FAQ's ImmunoSABR

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A. Background

1. Why the combination SABR/RT and L19-IL2?

We know that the combination therapy of radiotherapy with L19-IL2 can enhance the immune response against various solid tumours (see figure 1), providing an additive or synergistic antitumor effect in the presence of ED-B. We got these findings also from our recent phase I clinical study containing patients with an oligometastatic solid tumour.

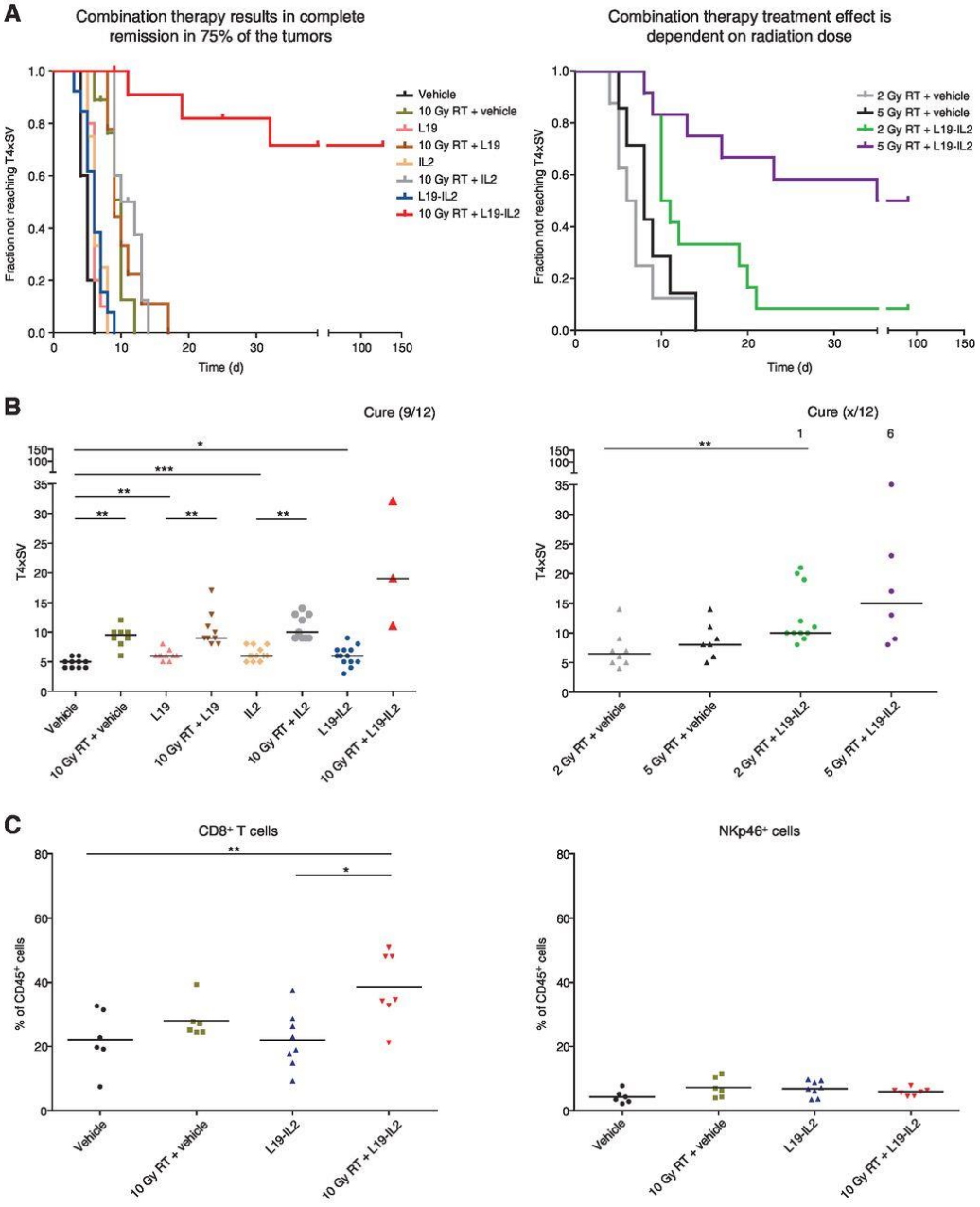


Figure 1: Combination therapy results in complete remission of 75% in the C51 model. A, fraction of tumours not reaching 4 times start volume (T4 × SV). B, time to reach 4 times start volume for the different treatment groups. C, results of flow cytometry analysis; shown is the percentage of CD8+ and NKp46+ cells of all CD45+ cells present in the tumour. Data represent the mean of 6 to 12 tumours. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. [Zegers et al. 2015]

2. Why the combination Immunocytokines and checkpoint inhibitors instead of monotherapy IO or checkpoint inhibitors like the rest of the world?

In vivo, in preclinical models, we found that the synergy of radiation with L19-IL2 is superior to the combination of radiation with checkpoint inhibitors. We have shown this in three different tumour models (see under).

