemic steroids 1-2 mg/kg/d + consider methimazole  Symptomatic hypothyroidism + abnormal laboratory results + hormone replacement	Symptomatic hyperthyroidism: betablockers (if tachycardia), methimazole only if anti-TPO antibodies are detected  Symptomatic hypothyroidism + abnormal laboratory results + hormone replacement

## Article highlights

- Therapy with anti-PD-1 antibodies is a relatively novel treatment option now recommended as first line therapy for metastasized melanoma, independent of *BRAF* mutation
- Anti-PD-1 antibodies prevent PD-1 from binding to PD-L1 and following downregulation of T-cells
- Approved anti-PD-1 antibodies, pembrolizumab and nivolumab, show good response rates and tolerability
- Majority of adverse events associated with anti-PD-1 therapy are likely immune related
- They are usually mild in severity and can be managed with immunomodulatory medications and treatment interruption