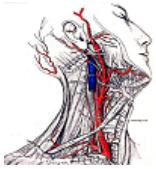


Head and Neck Cancer International Group (HNCIG)

16 March 2017
17:30 to 19:30h

Ayre Gran Via Hotel
Room: TIBIDABO I
Barcelona, Spain

Minutes

Group Chair: Quynh Le
Group Secretary: Hisham Mehanna

Phone: Chris Holsinger, Jeff Buchsbaum, Yook Lim Soong, Barbara Burtness, Amanda Psyrri, Yelena Shnayder

Present: Bob Ferris, Tahara Makoto, Vincent Grégoire, Quynh Le, Jan Vermorken, Hisham Mehanna, Jens Overgaard, Lisa Licitra, Jorgen Johansen, Jens Overgaard, Lara Iglesias, Nadejda Vintonenko, Anne Auperin, Stephan Teman, Hans Kaanders, Cai Grau, Sarbani Ghosh Laskar, Robert Takes, Jean Bourhis, Pierre Blanchard

1. Introductions
    a. Those present in the room and on the phone were asked to introduce themselves with institutional affiliations.

2. Review of minutes from October 2016 (Copenhagen) meeting
    a. The previous minutes with amended. Under the section concerning fund raising support, they should read “European COST (Cooperation in Science and Technology) Application” rather than “European HNS”.
    b. With this amendment, Jan Vermorken moved to approve minutes, with second by Vincent Grégroire, and approval by acclamation.

3. Prioritized Committees
    a. Membership Committee
        i. Readout from 2 March 2017 meeting:
            1. The Committee agree that all the groups present at the initial meeting in Nice, France plus ICORG are considered full members of HNCIG
            2. An application form was provided to Ricardo Mesia Nin, of the Spanish Head and Neck Group, TTCC; he has shared it with the group secretary, and the Committee awaits its submission.
            3. The Committee agreed on a definition of membership consistent with the HNCIG statutes.
            4. The Committee will conduct ongoing review of memberships.
                - Each year, groups will be asked to provide brief status updates including accrual statistics, an affirmation of compliance with GCP, and when dues

are accessed, assurance that dues are up to date. From these data, the Committee will prepare an annual membership update presentation for the Board.

- Every three years, specific groups will be evaluated for continued membership. Groups will be notified six months in advance of this evaluation.
- Since the HNCIG is still in a set up period, the Committee agreed that the routine review process will start after two years. Thereafter group reviews will be staggered and conducted on a rolling basis.

5. The Committee needs a definition of which trials are to be considered HNCIG trials for evaluating "participation in HNCIG trials".
    - From discussion, it was agreed that HNCIG trials are those trials in which more than one HNCIG member group participates and which are in principle "open door" (but which may in fact be limited due to external factors such as drug availability, financing, regulatory concerns, etc.).
    - Trials should be tagged consecutively, e.g., "HN0001, HN0002, …" in addition to whatever other designation they are known by.
    - Ideally, the HN#### designator should appear in the title of the trial, on the protocol front page, and should be indexed in online clinical trial databases such as clinicaltrials.gov. However, at the minimum, it should be on the protocol front page and indexed in online clinical trial databases.
    - HNCIG trials when published should ideally include a reference to HNCIG in the title, but minimally, should reference the group in acknowledgements.
    - As the list of trials builds, each trial should be added to a central table on the HNCIG website.
    - Prior to a HN#### becoming official, HNCIG must receive communication from the lead clinical trial group that consents to such designation.
    - The HNCIG website now has a permanent location: hnc.intergroup.info

Some trials proposed as HNCIG during the meeting (not yet official):

Tenative HN####	NCT	Title	Lead Group	Cooperating Groups
HN0001	NCT02254278	NRG HN002: Reduced-Dose Intensity-Modulated Radiation Therapy With or Without Cisplatin in Treating Patients With Advanced Oropharyngeal Cancer	NRG	NRG, ECOG-ACRIN, CCTG
HN0002	NCT01880359	EORTC 1219: AF CRT +/- Nimorazole in HNSCC	EORTC	EORTC, DAHANCA
HN0003	NCT02135042	NRG HN001: Individualized Treatment in Treating Patients With Stage II-IVB	NRG	NRG, ECOG-ACRIN, HKNPCSG, CCTG,

