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Oncology Gold Standard® practical consensus recommendations for the use of monoclonal antibodies in the management of squamous cell carcinoma of head and neck

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Abstract

We present the 2017 Oncology Gold Standard Practical Consensus Recommendation for use of monoclonal antibodies in the management of advanced squamous cell carcinoma of head neck region.

Key words: Combination therapy, guidelines, outcome, survival, targeted therapy

Introduction

The Oncology Gold Standard (OGS) Expert Group on Squamous Cell Carcinoma of Head Neck (SCCHN) met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines on the management of advanced SCCHN. Their discussions were based on the scenario as exists currently in India. The mandate was to develop practical consensus recommendations (PCR) applicable globally with emphasis on countries with limited resources. The expert group members included members of Indian Cooperative Oncology Network Trust, Molecular Oncology Society, Indian Society of Medical and Pediatric Oncology, Association of Radiation Oncologists of India, Indian Society of Oncology, and Indian Association of Surgical Oncology.

The manuscript is developed with the help of domain expertise of the expert group, published evidence and practical experience in real life management of such patients. Secretarial, academic, and educational support was provided by OGS.

The OGS PCR 2017 will, therefore, serve to optimize management of SCCHN in conjunction with evolving literature, good clinical judgment, and individual patient characteristics and preferences.

As part of the background work, current published evidence, and landmark papers was provided to the expert group panel members for review.[1-4] Members of the core and extended panel were encouraged to share their personal experiences, take into consideration unique features particular to countries with limited resources, make comments, and record dissent while voting for the consensus statements. Thus, the final manuscript is applicable globally.

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SCCHN is one of the most common cancers globally, in south Asia as well as in India.[5,6] In fact, some parts of India have the dubious distinction of having the world's highest incidence of the disease.[7,8] It is a disease of our lifestyle, with tobacco, alcohol, and HPV as well recognized causative agents.[7] Of unique interest on South Asia is the role of smokeless tobacco and betel nut.[8] The management of advanced SCCHN requires a multidisciplinary approach to optimize outcome. For several decades, progress in this field was painfully slow. For instance, the 2011 meta-analysis of concomitant chemoradiotherapy by Blanchard *et al*. included 16,192 patients and showed that the 5-year absolute benefits associated with the addition of chemotherapy was only 4%–8.9%.[9]

The first breakthrough, which led to substantial improvement in overall survival (OS), for patients with advanced SCCHN was with the use of monoclonal antibodies.[10] This was possible because of a better understanding of the molecular biology and specific pathways involved in carcinogenesis as well as disease progression, coupled with innovations in the development of targeted therapy using biological agents that could have a preferential impact on cancer cells. The initial promise of targeted therapy was cemented with a series of studies and publications spanning >10 years.[10-12] Substantial studies were also conducted in India, and the collective experience resulted in teasing out of several finer points that can help optimize outcome in individual patients.[13,14]

We, therefore, decided it was time to put the collective wisdom together and bring out a PCR on the use of currently available monoclonal antibody (MoAb) in the management of advanced SCCHN.

Is the use of monoclonal antibody in squamous cell carcinoma of head neck based on epidermal growth factor receptor biomarker testing?

The HER (erbB) family of transmembrane receptor tyrosine kinases play a vital role in tumor cell growth and survival of

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several cancers. This family includes epidermal growth factor receptor (EGFR), which has been demonstrated to have a pivotal role in normal cell growth, lineage determination, repair, and functional differentiation.

The benefit of targeted therapy in several cancers has been found to be associated with their use in a subpopulation of patients whose tumor cells demonstrated high expression of the target receptor, for instance, Her2 in breast cancer and EGFR in lung cancer. In SCCHN, overexpression of EGFR is easily detected by immunohistochemistry. Such an overexpression exists in almost all cases of SCCHN[10] and is also associated with poor prognosis.[14]

Because it is so ubiquitously expressed, studies have shown that EGFR testing is neither necessary nor does it provide additional information while treating SCCHN with targeted therapy, including the use of MoAb.[15]

What are the ways to target the overexpressed epidermal growth factor receptor in squamous cell carcinoma of head neck?

