Subject: International expert panel for the development of guidelines for the definition of survival endpoints in clinical trials (**DATECAN project - Définition, évaluation et Analyse des criTères de survie dans les Essais randomisés en CANcérologie**)

Dear Colleague,

Thank you for agreeing to participate to the International DATECAN expert panel that will develop ***guidelines for the definition of survival endpoints in clinical trials***. These guidelines will be developed using a consensus methodology based on experts' opinions obtained in a systematic manner. This method has been validated and is now commonly used to elaborate recommendations and guidelines. The protocol of the DATECAN project has been recently published in the European Journal of Cancer (Bellera et al. Eur J Cancer 2013;49(4):769-81).

Specifically, you have been selected to participate as member of the ***Head and Neck cancer Rating Committee of the DATECAN project***. As one of the many experts of this committee, you have thus accepted to participate in up to two rounds of rating. Items for which no strong consensus was reached at the end of the second round are discussed during an in-person meeting involving all experts.

Please note that all your answers will be kept confidential and will be communicated only on an aggregated basis.

We are contacting you due to your implication and your expertise in clinical research and in the treatment of head and neck cancer.

We are pleased to enclose the materials that you will need for the first round of this consensus panel:

- Page 3-5: Presentation of the questionnaire and rating instructions
- Page 6-7: Mailing instructions and definitions of terms
- Pages 8-19: ***Head and Neck*** cancer DATECAN scoring form
- Page 20-22 : The ***Head and Neck*** cancer participants

We are asking you to fill out the scoring forms and return them by regular mail service, fax, or email within 4 weeks, that is, no later **than 31st December, 2016**. Note, that the form can also be completed online. Instructions for sending the forms are detailed on page 6.

We thank you for your active participation in this project. Should you have any questions, we can be reached at the e-mail listed on page 7.

Yours sincerely,

On behalf of the Head and Neck cancer Steering Committee

Dr. Lisa Licitra, Medical Oncologist, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milano, Italy.

Prof. Kian Ang, Radiation Oncologist, MD Anderson Cancer Center, Houston, USA. Pr Ang unfortunately passed away in June 2013. We are so much grateful for his contribution to this project.

Dr. Bertrand Baujat, Surgeon, Hôpital Tenon, Paris, France.

Prof. Gregory Pond, Biostatistician, Ontario Clinical Oncology Group OCOG / CTMG Henderson Research Centre, Hamilton, Canada.

Dr Christophe Le Tourneau, Medical Oncologist, Institut Curie, Paris, France.

Dr Anne Auperin, Biostatistician, Institut Gustave Roussy, Villejuif, France.

Catherine Fortpied, Senior Biostatistician, EORTC, Brussels, Belgium.

This study was supported by a grant from
Ligue Nationale Contre le cancer (APP 2009)

DATECAN scoring form for Head and Neck cancer

On the next pages, we ask you to please fill out a scoring form to judge which events (such as appearance of metastases, treatment-related deaths, etc…) should be included when evaluating various survival/time-to-event endpoints.

The outcomes and events listed have been selected by the ***Head and Neck*** cancer steering committee.

Following the recommendations of the steering committee, five different clinical settings are defined, representing the patient clinical status at the time he/she is recruited in the trial:

- Initial curative surgery (Surg)
- Initial curative radiotherapy (+/-chemotherapy) (RT-CT)
- Recurrence and/or metastatic disease not suitable for local therapy (R/M)
- Organ preservation setting (Preserv)
- Prevention (Prev)

In the framework defined above, the question that we ask you to answer is thus "which events should be considered in the definition of that particular endpoint"

Survival endpoints considered for consensus

The following survival endpoints are considered (and settings in which they apply):

Settings: Endpoints:	Surg	RT-CT	R/M	Preserv	Prev
Overall survival	X	X	X	X	
Time to local progression	X	X		X	
Local control	X	X		X	
Local progression-free survival	X	X		X	
Time to regional progression	X	X		X	
Regional control	X	X		X	
Regional progression-free survival	X	X		X	
Time to locoregional progression	X	X		X	
Locoregional control	X	X		X	
Locoregional progression-free survival	X	X		X	
Time to death without any carcinologic event	X	X		X	
Time to distant metastases	X	X		X	
Distant metastasis-free survival	X	X	X	X	
Disease-free survival	X				
Progression-free survival	X	X	X	X	
Event-free survival	X	X	X	X	X
2nd cancer-free survival	X	X	X	X	X
Time to second cancer	X	X	X	X	X
Precancerous lesions-free survival					X

