ANNEXES

ANNEX 1 CLINICAL TRIALS

Study n°	Study Title	Coordinating investigator[1]		Patients
		MM	NVB	
Closed trials				
LB 93-001	Immunization with MAGE-1.A1 peptide of HLA-A1 positive cancer patients whose tumors express *MAGE-1* gene.			10
LB 94-001 *	Immunization with MAGE-3.A1 peptide of HLA-A1 positive cancer patients whose tumors express *MAGE-3* gene.			53
LUD 94-002	Pilot study of immunization with MAGE-1.Cw*1601 peptide in patients with malignant melanoma, non small cell lung cancer, head and neck squamous cell carcinoma or bladder carcinoma.			3 **
LUD 95-002	Pilot study of immunization with the MAGE-3.A1 peptide plus immunological adjuvantS QS21 and MPL in patients with malignant melanoma, non small cell lung cancer, head and neck squamous cell carcinoma or bladder carcinoma.			10
LUD 95-004	Pilot study of immunization with the MAGE-3.A2 peptide in patients with malignant melanoma, non small cell lung cancer, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma or bladder carcinoma.	PW		39
LUD 96-007	Pilot study of immunization with the MAGE-1.A1 and MAGE-3.A1 peptides in patients with malignant melanoma, non small cell lung carcinoma, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma or bladder carcinoma.			28
LUD 97-002 * (EORTC 18972-13971)	Phase I/Early II study of immunization with a MAGE-3 protein based vaccine plus immunological adjuvant SB AS-2 in HLA class I selected patients with *MAGE-3* positive tumors.			57
LUD 97-004	Phase I/II study of high-frequency and prolonged immunization with the MAGE-3.A1 and/or MAGE-3.DP4 peptide in stage III/IV patients with malignant melanoma.			45 **
LUD 97-005 *	Pilot study of prime-boost immunization with recombinant canarypox virus expressing the MAGE-1.A1 and MAGE-3.A1 cytolytic T lymphocytes epitopes [ALVAC-MAGE-1,3 Minigene (vCP1469A)] followed by MAGE-1.A1 and MAGE-3.A1 peptides in cancer patients.			40
LUD 99-003 *	Phase I/II study of intradermal and subcutaneous immunization with the recombinant MAGE-3 protein in patients with *MAGE-3*-positive measurable non-visceral metastatic melanoma followed in selected patients by immunization with the MAGE-3 protein combined with antigenic peptides.			30
LUD 99-006	Phase I study of Immunization with autologous PBMC pulsed with the MAGE-4.A2 and MAGE-10.A2 peptides in combination with low-dose recombinant human Interleukin-12 in patients with advanced malignant disease.			5 **
LUD 01-006	Determination of MAGE-3.A1- or MAGE-10.A2 peptide-induced immune response in patients with resected primary or regional melanoma at high risk of relapse.			19

ANNEX 1 CLINICAL TRIALS

Study n°	Study Title	Coordinating investigator[1]		Patients
		MM	NVB	
Ongoing Trials				
LUD 02-002	Phase I/II study of immunization with recombinant MAGE-3 protein combined to AS15 adjuvant containing CpG/QS21/MPL and with peptides, in patients with *MAGE-3* positive metastatic cutaneous melanoma.			11 **
LUD 02-001	Phase I/II study of immunization with the MAGE-3.A1 peptide mixed with the immunological adjuvant CpG 7909 in patients with metastatic melanoma.			1
LUD 03-007	Phase I/II study of immunization with multiple peptides mixed with the immunological adjuvant CpG 7909 in HLA-A2 patients with metastatic cutaneous melanoma.			12
Trials in Preparation				
LUD 02-016	Phase I/II study of immunization with escalating doses of a recombinant ALVAC virus encoding the MAGE-1.A1 and MAGE 3.A1 epitopes, in patients with metastatic melanoma.			
TOTAL		**15**		**363**

1) Coordinating investigator
MM = Marie Marchand
NVB = Nicolas van Baren
PW = Patrick Weynants[†]

* Clinical results of these studies were published [Marchand 1995, 1999; Marchand 2003; Van Baren 2005; Kruit 2005]

** Early study closure

ANNEX 2

PERFORMANCE STATUS SCALES

WHO* SCALE		KARNOFSKY SCORE	
0	Fully active, able to carry out all pre-disease performance without restriction	**100**	Normal; no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity, but ambulatory and able to carry out light work	**80**	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or do active work
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about , more than 50% of waking hours	**60**	Requires occasional assistance and frequent medical care
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited selfcare, confined to bed or chair, more than 50% of waking hours	**40**	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization is indicated though death not imminent
4	Completely disabled. Cannot carry out any selfcare. Totally confined to bed or chair	**20**	Very ill, hospitalization necessary
		10	Moribund; fatal processes progressing rapidly
5	Death	**0**	Death

* World Health Organization

Protocol LB 94-001

Immunization with MAGE-3.A1 peptide of HLA-A1 positive cancer patients whose tumor express the *MAGE-3* gene.

