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A pilot trial evaluating lenalidomide and oral azacitidine with radiotherapy for patients with newly diagnosed and relapsed plasmacytoma

Running Title – LENAZART trial for patients with plasmacytoma

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Keywords

Plasmacytoma, Lenalidomide, Azacitidine, Radiation Therapy, Myeloma, Plasma Cell Disorder

Data Sharing Statement

The de-identified data generated in this study are provided in the manuscript. Additional data may be requested from the corresponding author.

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Contribution: U.A.S., A.D., A.M.L., S.D. designed the study, initiated this work, developed the statistical analysis plans and analyzed the data; U.A.S. and A.M.L. wrote the manuscript; and all authors made substantial contributions to design of the study, conduct of the study, interpretation of results, revised the manuscript critically, and gave final approval of the manuscript to be submitted.

Disclosure of Conflicts of Interest

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Solitary plasmacytoma of the bone (SPB) is a rare entity representing 5% of all plasma cell dyscrasias. SPB treated with radiation therapy (RT) has a 10% risk of progression to multiple myeloma (MM) over 3 years if there is no marrow involvement, whereas there is a 60% chance of progression over 3 years in patients with minimal marrow involvement.(1-4) Median time to progression (TTP) in the latter group is 26 months.(5, 6) Presently, despite mounting evidence of a significant risk of progression to MM, there is no FDA-approved therapy and patients are usually treated with localized RT. This is an area of unmet need.

A similar opportunity exists in the setting of MM patients relapsing with localized disease amenable to RT. This group of patients may not immediately require long-term systemic therapy especially if RT combined with epigenetic modulation and lenalidomide results in therapeutically relevant immune responses.

A few studies combining lenalidomide and azacitidine have shown responses even in a lenalidomide refractory population with upregulation of cancer testis antigen (CTA) as well as CTA specific T cell responses, lower plasma cytidine deaminase levels and higher tumor cereblon expression.(7-9) These synergistic mechanisms focus on manipulating antigen expression and enhancing antigen presentation (both neoantigens and cancer testis antigens) with oral azacitidine (CC-486), and augmentation of antigen specific immune responses via increased IL2 production leading to an increase in the proliferation of T cells with lenalidomide.(7)

We hypothesized that this combination with RT in plasmacytomas would serve to inflame the tumor microenvironment and potentially lead to therapeutically active systemic immune responses via an abscopal effect.

The LENAZART trial was an open-label, single center, single-arm study of lenalidomide (LEN), oral azacitidine (AZA; CC-486), and RT that enrolled 22 patients in 2 cohorts (NCT04174196; **Figure 1**). The study was approved by the institutional review board (IRB#19-284). Cohort 1 enrolled patients with histologically confirmed newly diagnosed or recurrent solitary plasmacytoma of the bone with minimal marrow involvement (detectable clonal bone marrow (BM) plasma cells by multicolor flow cytometry and ≤ 10% clonal plasma cells in a BM biopsy by immunohistochemistry, morphology, or flow cytometry) and secretory M protein < 3 g/dL. Cohort 2 enrolled relapsed or progressive MM per IMWG criteria(10) with plasmacytomas appropriate for RT on imaging and BM involvement for clonal plasma cells by immunohistochemistry. Enrollment did not require measurable disease by IMWG criteria. Any prior number of therapies including lenalidomide refractory disease was permitted, including prior RT and allogeneic transplant.

In the study, patients were treated with oral azacitidine 100 mg on day 1-21 and lenalidomide 25 mg on day 1-21 of a 28-day cycle for 6 cycles. Concurrent RT to the plasmacytoma was initiated after cycle 2. It could commence earlier should the physician deem it necessary due to worsening pain, neurologic involvement or rapid progression. Total dose could vary between 45-50 Gray (Gy) for cohort 1 and 30-50 Gy for cohort 2 based on clinical judgement.