Settings: Endpoints:	Surg	RT-CT	R/M	Preserv	Prev
Laryngeal dysfunction-free survival				X	
Laryngeal dysfunction-free and disease free survival				X	
Laryngo-esophageal dysfunction-free survival				X	
Laryngo-esophageal dysfunction-free and disease free survival				X	
Time to laryngectomy				X	
Time to tracheotomy				X	

Overall Survival will not be considered in the questionnaire because there is no ambiguity in its definition.

Scoring Instructions

For each endpoint, several events will be proposed to you (e.g. local progression, etc). For each of them, we will ask you to score, on a scale ranging from ***1 (totally disagree)*** to ***9 (totally agree)*** if, according to you, that event should be considered in the definition of this endpoint.

EXAMPLES

Example 1. PLEASE INDICATE ON A SCALE OF ***1 (TOTALLY DISAGREE)*** TO ***9 (TOTALLY AGREE)*** WHETHER THE EVENTS BELOW SHOULD BE CONSIDERED FOR EACH SURVIVAL OUTCOME.

EVENT: **OUTCOME:**	**Local progression**	**Occurrence of distant metastases**	**Death related to primary cancer**	**Death related to a second cancer**	**Death related to acute toxicity of protocol treatment**	**Death related to non acute toxicity of protocol treatment**	**Death related to causes other than primary cancer, second cancer and toxicity**
Overall survival	**1**	**1**	**9**	**9**	**9**	**9**	**9**

Since according to us, all deaths should be considered an event for this endpoint but local progression and occurrence of distant metastases should not at all, we complete a '1' in the columns corresponding to the first two events, and a '9' in all other columns.

Example 2. PLEASE INDICATE ON A SCALE OF ***1 (TOTALLY DISAGREE)*** TO ***9 (TOTALLY AGREE)*** WHETHER THE EVENTS BELOW SHOULD BE CONSIDERED FOR EACH SURVIVAL OUTCOME.

EVENT: **OUTCOME:**	**Local progression**	**Occurrence of distant metastases**	**Death related to primary cancer**	**Death related to a second cancer**	**Death related to acute toxicity of protocol treatment**	**Death related to non acute toxicity of protocol treatment**	**Death related to causes other than primary cancer, second cancer and toxicity**
Time-to-event 'X'	**3**	**3**	**8**	**1**	**1**	**1**	**1**

When considering time-to-event 'X', if you strongly believe that death related to the primary cancer site should be considered, you definitely think that deaths of other cause should not be included but you are not fully convinced that local progression and occurrence of distant metastases should be included, then you may wish to score '8' for "death due to primary cancer site", "1" for "death related to other cause" and '3' for "local recurrence" and "appearance of metastases".

Returning the scoring form

(No later than 31st December, 2016)

Please, keep a photocopy or a scan of your completed scoring forms in your records. Once the forms are completed, please return them via **post**, **fax, e-mail or online (e-crf)** to:

DATECAN Project / Data Management Unit
Ms Adèle CUEFF (Data manager)
Biostatistics and epidemiological unit
Georges François Leclerc Cancer Care Center
1 rue du Pr Marion
BP 77980
21079 Dijon cedex
FRANCE
Fax : +33 3 80 73 77 84
Phone : +33 3 80 73 77 89 (poste 37 89)
Email: acueff@cgfl.fr

Should you have any questions regarding our on-line questionnaire, please do not hesitate to contact our data management unit (above).

To complete the questionnaire online, send an email to Adèle Cueff (acueff@cgfl.fr). She will send you by return an email that will explain how to proceed with link for e-crf as well as login and password to complete online the questionnaire.

Publication rules

The principal publication will be made in the name of the DATECAN group with names of the members of the coordinating and steering committees identified as co-authors. All experts who contributed to the consensus by completing the questionnaires will be indexed in PubMed both as participating investigator and as member of DATECAN.

Definitions of terms used in the questionnaire

Before completing the questionnaire, please consider the following definitions:

- **Acute toxicity of protocol treatment** is defined as toxicity occurring within 30 days after the end of treatment.
- **Progression:** this term refers to recurrence, relapse or failure, indistinctly.

