Prospective primary human lung cancer tumoroids to predict treatment response

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To establish matched normal and primary human lung cancer organoids from patient-derived lung (tumor) material.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON54034

Source
ToetsingOnline

Brief title
Lung cancer tumoroids

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung cancer, tumour material

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: KOFL grant

Intervention

Keyword: Lung cancer, Material, Tumoroids, Tumour

Outcome measures

Primary outcome

To establish matched normal and primary human lung cancer tumoroids from patient-derived (tumor) tissue material

Secondary outcome

1. To define oncogenic drivers in lung cancer tumoroids

2. To investigate the stability of (epi-) genetic and phenotypic tumor heterogeneity of cultured tumoroids compared to a primary/secondary biopsy.

3. To predict sensitivity and to get insight in the molecular biology of the response to immunotherapy, radiotherapy, cytotoxic and targeted agents.

4. To compare treatment response in normal lung organoids and lung cancer tumoroids

5. To develop biomarker(s) of tumor response to be able to select patients who will benefit from novel treatment strategies.

6. To analyze (ct)DNA, RNA, proteins, metabolites, and microvesicles secreted by lung cancer cells in tumoroids-derived culture supernatants and corresponding patient-derived blood samples.

Study description

Background summary

The 5-year survival of advanced lung cancer is between 1-5% and there is an urgent need for new therapeutic options that improve survival and quality of life. While precision medicine now enables the identification of driver mutations in tumors, treatments with *targeted* small molecules or antibodies

lead to responses that are nearly always not durable and come with serious adverse effects in a sizable minority of the patients. Also in immune therapy, responses are only observed in a minority of patients, and although they may last for many years, resistance is still the rule. The main reason for resistance is that clonal evolution and selection of resistant cancer cells during treatment cannot be predicted prospectively in patients. Currently no method exists which enables the prediction of durable responses prior to a specific treatment and therapy modification during relapse. The prediction would not only be of significant value for individual patients for they would not be exposed to ineffective and costly therapy, but it would give insight in the molecular mechanisms for resistance and hence could lead to new ways or targets to overcome this.

One of the most important barriers to achieve durable responses in advanced lung cancer is intra- and inter-tumor heterogeneity, a common feature of human solid cancers. Tumor heterogeneity is thought to be driven by a subpopulation of tumor cells termed lung cancer initiating cells or lung cancer stem cells that reflect the *cell of origin* and maintain self-renewal and multipotent properties of these cells but that are transformed.
Tumoroid technology has enabled the culturing of normal and transformed *stem cells* directly from patients without any genetic manipulation (i.e. IPS) (1). Such normal and cancer tumoroids maintain many of the properties of the tumors and are thought to be an excellent in vitro 3D model system.
Only recently patient-derived tumoroidshave been exploited to establish prospective tumor tissue banks that can be used for drug screening (1). In our lab we have successfully established primary 2D and 3D cell culture systems, tumoroids, including organoids from the proximal bronchus coming from lobectomies. We are using these systems to predict normal tissue complication to combination treatments.

We and others have demonstrated that lung stem cell pathways such as the NOTCH signaling pathway is frequently deregulated in lung cancers and is associated with a worse outcome. In vitro and in preclinical models deregulation of the NOTCH pathway is associated with resistance to radiotherapy and first-line chemotherapy (2). Thus, blocking the NOTCH pathway may improve treatment response. Clinical trials using NOTCH inhibitors have unfortunately been unsuccessful in part because of limited response and lack of biomarkers for patient selection.
Checkpoint inhibitors have changed the outcome of patients with metastatic non-small cell lung cancer (NSCLC) in first and later lines, with improved progression-free survival (PFS), overall survival (OS) and quality of life (3). Radiotherapy has consistently been shown to activate key elements of the immune system that are responsible for resistance for immune therapy (4-8). Radiation upregulates MHC-class I molecules that many cancer cells lack or only poorly express, tumor-associated antigens, provokes immunogenic cell death, activates dendritic cells, decreases regulatory T-cells (Tregs) in the tumor, broadens the T-cell repertoire and increases T-cell trafficking, amongst many other

