

Supplementary Online Content

Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 Trial [published online February 13, 2020]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.6650

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

eMethods

Using Contemporary Controls and Adjusting for Time Trends in I-SPY2: The “Time Machine”

The initial statistical analyses in I-SPY2 compared investigational arms with concurrently randomized controls. The approach applied to the first five investigational arms: neratinib, veliparib+carboplatin, trebananib, ganitumab, and Akt inhibitor MK2206. In September 2013 the FDA granted accelerated approval for pertuzumab + trastuzumab + docetaxel as neoadjuvant therapy for high risk HER2+ breast cancer. Our investigators and DSMB required dropping the I-SPY 2 control arm for HER2+ subtypes because it did not contain pertuzumab, which we did by amendment in early 2014. At the time pertuzumab+trastuzumab+paclitaxel (for the first 12 weeks of neoadjuvant therapy) was an investigational arm in the trial, but it had accrued only 6 patients with none through surgery.

We wanted to be able to use the results for the original control arm but were concerned about the possibility of a drift in the prognosis of patient population over time and within patient subtype. We built a model that we call “the time machine” that adjusts for the results over time within each arm, including result for the investigational arms as well as those for control. Having multiple arms in the trial with different time periods during which they are accruing patients enabled bridging across the different eras of trial accrual. The time machine discounts results from the past, with more discounting if they are further in the past. The mathematical basis and motivation was a statistical model for bridging eras in sports.¹ We have used the time machine in all analyses in I-SPY2 since August 2015. The model description follows.

The control rate for an investigational arm is adjusted to the time period when the arm was being randomized to patients. Each investigational arm is compared directly against its concurrently randomized controls. The time machine strengthens this comparison by bridging to earlier controls via a series of direct comparisons. These direct comparisons are the various comparisons of arms that have been randomized in the trial, including comparisons of investigational arms against each other as well as against controls. The strength of this borrowing depends on the time-period overlaps among the various arms, both control and investigational arms. The greater uncertainty associated with results during periods of relatively low accrual and when fewer arms are being randomized is incorporated into the final analyses of the various arms.

Although the time-machine algorithm compares investigational arms against each other, between investigational arm comparisons will not be published or otherwise disclosed, not even to I-SPY2 personnel and investigators.

The time machine can be applied at any time to the totality of results in I-SPY2, including well after all the pCR results are available for an investigational arm. Indeed, the I-SPY2 DSMB has requested these analyses in their monthly reports, partly to help them understand how the time machine works. But the final analysis of pCR results for any investigational arm includes only the data available up until the results of surgery are available for all patients in that arm. As a consequence the published estimated pCR rates of the control arm within disease subtype vary somewhat over time. And because the effective control sample size increases over time, the precision of such estimates increases over time (this is, the width of the probability interval decreases).

We explicitly incorporate terms in the model to account for potential time trends in the pCR rate; we account for molecular subtype and treatment as well. This is accomplished using time-dependent offset terms in a logistic model. Time is set to 0 at each analysis. We partition time in the past into bins of 90 days each. The index of the most recent bin, that for the previous 0–90 days, is 1. The index of the bin 91–180 days in the past is 2. And so on. Let t_i be the index of the bin for the randomization time of patient i .

We model time-trend parameters $\delta(t)$ within each bin t . These are additive parameters in the model for the log-odds ratio of pCR rate for each investigational arm compared with control. We use two sets of time-trend parameters $\delta_+(t)$ for HER2-positive and $\delta_-(t)$ for HER2-negative. Consider patient i who has subtype (HR–, HER2+, MP–) and was randomized 750 days before present. Her bin t_i is 9 and her time-trend offset is $\delta_+(9)$.

Suppressing subscripts + and – for both HER2+ and HER2–, we set $\delta(t) = 0$ for $t=1,2,3,4$. That means the previous year’s results count fully in the analysis. Further in the past, that is, for $t > 4$, $\{\delta(t)\}$ is a second-order Normal Dynamic Linear Model (NDLM).² The NDLM uses the data within bins to estimate the respective log-odds ratios, but it also serves to smooth the effect across bins.

The time machine has the following structure for both HER2+ and HER2-, again suppressing the + and - subscripts:

$$\begin{aligned}\delta(1) &= \delta(2) = \dots = \delta(4) = 0 \\ \delta(5) &\sim N(\mu_0, \tau_0^2) \\ \delta(6) - \delta(5) &\sim N(\mu_1, \tau_1^2) \\ \delta(t) - 2\delta(t-1) + \delta(t-2) &\sim N(0, \tau^2) \text{ for } t > 6 \\ \tau^2 &\sim IG(\alpha, \beta)\end{aligned}$$

In this notation, $N(\mu, \sigma^2)$ refers to a normal distribution with mean μ and standard deviation σ and IG stands for inverse gamma. The parameters of the prior distributions are $\mu_0 = \mu_1 = 0$, $\tau_0^2 = \tau_1^2 = 0.001$, $\alpha=1$, and $\beta=0.001$.

