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Original Article

Safety and Effectiveness of Nimotuzumab in the Treatment of Advanced Head and Neck Cancer Patients. Phase IV Clinical Trial: Final Results

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Abstract

Objective: Epidermal Growth Factor Receptor (EGFR) can be overexpressed in head and neck cancer (HNC). Nimotuzumab is a humanized monoclonal antibody (hMab) that binds to the EGFR. A phase IV study was conducted in advanced head and neck newly diagnosed and recurrent cancer patients to evaluate safety and efficacy of nimotuzumab.

Methods: Four therapeutic schemes were evaluated: nimotuzumab, nimotuzumab+Chemotherapy (Nimo+CT), nimo-

tuzumab+Radiotherapy (Nimo+RT) and nimotuzumab+Chemo+Radiotherapies (Nimo+CRT). Common Toxicity Criteria to Evaluate Adverse Events (AEs) (version 3.0) was used to classify AEs; Kaplan-Meier curves were compared by the non-parametric Log-rank method and Cox regression was applied for subgroup analyses.

Results: A total of 225 patients were included. Most AEs were classified as grade I, AEs related to the product were reported in 36 patients. In this subgroup, most frequent events were anemia, leukopenia, neutropenia, anorexia, nausea, vomiting, asthenia and fever. In the newly diagnosed subset (n=155), although no significant difference was shown in the Intent-to-treat (ITT) analysis, there was a trend toward a benefit in favor of Nimo+CRT, not just related to Progression-Free-Survival (PFS) (22.4 months; p=0.065), but also to Overall Survival (OS) (24.3 months; p=0.089), with higher survival rates at 12 and 24 months for PFS (67.3% and 46.3%, respectively) and OS (70.1% and 50.3%, respectively), compared to the other regimens.

Conclusions: Administration of nimotuzumab was safe in the treatment of advanced HNC patients and well tolerated despite the combination with CRT.

Trial registration: RPCEC00000145 (Cuban Registry of Clinical Trials; http://registroclinico.sld.cu/en/home). Registered 1 February 2013 – Retrospectively registered.

Keywords: EGFR; HNC; Nimotuzumab; Monoclonal antibody; Chemotherapy; Radiotherapy; Safety; Survival

Introduction

HNC is the seventh most common cancer worldwide. This type of cancer comprises a heterogeneous group of malignant tumors that originate in the upper region of the respiratory and digestive tracts, which includes the oral cavity and lips, pharynx, larynx, salivary glands, ear, nasal cavity and paranasal sinuses [1-3]. It is more evident that the oncogenesis of HNC and its evolution is characterized by profound immune defects, since cancer cells evade immunosurveillance due to the accumulation of genetic mutations and tumor heterogeneity [4]. In the last two decades, there has been a better understanding of the underlying molecular mechanisms in HNC, and advances in molecular biology have led to the development of new targeting agents [2].

EGFR can be overexpressed in HNC [5]. Nimotuzumab is a hMab developed at the Center of Molecular Immunology, that targets and binds to the EGFR with intermediate affinity [6]. Nimotuzumab has antiproliferative, pro apoptotic and antiangiogenic effects, induces natural killer (NK) cell activation, cytotoxicity and dendritic cell (DC) maturation [7].

Evidence of efficacy and low toxicity of nimotuzumab has been previously documented [8-10]. Since 2007 the Regulatory Authority for Medicines and Medical Devices of the Republic of Cuba, CECMED, approved the use of nimotuzumab concomitant with RT and/or CT in patients with advanced malignant head and neck tumors of epithelial origin. A phase IV clinical trial was designed and conducted in newly diagnosed and recurrent advanced HNC patients, to evaluate safety and efficacy in open population.

Materials and Methods

Study design

A phase IV multicenter, uncontrolled nor randomized, and open clinical trial was designed to evaluate safety, PFS and OS in advanced HNC patients treated with four therapeutic regimens of nimotuzumab: as monotherapy, Nimo+CT, Nimo+RT, and Nimo+CRT. A total of 225 patients were recruited. The hMab was administered by intravenous route (200 mg/dose), with six weekly doses during the induction phase, and subsequent doses every two weeks up to 24 months in the maintenance period. RT consisted in administration of 50.4-77 Gy with linear accelerators and Cobalt-60. Intensity-Modulated Radiation Therapy was not used. CT comprised of different drugs such as Cisplatin, Methotrexate, Docetaxel and 5-fluorouracil. The study was registered at the Cuban Registry of Clinical Trials (http://registroclinico.sld.cu/en/home; ID: RPCEC00000145).

