



*Meta-Analysis of Amifostine  
in RadioTherapy*

**META-ANALYSIS  
OF  
AMIFOSTINE  
IN  
RADIOTHERAPY**

**Initiated by the Groupe d'Oncologie Radiothérapie Tête et Cou  
(GORTEC) and Institut Gustave Roussy  
Villejuif, France**

**Protocol**

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## 1. INTRODUCTION AND BACK GROUND

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Amifostine (WR-2721, YM-08310, chemical name: S-2-(3-aminopropylamino)-ethylphosphorothioic acid) is an inorganic thiophosphate functioning as cytoprotector of normal tissues against ionizing radiation and chemotherapeutic agents. This drug was used initially for radiation protection as military purpose. Nowadays, this agent has been approved by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as routine use during platinum chemotherapy and during radiotherapy for head and neck cancer. The main feature of this agent is to protect normal tissue from radiotherapy and/or chemotherapy by the mechanism of “selective cytoprotection”. This protection of normal tissues is generally associated with a preservation of cytotoxic effect of tumor by either radiotherapy or chemotherapy and hence is likely to increase therapeutic index. In other words if this selective cytoprotection is definitely proved, we could use this agent confidently to give more toxic therapy with expected lower toxicity and so the possibility of cure for cancer could be increased.

In the past three decades, numerous clinical studies have investigated the effect of cytoprotection with Amifostine. Evidence for normal tissue protection or reduction of acute toxicity from radio/chemotherapy is relatively clear; however, the issue of tumor protection has been continuously discussed<sup>1,2</sup>. With the available evidence, there are several difficulties to resolve this concern. Firstly, most of the published studies planed to detect only difference in acute toxicity, had small sample size and so not enough statistical power to answer this question. Secondly, most of the trials report short term outcome for cancer treatment (median follow up 1-2 year) and therefore further follow up is needed to answer this question.

This project will be focused on effect of Amifostine administered within the course of radiotherapy. The best way to overcome these difficulties and to get the final answer is to perform meta-analysis on survival outcome from individual patient data<sup>3</sup>. This will be more useful than literature based meta-analysis in this particular case because of the superiority of the reliable longer follow up data. It will be also possible to study the effect of Amifostine in different type of cancer.

Therefore, the meta-analysis will be based on individual patient data<sup>3</sup> and will used methodology similar to that used in the MACH-NC study<sup>4</sup>, the Breast Cancer Overview<sup>5</sup>, the Prophylactic Cranial Irradiation Overview<sup>6</sup>, and the Non Small Cell Lung Cancer Overview<sup>7</sup>.

A similar collaborative group comprising those involved in trials included in the project will be established and the meta-analysis will be conducted and reported on its behalf.

Both published and unpublished studies will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results<sup>8</sup>. Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion<sup>3,9</sup>. Updated follow-up information will be sought which will enable us to report on long-term survival.

In summary, the constitution of this unique database aims to answer the most important clinical issue for Amifostine, i.e. the controversial question of tumor protection effect. It should provide a reliable contribution to this issue, ultimately useful for clinical practice.

## 2. OBJECTIVES

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**Assessment of the role of amifostine with radiotherapy in the treatment of cancer by studying the following comparison :**

Radiotherapy



Radiotherapy + Amifostine

Or

Radiotherapy Chemotherapy



Radiotherapy Chemotherapy + Amifostine

### 3. TRIALS SELECTION CRITERIA

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#### 3.1 INCLUSION CRITERIA

All trials must satisfy the following criteria:

**Trials must**

- o Include patients with one of the following cancer : Lung Cancer, Head and Neck Cancer or Pelvic Carcinoma.
- o Include patients with non metastatic disease and no previous treatment for the current cancer
- o Be randomized in a way which precludes prior knowledge of treatment assignment.
- o Have started accrual in 1990 or after.
- o Have completed accrual before June 2002.
- o Compare between radiotherapy with Amifostine and radiotherapy without Amifostine or between radiotherapy plus chemotherapy with Amifostine and radiotherapy plus chemotherapy without Amifostine
- o Administer Amifostine during only the course of radiotherapy or during the course of concurrent chemoradiotherapy
- o Use radiotherapy with curative intent

#### 4. TRIAL SEARCH

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Data from all published and unpublished randomized trials making the above comparisons in cancer patients will be sought using electronic database searching for the period 1966-2003 (Medline, Embase, Cancerlit, CINAHL, ACP Journal Club, Cocharne DSR, DARE, CCT meta-register, HealthSTAR/Ovid HealthSTAR), hand searching (review articles, meeting proceedings of ASCO, ASTRO, ECCO, ESTRO, ECCO, ESMO from 1994-2003) and by contacting experts in the field.

The search strategy used was

1. for MEDLINE/ EMBASE/HealthSTAR/ CINAHL/ Cancerlit :

(EXP "Amifostine" OR "Ethyol".mp OR "WR-2721".mp OR "YM-08310".mp OR "S-2-(3-aminopropylamino)-ethylphosphorothioic acid 2").tw) AND (Cochrane Maximally Sensitive Search Strategy for Randomized Controlled Trial)

2. for ACP Journal Club, Cochrane DSR, DARE, CCT

(EXP "Amifostine" OR "Ethyol".mp OR "WR-2721".mp OR "YM-08310".mp OR "S-2-(3-aminopropylamino)-ethylphosphorothioic acid 2").tw)

## 5. DESCRIPTION OF THE TRIALS INCLUDED

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**Appendix A** describes the trials comparing radiotherapy (+ chemotherapy) + Amifostine versus radiotherapy (+ chemotherapy) alone which accrued during the period 1995-2002 and are potentially eligible for the meta-analysis. Twenty-two trials including 2 341 patients were identified. Two categories of trials have been identified: 1) trials in which only radiotherapy is the treatment ; 2) trials in which chemo + radiotherapy is the treatment.

## 6. CRITERIA OF EVALUATION

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### 6.1 ENDPOINTS

The main endpoint will be **overall survival**, because of expected availability of data, its importance and because of the reliability of the measurement.

Secondary endpoints as failure-free survival will be also considered as well as the type of first recurrence by type of cancer.

### 6.2 PROGNOSTIC FACTORS

The prognostic factors (groups) that will be considered are :

- o Age (50 or less, 51-60, 61+).
- o Sex (male, female).
- o Site (lung, head and neck, pelvis)
- o Histology (squamous cell, adenocarcinoma, other)
- o Stage (Early, I or II versus late, III, IV)

## 7. DATA COLLECTION AND QUALITY CONTROL

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For each eligible trial, the main investigator will be asked to provide the following basic data for survival and prognostic factors for **all** randomized patients.