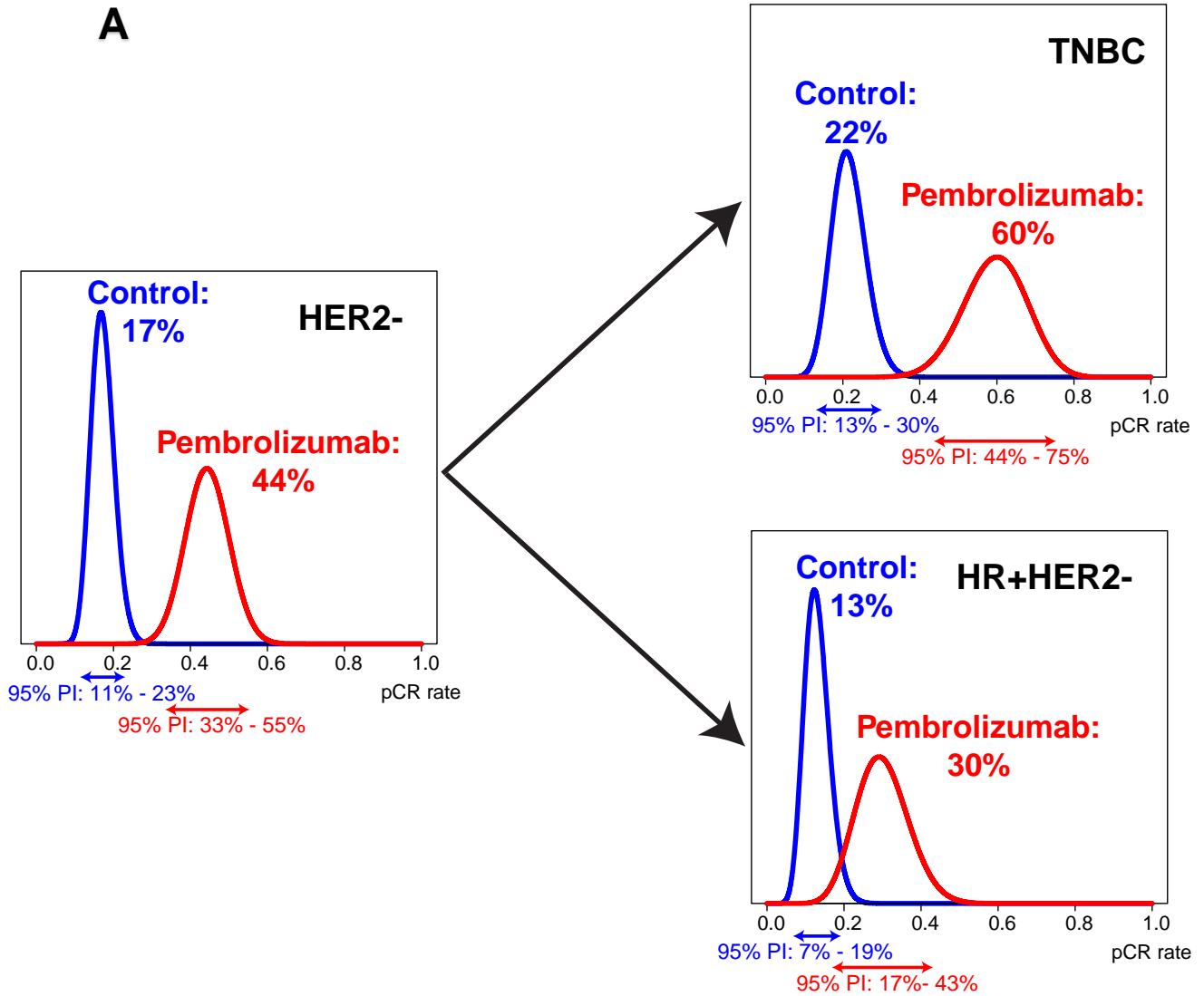
eTable 1: Baseline characteristics of participants in the pembrolizumab and control arms.

Characteristic	Pembrolizumab (n = 69)	Control (n=181)
Median age (range) - years	50 (27-71)	47 (24–77)
Ethnicity, n (%)		
White	56 (81%)	138 (76%)
African American	6 (9%)	27 (14.9%)
Asian	3 (4%)	13 (7%)
Other/Mixed	4 (6%)	3 (2%)
HR Status, n (%)		
Positive	40 (58%)	96 (53%)
Negative	29 (42%)	85 (47%)
Median Longest Tumor size by MRI , cm (range)	3.6 (1.9-13.0)	3.9 (1.2-15.0)
Node status , n (%)		
Palpable	30 (43%)	75 (41%)
Non-palpable	36 (52%)	79 (44%)
Missing	3 (4%)	27 (15%)

eFigure 1: Final probability distributions and RCB classifications.

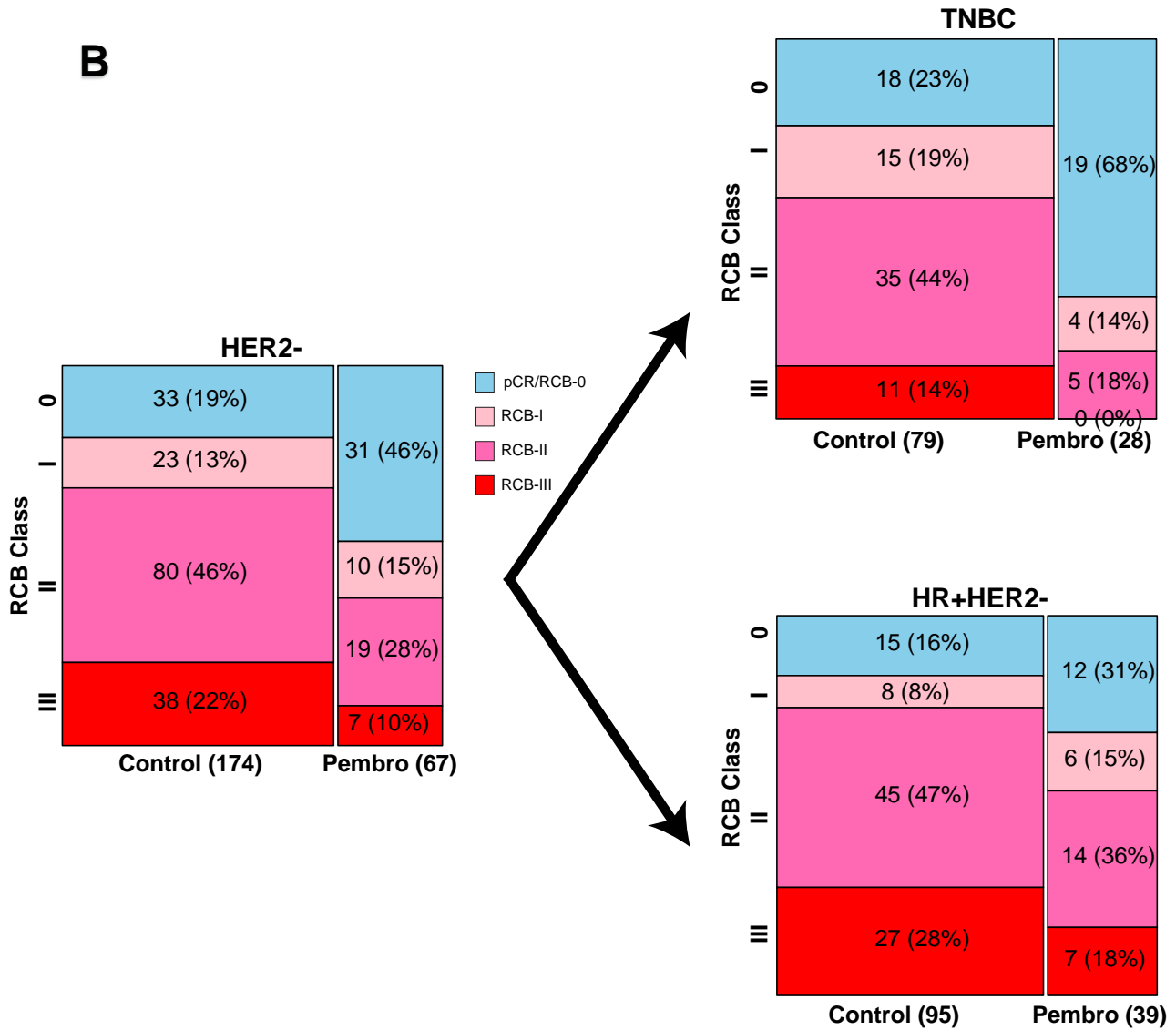
(A) Probability distributions for the pembrolizumab and control arms within each of the predefined biomarker signatures. The corresponding 95% probability intervals (PIs) are represented by the arrows along the x axis for each. The mean of each distribution is the estimated pathological complete response rate.