Patient's code:…….

Inclusion Criteria must be answered with 'yes'.		**yes**	**no**
Be HLA-A1 according to lymphocyte HLA typing.		☐	☐
Histologically confirmed diagnosis of one of the following cancer type and AJCC 1992* stage: Melanoma, Head and Neck, NSCLC, Esophagus or Bladder cancer Stage III (regional) or IV (distant, except brain metastases) disease free or tumor bearing.		☐	☐
MAGE-3 gene expression by tumor (determined by RT-PCR).		☐	☐
Fully recovered from toxic manifestations of prior treatment and at least 4 weeks after treatment cessation (and 6 weeks if nitrosoureas).		☐	☐
WHO scale ≤ 1 and a life expectancy ☐ 3 months.		☐	☐
Age ≥ 18 years old and able to give written informed consent.		☐	☐
WBC	☐ 3.000/mm^3	☐	☐
Haemoglobin	☐ 10,5 g/dl	☐	☐
Platelets	☐ 100.000/mm^3	☐	☐
Bilirubine	≤ 1,5 mg/dl	☐	☐
Creatinine	≤ 1,5 mg/dl	☐	☐
Alkaline phosphatase, gamma glutamy transpeptidases SGOT and SGPT: within the institutions normal range.		☐	☐
Exclusion Criteria must be answered with 'no'.		**yes**	**no**
Cardiovascular disease (e.g. uncontrolled congestive heart failure or hypertension, unstable coronary artery disease or serious arrhythmias).		☐	☐
Serious active infections requiring antibiotic therapy.		☐	☐
Recipients of major organ allograft or affected by autoimmune disease.		☐	☐
Affected by neurological or psychiatric alterations.		☐	☐
Pregnant or lactating women.		☐	☐
Concomitant chemotherapy or immunotherapy.		☐	☐
Prior radiotherapy during the last four weeks except for low energy radiotherapy of skin tumors.		☐	☐
Concomitant corticosteroids or NSAIDS (except as administered for life-threatening circumstances).		☐	☐
Known allergic disease.		☐	☐

*American Joint Committee on Cancer, Manual for Staging of Cancer, 4th edition, 1992

Protocol LUD 97-002

Phase I/Early II study of immunization with a MAGE-3 protein based vaccine plus immunological adjuvant SB AS-2 in HLA class I selected patients with MAGE-3 positive tumors