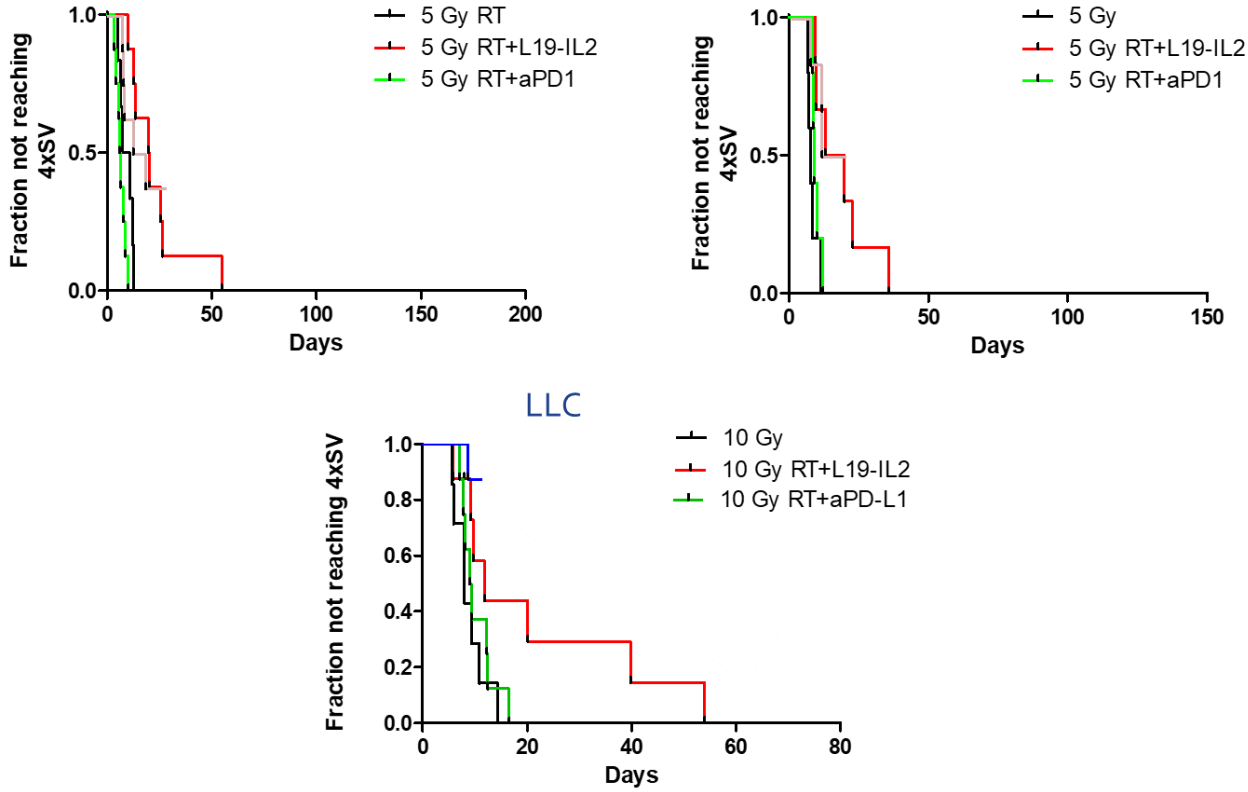


Figure 2: Radiation with L19-IL2 vs radiation with checkpoint inhibitors in Lewis Lung Carcinoma (LLC) model. [Markus et al., submitted]

However, if you **<u>combine immunocytokine with checkpoint inhibitors,</u>** the PFS and OS increased even more!

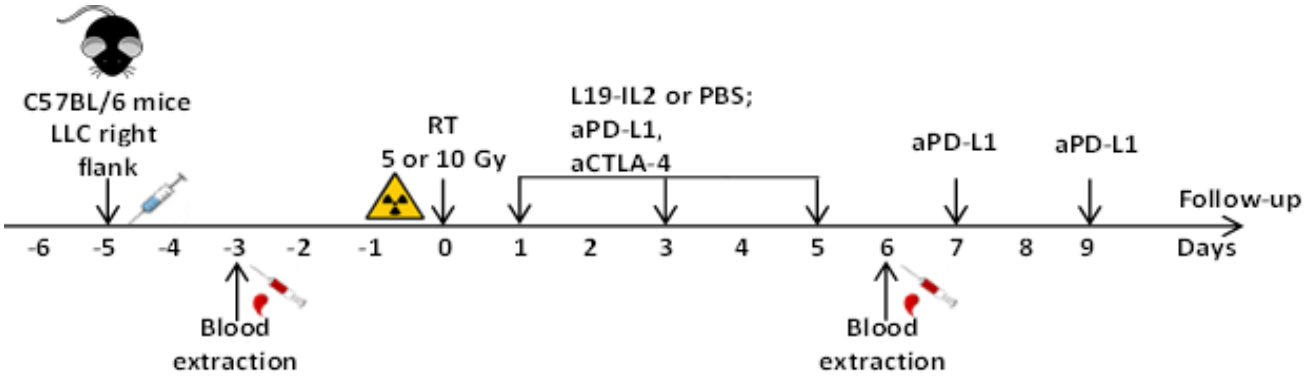


Figure 3: Study design of Olivo Pimentel et al. (submitted). Upon an average volume of 200mm3, animals were randomised in different treatment groups: RT + vehicle/L19-IL2 (1 mg/kg) + IgG or RT + vehicle/L19-IL2 + aPD-L1/aPD1/aCTLA-4 (all 10 mg/kg). Tumours were irradiated with 5Gy (C51 and CT26) or 10Gy (LLC), as the latter is less immunogenic. Vehicle/L19-IL2, aCTLA-4 and IgG were given i.v. on day 1, 3 and 5 after RT; aPD-1, aPD-L1 and IgG were given i.p. 1, 3, 5, 7 and 9 days after RT. Tumour response was quantified as time to reach 4 times starting tumour volume (T4xSV).

