

## **Supplemental Information: Protocol for systematic review**

**Title:** Autoimmune retinopathy with associated anti-retinal antibodies as a potential immune-related adverse event associated with immunotherapy in patients with advanced cutaneous melanoma: case series and systematic review

**Registration:** None

**Amendments:** None

### **Introduction**

**Rationale:** Immune-related adverse events (irAEs) are common after the initiation of immunotherapy for advanced cutaneous melanoma. Autoimmune retinopathy (AIR) is an underappreciated irAE in this context.

**Objective:** To demonstrate the spectrum of autoimmune retinopathy (AIR) following immunotherapy for advanced cutaneous melanoma

### **Methods**

#### **Inclusion criteria**

- PubMed indexed
- Written in English
- Visual symptoms began after the initiation of immunotherapy for cutaneous or non-ocular mucosal melanoma
- Clinical evidence of autoimmune retinopathy

#### **Exclusion criteria**

- Immunotherapy for malignancies other than cutaneous or non-ocular mucosal melanoma
- Onset of visual symptoms or ocular findings prior to initiation of immunotherapy

**Information source(s):** PubMed

#### **Search strategy:**

Searches were carried out with the following search terms: “melanoma” AND (“retinopathy” OR “maculopathy”) AND (“immunotherapy” OR “checkpoint inhibitor” OR “pembrolizumab” OR “nivolumab” OR “ipilimumab”)

**Data management:** Records will be stored in an Excel spreadsheet

**Selection process:** Studies will be screened and assessed for eligibility by a single reviewer. Studies selected for inclusion are then reviewed by two independent reviewers.

**Data collection process:** Data will be collected in a spreadsheet

**Variables sought:**

- Patient's sex
- Patient's age
- Immunotherapy at the onset of visual symptoms
- Visual symptoms
- Onset of visual symptoms after initiation of immunotherapy
- BCVA at presentation
- Ocular finding(s)
- Anti-retinal antibodies detected
- Concurrent systemic irAE
- Treatment for AIR
- Cessation of immunotherapy
- Duration of follow-up