		Nasopharyngeal Cancer Based on EBV DNA		Singapore, Fudan
HN0004	NCT01969578	EORTC 1206: Androgen Deprivation Therapy in Advanced Salivary Gland Cancer	EORTC	EORTC, XXX
HN0005	NCT01898494	ECOG 3311: Transoral Surgery Followed By Low-Dose or Standard-Dose Radiation Therapy With or Without Chemotherapy in Treating Patients With HPV Positive Stage III-IVA Oropharyngeal Cancer	ECOG-ACRIN	NRG, CCTG?
HN0006	NCT02268695	Platinum-Cetuximab Combined With Docetaxel or With 5FU in Patients With Recurrent/Metastatic HNSCC (TPExtreme)	GORTEC	GORTEC, TTCC, AIO?
HN0007	NCT02984410	EORTC 1420: Study Assessing The "Best of" Radiotherapy vs the "Best of" Surgery in Patients With Oropharyngeal Carcinoma (Best Of)	EORTC	EORTC, SAKK?
HN0008	NCT01874171	Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events in HPV+ OPSCC (De-ESCALaTE)	NCRI	NCRI, ICORG
HN0009	**ISRCTN41478539**	CompARE: Phase III randomised controlled trial Comparing Alternative Regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer	NCRI	NCRI, TMC
HN0010	NCT02215265	Post-operative Adjuvant Treatment for HPV-positive Tumours (PATHOS)	NCRI	NCRI, EORTC

b. Harmonization Committees
   i. Endpoints Committee
      1. Appointment of Group Representatives
         - Need endpoint lead assigned from the groups highlighted below

Currently assigned group representatives for Endpoint Committee {note, this has been updated to reflect updates available after the meeting, while the minutes were being drafted}:

ECOG-ACRIN	Burtness	Sharon Spencer
TROG	Porceddu	Sandro Porceddu
HeCOG	Psyrri	Urania Dafni
GONO	Licitra	Lisa Licitra
IGR	Pignon	Anne Aupérin
NRG	Le	Stu Wong
EORTC	Grégoire	Catherine Fortpied

NWHHT	Takes	Robert Baatenburg de Jong
DAHANCA	Johansen	Jens Overgaard
GORTEC	Bourhis	Jean Bourhis
TCOG (Taiwan)	Chen	Mu-Hung Tsai
IAG KHT	Rainer	Need to appoint
TMC	drpspai@gmail.com	drpspai@gmail.com
NCRI UK	Mehanna	Hisham Mehanna
CCTG	Waldron	John Waldron
Fudan	Hu	Guo Ye
NCC Singapore	Soong	Yoke Lim Soong
HK NPC	Kwong	Dora Kwong
Clinical Trials Ireland	Brennan	Sinead Brennan
TTCC	pending	Need to appoint

**Note: ICORG is now known as Clinical Trials Ireland.*

2. DATECAN Update
   - Guidelines for endpoint definitions in cancer trials: aim is to develop standardized definitions of time to endpoints for oncology based on an international consensus process (EJC 24:769; 2013).
   - The process has already been applied and results published for pancreatic cancer, breast cancer, GIST, and renal cell carcinoma. Several others are now in progress including head and neck cancers.
   - The consensus process employs the Delphi method with two rounds of ratings.
   - The HNC process is under leadership of a steering committee (Lisa Licitra, Bertrand Baujat, Gregory Pond, Christophe Le Toureau, Catherine Fortpied, and Anne Auperin).
   - Lack of standardization for locally advanced SSCHN demonstrated in JCO 27:5965;2009.
   - First round questionnaire distributed so far to 49 experts. Regionally, mostly EU, but also Asia and Americas. Roughly balanced across surgical, radonc, and statistical specialties.
   - Questionnaires distributed to HNCIG participants prior to current meeting.
   - Next step is to analyze first-round questionnaires.
   - Discussion Points
     i. Need some subsets within recurrent/met disease whether curative intent or not.
     ii. Consider adding immune-response endpoints to the second round
     iii. Consider surrogate endpoints
     iv. Can we validate against existing databases?

v. Get endpoint paper out soon; may help gain access to company databases
vi. Need to get away from local discretion about endpoints
vii. Consider adding radiographic response markers.
viii. HNCIG Endpoints Committee should align with DATECAN group.