EGFR overexpressing SCCHN tumors can be targeted in several ways. The most common is the use of large (syn MoAb) or small (syn tyrosine kinase inhibitors [TKIs]) molecules. The large MoAbs bind to the extracellular domain of the EGFR receptor. Apart from blocking the downstream EGFR signaling, they also recruit Fc-receptor-expressing immune effector cells and trigger the antibody-dependent cellular cytotoxicity to facilitate tumor lysis. The small-molecule TKIs enter the cell and act on the intracellular domain by typically competing with native adenosine triphosphate for binding.

In addition, recent advances have also documented the potential role of gene therapy as well as nucleic acid-based molecules (antisense oligodeoxynucleotides and small interfering mRNA).[16]

Of all the options currently available, use of MoAb in combination with conventional modalities of therapy provides the best outcome.

What are the currently available monoclonal antibodyies that target epidermal growth factor receptor in squamous cell carcinoma of head neck with meaningful clinical benefit?

The various MoAb approved for or under development for SCCHN have one thing in common that they target the EGFR. Cetuximab, nimotuzumab, and panitumumab are currently available and shall be the focus of these recommendations.[10,11,13,17]

Cetuximab was the first MoAb to be developed, studied and approved in SCCHN. It belongs to the first generation of chimeric MoAb and binds monovalently to EGFR.

The EXTREME trial in 442 patients with untreated recurrent or metastatic SCCHN showed that addition of cetuximab to platinum – fluorouracil prolonged the median OS from 7.4 to 10.1 months (hazard ratio [HR] 0.80; $P = 0.04$) Table 1. The median progression-free survival (PFS) time also improved from 3.3 to 5.6 months (HR 0.54; $P < 0.001$) and the increase in relative risk RR was from 20% to 36% ($P < 0.001$).[18]

In 2006, the landmark multicentric randomized controlled trial by Bonner *et al*. studied the role of cetuximab in 424 patients receiving radiotherapy for locoregionally advanced SCCHN. Updated 5-year follow-up confirmed that addition of cetuximab increased median PFS (24.4 mo vs. 14.9 mo) as well as median OS (49 mo vs. 29.3 mo; $P = 0.018$) and conclusively proved the value of MoAb in SCCHN – being superior to radiotherapy alone.[11]

Nimotuzumab, the second MoAb developed for SCCHN, is a humanized IgG1 isotype MoAb with bivalent binding to EGFR. In nimotuzumab, the complementarity determining regions of the murine IgG2a monoclonal ioregf/r3 is combined with the human framework assisted by computer modeling.

In 2010, a randomized, placebo-controlled, multicenter trial was published on 106 patients with advanced locoregional (unresectable) platinum ineligible SCCHN. Both arms received RT and patients were randomized to receive additional nimotuzumab ($n = 54$) or placebo ($n = 52$) Table 2. About 59.5% of patients receiving nimotuzumab plus irradiation achieved complete response while it was only 34.2% of the individuals treated with irradiation plus a placebo. In the intent to treat analysis, the median survival of the patients treated with nimotuzumab and RT was 12.50 months while individuals treated with the placebo plus irradiation had a median of 9.47 months ($P = 0.049$).[12]

Another randomized multicentric clinical trial with 92 patients by Reddy *et al*., studied the role of nimotuzumab to two standard of care regimen, namely, radiotherapy and chemoradiotherapy [Table 3]. Overall response at month 6 posttreatment was 100% and 70% with CRT + nimotuzumab and CRT while its 76% and 37% with RT + nimotuzumab and RT, respectively. At month 60, OS was 57% with CRT + nimotuzumab, 26% with CRT ($P = 0.03$), 39% with RT + nimotuzumab, and 26% with RT ($P > 0.05$). Median OS was not reached for CRT + nimotuzumab; it was 21.94 months for CRT ($P = 0.0078$), 14.36 months for RT + nimotuzumab, and 12.78 months for RT ($P = 0.45$). Nimotuzumab did not deteriorate the Karnofsky performance score (KPS) of the patient when it was added to either CT + RT or RT.[13]

Panitumumab, the third MoAb, has been studied in SCCHN with modest or no benefit.