The primary endpoint was the rate of stringent complete response (sCR) by 2016 IMWG criteria on post-treatment BM biopsy and aspirate specimens and absence of new lesions by PET.(10) We estimated the historical rate of sCR as approximately 5% (based on the rate for newly diagnosed myeloma with lenalidomide and dexamethasone per the MAIA study of 7.3%(11) and for relapsed myeloma with lenalidomide dexamethasone per the POLLUX study of 4.6%).(12)

The primary endpoint was evaluated separately for the two cohorts. With 10 patients in each cohort, the maximum half-width of the exact 95% confidence interval (CI) for the response rate was +/- 0.31. A sCR rate of ≥20% would be considered promising for either cohort. Secondary endpoints included safety and progression free survival (PFS).

Planned enrollment was 10 patients per cohort. Patients removed from the study prior to day 30 were replaced if they did not receive both study drugs or if they withdrew consent for non-toxicity related reasons such as progression or patient preference at the discretion of the investigator. Otherwise, patients removed from study after day 30 and before the ascertainment of the primary endpoint were considered as not achieving sCR.

The study treated 8 patients in cohort 1 of which all were evaluable. In cohort 2 there were 12 patients treated (all lenalidomide exposed and 75% lenalidomide refractory) with 9 of them being evaluable. Three participants in cohort 2 were not evaluable as they withdrew prior to C2D1 due to progression of disease (n=2) and patient preference (n=1) (**Table S1; Figure S1**). The median age of the treated study participants was 67 years (range 50-81), with 45% females and 10% Hispanic or Latinx. The study was diverse with 65% White, 25% Black and 10% Asian participants. In cohort 1, 37.5% participants had received prior RT for prior plasmacytomas. In cohort 2, participants had a median of 2 (range 1-3) prior lines of therapy.

Six planned treatment cycles on study were completed in 75% evaluable participants in cohort 1 and 78% in cohort 2. Median RT dose on trial was 45 Gy in cohort 1 and 34.5 Gy in cohort 2. Only one patient had a dose reduction in lenalidomide from baseline dose on study. There were no dose reductions for azacitidine, and all patients tolerated 100 mg daily. All participants in cohort 2 were exposed to lenalidomide previously with 75% refractory to lenalidomide and received it in the immediate prior line. Best response in cohort 1 was partial response and in cohort 2 was very good partial response and no participants achieved sCR, therefore the primary endpoint was not met (**Table S1**). The plasmacytoma was radiated and therefore not included in the response assessment. Median PFS or TTP was 16.3 months (95%CI 14.3 months-not reached) in cohort 1 (**Figure 2**) and median PFS was 10.4 months (95%CI 6.4 months-not reached) in cohort 2 (**Figure 3**). PFS duration was not linked to depth of response. One participant in cohort 2 died in remission from an infection while on lenalidomide maintenance.

The combination was well tolerated with ≥grade 3 neutropenia seen in 20%. Other common adverse events ≥20% of any grade included constipation (45%), nausea (20%), diarrhea (20%), maculopapular rash (20%) and fatigue (50%). There were four serious adverse events on study – basal cell carcinoma (unrelated), stroke (possible - lenalidomide and unlikely - azacitidine), colon obstruction (unlikely) and diarrhea (possible) (**Table S2**).

This was the first prospective trial that enrolled a diverse population in solitary plasmacytoma with minimal marrow involvement and relapsed myeloma with plasmacytomas that utilized an immunomodulatory approach. A similar phase 3 trial run through a cooperative group evaluating the combination of zoledronic acid, ixazomib, lenalidomide, and dexamethasone compared to zoledronic acid alone after RT enrolled 11 patients and was closed early due to lack of accrual (NCT02516423).