(B) next page

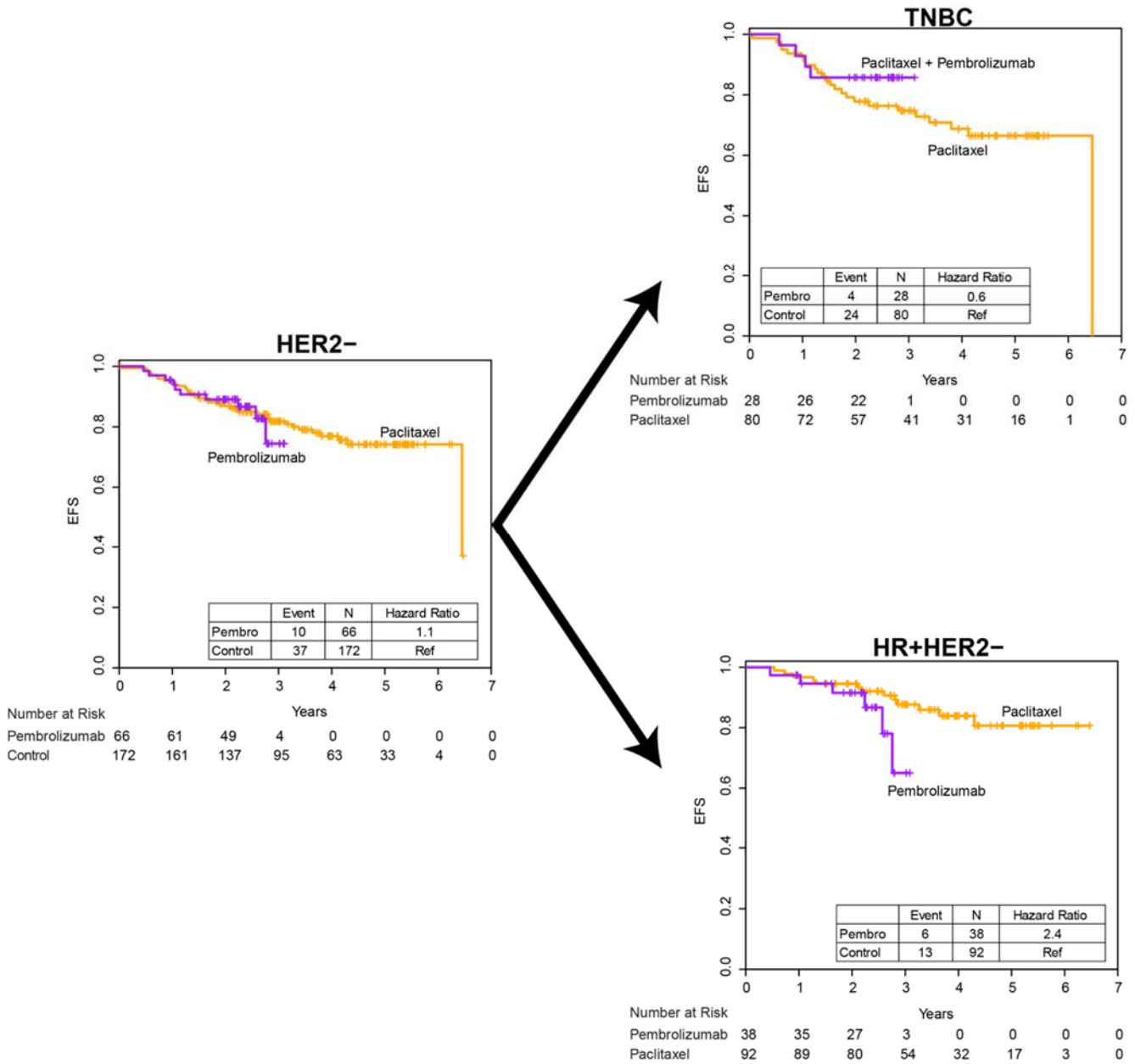


eFigure 1 ... continued

(B) Residual cancer burden classifications assessed in surgical specimens for each of the three biomarker signatures. In both panels (A) and (B), the triple-negative (top right) and HR-positive/HER2-negative (bottom right) signatures are subsets of the HER2-negative signature (left). Two patients in the pembrolizumab arm and seven in the control arm did not proceed to surgery and are thus not included in the RCB analysis.



eFigure 2: Event-free survival (EFS) by signature. Kaplan-Meier plots of event-free survival for participants in the pembrolizumab 4-cycle arm (purple) and control population (orange). Median follow up in the pembrolizumab arm is 2.4 years and 3.5 years for the control arm. The HER2- cohort is shown on the left, the triple-negative (TNBC) on upper right and HR-positive/HER2-negative on lower right.



eTable 2: All Adverse events reported within 180 days of last treatment. Adverse events (any grade) reported within 180 days of last investigational agent dose* with >1% frequency in either arm. AEs were subdivided into those that occurred within 30 days and between 30-180 days of last dose.