Inclusion Criteria

Patients were eligible if they were older than 18 years old and had life expectancy ≥ 6 months. Other inclusion criteria were: patients who signed the informed consent model to participate in the study, with Eastern Cooperative Oncology Group (ECOG) scale of Performance Status ≤ 3, and with normal functioning of organs and bone marrow defined by laboratory parameters.

Exclusion Criteria

The exclusion criteria comprised patients who were pregnant or breastfeeding; with decompensated chronic diseases; with brain metastases; the presence of a second primary tumor, with the exception of basal or squamous cell carcinomas of the skin and treated carcinoma in situ of the neck; patients who were receiving another investigational product; who had been treated with nimotuzumab within 6 months prior to inclusion; and with a history of allergy attributed to compounds of chemical or biological composition similar to it.

Ethical considerations

The study was approved by the Ministry of Public Health (Cuba), the Institutional Ethics Committees and Cuban Regulatory Agency CECMED, and complied with the principles of the Declaration of Helsinki and Good Clinical Practice. A written consent for participating was required from each patient before his/her inclusion.

Evaluation during the study

PFS and OS were estimated for all patients. PFS was defined as the time from randomization until progression, and OS as the time from randomization until death from any cause; Kaplan-Meier curves were compared by the non-parametric Log-rank method [11]. Cox regression [12] was applied for subgroup analyses and Forest Plots were constructed. Common Toxicity Criteria to Evaluate AEs (version 3.0) was used to classify according to intensity, and AEs were also classified according to the System Organ Class affected.

Results

Patient population

A total of 225 patients were recruited in the study (Figure 1). Patients´ characteristics were analyzed according to age, sex, type of tumor (new diagnosis or recurrent), smoking and drinking status, ECOG performance status, stage, CT, RT and Second-line treatment (Table 1). The highest median age (72 years old) corresponded to Nimo+RT group. Patients were predominantly men. Newly diagnosed patients prevailed in Nimo+RT (71.4%) and Nimo+CRT (92.3%) regimens. Most patients were classified with ECOG 0 and 1 for all groups.

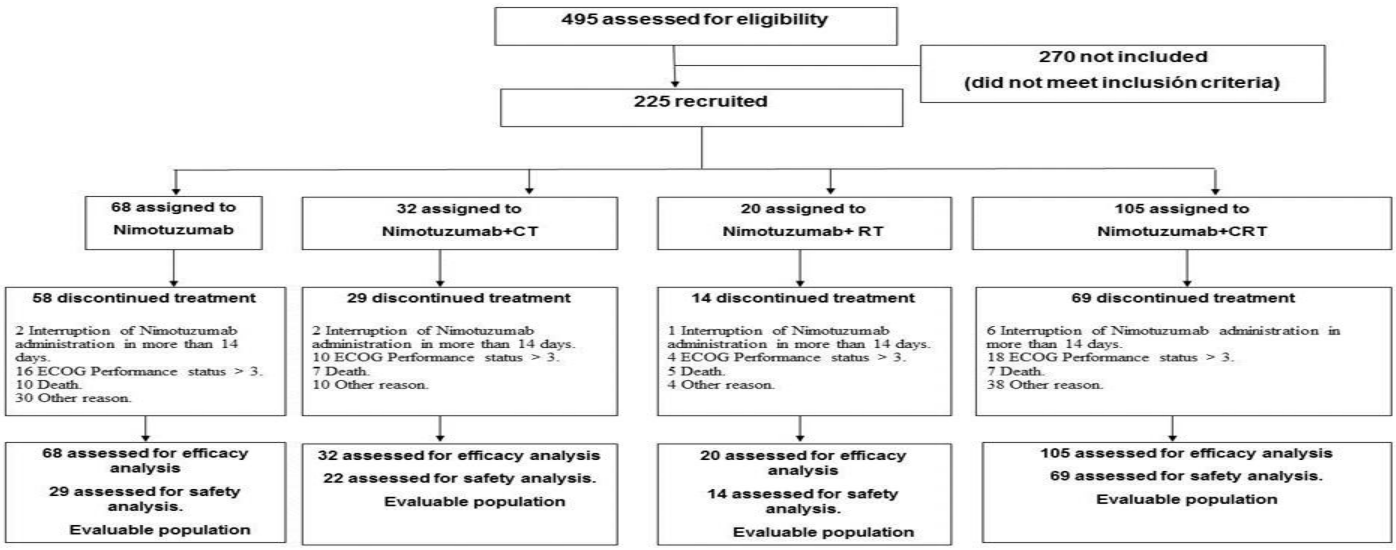

Figure 1: CONSORT Diagram.