LEWIS LUNG CARCINOMA MODEL

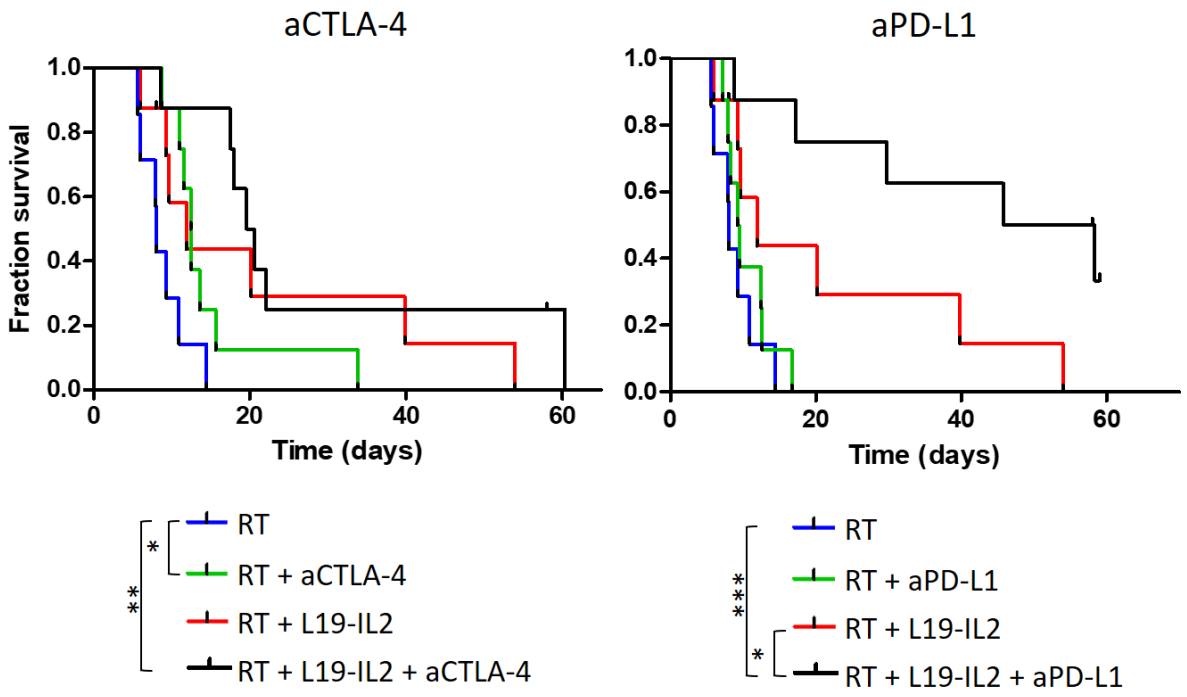


Figure 4: Radiation with L19-IL2 vs radiation with checkpoint inhibitors in Lewis Lung Carcinoma (LLC) model. [Olivo Pimentel et al., submitted] RT+L19-IL2+aPD-L1 improved outcome compared to RT + L19-IL2 and was associated with increased infiltration of NK and CD44+ CD8+ T cells. (Data not shown)

3. Is there a memory effect? And if yes are there biomarkers?

Yes there is a memory effect on all our preclinical models and there is a subgroup of memory T cells that can be used as biomarkers: the minority of mice without memory effect had no increase ot memory T cells. We intend to measure memory T cells in the translational research project.

4. Are there more clinical trials combining immunocytokine IL2 with a checkpoint inhibitor (anti-PDL-1)?

Yes there are. Here a list which keep increasing.

NCT	Phase	Drug	Stage	Study design	Pembro	IL2
NCT02748564	2 (1b+2)	IL2 (aldesleukin) +Pembro	Stage 3-4 Melanoma	Phase Ib: To determine the safety and side effects of increasing doses of IL-2 in combination with pembrolizumab Phase II: Once the maximum tolerated dose of IL-2 is determined, additional patients will be treated to determine if it is effective against the cancer.	30 min on day 1 every 3 wks	every 8 hours for up to 14 doses at weeks 4, 7, 16, 19, 28, and 31
NCT02964078	2	IL2 +Pembro	Stage 3-4 RCC	Organised into blocks of 9 weeks, with pembro treatment planned for weeks 1, 4 and 7. On the second and third blocks, interleukin-2 is added, for 5 doses at a time, one dose every 8 hours, on a weekly schedule on the two weeks after the week 1 and the week 4 pembro doses.	The dose of pembrolizumab is fixed, flat dose 200 mg/dose.	There is no dose escalation portion: The dose and schedule of IL-2 is fixed, 600,000 IU/kg/dose, with a cap of 66 mIU/dose. Doses may be omitted for safety.
NCT03260504	1	IL2 +Pembro	Stage 3-4 RCC	Unknown	30 min on day 1 every 3 wk	days 2-6 every 3wk (2 cycles)
NCT02303990 (RADVAX)	1	Pembro + HFRT	Stage 3-4 NSCLC/ melanoma	Patients were stratified by histology and whether they had received prior PD-1 or PDl-1 therapy. Within each stratum, the first six patients received 8 Gy × 3 to a single lesion and the second six patients received 17 Gy × 1. After that pembro.	Pembro (200mg) ever 3 wks for 6 cycles	-

NCT02830594	1	RT + Pembro	Gastroesophageal Cancer (GEC)	Standard palliative RT 30 Gy over 10 fractions to a single site of disease.	200 mg was given concurrently with RT with first dose concordant with the first fraction. Cycles repeated every 3 weeks for up to 35 cycles in the absence of disease progression or unacceptable toxicity	

5. What is the pathway behind the combination SABR/RT, L19-IL2 and pembrolizumab?

L19-IL2 and pembrolizumab induced anti-tumour effects (see figure 5). (1) Radiotherapy induces immunogenic cell death, thereby releasing DAMPs and antigens (2), creating an *in situ* vaccine. Tumour-associated antigens are picked up by dendritic cells (3) that migrate to lymph nodes to activate CD8+ T cells (4). L19-IL2 can stimulate the proliferation of tumour specific CD8+ T cells (5) that can now target the irradiated tumours (6), non-irradiated tumours (7) and prevent the formation of new tumours months after tumour cure and termination of the treatment (8). To increase the effect of the CD8+ T cells, the PDL-1 on tumours that normally inhibit CD8+ T cells will also be blocked by Pembrolizumab (9).

