Tests for detection of ROS1 gene alterations in patients with locally advanced or metastatic non-small cell lung-cancer (NSCLC)

Project plan for an evaluation of tests

Sammendrag

Kort beskrivelse av bestillingen:

Folkehelseinstituttet har fått i oppdrag å evaluere genomiske tester relevante for identifisering av somatiske ROS1-genforendringer hos pasienter med lokalavansert eller metastasert ikke-småcellet lungekreft. Statens legemiddelverk (SLV) vil vurdere behandlingseffekten og sikkerheten av legemidlet Entrectinib (Rozlytrek) i samme populasjonen.

Tittel:
Tester for deteksjon av ROS 1 genforendringer blant pasienter med ikke-småcellet lungekreft

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Prosjektplan for
Vurdering av tester

Oppdragsgiver:
Bestillerforum RHF

Startdato:
23.09.2020

Sluttdato:
01.02.2021

Lag:
Gerd.M.Flodgren, forsker og lagleder
Vida Hamadi, helseekonom
Elisabet Hafstad, bibliotekar

Fagfeller:
Kjetil Brurberg, FHI

Godkjent av:
Kjetil Brurberg, avdelingsdirektør, FHI
Kåre Birger Hagen, fagdirektør, FHI

Summary

Short description of the commission:
The Institute of Public Health has been commissioned to evaluate genomic tests relevant for the identification of somatic ROS1 gene alterations in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). The Norwegian Medicines Agency (NoMA) will evaluate the treatment effect and safety of the drug Entrectinib (Rozlytrek) in the same population.

Title:
Tests for detection of ROS1 gene alterations in patients with non-small cell lung cancer
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Protocol for
A rapid review

Commissioner:
Commissioning forum RHF

Start date:
23.09.2020
End date:
01.02.2021

Team:
Gerd.M.Flodgren, researcher, and team leader
Vida Hamadi, health economist
Elisabet Hafstad, information specialist

Peer reviewers:
Kjetil Brurberg', NIPH

Approved by:
Kjetil Brurberg, NIPH
Kåre Birger Hagen, Specialist director, NIPH

Mandate/commission

The Commissioning Forum, representing the four Norwegian health regions (RHFs) has through the Nye Metoder system commissioned an evaluation to be jointly carried out by the National institute of Public Health (NIPH) and the Norwegian Medicines Agency (NoMA). NIPH will be responsible for assessing genomic tests relevant for the detection of ROS1 alterations in patients with NSCLC. NoMA will be responsible for evaluating the treatment effectiveness and safety of the drug Entrectinib (Rozlytrek) in the same population.

Background

Condition/disease

Epidemiology

Lung cancer constitute approximately 10% of all new cancer cases in Norway. It is the second most common cancer among men and the third most common in women (1). Non-small cell lung cancer (NSCLC) dominates, and among its sub-types, adenocarcinoma is most prevalent. The five-year survival for NSCLC is less than 10% (1).

ROS1 (proto-oncogene tyrosine-protein kinase fusion protein) is a receptor tyrosine kinase (RTK)(2). ROS1 gene alterations occur almost exclusively in adenocarcinomas. In NSCLC a number of fusion partners have been identified, of which the most common are CD74-ROS1, SLC34A2-ROS1, TPM3-ROS1, and SDC4-ROS1 (2). Patients with ROS1 alterations probably make up 1-2% of NSCLC adenocarcinoma cases, which corresponds to around 10 patients per year in Norway (4).

Expression of the ROS1 fusion protein results in hyperactivation of downstream signaling pathways, which in turn leads to uncontrolled cell division and increased tumor tissue survival (2). Treatment with the tyrosine kinase inhibitor (TKI) Entrectinib has in a small one-armed study, including mostly previously treated patients with NSCLC, been shown to shrink tumours and slow down the disease progression (3, 4). Entrectinib is approved for treatment of ROS1 fusion positive NSCLC by the European Medicines Agency (EMA) (5), and the US Food and Drug Administration (FDA) (6), but is currently not approved for medical use in Norway.

Accurate and reliable detection of ROS1 gene alterations is important to ensure that people who may benefit from treatment are correctly identified, as well as ROS1 negative patients, to avoid provision of unnecessary and costly treatment.