An open-label randomized control phase III trial in recurrent and metastatic SCCHN included 657 patients of which 330 patients were randomized to chemotherapy alone (CDDP + 5FU) and 327 to CT plus panitumumab. There was no improvement of median OS by adding panitumumab (11.1 mo vs. 9 mo, $P = 0.14$), though the median PFS was better by 1.2 months (5.8 months vs. 4.6 months, $P = 0.0036$).[17]

Table 1: Cetuximab results of EXTREME trial

	Cetuximab + CT	CT alone	*P*
Number of patients	222	220	
Median PFS	5.6 months	3.3 months	<0.01
Median OS	10.1 months	7.4 months	0.04

CT=Chemotherapy, PFS=Progression-free survival, OS=Overall survival

Table 2: Nimotuzumab results in trial by Rodriguez

	Nimotuzumab + RT	Placebo + RT	*P*
Number of patients	54	52	
CR	59.5%	34.2%	
Median OS	12.5 months	9.47 months	0.0491

RT=Radiotherapy, CR=Complete response, OS=Overall survival

Table 3: Reddy *et al.* study results in 92 randomized patients (2014)

	Nimotuzumab + CRT	CRT alone	*P*	Nimotuzumab + RT	RT alone	*P*
ORR	100%	70%	0.02	76%	37%	0.023
5 years OS	57%	26%	0.03	39%	26%	NS
Median OS	Not reached	22 months	0.036	14.4 months	12.8 months	NS

OS=Overall survival, CRT=Chemoradiotherapy, RT=Radiotherapy, ORR=Objective response rate, NS=Not significant

Another trial with panitumumab conducted by Canadian cancer trials group consisted of 320 patients with locally advanced SCCHN [Table 4]. This compared panitumumab with accelerated-fractionation RT (Arm A) versus standard chemoradiotherapy (Arm B). The results did not show any benefit by the addition of panitumumab. In intention-to-treat population, 2-year PFS was 73% in arm A and 76% in arm B ($P = 0.83$). Two-year OS was 85% in arm A and 88% in arm B ($P = 0.66$).[19]

Other monoclonal antibody in Squamous Cell Carcinoma of Head Neck

In addition, other MoAb such as zalutumumab, necitumumab, and duligotuzumab also target EGFR, are under development, and regulatory approval submission is pending.[20]

In 2016, US FDA approved two new MoAb, nivolumab, and pembrolizumab with a mechanism of action that is different – the new immunotherapeutic drugs. Currently, they are approved only after standard of care has failed.[21,22]

Pembrolizumab is a humanized MoAb that binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. It has currently received accelerated approval for patients with disease progression on or after platinum-containing chemotherapy.[21]

Nivolumab is another human PD-1 receptor blocking humanized MoAb. Its approval is based on the phase III study having 361 patients with previously treated metastatic or recurrent SCCHN. The median OS with nivolumab was 7.5 months compared with 5.1 months with investigator's choice (HR, 0.70; 95% confidence interval [CI], 0.51–0.96; $P = 0.0101$). The objective response rate (ORR) was 13.3% with nivolumab and 5.8% for investigator's choice in.[22]

Atezolizumab and durvalumab are other immunotherapeutic agents which are currently being evaluated in head and neck cancer.[23]

What are the fundamental differences between cetuximab and nimotuzumab monoclonal antibodies?

Cetuximab belongs to the older first generation of chimeric MoAb. Therefore, it binds to the EGFR in a monovalent as well as bivalent fashion stably. Its binding to EGFR also seems to be independent of expression density of EGFR. As a result, it has tendency to bind to cells expressing low levels of EGFR (some normal cells) as well as those with high levels of EGFR (malignant cells, SCCHN).[10,11]

Nimotuzumab, on the other hand, is a humanized IgG1 isotype MoAb that has an intermediate affinity toward EGFR. Therefore, it requires bivalent binding with EGFR for stable attachment to the cellular surface. Hence, nimotuzumab can bind to EGFR overexpressing cells at high spatial density (overcrowding) of EGFR, thus making the high EGFR overexpressing cancer cells a selective target for nimotuzumab.[24]