Table 1: Patients´ characteristics.

Patients characteristics	Therapeutic scheme			
	Nimotuzumab (n=68)	Nimo+CT (n=32)	Nimo+ RT (n=20)	Nimo+CRT (n=105)
Age (median /p25-p75)	66 (60; 76)	58(48.5;64.5)	72 (63; 76)	57 (52; 63.5)
Sex				
Male	54 (79.4%)	28 (87.5%)	18 (85.7%)	92 (88.5%)
Female	14 (20.6%)	4 (12.5%)	3 (14.3%)	12 (11.5%)
Type of patient				
New diagnosis	30 (44.1%)	14 (43.8%)	15 (71.4%)	96 (92.3%)
Recurrent	38 (55.9%)	18 (56.3%)	6 (28.6%)	6 (5.8%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
Smoking status				
Ex - smoker	33 (48.5%)	12 (37.5%)	6 (28.6%)	48 (46.2%)
Smoker	21 (30.9%)	15 (46.9%)	10 (47.6%)	43 (41.3%)
Non - smoker	14 (20.6%)	5 (15.6%)	4 (19.0%)	11 (10.6%)
Not available	0 (0.0%)	0 (0.0%)	1 (4.8%)	2 (1.9%)
Drinking status				
Alcoholic beverage	25 (36.8%)	16 (50.0%)	13 (61.9%)	46 (44.2%)
Non- alcoholic beverage	43 (63.2%)	16 (50.0%)	7 (33.3%)	55 (52.9%)
Not available	0 (0.0%)	0 (0.0%)	1 (4.8%)	3 (2.9%)
Performance status (ECOG)				
0	28 (41.2%)	18 (56.3%)	12 (57.1%)	73 (70.2%)
1	26 (38.2%)	11 (34.4%)	7 (33.3%)	26 (25.0%)
2	12 (17.6%)	2 (6.3%)	1 (4.8%)	3 (2.9%)
3	2 (2.9%)	1 (3.1%)	1 (4.8%)	0 (0.0%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
Stage				
I	5 (7.4%)	3 (9.4%)	0 (0.0%)	0 (0.0)
II	6 (8.8%)	3 (9.4%)	2 (9.5%)	3 (2.9%)
III	28 (41.2%)	10 (31.3%)	12 (57.1%)	44 (42.3%)
IV	29 (42.7%)	16 (51.0%)	7 (33.4%)	55 (52.9%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
CT				
1st line	1 (1.5%)	18 (56.3%)	2 (9.5%)	77 (74.0%)
2nd line	3 (4.4%)	12 (37.5%)	0 (0.0%)	8 (7.7%)
No	64 (94.1%)	2 (6.3%)	19 (90.5%)	17 (16.3%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
RT				
Yes	2 (2.9%)	3 (9.4%)	20 (95.2%)	81 (77.9%)
No	66 (97.2%)	29 (90.6%)	1 (4.8%)	21 (20.2%)
Not available	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.9%)
2nd line treatment				
CT	3 (4.4%)	6 (18.8%)	0 (0.0%)	8 (7.7%)

RT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CRT	2 (2.9%)	0 (0.0%)	0 (0.0%)	4 (3.8%)
Surgery/				
RT/CT	2 (2.9%)	1 (3.1%)	1 (4.8%)	3 (2.9%)
No	44 (64.7%)	17 (53.1%)	15 (71.4%)	73 (70.2%)
Not available	17 (25.0%)	8 (25.0%)	5 (23.8%)	16 (15.4%)

Efficacy results

Nimo+CRT regimen offered higher medians of PFS and OS, as well as greater survival rates at 12 and 24 months (Tables 2,3 and Figures 2,3), with respect to the other therapeutic schemes evaluated in the clinical trial by ITT (n=155) in the newly diagnosed subgroup of patients. PFS and OS for those treated with Nimo+CRT were 22.4 months (p=0.065) and 24.3 months (p=0.089), respectively. In recurrent patients, this difference was not demonstrated between the regimens.