While the current study didn't meet its primary sCR endpoint, there were patients that achieved durable PFS and the combination of lenalidomide with azacitidine with RT was well tolerated. A rigorous comparison with published data on the natural history of patients presenting with a

solitary plasmacytoma and occult marrow disease is limited by the wide confidence intervals for TTP in cohort 1. Our inclusion of participants with recurrent solitary plasmacytoma with minimal marrow involvement may have also contributed to a TTP of 16 months compared to historical cohorts with newly diagnosed plasmacytomas and a TTP of 26 months.(5, 6)

The small sample size highlights the challenges with conducting prospective clinical trials in rare diseases. The overall lack of deep durable responses suggests that alternative approaches should be explored in these patients. Future studies may consider multicenter cooperative group approaches to prospective trial enrollment for this rare condition evaluating novel immune therapies such as bispecific antibodies in conjunction with RT. One such study is recruiting in China (NCT07115667; n=21).

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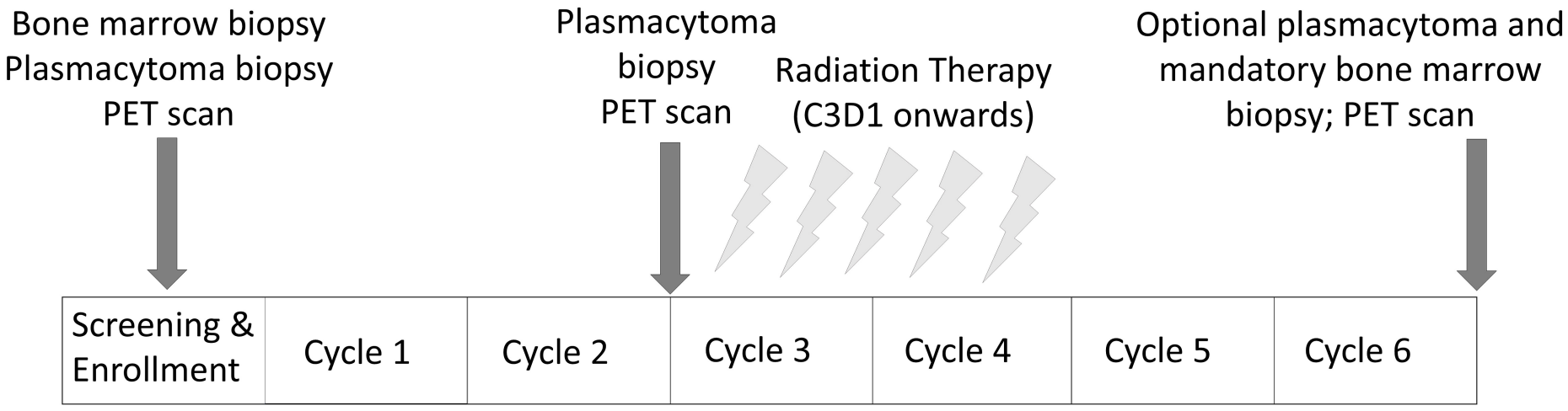
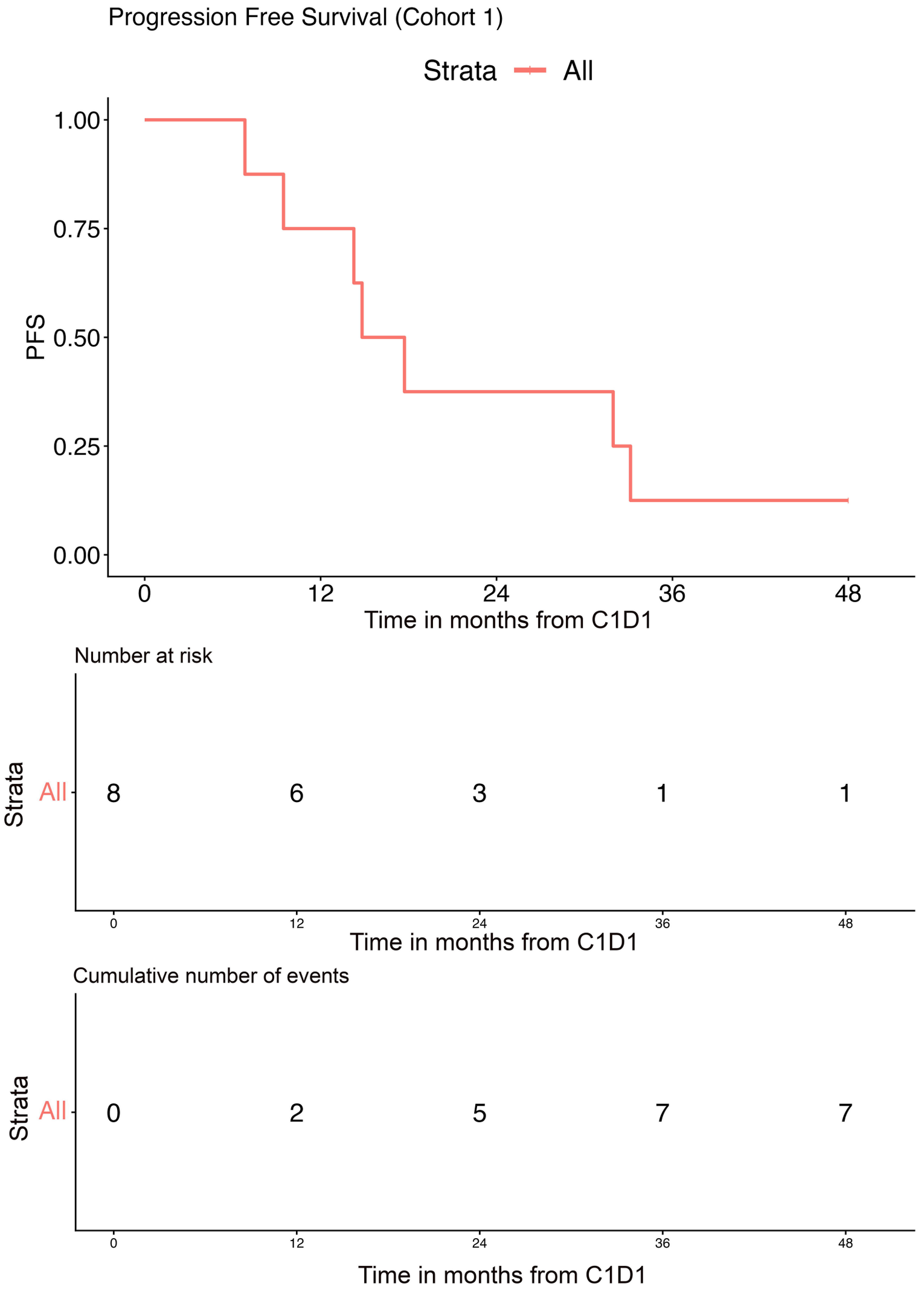
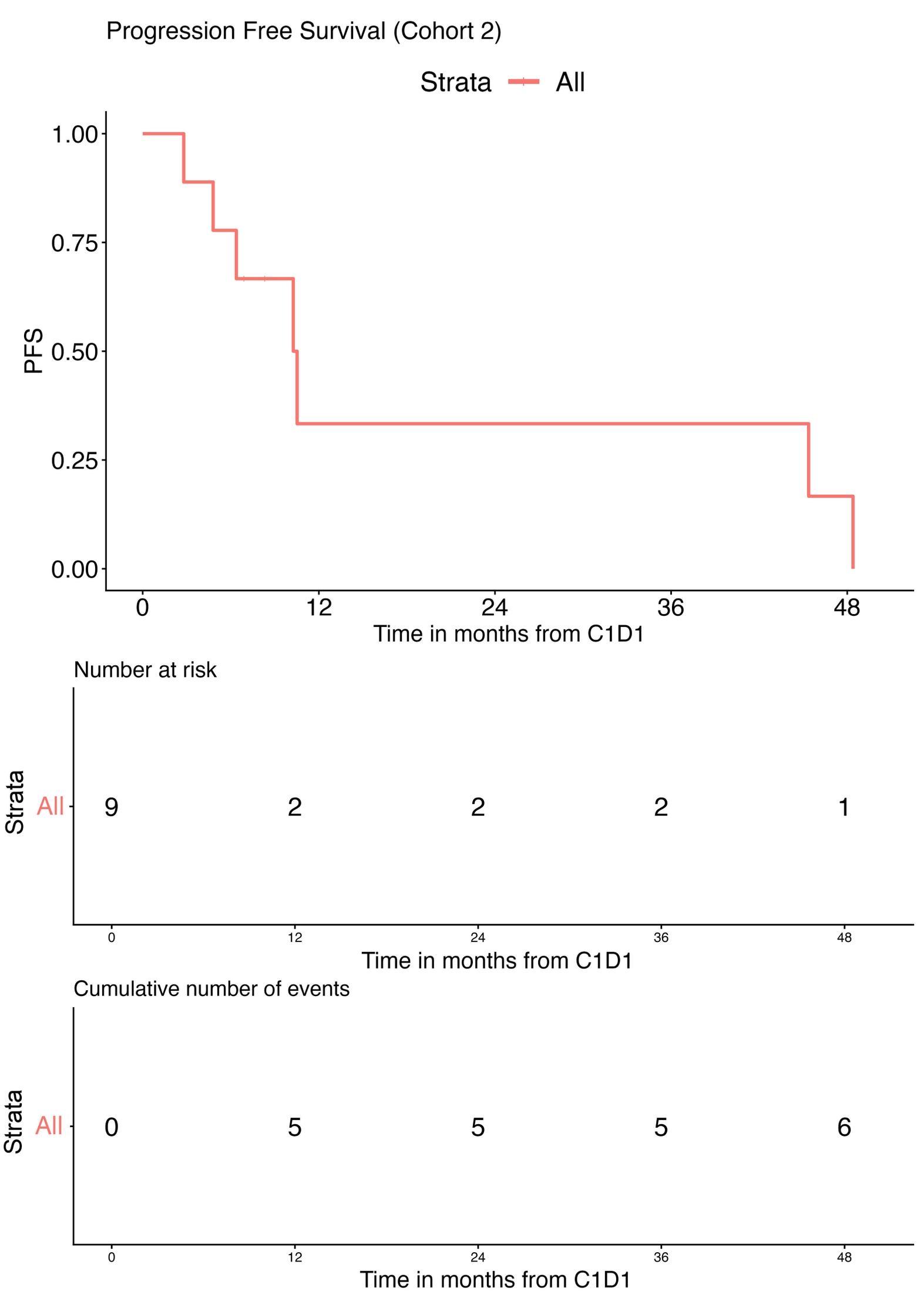
Figures



