Antibody Therapeutics

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ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

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Antibody immune checkpoint inhibitor success story «Keytruda»

Relevant for exam: Figure 1, 2 and Table 1, 2, 3

Immuno-checkpoint inhibitor successes before lambrolizumab

- Antibodies against CTLA-4 (e.g. ipilimumab) showed good results in melanoma and other cancer patients
- Nivolumab (also anti-PD-1) showed good results in Phase 1 with melanoma and other cancer patients
- BMS936559 (anti-PD-1L) showed good results in Phase 1 with melanoma and other cancer patients

Antibody name

- Name in pre-clinical research: MK-3475
- Name in this paper: Lambrolizumab
- New name (generic name): Pembrolizumab
- Market name: Keytruda

Development of Lambrolizumab

- Where does the antibody bind? PD-1 or PD-1L?
- Derived from mouse (Kd = 28 pM) and human antibody (IgG4): how was lambrolizumab engineered from the two pre-cursors?
- Binding affinity of lambrolizumab (50% effective concentration)?

Antibody humanization

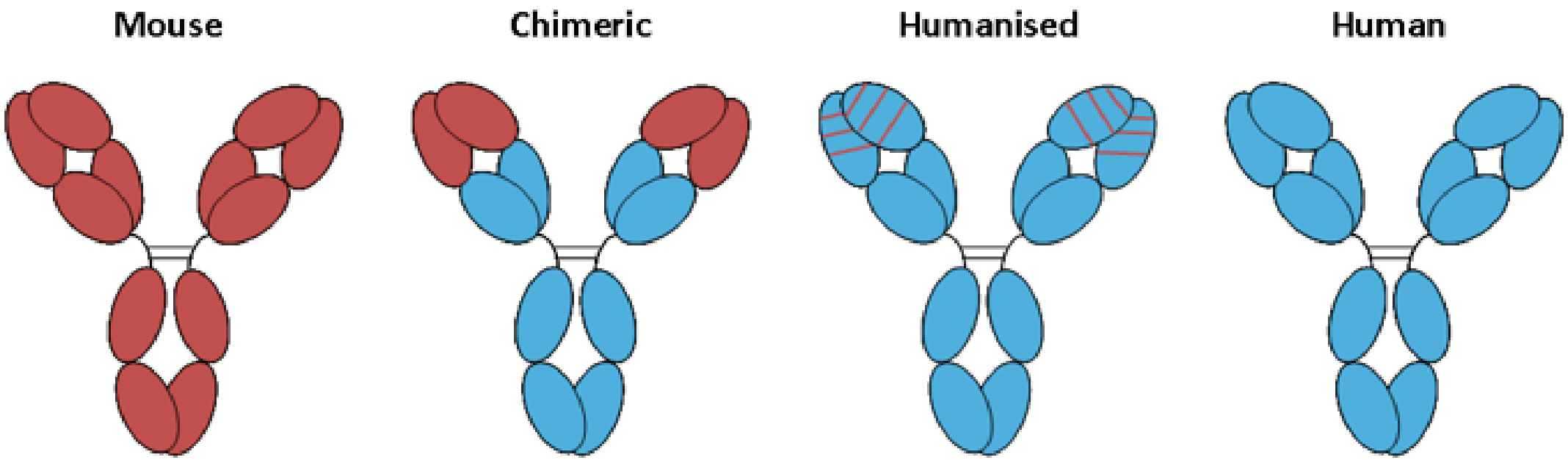

Table 1

Table 1. Baseline Characteristics of the Patients, According to Cohort.

Characteristic	10 mg/kg Every 2 Wk		10 mg/kg Every 3 Wk		2 mg/kg Every 3 Wk	Total (N=135)
	No Prior Ipilimumab (N=41)	Prior Ipilimumab (N=16)	No Prior Ipilimumab (N=24)	Prior Ipilimumab (N=32)	No Prior Ipilimumab (N=22)	
	number (percent)					
Sex						
Male	23 (56)	9 (56)	16 (67)	17 (53)	14 (64)	79 (59)
Female	18 (44)	7 (44)	8 (33)	15 (47)	8 (36)	56 (41)
Age (yr)						
Mean	60.4	59.4	67	57.3	58.6	60.4
Range	25–94	29–87	37–87	32–77	30–79	25–94
Race*						
Asian	0	0	2 (8)	0	0	2 (1)
White	41 (100)	16 (100)	22 (92)	32 (100)	22 (100)	133 (99)

- How many patients?
- Three treatment groups: which ones?
- Clinical trial phase 1, 2 or 3?
- Age of patients?

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	number (percent)					
ECOG performance status†						
Unknown	1 (2)	0	0	0	0	1 (1)
0	32 (78)	13 (81)	18 (75)	21 (66)	13 (59)	97 (72)
1	8 (20)	3 (19)	6 (25)	11 (34)	9 (41)	37 (27)
BRAF mutation status						
Mutant	13 (32)	1 (6)	1 (4)	5 (16)	6 (27)	26 (19)
Nonmutant	23 (56)	14 (88)	21 (88)	21 (66)	14 (64)	93 (69)
Unknown	5 (12)	1 (6)	2 (8)	6 (19)	2 (9)	16 (12)
Brain metastasis						
Yes	3 (7)	3 (19)	0	4 (12)	2 (9)	12 (9)
No	38 (93)	13 (81)	24 (100)	28 (88)	20 (91)	123 (91)

- What is ECOG?
- Disease state of patients?