Progress, treatment, and care pathway for locally advanced or metastatic NSCLC

Patients with NSCLC are typically diagnosed at a late stage in the disease process where curative treatment is not feasible, and when survival is very low (7). Treatment for these patients therefore focus on interventions to prolong life and prevent or alleviate symptoms. Radiation therapy and/or drug treatment is given to most of these patients (7). It is recommended that all patients with NSCLC are tested for PD-L1 expression, and non-squamous cell carcinoma group are tested for EGFR, ALK, and ROS1 alterations. In adenocarcinoma with a detected mutation, targeted treatment is offered in the first line (e.g. TKI treatment with Crizotinib for ROS1), and in some cases second-line treatment is also offered(7). See Fig. 1

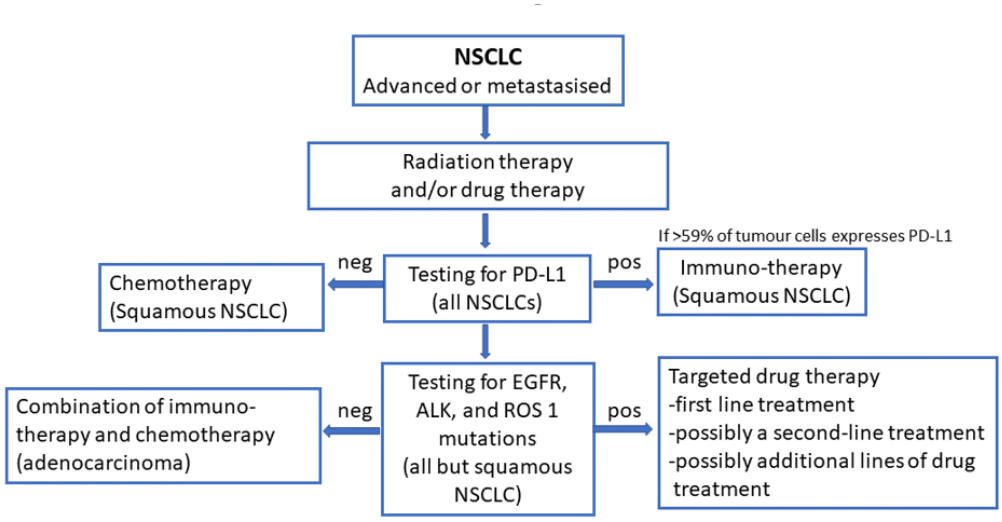

Figure 1. The recommended testing and treatment algorithm for patients with advanced NSCLC by Norwegian guidelines (7).

Genomic test (s) for detection of ROS1gene alterations

Genomic test(s)under study

There are four main methods that may be used to detect ROS 1 alterations in patients with NSCLC: immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), real time-polymerase chain reaction (RT-PCR), and next generation sequencing (NGS) (2). IHC is routinely used at Norwegian hospitals to screen for increased ROS1 gene alteration protein expression in patients with NSCLC. While IHC, FISH, and PCR are single protein/gene tests, NGS includes multi-gene panels, by which alterations in a number of genes can be detected at the same time. FISH is by many considered the gold standard test for the identification of ROS 1 gene alterations (8). The pros and cons of the different tests will be addressed in detail in the full review.

Companion diagnostic tests

There is at present no companion diagnostic test for Entrectinib approved by the FDA.

Why is it important to conduct this assessment?

In this review we will summarise the evidence of the accuracy, advantages, disadvantages and costs of different tests for the detection of ROS1 alterations. We will also if feasible, and together with experts, address possible barriers and challenges to the implementation of new tests/test systems in a Norwegian context. This assessment is conducted to assist decision makers to make informed decisions regarding the delivery and organization of genomic tests services in Norway.

Objectives

Our main objective is to summarise available evidence on the analytical validity, clinical validity, clinical utility, and the feasibility related to relevant genomic tests (single protein/gene tests or multiple gene panels) used for the detection of ROS1 alterations in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

In addition, we will address (i) Service delivery/organisational aspects, (ii) ethical, legal and social implications (ELSI), (iii) the patient perspective, and (iv) costs.

