

Supplementary Online Content

George S, Motzer RJ, Hammers HJ, et al. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression: a subgroup analysis of a randomized clinical trial. *JAMA Oncol*. Published online May 12, 2016.
doi:10.1001/jamaoncol.2016.0775

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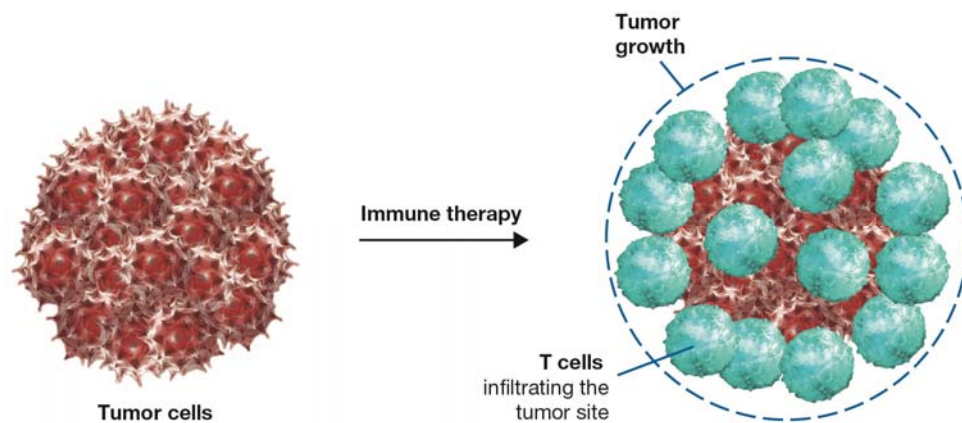
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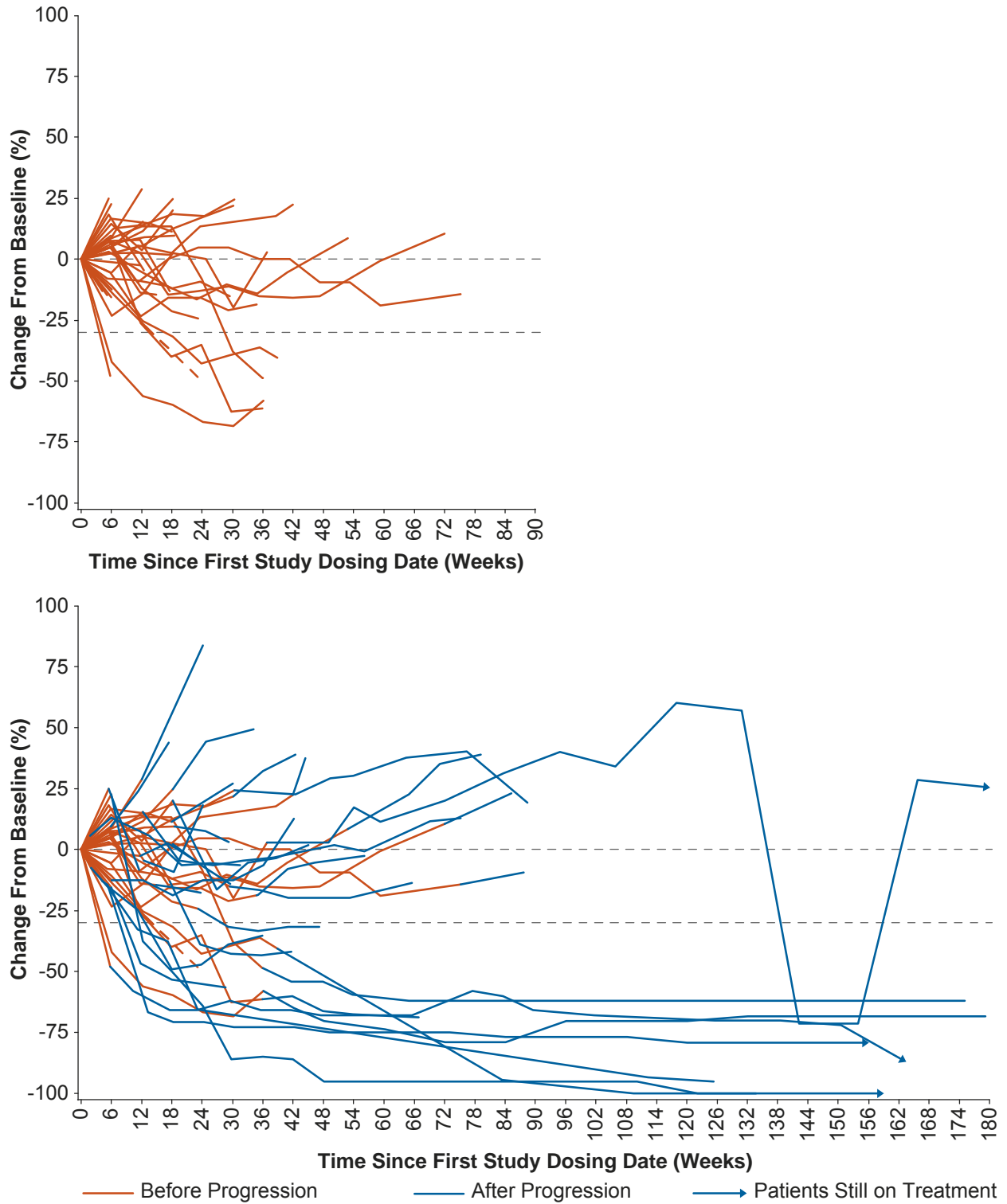
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Potential Mechanism for Tumor Flare Associated With Immunotherapy