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	number (percent)					
Lactate dehydrogenase						
Normal	23 (56)	11 (69)	16 (67)	17 (53)	13 (59)	80 (59)
Elevated‡	13 (32)	5 (31)	6 (25)	7 (22)	5 (23)	36 (27)
Unknown	5 (12)	0	2 (8)	8 (25)	4 (18)	19 (14)
M staging of extent of metastasis						
MX	0	0	0	1 (3)	0	1 (1)
M0	7 (17)	2 (12)	2 (8)	3 (9)	1 (5)	15 (11)
M1a	1 (2)	3 (19)	6 (25)	3 (9)	1 (5)	14 (10)
M1b	11 (27)	3 (19)	7 (29)	5 (16)	2 (9)	28 (21)
M1c	20 (49)	8 (50)	9 (38)	18 (56)	18 (82)	73 (54)
Unknown	2 (5)	0	0	2 (6)	0	4 (3)

- Most patients have metastasis at stage M1c. What is M1c?

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	number (percent)					
Previous treatment§						
No prior systemic treatment	16 (39)	0	12 (50)	0	14 (64)	42 (31)
Immunotherapy, excluding ipilimumab	11 (27)	4 (25)	5 (21)	10 (31)	4 (18)	34 (25)
Chemotherapy	11 (27)	8 (50)	9 (38)	14 (44)	5 (23)	47 (35)
BRAF inhibitor	4 (10)	0	1 (4)	4 (12)	1 (5)	10 (7)

- How were patients treated before?

Table 2

Table 2. Drug-Related Adverse Events.*

Drug-Related Event	All Grades (N=135)	Grade 3 or 4 (N=135)
	number (percent)	
Any	107 (79)	17 (13)
Hypothyroidism	11 (8)	1 (1)
Gastrointestinal disorder		
Diarrhea	27 (20)	1 (1)
Nausea	13 (10)	0
Abdominal pain	7 (5)	1 (1)
Generalized symptom		
Fatigue	41 (30)	2 (1)
Myalgia	16 (12)	0
Headache	14 (10)	0
Asthenia	13 (10)	0
Pyrexia	10 (7)	0
Chills	9 (7)	0
Decreased appetite	6 (4)	1 (1)
Increase in aminotransferase level		
AST	13 (10)	2 (1)
ALT	11 (8)	0
Renal failure	3 (2)	2 (1)
Respiratory disorder		
Cough	11 (8)	0
Dyspnea	6 (4)	0
Pneumonitis	6 (4)	0
Skin disorder		
Rash	28 (21)	3 (2)
Pruritus	28 (21)	1 (1)
Vitiligo	12 (9)	0

- What are adverse events «grade 1 to 4»?

Adverse events

Table Common Terminology Criteria for Adverse Events Grade and Clinical Severity[1]

Grade	Clinical severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

ADL indicates activities of daily living.

Table 3

Table 3. Objective Response Rate, According to Dosing Regimen and Status with Respect to Prior Therapy with Ipilimumab, as Assessed According to Two Criteria.*

Regimen and Ipilimumab Status	RECIST				Immune-Related Response	
	No. of Patients	Confirmed and Unconfirmed Objective Response	Confirmed Objective Response	Duration of Response†	No. of Patients	Confirmed Objective Response
		no. (% [95% CI])		*mo*		*no. (% [95% CI])*
10 mg/kg every 2 wk						
No prior ipilimumab	39	21 (54 [37–70])	19 (49 [32–65])‡	1.9–10.8	41	23 (56 [40–72])
Prior ipilimumab	13	8 (62 [32–86])	8 (62 [32–86])§	2.8–8.3	16	9 (56 [30–80])
Total	52	29 (56 [41–69])	27 (52 [38–66])	1.9–10.8	57	32 (56 [42–69])
10 mg/kg every 3 wk						
No prior ipilimumab	19	7 (37 [16–62])	5 (26 [9–51])	2.6–5.6	24	8 (33 [16–55])
Prior ipilimumab	26	9 (35 [17–56])	7 (27 [12–48])	2.8–8.3	32	7 (22 [9–40])
Total	45	16 (36 [22–51])	12 (27 [15–42])	2.6–8.3	56	15 (27 [16–40])
2 mg/kg every 3 wk, no prior ipilimumab	20	7 (35 [15–59])	5 (25 [9–49])¶	2.1–5.5	22	3 (14 [3–35])
Total‖	117	52 (44 [35–54])**	44 (38 [25–44])	1.9–10.8	135	50 (37 [29–45])

Table 3

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Regimen and Ipilimumab Status	RECIST				Immune-Related Response	
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10 mg/kg every 3 wk						
No prior ipilimumab	19	7 (37 [16–62])				
Prior ipilimumab	26	9 (35 [17–56])				
Total	45	16 (36 [22–51])	1			
2 mg/kg every 3 wk, no prior ipilimumab	20	7 (35 [15–59])				
Total‖	117	52 (44 [35–54])**	44			

- What is «RECIST»?
- What is «confirmed» versus «non-confiremd» objective response?

