SupPRESs - NSCLC

Stereotactic Ablative Radiotherapy for Oligo-**P**rogressive Disease **RE**fractory to **S**ystemic Therapy in **N**on **S**mall **C**ell **L**ung **C**ancer: A Registry-based Phase II Randomized Trial

(PERa Lung 2.0)

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1.0 INTRODUCTION

Lung cancer is the most commonly diagnosed cancer in Canada and remains associated with high mortality. Nevertheless, advances over the last decade in the fields of immuno-oncology, targeted therapy, radiotherapy and precision medicine have led to significant improvements in clinical outcomes of non-small cell lung cancer (NSCLC). The use of immune checkpoint inhibitors (ICI) has introduced a paradigm shift in the treatment of many cancers and represents the treatment backbone for first line therapy in NSCLC lacking a driver mutation [1]. Despite the unprecedented results from ICI, even in patients with initial benefit, many patients eventually develop secondary resistance to immunotherapy[2, 3]. On the other hand, patients with NSCLC harboring a driver mutation such as EGFR, ALK, ROS benefit from tyrosine kinase inhibitors (TKIs) as part of first line therapy[4]. Although the introduction of TKIs has greatly improved the prognosis of these patients, secondary progression secondary to novel downstream genetic alterations after targeted therapy initiation almost invariably occurs after a median of 9-12 months [5-7].

Oligoprogressive disease is loosely defined as secondary progression to a limited number of sites after a systemic therapy has resulted in a period of stable disease, partial or complete response [8]. The frequency of occurrence of oligoprogression after ICI is not well documented, but after TKIs, it is estimated to occur in 20-50% of cases [8, 9]. It has been hypothesized that oligoprogression results from tumor heterogeneity, whereby progression is observed in drug resistant subclones in a small number of sites, while the efficacy is maintained for the rest of the cancer. Current management of patients developing secondary resistance in the form of oligoprogression remains controversial and backed by little evidence. Both NCCN and ESMO recognize local ablative therapy (stereotactic ablative radiotherapy- SABR or surgery) as an option in patients presenting oligoprogressive disease and the often-favoured non-invasive approach of SABR is a strategy routinely discussed at multidisciplinary tumor board and frequently used in our clinics.

SABR is defined as a highly conformal imaged-guided radiotherapy technique allowing for precise delivery of an ablative dose of radiotherapy in a small number of fractions (typically 1 to 10)[10]. The accuracy of SABR allows for the treatment of multiple lesions within the same organ or metastatic lesions that are in close proximity. The use of SABR as a radical approach in oligometastatic or oligroprogressive disease is particularly interesting given its non-invasive

nature, its excellent local control rates, approaching 90% in many series [11, 12], and its safety with < 5-10% risk of grade ≥ 3 toxicities [13-16]. In the past year, the use of SABR for local ablation in upfront oligometastatic disease has gained significant momentum after the recent demonstration of overall survival benefit from comprehensive local ablation of all metastatic disease sites in 2 recent randomized phase II trials – the trial by Gomez et al. focused specifically in NSCLC [17] as well as SABR-COMET, evaluating a SABR approach in oligometastatic disease from various solid histologies[18]. In the specific context of ICI and TKI oligo-refractory tumors, the rationale for the use of SABR relies on controlling those lesions that progress on systemic therapy, while allowing keep immune/target pressure with the same systemic therapy line on the remaining sensitive tumor cells. At the cellular level, local radiation may trigger immunogenic cell death, which can promote systemic inflammation and immune-mediated activation of antigen-presenting dendritic cells and immune CD4 Th1 and CD8 cytotoxic T cells, and ultimately anti-cancer immunity [19, 20 21-23]. Specifically, a phenomenon of antigen release with use of high dose per fraction (10-15 Gy) was previously demonstrated, suggesting that SABR may work synergistically with ICI [24].

Despite these theoretical benefits, a closer look to the supporting literature for the use of SABR in oligoprogressive disease reveals that this strategy is supported by only retrospective studies including small numbers of patients[25-27]. Contrary to the situation of upfront oligometastatic disease, there is no data regarding an overall survival benefit from the addition of SABR to patients presenting an oligo-refractory NSCLC. There are currently 3 on-going prospective clinical studies looking at the role of SABR for oligoprogression:

1- the STOP trial, a Canadian-based phase II randomized trial (54 patients) of SABR in oligoprogressive disease to 5 or less metastasis with the primary endpoint being progression free survival (PFS) (NCT02756793),
2- the HALT trial, a phase II/III randomized trial of 110 patients looking at NSCLC with actionable mutation receiving TKI, with 3 or less oligropressive lesions (NCT03256981) and
3- the recent PROMISE trial, a Sloan Kettering study of SABR for oligoprogressive NSCLC and breast cancers with PFS as primary endpoint (NCT03808662).