Code Term	Pembrolizumab (n=69)			Control (n=181)		
	<30 Days	30-180 Days	Total	<30 Days	30-180 Days	Total
Abdominal discomfort	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Abdominal distension	4 (5.8%)	1 (1.4%)	5 (7.2%)	4 (2.2%)	0 (0%)	4 (2.2%)
Abdominal pain	21 (30.4%)	1 (1.4%)	22 (31.9%)	9 (5%)	9 (5%)	18 (9.9%)
Abdominal pain upper	4 (5.8%)	1 (1.4%)	5 (7.2%)	8 (4.4%)	1 (0.6%)	9 (5%)
Acne	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Adnexa uteri pain	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Adrenal insufficiency**	1 (1.4%)	5 (7.2%)	6 (8.7%)	0 (0%)	0 (0%)	0 (0%)
Agitation	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Akathisia	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Alanine aminotransferase increased	15 (21.7%)	0 (0%)	15 (21.7%)	14 (7.7%)	3 (1.7%)	17 (9.4%)
Alopecia	44 (63.8%)	2 (2.9%)	46 (66.7%)	117 (64.6%)	12 (6.6%)	129 (71.3%)
Amenorrhoea	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	3 (1.7%)	6 (3.3%)
Amnesia	1 (1.4%)	0 (0%)	1 (1.4%)	3 (1.7%)	0 (0%)	3 (1.7%)
Anaemia	14 (20.3%)	9 (13%)	23 (33.3%)	17 (9.4%)	18 (9.9%)	35 (19.3%)
Anal abscess	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Angina pectoris	1 (1.4%)	0 (0%)	1 (1.4%)	4 (2.2%)	3 (1.7%)	7 (3.9%)
Anorexia	14 (20.3%)	3 (4.3%)	17 (24.6%)	26 (14.4%)	12 (6.6%)	38 (21%)
Anxiety	8 (11.6%)	5 (7.2%)	13 (18.8%)	31 (17.1%)	9 (5%)	40 (22.1%)
Aphthous stomatitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Arthralgia	23 (33.3%)	1 (1.4%)	24 (34.8%)	47 (26%)	2 (1.1%)	49 (27.1%)
Arthritis	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Arthropod bite	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Aspartate aminotransferase increased	9 (13%)	0 (0%)	9 (13%)	10 (5.5%)	3 (1.7%)	13 (7.2%)
Asthenia	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Axillary pain	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Back pain	11 (15.9%)	2 (2.9%)	13 (18.8%)	19 (10.5%)	10 (5.5%)	29 (16%)
Balance disorder	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Band neutrophil count increased	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Blepharospasm	2 (2.9%)	0 (0%)	2 (2.9%)	4 (2.2%)	0 (0%)	4 (2.2%)
Blister	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Blood alkaline phosphatase increased	1 (1.4%)	1 (1.4%)	2 (2.9%)	7 (3.9%)	0 (0%)	7 (3.9%)

Blood bilirubin increased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Blood creatinine increased	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	0 (0%)	3 (1.7%)
Blood glucose	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Blood thyroid stimulating hormone decreased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Bone pain	17 (24.6%)	5 (7.2%)	22 (31.9%)	47 (26%)	9 (5%)	56 (30.9%)
Breast discomfort	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Breast oedema	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Breast pain	8 (11.6%)	2 (2.9%)	10 (14.5%)	22 (12.2%)	8 (4.4%)	30 (16.6%)
Breast tenderness	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Bronchitis	1 (1.4%)	1 (1.4%)	2 (2.9%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Burning sensation	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Bursitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Candidiasis	3 (4.3%)	1 (1.4%)	4 (5.8%)	4 (2.2%)	0 (0%)	4 (2.2%)
Catheter related complication	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Catheter site erythema	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Catheter site infection	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Catheter site inflammation	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Catheter site pain	3 (4.3%)	0 (0%)	3 (4.3%)	7 (3.9%)	1 (0.6%)	8 (4.4%)
Catheter site pruritus	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Catheter site rash	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Cellulitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Cheilitis	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Chest discomfort	2 (2.9%)	1 (1.4%)	3 (4.3%)	1 (0.6%)	0 (0%)	1 (0.6%)
Chest pain	1 (1.4%)	0 (0%)	1 (1.4%)	3 (1.7%)	2 (1.1%)	5 (2.8%)
Chills	5 (7.2%)	0 (0%)	5 (7.2%)	10 (5.5%)	2 (1.1%)	12 (6.6%)
Cholecystitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Claustrophobia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Cognitive disorder	3 (4.3%)	0 (0%)	3 (4.3%)	7 (3.9%)	1 (0.6%)	8 (4.4%)
Colitis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Computerised tomogram abnormal	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Constipation	28 (40.6%)	10 (14.5%)	38 (55.1%)	74 (40.9%)	15 (8.3%)	89 (49.2%)
Contusion	0 (0%)	2 (2.9%)	2 (2.9%)	12 (6.6%)	1 (0.6%)	13 (7.2%)
Cough	19 (27.5%)	5 (7.2%)	24 (34.8%)	29 (16%)	10 (5.5%)	39 (21.5%)
Decreased appetite	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Dehydration	1 (1.4%)	2 (2.9%)	3 (4.3%)	7 (3.9%)	3 (1.7%)	10 (5.5%)
Depressed mood	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Depression	9 (13%)	3 (4.3%)	12 (17.4%)	14 (7.7%)	7 (3.9%)	21 (11.6%)
Dermatitis	2 (2.9%)	0 (0%)	2 (2.9%)	4 (2.2%)	0 (0%)	4 (2.2%)
Dermatitis acneiform	13 (18.8%)	1 (1.4%)	14 (20.3%)	29 (16%)	5 (2.8%)	34 (18.8%)
Dermatitis bullous	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Dermatitis contact	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)