Table 4: Panitumumab results from study by Vermorken *et al.*

	Panitumumab + RT	CRT	*P*
n	160	160	
2 year PFS	73%	76%	0.83
2 year OS	85%	88%	0.66

PFS=Progression-free survival, OS=Overall survival, CRT=Chemoradiotherapy, RT=Radiotherapy

Garrido *et al*. have clearly demonstrated the implications of this difference in binding to EGFR [Figure 1]. They have shown that when a cells EGFR expression is low [as in certain nonmalignant cells – Figure 1a], in the level of accumulation, with very little binding occurring with nimotuzumab binding of cetuximab is significantly higher than that of nimotuzumab as it binds to EGFR monovalently. On the other hand, when cells have high EGFR expression, [as in SCCHN cells – Figure 1b], both cetuximab, as well as nimotuzumab, binds equally.

What is the clinical implication of monovalent binding with cetuximab versus bivalent binding with nimotuzumab?

The difference between nimotuzumab and cetuximab in how these MoAbs bind to some normal cells – a factor related to spatial density of binding ligands. As is well established, drug effect on normal cells results in toxicity and for patients with advanced disease, toxicity is a major concern. While improving outcome, attention to preserving/improving quality of life (QoL) is of importance.

Because cetuximab binds with equal affinity to low EGFR expressing normal cells, skin toxicity (rash) is significantly higher. This occurs in some patients and has been often considered as a biomarker of response. On the other hand, there is hardly any skin toxicity reported with nimotuzumab. The difference in binding mechanism explains why skin toxicity does not occur with nimotuzumab. It is also the scientific basis for establishing that lack of skin toxicity has no implication about the efficacy of nimotuzumab.[10,11,13,24]

Such dermatitis can be a potentially significant toxicity. This was seen in the Italian study on locally advanced SCCHN where 73% patients receiving radiotherapy plus concurrent weekly cetuximab developed grade 3 dermatitis.[25] Merlano *et al*. also highlighted the occurrence of stomatitis and radiodermatitis in their study. It occurred in each and every one of their patients and in 49% (22/45), it was so severe that they required parenteral nutrition.

Other toxicities also need to be taken into consideration. For instance, the original landmark Bonner *et al*. study with cetuximab showed significantly higher grade 3+ infusion reactions.[11]

Ang *et al*. reported on what happens to toxicity when cetuximab is added to standard cisplatin-RT (CRT) in a prospective randomized study involving 940 patients. Besides the usual skin reactions (dermatitis/mucositis),

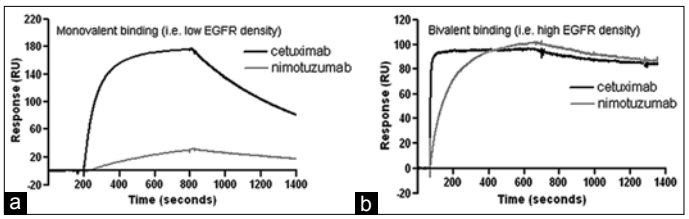

Figure 1: EGFR binding with cetuximab and niomtuzumab (reproduced from Garrido *et al* Cancer Biol Ther 2011)

Table 5: Toxicity comparison between nimotuzumab and CDDP in squamous cell carcinoma of head and neck

	Nimotuzumab arm	CDDP arm	*P*
n	82	73	
GI toxicity (Group 3 or 4)	4.2%	33.7%	<0.001
Hematological toxicity (Group 2-4)	9.7%	59%	<0.001
Mucositis/dermatitis (Group 3 or 4)	28%	41%	0.13

GI=Gastrointestinal, CPPD=Cisplatin

they also reported statistically significant higher headache, hypomagnesemia, and hypocalcemia in the cetuximab arm.[26]

A study by Magrini *et al*. (comparator arm cisplatin + RT) showed lower compliance and increased acute toxicity in the cetuximab + RT arm without better efficacy.[27]