- o Date of birth or age.
- o Sex.
- o Site.
- o Histology.
- o Stage.
- o Allocated treatment.
- o Date of randomization.
- o Date of last follow-up.
- o Survival status.
- o Date and type (loco-regional or distant) of first failure.
- o Whether excluded from trial analysis.
- o Reason for exclusion (if applicable).
- o Whether received at least one dose of amifostine.

**Appendix B** gives the suggested format and coding to send the data to the Secretariat. All data will be checked for internal consistency and consistency with trial protocol and published report. Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trialists for verification.



## 8. STATISTICAL ANALYSIS PLAN

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The aim of the analysis is to obtain and analyse data from all randomized patients included in all of the relevant randomized trials.

With more than 2 000 patients it would be possible to detect, with a power of 80% (two-sided test), an absolute reduction in survival from 50 % to 44 % at 2-years. Therefore, the study will have enough power to exclude clinically important difference.

The principal analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on the endpoints of failure-free survival.

The analysis will be performed on an **intention-to-treat** basis, that is, patients will be analysed according to the treatment allocated, irrespective of whether they received that treatment. The stratified (by trial) logrank test will be used. The hazard ratio for individual trials and for overall comparison will be computed using fixed effect model. The hazard ratio will be reported with their 95% confidence interval.

Results will also be presented as absolute differences at relevant time points calculated from the hazard ratio and baseline event rate for patients not allocated amifostine<sup>9</sup>; proportional hazards are assumed.  $\chi^2$  heterogeneity tests<sup>7</sup> will be used to test for gross statistical heterogeneity. Survival curves will be presented as simple (non-stratified) Kaplan-Meier curves. All p-values will be two-sided.

Several comparisons of the results of amifostine in **groups of trials** classified according to the type of cancer are planned as exploratory analyses :

- Head and neck cancer versus Lung cancer versus cancer in the pelvic area.
- Intravenous infusion of Amifostine versus subcutaneous injection of Amifostine
- Effect of Amifostine in radiotherapy alone versus effect in chemo-radiotherapy

For these analyses a hazard ratio will be calculated for each trial and a pooled hazard ratio calculated for each treatment category. A test for interaction will be used to investigate if there are any substantial differences in the effect of treatment between these treatment categories.

To study the interaction between treatment effect and **covariates**, e.g. sex, analyses stratified by trial will be performed for each value of this covariate. The results will be then combined to give overall hazard ratios for male and female and compared by a test for heterogeneity.

Given the large number of trial characteristics, there may be interactions between them that could potentially confound these analyses. If we encounter substantial heterogeneity within main meta-analysis we will further explore the potential influence of these factors using multi-level modelling techniques. Hazard ratios for overall survival will also be calculated excluding any trials that are clear outliers as sensitivity analyses.

Before analyzing the data, the analysis plan will be finalized following discussion between the members of the secretariat and of the steering committee.

## **9. WORKING PARTIES IN THE META-ANALYSIS**

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In order to complete the meta-analysis successfully, three groups with specific functions have been created : 1) the Secretariat 2) the Steering Committee 3) the Meta-analysis of Amifostine in RadioTherapy (MAART) Trialists' Collaborative Group.

The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in very close collaboration with the Steering Committee.

The Steering Committee will include international experts in the field of oncology, and radiotherapy, and experts in meta-analysis. The list of its members is given on the following page. The Steering Committee will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

The MAART Trialists' Collaborative Group will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Steering Committee will also be included in this group. It will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Steering Committee and the Secretariat.

## **10. PRACTICAL CONSIDERATIONS**

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The Secretariat, located in the Biostatistics Department at Institut Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. All supplied data will remain confidential and used exclusively for the meta-analysis. At the request of MedImmune which supported the project by an unrestricted grant, the database may be sent to an independent expert for the purpose of checking the analysis. This expert will destroy the database after his work. A meeting of all group members will be organized by the Secretariat to discuss the preliminary results.

### **Timetable**

- June 2004: Invitation of the investigators to collaborate
- July 2004-March 2005: data collection and checking
- April 2005: preliminary analysis and trialists meeting
- October 2005: presentation of preliminary results at the ESTRO meeting

## **11. PUBLICATION POLICY**

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Any publication arising from this project will be made in the name of the MAART Group and include a list of all collaborators.

### **Acknowledgment**

The project is supported by an unrestricted grant for MedImmune Oncology. Funding sources will not have any role in the data collection, analysis, interpretation or writing of the report.

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## REFERENCES

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- 1 Koukourakis MI. Amifostine in clinical oncology: current use and future applications. *Anti-Cancer Drugs* 2002;13:181-209.
- 2 Lindergarrd JC, Grau C. Has the outlook improved for Amifostine as a clinical radioprotector ? *Radiother Oncol* 2000;57:113-8.
- 3 Pignon JP, Hill C. Meta-analysis of randomised clinical trials in oncology. *Lancet Oncology* 2001 ;2 :475-82.
- 4 Pignon JP, Bourhis J, Domenge C, Désigné L on behalf of the MACH-NC Collaborative Group. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analysis of updated individual data. *Lancet* 2000;255: 949-955.
- 5 Early Breast Cancer Trialists Collaborative Group. Effect of Systemic treatment of early breast cancer by hormonal, cytotoxic, or immunotherapy therapy : 133 randomized trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992;339:1-15,71-85.
- 6 Auperin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, Kristjansen PEG, Johnson B, Ueoka H, Wagner H, Aisner J. Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission : a meta-analysis of individual data from 987 patients. *N Engl J Med* 1999;341: 476-484.
- 7 The Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated individual patient data from 56 randomised clinical trials. *Br Med J* 1995;311:899-909.
- 8 Begg CB, Berlin A. Publication bias and the dissemination of clinical research. *J Natl Cancer Inst* 1989;18:107-115.
- 9 Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual data: is there a difference? *Lancet* 1993;341:418-422.

## Appendix A1: Description of the trials comparing radiotherapy (+ chemotherapy) + Amifostine versus radiotherapy (+chemotherapy) alone

See abbreviations on page 20 and references on pages 21-26.