eFigure 2. Change in Tumor Burden Over Time (Before and After First Progression)



eFigure 3. Narratives and Radiographic Scans of Patients Treated Beyond First Progression

A. The images are of a 70-year-old man, enrolled in the nivolumab trial described in this report, who was previously treated with sunitinib, everolimus, and pazopanib for metastatic RCC. While receiving nivolumab treatment, the patient had an initial increase in size of the metastatic lesions. The patient also demonstrated clinical benefit (maintained performance status and general well-being) and was tolerating treatment. Based on these results, the treating clinician determined that the patient could continue treatment beyond RECIST-defined progression. The patient improved clinically and had significant tumor shrinkage over several months. Seven months after initiating nivolumab treatment, the patient decided to discontinue treatment due to travel constraints involved with receiving nivolumab treatment. He was then switched to another medication after nivolumab discontinuation.

Patient 1

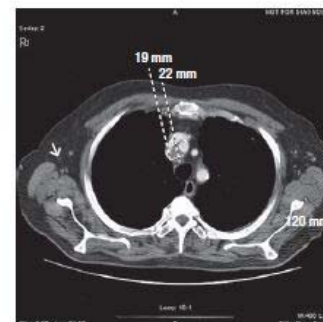
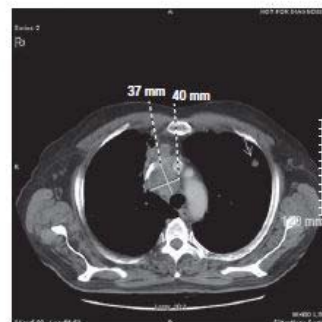
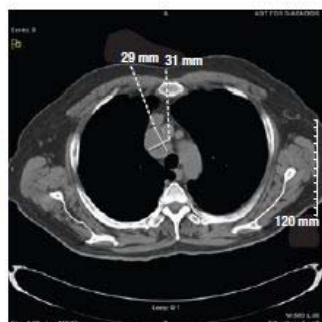
Baseline

6 weeks

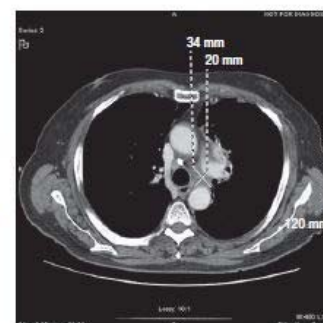
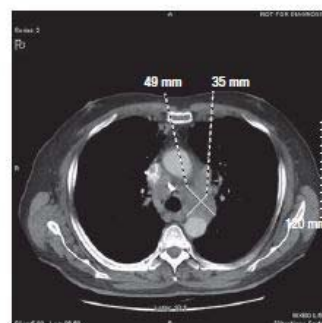
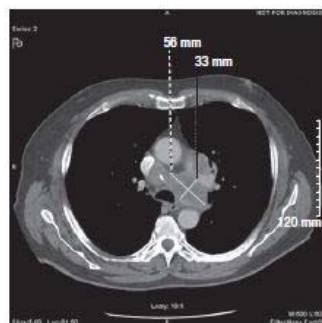
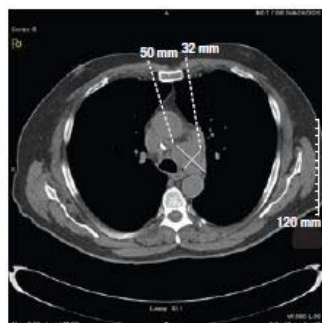
3 months

7 months

Lesion A
(lymph node)