Dermatosis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	29 (42%)	10 (14.5%)	39 (56.5%)	60 (33.1%)	10 (5.5%)	70 (38.7%)
Disturbance in attention	7 (10.1%)	0 (0%)	7 (10.1%)	7 (3.9%)	0 (0%)	7 (3.9%)
Dizziness	19 (27.5%)	2 (2.9%)	21 (30.4%)	26 (14.4%)	8 (4.4%)	34 (18.8%)
Drug tolerance decreased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Dry eye	5 (7.2%)	1 (1.4%)	6 (8.7%)	10 (5.5%)	4 (2.2%)	14 (7.7%)
Dry mouth	7 (10.1%)	3 (4.3%)	10 (14.5%)	13 (7.2%)	2 (1.1%)	15 (8.3%)
Dry skin	16 (23.2%)	2 (2.9%)	18 (26.1%)	23 (12.7%)	2 (1.1%)	25 (13.8%)
Dysgeusia	16 (23.2%)	6 (8.7%)	22 (31.9%)	34 (18.8%)	7 (3.9%)	41 (22.7%)
Dyskinesia	2 (2.9%)	1 (1.4%)	3 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Dysmenorrhoea	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Dyspareunia	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Dyspepsia	10 (14.5%)	1 (1.4%)	11 (15.9%)	21 (11.6%)	5 (2.8%)	26 (14.4%)
Dysphagia	2 (2.9%)	1 (1.4%)	3 (4.3%)	4 (2.2%)	0 (0%)	4 (2.2%)
Dysphasia	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Dysphonia	3 (4.3%)	0 (0%)	3 (4.3%)	3 (1.7%)	0 (0%)	3 (1.7%)
Dyspnoea	17 (24.6%)	3 (4.3%)	20 (29%)	23 (12.7%)	12 (6.6%)	35 (19.3%)
Dysuria	4 (5.8%)	0 (0%)	4 (5.8%)	4 (2.2%)	1 (0.6%)	5 (2.8%)
Ear discomfort	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Ear pain	3 (4.3%)	1 (1.4%)	4 (5.8%)	11 (6.1%)	0 (0%)	11 (6.1%)
Ecchymosis	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Ejection fraction decreased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (1.1%)
Embolism	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Emotional disorder	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Epistaxis	17 (24.6%)	0 (0%)	17 (24.6%)	29 (16%)	1 (0.6%)	30 (16.6%)
Eructation	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Erythema	3 (4.3%)	2 (2.9%)	5 (7.2%)	13 (7.2%)	3 (1.7%)	16 (8.8%)
Erythema multiforme	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Eye discharge	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Eye irritation	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Eye pain	3 (4.3%)	1 (1.4%)	4 (5.8%)	1 (0.6%)	0 (0%)	1 (0.6%)
Eye pruritus	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Eye swelling	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Eyelid function disorder	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Face oedema	4 (5.8%)	0 (0%)	4 (5.8%)	3 (1.7%)	0 (0%)	3 (1.7%)
Faecal incontinence	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Fall	1 (1.4%)	1 (1.4%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Fatigue	51 (73.9%)	9 (13%)	60 (87%)	133 (73.5%)	19 (10.5%)	152 (84%)
Febrile neutropenia	1 (1.4%)	5 (7.2%)	6 (8.7%)	7 (3.9%)	6 (3.3%)	13 (7.2%)
Feeling abnormal	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Flank pain	3 (4.3%)	1 (1.4%)	4 (5.8%)	0 (0%)	0 (0%)	0 (0%)

Flatulence	2 (2.9%)	0 (0%)	2 (2.9%)	3 (1.7%)	2 (1.1%)	5 (2.8%)
Flushing	8 (11.6%)	0 (0%)	8 (11.6%)	18 (9.9%)	0 (0%)	18 (9.9%)
Folliculitis	4 (5.8%)	0 (0%)	4 (5.8%)	11 (6.1%)	1 (0.6%)	12 (6.6%)
Fracture	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Frequent bowel movements	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Fungal infection	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Furuncle	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Gait disturbance	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Gastritis	4 (5.8%)	0 (0%)	4 (5.8%)	4 (2.2%)	0 (0%)	4 (2.2%)
Gastrointestinal pain	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Gastroesophageal reflux disease	8 (11.6%)	2 (2.9%)	10 (14.5%)	29 (16%)	5 (2.8%)	34 (18.8%)
Genital herpes	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Gingival infection	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Granulocyte percentage	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Groin pain	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Haematochezia	2 (2.9%)	1 (1.4%)	3 (4.3%)	4 (2.2%)	0 (0%)	4 (2.2%)
Haematocrit decreased	1 (1.4%)	1 (1.4%)	2 (2.9%)	3 (1.7%)	5 (2.8%)	8 (4.4%)
Haematoma	2 (2.9%)	1 (1.4%)	3 (4.3%)	2 (1.1%)	3 (1.7%)	5 (2.8%)
Haematuria	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Haemoptysis	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Haemorrhoidal haemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (1.1%)
Haemorrhoids	4 (5.8%)	2 (2.9%)	6 (8.7%)	3 (1.7%)	6 (3.3%)	9 (5%)
Hallucination	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Headache	31 (44.9%)	4 (5.8%)	35 (50.7%)	60 (33.1%)	11 (6.1%)	71 (39.2%)
Heart rate increased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Heart rate irregular	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Hepatitis***	1 (1.4%)	1 (1.4%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Herpes simplex	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Herpes zoster	1 (1.4%)	3 (4.3%)	4 (5.8%)	1 (0.6%)	0 (0%)	1 (0.6%)
Hordeolum	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Hot flush	21 (30.4%)	2 (2.9%)	23 (33.3%)	53 (29.3%)	11 (6.1%)	64 (35.4%)
Human papilloma virus test positive	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Hyperacusis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Hypercalcaemia	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Hyperglycaemia	2 (2.9%)	1 (1.4%)	3 (4.3%)	4 (2.2%)	0 (0%)	4 (2.2%)
Hyperhidrosis	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	4 (2.2%)	6 (3.3%)
Hyperkalaemia	3 (4.3%)	0 (0%)	3 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Hypernatraemia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Hypersensitivity	5 (7.2%)	1 (1.4%)	6 (8.7%)	7 (3.9%)	0 (0%)	7 (3.9%)
Hypertension	6 (8.7%)	0 (0%)	6 (8.7%)	26 (14.4%)	9 (5%)	35 (19.3%)
Hyperthyroidism	2 (2.9%)	2 (2.9%)	4 (5.8%)	0 (0%)	0 (0%)	0 (0%)