While the treatment of highly selected oligoprogressive patients ‘’off-protocol’’ has entered our practice, there remains a concern that the combination of therapies may increase the toxicities through the synergistic effect of systemic and local therapies. In some prospective reports, the combination of ICI and SABR resulted in 20-25% grade 3 toxicities [28, 29], while small studies reported from 0 to 40% grade ≥ 3 toxicity from the combination of TKI and SABR [30-32]. For these reasons, there is a critical need to carefully examine the efficacy, safety and quality of life impact of this approach, as well as to define immunogenic and immune surrogate makers.

2.0 STUDY DESIGN

The CHUM has initiated a NSCLC lung cancer biobank and registry initiative of early stage, locally advanced and metastatic lung cancers funded by Institut du Cancer de Montreal and AstraZeneca respectively (Ethics #18.085-17.035 and #18-104). Herein, we propose a registry-based randomized screening phase II trial. A total of 68 patients with metastatic NSCLC on ICI or TKI with oligoprogression to 1-5 extracranial lesions will be randomized using a 1:1 ratio to standard of care (begin next-line systemic therapy, best supportive care, continue current systemic line, based on treating physician decision) vs. receive SABR to all oligoprogressive lesions while continuing their current systemic therapy. Enrolled patients will be stratified by the presence or

absence of a driver mutation, as well as by the presence or absence of brain metastasis. Brain metastasis will be treated as per standard of care and will not be counted toward the total of 5 lesions. We hypothesize that use of SABR to oligoprogressive extracranial lesions will result in a 5 month increase in PFS compared to standard of care (primary endpoint), as well as a 3 month improvement in OS compared to standard of care (co-primary endpoint). This study utilizes cohort multiple randomized controlled trial in companion to PERa (Partnership initiative for the Evaluation of technological innovation in Radiotherapy)

3.0 OBJECTIVES

3.1 Primary endpoint:

To compare progression free survival between NSCLC patients treated with SABR to all oligoprogressive lesions with continuation of current systemic therapy vs. those treated with standard of care (which can include switch to next line of systemic, observation or continue current systemic therapy without SABR).

- Outcome measure*:* Median PFS, with PFS defined from randomization to disease progression at any site or death
- Progression is defined as per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines. The distinction of pseudoprogression or fibrosis from a local recurrence after SABR can be difficult. In cases where the RECIST 1.1 criteria for progression are met but there is a substantial doubt based on radiological imaging that the tumor size increase is due to pseudoprogression or fibrosis, the situation should be counted as progression unless there is imaging follow-up with stability of the imaging findings for at least 6 months.
- As per RECIST 1.1, when findings of progression are equivocal (e.g. small new lesions of uncertain etiology), the patient should still be followed. If progression is confirmed at the next assessment, the date of progression assigned is the earlier date when progression was first suspected.

3.2 Co-primary endpoint:

To compare overall survival (OS) between NSCLC patients treated with SABR to all oligoprogressive lesions with continuation of current systemic therapy vs. those treated with standard of care (which can include switch to next line of systemic, observation or continue current systemic therapy without SABR).

- Outcome measure: Median OS, with OS defined as time from randomization to time of death from any cause.