Definitions*:

Analytical validity (technical performance) = a test's ability to accurately and reliably *measure* a biomarker of interest (sensitivity, specificity, assay robustness, and quality control)

Clinical validity (strength of clinical correlation) = a test's ability to accurately and reliably identify or *predict* the disorder of interest (sensitivity, specificity, positive predictive value, negative predictive value)

Clinical utility (impact on patient outcomes)= refers to how likely it is that using the test to guide clinical decisions will significantly improve outcomes related to patients health and well-being (benefits vs. harms, whether using the tests gives added value to not using it, effectiveness, and efficacy)

* According to EGAPP definitions https://www.cdc.gov/genomics/gtesting/egapp/recommend/method.htm

Methods

Due to time constraints we will use a rapid overview of reviews in this assessment. The purpose of the genomic applications/tests that will be assessed is pharmacogenomic prediction of treatment response or adverse events. We will use the EGAPP framework (9, 10), and the extended framework described by Pitini et al. to guide our assessment (11).

Objectives/Research questions

The main objective of this evaluation is to summarise available evidence on the analytical validity, the clinical validity, and the clinical utility of tests (IHC, FISH, RT-PCR, and PCR) for the detection of ROS 1 alterations.
More precisely we wanted to answer the following research questions:

- How accurately and reliably do each of these tests detect the biomarker in the laboratory (technical performance)?
- How accurately and reliably do each of these tests detect the biomarker in samples from patients with locally advanced or metastasised NSCLC (e.g. tumour tissue, circulating cells, or cytology samples)?
- How well do each of these tests predict the effectiveness of treatment (e.g. shrinking of tumour, slowing down the disease process)?
- How well do each of these tests predict outcomes of importance to the patient (e.g. overall survival, and quality of life)?
- What are the potential adverse effects of using these tests to guide treatment decisions affecting patients?
- What are the pros and cons of the different tests (i.e. the feasibility of tests in terms of biological material requirements, turnarond time, invasiveness, training/expertise needed for interpretation of test results)

Secondary aims include assessing (i) the existing organization and delivery of genomic test services across health regions in Norway, (ii) the ethical, legal, and social implications (ELSI) of testing, and (iii) patient preferences.

Criteria for considering reviews for this assessment

We will use the PICO (population, intervention, comparison and outcomes) framework to describe the inclusion criteria (12).

Population:	People with locally advanced or metastatic non-small cell lung cancer (NSCLC)

Intervention (index test (s)):	Immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), real-time polymerase chain reaction (RT-PCR), next generation sequencing (NGS)
Comparison (reference test(s)):	As per above
Outcomes:	Analytical validity, clinical validity, clinical utility, feasibility, ELSI, and patient preferences
Language:	English, Norwegian, Swedish, Danish, Icelandic and Persian
Study design:	Systematic reviews, and non-systematic reviews

Exclusion criteria

- Studies in other languages than those listed above
- Studies that do not report a comparison between tests, or with cell-lines with known mutation status

Searching the literature

Information specialist Elisabet Hafstad (EH) will develop the search strategy with input from the authors, and run the searches. Another information specialist will peer review the search strategy. After a simplified search after systematic reviews (and original papers), relevant studies identified by the lead author was used to identify search terms and to determine the search cut-off . We will, based on the identification of a relevant evidence summary by Bubendorf from 2016 (13) search for systematic and non-systematic reviews from January 2015 and up to present. The search will not have any language restrictions. Relevant reviews in other languages than those mentioned above, but with an English abstract, will be listed in an appendix. The search strategy is provided in appendix 1.

Electronic searches

We will search the following electronic databases:

- Epistemonikos
- MEDLINE (Ovid)
- Embase (Ovid)
- INAHTA database
- EUnetHTA Relative Effectiveness Assessments
- Guidelines International Network (GIN)
- HTAi vortal+IQWIG, AIHTA, and KCE
- NIHR Journal Library

Searching other resources

We will search the reference lists of included studies and contact experts in the field.

Selection of reviews

We will search for reviews reporting analytical validity, clinical validity, clinical utility and/or feasibility of relevant genomic tests (i.e. IHC, FISH, PCR, NGS) that are used for the detection of ROS1 alterations in people with advanced NSCLC. We will also, if time and resources allow it, search for reviews reporting on ELSI, and/or patient preferences.

We will download all titles and abstracts retrieved by the electronic searches into the reference management program EndNote (14) and remove duplicates. Two review authors (GMF and VH) will independently assess the remaining titles and abstracts against the inclusion criteria using the reference management program Rayyan (15). We will obtain full text copies of potentially relevant reviews, and assess them in duplicate. We will resolve disagreements by discussion, or if necessary, by the use of an arbitrator. We will document reasons for exclusion of seemingly relevant reviews read in full text but subsequently excluded, in an appendix.

