SUMMARY

Rationale:
We hypothesized that combining Immunocytokines with (Stereotactic Ablative Body) Radiotherapy (SAB)R will lead to:

- A direct cytotoxic effect of SABR to all irradiated metastatic lesions in the irradiation field;
- An immunogenic cell death (ICD) induced by radiation which will, in combination with L19-IL2, create a systemic out of field radio-immune (OFRI) effect thus eliminating micrometastases and macrometastases outside the irradiation field (watch the animation on https://youtu.be/6wDE6RkrikA);
- A memory effect, induced by the ICD, subsequently leading to less long term relapses.

Preclinical studies have shown that immunocytokines on their own, have no significant effect. but the combination of radiotherapy and immunocytokines does. Radiotherapy in the standard arm will depend on the local guidelines. This is a European multi centric study and as the use of radiotherapy in metastatic lung cancer patients varies significantly from country to country,
it has been decided not to be prescriptive and ask the research doctors to follow the local guidelines. To correct for the heterogeneity that might occur, we will stratify per centre.

Objective:
The main objective of the trial is to test if the combination of (SAB)R and the immunocytokine L19-IL2 has clinically meaningful activity in patients with limited metastatic non-small cell lung cancer (NSCLC): (≤10 sites, WHO 0-1). The expected activity is a systemic immune response preventing disease progression and resulting in an improvement of progression-free survival (PFS) at 1.5 years.

Study design:
It is a multicentre, randomised controlled open-label phase II clinical trial testing the hypothesis that a combination of (SAB)R and immunocytokine L19-IL2 increases the progression-free survival in patients with limited metastatic NSCLC. After randomisation by minimization, patients will be assigned either to the experimental arm (E-arm) or to the control arm (C-arm).

Study population:

The trial will consist of one cohort of adult patients with Stage IV metastatic NSCLC. Treatment will be different for patients with oligometastatic NSCLC and patients with poly-metastatic NSCLC. Therefore, number of metastases will be used as stratification factor for the randomisation procedure.

- Oligometastatic patients with a maximum of 5 metastases, amenable to SABR to all metastatic lesions.
- Patients with poly-metastatic NSCLC 6 to 10 metastases, amenable to SABR to maximal 5 metastatic lesions, with either no previous treatment or following chemo- and/or immunotherapy first line or second line. More explanation is given in section 5 and 6.

Patients with limited (stage IV) metastatic NSCLC (max 10 metastases) will be randomised (using ALEA software) by minimisation (stratification factors: centre, gender, histology, oligo/poly, anti-PD(L)1 maintenance, driver mutation) in 2 arms: E-arm or C-arm.

Intervention:

- **C-arm**: Standard of Care (SOC) according to the local and national guidelines.
  - SABR or hypofractionated RT to all lesions is highly recommended for the oligo metastatic group with ≥1 to 5 metastases, based on the Gomez et al(1) and other trials (2-4).
  - For the polymetastatic group, ≥ 6 and ≤10, radiotherapy to symptomatic lesion(s) and/or systemic therapy is given as standard with immunotherapy, immuno-chemotherapy or chemotherapy.
- **E-arm**:
  - Preferably SABR to all lesions for the oligo metastatic group (up to 5 metastases) (1-4) followed by treatment with the experimental drug L19-IL2 up to 6 cycles. *(+ anti-PD(L)1 treatment is given, if this is a part of local SOC).*
  - For the polymetastatic group (≥ 6 and ≤10) SABR and/or conventional radiotherapy to maximum 5 lesions followed by treatment with the experimental drug L19-IL2 up to 6 cycles *(+ anti-PD(L)1 treatment is given, if this is a part of local SOC).*

After randomisation in both arms:

- there will be a follow-up CT-scan and Quality of Life questionnaires to be completed every 12 weeks in Belgium. A deviation of maximum 4 days from the originally planned date is allowed, always start counting form randomisation date.

After randomisation in C-arm and after study treatment in Ee-arm:

- Patients will receive standard of care treatment, according to local protocol.

Inclusion criteria:

Inclusion criteria for oligometastatic disease (max 5 metastases) or poly-metastatic disease (6-10 metastases) are different.

- For patients with **oligometastatic disease**:

  - Histological/Cytological confirmed limited metastatic adult NSCLC patients, regardless of the PD-L1 status.

    - Maximum of 5 metastatic lesions, maximum two brain lesion with a total cumulative diameter of 5cm is allowed.

Largest Lesion Diameter	Second Met Diameter
3cm	≤2cm
2.8cm	≤2.2cm
2.4cm	≤2.6cm

      - SOC baseline imaging e.g MRI and/or PET-CT and CT-brain or MRI brain and/or CT-scan with at least covering thorax-upper abdomen-brain, within 6 weeks prior to randomisation.