**Outcome measures:**

- Ocular outcome
- Systemic outcome if reported

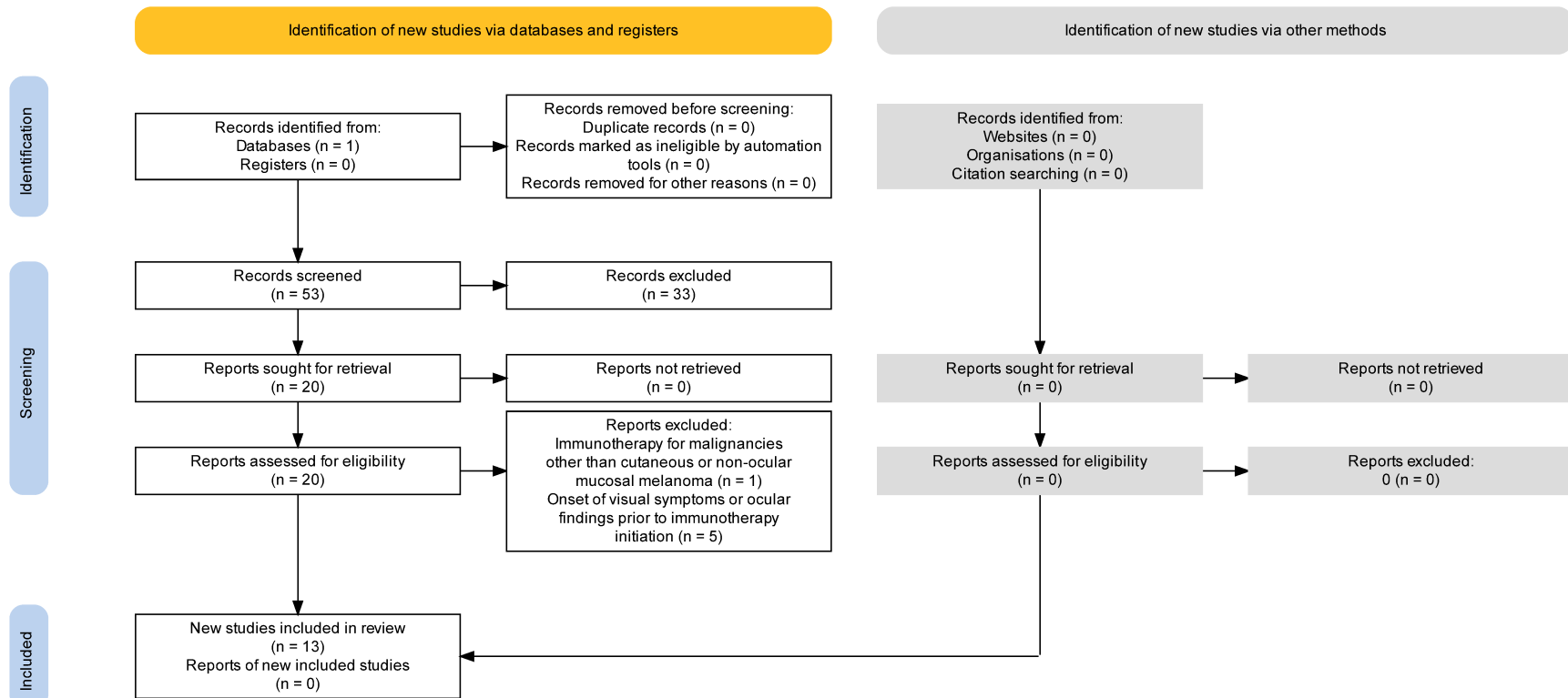
**Risk of bias in individual studies:**

Bias in individual studies can be presumed from omission of ocular outcomes. Studies with unexplained omission of ocular outcomes will be excluded from the final data synthesis.

**Data synthesis:**

Simple percentages of outcome measures will be reported. For measures involving time, median and interquartile range will be reported. Missing data will be reported as "not reported". The synthesized data will be presented in a table.

## Supplemental Figure 1. Systematic review flow diagram



**Supplemental Table 1.** Summary of published cases in systematic review

Publication	Sex	Age	Immuno-therapy	Visual symptom(s)	Symptom onset after starting immuno-therapy	BCVA at presentation		Ocular finding(s)	Anti-retinal antibodies detected	Concurrent systemic irAE	Treatment	Immuno-therapy stopped	Ocular outcome	Systemic outcome	Duration of follow-up
						OD	OS								
Mantopoulos et al. 2015 [22]	F	Early 70s	Ipilimumab for CM	Unspecified vision loss, photophobia	12 weeks	6/12	6/12	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Pruritis	Topical corticosteroids, oral corticosteroids	Yes	Complete resolution; 6/7.5 OD, 6/7.5 OS	Not reported	6 months
Crews et al. 2015 [23]	M	46	Ipilimumab for CM	Unspecified vision loss, photophobia	6 weeks	6/30	6/30	Serous retinal detachments OU	Not tested	Transaminitis	IV corticosteroids	Yes	Partial resolution; 6/18 OD, 6/12 OS,	Not reported	2 weeks
Theillac et al. 2017 [24]	M	55	Nivolumab for CM	Blurred vision	6 weeks	6/6	6/12	Bilateral granulomatous anterior uveitis, bilateral papillitis, serous retinal detachment OS	Not tested	Not reported	Oral corticosteroids, topical corticosteroids	Yes	Complete resolution; BCVA 6/6 OU	Not reported	1 month
Tsui et al. 2017 [25]	M	Late 60s	Ipilimumab, Nivolumab for CM	Unspecified vision loss, photopsia	5 weeks	6/45	6/45	Serous retinal detachments and choroidal detachments OU	Not tested	Not reported	Oral corticosteroids	Yes	Partial resolution of serous RDs and choroidal effusion; 6/15 OD, 6/12 OS	Not reported	7 weeks
Acaba-Berrocal et al. 2018 [26]	F	65	Pembrolizumab for CM	Blurred vision	2 years	6/12	6/30	Birdshot-like chorioretinopathy OU	Not tested	Not reported	subTenon's triamcinolone injection OU	Not reported	Partial resolution; BCVA 6/12 OD, 6/18 OS	Not reported	6 months
Sandhu et al. 2019 [27]	F	55	Ipilimumab, pembrolizumab (+ trametinib + vemurafenib) for CM	Blurring of central vision	7 months	6/12	6/12	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Not reported	Topical corticosteroids, dorzolamide	Yes	Complete resolution; BCVA 6/6 OD, 6/7.5 OS	POD	4 months
Golash et al. 2020 [28]	F	82	Pembrolizumab for CM	Blurred vision	3 days	6/12	6/18	Serous retinal detachments and choroidal detachments OU, panuveitis OU, hypotony OU	Not tested	None	Topical corticosteroids, oral steroids, cataract surgery with intravitreal dexamethasone implant OU	Not reported	Initial decline to CF OD, 2/36 OS. Partial resolution. 6/24 OD, 6/24 OS	Not reported	6 months
Kemels et al. 2020 [29]	M	74	Nivolumab for NOMM	Unspecified vision loss	3 weeks	6/7.5	6/9.5	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Not reported	Oral corticosteroids	Yes	No reported change in vision	POD	1 month
Kemels et al. 2020 [29]	F	51	Nivolumab for NOMM	Unspecified visual loss, photopsia	1 month	6/9.5	6/6	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Sarcoid-like granulomatous reaction	Periocular corticosteroids OU, intravitreal corticosteroid implants OU, resection of primary tumor	Yes	Partial resolution, 6/7.5 OD, 6/7.5 OS	PR	10 months