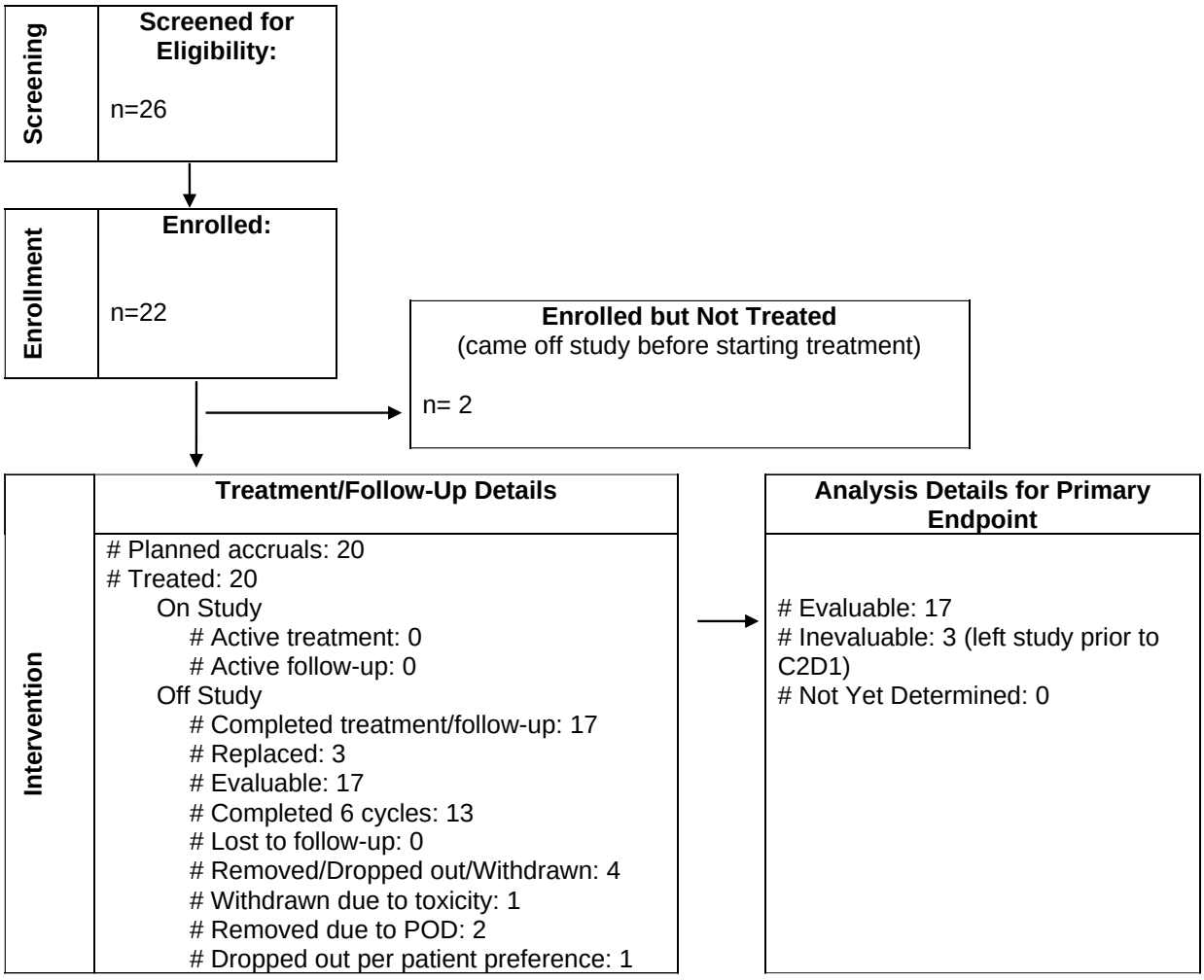
COHORT 1: Solitary plasmacytoma of the bone with minimal marrow involvement
COHORT 2: Relapsed multiple myeloma with plasmacytomas