      - If a patient has unclear lesions in the liver or brain an MRI would be advised following the ESMO guidelines.

    - In patients with 2 lung tumours, it can be unclear if the patient has 2 concurrent primary tumours or a primary lung tumour with 1 metastasis. In this case, the local multidisciplinary tumour board will decide whether the patient has an M1 disease or not.

  - Previous treatment:
    - Patient inclusion is allowed from 4 weeks Following the last chemo-and/or immunotherapy infusion (first line or second line, excl aPD(L)1 treatment).In case of maintenance chemotherapy, this can continue during the C-arm and **not** allowed in the E-arm.
  - Patient received a (last gift) of live vaccine need to wait 8 weeks before they can be randomised and receive aPD(L)1 treatment
  - Age of 18 years or older.

- WHO performance status 0-1;
- Adequate bone marrow function, evaluated in the local laboratory (Lab): Absolute Neutrophil Count (ANC) of $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, Haemoglobin (Hb) ≥ 6.0 mmol/L (or 9.67 g/dL) /L (it is allowed to give a blood transfusion if Hb is initially too low);
- Adequate hepatic function (evaluated in the local lab): total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase ≤ 2.5 x ULN for the institution or ≤ 5 in case of liver metastasis);
- Adequate renal function (evaluated in the local lab): creatinine clearance of at least 40 ml/min;
- Adequate endocrine function: TSH 0.35-4.8 mU/L or for 80+ patients till 9mU/L, FT4 8,0-24,0 pmol/l or 0.7-2Ng/dL. Make sure lower/higher values are not the cause of medication (e.g. heparin i.v. amiodarone, lithium).
- The patient is capable of complying with study procedures;
- Life expectancy of at least 12 weeks;
- Negative serum pregnancy test for women of childbearing potential.
- Ability to comply with contraception requirements:
  Non-sterilised, sexually active male patient with a female partner who is of child-bearing age, must use two acceptable birth control methods like a condom combined with spermicidal cream or gel, and a partner who is WOCBP must use effictive contraception as definied for WOCBP who are participants in the study as per the next paragraph. From the first dose of study medicine, during the study and at least up to 12 weeks after the last administration of the study medicine and up to 5 months after the last dose of the medicine with anti-PDL)1 as an action mechanism (if you get this product besides the study medicine), as an addition to the use, by the female partner, of as described in the following section:
  Women of childbearing potential (WOCBP) and WOCBP partners of male patients must be using, from the screening to three months following the last study drug administration and 5 months after last dose of anti-PD(L)1 maintenance treatment, effective contraception methods (a) IUD (IUD) or intrauterine hormone delivery system (IUS), b) combined (with estrogen and progesterone) hormonal contraception associated with ovulation inhibition (oral, intravaginal, transdermal), c) hormonal contraception with progesterone only associated with ovulation inhibition (oral, injectable, implantable), Reference: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- Signed and dated written informed consent;

- For patients with **poly-metastatic disease** (6 to 10 metastases)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Histological/Cytological confirmed limited metastatic adult NSCLC patients, regardless of the PD-L1 status.
    - A minimum of 6 and maximum of 10 metastatic lesions, maximum two brain lesion with a total cumulative diameter of 5cm is allowed.

Largest Lesion Diameter	**Second Met Diameter**
3cm	≤2cm
2.8cm	≤2.2cm
2.4cm	≤2.6cm

        - SOC baseline imaging e.g MRI and/or PET-CT and CT-brain or MRI brain and/or CT-scan with at least covering thorax-upper abdomen-brain, within 6 weeks prior to randomisation.
        - If a patient has unclear lesions in the liver or brain an MRI would be advised following the ESMO guidelines.
    - At least one measurable lesion (according to RECIST 1.1) that has no overlap with the PTV of the lesion subjected to radiotherapy.
- Previous treatment:
    - Patient inclusion is allowed from 4 weeks following the last chemo- and/or immunotherapy infusion (first or second line excl aPD(L)1 treatment). In case of maintenance chemotherapy, this can continue during the C-arm and **not** allowed in the E-arm;
- Patient received a (last gift) of live vaccine need to wait 8 weeks before they can be randomised and receive aPD(L)1 treatment
- Age of 18 years or older;
- WHO performance status 0-1;
- Adequate bone marrow function (evaluated in the local lab): Absolute Neutrophil Count (ANC) of $\geq 1.0 \times 10^9$ /L, platelet count $\geq 100 \times 10^9$/L, Hb ≥ 6.0 mmol/L (or 9.67 g/dL) (it is allowed to give a blood transfusion if Hb is initially too low);
- Adequate hepatic function (evaluated in the local lab): total bilirubin ≤ 1.5 x upper limit of normal (ULN) for the institution; ALT, AST, and alkaline phosphatase ≤ 2.5 x ULN for the institution or ≤ 5 in case of liver metastasis);
- Adequate renal function (evaluated in the local lab): creatinine clearance of at least 40 ml/min;
- Adequate endocrine function: TSH 0.35-4.8 mU/L or for 80+ patients till 9mU/L, FT4 8,0-24,0 pmol/l or 0.7-2Ng/dL. Make sure lower/higher values are not the cause

of medication (e.g. heparin i.v. amiodarone, lithium).