TABLE A1: RANDOMIZED TRIALS OF RADIOTHERAPY (+ CHEMOTHERAPY) + AMIFOSTINE VERSUS RADIOTHERAPY (+ CHEMOTHERAPY) IN NSCLC

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
Lung <sup>‡</sup>	146	1997-99	RT: 55-60 Gy, 2 Gy/F, 5 F/ week	340 mg/m <sup>2</sup> iv. 15-30 mins before RT	# 1, Antonadou (Sem Rad Onc 2002) (IJROBP 2001)
NSCLC	73	1997-99	RT: 55-60 Gy, 2 Gy/F, 5F/ week CT concurrently: P 60 mg/m <sup>2</sup> weekly <b>or</b> Cb AUC 2 weekly	300 mg/m <sup>2</sup> iv. over 10 mins 15 mins before RT	# 2, Antonadou (IJROBP 2003) (ASCO 2000)
Lung <sup>%</sup>	45	1998-99	RT:55-60 Gy to the primary site CT induction: 3-4 cycles of platinum based CT	340 mg/m <sup>2</sup> daily iv. over 10 mins 15-30 mins before RT	# 3, Antonadou (Sem Rad Onc 2002)
Lung*	60	1997-99	RT: 64 Gy for NSCLC RT: 50-60 Gy for SCLC	500 mg <b>sc</b> 20 mins before each RT	# 4, Koukourakis (JCO 2000) (ECCO 1999)

<sup>‡</sup> 23 patients with SCLC, <sup>%</sup> 19 patients with SCLC, \* NSCLC, 36 patients, SCLC, 20 patients, thymoma, 3 patients, neuroendocrine mediastinal tumor, one patient. Trial stratified by site (lung, head and neck, pelvis) with 140 patients overall.

TABLE A1 (followed)

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
NSCLC	62	1998-2001	RT: 69.6 Gy/ 6 weeks, 1.2 Gy/F, 2 F/d CT concurrently: E oral, 50 mg bid 30 mins before each RT day 1-10, d29 C 50 mg/m <sup>2</sup> iv d1,8,29,36	500 mg iv twice weekly before chemo-RT	# 5, Komaki (ASCO 2004) (Sem Rad Onc 2002) (ASTRO 2002, 2001) (ASCO 2001)
NSCLC	60	1997-2000	RT: 60-66 Gy, 2 Gy/F, 5 F/ week CT induction: P 175 mg/m <sup>2</sup> d1,22 Cb AUC 6 d1,22 CT concurrently: P 60 mg/m <sup>2</sup> d43,50,57,64,71,78	During induction CT, 740 mg/m <sup>2</sup> iv day1, 22 over15 min, 30 mins before CT During concurrent CT-RT 740 mg/m <sup>2</sup> iv over 15 min d43,50,57,64,71,78 30mins before CT	# 6, Leong (JCO 2003) (ASCO 2001)
NSCLC	243	1998-2002	RT: 69.6 Gy, 1.2 Gy/F, 2 F/ day CT Induction: P 225 mg/m <sup>2</sup> /3hr iv d1,22 Cb AUC 7.5 d1, 22 CT concurrently: P 50 mg/m <sup>2</sup> d43,50,57,64,71,78 Cb AUC 2 d43,50,57,64,71,78	500 mg iv over 5 mins x 4/ week during course of RT	# 7, Movsas(RTOG 98-01) Werner-Wasik (ASTRO 2003) (ASCO 2003) (Sem Rad Onc 2002)

TABLE A1 (followed)

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
NSCLC	123	1998-2002	RT: 64.8 Gy/ 36 F/ 7.5 week CT concurrently: P 50 mg/m <sup>2</sup> and Cb AUC 2 weekly x 7 CT adjuvant: G 1000 mg/m <sup>2</sup> d1,8,15 every 28 days C 80 mg/m <sup>2</sup> d8	500 mg iv weekly 15-30 mins before CT 200 mg iv daily 15-30 mins before RT Initially over 10 mins then bolus	# 8, Senzer (Sem Onc 2002)



TABLE A2: RANDOMIZED TRIALS OF RADIOTHERAPY (+ CHEMOTHERAPY) + AMIFOSTINE VERSUS RADIOTHERAPY (+ CHEMOTHERAPY) IN HNSCC

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
HNSCC	315	1995-97	RT: definitive 66-70 Gy : postop high risk 60-64 Gy : postop low risk 50-54 Gy , 1.8-2 Gy/ F	200 mg/m <sup>2</sup> iv. over 3 mins 15-30 mins before each RT	# 9, Brizel (JCO 2000) (IJROBP 2000) (ASCO 1998, 1999) (ASTRO 1998, 1999) (ESTRO 1998) (JCRCO 1998) (ASTRO 1997) Momm (IJROBP 2001)
HNSCC	26	1996-98	RT: 64 Gy / 22-23 days, 2Gy/F, 2 F/d	150 mg/m <sup>2</sup> iv over 3 mins 15-30 mins before each RT	# 10, Bourhis (IJROBP 2000) (ASCO 1999)
HNSCC	67	Not available	RT: conventional fractionation dose not specified	200 mg/m <sup>2</sup> 30 mins before each RT	# 11, Veerasarn (ECCO 2003)
HNSCC*	40	1997-99	RT: 64-70 Gy	500 mg <b>sc</b> 20 mins before each RT	# 4, Koukourakis (JCO 2000) (ECCO 1999)

\* Trial stratified by site (lung, head and neck, pelvis) with 140 patients overall.

TABLE A2: (followed)

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
HNSCC	50	1997-98	RT : 60-74 Gy, 2 Gy/ F, 5F/ week CT concurrently : Cb 90 mg/m <sup>2</sup> once a week	300 mg/m <sup>2</sup> iv. 30 mins before each RT	# 12, Antonadou (IJROBP 2002) (ASTRO 1998)
HNSCC	28	1995-96	RT: 60 Gy, 2 Gy/ F, 5 F / week CT concurrently: Cb 70 mg/m <sup>2</sup> d1-5, 29-34	500 mg iv. immediately before carboplatin only not given during RT alone	# 13, Buntzel (Sem Rad Onc 2002) (Cancer Invest 2001) (ECCO 1999) (Annal Oncol 1998) (ASCO 1997, 1998) (ORLN 1997) (abst.ORLN 1997) (Supportive care in cancer 1998) (abst.JCRCO 1998) (abst. Annal Hem 1998) (abst. Supportive Care Cancer 1997) (ESMO 1996)

TABLE A2: (followed)