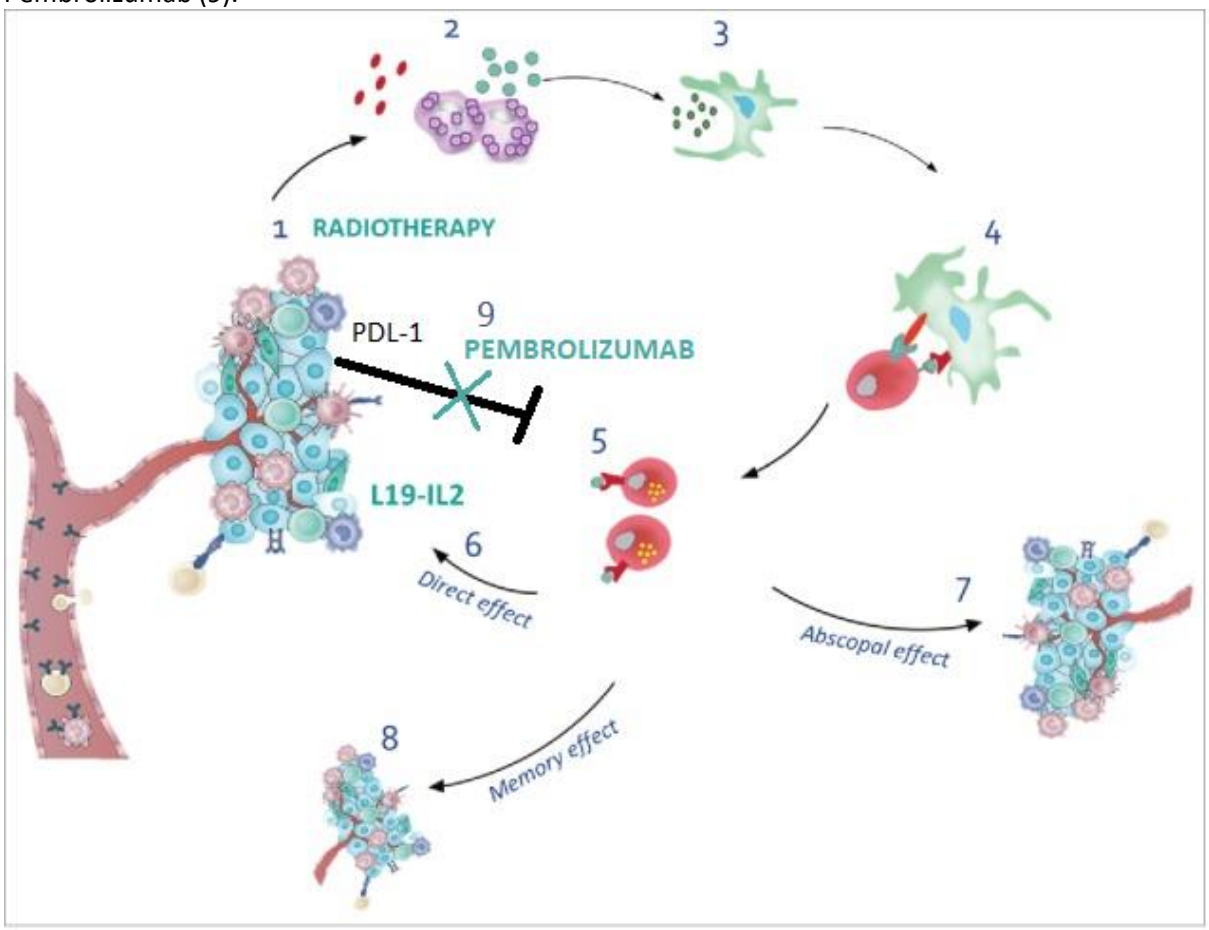
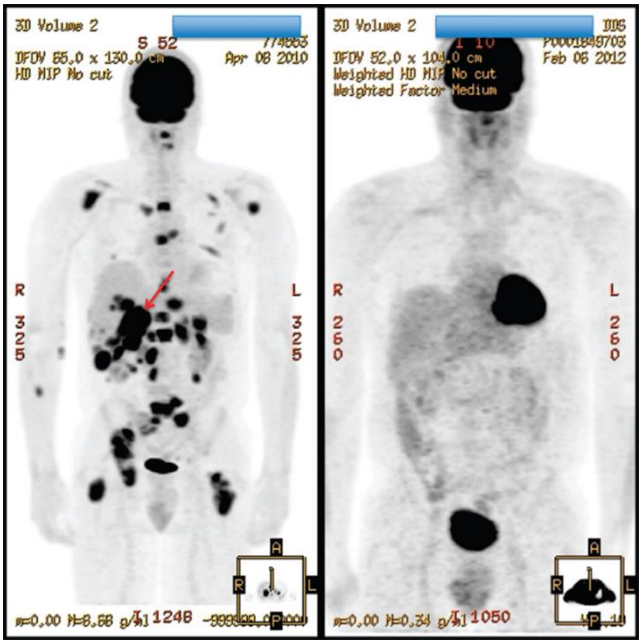


Figure 5: Pathway of the combination (SAB)R + L19-IL2 + Pembrolizumab

In the study of Rekers et al., they showed for the first time that irradiation results in a curative abscopal effect when combined with systemic L19-IL2 treatment dependent on T cells, in 20–30% of the mice. Single dose RT combined with L19-IL2 led to an elevation of T cell infiltration in the non-irradiated tumours with a more immunosuppressive phenotype, a phenomenon which is enhanced upon fractionated irradiation. We suggest that diminished abscopal effect in fractionated irradiation is likely due to fractionation than to the total radiation dose since the total dose, biologically equivalent to the large single dose, has been applied. Finally, they showed that RT + L19-IL2 could induce long-lasting immunological protection against tumours (the so-called “memory effect”), which is associated with the presence of effector and central memory T cells.

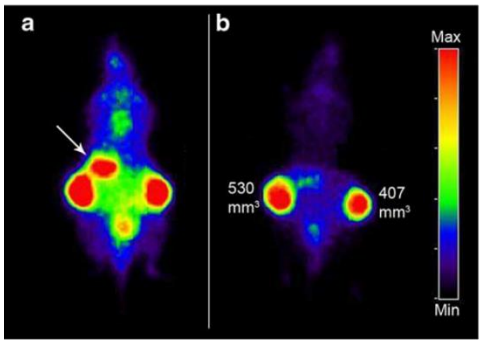
6. Are there already clinical data of IL2 + radiation?

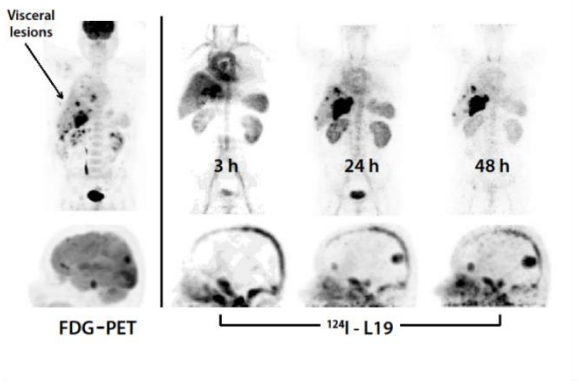
Yes, the abscopal effect has been shown in clinical trials with metastatic melanoma patients at the price of a certain toxicity. By using IL2, the burden of proof is lower: we know it works in patients (see Figure: Before and after treatment (SBRT + IL2) PET imaging in a patient with widely metastatic melanoma (ref: Steven K. Seung et al., Sci Transl Med 2012;4:137ra74). L19-IL2 is a targeted IL2 which concentrate in the tumours and therefore is less toxic than naked IL2.
(More information can be found in the Investigator Brochure)