- Jack – will get endpoint leads from remaining groups and circulate as soon as possible

ii. Radiation

1. Guidelines for CTV delineation of the primary tumor target volumes in laryngeal, hypopharyngeal, oropharyngeal, and oral cavity SCC, v5.1 (Vincent Grégoire and Cai Grau)
    - Lack of agreement on volume definitions by clinicians (Harari et al., Radiother Onc 103:92;2012)
    - Previous work on delineation of neck node levels for HN tumors – (Grégoire et al., Radiother Onc 110:172;2014).
    - Two camps: anatomical margins (and understanding of anatomical borders and typical extension/infiltration pattern) vs geometry: GTV plus a margin defined by distance up to any demarcating barrier such as air or bone (Danish approach)
    - Danish approach has decreased in observer variability
    - Biological basis: a few studies demonstrate roll-off of cell density versus distance from GTV (Campbell et al., IJROBP 82:574;2012 and Fleury Cancer Radiother 18:666;2014).
    - GVT to CTV-T delineation
        i. Planning CT + contrast;
        ii. Accurate diagnostics for GTV: clinical examination including fiberoptic, endoscopic examination with drawings/pictures, diagnostics imaging (CT/MRI/FDG-PET).
        iii. High dose prescription (GTV +5 mm);
        iv. Intermediate/prophylactic dose prescription GTV + 10mm. Editing for air cavities, anatomy, barriers, experience in endoscopic surgery.
        v. Need to consider PTV taking in to consideration immobilization
        vi. CTV-T is meant for primary not post-op radiation
            1. CTV: Addition of a concentric margin around the GTV, including head and neck compartments (e.g., pre-epiglottic space, para-pharyngeal space), modified for natural borders (e.g., cartilage, bone, air, muscular fascia) unless invaded.
            2. Elective CTV: GTV + 1 cm (1.5 cm of mucosal extension for hypopharyngeal SCC)
            3. High Dose CTV: GTV+0.5 cm
        vii. Caveats

1. Consider how to handle SCC p16+ vs p16-
2. Currently includes oral, pharynx, larynx
3. Not valid for recurrent tumors or when information is missing

viii. Discussion

1. Need for RTQA harmonization; certification of sites for participation in clinical trials; how to assure real time checks for compliance with planning guidelines.

- [Quynh] Ask each group to take this (version 6) to appropriate person in group for review; then endorsement by HNCIG; would like to put final version of manuscript on website.
- [Lisa L] For discussion in paper – will conditions such as tumor hypoxia require different dose?
- Anne Lee and colleagues will generate a similar guideline for nasopharynx cancer

4. Presentation of ECOG Proposal – De-escalation of post-operative adjuvant therapy for patients with "high-risk" lymphatic metastasis from p16+ oropharyngeal carcinoma (Chris Holsinger)
   a. Trend towards primary surgical treatment of T1 and T2 oropharygneal SCC from 2004 to 2014 (Cracchioto et al., Cancer 122:1523;2016)
   b. Current trials E3311 and NRG HN002 suggest that there is consensus for de-escalation of treatment for HPV- associated p16+ SCC of the oropharynx.
      i. In E3311, patients with certain adverse biological features (e.g., 5 or more nodes, extracapsular spread, extranodal extension) receive post-op chemoradiation, reflecting current practice
   c. Retrospective evidence
      i. These patients might have similar outcomes with post-op RT alone
      ii. Extracapsular spread as a risk factor might not apply to p16+ population (Sinha P et al, Cancer 118:3519; 2012 and Maxwell JH et al, Cancer 119:3302; 2013).
      iii. There is no post-op trial
   d. Proposal
      i. Phase III RCT
      ii. Treatment comparing two post-op regimens:
         1. Standard: IMRT (60Gy/30fx) + Cispt (40mg/m^2 weekly)
         2. Experimental (de-escalated): IMRT (60 Gy/30fx) + cetuximab (400mg/m^2 loading then 250mg/m^2 weekly)
      iii. Eligibility:
         1. "High-Risk": Any extranodal extension or greater than 4 lymph nodes
         2. P16+ oropharyngeal cancer
         3. After open or transoral endoscopic HN surgery
      iv. Design:
         1. Non-inferiority design
         2. Primary endpoint OS