Moreover, Pfister *et al*. found that addition of cetuximab to standard chemoradiotherapy (CRT) lead to such unacceptable toxicity that the study had to be terminated prematurely, two patients developed acute toxicity leading to death and two others were diagnosed with grade 4 cardiac events.[28]

In contrast, a nimotuzumab study of 150 patients with locally advanced SCCHN involved the use of the MoAb with RT and/or CRT. This study reported six adverse events (8%) related to nimotuzumab alone and 4 (5.33%) adverse events were reported to be related to nimotuzumab in combination with RT/CRT.[12]

This was collaborated by Reddy *et al*.'s study which documented that nimotuzumab resulted in skin rash in only 6.5% of their patients.[13]

In fact, the study by Rodríguez even evaluated QoL in 42 patients using EORTC QLC-C30 and QLQ-H and N35 questionnaires. It found that QoL was similar in the nimotuzumab as well as the placebo arms at baseline whereas the nimotuzumab arm showed the highest health score after treatment.[12]

In study by Ramakrishnan *et al*. all nimotuzumab related adverse events were mild-to-moderate, self-limiting, and reversible. The only nimotuzumab-related SAE was infusion reaction in a single patient.[29]

In a study of 155 patients, toxicity was as shown in Table 5.

Thus, all toxicities are significantly lower with nimotuzumab as compared to cetuximab. This not only includes rash/dermatitis but also more severe ones such as cardiotoxicity, acute death (necessitating premature termination of the study).[30]

What does the published Indian data on cetuximab and nimotuzumab show?

Apart from pivotal/international/regulatory clinical trials, many clinicians from India have published or presented studies on cetuximab and/or nimotuzumab in SCCHN. Following is the compilation of such studies. Table 6 shows the published Indian data on cetuximab in SCCHN.[14,31-38]

Similarly, Table 7 shows the published Indian data on nimotuzimab in SCCHN.[39-47]

What are the efficacy differences between cetuximab and nimotuzumab?

There are no head-to-head comparison trials of cetuximab versus nimotuzumab, and they are unlikely to ever happen. Hence, the expert group made indirect comparisons and assumptions based on available published data. Trends in worldwide use and limitations in the application of the published treatment guidelines are also hard facts that were taken into consideration.

Published Indian data clearly shows that, in SCCHN, a significantly higher number of patients achieve CR with nimotuzumab (ranging from 49% to 90%) than with Cetuximab.[10-13]

Development of significant rash while receiving cetuximab is a predictor of response. The five-year follow-up update of the Bonner study showed that acneiform rash (grade 2 and higher) predicted improved OS as compared to those with absent or grade 1 rash (HR 0.49; CI 0.34–0.72; $P = 0.002$).[11]

Since rash is rare with Nimotuzumab, we cannot comment on any correlation.[12]

Ang *et al*. reported on the RTOG 0522, a randomized Phase III Trial ($n = 940$) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV H and N carcinoma concluded that adding cetuximab to radiation-cisplatin did not improve outcome and hence should not be prescribed routinely. PFS and OS did not differ by EGFR expression. This is also the same experience in the Indian study by Rawat S wherein the outcome was worse in the cetuximab arm.[14,26]

The efficacy data from GSTTC Italian Group's study compared concurrent cetuximab-radiation with concurrent-cisplatin radiation with or without induction in a 2 × 2 design showed that addition of cetuximab did not lead to any significant differences for RR, PFS, and OS.[48]

In the study by Ghi *et al*., 421 patients were randomized to CRT (standard arm; $n = 261$) versus Cetuximab-RT (experimental arm; $n = 160$). There was no difference between the two arms for ORR, PFS, or OS.[49]

Thus, cetuximab should not be added to chemoradiotherapy regimen. Furthermore, cetuximab-RT is no better than CRT combination.