Taking into account the 155 newly diagnosed patients, subgroup analyses were performed considering patients included in Nimo+CRT versus nimotuzumab, Nimo+CT and Nimo+RT arms (Figures 4,5). In terms of PFS and OS, patients who received Nimo+CRT were benefited. Those who obtained the greatest benefit in PFS were men (HR 0.55; 0.43-0.71), ex-smokers (HR 0.49; 0.35-0.68), non-drinkers (HR 0.55; 0.39-0.78), patients with ECOG 0 (HR 0.37; 0.29-0.46), stage IV (HR 0.33; 0.27-0.39) and those who received RT (HR 0.46; 0.34-0.61) and First line of CT (HR 0.41; 0.30-0.57). Regarding OS, ex-smokers (HR 0.53; 0.36-0.76), ECOG 0 (HR 0.48; 0.35-0.65), stage IV (HR 0.30; 0.25-0.35) and patients with RT (HR 0.63; 0.41-0.97) and First line of CT (HR 0.43; 0.30-0.62) were benefited.

Table 2: PFS according to therapeutic schemes

PFS	Median (months)	12 months rate (%)	24 months rate (%)
New diagnosis (n=155)			
Nimotuzumab	9,902	42.1	34.4
Nimo-CT	8,885	28.1	28.1
Nimo-RT	5,279	42.9	28.6
Nimo-CRT	22,492	67.3	46.3
Log rank p=0.065			
Recurrent (n=68)			
Nimotuzumab	4,164	27	9
Nimo-CT	7,049	30.6	18.3
Nimo-RT	3,213	50	16.7
Nimo-CRT	7,344	16.7	16.7
Log rank p=0.713			

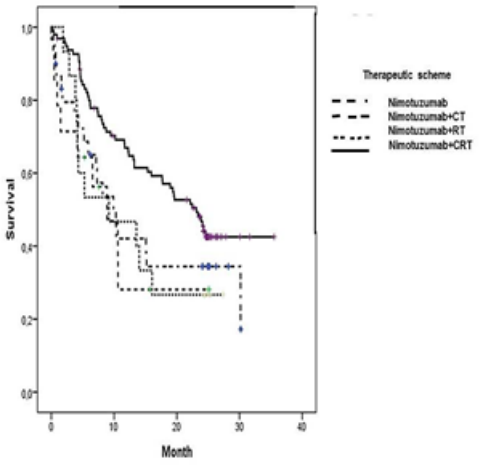

Figure 2: PFS Kaplan-Meier curves for newly diagnosed patients.

Table 3: OS according to therapeutic schemes.

OS	Median (months)	12 months rate (%)	24 months rate (%)
New Diagnosis (n=155)			
Nimotu-zumab	11,279	49.3	34.2
Nimo-CT	10,590	40.8	27.2
Nimo-RT	12,623	64.3	42.9
Nimo-CRT	24,393	70.1	50.3
Log rank p=0.089			
Recurrent (n=68)			
Nimotu-zumab	11,213	35.7	22.3
Nimo-CT	10,098	39.4	26.3
Nimo-RT	13,082	60	40
Nimo-CRT	11,607	50	16.7
Log rank p=0.750			