RECIST

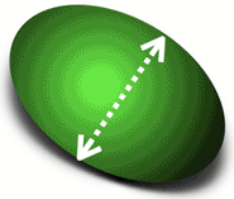
Criteria for target lesions

Tumours

CT scan: long axis ⩾ 10mm
Chest X-ray: long axis ⩾ 20mm

Malignant lymph nodes

Short axis diameter ⩾ 15mm



Selection of lesions

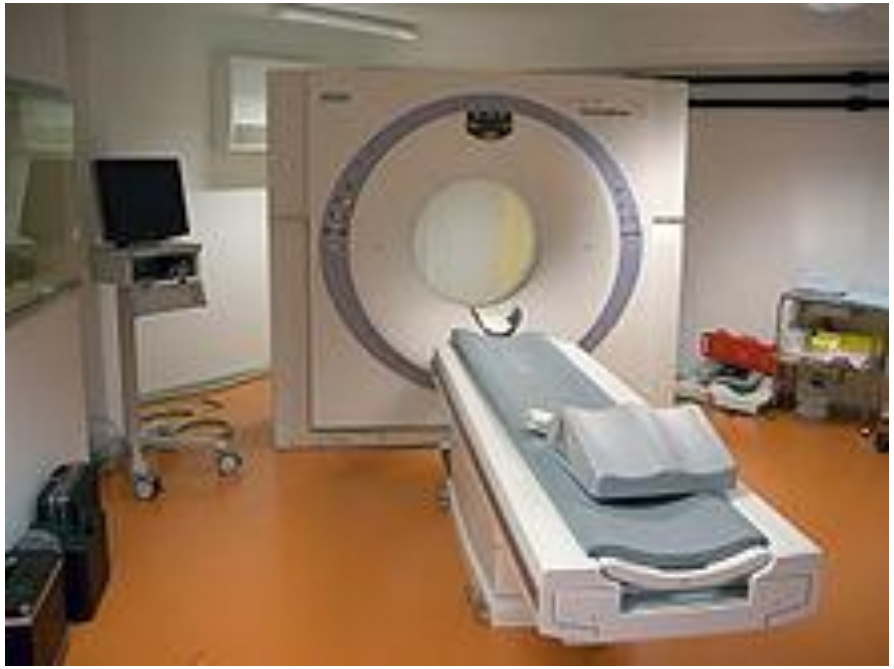
Choose 1 to 5 target lesions, equally distributed over affected organs (with a maximum of 2 per organ)

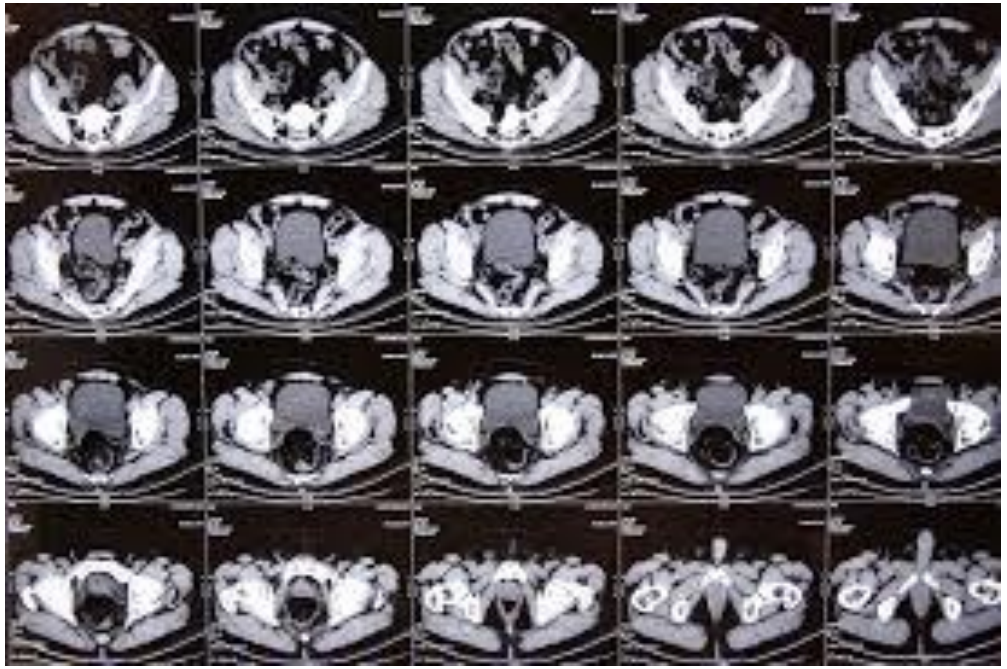
Preferably choose largest lesions

Preferably choose well-described lesions that are easy to measure

	WHO	RECIST 1.0	RECIST 1.1
Lesion measurement			
Imaging modality	No particular mention of imaging modality	CT, MRI and chest radiography are recommended modalities	Update with detailed guidance on use of MRI, PET/CT
Definition of measurable lesions	No limitation on minimal size of the lesion	CT: 10 mm spiral, 20 mm non-spiral	CT: 10 mm; delete reference to spiral scan
		Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)
Lymph node	Not mentioned	Not mentioned	CT: ≥ 15 mm short axis for target ≥ 10 - < 15 mm for non-target < 10 mm is non-pathological
Method of measurement	Cross-product of the longest diameter and the greatest perpendicular diameter	Longest diameter in the axial plane	Longest diameter in the axial plane
No. lesions to be measured	No particular no. lesions specified	10 lesions (5 per organ)	5 lesions (2 per organ)
Response evaluation			
Complete Response (CR)	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions and pathologic lymph nodes
Partial Response (PR)	≥ 50% decrease in the sum of the area (longest diameters multiplied by longest perpendicular diameters)	≥ 30% decrease in the sum of the longest diameter	≥ 30% decrease in the sum of the longest diameter
Stable Disease (SD)	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
Progressive Disease (PD)	≥ 25% increase in the sum of the area	≥ 20% increase smallest sum on study or new lesions	≥ 20% increase smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions

CT Scan





- What is «immune-related response»?
- What % of patients showed a «response»?