7. Are there imaging data with labelled L19 providing a specific tumour uptake?

L19-IL2 is a targeted IL2 which concentrate in the tumours rich in EDB; this has been shown with imaging in mice and patients (see figure hereunder). The hypothesis is that L19-IL2 will have the same effect as IL2 but with fewer side effects. (More information can be found in the Investigator Brochure)





8. Has L19-IL2 already been given in patients? At which dose?

Yes, starting form 10 Mio IU up till 56 Miu IU.
The recommended dose in this trial of 15 Mio UI is lower than the dose which was found in earlier phase I dose escalation approaches, where L19-IL2 was proven safe in a variety of stage IV malignancies with a recommended dose of 22.5 Mio IU(1, 7). Furthermore, it was safely combined with dacarbazine in stage IV melanoma patients maintaining the same recommended dose level (7). However, later studies of L19-IL2 in combination with dacarbazine conducted using a different premedication protocol and slower drug infusion (3 hours) have demonstrated that the product can be safely administered up to 56 Mio IU in Stage IV melanoma patients (Eudra-CT nr. 2012-004495-19) (unpublished results). Here we are going to administered 27% of the MTD.

9. Do we have pre-/clinical data regarding the combination chemotherapy followed by L19-IL2?

Pre-clinical: It is not doable to do sequential chemo-RT-immunotherapy in an animal study; right strain, study design, the lifespan of a mouse, chemo, frequency, dose, a period of rest, RT (fx+dose), L19-IL2, translational, financial.

Clinical data: L19IL2 has been administered in the context of different clinical trials to over 150 patients, as monotherapy or in combination with chemotherapeutics or radiotherapy showing excellent tolerability and clinical benefit in a substantial proportion of treated patients with different kind of advanced tumours. (More information can be found in the Investigator Brochure).

B. The clinical trial "ImmunoSABR"

General remark

- **The field** of metastatic lung cancer is **evolving rapidly** & **is not synchronized across Europe**:
  - The reimbursement policies and the definition of SOC are different.
- This is a randomized **phase 2** typically **more flexible** and **more exploratory** than a randomized phase 3
- **Treating Physician** makes the **final decision** what is best for the patient
- The field is **very competitive**: accrual of enough patients will be crucial

10. Is it an Investigator Initiated Trial?

Yes and it is funded by a Horizon 2020 grant. As a consequence our budget is about 20% of a comparable company sponsored trial and have few restrictions (e.g. duration, reporting, budget…).

11. In a nutshell what are the main inclusion criteria for ImmunoSABR?

The study population consists of adult, squamous and non-squamous, non-small cell lung cancer patients with Stage IV metastatic disease (up to 10 metastases) with either no previous treatment or with stable disease or response following chemo- and/or immunotherapy first line or second line.

12. Is "progression" an exclusion criteria?

No. To make the trial simple and patient population correlates with real-life treatment

- L19-IL2 will increase the PFS
- This effect should be the same for every patient in this population
- No indication that it might not work in a certain population

All visible metastatic lesions count as a metastatic lesion. So not only the lesions that are measurable regarding RECIST.

13. Should all the potential patients be registered before randomisation?

No, it would too much work and we do not have the budget to do so. That could be considered for the phase III trial**. If patient is eligible, only then the patient will be registered in Open Clinica and will be directly manually randomised into the trial.**

14. Do we have clinical data regarding the combination chemotherapy followed by L19-IL2 in NSCLC patients?

Yes, our phase 1 trial (*"Toxicity report of a phase I dose-finding study combining Stereotactic Body Radiotherapy with escalating doses of L19-IL2" NCT02086721. Van Limbergen et al.)*

Using a 3+3 dose escalation design, escalating doses of L19-IL2 were administered following SBRT in patients with oligometastatic solid tumour **(n1-5)**. Patients could receive, if appropriate, first radical treatment of the primary tumour and/or nodal sites using radiotherapy (n3), chemo(n3) or surgery(n5). Then stereotactic body radiotherapy (SBRT) was administered to all remaining oligometastatic tumour lesions.

A total of 6 patients (2 with NSCLC) were treated with predefined doses of L19-IL2 following SBRT. The 15 Mio UI dose level was well tolerated with no related ≥ gr III toxicity.
SABR:

- **4x 12Gy**
- **3 x 18 Gy**

At least 2 patients are progression-free and 1 patient will receive his last CT-scan to see if he is also progression free. If that is the case a success rate of 50%!

15. Following the ESMO guideline of OCT-2018, SOC will change soon in all countries: how do you integrate SOC in ImmunoSABR?

2019 SOC – OLIGO (n1-2):

1. Sequential chemoradiotherapy 66Gy on primary tumour
2. Concurrent chemoradiotherapy 66Gy on primary tumour
3. Chemotherapy followed by surgery on primary tumour

ImmunoSABR setup:
PET-CT → start ImmunoSABR → randomisation
C-arm: wait and see
E-arm: SABR (30-60Gy on all meta's) followed by 6x L19-IL2

2019 SOC – OLIGO (n3-5)*:

1. Sequential chemoradiotherapy 66Gy on primary tumour
2. Concurrent chemoradiotherapy 66Gy on primary tumour
3. Chemotherapy followed by surgery on primary tumour

ImmunoSABR setup:
PET-CT → start ImmunoSABR → randomisation
C-arm: maintenance

- Non-squamous: pemetrexed-pembrolizumab
- Squamous: pembrolizumab

E-arm: 1x Pembro followed by SABR (30-60Gy on 3 meta's) followed by 6x L19-IL2 and Pembro

*After the first 15 included patients in the E-arm in the NL or BE, an extended toxicity check takes place. Recruiting of new patients will continue after it is found safe.

2019 SOC – POLY (n6-10)*:

1. Chemotherapie
    a. Non-squamous: 4x platinum-pemetrexed-pembro
    b. Squamous: 4x platinum-pacli-pembro

ImmunoSABR setup:

PET-CT → no progression → start ImmunoSABR → randomisation
C-arm: maintenance
- Non-squamous: pemetrexed-pembrolizumab
- Squamous: pembrolizumab

E-arm: 1x Pembro followed by SABR (30-60Gy on 3 meta's) followed by 6x L19-IL2 and Pembro

*After the first 15 included patients in the E-arm in the NL or BE, an extended toxicity check takes place. Recruiting of new patients will continue after it is found safe.