You are now ready to complete the scoring forms!

We thank you for your participation!

Should you need any further information or help to complete the next pages, please do not hesitate to contact us:

Christophe Le Tourneau	+33(0)1.4432.4086	christophe.letourneau@curie.fr
Anne Auperin	+33(0)1.4211.5499	anne.auperin@gustaveroussy.fr
Catherine Fortpied	+32(0)2.774.16.81	Catherine.Fortpied@eortc.be

Evaluation of survival outcomes in Head and Neck Cancer patients

Round 1

Before proceeding to the scoring forms, we would appreciate if you could please provide us with some information about you:

Expert (Surname, First name):

_____

Specialty (please select one):

- ☐ Medical Oncology
- ☐ Radiation Oncology
- ☐ Surgery
- ☐ Pathology
- ☐ Imaging
- ☐ Methodology
- ☐ Other:

_____

_____

Number of years of experience in the specialty: _____

Principal investigator in clinical trials:

☐Yes, (also currently) ☐ Yes, only in the past ☐No

Current affiliation (Name of institution, City, Country):

_____

_____

Co-operating groups (please list all of them):

_____

_____

PLEASE INDICATE ON A SCALE OF ***1 (TOTALLY DISAGREE)*** TO ***9 (TOTALLY AGREE)***
WHETHER THE EVENTS BELOW SHOULD BE CONSIDERED FOR EACH OUTCOME.

Table 1: Outcomes applicable to Initial curative surgery (Surg), Initial curative radiotherapy (+/- chemotherapy) (RT-CT) and Organ preservation (Preserv) settings

EVENT: / OUTCOME:	Local progression	Regional progression	Occurrence of distant metastases	Progression of distant metastases	Second cancer of the head and neck	Second cancer other than head and neck
Time to local progression						
Local control						
Local progression-free survival						
Time to regional progression						
Regional control						
Regional progression-free survival						
Time to locoregional progression						
Locoregional control						
Locoregional progression-free survival						
Time to death without any carcinologic event						
Time to distant metastases						

EVENT: OUTCOME:	Salvage surgery of primary tumor with viable tumor (RT-CT only)	Salvage surgery of primary tumor without viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment without viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment without viable tumor (RT-CT only)
Time to local progression						
Local control						
Local progression-free survival						
Time to regional progression						
Regional control						
Regional progression-free survival						
Time to locoregional progression						
Locoregional control						
Locoregional progression-free survival						
Time to death without any carcinologic event						
Time to distant metastases						

EVENT: OUTCOME:	Death related to primary cancer	Death related to a second cancer	Death related to acute toxicity of protocol treatment	Death related to non acute toxicity of protocol treatment	Death related to causes other than primary cancer, second cancer and toxicity	Death, unknown cause	Other Specify .... and score
Time to local progression							
Local control							
Local progression-free survival							
Time to regional progression							
Regional control							
Regional progression-free survival							
Time to locoregional progression							
Locoregional control							
Locoregional progression-free survival							
Time to death without any carcinologic event							
Time to distant metastases							

Table 2: Outcomes applicable to <u>Surg / RT-CT / Preserv</u> and <u>Recurrence and/or metastatic disease not suitable for local therapy (R/M)</u>

Event-free survival, 2nd cancer-free survival and time to second cancer are also applicable to <u>Prevention</u>

EVENT: / OUTCOME:	Local progression	Regional progression	Occurrence of distant metastases	Progression of distant metastases	Second cancer of the head and neck	Second cancer other than head and neck
Distant metastasis-free survival						
Progression-free survival						
Event-free survival						
2nd cancer-free survival						
Time to second cancer						

EVENT: / OUTCOME:	Salvage surgery of primary tumor with viable tumor (RT-CT only)	Salvage surgery of primary tumor without viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment without viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment without viable tumor (RT-CT only)
Distant metastasis-free survival						
Progression-free survival						
Event-free survival						

EVENT: OUTCOME:	Salvage surgery of primary tumor with viable tumor (RT-CT only)	Salvage surgery of primary tumor without viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection ≤15 weeks from end of treatment without viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment with viable tumor (RT-CT only)	Elective neck dissection >15 weeks from end of treatment without viable tumor (RT-CT only)
2nd cancer-free survival						
Time to second cancer						