Inclusion Criteria must be answered with 'yes'.	**yes**	**no**
Histologically confirmed diagnosis of one of the following cancer type and AJCC 1992* stage: Cutaneous melanoma (Stage III or IV), NSCLC (Stage IIIB or IV); Head and neck carcinoma (Stage IV with high risk for recurrence, any T -N3, T4-N1, T4-N2); Esophageal carcinoma (Stage IIB, III or IV); Bladder carcinoma (Stage III or Stage IV).	☐	☐
Expression of least one of the 3 class I HLA alleles : HLA-A1, HLA-A2 or HLA-B44.	☐	☐
MAGE-3 gene expression by tumor (determined by RT-PCR analysis).	☐	☐
Age ≥ 18 years old able to give written informed consent.	☐	☐
Negative pregnancy test for women of childbearing age.	☐	☐
If potentially fertile: - Agreement to use effective contraception until 3 months have elapsed after the last - Negative urine or serum pregnancy test (women of childbearing)	☐ ☐	☐ ☐
Fully recovered from surgery.	☐	☐
WHO performance status of 0 or 1.	☐	☐
Hemoglobin ≥ 5 mmol/L or ≥ 8 g/100 ml	☐	☐
Granulocytes ≥ $2{,}000/mm^3$	☐	☐
Lymphocytes ≥ $700/mm^3$	☐	☐
Platelets ≥ $100{,}000/mm^3$	☐	☐
Prothrombin time within the Institution's normal range.	☐	☐
Partial thromboplastin time within the Institution's normal range.	☐	☐
Serum creatinine ≤ 177 μmol/L or ≤ 2 mg/100 ml	☐	☐
Serum bilirubin ≤ 34.2 μmol/L or ≤ 2 mg/100 ml	☐	☐
ASAT and ALAT ≤ 2 x the normal upper limit or ≤ 5 x the normal upper limit if due to liver metastases.	☐	☐
HIV Negative antibodies.	☐	☐
HBV Negative antigens; antibodies may be positive.	☐	☐
HCV Negative antibodies.	☐	☐
Exclusion Criteria must be answered with 'no'.	**yes**	**no**
Cardiovascular disease (e.g. uncontrolled congestive heart failure or hypertension, unstable coronary artery disease, serious arrythmias) or major respiratory diseases.	☐	☐
Serious acute or chronic illnesses, e.g. active infections requiring antibiotics, bleeding disorders, or other conditions requiring concurrent medications not allowed in this study.	☐	☐
Second active cancer with the exception of skin basocellular cancer.	☐	☐
Recipients of major organ allograft.	☐	☐
Autoimmune disease such as, but not limited to, inflammatory bowel disease or multiple sclerosis. (Vitiligo is not an exclusion criterion).		
Brain metastases.	☐	☐
Organic brain syndrome or significant psychiatric abnormality which would preclude participation in the full protocol and follow up.	☐	☐
Chemotherapy, radiotherapy or immunotherapy within the preceding 4 weeks (6 weeks for nitrosoureas and mitomycin C).	☐	☐
Prior treatment with MAGE-3 based vaccines, or other tumor vaccines within the preceding 8 weeks.	☐	☐
Immunodeficiency, previous splenectomy or radiation therapy to the spleen.	☐	☐
Lactation.	☐	☐

*American Joint Committee on Cancer, Manual for Staging of Cancer, 4th edition, 1992

Protocol LUD 99-003

Phase I/II study of intradermal and subcutaneous immunization with the recombinant MAGE-3 protein in patients with *MAGE-3*-positive measurable non-visceral metastatic melanoma followed in selected patients by immunization with the MAGE-3 protein combined with antigenic peptides

Inclusion Criteria must be answered with 'yes'.	**yes**	**no**
Patient with evaluable melanoma belonging to one of the following AJCC 1997* categories: Stage III or IV M1a malignant melanoma, histologically confirmed.	☐	☐
MAGE-3 gene expression by tumor (determined by RT-PCR analysis).	☐	☐
Age ≥ 18 years old, able to give written informed consent.	☐	☐
If potentially fertile: - Agrees to use effective contraception until 3 months have elapsed after the last injection. - Negative urine or serum pregnancy test (women of child bearing age).	 ☐ ☐	 ☐ ☐
Fully recovered from surgery.	☐	☐
Ambulatory (WHO/ECOG performance status 0 or 1**)	☐	☐
Hemoglobin ≥ 5 mmol / L or ≥ 8 g/100 ml	☐	☐
Granulocytes ≥ 2,000 / mm^3	☐	☐
Lymphocytes ≥ 700 / mm^3	☐	☐
Platelets ≥ 100,000 / mm^3	☐	☐
Serum Creatinine ≤ 177 μmol / L or ≤ 2 mg / 100 ml	☐	☐
Serum bilirubin ≤ 34.2 μmol / L or ≤ 2 mg / 100 ml	☐	☐
AST (GOT), ALT (GPT) ≤ 2 x normal upper limit	☐	☐
HBV Negative for serum antigens (antibodies may be positive)	☐	☐
HCV Negative for serum antibodies	☐	☐
HIV Negative for serum antibodies	☐	☐
Informed consent signed	☐	☐

Exclusion Criteria must be answered with 'no'.	**yes**	**no**
Visceral metastases.	☐	☐
Chemotherapy (more than 2 regimens) combined or not with non-specific immunotherapy, or radiotherapy within the preceding 4 weeks (6 weeks for nitrosoureas).	☐	☐
Prior treatment with MAGE tumor vaccines or any other tumor vaccines within the preceding 8 weeks.	☐	☐
Cardiovascular disease (e.g. uncontrolled congestive heart failure or hypertension, unstable coronary artery disease or serious arrhythmias) or major respiratory disease.	☐	☐
Serious acute or chronic illnesses, e.g. active infections requiring antibiotics, bleeding disorders.	☐	☐
Second active cancer with the exception of in situ carcinoma of the cervix or skin basal cell carcinoma.	☐	☐
Recipient of major organ allograft.	☐	☐
Autoimmune diseases such as, but not limited to, inflammatory bowel disease or multiple sclerosis (Vitiligo is not an exclusion criteria).	☐	☐
Organic brain syndrome or significant psychiatric abnormality wich would preclude participation in the full protocol and follow-up.	☐	☐
Immunodeficiency, previous splenectomy or radiationtherapy to the spleen.	☐	☐
Pregnancy or lactation (nursing mothers).	☐	☐