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16. Is it possible to modify the Standard of Care (SoC) during the trial?

Yes we expect this because the guidelines are evolving rapidly. This is one of the reason why we stratify per center.

17. If we have an oligo patient, should we treat the primary?

Pre-treatment of the primary tumour is not mandatory, however, during the I-SABR trial, the primary tumour can't be treated. Only metastatic lesions. So if you want to treat the primary tumour, it must be done **before** ImmunoSABR trial inclusion. ImmunoSABR is focussing on metastatic lesions. If you administer chemo-radiotherapy you have to wait 4 weeks before starting SABR on the metastasis followed by L19-IL2. **Lymph nodes are not counted as metastatic lesion. All visible metastatic lesions count as a metastatic lesion. So not only the lesions that are measurable regarding RECIST.**

1. **Before I-SABR:** chemo + immune before the trial as 1ste line. Chemo stops, and I-SABR can be 2nd line treatment. Note: between the last chemo and randomisation, a period of at least 4 weeks is needed.
2. **During I-SABR:** When the patient is randomised into the c-arm, because it is SOC. (Be aware that the patient can't have chemo in the e-arm)
3. **After I-SABR:** If the patient, randomised into the e-arm, is progressive after 3-5 cycles of L19-IL2, the study stops and the patient can have SOC regarding local protocol.

- I-SABR can act as 1st, 2nd or max 3rd line treatment.

18. Our oligo patient do not receive Pembro, is that a problem?

No. If Pembro is not SoC you do not have to administer it.

19. Why not make Pembrolizumab mandatory instead of optional?

This is not possible. Not all sites/ countries will have Pembrolizumab as SOC. This means the sponsor needs to pay for every centre where Pembro is not SOC. Later in an (eventual) phase 3 trial, this can be mandatory.

20. Why not to give a placebo?

Because it is a randomized phase 2 trials. If the trial is positive and continue in a randomized phase 3 we would.

21. Is it allowed to give the combination maintenance therapy 'chemo-pembro' if it is SOC?

No, it's not allowed to give chemo-pembro (e.g. pemetrexed-pembro; not-squamous) as maintenance therapy to E-arm patients. Pembro alone is allowed if SOC.

22. In the protocol it's allowed to use SABR on 5 metastatic lesions as SOC in poly metastatic patients?

In most cases, conventional RT will be used as SOC, but in some situations, the use of SABR on one or more lesions is preferred. We will leave the decision to the treating physician level and we will not interfere with the local protocol.

23. Can patients only be included when ImmunoSABR is 1st line treatment?

No, patients who are already treated with 1st or 2nd line treatment (e.g. chemo, chemo-pembro, immune or target therapy) can still participate. **ImmunoSABR will be max 3rd line treatment.**
The only remark is that the timeframe between last (cancer) treatment and randomisation (start trial) is at least 4 weeks.

24. The population is heterogeneous, why?

This is not uncommon in a Phase II trial. We specifically choose for this study population because **we expect that:**

- Patient population correlates with real-life treatment
- L19-IL2 will increase the PFS
- This effect should be the same for every patient in this population
- No indication that it might not work in a certain population

25. Are the in- and exclusion criteria not too flexible?

We specifically used for more flexible criteria because there will be differences in SOC per country but also between centres. By using specific minimisation factors, we can compare the c- and e-arm with enough power (85%). It's also common under a phase 2 study.

26. You use 6 stratification factors for a total of 126 patients?

We apply the method ***"randomisation by minimisation".*** This method is specifically applicable for smaller trials with multiple stratification factors. This procedure will help to create homogenous arms based on these 6 prognostic factors:

- Centre
- Oligo-Poly
- Histology (squamous/none-squamous)
- Pembro maintenance YES/NO.
- Gender
- Driver mutation (EGFR, ALK, ROS, MET or Other/unknown)

27. Patients with a driver mutation can be included?

Yes, all driver mutations but also "de novo". However, it must be recorded in the eCRF what type it is.

28. When the patient is randomized in the experimental group, is the L19-IL2 automatically ordered?

No you need to fill the form and send it to Philogen OR you ask the pharmacy to do it. The last option is probably better. Philogen, a swiss SME, will directly send the drug to your hospital: they are experienced to do so.

29. There are 6 cycles of L19-IL2, is it possible to give less?

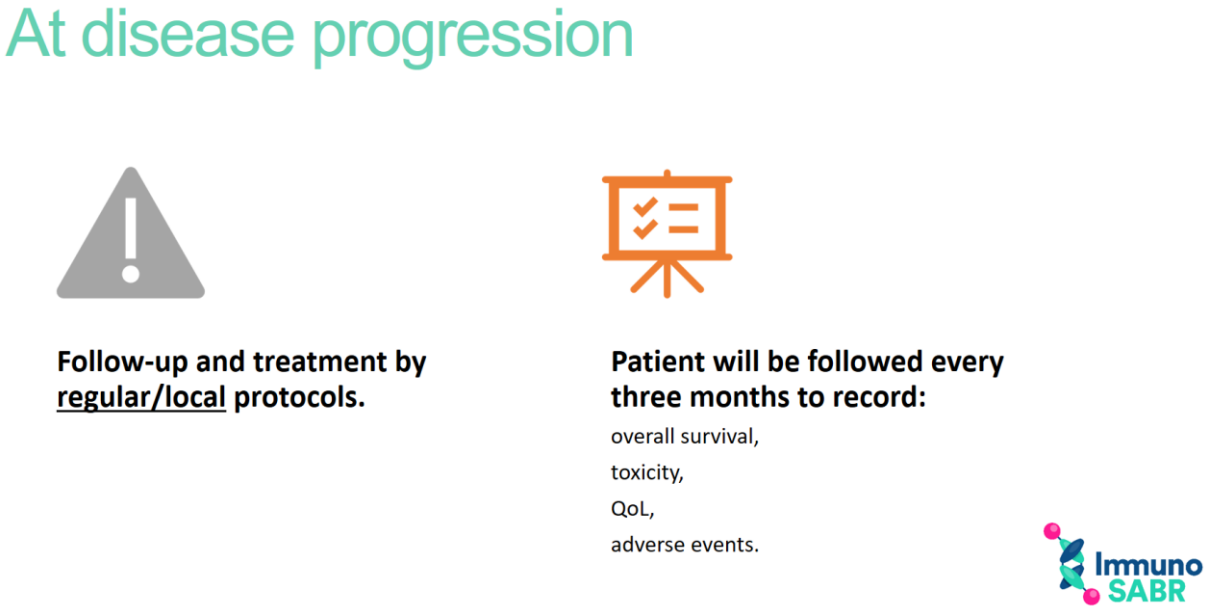
The study protocol defines that 6 cycles should be given (also to exclude pseudoprogression). However, if the patient or the treating physician decides to stop the immunotherapy (L19-IL2) due to side effects, progression, etc, fewer cycles can be given. This will be noted as a protocol deviation in the eCRF. Note that the number of administration are much less than checkpoint inhibitors (often administered over several years).