Lesion B
(lymph node)



B. The images are of a 51-year-old man who had primary refractory disease that progressed on sunitinib within 3 months of initiation. This patient was treated with nivolumab in the trial described in this report. He presented with homonymous hemianopsia after 2 cycles (6 weeks) of nivolumab. The workup revealed 2 brain metastases (left occipital and left frontal) with surrounding edema. The restaging CT scan demonstrated minimal shrinkage of the marker lesions. After gamma knife therapy and steroid taper, he continued nivolumab beyond RECIST-defined first progression as he was tolerating the treatment and was deemed to have clinical benefit (tumor shrinkage of the target lesions, maintained performance status). Over the course of treatment this patient experienced a complete resolution of brain symptoms and continuing tumor shrinkage. At the 4-year mark (as of this report), he has no measurable tumors and is still on treatment.

Patient 2

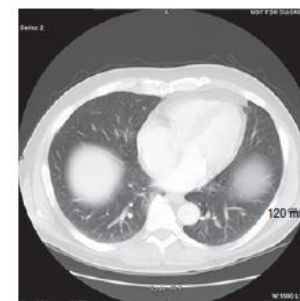
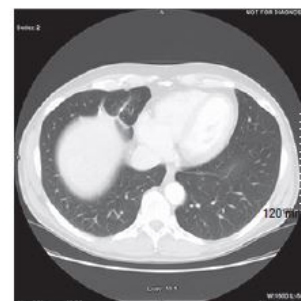
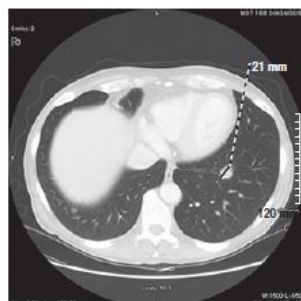
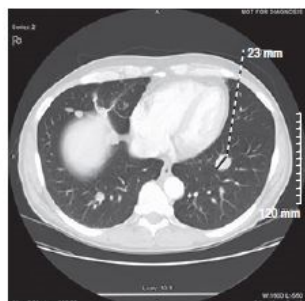
Baseline

6 weeks

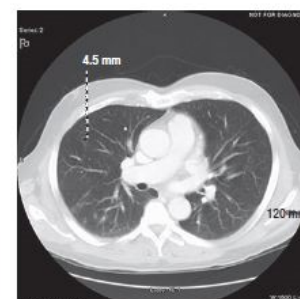
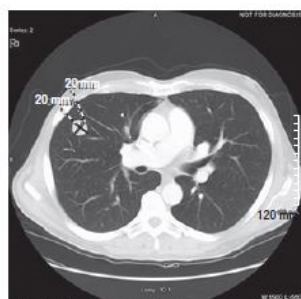
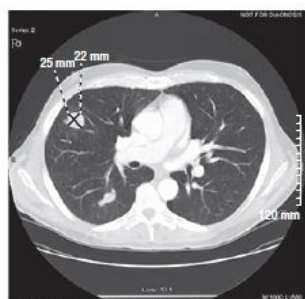
8 months