Data extraction and management

Two reviewers (GMF and VH) will independently extract data from each included review into a standardised data extraction form, which will be adapted and piloted for use in this overview. We will extract the following data: full citation, year of publication, setting, country of origin, study funding and potential conflicts of interest, study designs, language, and details on the PI-COs:

- *Participants*: number, age, gender, race/ethnicity, SES, time since diagnosis, previous treatment received, concomitant therapy/medication etc.
- *Genomic tests*: technical details of tests, regulatory status, in-house or commercial test, previous tests conducted, sequence of tests if more than one test are conducted, turnaround time, biological material needed, etc.
- *Comparisons*: head-to-head-comparisons, index test(s) versus reference tests if applicable, or cell-lines with known mutation status
- *Outcomes*: analytical validity (sensitivity, specificity, assay robustness, quality control), clinical validity (i.e. sensitivity and specificity, positive and negative predictive values), clinical utility outcomes related to the test (e.g. response rate to treatment, overall survival, quality of life), pros and cons of the included tests etc.

Quality assessment

There will be no quality assessment as this is a rapid overview of reviews.

Delivery of services and organizational aspects

We aim to map tests/test systems that are in use (or that may come to be used) in the different health regions in Norway and retrieve information regarding existing delivery and organization of genomic test services (including variability in delivery and organisation of services across health regions). If time and resources allow, we will also, if considered relevant for a specific test showing promise, seek the views of experts regarding potential challenges and barriers to implementation of this new technology in a Norwegian context.

Ethical, legal, and social implications

We will, if time and resources allow it, collect information concerning any ethical, legal or social implications related to the genomic tests under study.

Patient preferences

We will, if time and resources allow it, collect information concerning patient preferences regarding different genomic tests.

Compilation of results

We will provide a narrative summary of the evidence from included reviews, and from data received from the test suppliers, on the analytical validity, the clinical validity, and the clinical utility of the different tests in text and tables. Results related to delivery/organizational aspects, resource use, ELSI and patient preferences will also be reported narratively.

Health economic analysis

Preferably, a cost-effectiveness analysis should be performed to follow the NSCLC patient from diagnostic test for the detection of ROS1 mutations via treatment to final clinical outcomes based on so called end-to-end studies. Based on the feedback from the suppliers of the diagnostic methods and the relevant pharmaceutical company, there are no end-to-end studies available for the detection of ROS1 mutations in patients with NSCLC. If our review identifies end-to end studies, we will perform a cost-effectiveness analysis based on an integrated test-treatment model.

We will in collaboration with the experts from the reginal health authorities estimate the costs associated with each diagnostic method in Norway based on the micro-costing method (16). Micro-costing is a highly detailed health economic costing approach in which all of the underlying resources required for an intervention or activity, such as equipment, consumables, and staff time, are identified, and then unit costs are attached to this resource use to generate an overall cost (16). In the estimation of the costs related to the diagnostic methods, we will also consider the multigene testing and testing samples from multiple patients.

Acknowledgements

We wish to acknowledge information scientist Elisabet Hafstad for developing the search strategy, internal peer reviewer Kjetil Brurberg, NIPH and the clinical experts: Tormod K Guren, OUH, Åslaug Helland, OUH, Emilius AM Janssen, UiS, Hege LG Russnes, OUH, for helpful comments on the protocol. We also wish to acknowledge Øyvind Melien for his contribution to this project.

Conflict of interest

Gerd M Flodgren and Vida Hamidi (review authors) declare no conflict of interest.

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Contributions of authors

GMF wrote the project plan, apart from the paragraph on health economics which was written by VH.

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Appendix 1 Search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 30, 2020; Embase 1974 to 2020 September 30

