SUMMARY

Patient use

Between August 22, 2016 and July 30, 2018, 276 patients were evaluated. Of these, 111 were included in study (Figure 3). Only 67 patients (60.4%) completed the induction treatment and went on to maintenance, of these 61 of the newly diagnosed stratum.

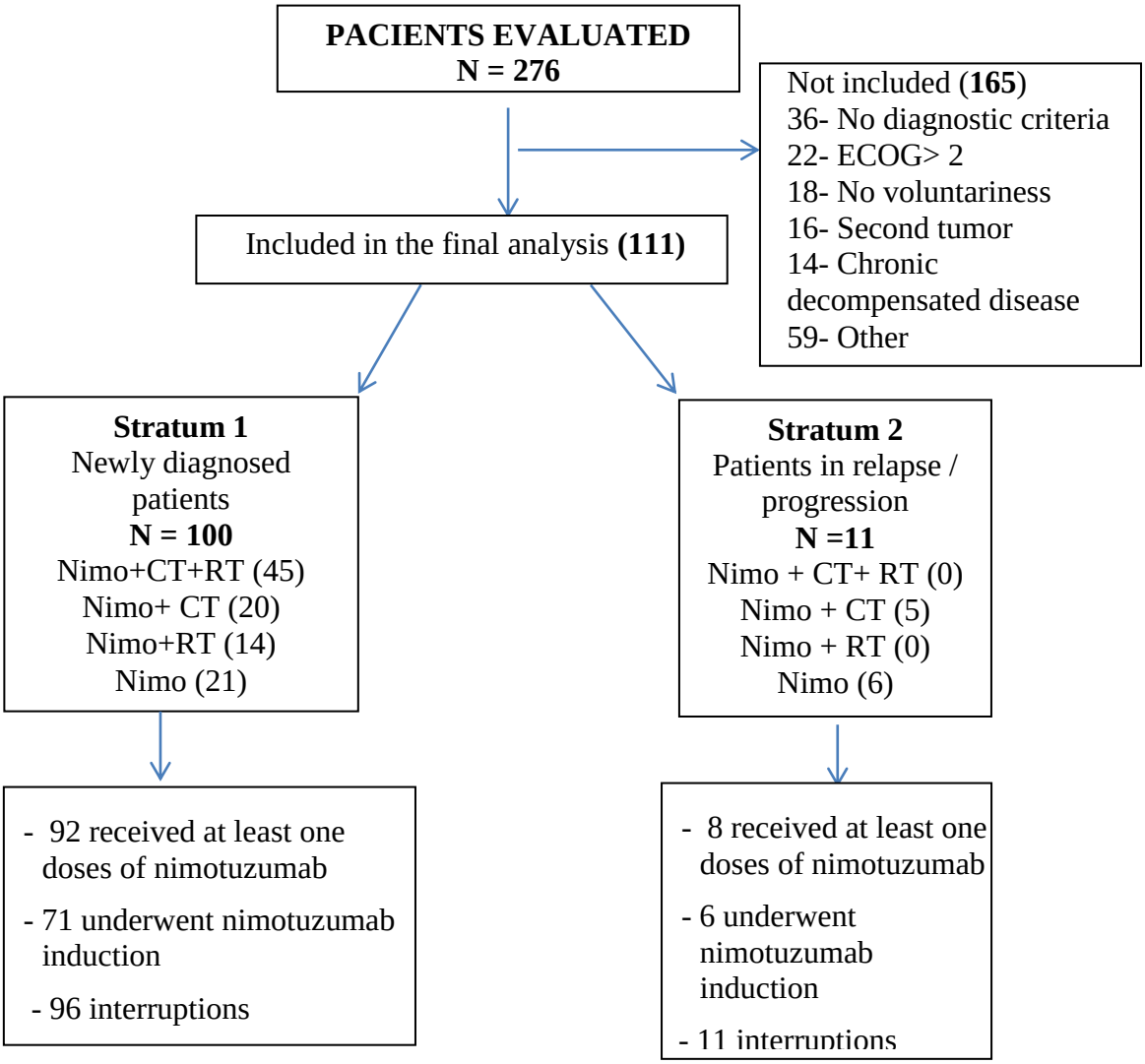

Figure 1: Distribution of study patients

The number of patients included in this period came from 13 sites. The Conrado Benítez (CB) hospital in Santiago de Cuba was the most inclusive when recruiting 17.1% of the patients, followed by Vladimir Ilich hospital in Holguín, with 12.6% of the total included.