- The patient is capable of complying with study procedures;
- Life expectancy of at least 12 weeks;
- Negative serum pregnancy test for women of childbearing potential;
- Ability to comply with contraception requirements:
  Non-sterilised, sexually active male patient with a female partner who is of child-bearing age, must use two acceptable birth control methods like a condom combined with spermicidal cream or gel, and a partner who is WOCBP must use effictive contraception as definied for WOCBP who are participants in the study as per the next paragraph. From the first dose of study medicine, during the study and at least up to 12 weeks after the last administration of the study medicine and up to 5 months after the last dose of the medicine with anti-PDL)1 as an action mechanism (if you get this product besides the study medicine), as an addition to the use, by the female partner, of as described in the following section:
  Women of childbearing potential (WOCBP) and WOCBP partners of male patients must be using, from the screening to three months following the last study drug administration and 5 months after last dose of ant-PD(L)1 maintenance treatment, effective contraception methods (a) IUD (IUD) or intrauterine hormone delivery system (IUS), b) combined (with estrogen and progesterone) hormonal contraception associated with ovulation inhibition (oral, intravaginal, transdermal), c) hormonal contraception with progesterone only associated with ovulation inhibition (oral, injectable, implantable), Reference: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
- Signed and dated written informed consent.

Exclusion criteria (for both groups; oligometastatic and poly-metastatic disease):

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- More than 10 metastatic lesions.
- More than 2 brain metastatic lesions.
- 2 brain metastases with a cumulative diameter larger than 5 cm.
- Patients with non-infectious pneumonitis, uncontrolled thyroid disease, pleuritis, pericarditis and peritonitis carcinomatosis. Or other mild/serious infection at screening that might need antibiotic therapy. (First treat infection, so patient can still participate after it is cleared.)
- Patients who received live vaccines 30 days or fewer prior to enrolment.

- Patients who are already actively participating in another interventional study with an investigational product.
- Patients who need simultaneous radiation on the primary tumour and metastatic lesion(s). For these patients it might be an option to treat the primary tumour first although this is not mandatory for this study. There must be minimal 4 weeks between last treatment and randomisation.
- Whole brain radiotherapy (WBRT) is not allowed, although it is accepted when given at least 4 weeks prior to randomisation or after the treatment period. Patients with stable brain metastases are not excluded.
- Previous radiotherapy to an area that would be re-treated by (SAB)R, resulting in overlap of the high dose areas.
- Maintenance therapy with anti-PD(L)1 treatment combined with chemotherapy is not allowed during treatment ((SAB)R and L19-IL2 cycles).
- Other active malignancy or malignancy within the last 2 years (except localised skin basal/squamous cell carcinoma, non-muscle invasive carcinoma of the bladder or in situ carcinoma from any site).
- Concomitantly administered **glucocorticoids** may decrease the activity of IL2 and therefore should be avoided. However, patients who develop life-threatening signs or symptoms may be treated with dexamethasone until toxicity resolves or reduces to an acceptable level (generally grade 1 and 2, however must be based at the research physician's discretion).
- History of allergy to intravenously administered L19-IL2/proteins/peptides/antibodies/ radiographic contrast media.
- HIV positive; active HIV infection, or active hepatitis B or C (assessed in local lab).
    - For HBV serology: the determination of HBsAg, anti-HBsAg-Ab and anti-HBCAg-Ab is required. In patients with serology documenting previous exposure to HBV (i.e., anti-HBs Ab with no history of vaccination and/or anti-HBc Ab), negative serum HBV-DNA is required. For HCV: HCV RNA or HCV antibody test. Subjects with a positive test for HCV antibody but no detection of HCV RNA indicating no current infection are eligible.
- Systemic treatment with either corticosteroid (>10 mg daily prednisone equivalents) or Interferon alpha or immunosuppressive medications within 14 days prior to randomisation. Topical or inhalation steroids are allowed. If a patient needs to take unexpectedly immunosuppressive medication during the trial, it will be allowed but decreasing the dose as soon as possible is strongly advised.
- Prior history of organ transplant, including allogenic stem cell transplant.