Table 3

egimen and Status with Respect to Prior Therapy with Ipilimumab, as Assessed

Regimen and Ipilimumab Status	RECIST				Immune-Related Response	
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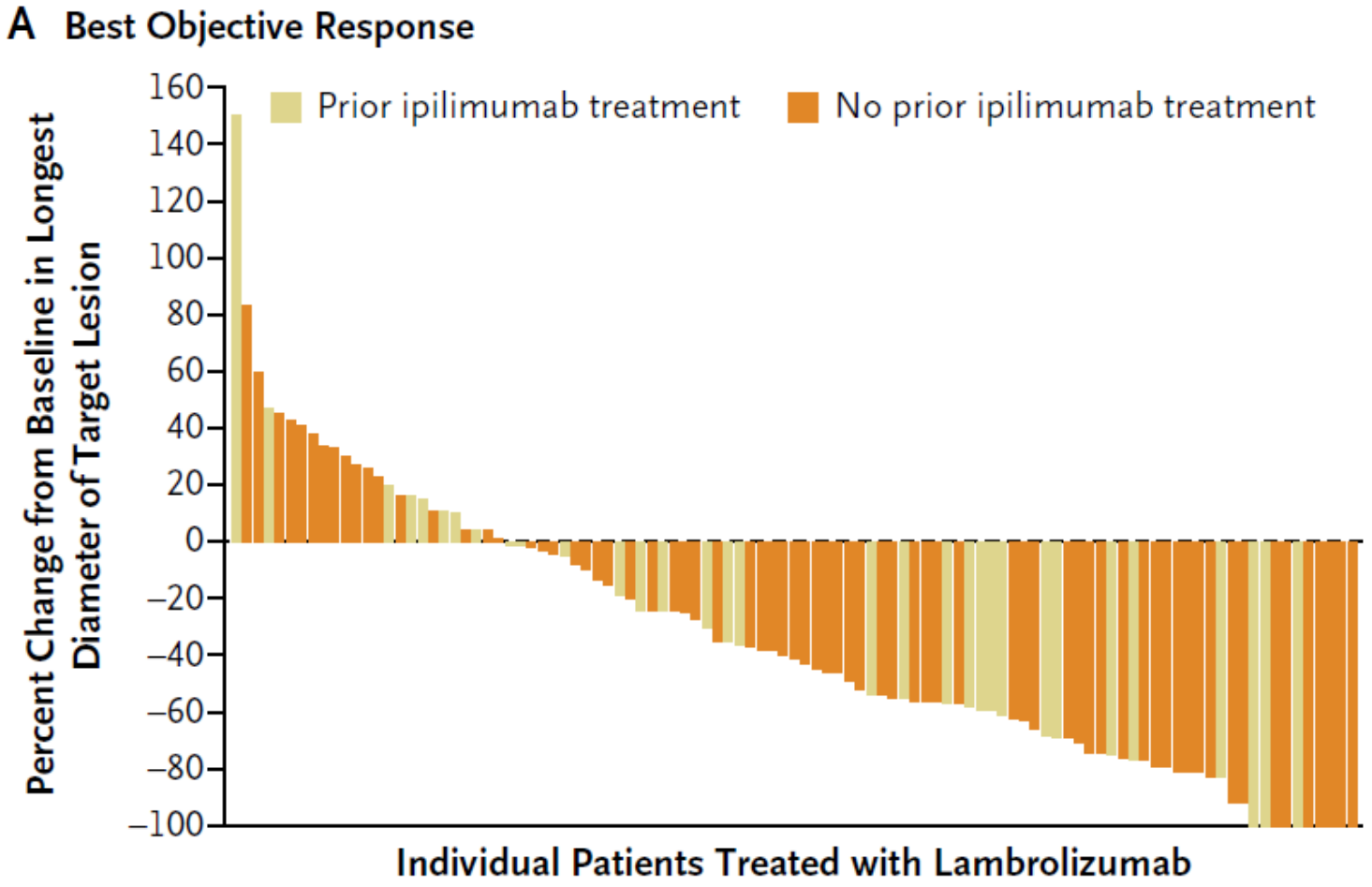
Immune-related response

Response	Definition	
	Choi criteria[20]	RECIST 1.1[28]
Complete response	Disappearance of all lesions No new lesions	Disappearance of all target lesions, all nodal lesions have short axis <10 mm
Partial response	A decrease in size ≥10% or a decrease in tumor attenuation (HU) ≥15% on CT No new lesions No obvious progression of nonmeasurable disease	≥30% decrease in the sum of diameters from baseline sum diameters
Progressive disease	An increase in tumor size ≥10% and does not meet criteria of PR by tumor attenuation on CT New lesions	≥20% increase in the smallest sum of diameters as reference with an absolute increase of ≥5 mm
Stable disease	Does not meet the above criteria	Does not meet the above criteria