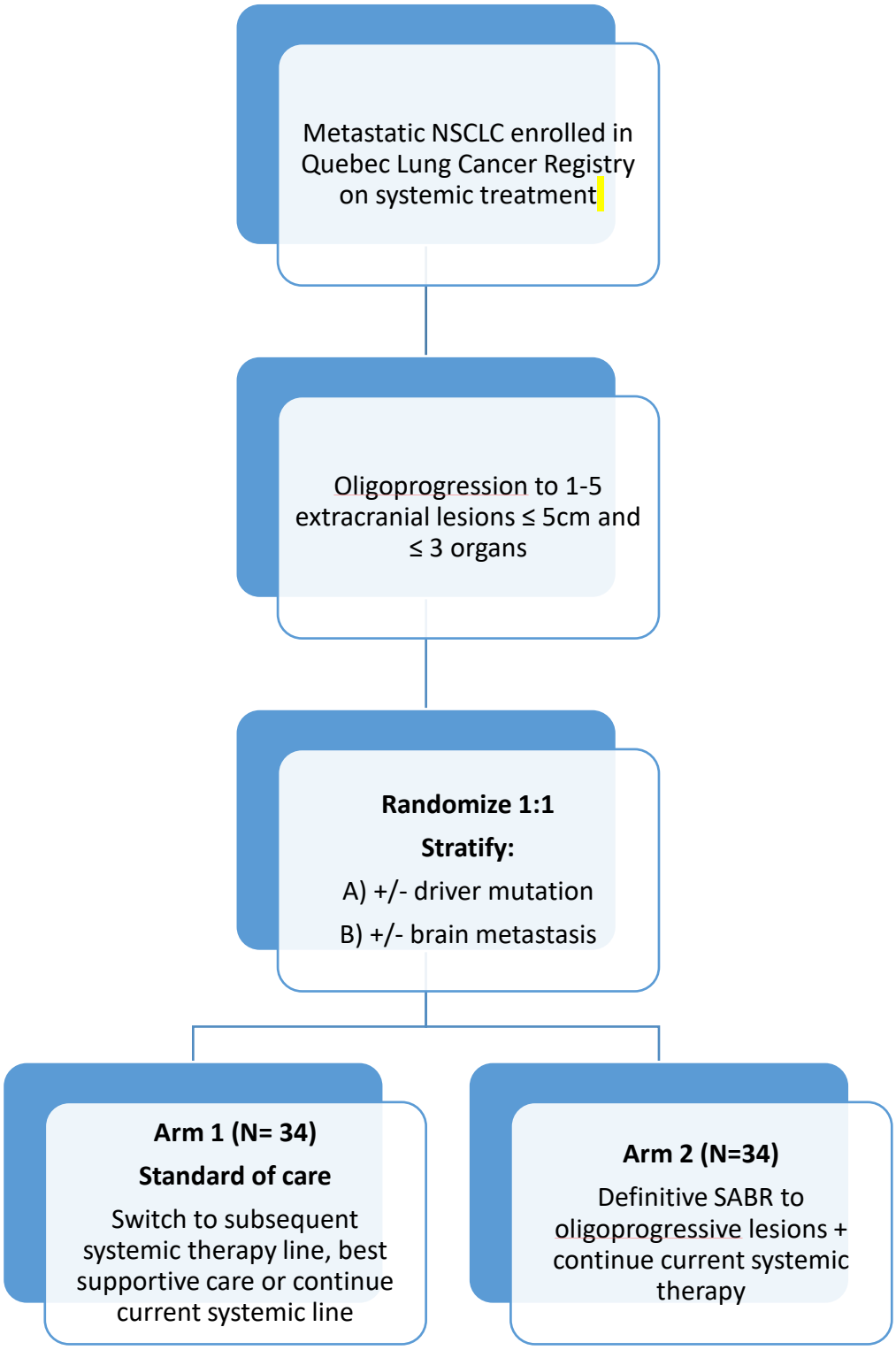
3.3 Secondary endpoints:

- Quality of life
  - Measured using the EORTC core and lung specific tools, lung cancer-related patient reported outcomes- CTCAE (PRO-CTCAE) version 5.0 and the 5-level EQ-5D (EQ-5D-5L)
- Grade ≥ 3 toxicity
  - Measured using the Common Terminology Criteria for Adverse Events (CTCAE v5.0)
- Time to next systemic therapy
  - Defined as time from randomization to time of subsequent therapy line
- Cost-utility analysis

3.4 Ancillary studies:

- Flow cytometry analysis to analyze the immunomodulatory effect on innate and adaptive responses in the peripheral blood
- Immunogenic cell death markers in serum

Figure 1. Study Diagram



4.0 STUDY POPULATION

Patients with metastatic NSCLC on systemic treatment included in the CRCHUM lung cancer registry and who present progressive disease will be identified by the research assistant responsible of the registry. The charts of these patients will be reviewed to identify eligible patients to the randomized trial. Eligible patients will be proposed participation to the PERa registry, where they would be randomized to the current trial if they agree to participate. Patients who fit eligibility criteria and decline participation to the study, will be followed within the PERa registry.