Hypoaesthesia	1 (1.4%)	2 (2.9%)	3 (4.3%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Hypoalbuminaemia	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Hypocalcaemia	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Hypokalaemia	4 (5.8%)	2 (2.9%)	6 (8.7%)	10 (5.5%)	7 (3.9%)	17 (9.4%)
Hypomagnesaemia	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Hyponatraemia	0 (0%)	1 (1.4%)	1 (1.4%)	3 (1.7%)	0 (0%)	3 (1.7%)
Hypophosphataemia	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Hypotension	3 (4.3%)	4 (5.8%)	7 (10.1%)	0 (0%)	0 (0%)	0 (0%)
Hypothyroidism	3 (4.3%)	4 (5.8%)	7 (10.1%)	0 (0%)	0 (0%)	0 (0%)
Hypoxia	0 (0%)	2 (2.9%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Increased appetite	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Infection	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Influenza like illness	5 (7.2%)	2 (2.9%)	7 (10.1%)	8 (4.4%)	4 (2.2%)	12 (6.6%)
Infusion related reaction	11 (15.9%)	0 (0%)	11 (15.9%)	15 (8.3%)	0 (0%)	15 (8.3%)
Injection site reaction	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Insomnia	23 (33.3%)	5 (7.2%)	28 (40.6%)	56 (30.9%)	9 (5%)	65 (35.9%)
Irritability	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Joint effusion	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Joint range of motion decreased	0 (0%)	2 (2.9%)	2 (2.9%)	0 (0%)	2 (1.1%)	2 (1.1%)
Joint swelling	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Keratitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Lacrimation increased	6 (8.7%)	5 (7.2%)	11 (15.9%)	6 (3.3%)	9 (5%)	15 (8.3%)
Laryngeal inflammation	4 (5.8%)	0 (0%)	4 (5.8%)	2 (1.1%)	0 (0%)	2 (1.1%)
Laryngitis	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Leukocytosis	2 (2.9%)	2 (2.9%)	4 (5.8%)	0 (0%)	1 (0.6%)	1 (0.6%)
Localised oedema	5 (7.2%)	1 (1.4%)	6 (8.7%)	7 (3.9%)	4 (2.2%)	11 (6.1%)
Loss of proprioception	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Lung infection	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Lymph node pain	1 (1.4%)	0 (0%)	1 (1.4%)	3 (1.7%)	0 (0%)	3 (1.7%)
Lymphadenopathy	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Lymphocyte count decreased	1 (1.4%)	3 (4.3%)	4 (5.8%)	7 (3.9%)	4 (2.2%)	11 (6.1%)
Lymphocyte count increased	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Madarosis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Malaise	4 (5.8%)	0 (0%)	4 (5.8%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
Melaena	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Melanocytic naevus	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Memory impairment	3 (4.3%)	2 (2.9%)	5 (7.2%)	3 (1.7%)	0 (0%)	3 (1.7%)
Menorrhagia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Menstruation irregular	5 (7.2%)	2 (2.9%)	7 (10.1%)	5 (2.8%)	2 (1.1%)	7 (3.9%)
Metamyelocyte count increased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Metrorrhagia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)

Micturition urgency	2 (2.9%)	1 (1.4%)	3 (4.3%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Monocyte count decreased	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Mood swings	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Mouth haemorrhage	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Mouth ulceration	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Mucosal infection	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Mucous stools	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Muscle spasms	2 (2.9%)	1 (1.4%)	3 (4.3%)	7 (3.9%)	0 (0%)	7 (3.9%)
Muscle tightness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Muscular weakness	5 (7.2%)	1 (1.4%)	6 (8.7%)	8 (4.4%)	2 (1.1%)	10 (5.5%)
Musculoskeletal chest pain	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Musculoskeletal pain	2 (2.9%)	0 (0%)	2 (2.9%)	6 (3.3%)	1 (0.6%)	7 (3.9%)
Musculoskeletal stiffness	2 (2.9%)	1 (1.4%)	3 (4.3%)	0 (0%)	0 (0%)	0 (0%)
Myalgia	24 (34.8%)	3 (4.3%)	27 (39.1%)	43 (23.8%)	7 (3.9%)	50 (27.6%)
Nail bed inflammation	1 (1.4%)	1 (1.4%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Nail bed tenderness	0 (0%)	1 (1.4%)	1 (1.4%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Nail discolouration	19 (27.5%)	4 (5.8%)	23 (33.3%)	34 (18.8%)	9 (5%)	43 (23.8%)
Nail discomfort	4 (5.8%)	0 (0%)	4 (5.8%)	4 (2.2%)	0 (0%)	4 (2.2%)
Nail disorder	2 (2.9%)	1 (1.4%)	3 (4.3%)	3 (1.7%)	6 (3.3%)	9 (5%)
Nail dystrophy	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Nail infection	3 (4.3%)	2 (2.9%)	5 (7.2%)	3 (1.7%)	7 (3.9%)	10 (5.5%)
Nasal congestion	12 (17.4%)	3 (4.3%)	15 (21.7%)	22 (12.2%)	5 (2.8%)	27 (14.9%)
Nasal dryness	2 (2.9%)	0 (0%)	2 (2.9%)	4 (2.2%)	0 (0%)	4 (2.2%)
Nasopharyngitis	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	3 (1.7%)	4 (2.2%)
Nausea	44 (63.8%)	11 (15.9%)	55 (79.7%)	117 (64.6%)	14 (7.7%)	131 (72.4%)
Neck pain	3 (4.3%)	1 (1.4%)	4 (5.8%)	4 (2.2%)	1 (0.6%)	5 (2.8%)
Nervousness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Neuralgia	3 (4.3%)	0 (0%)	3 (4.3%)	3 (1.7%)	2 (1.1%)	5 (2.8%)
Neuropathy peripheral	6 (8.7%)	1 (1.4%)	7 (10.1%)	7 (3.9%)	0 (0%)	7 (3.9%)
Neutropenia	5 (7.2%)	2 (2.9%)	7 (10.1%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Neutrophil count decreased	12 (17.4%)	3 (4.3%)	15 (21.7%)	18 (9.9%)	13 (7.2%)	31 (17.1%)
Neutrophil count increased	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Night blindness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Night sweats	1 (1.4%)	1 (1.4%)	2 (2.9%)	4 (2.2%)	1 (0.6%)	5 (2.8%)
Nitrite urine present	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Nocturia	4 (5.8%)	0 (0%)	4 (5.8%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
Non-cardiac chest pain	4 (5.8%)	1 (1.4%)	5 (7.2%)	9 (5%)	3 (1.7%)	12 (6.6%)
Ocular hyperaemia	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Oedema	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Oedema peripheral	12 (17.4%)	2 (2.9%)	14 (20.3%)	17 (9.4%)	6 (3.3%)	23 (12.7%)
Oesophageal pain	2 (2.9%)	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)