Progression Free Survival (Cohort 1)
Strata
All
1.00
0.75
0.50
0.25
0.00
PFS
0
12
24
36
48
Time in months from C1D1
Number at risk
Strata
All
8
6
3
1
1
0
12
24
36
48
Time in months from C1D1
Cumulative number of events
Strata
All
0
2
5
7
7
0
12
24
36
48
Time in months from C1D1


Progression Free Survival (Cohort 2)
Strata
All
1.00
0.75
0.50
0.25
0.00
PFS
0
12
24
36
48
Time in months from C1D1
Number at risk
Strata
All
9
2
2
2
1
0
12
24
36
48
Time in months from C1D1
Cumulative number of events
Strata
All
0
5
5
5
6
0
12
24
36
48
Time in months from C1D1

Supplementary Figures

Figure S1: Consort Diagram



Supplementary Tables

Table S1: Response assessments by cohort

Table legend

N/A: Not applicable or available

RT: Radiation Therapy

cGy: centi Gray

BL: Baseline

EOS: End of Study

IMWG: International Myeloma Working Group

MRD: Minimal Residual Disease

PFS (m): Progression Free Survival in months

POD: Progression of Disease

COHORT 1																					
Patient ID	**Age Range**	**Sex**	**Evaluable**	**Diagnosis Year**	**Cytogenetics**	**Prior RT site**	**BL lesion**	**C1D1 Year**	**RT dose cGy**	**RT fraction**	**BL SUV**	**EOS SUV**	**BL Len Dose**	**EOS Len Dose**	**Cycles completed**	**BL BM**	**EOS BM**	**EOS MRD**	**IMWG Response**	**Relapsed**	**PFS (m)**	**Off study (reason)**
4	41-50	F	Yes	2020	N/A	NA	sternum	2020	4400	22	2.8	0	25	25	6	5%	< 5%	Positive	MR/ non measurable	N	48+	N/A
9	61-70	M	Yes	2021	t(4;14); del13	NA	L clavicle	2021	3600	12	5.7	3	25	25	6	<5 %	<10%	Positive	MR/ measurable	Y	14.8	N/A
11	71-80	F	Yes	2017	gain11q	T10	T6	2021	4500	25	7.1	0	25	NA	4	<5 %	NA	NA	MR/ non measurable	N	33.1	Withdrawn (patient preference)
12	51-60	M	Yes	2022	Negative	NA	R ischium	2022	4600	23	9.1	5.7	25	25	6	<5 %	MRD neg (limited/fragmented)	Negative	PR/ measurable	N	17.7	N/A
13	51-60	M	Yes	2021	Negative	L2	L2	2022	2400	5	NA	NA	25	25	6	5%	<5%	Positive	SD/ non measurable	Y	32	N/A
14	61-70	M	Yes	2022	17del; del13; hyperdiploidy	NA	T12	2022	4500	25	12.8	2.9	25	5	6	5-9%	10-15%	Positive	SD/ measurable	N	14.3	N/A
16	61-70	F	Yes	2018	t(11;14)	L3	L scapula	2022	4600	23	2.3	NA	25	NA	2	<5 %	NA	NA	SD/ non measurable	N	6.8	Withdrawn (stroke)
17	61-70	F	Yes	2022	t(4;14); del13	NA	L humerus	2022	4600	23	2.6	NA	25	25	6	<5 %	5%	Positive	PR/ measurable	Y	9.5	N/A
COHORT 2																						
Patient ID	**Age Range**	**Sex**	**Evaluable**	**Diagnosis Year**	**Cytogenetics**	**Prior lines of chemo**	**BL lesion**	**C1D1 Year**	**RT dose cGy**	**RT fraction**	**BL SUV**	**EOS SUV**	**BL Len Dose**	**EOS Len Dose**	**Cycles completed**	**BL BM**	**EOS BM**	**EOS MRD**	**IMWG Response**	**Relapsed**	**PFS (m)**	**Off study (reason)**
1	71-80	M	Yes	2011	t(11;14); gain13	1	L iliac	2020	3000	10	4.8	NA	10	10	3	10-15%	POD	Positive	POD	Y	3.7	Withdrawn (POD)