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
HNSCC	137	Not available	RT: 60-70 Gy, 2 G/F CT concurrently: Cb 70 mg/m <sup>2</sup> d1-5, 21-25	300 mg/m <sup>2</sup> iv d1-5, 21-25 over 3 mins before CT 60 mins before RT 60 Day of RT alone: 200 mg/m <sup>2</sup> iv Over 3 mins, 30 mins before RT	# 14, Buntzel (ASTRO 2001)
HNSCC	56	1996-99	RT: 60 Gy (R0), 70 Gy (R1/2) CT concurrently: Cb 70 mg/m <sup>2</sup> d1-5 week 1 and 5	250 mg iv daily before each RT	# 15, Vacha (Strahlen Onk 2003) (Strahlen Onk 1999) (ESTRO 1998) Marx (JCRCO 2000)
HNSCC	48 (planned 60)	Not available	RT: 72 Gy (46 Gy + Boost) CT concurrently : P 60 mg/m <sup>2</sup> d1,8,15,22	500 mg <b>sc.</b> 15-30 min before each RT	# 16, Braaksma (ESTRO 2002) (ASTRO 2002)

TABLE A2: (followed)

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
HNSCC	38	1995-96	RT: 80 Gy, 2Gy/d week 2-3 1.5 Gy/F 2 F/d week 5-6, 8-9 CT alternating with RT: C 20 mg/m <sup>2</sup> + Fu 300 mg/m <sup>2</sup> + FA 20 mg/m <sup>2</sup> d1-4 at week 1-4-7-10	200 mg/m <sup>2</sup> iv over 15 mins 15 mins before CT 100 mg/m <sup>2</sup> before each RT	# 17, Giglio (ASCO 1997)
HNSCC	170	19??-2002	RT: 66-72 Gy CT: C 40 mg/m <sup>2</sup> weekly	250 mg/m <sup>2</sup> iv 10 min Before RT 4 days/ week	# 18, Patni (ASCO 2004)

TABLE A3: RANDOMIZED TRIALS OF RADIOTHERAPY (+ CHEMOTHERAPY) + AMIFOSTINE VERSUS RADIOTHERAPY (+ CHEMOTHERAPY) IN PEVIS CANCER

Sites	Number of patients randomized	Inclusion period	Treatment description	Amifostine	Reference
Pelvis	207	1999-2000	RT: definitive 65-70 Gy : postop 50 Gy 1.8-2 Gy/ F, 5 F / week	340 mg/m <sup>2</sup> iv. over 3-5 mins 15-30 mins before RT	# 19, Athanassiou (IJROBP 2003) (ECCO 2001)
Pelvis*	40	1997-99	RT: 50 Gy + brachytherapy	500 mg sc 20 mins before each RT	# 4, Koukourakis (JCO 2000) (ECCO 1999)
Pelvis	47	2000-01	RT: 50 Gy, midline 2 Gy/F, 5 F / week	500 mg daily iv over 6 mins 15-30 mins before RT	# 20, Kouvaris (Strahlen Onk 2003)
Colorectal	124	Not available	RT: 50-60 Gy, 2Gy/F, 5 F/ week CT concurrently: Fu based once weekly or during the first and the last week of RT	300 mg/m <sup>2</sup> iv daily	# 21, Antonadou (ECCO 2003) (ASCO 2003)
Cervix Uteri	20	Not available	RT: external beam RT and intracavitary RT CT: C 20 mg/m <sup>2</sup> for 5 days in 2 cycles during intracavitary RT C 100 mg/m <sup>2</sup> x 2 cycles during external beam RT	825 mg/m <sup>2</sup> 15 min before CT	# 22, Gallardo (Int J Gyn Cancer 1999)

\* Trial stratified by site (lung, head and neck, pelvis) with 140 patients overall.

## Abbreviations

CT = Chemotherapy,  
d = day,  
F = Fraction,  
RT = Radiotherapy.

HNSCC= Head and neck squamous cell carcinoma,  
NSCLC = Non-small cell lung cancer,  
SCLC = Small Cell Lung Cancer,  
sc = subcutaneous.

C = cisplatin,  
Cb = carboplatin,  
E = Etoposide (VP-16),  
FA= Folinic Acid,  
Fu = 5-FU,  
G = Gemcitabine,  
P = Paclitaxel.

## REFERENCE:

**Trial #1**

Antonadou D. Radiotherapy or Chemotherapy Followed By Radiotherapy with or without Amifostine in Locally Advanced Lung Cancer. *Sem Rad Onc* 2002;12(1) suppl 1 : 50-8.

Antonadou D, Coliarakis N, Syndodinou M et al. Randomized. Phase III trial of Radiation Treatment +/- Amifostine in Patients with Advanced-stage Lung Cancer *Int J Radiation Oncol Biol Phys* 2001;51(4):915-22.

**Trial #2**

Antonadou D, Throuvalas N, Pertridis A et al. Effect of Amifostine on Toxicities Associated with Radiochemotherapy in Patients with Locally Advanced Non-Smal-Cell Lung Cancer. *Int J Radiation Oncology Biol Phys* 2003;57(2):402-8.

Antonadou D, Synodinou M, Boufi M et al. Amifostine Reduces Toxicity During Radiochemotherapy in Patients with Localized Advanced Stage Non Small Cell Lung Cancer. *Proc Am Soc Clin Oncol* 2000;19:501a.

**Trial #3**

Antonadou D. Radiotherapy or Chemotherapy Followed By Radiotherapy with or without Amifostine in Locally Advanced Lung Cancer. *Sem Rad Onc* 2002;12 suppl 1 : 50-8.

**Trial #4**

Koukourakis MI, Kyrias G, Kakolyris S et al. Subcutaneous Administration of Amifostine During Fractionated Radiotherapy: A Randomized Phase II Study. *J Clin Oncol* 2000;18:2226-33.

Koukourakis MI, Frangiadaki C, Stavroulaki A et al. Subcutaneous Amifostine during Fractionated Radiotherapy : A Randomized Phase II Study in Pelvic tumors. *Eur J Cancer* 1999;35 (suppl 4): S98.

**Trial #5**

Komaki R, Spitz MR, Wu JX Mutagen Sensitivity (MS) may predict lung protection by amifostine for patients with locally advanced non-small cell lung cancer (NSCLC) treated by chemoradiotherapy. *Proc Am Soc Clin Oncol* 2004;23:671.

Komaki R, Lee JS, Kaplan B et al. Randomized Phase III Study of Chemoradiation with or without Amifostine for Patients with Favorable Performance Status Inoperable Stage II-III Non-Small Cell Lung Cancer: Preliminary Results. *Sem Rad Onc* 2002;12(1):46-9.

Komaki R, Lee JS, Mila L et al. Phase III Trial of Amifostine With Chemoradiation for Inoperable Non-Small Cell Lung Cancer (NSCLC): Does Amifostine Protect Cancer Cells. *Int J Rad Oncol Biol Phys* 2002;54 (Suppl):105.

Komaki R, Lee J S, Kaplan B et al. Randomized Phase III Study of Chemoradiation +/- Amifostine in Patients with Inoperable stage II-III Non-Small Cell Lung Cancer (NSCLC). *Proc Am Soc Clin Oncol* 2001;20:325a.