*American Joint Committee on Cancer, Manual for Staging of Cancer, 5th edition, 1997

Protocol LUD 02-002

Phase I/II study of immunization with recombinant MAGE-3 protein combined to AS15 adjuvant containing CpG/QS21/MPL and with peptides, in patients with MAGE-3 positive metastatic cutaneous melanoma

Inclusion Criteria must be answered with 'yes'.	**yes**	**no**
Patient with evaluable cutaneous melanoma belonging to one of the following AJCC 2002* categories: Stage IIIN2b, III N2c,III N3,IV M1a,IV M1b or M1c malignant melanoma, histologicallyconfirmed.Please circle the stage	☐	☐
MAGE-3 gene expression by tumor (determined by RT-PCR analysis).	☐	☐
HLA-typing: at least one of the three following conditions must be fulfilled (see section 4.1.3): 1° If tumor only MAGE-3 positive, than patients must have A1, A24, B18, B44, DP4 or DR13 2° If tumor NA17 or MAGE-10 positive , than patient must have A2 to receive corresponding peptides 3° If tumor MAGE-12 positive, than patient must be Cw7 to receive corresponding peptide	☐	☐
Presence of least one evaluable melanoma lesion	☐	☐
Age ≥ 18 years old, able to give written informed consent.	☐	☐
If potentially fertile agrees to use effective contraception until 3 months have elapsed after the last injection. NA ☐	☐	☐
Fully recovered from surgery.	☐	☐
Ambulatory (WHO/ECOG performance status 0 or 1**).	☐	☐
Hemoglobin ≥ 6,25 mmol / L or ≥ 10 g/100 ml	☐	☐
Granulocytes ≥ 2,000 / mm^3	☐	☐
Lymphocytes ≥ 700 / mm^3	☐	☐
Platelets ≥ 100,000 / mm^3	☐	☐
Serum Creatinine ≤ 177 μmol / L or ≤ 2 mg / 100 ml	☐	☐
Serum bilirubin ≤ 34.2 μmol / L or ≤ 2 mg / 100 ml	☐	☐
Prothrombin time within the Institution's normal range	☐	☐
Partial thromboplastin time within the Institution's normal range	☐	☐
AST (GOT), ALT (GPT) ≤ 2 x normal upper limit	☐	☐
LDH ≤ normal institutional limit in patients with distant metastasis	☐	☐
HBV Negative for serum antigens (antibodies may be positive)	☐	☐
HCV Negative for serum antibodies	☐	☐
HIV Negative for serum antibodies	☐	☐
Informed consent signed	☐	☐
Exclusion Criteria must be answered with 'no'.	**yes**	**no**
Brain metastasis	☐	☐
Chemotherapy, radiotherapy or immunotherapy within the preceding 4 weeks (6 weeks for nitrosoureas) or more than one chemotherapy regimens prior to trial.	☐	☐
Clinically significant heart disease (NYHA Class III or IV)	☐	☐
Serious acute or chronic illnesses, e.g. active infections requiring antibiotics, bleeding disorders or other conditions requiring concurrent medications.	☐	☐
Second active cancer with the exception of in situ carcinoma of the cervix or skin basal cell carcinoma.	☐	☐
Active immunodeficiency disease or autoimmune disease (Vitiligo is not an exclusion criteria).	☐	☐
Organic brain syndrome or significant psychiatric abnormality which would compromise the ability to give informed consent.	☐	☐
Pregnancy or lactation (nursing mothers) NA ☐	☐	☐
Lack of willingness to comply with the study requirements.	☐	☐

American Joint Committee on Cancer, Manual for Staging of Cancer, 6th edition, 2002

ANNEX 4

Response Evaluation Criteria in Solid Tumors (RECIST)
Quick Reference

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
    - **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
    - **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
    - **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated

equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions:

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions:

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions Although a clear progression of "non target" lesions only is

exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

The 95% confidence intervals should be provided.