For patients who are not suitable for cisplatin as part of the treatment, the subgroup analysis in 5-year update of the Bonner trial gives important insight. It showed that there is no benefit of the addition of cetuximab to radiotherapy for patients who are older than 65 or whose KPS is <90.[11]

RCT on 106 platinum ineligible patients showed 59.5% of patients receiving nimotuzumab plus irradiation achieved complete response while it was only 34.2% of patients treated with irradiation plus a placebo. In the intent to treat analysis, the median survival of the patients treated with nimotuzumab and RT was 12.50 months while individuals

Table 6: Additional cetuximab data from India

Study title	Author	Patients	Results
Comparison between weekly cisplatin-enhanced RT and cetuximab-enhanced RT in locally advanced SCCHN: First retrospective study in Asian population	Rawat S	53	Median OS worse with cetuximab (32.5 months vs. 53.6 months; *P* 0.044)
Chemoradiation with elderly with head neck cancer: A single institution experience	Kataria T	32	3 patients received cetuximab
Cetuximab and cancers of the head and neck: Tapping the circadian rhythm	Shukla P	NA	Cetuximab should be administered between 11 am and 3 pm to minimize toxicity
Cetuximab with RT in patients with locoregionally advances SCCHN unsuitable or ineligible for concurrent CRT: Ready for routine clinical practice?	Agarwal JP	37	15 (40.5%) developed >Group 3 dermatitis; 2 year DFS and OS were 29.5% and 44.4%
Cetuximab plus RT in patients with unresectable locally advanced SCCHN - an open labeled single arm Phase II study	Dattatreya S	19	ORR 68.4%, 2 years OS 84%
Palliative weekly CT along with cetuximab in recurrent and metastatic SCCHN: A retrospective study	Rangaraju RR	35	ORR 18 (56.2%); median OS 8.02 months
A retrospective analysis of patients with head neck cancer treated with radiation, hyperthermia and cetuximab: A brief report of outcome	Huilgol NG	6	CR 100%
Efficacy and toxicity of cetuximab with CT in recurrent and metastatic SCCHN: A prospective observational study	Tiwari S	50	ORR 25 (50%); median PFS 5.3 months; median OS 9.9 months
A tertiary care experience with paclitaxel and cetuximab as palliative CT in SCCHN	Noronha V	100	ORR 38.5%; median PFS 152 days; median OS 314 days
Total patients in the pooled analysis		332	

SCCHN=Squamous cell carcinoma of head and neck, CT=Chemotherapy, CRT=Chemoradiotherapy, RT=Radiotherapy, DFS=Disease-free survival, OS=Overall survival, ORR=Objective response rate, PFS=Progression-free survival, CR=Complete response

Table 7: Additional nimotuzumab data from India

Study title	Author	Patients	ORR (%)	CR (%)
Nimotuzumab with concurrent CRT				
Results from a pilot study of nimotuzumab with concurrent CRT in patients with LASCCHN	K T Bhowmik	31	87	65
Retrospective analysis of head and neck cancer patients successfully treated with chemoradiation plus nimotuzumab	S M Karandikar	16	75	75
A comparative study of MoAb against EGFR (nimotuzumab) used in combination with CRT versus CRT alone in the treatment of LASCCHN	Aseem Bhatnagar	25	96	N/A
To assess the possibility of combining MoAb (Nimotuzumab) with concurrent CRT in patients with LASCCHN	Kumar A	11	90	60
Nimotuzumab in concurrent CRT in patients with LASCCHN	Naresh Somani	57	81	60
Nimotuzumab with concurrent chemoradiation in inoperable locally advanced squamous cell carcinoma of head and neck: An Indian experience	Ankur Bahl	35	97	49
BEST trial		20	100	90
Total in CRT + nimotuzumab studies		195	89	63
Study title	**Author**	**Patients**	**Results**	
Other studies				
Nimotuzumab in induction CT and chemoradiation in patients with advanced head and neck cancer - retrospective study	S Subramanian	16	CR in 6 patients, PD in 6 patients, 4 patients lost to follow-up	
Nimotuzumab and IMRT in the concurrent setting of locally advanced head and neck cancers: Early results of a prospective trial in India	Kaustav Talapatra	25	Locoregional control in 72% patients, residual at primary in 12% patients, residual disease at node in 8%, and progress of disease in 8%	
Therapeutic effect of concurrent radiation with single agent nimotuzumab in locally advanced and recurrent HNSCC: Retrospective analysis	Kondaveeti SS	23	CR 65.2%, PR 13%, SD 4.4%	
Total patients in the pooled analysis		259		