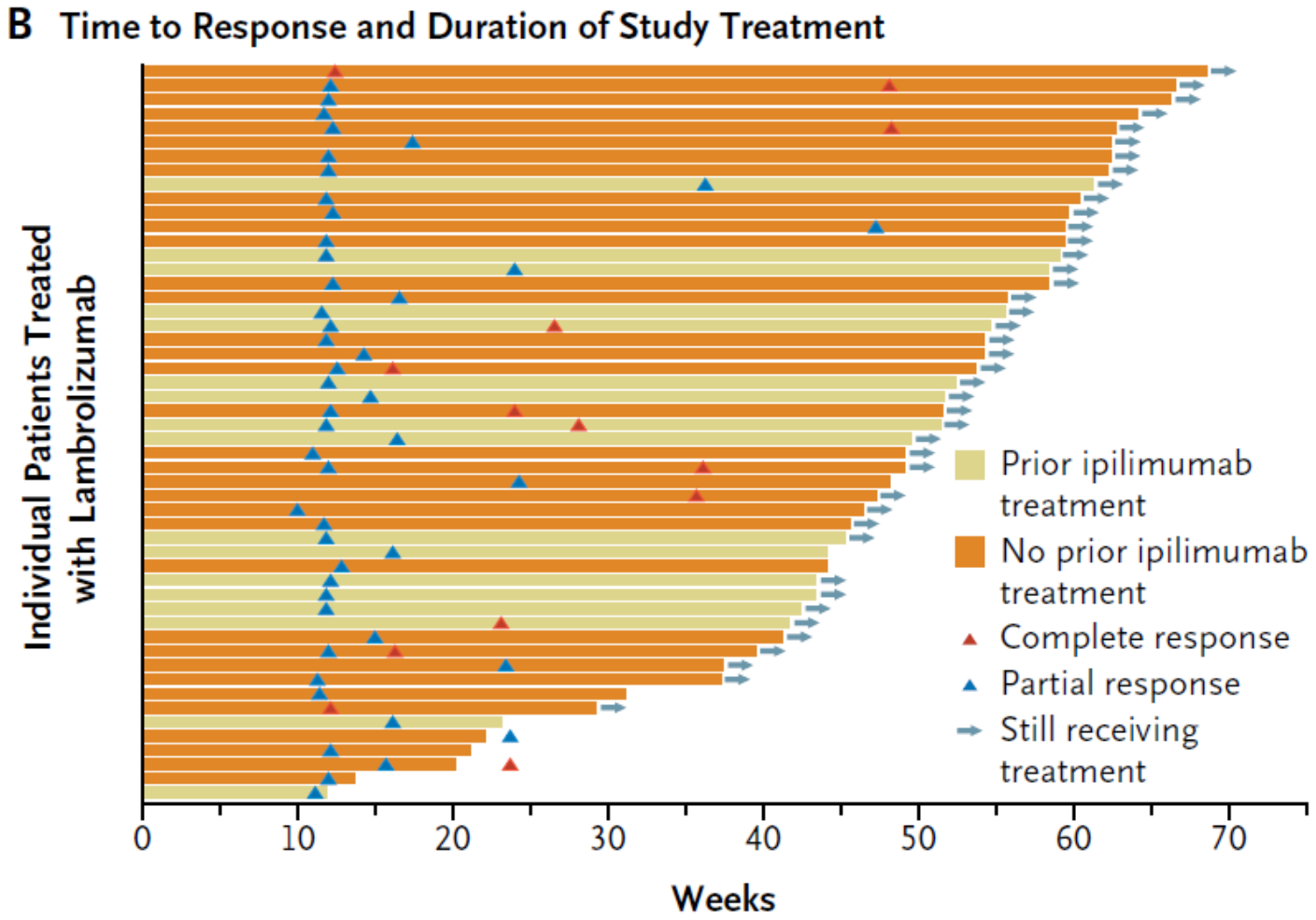
Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumors; CT, computed tomography; PR, partial response.