Onychalgia	2 (2.9%)	0 (0%)	2 (2.9%)	10 (5.5%)	3 (1.7%)	13 (7.2%)
Onychoclasia	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Onycholysis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Onychomadesis	1 (1.4%)	8 (11.6%)	9 (13%)	4 (2.2%)	15 (8.3%)	19 (10.5%)
Onychomycosis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Oral candidiasis	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	0 (0%)	3 (1.7%)
Oral disorder	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Oral dysaesthesia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Oral herpes	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Oral pain	5 (7.2%)	4 (5.8%)	9 (13%)	9 (5%)	0 (0%)	9 (5%)
Oropharyngeal pain	13 (18.8%)	2 (2.9%)	15 (21.7%)	24 (13.3%)	5 (2.8%)	29 (16%)
Oropharyngeal swelling	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Otitis externa	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Pain	13 (18.8%)	2 (2.9%)	15 (21.7%)	23 (12.7%)	2 (1.1%)	25 (13.8%)
Pain in extremity	7 (10.1%)	2 (2.9%)	9 (13%)	18 (9.9%)	6 (3.3%)	24 (13.3%)
Pain in jaw	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Pain of skin	6 (8.7%)	3 (4.3%)	9 (13%)	10 (5.5%)	1 (0.6%)	11 (6.1%)
Palmar-plantar erythrodysaesthesia syndrome	1 (1.4%)	1 (1.4%)	2 (2.9%)	1 (0.6%)	3 (1.7%)	4 (2.2%)
Palpitations	6 (8.7%)	1 (1.4%)	7 (10.1%)	4 (2.2%)	7 (3.9%)	11 (6.1%)
Panic attack	1 (1.4%)	1 (1.4%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Paraesthesia	8 (11.6%)	1 (1.4%)	9 (13%)	24 (13.3%)	3 (1.7%)	27 (14.9%)
Paronychia	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Parosmia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	2 (1.1%)	2 (1.1%)
Pelvic pain	5 (7.2%)	0 (0%)	5 (7.2%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Periorbital oedema	3 (4.3%)	0 (0%)	3 (4.3%)	2 (1.1%)	0 (0%)	2 (1.1%)
Peripheral motor neuropathy	6 (8.7%)	3 (4.3%)	9 (13%)	7 (3.9%)	2 (1.1%)	9 (5%)
Peripheral sensory neuropathy	36 (52.2%)	3 (4.3%)	39 (56.5%)	101 (55.8%)	14 (7.7%)	115 (63.5%)
Personality change	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Petechiae	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Pharyngeal erythema	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Pharyngitis	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Pharyngitis streptococcal	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Photophobia	2 (2.9%)	1 (1.4%)	3 (4.3%)	2 (1.1%)	0 (0%)	2 (1.1%)
Photosensitivity reaction	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Platelet count decreased	0 (0%)	3 (4.3%)	3 (4.3%)	1 (0.6%)	7 (3.9%)	8 (4.4%)
Pneumonitis	2 (2.9%)	1 (1.4%)	3 (4.3%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Pollakiuria	5 (7.2%)	0 (0%)	5 (7.2%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Post procedural discharge	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (1.1%)
Post procedural drainage	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Postnasal drip	3 (4.3%)	0 (0%)	3 (4.3%)	4 (2.2%)	5 (2.8%)	9 (5%)
Premature menopause	4 (5.8%)	0 (0%)	4 (5.8%)	2 (1.1%)	1 (0.6%)	3 (1.7%)

Presyncope	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Procedural pain	0 (0%)	1 (1.4%)	1 (1.4%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
Proctalgia	4 (5.8%)	3 (4.3%)	7 (10.1%)	1 (0.6%)	3 (1.7%)	4 (2.2%)
Productive cough	3 (4.3%)	1 (1.4%)	4 (5.8%)	1 (0.6%)	0 (0%)	1 (0.6%)
Protein total decreased	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	22 (31.9%)	0 (0%)	22 (31.9%)	19 (10.5%)	3 (1.7%)	22 (12.2%)
Purpura	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Pyrexia	10 (14.5%)	4 (5.8%)	14 (20.3%)	16 (8.8%)	10 (5.5%)	26 (14.4%)
Rash	8 (11.6%)	4 (5.8%)	12 (17.4%)	18 (9.9%)	0 (0%)	18 (9.9%)
Rash erythematous	1 (1.4%)	0 (0%)	1 (1.4%)	1 (0.6%)	0 (0%)	1 (0.6%)
Rash follicular	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Rash maculo-papular	15 (21.7%)	1 (1.4%)	16 (23.2%)	30 (16.6%)	5 (2.8%)	35 (19.3%)
Rash papular	1 (1.4%)	0 (0%)	1 (1.4%)	3 (1.7%)	0 (0%)	3 (1.7%)
Rash pustular	0 (0%)	0 (0%)	0 (0%)	4 (2.2%)	1 (0.6%)	5 (2.8%)
Rectal haemorrhage	3 (4.3%)	1 (1.4%)	4 (5.8%)	1 (0.6%)	2 (1.1%)	3 (1.7%)
Rectal ulcer	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Red blood cell count decreased	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Renal failure acute	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	2 (1.1%)	2 (1.1%)
Respiratory tract congestion	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Restless legs syndrome	1 (1.4%)	0 (0%)	1 (1.4%)	5 (2.8%)	0 (0%)	5 (2.8%)
Restlessness	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Retching	1 (1.4%)	1 (1.4%)	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Retinal tear	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Rhinitis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Rhinitis allergic	6 (8.7%)	1 (1.4%)	7 (10.1%)	8 (4.4%)	2 (1.1%)	10 (5.5%)
Rhinorrhoea	7 (10.1%)	0 (0%)	7 (10.1%)	3 (1.7%)	2 (1.1%)	5 (2.8%)
Rosacea	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Scleral discolouration	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Scratch	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Secretion discharge	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Sensory disturbance	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Sepsis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Seroma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (1.1%)
Serum sickness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Sinus congestion	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Sinus headache	2 (2.9%)	1 (1.4%)	3 (4.3%)	3 (1.7%)	0 (0%)	3 (1.7%)
Sinus tachycardia	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	5 (2.8%)	7 (3.9%)
Sinusitis	3 (4.3%)	1 (1.4%)	4 (5.8%)	7 (3.9%)	1 (0.6%)	8 (4.4%)
Skin burning sensation	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Skin discolouration	1 (1.4%)	2 (2.9%)	3 (4.3%)	2 (1.1%)	2 (1.1%)	4 (2.2%)
Skin disorder	2 (2.9%)	0 (0%)	2 (2.9%)	3 (1.7%)	1 (0.6%)	4 (2.2%)