4.1 Eligibility criteria

- Age ≥18 years
- Metastatic NSCLC enrolled in our CRCHUM Lung Cancer Registry and co-enrolled to the PERa registry
- Ability to provide written informed consent
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Progressive disease while on systemic treatment (any line), defined as per RECIST criteria 1.1 on CT metrics as a greater than 20% increase in the sum measurement of lesions, non-target unequivocal progressive disease or a new lesion on CT.
- Oligoprogression to 1-5 extracranial lesions ≤ 5cm and involving ≤ 3 organs. Progression at the primary tumor site should be counted within the total of 5 lesions. For patients with lymph node metastases, each node is counted as one site of metastasis.
- Patients with brain metastasis are allowed; brain metastasis are not counted in the maximum number of lesions and should be treated as per standard of care
- All sites of disease can, in the opinion of the investigator, be safely treated and targetable with SABR (taking into account prior local therapy, organ function and underlying medical condition such as inflammatory bowel disease, pulmonary fibrosis, etc.)
- Patients with prior metastases that have been treated with ablative therapies (e.g. radiotherapy, surgery or radiofrequency ablation) before their current line of systemic therapy, are eligible.

4.2 Exclusion criteria

- Any lesion > 5 cm
- Pregnancy or breastfeeding
- Any medical condition that could, in the opinion of the investigator, preclude radiotherapy or prevent follow-up after radiotherapy.
- Presence of spinal cord compression
- Metastatic disease that invades the GI tract (including esophagus, stomach, small or large bowel)

4.3 Note regarding lesions with equivocal or slow progression on CT

Lesions that present an equivocal or slow progression on CT (e.g. unspecific millimetric increase in size) but that do not fit the RECIST criteria for progression should be counted within the 5 oligoprogressive lesions. If the patient meets the criteria for overall progressive disease, the decision to either treat such lesions with equivocal progression upfront or to proceed to close radiological follow-up will be at the discretion of the treating physician. The presence of such lesions will be noted at study entrance. For patients randomized to the experimental arm and who present lesions with equivocal progression left untreated, these lesions should be followed radiologically and a SABR treatment should be offered at time of further progression if deemed safe by the treating physician. This would not be counted as a progression under the protocol.

5.0 PRE-TREATMENT EVALUATION

- History and Physical Examination
    - Including prior cancer therapies and concomitant cancer-related medications
- Restaging within 8 weeks prior to randomization:
    - Brain: CT or MRI
    - Body: CT of the neck, chest, abdomen OR FDG-PET/CT.
- Pregnancy test for women of child-bearing age

6.0 TREATMENT ARMS

6.1 Arm 1 (Standard arm):

Patients on the standard arm will be treated as per standard of care in our institution. Treatment options could include switching to next systemic therapy line, best supportive care or continuing on current systemic therapy. The decision will be at the discretion of the treating medical oncologist. Palliative radiotherapy to brain metastases, symptomatic lesions or spinal cord compressions is allowed. The subsequent systemic therapy could be next-line TKI, ICI, or chemotherapy, or a combination of both. Patients eligible to a systemic therapy within the context of a clinical trial could be included.

6.1.1 *Further radiotherapy for progressive disease at new metastatic sites*: Patients in the standard arm who develop new metastasis should be treated ~~with~~ as per standard-of-care. SABR to those sites is not permitted, except if it would be considered standard of care (e.g. brain metastasis).

6.2 Arm 2 (Experimental arm): *SABR to oligoprogressive lesions + current systemic therapy*

The experimental arm will involve SABR to all oligoprogressive lesions + continuation of current systemic therapy.

6.2.1 *SABR treatment planning:* Patients positioning and immobilization device will be as per treating physician. Positioning should be stable to avoid uncontrolled movement during treatments and maintain treatment accuracy. All patients will undergo planning CT of the region containing the treated lesion. CT scan range will be as per standard limits used in our department for each anatomical site. Use of intravenous contrast (iodine or gadolinium) is be required for liver metastases, but will be as per treating physician for all other sites. In addition, a 4D planning CT scan should be obtained for all metastases with potential for respiratory motion. ITV technique, tracking, as well as abdominal compression, active breathing control, gating, breath hold, etc. should be used. Patients could be treated using: (1) Cyberknife robotic device, using fiducial markers (Synchrony), XsightLung technique; (2) volumetric arc therapy or (3) helical tomotherapy. Image guided radiotherapy technique will therefore include orthogonal in-room 2D kV X-rays, kV cone beam computed tomography and MV computed tomography. MRI will be required for patients with

vertebral or paraspinal metastases for planning. The MRI needs to image the area being treated and one vertebrae above and below as a minimum, but does not need to be a whole spine MRI unless clinically indicated.