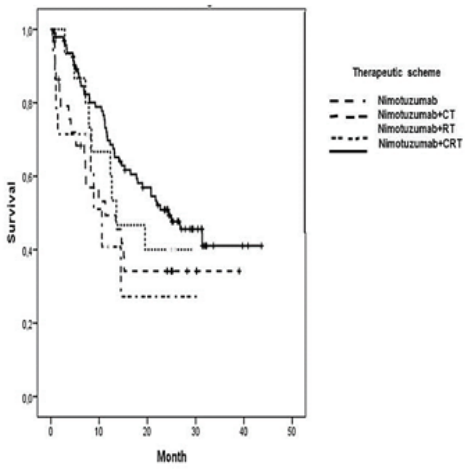

Figure 3: OS Kaplan-Meier curves for newly diagnosed patients

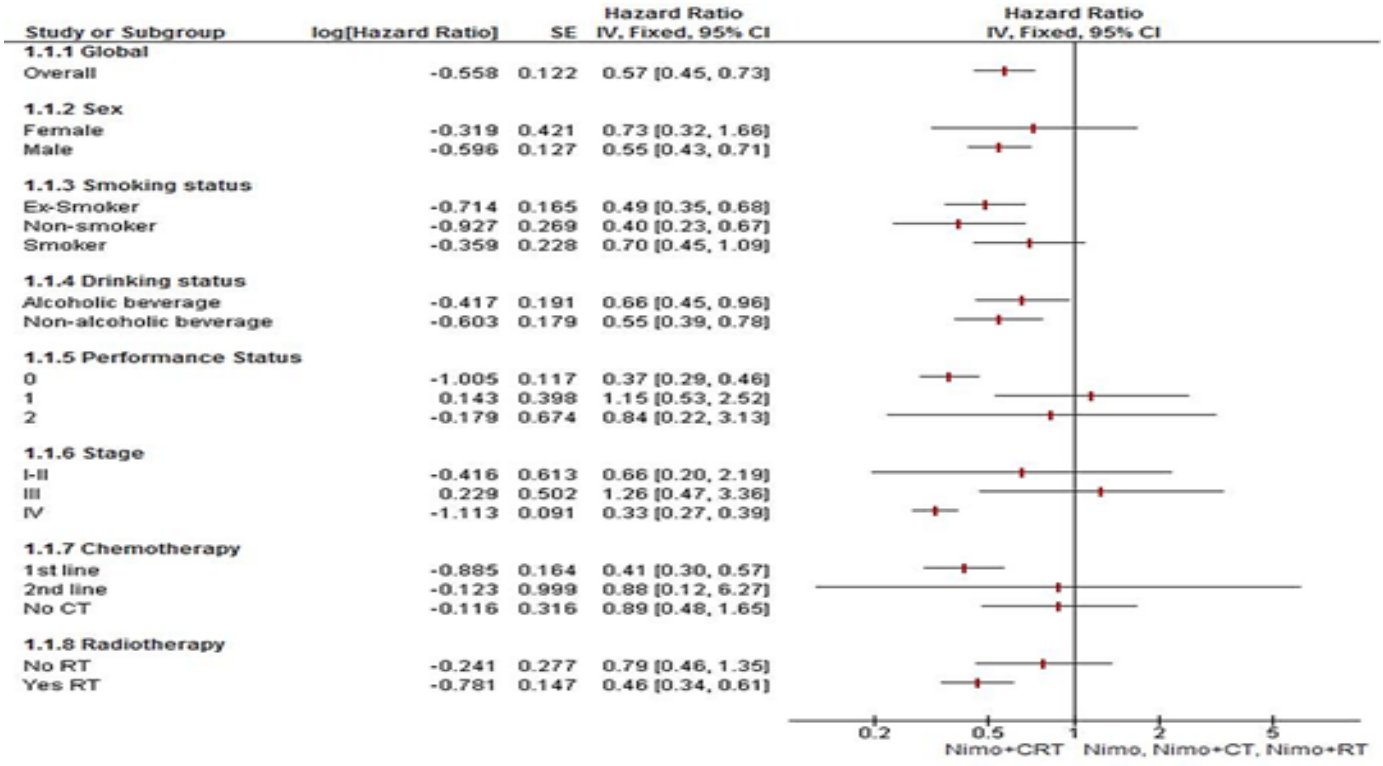

Figure 4: Subgroup analyses for PFS in newly diagnosed patients.