Figure 1a



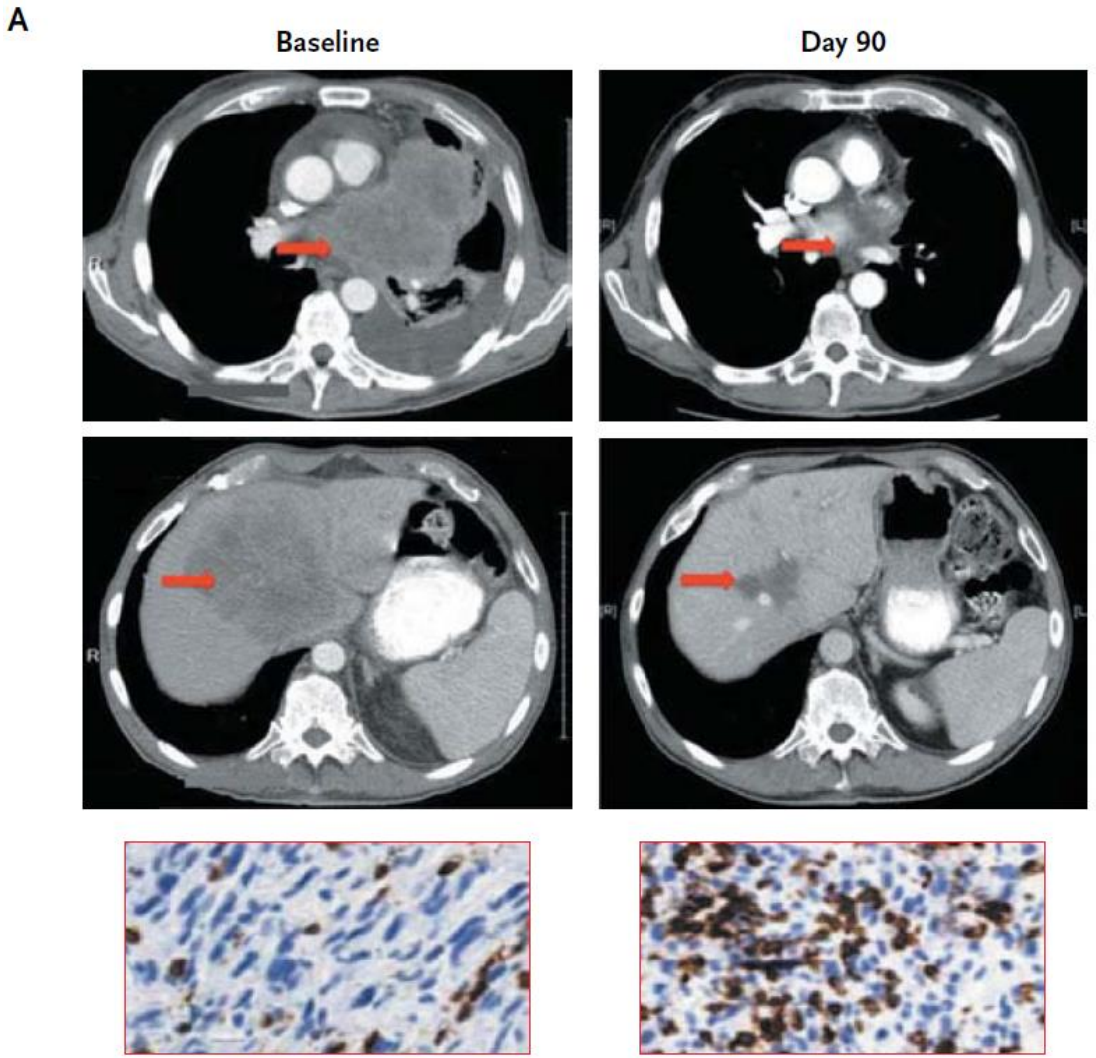
- What is «percent change from baseline in longest diameter of target lesion»?
- At which timepoints was this measured?
- How many patients showed a complete response (100%)?
- Are all 135 patients shown?

Figure 1b



- Which patients are shown here?
- How many patients shown here continued the treatment (at the end of the study)?
- For two patients, the «triangles» (= responses) are outside the treatment period. Why?

Figure 2a



- What do the «red» arrows show?
- The tissue sections (lower panels) show CD8 T-cell infiltrates (brown color). Why were they analyzed?