Gopal P, Starkschall G, Tucker S et al. The Effects of Radiation Therapy, Chemotherapy and the Radioprotector Amifostine on the Diffusion Capacity of Patients with Non-Small Cell Lung Cancer (NSCLC). *Int J Rad Oncol Biol Phys* 2001;51 (Suppl 1):22.

**Trial #6**

Leong SS, Tan EH, Fong KW et al. Randomized Double-Blind Trial of Combined Modality Treatment with or without Amifostine in Unresectable Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol* 2003;21:1767-74.

**Trial #7**

Movsas B. Exploring the Role of the Radioprotector Amifostine in Locally Advanced Non-small Cell Lung Cancer: Radiation Therapy Oncology Group Trial 98-01. *Semin Radiat Oncol* 2002; 12 (Suppl 1) : 40-5.

Werner-Wasik M, Scott C, Movsas B et al. Amifostine as Mucosal Protectant in Patients with Locally Advanced Non-Small Cell Lung Cancer (NSCLC) Receiving Intensive Chemotherapy and Thoracic Radiotherapy (RT): Results of the Radiation Therapy Oncology Group (RTOG) 98-01 Study. *Int J Rad Oncol Biol Phys* 2003;57 (Suppl):S216.

Movsas B, Scott C, Langer C et al. Phase III Study of Amifostine in Patients with Locally Advanced Non-small Cell Lung Cancer (NSCLC) Receiving Chemotherapy & Hyperfractionated Radiation (Chemo/ HfxRT): Radiation Therapy Oncology Group (RTOG) 98-01. *Proc Am Soc Clin Oncol* 2003;22:636.

**Trial #8**

Senzer N. A Phase III Randomized Evaluation of Amifostine in Stage IIIA/ IIIB Non-Small Cell Lung Cancer Patients Receiving Concurrent Carboplatin, Paclitaxel, and Radiation Therapy Followed by Gemcitabine and Cisplatin Intensification: Preliminary Findings. *Semin Oncol* 2002;29(6)suppl 19:38-41.

**Trial #9**

Brizel DM, Wasserman T. The influence of intravenous amifostine on xerostomia and survival during radiotherapy for head and neck cancer: Two year follow-up of a prospective randomized trial. *Proc Am Soc Clin Oncol* 2004;23: 495

Brizel DM, Wasserman TH, Henke M et al. Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer. *J Clin Oncol* 2000;18:3339-45.

Wasserman T, Mackowiak JI, Brizel DM et al. Effect of Amifostine on Patient Assessed Clinical Benefit in Irradiated Head and Neck Cancer. *Int J Radiation Onc Biol Phys* 2000;48(4):1035-9.

Rudat V, Meyer J, Momm F et al. Protective effect of Amifostine on Dental Health after Radiotherapy of the Head and Neck. *Cancer* 2000; 48: 1339-43.

Momm F, Bechtold C, Rudat V et al. Alteration of Radiation Induced Hematotoxicity by Amifostine. *Int J Radiat Oncol Biol Phys* 2001;51:947-51.

Momm F, Bechtold C, Fisher K et al. Alteration of Radiation Induced Hematotoxicity by Amifostine. *Strahl Onkol* 1999;175 (suppl 4):2-5.

Sauer R, Wannemacher W, Wasserman T et al. Randomized Phase III trial of Radiation +/- Amifostine in Patients with Head and Neck Cancer. *Proc Am Soc Clin Oncol* 1999;18:392a.

Brizel DM, Wasserman TH, Strnad V et al. Final Report of a Phase III Randomized Trial of Amifostine as a Radioprotectant in Head and Neck Cancer. *Int J Rad Oncol Biol Phys* 1999;45 (Suppl 1):147.

Brizel D, Sauer R, Wannemacher et al. Randomized Phase III trial of Radiation + /- Amifostine in Patients with Head and Neck Cancer. *Proc Am Soc Clin Oncol* 1998;17:386a.



Brizel D, Sauer R, Wannemacher M et al. Randomized Phase III Trial of Radiation +/- Etyol (Amifostine) in Patients with Head and Neck Cancer. *Int J Rad Oncol Biol Phys* 1998;42 (Suppl 1):224.

Sauer R, Wannemacher W, Brizel D et al. Randomised Phase III trial of Radiation +/- Etyol (Amifostine) in Patients with Head and Neck Cancer. *Radiother Oncol* 1998;48 (Suppl. 1):S181.

Strnad V, Sauer R, Krafft T. Preliminary results of a randomised study using WR-2721 in radiation therapy alone in patients with head and neck cancer. *Eur J Cancer* 1997;33 (Suppl. 8):S189.

Sauer R et al Randomized phase III trial of radiation (RT)+/- Etyol (Amifostine) in patients with head and neck cancer. *Int J Rad Oncol Biol Phys* 1997;39 (Suppl):234.

Strnad V, Wannemacher M, Brizel D et al. Randomized Phase III trial of Radiation +/- Amifostine in Patients with Head and Neck Cancer. *Proceeding Of Journal of Cancer Research and Clinical Oncology* 1998;124 (Suppl.): R106.

#### **Trial #10**

Bourhis J, Crevoisier RD, Abdulkarim B et al. A Randomized Study of Very Accelerated Radiotherapy with and without Amifostine in Head and Neck Squamous Cell Carcinoma. *Int J Radiat Onc Biol Phys* 2000;46(5):1105-8.

#### **Trial #11**

Veerasarn V, Phromratanapongse P, Suntornpong N et al. Effect of amifostine to prevent radiotherapy-induced acute and late toxicity in head and neck cancer patients who had normal or mild impaired salivary gland function. *Eur J Cancer Suppl* 2003;1: S273.

#### **Trial #12**

Antonadou D, Pepelassi M, Synodinou M et al. Prophylactic use of Amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. *Int J Radiation Onc Biol Phys* 2002;52(3):739-47.

Antonadou D, Pepelassi E, Synodinou M et al. The Prophylactic Use of Amifostine in the Prevention of Chemoradiation Induced Mucositis and Xerostomia in Head and Neck Cancer. *Int J Rad Oncol Biol Phys* 1998;42 (Suppl 1):224.

#### **Trial #13**

Buntzel J, Glatzel M, Kuttner K et al. Amifostine in Simultaneous Radiochemotherapy of Advanced Head and Neck Cancer. *Sem Rad Onc* 2002;12 : 4-13.