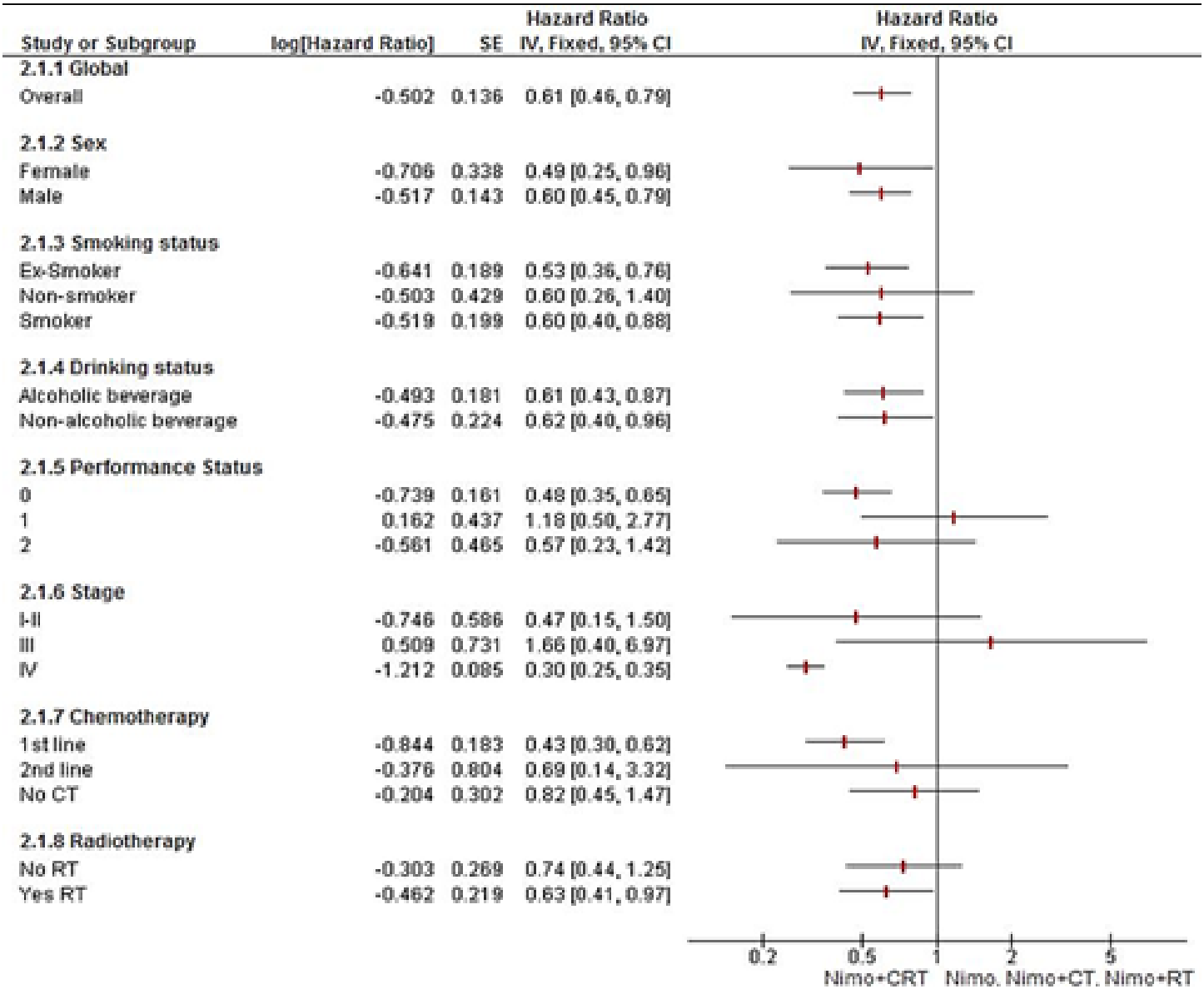

Figure 5: Subgroup analyses for OS in newly diagnosed patients. Figure 5: Subgroup analyses for OS in newly diagnosed patients.

Safety results

A total of 961 AEs were reported, 118 of them were related to the product administration, and were reported in 36 patients. In this subset, most frequent events related to the product were nausea (25% of patients), leukopenia/neutropenia (13.9%), anorexia (19.4%), fever (11.1%), anemia (13.9%), asthenia (16.7%) and vomiting (8.3%). AEs were classified according to the System Organ Class (Table 4), and the majority of AEs classified as grade I (Table 5) and non-serious.

Table 4: System Organ Class classification of related AEs according to the number of patients.