Figure 2b

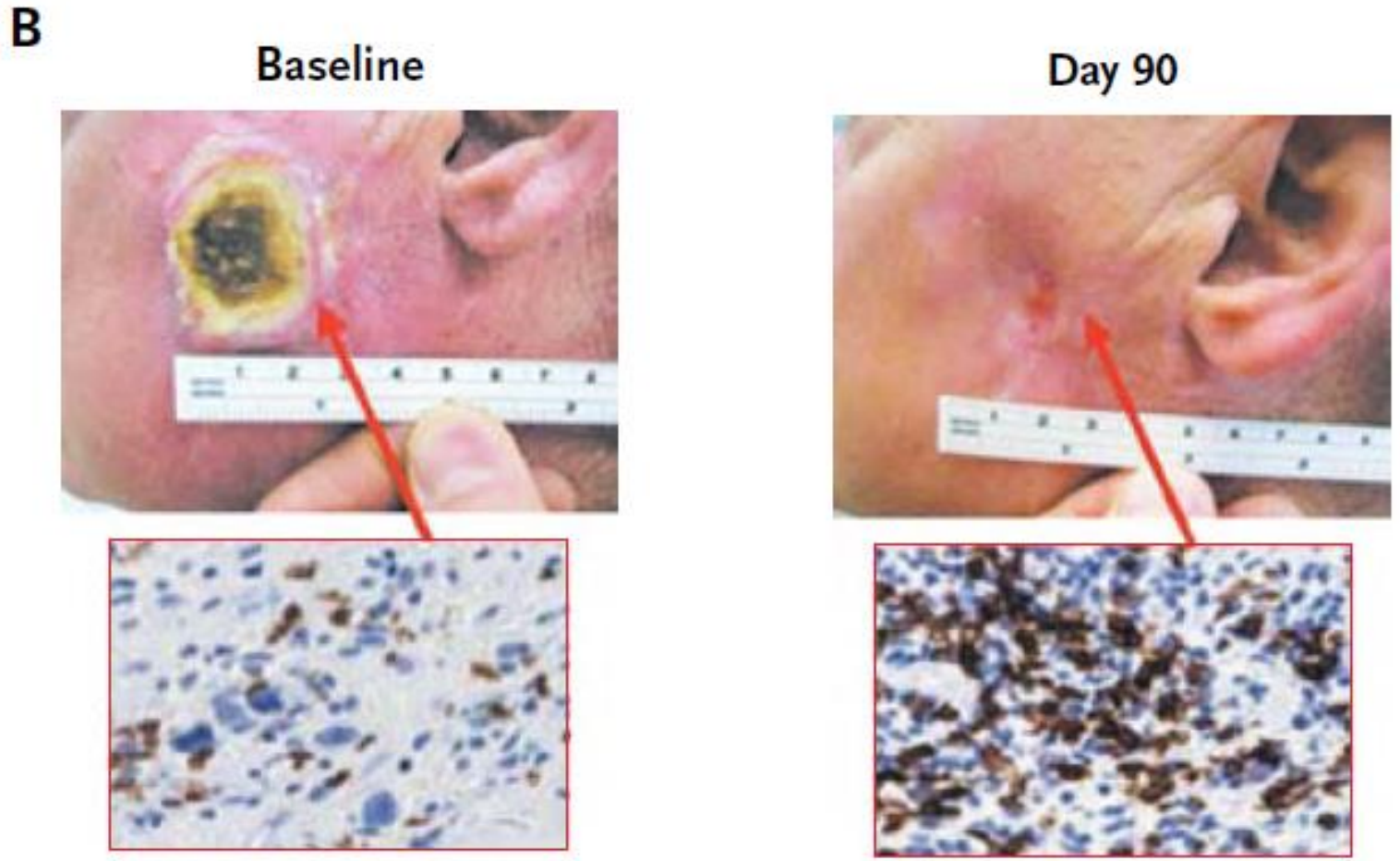
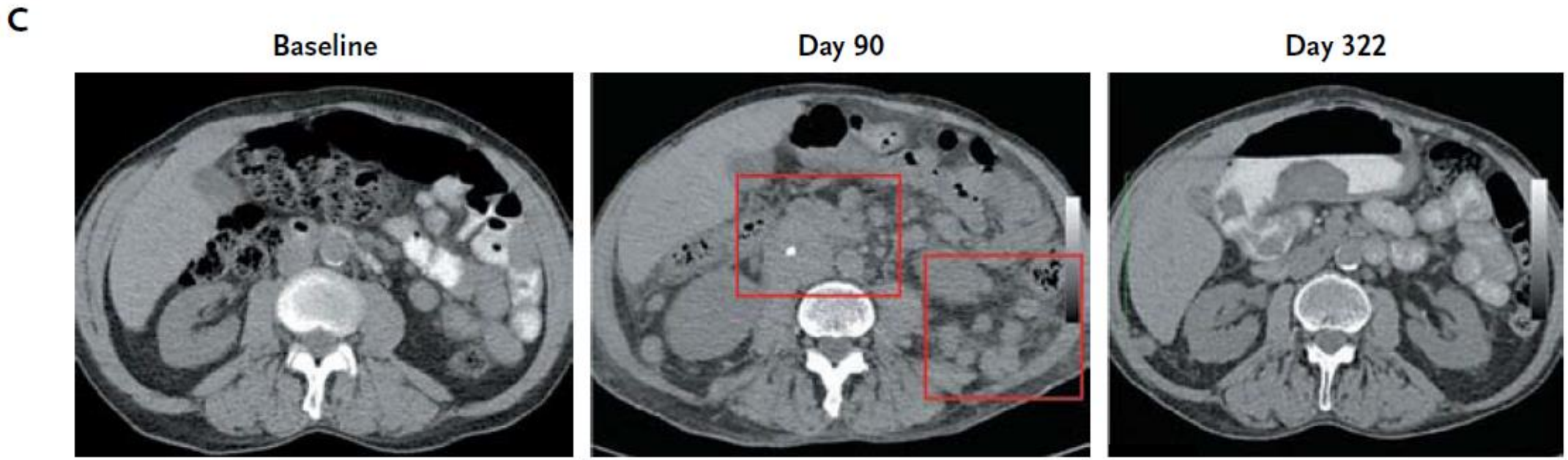