Bennett CL, Lane D, Stinson T et al. Economic Analysis of Amifostine as Adjunctive Support for Patients with Advanced Head and Neck Cancer : Preliminary Results from a Randomized Phase II Clinical Trial from Germany. *Cancer Investigation* 2001;19:107-13.

Buntzel J, Glatzel M, Weinaug R et al. Amifostine in Combined Radio – and Chemomodality for Head and Neck Cancer. *Eur J Cancer* 1999;35 (suppl 4): S363.

Buntzel J., Kuttner K, Frohlich D et al. Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer. *Ann Oncol* 1998 ;9(5):505-9.

Buntzel J. Clinical Experience with Amifostine in RadioChemotherapy of Head and Neck Cancer. *Proceeding in Journal of Cancer Research and Clinical Oncology* 1998;124 (Suppl 1): R113.

Buntzel J. Cytoprotection with amifostine (A) as the base for intensification of radiochemotherapy (RCT) in head and neck cancer. *Proceeding in Annals of Hematology* 1998; S197.

Buntzel J; Schuth J; Kuttner K. Radiochemotherapy with amifostine cytoprotection for head and neck cancer. *Supportive Care in Cancer* 1998; 6:155-60.

Buntzel J, Kuttner K, Kuttner K et al. Selective cytoprotection with amifostine (A) in the treatment of head and neck with simultaneous radiochemotherapy (RCT). *Eur J Cancer* 1997;33 (Suppl. 8):S189.

Buntzel J, Kuttner K, Frohlich D et al. Amifostine in simultaneous radiochemotherapy for head and neck cancer. *Oto-Rhino-Laryngologia Nova* 1997; 7: 204-210.

Buntzel J; Glatzel,M.; Schuth J et al. Selective cytoprotection with amifostine: A new strategy in supportive care of head and neck malignancies. *Oto-Rhino-Laryngologia Nova*.1997;7:276-280.

Buntzel J, Kuttner K, Russell L et al. Selective Cytoprotection by Amifostine in the Treatment of Head and Neck Cancer with Simultaneous Radio-Chemotherapy. *Proc Am Soc Clin Oncol* 1997;16:393a.

Buntzel,J.Glatzel. Amifostine provides protection against mucositis and other toxicities induced by radiochemotherapy (RCT) of head and neck cancer *Supportive Care in Cancer* 1997. 5 (Suppl.):165 (Abstr.47).

Buntzel J, Glatzel M, Kuttner K et al. Selective Cytoprotection with Amifostine in Simultaneous RadioChemotherapy of Head Neck Cancer. *Ann Oncol* 1996; 7 (Suppl 5): 81

#### **Trial #14**

Buentzel J, Monnier A, Ammon J et al. Phase III Randomized Double Blind Placebo Controlled Trial of Carboplatin and Radiation Therapy \_Amifostine in Patients with Head and Neck Cancer. *Int J Rad Oncol Biol Phys* 2001;51 (Suppl1):85.

#### **Trial #15**

Vacha P, Fehleuer F, Mahlmann B et al. Randomized phase III trial of postoperative radiochemotherapy +/- amifostine in head and neck cancer: Is there evidence for radioprotection? *Strahlenther Onk* 2003;179:385-9.

Marx M. Acute toxicity of postoperative radiochemotherapy (RCT) alone versus RCT plus in Amifostine in Head and Neck Cancer Patients: Preliminary Results of a Randomized Trial. *Journal of Cancer Research & Clinical Oncology* 2000;126(suppl 1):R82.

Vacha P, Marx M, Engel A et al. Side Effects of Postoperative Radiochemotherapy with Amifostine versus Radiochemotherapy Alone in Head and Neck Tumors. Preliminary Results of a Prospective Randomized Trial. *Strahlenther Onkol* 1999.175 (suppl. 4):18-22.

Vacha P. Acute toxicity of postoperative radiochemotherapy plus amifostine vs. radiochemotherapy alone in head and neck cancer patients: preliminary results of a randomized trial. *Rad Oncol* 1998;48 (Suppl 1):S40.

#### **Trial #16**

Braaksma M, Levendag P, M De Jonge et al. Organ Preservation with Chemoradiation in Advanced Head and Neck Cancer Concomitant Paclitaxel With or Without Subcutaneous Amifostine Prior to Radiation Preliminary Results on Toxicity of a Randomized Clinical Trial. *Int J Rad Oncol Biol Phys* 2002;54 (Suppl):291.

Braaksma M, Levendag P, M De Jonge et al .Subcutaneous amifostine. Does it reduce the acute toxicity of a concomitant chemoradiation scheme in advanced head and neck cancer? Preliminary results of a randomized clinical trial. *Radiother Oncol* 2002;64 (Suppl. 1): S247.

**Trial #17**

Giglio R, Mickiewicz E, Pradier E et al. Alternating Chemotherapy (CT) + radiotherapy (RT) with Amifostine (A) Protection for Head and Neck Cancer (HN) . Early Stop of A Randomized Trial. Proc Am Soc Clin Oncol 1997;16: 384a.

**Trial #18**

Patni N, Patni S, Bapna A et al. The role of amifostine in prophylaxis of radiotherapy induced mucositis and xerostomia in head and neck cancer. Proc Am Soc Clin Oncol 2004;23:503

**Trial #19**

Athanassiou H, Antonadou D, Coliarakis N et al. Protective Effect of Amifostine during Fractionated Radiotherapy in Patients with Pelvic Carcinomas : Results of a Randomized Trial. Int J Radiat Onc Biol Phys 2003;56(4):1154-60.

Athanassiou E, Antonadou D, Coliarakis N et al. Protective Effect of Amifostine during Fractionated Radiotherapy in Patients with Pelvic Carcinomas : Results of a Randomized Trial. Eur J Cancer 2001;37 (suppl. 6): S358.

**Trial #20**

Kouvaris J, Kouloulis V, Malas E et al. Amifostine as Radioprotector Agent for the Rectal Mucosa during Irradiation of Pelvic Tumors. A Phase II Randomized Study Using Various Toxicity Scales and Rectosigmoidoscopy. Strahlentherapie Und Onkologie 2003;179:167-74.

**Trial #21**

Antonadou D, Athanassiou H, Sarris G et al. Randomized Phase III Trial of Chemoradiation treatment +/- Amfiostine in Patients with Colorectal Cancer. Proc Am Soc Clin Oncol 2003;22:293.