effects. Radiation may convert a completely or partly poorly or non-immunogenic tumor immunogenic. Radiotherapy in combination with different forms of immune therapy such as anti-PD-(L)1, anti-CTLA4, immunocytokines, dendritic cell vaccination and Toll-like receptor agonists improved consistently local tumor control and very interestingly, lead to better systemic tumor control (the *abscopal* effect) and the induction of specific anti-cancer immunity with a memory effect. Moreover, as PD1/PD-L1 is upregulated by radiation and radiation can overcome resistance for PD-(L)1 blockage, their combination is logical (9). The best timing, sequencing and dosing of all modalities is a matter of intense research, but in pre-clinical models, the concurrent administration of anti-PD-(L)1 was superior to sequential (8). The recently published subgroup analysis of the phase 1 KEYNOTE-001 trial at a single institution, aimed to investigate if prior radiotherapy would affect the PFS or the OS (10,11). In patients having received prior extra-cranial radiotherapy, the six-month PFS rate was 54.3% vs. 21.4% among never irradiated patients. The median OS was 11.6 months and the six-month OS estimate was 75.3% among patients who previously received extra-cranial radiation therapy vs. a median OS of 5.3 months and a six-month OS estimate of 45.3% among patients who did not receive extra-cranial radiation therapy. Although in pre-clinical models the best way for combining radiation with anti-PD-(L)1 is to give it concurrently or at least very close to each other (8), in this study, radiotherapy was delivered in median 9.5 months prior to the first cycle of pembrolizumab. Still, a beneficial effect may have occurred.
Supporting an enhancing effect of radiotherapy on the immune system in combination with pembrolizumab, patients with prior thoracic radiotherapy had more overall pulmonary toxicity compared to never irradiated patients: 12.5% vs. 1.4%.
It is clear that radiotherapy may well become an integral part of immune therapy against cancer. Nevertheless, as with all treatments, optimal biomarkers for response are lacking. They would not only allow patient selection, but would also give insight in resistance mechanisms and the identification of new targets or the optimal use of current medications and radiation, such as dosing and sequencing. Moreover, not only biomarkers for tumor response, but also for side effects are needed, for the latter may be dose-limiting and result in the omission of therapy in the more frail and older patient population. Putative biomarkers for immune response are those associated with immunogenic cell death (ICD) (12-15). These and other immune-related markers are currently evaluated within a clinical trial at Maastro.

Tumoroids are generated from tissue biopsies, and are a collection of organ-specific cell types that are able to self-organize in-vitro in a manner similar to the in-vivo situation (3D). They have the capability to facilitate in-depth analysis of patient*s own tumor material at point of diagnosis and during progressive/recurrent disease. There is currently no published protocol to establish short and long-term lung cancer tumoroids from lung cancer patients. Such a methodology would enable the prospective identification of

patient tailored optimal treatments as well as the derivation of predictive biomarkers for response and relapse.

For this study, we will also be using data, derived from the non WMO trial: *Prospective primary human lung cancer organoids to predict treatment response*. This trial was approved by the Ethics Committee of Zuyderland Hospital in Heerlen (trial number 17-N-139). Surgically obtained tumor tissue samples have predominantly been used for the optimization of the current protocol for the establishment of long tumor organoid cultures. Data of this trial that will be used for further validation and optimization of the current protocol include the definitive diagnosis and FFPE material to compare the morphology of the cultured 3D tumor structures with the morphology of the primary tumor.

Study objective

To establish matched normal and primary human lung cancer organoids from patient-derived lung (tumor) material.

Study design

Preclinical study, using patient derived lung (tumor) material to establish tumoroids.

Study burden and risks

From patients who will ondergo a bronchoscopy during standard care, left-over tumor tissue will be derived during this standard procedure as well as 10ml of extra blood through an existing bloodline.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• All patients selected to undergo primary surgical resection of a primary lung cancer. All types of resection are eligible, e.g. wedge resection, segmental resection, lobectomy, pneumonectomy.
• All patients with (suspected) lung cancer that will undergo a bronchoscopy or endobronchial ultrasound guided transbronchial needle aspiration (EBUS/EUS-TBNA) bronchoscopy.

Exclusion criteria

- Incompetent
- <18 years of age

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-11-2022
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	13-06-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-07-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-04-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05092009
CCMO	NL79010.068.21