6.2.2 *SABR dose*: SABR doses will vary based on tumor location and physician's preference. Patients will receive between 1 or 8 fractions. The following table details suggested dose per tumor site:

Site	Dose (Gy)	Fractions	Frequency
Lung-peripheral	30-34	1	Single dose
	45-54	3	Every 2nd day
Lung-central*	60	8	
	35-50	5	Every 2nd day
Mediastinal/cervical lymph node	35-40	5	Every 2nd day
Liver	35-50	3-5	Every 2nd day
Osseous/Spinal/paraspinal	24	2	Every day
	30	3	Every day
	35	5	Every day
	16-20	1	Single dose
Abdominal-pelvic metastasis (lymph node/adrenal gland)	30-45	3-5	Every 2nd day

***Lung-central lesion defined as per RTOG 0813, as tumors within or touching the zone 2 cm around the proximal bronchial tree or immediately adjacent to the mediastinal or pericardial pleura.*

The prescription isodose line covering 95% the PTV may range from 60-90% where the maximum dose is 100%. All dose calculations will be performed using corrections for tissue heterogeneities. Constraints for 1 to 5 fraction regimens will derived from Timmerman *et al.* [33], whereas constrains for 8 fraction regimen will be derived from the SUNSET protocol[34].

6.2.3 *Target volume determination:* Gross tumor volume definition will be based on planning CT as well as any other standard multi-modality imaging used in the clinic. With the exception of vertebral body lesions which could include a clinical target volume as per the consensus guidelines by Cox et al.[35], no additional margin will be added for microscopic spread of disease in all other sites. A Planning Target Volume margin of 2-5 mm will be added depending on site of disease, immobilization, and institutional set-up accuracy.

6.2.4 *Further radiotherapy for progressive disease at new metastatic sites:* Patients in the experimental arm who develop new, untreated metastasis should be considered for SABR at those sites, if these lesions can be treated safely with SABR. If SABR is not possible, then palliative RT can be delivered if indicated.

7.0 ANCILLARY STUDY

In addition, to closely monitor toxicity and clinical outcome, extensive immunological profile will be performed to understand the difference in both arms for innate and adaptive immunity. Monitoring of immunogenic cell death will also be performed. Participation to the biobank will be optional and will be the subject of a separate consent form.

7.1 Blood collection and processing:

Blood samples will be drawn from participants 40 mL who have been through the informed consent process and have agreed to participate both in the study and the NSCLC lung cancer biobank. PBMC will be separated from the plasma using lymphocyte separation medium (LSM, Wisent) and following the SOPs from the Montreal Cancer Consortium (MCC) Biobank at the CHUM. Immune profiling and immune cell death analysis will be centrally performed at Dr. Routy's lab at the CRCHUM.

7.2 Time point:

1. At time of study initiation and before radiotherapy start
2. 1-month post radiotherapy or 1-month post study initiation
3. 3 months post radiotherapy or 3-month post study initiation
4. At time of further disease progression

7.3 Standard flow cytometry method:

As previously performed by our group, we plan to perform an immune profiling on the PBMC using the Fortessa BD flow cytometer. We will select the flow cytometry assessment by importance and the following panels will be performed to analyse the features of the adaptive and innate immune infiltrating cells (ranked by priority): 1. T cells: CD45, CD4, CD8, Foxp3, PD-L1, PD-1, TIM3, LAG3, FOXP3 2. Conventional NK cells and Innate Lymphoid Cells: CD16, CD56, CD39, CD127, CD117, CD161, CRTH2, NKp46, NKp44, CD94, CD16, CD56. 3. DC: CD11c, HLADR; 4. MDSC: CD11b, CD33.

7.4 Immunogenic cell death markers in plasma:

To analyse the immunogenic cell death, we will perform ELISA on patients' plasma to quantify the HMGB1 (Human HMG1 / HMGB1 ELISA Kit - LS-F4038, LSBio) that is released from dying cells and signals through TLR4-MyD88 axis on DCs, facilitating antigen processing and presentation leading to T cells activation.

7.5 Tumor samples- from achieved pathological blocs or optional rebiopsy upon progression

To map the tumor immune landscape and determine more specific tumor-driven immune changes, immunohistochemistry staining will be performed in collaboration of Histopathology and cellular imaging platforms at the CRCHUM. We will access all the initial tumor samples and in certain cases a biopsy at the time of progression will also be available. This protocol is already approved and performed for the Oncopole technology project.