Table 1: Distribution of patients included in the analysis by clinical site and treatment received (n=111)

	Stratum 1: New diagnostic								Stratum 2:Progression			
	Nimo+CT+RT		Nimo+CT		Nimo+RT		Nimo		Nimo+CT		Nimo	
Site	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
VIL	10	20,45	2	14,29	-	-	2	9,52	-	-	-	-
CB	8	18,18	-	-	5	35,71	4	19,05	-	-	2	33,33
JRLT	7	15,91	1	4,76	-	-	2	9,52	-	-	-	-
CCG	6	13,64	-	-	-	-	-	-	-	-	-	-
IIIC	5	11,36	-	-	-	-	1	4,76	-	-		-
MAD	3	6,82	-	-	5	35,71	3	14,29	-	-	-	-
CSM	3	6,82	4	19,05	-	-	-	-	4	80,00	2	33,33
CHR	2	4,55	4	19,05	-	-	-	-	-	-	-	-
ALI	1	2,27	2	9,52	2	14,29	1	4,76	-	-	-	-
EGS	-	-	4	19,05	-	-	3	14,29	1	20,00	-	-
CMC	-	-	2	9,52	-	-	1	4,76	-	-	-	-
GAL	-	-	1	4,76	-	-	3	14,29	-	-	-	-
AN	-	-	-	-	2	14,29	-	-		-	2	33,33
FP	-	-	-	-	-	-	1	4,76				
Total	45	100	20	100	14	100	21	100	5	100	6	100

Table 2: Distribution of patients who interrupted treatment according to the cause of interruption

Cause of interruption	No. of patients	%
1. Request or voluntary abandonment of the patient	23	21.50
2. Discontinuation of treatment with nimotuzumab in more than two weeks during the induction period or in more than three weeks during the maintenance period	15	14.02
3. Adverse events grade III or IV according to the toxicity scale of the CTCAE (version 4.0), which prevent further treatment	1	0.93
4. Deterioration of the general condition of the patient (ECOG) which, in medical judgment, prevents the administration of the treatment	29	27.10
5. Emergence of some exclusion criteria	4	3.74
6. Death	30	28.04
7. Other	5	4.67
Total of interruptions	107	96.4

In general, a male predominance was observed. The mean age was 60 years for patients treated with concurrent Nimo with chemoradiotherapy (Table 3).

Tabla 3: Distribution of patients according to demographic variables

Baseline characteristics		Stratum Previously untreated				Stratum 2 Progression/relapsed	
		Nimo+CRT	Nimo+CT	Nimo+RT	Nimo	Nimo+CT	Nimo
		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Gender	Male	40(89.9)	17(85.0)	13(92.9)	17(81.0)	5(100)	6(100)
	Female	5(11.1)	3(15.0)	1(7.1)	4(19.0)	-	-
Age	Mean ± SD	63.9±6.8	60.5±13.2	60.9±9.6	61.9±7.6	56.4±5.9	64.1±8.2
	Median ± R	64±10	57±23	62±15	61.0±11	56±11	67.0±16
	(Mín; Máx)	(48;77)	(42;86)	(47;76)	(49;76)	(49;64)	(53;75)
Smoking	Never	5(11.1)	3(15.0)	2(14.3)	2(9.5)	-	-
	Previous	10(22.2)	2(10.0)	5(35.7)	6(28.6)	1(20.0)	2(33.4)
	Current	30(66.7)	15(75.0)	7(50.0)	13(61.9)	4(80.0)	4(66.6)
Alcoho-lism	Yes	37(82.2)	15(75.0)	11(78.6)	16(76.2)	3(60.0)	3(50.0)
	No	8(17.8)	5(15.0)	3(21.4)	5(23.8)	2(40.0)	3(50.0)
	Total	44(100)	14(100)	14(100)	21(100)	5(100)	6(100)

In the newly diagnosed stratum, patients with tumor location in the middle intra-thoracic region and the clinical stage IIIb predominated in all treatment groups (Table 4).

Table 4: Baseline disease data for new diagnostic (stratum 1)

Baseline characteristics		Stratum Previously untreated			
		Nimo+CRT	Nimo+CT	Nimo+RT	Nimo
		No. (%)	No. (%)	No. (%)	No. (%)
Tumor location	Cervical portion	3 (6.8)	3(14.3)	1(7.1)	1(4.8)
	Intra-thoracic upper	6 (13.6)	5 (23.8)	4 (28.6)	3 (14.3)
	Intra-thoracic middle	33 (**75.0**)	11 (**52.4**)	9 (**64.3**)	15 (71.4)
	Not available	2 (4.5)	2 (9.5)	-	2 (9.5)
Histological type	Squamous cell	40 (**90.9**)	19 (90.5)	14(100.0)	17 (81.0)
	Adenocarcinoma	-	-	-	1 (4.8)
	Not available	4 (9.1	2 (9.5	-	3 (14.3
Clinical stage	Ia	3 (6.8)	1 (4.8)	-	-
	Ib	1 (2.3)	4 (19.0)	1 (7.1)	-
	IIa	3 (6.8)	2 (9.5)	1 (7.1)	1 (4.8)
	IIb	4 (9.1)	2 (9.5)	1 (7.1)	2 (9.5)
	IIIa	8 (18.2)	1 (4.8)	4 (28.6)	4 (19.0)
	IIIb	14 (**31.8**)	2 (9.5)	5 (**35.7**)	4 (19.0)