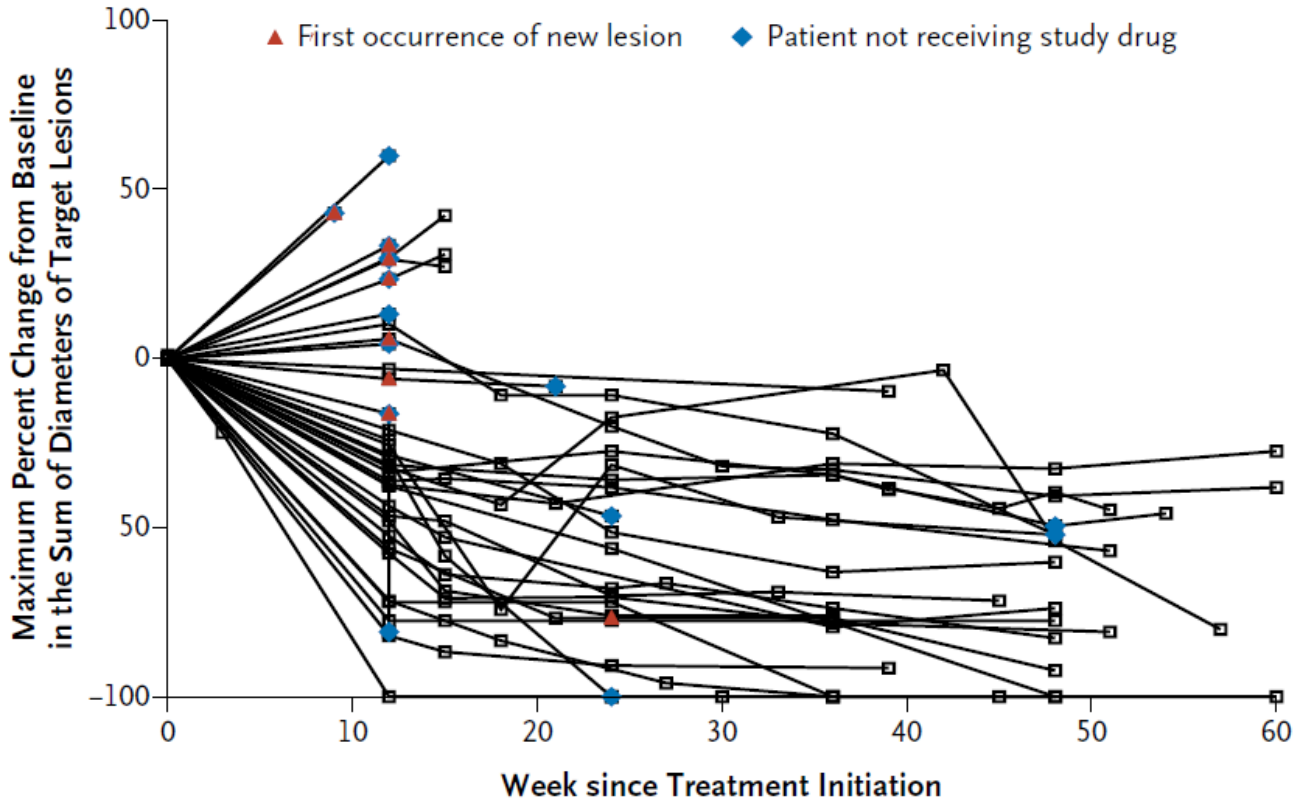
Figure 2c



- How was this patient treated? How did the disease develop?

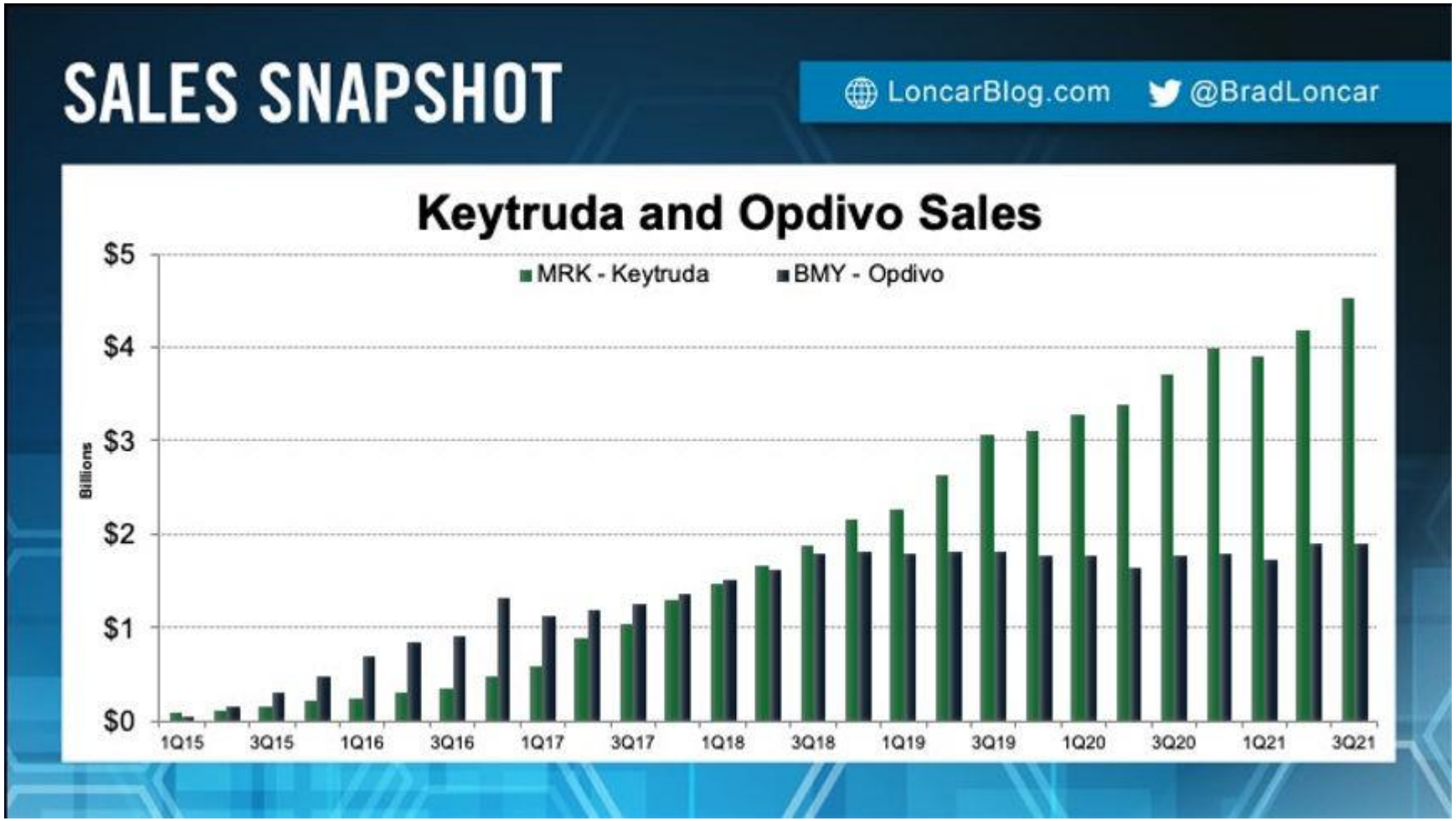
Figure 2d

D



- How were these patients treated? What does the Y-axis show?

Pembrolizumab (Keytruda) today



Pembrolizumab (Keytruda) today