48 months

**Lesion A
(lung)**



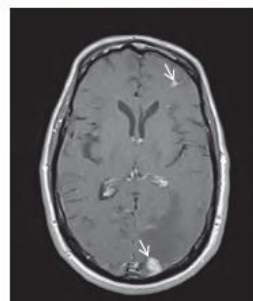
**Lesion B
(lung)**



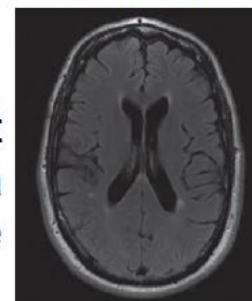
7 weeks

38 months

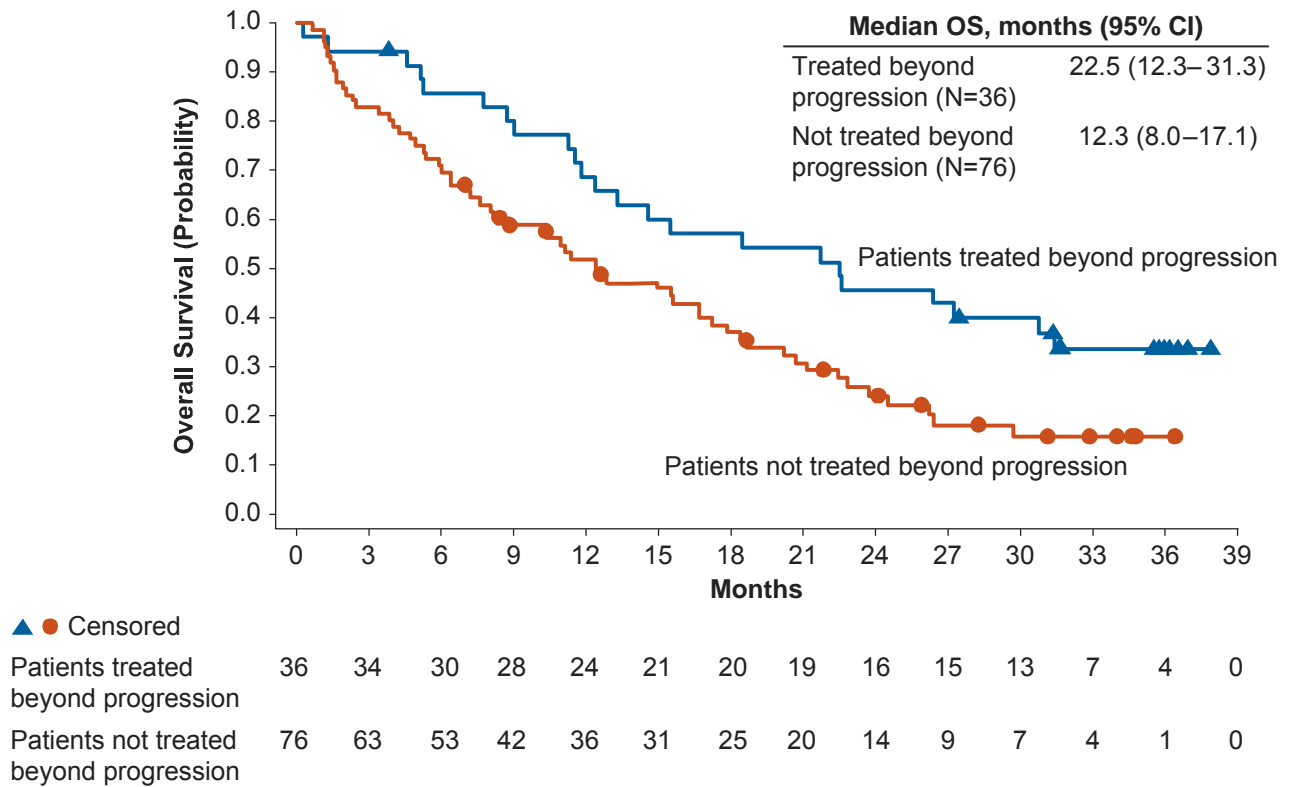
**New lesions C and D
(brain)**



**Post
gamma
knife**



eFigure 4. Landmark Analysis of Overall Survival 6 Weeks From First Progression



eTable 1. Summary of Patients Who Were Treated Briefly Beyond Progression

Patient Characteristics at Study Entry	Patients Treated Briefly Beyond Progression (n = 26)
Median age (range), years	60.5 (51.0-77.0)
Sex, n (%)	
Male	17 (65)
Female	9 (35)
MSKCC risk group, n (%)	
Favorable	8 (31)
Intermediate	12 (46)
Poor	6 (23)
Not reported	0
KPS, n (%)	
70 or 80	12 (46)
≥90	14 (54)
Number of evaluable sites, ^a n (%)	
1	5 (19)
≥2	21 (81)
Prior radiotherapy, n (%)	9 (35)
Number of prior systemic antiangiogenic regimens in the metastatic setting, n (%)	
1	8 (31)
2	5 (19)
≥3	13 (50)
Doses Received Overall and After Progression	Patients Treated Briefly Beyond Progression (n = 26)
Median number of doses received overall (range)	6 (3-15)
Median number of doses received after first progression (range)	2 (1-2)

eTable 2. Patient Disposition

Measure	Patients Treated Beyond Progression (n = 36)	Patients Not Treated Beyond Progression (n = 92)
Discontinued treatment, n (%)	32 (89)	92 (100)
Reasons for not continuing treatment, n (%)		
Disease progression	28 (78)	78 (85)
Drug toxicity	2 (6)	8 (9)
Adverse event unrelated to study drug	2 (6)	4 (4)
Death	0	1 (1)
Patient request	0	1 (1)

eTable 3. Karnofsky Performance Status and Target Lesion Status at First Progression

Characteristics	Patients Treated Beyond Progression (n = 36)	Patients Not Treated Beyond Progression (n = 92)
KPS, n (%)		
50 or 60	0	4 (4)
70 or 80	13 (36)	46 (50)
≥90	21 (58)	37 (40)
Not reported	2 (6)	5 (5)
Target lesion status at progression, n (%) ^a		
Increase in target lesions ^b	13 (36)	34 (37)
Appearance of new lesions	22 (61)	41 (45)
Increase in target lesions and appearance of new lesions	2 (6)	14 (15)

Abbreviation: KPS, Karnofsky performance status.