Baseline characteristics		Stratum Previously untreated			
		Nimo+CRT	Nimo+CT	Nimo+RT	Nimo
		No. (%)	No. (%)	No. (%)	No. (%)
	IIIc	1 (2.3)	1 (4.8)	-	1 (4.8)
	IV	8 (18.2)	6 (28.6)	2 (14.3	7 (**33.3**
	Not available	2 (9.5)	2 (9.5)	-	2 (9.5)
	Total	44(100)	21 (100)	14 (100)	21 (100)

In the stratum of patients in relapsed/progression the behavior was similar (Table 5).

Table 5: Baseline disease data for relapsed/progression stratum 2

Baseline characteristics		Stratum 2 Progression/relapsed	
		Nimo+CT	Nimo
		No. (%)	No. (%)
Tumor location	Cervical portion	-	-
	Intra-thoracic upper	-	-
	Intra-thoracic middle	4 (80.0)	6(100.0)
	Not available	1(20.0)	-
Histological type	Squamous cell	3 (60.0	3 (50.0)
	Adenocarcinoma	1 (20.0)	1 (16.7)
	Not available	1 (20.0	2 (33.3)
Clinical stage	Ia		
	Ib	1 (20.0)	-
	IIa		
	IIb	1 (20.0)	-
	IIIa	-	1 (16.7)
	IIIb	1 (20.0)	1 (16.7)
	IIIc	-	1 (16.7)
	IV	2 (40.0	3 (50.0)
	Not available	-	-
Total		5 (100)	6 (100)

Table 6 shows the distribution of the study patients according to the treatment received and the disease status (strata) at the time of inclusion in the study. In the newly diagnosed stratum, 35.1% of the patients received concurrent nimotuzumab with chemoradiotherapy. In the progression stratum, 54.5% of the patients received the monoclonal as monotherapy.

Table 6: Treatment received according to disease status (strata) at the time of inclusion in the study.

Treatment received	New diagnostic		Relapsed/ Progression	
	No.	%	No.	%
Nimo+CT+RT	45	45,0	-	-
Nimo+CT	20	20,0	5	45,5
Nimo+RT	14	14,0	-	-
Nimo	21	27,0	6	54,5
Total	100	100	11	100

SAFETY RESULTS

The safety profile analyzed showed that nimotuzumab remains as a safe medication.

The proportion of serious AE related (very probable, probable or possible) with the use of nimotuzumab was 1.3%, so the hypothesis raised in the study that the incidence of these events was lower than 10% was fulfilled. No patient died due to an adverse event associated with the use of nimotuzumab. Most of the related AE were mild and moderate and evolved towards recovery or improvement. The most frequent and related adverse events were diarrhea, chills and tremors with 0.9% each of them.

EFFECTIVENESS RESULTS

As a result of the intention-to-treat (ITT) response analysis, 16.0% of complete remission (16 patients) and 8.0% of partial remission (8 patients) were obtained, which resulted in an objective response of 24.0% in the analysis by ITT. 56% of the patients were not evaluated for the response to treatment, because they interrupted the study before 18 weeks, the moment of evaluation provided for in the protocol. In the PP analysis, 20.0% of complete remission and 10.8% of partial remission were obtained, which contributed to an objective response of 30.8% (20 patients).

Previously untreated patients who received nimotuzumab concurrent with chemoradiotherapy, reached in the ITT analysis a median OS of 12.2 months (95% CI, 6.9-17.5), and the 12- and 24-months OS rates were 51% and 17% respectively. Median PFS was 7.8 months (95% CI, 6.2-9.5) and the 12- and 24-months PFS rates were 39.3% and 11.2% respectively.

For these previously untreated patients, in the PP setting, those who received nimotuzumab concurrent with chemoradiotherapy (36 patients), reached a median OS of 12.3 months (95% CI, 9.6-15.1), and the 12- and 24-months OS rates were 55.3% and 17.1% respectively. Median PFS was 8.0 months (95% CI, 4.9-11.0) and the 12- and 24-months PFS rates were 41.3% and 9.2% respectively.

When analyzing the quality of life, a favorable evolution of the general state of health of these patients was obtained from the beginning of treatment until month 12, with a significant reduction in the appearance of nausea, insomnia and constipation.

CONCLUSIONS

1. The product is safe and well tolerated. Most adverse reactions are of mild intensity, and reversible.

2. The MAb nimotuzumab administered concurrently with CT and RT is consolidated as the therapy that benefits the survival of these patients and improves their quality of life.