Slides from biopsies will be stained using standard Autostainer protocol with Dako EnVision FLEX+ kit reagents. The expression of immune checkpoints (PD-L1, LAG3, TIM3 and TIGIT), T/NK-cells markers (CD4, CD8, FOXP3, CD56), and macrophages (CD163) will be assessed and quantified under light microscopy as the number of positive cells/mm2. An H&E slide will also be prepared for pathology reference, if needed. Digital images of H&E and immunohistochemistry slides will be obtained at 20X magnification using a slide scanner (NanoZoomer 2.0-HT, Hamamatsu, Bridgewater, NJ, USA). Whole slide images will be visualized using the Hamamatsu NDPviewer software. The CaloPix software (TRIBVN, Châtillon, France) will be used to perform the scoring of IHC slides using image analysis as the number of positive cells/mm2. Budget for

ancillary experiments and salary for dedicated post-doc will be provided in-kind by Dr. Routy's lab.

8.0 REGISTRATION PROCEDURE AND DATA COLLECTION

8.1 Registration and randomization

Registration and randomization will be performed on the CASTOR EDC platform, a secure web application for building and managing online surveys and databases, as part of the PERa registry. Randomization will be performed after confirmation of eligibility to the study and signature of the consent.

8.2 Data Collection

8.2.1 Captured data will be recorded and stored using CASTOR EDC and will include:

a) Patients demographics, smoking history, comorbidities, prior auto-immune disease, concomitant medications (antibiotics, prednisone up to 2 months prior to treatment initiation)

b) Cancer stage, number of lesions and size (cancer burden), histological type, PD-L1 expression and molecular status

c) Treatment details (radiotherapy, chemotherapy, targeted therapies, immunotherapy)

d) Patient-reported outcomes (EORTC QLQ, PRO-CTCAE and EQ-5D-5L)

e) Treatment toxicity (CTCAE version 5.0)

f) Clinical outcome: local control, overall survival, response rate, and progression free survival.

8.2.2 All SAEs will be reported to the institution's Research Ethic Board (REB) per institution guidelines and reported in CASTOR EDC.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence/AE that:

- Results in death;
- Is life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);

- Requires in-patient hospitalization and/or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities); a congenital anomaly or birth defect; or other medically important event.

9.0 SUBJECT WITHDRAWAL

Patients may withdraw from the study prior to the completion of study related procedures for the following reasons:

9.1 Patient withdraws consent for participation. Subjects may voluntarily discontinue participation in the study at any time.

9.2 It is deemed in the patient's best interest as determined by the attending/principal investigator.

10.0 FOLLOW-UP EVALUATION

Patients will be assessed at baseline, at 1-month, 3-, 6-, 12-, 18 and 24 months after randomization. At each assessment, patients will be assessed for local, regional and distant recurrence with standard of care CT of the chest, abdomen +/- neck, as well as for survival and toxicity grading. Toxicity will be graded by the treating physician at each follow-up, as per Common Toxicity criteria for adverse event version 5.0. *Follow-up and data collection will be as per ANNEXE 1.*

10.1 Patient-Reported Outcomes

Questionnaires regarding quality of life will be sent and filled on-line on the CASTOR EDC platform for patients that have and use an email address. Paper questionnaires will be filled with the help of a research assistant for all other patients. Quality of life questionnaires will include EORTC QLQ-C30 and lung module (QLQ-LC13) and lung-related PRO-CTCAE which will be filled at baseline, and at 1-, 3-, 6-, 12-, and 24-months after randomization.

The EORTC QLQ-C30 [36] is a core cancer-specific questionnaire containing 30 items on patients' functioning, global quality of life and disease- and treatment-related symptoms. The QLQ-LC13 [37]is a site-specific questionnaire consisting of 13 items on lung cancer symptoms (cough, haemoptysis, dyspnoea, site-specific pain) and its treatment-related side-effects (sore mouth, dysphagia, peripheral neuropathy, alopecia).

To improve precision and patient-centeredness in the capture of symptomatic AEs, the NCI developed a library of patient-reported outcome (PRO) items to supplement the CTCAE, called the PRO-CTCAE [38, 39]. The PRO-CTCAE item library consists of 78 symptomatic AEs represented by 124 distinct items. To limit burden, the PRO-CTACE survey in this study will include 20 core symptomatic AEs [38] determined on the basis of high prevalence in previous NCI-sponsored clinical trials [40] as well as the 11 AEs items related to respiratory/thoracic toxicity.