Skin hyperpigmentation	2 (2.9%)	1 (1.4%)	3 (4.3%)	6 (3.3%)	4 (2.2%)	10 (5.5%)
Skin hypopigmentation	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Skin infection	2 (2.9%)	1 (1.4%)	3 (4.3%)	5 (2.8%)	3 (1.7%)	8 (4.4%)
Skin lesion	1 (1.4%)	1 (1.4%)	2 (2.9%)	1 (0.6%)	0 (0%)	1 (0.6%)
Skin necrosis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Skin ulcer	0 (0%)	0 (0%)	0 (0%)	3 (1.7%)	0 (0%)	3 (1.7%)
Sleep disorder	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Sneezing	2 (2.9%)	0 (0%)	2 (2.9%)	1 (0.6%)	1 (0.6%)	2 (1.1%)
Soft tissue infection	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Somnolence	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	0 (0%)	2 (1.1%)
Stomatitis	10 (14.5%)	14 (20.3%)	24 (34.8%)	41 (22.7%)	18 (9.9%)	59 (32.6%)
Subcutaneous abscess	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Swelling	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Syncope	1 (1.4%)	1 (1.4%)	2 (2.9%)	1 (0.6%)	3 (1.7%)	4 (2.2%)
Tachycardia	3 (4.3%)	1 (1.4%)	4 (5.8%)	5 (2.8%)	2 (1.1%)	7 (3.9%)
Tachyphrenia	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Temperature intolerance	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
Tenderness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Thirst	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Throat tightness	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	1 (1.4%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Tongue discolouration	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Tongue injury	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Toothache	1 (1.4%)	0 (0%)	1 (1.4%)	3 (1.7%)	0 (0%)	3 (1.7%)
Transaminases increased	0 (0%)	2 (2.9%)	2 (2.9%)	0 (0%)	1 (0.6%)	1 (0.6%)
Tremor	4 (5.8%)	1 (1.4%)	5 (7.2%)	3 (1.7%)	0 (0%)	3 (1.7%)
Upper respiratory tract infection	6 (8.7%)	3 (4.3%)	9 (13%)	20 (11%)	6 (3.3%)	26 (14.4%)
Urinary incontinence	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Urinary retention	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Urinary tract infection	7 (10.1%)	3 (4.3%)	10 (14.5%)	8 (4.4%)	1 (0.6%)	9 (5%)
Urinary tract pain	1 (1.4%)	0 (0%)	1 (1.4%)	4 (2.2%)	0 (0%)	4 (2.2%)
Urticaria	4 (5.8%)	0 (0%)	4 (5.8%)	0 (0%)	0 (0%)	0 (0%)
Vaginal discharge	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	1 (0.6%)	1 (0.6%)
Vaginal haemorrhage	1 (1.4%)	1 (1.4%)	2 (2.9%)	4 (2.2%)	0 (0%)	4 (2.2%)
Vaginal infection	1 (1.4%)	1 (1.4%)	2 (2.9%)	3 (1.7%)	1 (0.6%)	4 (2.2%)
Varicella	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Venous thrombosis	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Vertigo	2 (2.9%)	1 (1.4%)	3 (4.3%)	4 (2.2%)	0 (0%)	4 (2.2%)
Viral infection	1 (1.4%)	0 (0%)	1 (1.4%)	2 (1.1%)	0 (0%)	2 (1.1%)
Vision blurred	11 (15.9%)	3 (4.3%)	14 (20.3%)	14 (7.7%)	4 (2.2%)	18 (9.9%)
Visual impairment	2 (2.9%)	3 (4.3%)	5 (7.2%)	2 (1.1%)	0 (0%)	2 (1.1%)

Vitiligo	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	18 (26.1%)	8 (11.6%)	26 (37.7%)	30 (16.6%)	6 (3.3%)	36 (19.9%)
Vulva cyst	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Vulvitis	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Vulvovaginal dryness	2 (2.9%)	0 (0%)	2 (2.9%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
Weight decreased	4 (5.8%)	5 (7.2%)	9 (13%)	6 (3.3%)	2 (1.1%)	8 (4.4%)
Weight increased	0 (0%)	0 (0%)	0 (0%)	7 (3.9%)	0 (0%)	7 (3.9%)
Wheezing	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	1 (0.6%)	3 (1.7%)
White blood cell count decreased	7 (10.1%)	2 (2.9%)	9 (13%)	11 (6.1%)	7 (3.9%)	18 (9.9%)
White blood cell count increased	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)	2 (1.1%)
White blood cells urine positive	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Wound dehiscence	1 (1.4%)	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
Wound infection	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)	2 (1.1%)

*from last pembrolizumab dose for the experimental arm and from last paclitaxel for the control arm

**includes primary and secondary causes of adrenal insufficiency (e.g. hypophysitis and hypopituitarism)

*** includes autoimmune hepatitis and hepatitis

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