Antonadou D, Athanassiou H, Sarris G et al. Randomized phase III trial of chemoradiation treatment amifostine in patients with colorectal cancer. Eur J of Cancer Supplements; 1(5): S325

**Trial #22**

Gallardo D, Mohar A, Calderillo G et al. Cisplatin, Radiation and Amifostine in Carcinoma of the Uterine Cervix. Int J Gyn Cancer 1999;9:225-30

## Appendix A2 : excluded trials

### **Trials too old (inclusion before 1990)**

#### **Trial #E1** (100 patients)

Kligerman MM, Liu T. Interim Analysis of a Randomized Trial of Radiation Therapy of Rectal Cancer with/without WR-2721. *Int J Radiat Oncol Biol Phys* 1992;22:799-802.

Liu T, Liu Y, He S, Zhang Z, Kligerman MM. Use of Radiation with or without WR-2721 in Advanced Rectal Cancer. *Cancer* 1992;69:2820-25

This trial is also excluded because it use palliative radiotherapy.

#### **Trial #E2** (60 patients)

Takahashi M, Abe M , Kawamura T et al. Clinical Study of Radioprotective Effects of ym-08310 in Patients with Carcinoma of the Cervix Uteri. *Nippon Igaku Hoshasen Gakkai Zasshi (Nippon Acta Radiologica)* 1982 ;42 :435-42.

#### **Trial #E3** (67 patients)

Nibbe N, Takahashi I, Miyaishi K. An Evaluation of the Clinical Usefulness of Amifostine (YM-08310), Radioprotective agent. A Double-blind Placebo-Controlled Study. 2.Abdominal and pelvic Tumor [Japanese] *Journal of Japan Society for Cancer Therapy* 1985;20:994-1001.

#### **Trial #E4** (37 patients)

Nibbe N. An Evaluation of the Clinical Usefulness of Amifostine (YM-08310) Radioprotective Agent. A Double-Blind Placebo-Controlled Study 1.Head and Neck Tumors [Japanese] *Nippon Gan Chiryō Gakkai Shi-Journal of Japan Society for Cancer Therapy* 1985; 20(5):984-993.

### **Trials with inappropriate randomization method**

#### **Trial #E5** (28 patients)

Peters K, Mucke R, Hamann D et al. Supportive use of amifostine in patients with head and neck tumors undergoing radio-chemotherapy. Is it possible to limit the duration of the application of amifostine? *Strahl Onk* 1999;175(suppl4):23-6.

Mucke R, Peters K, Hamann D et al. A Randomized Study of Concurrent Radiochemotherapy (RCT) versus RCT + Amifostine (A) in patients with Advanced Head and Neck Tumors: No Cytoprotective Effect of Time Limited Application of Amifostine. *Rad Oncol* 1998;48 (Suppl. 1)::S31.

### **Trials with other reason of exclusion**

#### **Trial #E6** (5 patients)

The EORTC 24981, a randomized on amifostine in patient with naso-pharynx carcinoma treated by radio-chemotherapy was excluded as it included only 5 patients (early stopping because of low accrual, Laurence Collette, personal communication)



## Appendix B : How to send data to the Secretariat.

### FORMAT FOR THE DATA

The preferred format for the information is described on the following pages. However, if a different format is more convenient for you, this should cause no great difficulty as long as it is fully specified.

### WAYS OF SENDING THE DATA

- EITHER:
1. As long as it will not cause delay, **the easiest way for us to receive the data is by e-mail<sup>1</sup>**. We should be able to read any standard floppy disk<sup>2</sup> or compact disk if you let us know its specification. Please accompany any disk with a printout of its contents.
- OR:
2. Send a lineprinter listing from your computer, (preferably with blank lines between each line of data to help us avoid punching errors), giving as much as possible of the information requested on the form.
- OR:
3. If you would prefer to enter the individual patient data onto forms, please contact the secretariat (tel: 33 1 42 11 45 65 ; fax: 33 1 42 11 52 58).

It is important when trying to achieve a synthesis of the results of many different trials to include **all patients** ever **randomized**, whether eligible or not, whether or not they received their allocated treatment, whether properly followed up or not. Please try to get as near as possible to that ideal (or, at least please indicate where post randomization exclusions or losses have occurred), as long as to do so will not delay you sending us data. If it will cause a delay, then send us what you can now, and send the extra information later.

**Please, fill out and mail (or fax) the enclosed form to the secretariat to facilitate data processing.**

-----

<sup>1</sup> Our e-mail address is : [jppignon@igr.fr](mailto:jppignon@igr.fr). If sending data via email, please encrypt the data and let us know how it has been encrypted in a separate email.

<sup>2</sup> The preferred specification would be PC compatible, 3.5" disk, ASCII Format. Data can be in other format (Excel, Dbase, SAS etc.), but please indicate which format has been used.

Meta-Analysis of Amifostine in Cancer

**Suggested coding and format for sending data by network mail or floppy disk**

<u>Column</u>	<u>Variable</u>	<u>Format/Coding</u>
2-11	Patient identifier	10 characters
13-20	Date of birth or age	dd/mm/yyyy, 99999999=Unknown 6 blanks (columns 13-18), 2 digits (columns 19-20), 99=Unknown
22	Sex	1=Male, 2=Female, 9=Unknown
24-25	Site of primary tumor	1 = Lung cancer, 2 = Mediastinal tumor (e.g. Thymoma), 3 = Head and neck cancer, 4 = Rectal cancer, 5 = Colon cancer 6 = Bladder cancer, 7 = Endometrial cancer, 8 = Uterine cervix cancer, 9 = Prostate cancer, 10 = Other pelvic tumor
27	Histology	1= Squamous cell carcinoma, 2=Adenocarcinoma, 3= Small cell lung cancer 4 = Transitional cell carcinoma (bladder cancer), 5= Sarcoma 6 = Other histology
29	Tumor stage	1 = Early stage (I, II), 2 = Late stage (III,IV)
31	Treatment allocated	1=No Amifostine, 2=Amifostine
33-40	Date of randomization	dd/mm/yyyy, 99999999=Unknown
42-49	Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
51	Survival status	0=Alive, 1=Dead

Suggested coding for sending data (followed)

**Meta-Analysis of Amifostine in Cancer**

<u>Column</u>	<u>Variable</u>	<u>Format/Coding</u>
53	Failure	0=No, 1=Yes
55-62	Date of first failure	dd/mm/yyyy, 99999999=Unknown
64	Type of failure	Loco-regional =1, Distant = 2, 9=Unknown
66	Excluded from your analysis	0=No, 1=Yes
68-79	Reasons for exclusion	12 characters
81	Received at least one dose of amifostine	0=No, 1=Yes



*Meta-Analysis of Amifostine  
in RadioTherapy*

**Meta-analysis of Amifostine in Radiotherapy**

Name of contact clinician :.....

Name of trial :.....