In addition, the EQ-5D-5L is a short questionnaire which will be used for cost-utility analysis. The questionnaire involves a short health description part measuring the 5 following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, as well as an evaluation of overall health status using a visual analogue scale [41].

11. STATISTICAL CONSIDERATIONS

11.1 Sample size

Primary endpoint: *Progression free survival*

The rapidly evolving lines of therapy as well as the heterogeneity of outcomes among NSCLC subgroups make prediction of outcomes after progression on first or second line therapy for metastatic NSCLC challenging. Based on Checkmate 057[42] and Checkmate 017[43], we can estimate a PFS of 3 months after second line systemic therapy- with the caveat that this PFS can be as high as 10 months in an expected minority of patients with drivers mutation treated with second line TKI[44].

Previous retrospective reports suggest improvement in PFS between 4-10 months with the addition of local ablation in oligoprogressive NSCLC [25, 27]. Most of these retrospective reports have assessed the role of local ablation in NSCLC associated with a driver mutation. We will therefore assume a conservative improvement in PFS of 3 months in the experimental arm (SABR to all extracranial oligoprogressive lesions + continued systemic therapy) compared to standard of care. For this screening trial, we will assume an accrual period of 4 years followed by a follow-up period of 1 year. Based on a median PFS of 3 months in the standard arm, using a two-sided alpha of 0.05 and a power of 80% to detect a 3 months difference, a sample size of 65 patients would be required. Taking into account an attrition rate of 5%, a total of 68 patients would be included in the study.

Co-primary: *Overall survival*

Based on Checkmate 057 (median OS 12 months (95% CI 10-15) [42], Checkmate 017 (Ref) (median OS 9 months (95% CI 7-13)) and a systemic review of real word patterns after second or third line therapy (median OS 5-12 months)[45], we can estimate that the median OS after initiation of second or third line systemic therapy will be 10 months. In a recent phase II trial of 24 patients with oligoprogressive NSCLC treated with SABR to up to six extracranial lesions and erlotinib after progression on first line therapy, median OS was 20 months, suggesting improved OS compared outcomes expected with systemic therapy alone[46]. In the subgroup of patients with EGFR mutations, this improvement in survival is further supported by retrospective data suggesting that continuing TKI beyond first progression is associated with improved survival benefit compared with patients who stop TKI[47, 48]. For this trial, we make the assumption that the median OS of patients treated with SABR at oligoprogression would be increased by 6 months compared to those treated on the standard arm. The proposed sample size will allow to detect a 6 months difference with a two-sided alpha of 0.2 and a power of 71%.

11.2 Analysis Plan

Patients will be analyzed in the groups to which they are assigned (intention-to-treat). PFS, OS and local control will be calculated using the Kaplan-Meier method with differences compared using the stratified log-rank test. Pre-planned subgroup analyses will occur based on the

stratification factors. A Cox multivariable regression analysis will be used to determine baseline factors predictive of survival endpoints. Quality of life differences between groups will be tested using the Student's t-test. A longitudinal analysis consisting of repeated measures mixed-effects models will be used. Differences in rates of grade 3 or higher toxicity between groups will be tested using the Fisher's Exact Test or Chi-Squared test, as appropriate. All *p* values from multilevel analysis will be 2 sided, and levels <0.05 will be considered statistically significant.

11.3 Economic evaluation

Economic evaluation will be completed through a cost-utility analysis, using a government payer perspective. The EQ-5D-5L will be used to calculate utilities, and quality adjusted life years (QALYs) will be calculated from the area under the preference-weighted survival curve. Costs will be abstracted from the available literature. The incremental cost effectiveness ratios (ICERs) between treatment arms will be compared, as is standard, using the ratio between differences in costs and QALYs.

11.4 Data Safety Monitoring Committee

The DSMC will meet annually after study initiation to review toxicity outcomes. If any grade 3-5 toxicity is reported, the DSMC will review the case notes to determine if such toxicity is related to treatment. If the DSMC deems that toxicity rates are excessive, then the DSMC can, at its discretion, recommend cessation of the trial, dose adjustment, or exclusion of certain treatment sites and/or delivery techniques that are deemed as high-risk for complications.