3. HR 1.3 (80% vs [not worse than] 75% OS at 3 yr
4. 94% power, 0.15 one-sided alpha
5. Assuming 7 year accrual, n = 1190

v. Concept Review
1. Submitted to the NCI Scientific Steering Committee for Head and Neck Cancer's PULA (Previously Untreated, Locally Advanced) Task Force in October 2016.
2. Submitted to ECOG-ACRIN Executive Committee in December 2016.
   - ExCo has recommended that proposal go to HNCIG for discussion about international accrual in hope of shortening trial
3. Comments
   - [J Bourhis] Control arm chemo dose may not be considered standard
   - [J Johansen] Concern about difference in delivery of prescribed doses
   - [J Overgaard] Concern about having effectively two experimental arms versus continuing stepwise.
   - [A. Psyrri, J. Vermorken] consider RT alone vs. RT + cisplatin design

5. Intergroup Funding
   a. Discussions with Oral Cancer Foundation (http://oralcancerfoundation.org/)
      i. OCF is a US-based 501c3 (not-for-profit) corporation with offices in California. They were approached about holding funds for HNCIG (e.g., from dues or trial-related grants).
      ii. After discussions with Drs. Le and Mehanna, the OCF willing to handle funds; at least while transaction volume is low.
      iii. Drs. Le, Mehanna, and Welch have performed some due diligence on the organization. A copy of their most recent available tax form is archived on the HNCIG website (2014 IRS Form 990).
   b. European funding (EU Cooperation in Science and Technology)
      i. The application was submitted requesting 500k Euro over a 5-year period.
      ii. The submission was rated highly but was criticized for lacked supporting documentation from international centers
      iii. Dr. Mehanna will resubmit, but need cooperating groups to register to show international support; Dr. Mehanna will send invitations.
   c. Approach to Industry
      i. There was a discussion of the willingness of the group to accept non-restricted funding from industry. Several members were leery of industry and potential to compromise the academic independence of the intergroup. It was agreed to only consider this if EU-based funding does not come through.

6. Other New Business
   a. None.

7. Next Meeting
   a. Alongside ASCO general meeting in Chicago. Date/Time TBD.

8. Adjourn

Action Items

(QL: Quynh Le, HM: Hisham Mehanna, JW: Jack Welch, YS: Yelena Shnayder; JVM: Jan Vermorken)

All Groups: Review list of HN#### trials in above table; provide any missing data, corrections, or additions.
All Groups: Submit DATECAN questionnaire ASAP.
All Groups: Review CTV delineation proposal, and provide comments to Vincent Grégoire for inclusion in version 6.0, which hopefully will be available before summer 2017. If no objections, HNCIG will discuss at next meeting and endorse. Endorsed version will be added to HNCIG website.

All Groups: Register to support the EU COST application when contacted by Hisham Mehanna, below.

IAG KHT, TMC, CCTG, TTCC: Identify lead person to participate in the Endpoints Committee.

QL: Set time and agenda for next HNCIG Membership meeting (prior to ASCO June 2016). To discuss annual collection of information from groups.

HM: Convene first teleconference of Endpoints Committee (prior to ASCO June 2016).
HM: Coordinate submission of EU COST application.

JW: Forward HNCIG application to Lara Iglesias on behalf of TTCC. [actioned]
JW: Forward completed DATECAN questionnaires to DATECAN contacts. [actioned]
JW: Meeting room request for June 2017. [actioned]
JW: Generate letter to respective groups asking that they confirm willingness to badge listed trials as HNCIG. Update website with trial listing.[actioned]

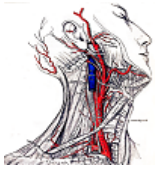
YS: Coordinate teleconference for membership committee (doodle poll, line reservation, notices).
YS: Coordinate teleconference for endpoints committee. [actioned]
YS: Coordinate teleconference for discussion of ECOG-ACRIN p16+ post-op de-escalation study. [actioned, pending response]

Publications

New HNCIG Publications (since last face to face meeting): None.

HNCIG Publications in Process:

- Endpoint harmonization in collaboration with Datecan.
- CTV delineation guidelines. Lead: Vincent Grégoire.



Head and Neck Cancer International Group (HNCIG)

- Featuring the newly formed HNCIG – invited publication in Oral Oncology. QL, JV, HM, JW