- Acute or sub-acute coronary syndromes within the last year, acute inflammatory heart disease, heart insufficiency NYHA > 2, or irreversible cardiac arrhythmias.
- A known impaired cardiac function defined as left ventricular ejection fraction (LVEF) < 50 % (or below the study site's lower limit of normal) as measured by MUGA or ECHO.
- Uncontrolled hypertensive disease; (systolic blood pressure (SBP) ≥160 or diastolic blood pressure (DBP) ≥100 mm Hg during two measurements).
- Uncontrolled and symptomatic hypotensive disease; (systolic blood pressure (SBP) <85 or diastolic blood pressure (DBP) <55 mm Hg during two measurements).
- History or evidence of active autoimmune disease.
- Severe diabetic retinopathy (neoangiogenesis targeted by L19 outside the tumour).
- Major trauma, including oncologic surgery, but excluding smaller procedures like the placement of porth-à-cath or surgical biopsy, within 4 weeks prior to randomisation (neoangiogenesis targeted by L19 outside a tumour).
- Any underlying mental, medical or psychiatric condition which in the opinion of the investigator will make administration of study drug hazardous or hinder the interpretation of study results. Unstable or serious concurrent uncontrolled medical conditions.
- Pregnancy or breast feeding; it is well known that ED-B, the target of both L19-IL2, is expressed in a variety of fetal tissues. Furthermore, anti-PD(L)1 treatment may increase the risk of immune-mediated disorders. Therefore, it will be contra-indicated for pregnant or lactating women.

Main study parameters/endpoints:
The main objective of the trial is to test if the combination of (SAB)R and the immunocytokine L19-IL2 will result in improved progression-free survival (PFS) at 1.5 years after randomisation, compared to the SOC. The secondary objectives will be assessment of 5-years PFS, 1,5-year and 5-year overall survival, and 1,5-year toxicity, Quality of Life, Out of Field Radio-Immune (OFRI) response, and In Field Radio-Immune (IFRI) response. Exploratory analyses will be performed to investigate biomarkers (e.g EDB expression on tumour biopsies and blood), diversity of the microbiota of faeces, CT radiomics, iRECIST, tumour grow kinetics and the changes of immunologic markers in repeated peripheral blood samples.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Standard of care for patients with metastatic NSCLC is a palliative systemic treatment (chemotherapy, immunotherapy). With this, progression-free survival and overall survival in this patient group are poor.

The ultimate aim of the combination of (SAB)R and L19-IL2 is to prolong PFS and OS by inducing an immune response which would be able to keep this systemic disease controlled. Known/potential risks additional to the standard of care treatment include:

- *L19-IL2 related side effects*:

Common (1 in 100): Fever with cold shivers, fatigue, nausea, vomiting, weakness, skin rash, itching, increased kidney function values, hypotenion, and high blood pressure.

Rare (1 in 10 000): (peripheral) oedema (accumulation of fluid elsewhere in the body), production of more fluid, pain in the torso, lack of oxygen, and pain in the tumour region.

There might be an increased risk of immune related toxicity for those patients receiving L19 -IL2 and radiotherapy in combination with standard treatment pembrolizumab. Immune related toxicity from standard of care pembrolizumab is rare but can be serious and life threatening.

Most of the adverse events were seen in studies using a higher dose of L19-IL2 (22.5-30 Mio IU) compared to our study dose of 15 Mio IU. We therefore expect, just as in our phase 1 trial, that the incidence and intensity of the adverse events is lower.

- *(SAB)R related side effects:* Side effects from (SAB)R vary from the localisation of the irradiated site. Toxicity is considered very low.

Common: Nausea, vomiting and diarrhoea when the abdomen is radiated, or local pain and discomfort when bones or soft tissue are radiated. When radiating the lungs/chest a cough, shortness of breath or broken ribs may occur.

Studies evaluating SABR to mixed oligometastatic sites report grade III toxicity rates below 3-5%, often bowel strictures.

There might be an increased risk of immune related toxicity for those patients receiving L19-IL2 and radiotherapy in combination with standard treatment pembrolizumab. Immune related toxicity from standard of care pembrolizumab is rare but can be serious and life threatening.

Taking into account that metastatic NSCLC is a mortal disease in the short term, the potential burden seems proportional to the potential gain.

1. INTRODUCTION AND RATIONALE

1.1 Background Disease Information

Lung cancer is the leading cause of cancer-related death worldwide (5, 6). Platinum-based chemotherapy, with or without maintenance therapy or aPD-1 directed immunotherapy (≥50 percent expression of programmed death-ligand 1, PD-L1), is the standard treatment for most patients with advanced NSCLC without targetable driver mutations (85-90% of the patient population). Despite these