EVENT: OUTCOME:	Death related to primary cancer	Death related to a second cancer	Death related to acute toxicity of protocol treatment	Death related to non acute toxicity of protocol treatment	Death related to causes other than primary cancer, second cancer and toxicity	Death, unknown cause	Other Specify .... and score
Distant metastasis-free survival							
Progression-free survival							
Event-free survival							
2nd cancer-free survival							
Time to second cancer							

Table 3: Outcomes specific to Organ preservation setting (Preserv)

EVENT: / OUTCOME:	Local progression	Regional progression	Occurrence of distant metastases	Progression of distant metastases	Second cancer of the head and neck	Second cancer other than head and neck
Laryngeal dysfunction-free survival						
Laryngeal dysfunction-free and disease free survival						
Laryngo-esophageal dysfunction-free survival						
Laryngo-esophageal dysfunction-free and disease free survival						
Time to laryngectomy						
Time to tracheotomy						

EVENT: / OUTCOME:	Total laryngectomy	Partial laryngectomy	Tracheotomy	Tracheotomy at 1 year or later	Feeding tube or gastrostomy at 1 years or later
Laryngeal dysfunction-free survival					
Laryngeal dysfunction-free and disease free survival					
Laryngo-esophageal dysfunction-free survival					

EVENT: OUTCOME:	Total laryngectomy	Partial laryngectomy	Tracheotomy	Tracheotomy at 1 year or later	Feeding tube or gastrostomy at 1 years or later
Laryngo-esophageal dysfunction-free and disease free survival					
Time to laryngectomy					
Time to tracheotomy					

EVENT: OUTCOME:	Death related to primary cancer	Death related to a second cancer	Death related to acute toxicity of protocol treatment	Death related to non acute toxicity of protocol treatment	Death related to causes other than primary cancer, second cancer and toxicity	Death, unknown cause	Other Specify .... and score
Laryngeal dysfunction-free survival							
Laryngeal dysfunction-free and disease free survival							
Laryngo-esophageal dysfunction-free survival							
Laryngo-esophageal dysfunction-free and disease free survival							
Time to laryngectomy							
Time to tracheotomy							

Table 4: Outcome specific to <u>Initial curative surgery (Surg)</u>

EVENT: / OUTCOME:	Local progression	Regional progression	Occurrence of distant metastases	Progression of distant metastases	Second cancer of the head and neck	Second cancer other than head and neck
Disease-free survival						

EVENT: / OUTCOME:	Death related to primary cancer	Death related to a second cancer	Death related to acute toxicity of protocol treatment	Death related to non acute toxicity of protocol treatment	Death related to causes other than primary cancer, second cancer and toxicity	Death, unknown cause	Other Specify .... and score
Disease-free survival							

Table 5: Outcome specific to <u>Prevention (Prev)</u>

EVENT: / OUTCOME:	Occurrence of precancerous lesions	Local progression	Regional progression	Occurrence of distant metastases	Second cancer of the head and neck	Second cancer other than head and neck
Precancerous lesions-free survival						

EVENT: / OUTCOME:	Death related to primary cancer	Death related to a second cancer	Death related to acute toxicity of protocol treatment	Death related to non acute toxicity of protocol treatment	Death related to causes other than primary cancer, second cancer and toxicity	Death, unknown cause	Other Specify .... and score
Precancerous lesions-free survival							

COMMENTS:

(Please indicate here any comment or suggestion regarding this questionnaire or the project in general)

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

.

Appendix: The Head and Neck cancer participants

Name	Specialty	Group	Group / Committee
Christophe Le Tourneau	Medical Oncology	UNICANCER	DATECAN Coordinating Committee Head & Neck cancer Steering Committee
Anne Auperin	Biostatistician	UNICANCER, GORTEC	
Catherine Fortpied	Biostatistician	EORTC Headquarters	
Lisa Licitra	Medical Oncology	EORTC	Head & Neck cancer Steering Committee
Kian Ang	Radiation Oncology	RTOG	
Bertrand Baujat	Surgical Oncology	GETTEC	
Gregory Pond	Biostatistician	OCOG	
			Head & Neck cancer Rating Committee