System	AEs	Therapeutic scheme								Total	
Organ		Nimotuzumab		Nimo+CT		Nimo+RT		Nimo+CRT			
Class		#	%	#	%	#	%	#	%	#	%
Blood and lymphatic system disorders	Anemia	0	0	0	0	0	0	5	25	5	13.9
Metabolism and nutrition disorders	Anorexia	0	0	1	20	1	25	5	25	7	19.4
Gastrointestinal disorders	Nausea	2	28.5	1	20	1	25	5	25	9	25
	Dysphagia	1	14.2	0	0	2	50	4	20	7	19.4
	Vomiting	0	0	0	0	0	0	3	15	3	8.3
	Diarrhea	1	14.2	0	0	0	0	1	1.7	2	5.6
				1	20	1	25	4	6.8	6	16.7
				0	0	0	0	3	15	4	11.1
				0	0	0	0	2	3.4	2	5.6
Investigations	Neutropenia/ leukopenia	0	0	0	0	0	0	5	25	5	13.9
	Weight loss	0	0	0	0	0	0	3	15	3	8.3
	Alanine amino transferase increased	0	0	0	0	0	0	1	5	1	2.7
	Creatinine increased	0	0	1	20	0	0	1	5	2	5.6
	Aspartate amino transferase increased	0	0	0	0	0	0	1	5	1	2.7
Nervous system disorders	Headache	1	14.2	0	0	0	0	3	15	4	11.1
	Dizziness	2	28.5	0	0	0	0	1	5	3	8.3
Musculoskeletal and connective tissue disorders	Arthralgia	0	0	1	20	0	0	1	5	2	5.6
Vascular disorders	Hypertension	0	0	1	20	0	0	1	5	2	5.6
Cardiac disorders	Tachycardia	0	0	0	0	0	0	1	5	1	2.7
Other		4	57.1	4	80	4	100	8	40	20	55.6
Total of patients		7	100	5	100	4	100	20	100	36	100

Table 5: Intensity of related AEs according to the number of patients.

Grade	Therapeutic scheme								Total	
	Nimotuzumab		Nimo+CT		Nimo+RT		Nimo+CRT			
	#	%	#	%	#	%	#	%	#	%
1	3	42.8	2	40	3	75	14	70	22	61.1
2	4	57.1	4	80	2	50	10	50	20	55.6
3	1	14.3	0	0	0	0	2	10	3	8.3
4	0	0	1	20	0	0	0	0	1	2.8
Not available	4	57.1	3	60	4	100	2	10	13	36.1
Total no of patients	7	100	5	100	4	100	20	100	36	100

Discussion

In previous clinical trials with nimotuzumab in patients with HNC [5, 9, 10] and other tumors [13-16], a favourable toxicity profile has been demonstrated. The most common AEs reported with intravenous infusion of nimotuzumab have been classified as grade I and II according to intensity and include fever, nausea, vomiting, muscle pain, headache and fatigue.

A previous multicenter phase IV study was conducted in Cuban patients with five treatment schemes that involved the oncospecific therapy combined with the ambulatory administration of nimotuzumab [17,18]. The five schemes were as follows: nimotuzumab as monotherapy, Nimo+RT, Nimo+CT, Nimotuzumab+concurrent CRT and Nimotuzumab+sequential CRT. A total of 439 patients were included with a pathological diagnosis of squamous cell carcinoma of head and neck in advanced stages, newly diagnosed or with progressive metastatic disease, tributaries to treatment with nimotuzumab in one of the schemes previously mentioned. Investigators concluded that the monoclonal antibody was safe, combined with different modalities of oncospecific therapy, since the majority of AEs classified as non-serious and were mild-intensity events.

In the present study, AEs related to the product were reported in 36 patients and most frequent events were anemia, leukopenia/neutropenia, anorexia, nausea, vomiting, asthenia and fever; the majority classified as grade I and non-serious. Although acneiform rash has been reported in treatment of squamous cell HNC patients with Cetuximab+platinum-based therapy with 5-Fluorouracil, and during therapy with Cetuximab+radiation [19], in the present study no acneiform rash was reported related to nimotuzumab. With these results, it is confirmed that nimotuzumab is safe, when administered to patients with this type of tumor and concomitant to CRT.

Patients with newly diagnosed advanced disease have a higher OS than recurrent patients [20]. The presence of distant disease or recurrent disease, in which patients are not candidates for surgery or RT, leads to a worse prognosis with an OS of 6-10 months [3].