The DSMC will conduct one interim analysis once the 34th patient is accrued and followed for 6 months. For this interim analysis, the DSMC will be blinded to the identity of each treatment arm, but median OS data will be presented for each arm. The DSMC will recommend stopping the trial if there is an OS difference that is statistically significant with a threshold of $p<0.001$ using the stratified log-rank test.

10.5 Timeline

It is expected that the registry would accrue approximately 15 patients yearly at CHUM, and that the study would be completed after 5 years.

12.0 PATIENTS DECLINING STUDY INTERVENTION

Patients who fit eligibility criteria and who decline enrollment on the trial will be followed as part of the PERa registry, which includes standard of care clinical and radiological follow-ups as well as quality of life data collection.

13.0 ETHICAL CONSIDERATIONS

12.1 Institutional Review Board (IRB) / Research Ethics Board (REB):

The protocol, the informed consent form, and any other written information to be given to subjects will be reviewed and approved by a properly constituted Institutional Review Board (IRB)/Research Ethics Board (REB), operating in accordance with federal laws and regulations. A letter to the investigator documenting the date of the approval of the protocol and informed consent form will be obtained from the IRB/REB prior to initiating the study.

13.1.1 Any amendment to the study will be submitted for review by the IRB/REB before any changes are implemented unless required to eliminate immediate hazard to the study participants.

13.1.2 Data derived from this study may be reported in scientific publications. Patients will not be indicated by name.

13.2 Informed consent:

The written informed consent form is to be provided to potential study subjects should be approved by the IRB/REB and adhere to ICH GCP and the ethical principles that have their origin in the Declaration of Helsinki. The investigator is responsible for obtaining written informed consent from each subject, or if the subject is unable to provide informed consent, the subject's legally acceptable representative, prior to beginning any study procedures and treatment(s). Patients who meet study eligibility criteria, and who are willing to participate in the study, will be consented by the trial coordinator. The consent form will be discussed with the patient in person. Informed consent will involve careful explanation of all items outlined in the consent form. It is our goal to be as explicit as possible in verbal and written consent procedures to ensure that all participants are joining the study without coercion. The informed consent must be signed and dated by the subject, or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form should

be given to the subject or the subject's legally acceptable representative. The process of obtaining informed consent should be documented in the patient source documents.

The subject should be given ample time and opportunity to ask questions prior to deciding about participating in the study and be informed that participation in the study is voluntary and that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

13.3 Confidentiality

Confidentiality of the information collected will be respected at all time. The principal investigator, the co-investigators and the research nurses will gather and record all collected information in a research record. All information collected will remain confidential to the extent permitted by law. In research records, subjects will be identified by enrolment number.

13.3.1 Research data will be stored on a secure server. There will be a user name and password to get access. If there should be paper copies, they will be kept under lock and key in the research office.

13.3.2 No records bearing patients identification will be provided to anyone outside of the institution except regulatory agencies.

13.3.3 Patients will not be identifiable as individuals in any publication or presentation that may result from this study.

Study records (safety reports, correspondence, etc.) will only identify the subject by initials and the assigned study identification number. The investigator will maintain a confidential subject identification list (Master List) during the course of the study. Access to confidential information (i.e., source documents and patient records) is only *permitted for direct subject management and for those involved in monitoring the conduct of the study* (i.e., Sponsors, CRO's, representatives of the IRB/REB, and regulatory agencies).

12.3.4 The data could also be used for other analyzes related to the project or for the development of future research projects. The subject's name will not be used in any public report of the study. This data will be retained for 10 years after the end of the study by the researchers in charge.

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ANNEXE 1. Schedule of assessments

	Baseline	**1mo**	**3mo**	**6mo**	**12mo**	**18mo**	**24mo**
History and Physical	X	X*	X*	X*	X*	X*	X*
Biopsy at time of progression (OPTIONAL)	X						
Serum biomarkers (OPTIONAL)	X	X	X				
CT chest/abdomen +/- neck Or PET/CT (as per standard of care)	X		X	X	X	X	X
Toxicity Grading CTCAE v5.0	X	X	X	X	X	X	X
EORTC QLQ-C30 + Lung module PRO-CTCAE EQ-5D-5L	X	X	X	X	X		X

- Clinical follow-up visits can be ± 2 weeks of the stated time points in Appendix 1
- * Optional- phone assessment allowed to assess patient's status, with physical assessment mandatory in the context reported symptoms.