30. Do you expect more adverse events compared to SOC?

Yes, we do expect a significant increase in adverse events (AE) compared to SOC. However, these AE will mostly be a grade 1-2 toxicity (based on the CTCAEv4) and for short period.

31. What to do at disease progression?

See protocol 5.2.5



32. What to do with a patient with an untreated primary tumour and oligometastasis?

We would then propose to treat the primary (chemo-radio) then wait until the lymphocyte count normalize than start SBRT followed within 72 hours by L19-IL2.
If the choice is made to treat primary tumour + metastasis in the same time, patient should be excluded.

33. Can patient with brain metastasis be included?

Yes, see table below. Maximum 2 lesions with a total diameter will be 5cm. Based on the SARON trial in the UK.

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

34. If all the lesions are irradiated, which lesion do you take to evaluate response?

As a general rule we are interested by progression not response. We are aware that in the group oligo (all the lesions can be irradiated) we will have no target lesions for response evaluation (RECIST) and sometimes progression is difficult to assess due to pseudo-progression. In case of doubt, we propose a panel discussion and radiomics analysis.

35. What about "migration from poly to oligo" after the SOC treatment? How should we deal with this?

It could indeed occur that a patient with 6 lesions receive chemo-immunotherapy and that two lesions get a CR. The patient has then 4 visible lesions at the moment of randomisation: should it be stratified in the group oligo or poly? Clearly in the oligo group we want to identify the patient with a favourable prognosis (see for example the trial of Gomez et al). So this patient should be stratified in the group "poly". In other words we randomize the patient after the SoC treatment but we **should count the number of metastasis at baseline.**

36. If you have an oligo patient e.g. 4 lesions and two have a CR after SoC treatment: which one should be irradiated?

The macroscopic lesions should be irradiated in any case. The irradiation of the lesions with CR is not compulsory (no GTV!) but the treating physician is free to administer an adjuvant consolidation radiation dose, if he is used to do so. If all the lesions have a CR, there is nothing to irradiate, then the patient can not be included: the hypothesis that we test in this trial is the combination irradiation-L19-IL2.

37. We have a patient with a NSCLC T3N2M1 (brain metastasis). We intend to treat the primary with radio-chemo. Do we have to delay the treatment of the brain metastasis?

Treatment to primary necessary? If yes → Prior to randomisation ImmunoSABR trial.
When primary is treated patient can be included into the trial (4 weeks between last gift chemo and randomisation) and receives SOC (c-arm) or SABR/R+L19-IL2 (e-arm) to the metastatic lesions.

If the patient has symptomatic brain lesion and that there is a need to treat the primary +brain simultaneously, the patient can not be included in the trial. The reason is that lymphopenia induced by chemo will decrease the effect of the immunotherapy and suppress the abscopal effect.

38. We have a patient with a NSCLC T2N3M1b (unique brain metastasis). We were wondering if we have to treat radically the primary/LN (chemorad) to include this patient in the ImmunoSABR, or can we just give a systemic treatment and then follow with the protocol, without consideration for radical treatment of the primary tumor?

You do not have to treat the primary with chemoradiation if your clinical judgement tells you it is not needed. You are free to treat the primary and/or the brain metastasis with radiation alone just before the L19-IL2. Just be aware that within the e-arm always a lesion needs to be treated with SABR/R. No overlap in RT field of prior irradiation is allowed.

39. The protocol prescribes to administer L19-IL2 for over 3 hours: how important is it? Can it be decreased?

It's very important because it reduces the risk of side effects. Philogen gave patients 56 Mio IU in 3 hours without any side effects. All 15 patients with triple treatment will have 3h IV infuse for every cycle.
For the combination treatment, the first 15 patients all cycles 3h IV. After these 15 patients → every first 2 cycles → 3h IV. If everything goes well, the 1.5h post measurements (vital signs) won't be obligatory anymore. PI's decision.
No side effects (no AE) → 3rd cycle could be done in 2.5h IV +1.5h post measurements (vital signs) if the patient handles it well.

40. Do we expect a "cytokine storm" with severe side effects?

No it is targeted IL2 with specific uptake in the tumour (see imaging above), the toxicity of phase 1 was very mild and we give a low dose of L19-IL2 (27% of the Recommended phase 2 dose in monotherapy).

41. The protocol prescribes to keep L19-IL2 in a freezer at -80°C: how important is it?

Activity will decrease after a couple of days, if L19-IL2 is stored above -80°C. Check if your hospital pharmacy has a -80°C fridge.

42. In case L19-IL2 is given after Pembro, are there restrictions or recommendations?

The only restriction for L19-IL2 administration are:

- Administration over 3 hours
- Administration within 72 hours after the last irradiation

We recommend however to administer the L19-IL2 about ***30 min after*** the end of the administration of Pembro.

43. In some cases we will start with chemo and Pembro as SoC: is it allowed? If yes should we stop transiently the administration of Pembro?

No, chemo is not allowed during (SAB)R or L19-IL2 treatment. After these treatment due to progression or SOC it is allowed to give chemo. Furthermore, giving chemo before the trial is also not a problem. The only thing is that at least 4 weeks is in between last chemo gift and randomisation.

44. If the patient is not an oligometastatic patient, we are not obliged to irradiate it with SABR? It can be with conventional RT?

If the patient is not Oligometastatic → so polymetastatic, SABR is not obligatory. In this case conventional radiotherapy can be used.