	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 30, 2020 **Embase** 1974 to 2020 September 30	
1	(Sequence Analysis, RNA/ OR Sequence Analysis, DNA/ OR High-Throughput Screening Assays/) use ppezv OR (exp Sequence Analysis/ OR High Throughput Screening/) use oemezd OR (NGS OR sequencing OR minisequenc* OR pyrosequenc* OR profiling OR molecular diagnostic* OR ((multigene OR multi-gene OR multiplex OR multi-plex) ADJ6 (assay* OR panel*)) OR ((fusion* OR mutation* OR rearrang* OR re-arrang* OR mRNA OR sequenc*) ADJ6 analys*) OR ((high-throughput OR messenger RNA OR mRNA OR phosphoproteomic*) ADJ3 screen*)).tw,kw,kf.	1698336
2	In Situ Hybridization, Fluorescence/ use ppezv OR Fluorescence In Situ Hybridization/ use oemezd OR ((fluorescen* in-situ ADJ (hybridisation OR hybridization)) OR FISH).tw,kw,kf.	454528
3	Reverse Transcriptase Polymerase Chain Reaction/ use ppezv OR Reverse Transcriptase Polymerase Chain Reaction/ use oemezd OR (polymerase chain reaction OR PCR OR ddPCR OR rtPCR).tw,kw,kf.	1693961
4	exp Immunohistochemistry/ use ppezv OR exp Immunohistochemistry/ use oemezd OR (antigen retrieval OR immunohistochemistry OR immunohistocytochemistry OR immunocytochemistry OR immunolabel* OR ((goodpasture OR immunogold* OR immunoproxidase OR immunophosphatase OR peroxidase) ADJ (stain* OR techni*)) OR immunostaining OR IHC).tw,kw,kf.	1514554
5	(Oncomine* OR FoundationOne* OR TruSight* OR TSO500* OR Caris Molecular* OR OncoDEEP* OR FusionPlex* OR MSK Impact* OR MSKImpact* OR "Archer DX" OR Illumina* OR ThermoFisher* OR Thermo Fisher* OR Qiagen* OR Therascreen* OR MassARRAY* OR Sequenom* OR SNaPshot* Multiplex* OR Rabbit* mAb* OR VENTANA*).tw,dm,dv.	216518
6	("proto-oncogene tyrosine-protein kinase" OR ROS1 OR "ROS-1" OR "ROS 1" OR "ROS proto-oncogene 1" OR MCF3).tw,kw,kf	5096
7	(("proto-oncogene tyrosine-protein kinase" OR ROS1 OR "ROS-1" OR "ROS 1" OR "ROS proto-oncogene 1" OR MCF3) ADJ6 (detect* OR screen* OR test*)).tw,kw,kf	950
8	(("proto-oncogene tyrosine-protein kinase" OR ROS1 OR "ROS-1" OR "ROS 1" OR "ROS proto-oncogene 1" OR MCF3) AND (detect* OR screen* OR test*)).ti	191

9	Carcinoma, Non-Small-Cell Lung/ use ppezv OR Non small cell lung cancer/ use oemezd OR (NSCLC OR ((lung OR pulmon*) ADJ3 (adeno-carcinoma* OR cancer* OR carcinoma*))).tw,kw,kf	535611
10	(Meta-Analysis.pt. OR Systematic Review.pt OR Review.pt. OR "Review Literature as Topic"/ OR "Meta-Analysis as Topic"/ OR "Technology Assessment, Biomedical"/ OR exp Guideline/ OR Cochrane Database of Systematic Reviews.jn.) use ppezv OR (Systematic Review/ OR Re-view/ OR Meta Analysis/ OR Biomedical Technology Assessment/ OR Practice Guideline/ OR Cochrane Database of Systematic Reviews.jn.) use oemezd OR (((systematic* OR evidence OR research OR literature) ADJ3 (overview* OR synthes*)) OR review OR reviews OR guideline* OR meta-anal* OR metaanal* OR metanal* OR technology assessment* OR HTA OR pubmed OR medline OR embase OR cinahl OR cinhal OR cochrane OR handsearch* OR ((comprehensiv* OR systematic* OR manual OR hand OR database) ADJ3 search*)).tw,kw,kf	8263382
11	(2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020).yr.	16055811
12	((OR/1-5) AND 6) OR 7 OR 8	3043
13	9 AND 10 AND 11 AND 12 [MEDLINE: 133; Embase 292	425

Epistemonikos

	Søkegrensesnitt: Advanced search – Title/Abstract Filters: Publication Year 2015-2020	
	ROS1 OR "ROS-1" OR "ROS 1" OR MCF3 OR "ROS proto-oncogene 1"	Broad Synthesis: 3 Structured Summary: 1 Systematic Review: 16

INAHTA database

	ROS1 OR "ROS-1" OR "ROS 1" OR MCF3 OR "ROS proto-onco-gene 1" OR "c-ros-1"	1