IMRT=Intensity Modulated Radiation Therapy, LASCCHN=Locally advanced squamous cell carcinoma of head and neck, CRT=Chemoradiotherapy, PD=Programmed death, MoAb=Monoclonal antibody, N/A=Not available, ORR=Objective response rate, CR=Complete response, EGFR=Epidermal growth factor receptor, CT=Chemotherapy, HNSCC=Head and neck squamous cell carcinoma, PR=Partial response, SD=Stable disease

treated with the placebo plus irradiation had a median of 9.47 months (P = 0.0491).[12]

Thus, nimotuzumab is efficacious in combination with chemoradiotherapy as well as RT alone.

Conclusions and Take Home Messages

Thus, the OGS Expert Group on SCCHN has provided this consensus practical recommendation for use in the community for the management of advanced SCCHN. This is

Table 8: Oncology Gold Standard practical consensus recommendations for monoclonal antibody in advanced squamous cell carcinoma of head and neck

MoAb are useful in SCCHN for 3 different patients populations having unresectable locally advanced head and neck cancers
With upfront concurrent CRT
With RT only for patients who cannot tolerate CT
For recurrent/metastatic patients
Selection of the MoAb is guided by the following three circumstances
Nimotuzumab is the preferred MoAb in combination with CRT for SCCHN patients
Cetuximab is the preferred MoAb for recurrent or metastatic SCCHN patients
Either nimotuzumab or cetuximab can be used with RT in platinum ineligible patients, the decision being based on what toxicity needs to be avoided

CRT=Chemoradiotherapy, CT=Chemotherapy, MoAb=Monoclonal antibody, SCCHN=Squamous cell carcinoma of head and neck, RT=Radiotherapy

applicable globally with emphasis on countries with limited resources.

The OGS PCR 2017 will, therefore, serve to optimize management of SCCHN in conjunction with evolving literature, good clinical judgment, and individual patient characteristics and preferences.

The availability of MoAb targeting EGFR is the first breakthrough in several decades that has led to improvement in the OS of patients with advanced SCCHN.

Out of the many MoAbs studied, cetuximab and nimotuzumab are currently recognized as part of standard management of SCCHN [Table 8].

Cetuximab is the first generation of chimeric MoAb that binds to EGFR monovalently whereas nimotuzumab is the second generation humanized IgG1 isotype MoAb that binds bivalently to EGFR.

Testing for EGFR does not have any role in deciding whether the patient will respond to/benefit from use of these MoAb.

Addition of these MoAb to conventional therapy (chemotherapy/RT/CRT) of advanced SCCHN is to be used judiciously and for selected patients only.

Selection of the appropriate MoAb depends on several factors – important ones being status of disease, intent of treatment, biological age, performance status, comorbidities, ability/willingness of the patient to tolerate potential side-effects, and family's ability to manage resources to complete planned therapy.

Both cetuximab and nimotuzumab can be used in combination with RT with similar benefit. The toxicity profile should help in deciding which MoAb to be used for individual patients.

Toxicity is significantly higher with cetuximab + RT as compared to nimotuzumab + RT for all patient types and groups.

For patients who are ineligible for cisplatin in combination with RT, replacing cisplatin with cetuximab does not provide any benefit.

For patients with age ≥65 years or for those with KPS <80, nimotuzumab plus radiation therapy is preferred over cetuximab plus radiation therapy as well as palliative radiation therapy alone.

Nimotuzumab is the only MoAb that can be currently used in combination with CRT.

In patients with metastatic/recurrent disease, cetuximab along with cisplatin plus 5-FU should be the choice of treatment. Currently, no data is available about nimotuzumab in these patients, and further evaluation is required to understand its precise role.

HPV-associated SCCHN – currently recommendation for the use of MoAb in SCCHN is not dependent on HPV status. They should, therefore, continue to be used as appropriate in both HPV positive as well as negative cases.

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Conflicts of interest

There are no conflicts of interest.

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