^aPercentages do not add up to 100% because not all factors attributed to progressive disease are shown (eg, progression of nontarget lesions).

^bAt least 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.

eTable 4. Treatment-Related Adverse Events in >10% of Patients

System Organ Class ^a	Patients Treated Beyond Progression (n=36)		Patients Not Treated Beyond Progression (n=92)	
	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Total patients with an event	29 (81)	2 (6)	61 (66)	13 (14)
Gastrointestinal disorders	16 (44)	0	23 (25)	3 (3)
Skin and subcutaneous tissue disorders	16 (44)	0	20 (22)	2 (2)
General disorders and administration-site conditions	15 (42)	1 (3)	32 (35)	3 (3)
Respiratory, thoracic, and mediastinal disorders	12 (33)	0	12 (13)	1 (1)
Musculoskeletal and connective tissue disorders	7 (19)	0	17 (18)	1 (1)
Metabolism and nutrition disorders	6 (17)	0	14 (15)	2 (2)
Nervous system disorders	6 (17)	0	13 (14)	2 (2)
Investigations (eg, blood tests, weight change)	5 (14)	0	11 (12)	3 (3)
Blood and lymphatic system disorders	4 (11)	0	8 (9)	2 (2)
Endocrine disorders	4 (11)	0	4 (4)	0
Immune system disorders	4 (11)	0	6 (7)	0
Infections and infestations	4 (11)	0	2 (2)	0

^a Includes events reported between the first dose and 30 days after last dose of study therapy.

eTable 5. Exposure-Adjusted Treatment-Related Adverse Events in >10% of Patients

System Organ Class^a	Patients Treated Beyond Progression (n = 36)	Patients Not Treated Beyond Progression (n = 92)
	Any grade, incidence rate/100PY^b	Any grade, incidence rate/100PY^b
Total incidence rate/100PY ^b for patients with an event	322.9	518.7
Skin and subcutaneous tissue disorders	63.1	73.7
Gastrointestinal disorders	59.3	69.5
General disorders and administration-site conditions	51.7	108.0
Respiratory, thoracic, and mediastinal disorders	32.7	33.5
Musculoskeletal and connective tissue disorders	18.1	52.1
Nervous system disorders	15.5	35.7
Metabolism and nutrition disorders	15.1	41.9
Investigations (eg, blood tests, weight change)	12.0	30.0
Endocrine disorders	9.9	10.3
Blood and lymphatic system disorders	9.8	19.8
Immune system disorders	9.2	15.1
Vascular disorders	6.9	14.7

^a Includes events reported between the first dose and 30 days after last dose of study therapy.

^b Number of patients with event × 100 person-years (PY) of exposure to first adverse event.

eTable 6. Treatment-Related Adverse Events in >2% of Patients Treated Beyond Progression

System Organ Class	Before Progression (n = 36)		After Progression (n = 36)	
	Any grade, n (%)	Grade 3 or 4, n (%)	Any grade, n (%)	Grade 3 or 4, n (%)
Total patients with an event	25 (69)	1 (3)	23 (64)	1 (3)
Skin and subcutaneous tissue disorders	11 (31)	0	8 (22)	0
Gastrointestinal disorders	10 (28)	0	10 (28)	0
General disorders and administration-site conditions	9 (25)	1 (3)	11 (31)	0
Respiratory, thoracic, and mediastinal disorders	4 (11)	0	8 (22)	0
Immune system disorders	3 (8)	0	1 (3)	0
Metabolism and nutrition disorders	3 (8)	0	3 (8)	0
Musculoskeletal and connective tissue disorders	3 (8)	0	5 (14)	0
Blood and lymphatic system disorders	2 (6)	0	2 (6)	0
Endocrine disorders	2 (6)	0	2 (6)	0
Infections and infestations	2 (6)	0	2 (6)	0
Injury, poisoning, and procedural complications	1 (3)	0	–	–
Nervous system disorders	1 (3)	0	5 (14)	0
Psychiatric disorders	1 (3)	0	1 (3)	0
Vascular disorders	1 (3)	0	2 (6)	1 (3)
Ear and labyrinth disorders	–	–	1 (3)	0
Eye disorders	0	0	1 (3)	0
Investigations (eg, blood tests, weight change)	0	0	5 (14)	0