Date trial opened for patient entry :..... (dd/mm/yy)

Date trial closed to patient entry .....

Please list the treatments used in each arm of the trial :

*Arm 1*.....

*Arm 3*.....

*Arm 2*.....

*Arm 4*.....

I am able to use suggested coding :            Yes        /        No

Please indicate :

. The TNM or staging classification used :

.....  
.....

. The Performance status coding used :            WHO                            ECOG                            Karnofsky                            Other

If other, specify : .....

**Guarantee of Confidentiality of Individual Trial Results**

Any data supplied will remain the property of the trialist(s) who supplied it.

This data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual trial data.

I wish my data to remain confidential :            Yes  /            No

I enclose a copy of the trial protocol :            Yes  /            No

Signature .....

Any data supplied will remain the property of the trialist(s) who supplied it, These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data

**Please return to Jean-Pierre Pignon – Institut Gustave Roussy  
39, rue Camille Desmoulins – 94805 Villejuif cedex France  
- Fax 33 1 42 11 52 58 – e-mail : jppignon@igr.fr**



# APPENDIX C



*Meta-Analysis of Amifostine  
in RadioTherapy*

Villejuif, June 28, 2004

Dear Colleague,

The purpose of this letter is to solicit your help and collaboration in the meta-analysis of amifostine in radiotherapy (MAART).

We have identified 22 randomized trials (around 2 000 patients) comparing Amifostine + radiotherapy to radiotherapy or Amifostine + chemo-radiotherapy to chemo-radiotherapy. The main objective is to study the impact of Amifostine on overall survival. We will also assess the impact of Amifostine separately on failure-free survival. Finally we will be able to study if some patients benefit more than other from the use of Amifostine.

You will notice that your trial(s) is (are) appropriate for the meta-analysis, and we would like very much to include it, should you have no objections.

The enclosed protocol gives further details on the background to the meta-analysis and details on the methodology that will be used to combine the results of all relevant randomized trials. The information to be collected for all randomized patients concerns age, sex, tumor site, histology, stage, treatment allocated, date of randomization, date of last follow-up, survival status, dates and type of first failure and whether to receive at least one dose of Amifostine. This information is also necessary for randomized patients excluded from your analysis. We would additionally like to know, if possible, the reason for exclusion.

We would be very grateful if you could complete and return the enclosed form giving details of whether you are willing to participate in this project and what data you would be able and willing to contribute. If you prefer that we contact a statistician or data center for further information we would appreciate if you could let us know whom we should get in touch with. We would very much appreciate receiving a copy of your protocol.

We do realize that each trial represents a great deal of hard work on the part of the investigators. Any data supplied will remain confidential and be used only for the purpose of the meta-analysis. Any publication arising from this project will be submitted in the name of *all* collaborators, and will in no way detract from publications of individual trials. We plan to present the results of the meta-analysis at an international meeting of collaborators to be held in 2005.

.../...


The protocol provides a list of publications which we have identified as being relevant to the meta-analysis. Should you know of any that we may have overlooked or unpublished studies which you or colleagues may have performed, we would be grateful if you could send us details of these on the form provided.

We hope that you are willing to participate in this important study which also aims to stimulate international collaboration between clinicians and research groups working in Amifostine.

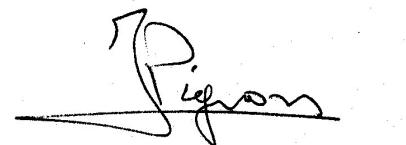
If you have any questions or would like further information about the meta-analysis, please do not hesitate to contact us.

We are looking forward to hearing from you.

Yours Sincerely,



Jean Bourhis, MD, PhD  
email : [bourhis@igr.fr](mailto:bourhis@igr.fr)



Jean Pierre Pignon, MD, PhD  
email : [jppignon@igr.fr](mailto:jppignon@igr.fr)

Kullathorn Thephamongkhol, MD, MSc  
email : [kullathorn@hotmail.com](mailto:kullathorn@hotmail.com)

enclosed



*Meta-Analysis of Amifostine  
in RadioTherapy*

## Registration form

Trial / Protocol number \_\_\_\_\_

Trial Publication \_\_\_\_\_

Name of Investigator \_\_\_\_\_

Address \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_

Email \_\_\_\_\_

Are you willing to take part in the Meta-analysis?      yes       no

Are the details of your trial correct?      yes       no

Is the most recent publication cited in the publication list?      yes       no

If no, please give correct details \_\_\_\_\_

Do you know of any other relevant trials not listed in the protocol?      yes       no

If yes, please provide details \_\_\_\_\_

Is a copy of the trial protocol enclosed?      yes       no

If different from above, please give details of the appropriate contact for the collection of trial data

Name \_\_\_\_\_

Address \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_

Email \_\_\_\_\_

Any data supplied will remain the property of the trialist(s) who supplied it, These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data

**Please return to Jean-Pierre Pignon – Institut Gustave Roussy  
39, rue Camille Desmoulins – 94805 Villejuif cedex France  
- Fax 33 1 42 11 52 58 – e-mail : [jppignon@igr.fr](mailto:jppignon@igr.fr)**



Meta-Analysis of Amifostine  
 in RadioTherapy

## Registration form (2)

Please indicate which of the following survival and prognostic factor information you would be able to supply for each patient randomized

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	<i>Treatment allocated</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Date of randomization</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Survival status</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Date of death/last follow-up</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Performance status</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Histology</i>

yes	no	
<input type="checkbox"/>	<input type="checkbox"/>	<i>Stage TNM</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Cause of death</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Date of first failure</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Type of failure</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Whether excluded from own analysis</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Reason for exclusion</i>
<input type="checkbox"/>	<input type="checkbox"/>	<i>Received at list 1 cycle of amifostine</i>

Did the trial have a target for patient accrual ?      yes       no       Target \_\_\_\_\_

Did the trial reach its target accrual ?      yes       no

What method was used to conceal randomization ?

Sealed envelope       Central telephone       Other

What method of randomization was used in this trial ?

Simple       Permuted Blocks       Minimization       Other

What, if any, stratification factors were used ? \_\_\_\_\_

What proportions was the trial designed to have in each arm ? (e.g.1:1) \_\_\_\_\_

Any data supplied will remain the property of the trialist(s) who supplied it, These data will remain confidential and will not be used, circulated or distributed in any way that allows access to individual patient data

**Please return to Jean-Pierre Pignon – Institut Gustave Roussy**  
**39, rue Camille Desmoulins – 94805 Villejuif cedex France**  
**- Fax 33 1 42 11 52 58 – e-mail : jppignon@igr**