45. In our system we already have an internal protocol for a (SABR) fractionation of 3x8 Gy, often used in trials, can we used it?

Yes you can. There is some literature suggesting that a dose per fraction of 8 Gy is the most immunogenic.
The protocol says: "The choice of dose-fractionation regimen will be made at the research physician's discretion. In any case the minimum dose per fraction to the metastasis should be 7 Gy (to ensure maximum immunogenicity) and maximum 18Gy, in total 30-60 Gy, preferably with minimum 24 hours – maximum 48 hours between fractions (fxs). (18, 19, 37-39) The dose constraints for various critical organs suggested by AAPM task group 101 should be respected (Appendix 14.2).(40)".

46. Are there specific requirements for the margins of the GTV?

No. The choice of margins will be made at the research physician's discretion. There is preclinical literature to suggest that margins in general are not critical to immunize a tumour (e.g. Markovsky et al. An Antitumor Immune Response Is Evoked by Partial-Volume Single-Dose Radiation in 2 Murine Models. Int J Radiat Oncol Biol Phys. 2019, DOI: 10.1016/j.ijrobp.2018.10.009).

47. Do we collect the simulation CT and the cone-beam CT?

No, only baseline scan form radiology and follow-up scans. We do not collect images form the radiotherapy Department.

48. Do we collect the dosimetry (DICOM, RTstruct)?

No it Is not necessary. We fully trust the quality of the participating centers. In case of a larger multicentric phase 3 we will do it.

49. How critical is the interval between the last fraction of radiation in the administration of L19-IL2 (max 72 hours interval)?

It is very critical. There are preclinical data suggesting that if this interval is longer the synergistic effect of the two treatment will be decreased. We are aware the coordination to ensure such short interval will be one of the main challenge of the trial. It will be important to decide at the level of each centre to decide what would be the preferred fractionation (e.g. 3x8 Gy). In practice if a patient is irradiated Monday, Wednesday and Friday or Wednesday to Friday, the administration of L19-IL2 must occur Monday morning at the latest. If the patient is irradiated Monday to Wednesday, the administration can start Wednesday

50. Can the interval between the last fraction of radiation in the administration of L19-IL2 be shorter than 72 hours? Can it be the same day?

Yes it can. It is probably even better. They key will be to maintain a 3 hours administration

51. Can the administration of L19-IL2 be given *during* radiation? E.g. if the radiation oncologist decide to increase the fractionation

According to the protocol no. It can not in any case be given *before* radiation. If the patient receive several fractions e.g. 5 fractions and L19-IL2 is administered after the third one it will be seen as a minor deviation.

52. Why is PFS the main endpoint and not OS?

It is common to take PFS as an endpoint in a randomized phase 2 and OS in randomized phase 3. Both are indeed very important. That's why we will collect the PFS as well as the OS. We even monitor the OS after the 1.5-year follow-up until the end of the study. PFS is a standard endpoint for phase II trials. However, we think that PFS is more specific compared to OS after 1st or 2nd line treatment prior to ImmunoSABR. Be aware that the field of metastatic lung cancer is evolving fast with new first and second line of treatment. The disadvantage of OS is that this endpoint is very much influenced by the various of treatment afterwards and therefore less "specific".
Thereby, we expect that most of the trial patients will receive prior treatment. So this is one of the main reasons why we use PFS as the primary endpoint

53. Why PFS at 1.5 years and not at 2 years or 1 year?

A PFS at 2 years was nor compatible with the constraints of the grants (budget and duration). A PFS at 1 year could be considered for the next amendment.

54. How is the payment organized?

There is a non-clinical budget and a clinical budget with a starting fee (25K€) and a fee per patient (4K€ per patient in the standard arm, 12K in the experimental arm). Hospital admission cannot be covered by the study. It is an academic study, 6million € max from H2020, no money to spare anymore. This is a project funded by the European commission so the centres are not allowed to make a "financial benefit" from this trial (e.g. the SBRT can not be reimbursed twice).

55. Are the 10 metastatic lesions based on PET/CT or CT?

Follow the protocol, the local guidelines, if needed the ESMO guidelines and common sense. The decision of the tumor board will be decisive.

C. The translational research part

56. What if a patient refuses to give faeces?

It's mandatory, but not a hard exclusion criteria

57. Why not a mandatory biopsy?

We got a lot of questions and feedback that realising this on a big scale was not feasible. Making it mandatory will lead to fewer to zero inclusions of patients.
Archived biopsies will be requested; 20 coupes on 10 slides and 2 coupes for RNA-later. And Optional biopsy at baseline.
A biopsy after treatment is strongly discouraged, especially if the lesion was treated with radiotherapy. This would could cause major problems with necrosis and impaired wound healing.

58. Are we collecting blood cfDNA?

Yes. At baseline an EDTA collecting tube will be filled with blood and processed by the SOP that UCL-London provided us.

59. Do we need to standardize the acquisition of CT? Why? Radiomics…

Yes, that would be ideal! The key is to have slice thickness to less than 3 mmm. However, we know this is not feasible with so many centres. And if we obligate every centre to deliver the images/scans in a certain way, we know it will not be in line with local protocol.

60. When do you collect the data and how?

Each year and at the end of the study → all CT, MRI and PET scans will be requested by the central study data manager.

- Information and SOP during site specific training by SILLAR (CRO)

61. How many scans are made during the ImmunoSABR trial?

A rough sketch of a possible timeline:

- Baseline (SOC imaging: MRI and/or PET/CT and/or CT with at least covering thorax-upper abdomen-brain)
- Randomisation
- + ~1 week later start radiotherapy
- + ~1-2weeks RT
- + 3 days; direct start immunotherapy after RT (<72h)
- + 22 days immunotherapy 1 cycle ***← first follow-up scan***
- + 22 days x 5 cycles (110 days) immunotherapy
- Start/continue follow-up till 1.5 years after randomisation

In total 10 CT-scans (/MRI if SOC) will be made after randomisation if SOC is CT-scan every 6wks.

62. When do we start with the FU-scans?

Start counting the weeks after randomisation date. There are 2 possible scan frequencies:

1. Every 6 weeks for first year and every 8 wks in second year (if SOC like in NL)
2. Every 12 weeks.

D. References:

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