3	51-60	M	Yes	2008	gain1q21; del13	1	sacrum	2020	3600	12	37.6	2.2	25	25	6	<5%	<5%	Positive	VGPR	Y	49.2	N/A
5	71-80	M	Yes	2019	t(11;14); del13	3	L iliac	2020	3600	12	11.1	4.1	25	25	6	<5%	<5%	Positive	SD	N	45.8	N/A (Death)
7	61-70	F	Yes	2013	17p deletion	2	T1	2021	3000	10	4.2	3.3	25	25	6	<5%	<5%	Positive	SD/ nonmeasurable	Y	7.4	N/A
8	61-70	F	Yes	2015	t(11;14)	1	T6	2021	2100	12	3.7	3.5	25	25	6	<5%	5-9%	Positive	SD	Y	6.7	N/A
15	81-90	M	Yes	2020	t(11;14); 17p del; del13; gain1q	1	T8	2022	3300	11	11.1	2.8	10	10	6	15-20%	10%	Positive	PR	Y	10.7	N/A
18	61-70	F	Yes	2007	hyperdiploidy	2	L rib	2023	4600	23	52	3.4	25	25	4	5%	50%	Positive	POD	Y	5.5	Withdrawn (POD)
22	61-70	M	Yes	2013	N/A	2	L mandible	2023	4400	22	6.9	3.7	25	25	6	<1%	8-15%	Positive	nonmeasurable	Y	8.9	N/A
23	71-80	M	Yes	2014	amp1q; del13	2	L sacrum	2023	3600	12	7.1	2.6	25	25	6	<5%	5-10%	Positive	POD	Y	10.5	N/A
6	51-60	M	No	2015	gain 1q21, del13q	1	L ischioacetabulum	2020	NA	NA	11.1	NA	5	5	1	5%	NA	NA	NA	NA	NA	Withdrawn & replaced (Patient preference)
20	71-80	F	No	2017	gain1q21, t(11;14), del13q, 17p del	3	L rib	2023	NA	NA	NA	NA	10	10	1	5-10%	POD	NA	POD	Y	NA	Withdrawn & replaced (POD)
10	51-60	F	No	2014	N/A	2	R parasternal	2021	NA	NA	4	6.2	25	20	1	<1%	POD	NA	POD	Y	NA	Withdrawn & replaced (POD)

Table S2: Adverse events

Adverse Events by CTCAE v5.0		All Adverse Events (All attributions)			Lenalidomide (Possibly, Probably and Definitely Related Attributions)			Azacitidine (Possibly, Probably and Definitely Related Attributions)		
SYSTEM_ORGAN_CLASS	**TOXICITY**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Gastrointestinal disorders	Constipation	6 (30%)	3 (15%)	0 (0%)	5 (25%)	3 (15%)	0 (0%)	5 (25%)	1 (5%)	0 (0%)
	Nausea	4 (20%)	1 (5%)	0 (0%)	4 (20%)	1 (5%)	0 (0%)	4 (20%)	1 (5%)	0 (0%)
	Diarrhea	4 (20%)	1 (5%)	0 (0%)	3 (15%)	1 (5%)*	0 (0%)	3 (15%)	1 (5%)*	0 (0%)
	Vomiting	1 (5%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)	1 (5%)	0 (0%)
	Small intestinal obstruction	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)
	Colonic obstruction*	0 (0%)	0 (0%)	1 (5%)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Belching	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Gastroesophageal reflux disease	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Hemorrhoids	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Mucositis oral	1 (5%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	Alopecia	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Skin hyperpigmentation	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Rash maculo-papular	3 (15%)	1 (5%)	0 (0%)	2 (10%)	1 (5%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Rash acneiform	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Discoloration of soles of feet	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Dry skin	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	non-healing wound on back	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma*	0 (0%)	1 (5%)*	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Investigations	Neutrophil count decreased	0 (0%)	0 (0%)	4 (20%)	0 (0%)	0 (0%)	4 (20%)	0 (0%)	0 (0%)	4 (20%)
	Blood bilirubin increased	2 (10%)	1 (5%)	0 (0%)	2 (10%)	1 (5%)	0 (0%)	2 (10%)	1 (5%)	0 (0%)
	Weight loss	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Creatinine increased	2 (10%)	0 (0%)	0 (0%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	Rhinovirus	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Thrush	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Urinary tract infection	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Wound infection	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	Dizziness	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Memory impairment	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Stroke*	0 (0%)	0 (0%)	1 (5%)*	0 (0%)	0 (0%)	1 (5%)*	0 (0%)	0 (0%)	0 (0%)
	Headache	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Peripheral sensory neuropathy	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	Myalgia	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)
	Back pain	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Joint effusion	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Pain in extremity	1 (5%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
General disorders	Fatigue	9 (45%)	1 (5%)	0 (0%)	9 (45%)	1 (5%)	0 (0%)	9 (45%)	1 (5%)	0 (0%)
	Non-cardiac chest pain	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Pain	0 (0%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Eye disorders	Floaters	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
*Serious Adverse Events										