**Supplemental Table 1.** Summary of published cases in systematic review (continued)

Publication	Sex	Age	Immuno-therapy	Visual symptom(s)	Symptom onset after starting immuno-therapy	BCVA at presentation		Ocular finding(s)	Anti-retinal antibodies detected	Concurrent systemic irAE	Treatment	Immuno-therapy stopped	Ocular outcome	Systemic outcome	Duration of follow-up
						OD	OS								
Miyamoto et al. 2020 [30]	M	73	Nivolumab for NOMM	Metamorphopsia OU	2 months	6/6	6/4.8	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Not reported	None	No	No follow up	POD	None
Elwood et al. 2021 [31]	F	65	Ipilimumab, Nivolumab for CM	Photopsia, visual field loss	18 months	6/12	6/15	MAR OU, chorioretinal leakage OU, venous leakage on FA OU, occult CNV OD	Anti-60 kDa retinal protein	Adrenal insufficiency	Intravitreal bevacizumab OD, subTenon's triamcinolone injection OS	Yes	Complete resolution of subretinal fluid OD; initial decline in BCVA OS to CF, partial resolution after subTenon's triamcinolone OS; improvement of visual field defects; BCVA 6/7.5 OD, 6/30 OS	Not reported	10 months
Whist et al. 2021 [32]	M	30	Ipilimumab + nivolumab for CM	Photopsia, floaters, nyctalopia	5 months	6/6	6/6	MAR OU; anterior & intermediate uveitis, CME, retinal periphlebitis OU	Not tested	Autoimmune hepatitis	IV and oral corticosteroids, mycophenolate, infliximab	Yes	No change in ERG deficits; BCVA 6/6 OU	Not reported	3 months
Lambert et al. 2021 [33]	F	54	Pembrolizumab for NOMM	Blurred vision, photopsia	3 months	6/6	6/6	Acute exudative polymorphous vitelliform maculopathy OU	Not tested	Autoimmune thyroiditis, Sarcoid-like granulomatous reaction	None	Yes	Complete resolution of subretinal fluid	PR	4 months
Yilmaz Tugan et al. 2021 [34]	M	60	Nivolumab for CM	Blurred vision	7 weeks	CF	CF	Serous retinal detachment OU, anterior uveitis OU	Not tested	Not reported	Oral corticosteroids, topical corticosteroids	No	Complete resolution, BCVA 6/6, 6/9.5	Not reported	6 months

CM = cutaneous melanoma; NOMM = non-ocular mucosal melanoma; MAR = melanoma-associated retinopathy; PR = partial response CR = complete response; POD = progression of disease