Incorporation of Cetuximab into 5-Fluorouracil and platinum containing regimens in metastatic HNC, is associated with higher PFS (5.6 vs 3.3 months) and OS (10.1 vs 7.4 months) [21]. In the present study with nimotuzumab, the majority of patients classified as newly diagnosed (n=155) and there were 68 recurrent patients included. When the 68 recurrent patients were analyzed, the OS showed no statistical significance between the treatment schemes (p=0.750) and the medians were 11.2 (nimotuzumab as monotherapy), 10.0 (Nimo+CT), 13.0 (Nimo+RT) and 11.6 months (Nimo+CRT). In contrast, the ITT efficacy analyses showed a trend towards a better PFS (p=0.065) and OS (p=0.089) in newly diagnosed patients treated with Nimo+CRT, exhibiting 22.4 and 24.3 months, respectively.

Historically, monotherapy with surgery or RT was the cornerstone of the treatment; however, in the last decades the treatment paradigm includes concurrent CRT2. This

therapy was used in the present study in combination with nimotuzumab, and it was the scheme that showed better efficacy results in the newly diagnosed subgroup, achieving the highest medians of PFS and OS in comparison to the other regimens. In addition, in this subset the results for these two variables were similar in the schemes with nimotuzumab as monotherapy, Nimo+RT and Nimo+CT. In the previous phase IV study conducted in Cuban patients [17,18], in the subgroup with new diagnosis the regimens that combined both oncospecific therapies (RT and CT) with the monoclonal antibody, showed the highest medians of PFS (17.2 and 20.7 months) and OS (19.4 and 22.8 months) for the regimens nimotuzumab+concurrent CRT and nimotuzumab+sequential CRT, respectively. In the present study this is confirmed, exhibiting similar results.

Although the risk factors most associated with squamous cell carcinoma of the head and neck are smoking and alcohol intake, also the human papillomavirus (HPV) is an important cause of this cancer. HPV has been identified as a causative agent in these tumors, mainly in the oropharynx, and is responsible for the increase in the worldwide incidence of cancer at this level. Patients with HPV+ oropharyngeal cancer generally have a better prognosis than patients with HPV- cancer [22, 23]. In the present study, there is no characterization of the sample according to HPV expression, so the survival results could not be analyzed taking into account the sub-classification of patients according to this factor, which influences the prognosis.

Treatments directed to EGFR are in medical practice. EGFR is expressed in more than 90% of this type of cancer, and its over-expression has been linked to a poor prognosis for these patients. Monoclonal antibodies and small tyrosine kinase inhibitor molecules are two currently used strategies [2,24]. On the other hand, in the treatment of advanced HNC, resistance to CT and anti-EGFR agents constitutes a major problem, and new drugs with action at a molecular level are needed [25]. In this regard, the combination of several immunotherapeutic strategies represents a challenge to improve the antitumor immune response [4,26].

Conclusion

This study confirms the improved effectiveness in terms of PFS and OS of the combination of Nimo+CRT in open population of newly diagnosed patients with advanced HNC, compared with the administration of nimotuzumab as monotherapy, Nimo+RT and Nimo+CT. The results of this trial also sustain that the administration of the monoclonal antibody is safe.

List of abbreviations

AE: Adverse Event.
CRT: Chemo- and Radio-therapy.
CT: Chemotherapy.
ECOG: Eastern Cooperative Oncology Group.
EGFR: Epidermal Growth Factor Receptor.
hMab: humanized monoclonal antibody.
HNC: Head and neck cancer.
HPV: Human papillomavirus.
ITT: Intent-to-treat.
Nimo+CRT: nimotuzumab+Chemo+Radiotherapies.
Nimo+CT: nimotuzumab+Chemotherapy.
Nimo+RT: nimotuzumab+Radiotherapy.
OS: Overall Survival.
PFS: Progression-Free-Survival.
RT: Radiotherapy.

Ethics Approval and Consent to Participate

The study was approved by the Ministry of Public Health (Cuba), the Institutional Ethics Committees and Cuban Regulatory Agency CECMED, and complied with the principles of the Declaration of Helsinki and Good Clinical Practice. A written consent for participating was required from each patient before his/her inclusion.

Competing Interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

PP and GS designed the study; LV, PV, ELD, MAR and AR included and treated patients; ARV, YA and CMC monitored the trial; CEV performed the statistical analyses; LV, PV, GS, AM, MR and TC interpreted the data and critically revised the manuscript; AMV analyzed and interpreted the data, and wrote the manuscript. All authors read and approved the final manuscript.

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