Alectinib as monotherapy for the first line treatment of adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC)

Project ID: PTJA03

Project description and planning

TLV, Sweden
HVB, Austria
AAZ, Croatia

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Contents:

A. VERSION LOG

Each (significant) modification should be marked with a new version number (Vx). Minor modifications may be marked within versions (Vx.y) Each new version to be communicated with the project team.

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	23/08/17	TLV, HVB, AAZ	1st version (draft)	
V2	03/10/17	TLV, HVB, AAZ	2nd version	Comments from the dedicated reviewers were incorporated

B. PROJECT PLAN

1.0 PARTICIPANTS

Table 1. Project participants

#	Agency	Role in the project	Country	Distribution of work
1.	Dental and Pharmaceutical Benefits Agency (TLV)	Author(s)	Sweden	• Develop the first draft and the final version of EUnetHTA project plan with co-authors • Perform the additional literature search (update) • Relative effectiveness and safety assessment • Send “draft versions” to reviewers, compile feedback from reviewers and perform changes according to reviewers comments • Prepare the final assessment including a final summary of the assessment
2.	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	Co-Author(s)	Croatia	• Develop the first draft and the final version of EUnetHTA project plan with 1st author and co-author • Carry out the assessment: answer assessment elements TEC Domain; support EFF and SAF Domains, Summary, Method and Discussion sections • Check and approve all steps
3.	Main Association of Austrian Social Security Institutions / Hauptverband der österreichischen Sozialversicherungsträger (HVB)	Co-Author(s)	Austria	• Develop the first draft and the final version of the EUnetHTA project plan with author(s) and co-author(s) • Carry out the assessment: answer assessment elements of the CUR Domain; support authors in EFF and SAF Domains, Summary, Method and Discussion sections • Check and approve all steps
4.	National Institute for Health and Care Excellence (NICE)	Reviewer	UK	Reviewers support the authors and co-authors by providing feedback on the draft Project plan and the Assessment report. They agree on the overall scope and on methods used; They accept the Project Plan and agree on timelines and ensure that the review is in accordance with
5.	Regione Veneto	Reviewer	Italy	
6.	Uniba	Reviewer	Slovakia	

7.	Andalusian Agency for Health Technology Assessment (AETSA)	Reviewer	Spain	EUnetHTA guidance. Their main role in the process is to ensure the quality of the rapid assessment.
8.	National Institute of Pharmacy and Nutricion (NIPN)	Reviewer	Hungary	
9.	Ministery of Health (MoH)	Observer	Malta	
10.	TBD	Editor/Medical writer		
11.	Zorginstituut Nederland [ZIN]	Project coordinator	Netherlands [NL]	Coordination between involved parties throughout the assessment duration
		External Expert(s)		

1.1 PROJECT STAKEHOLDERS

Please describe/list project stakeholders

Table 2. Project stakeholders

Organisation	Role	Contact details
F. Hoffmann - La Roche Ltd.	*Marketing Authorization Holder*	*Grenzacherstrasse 124* *4070 Basel, Switzerland*

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this pilot assessment report is to collaboratively produce structured rapid core HTA information on pharmaceuticals. In addition, the aim is to apply those collaboratively produced HTAs in the national or regional contexts.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	**Indicator (and target)**
1.	To collaboratively produce structured rapid core HTA	Production of 1 relative effectiveness assessment (REA)
2.	To apply these collaboratively produced rapid assessments into local (e.g. regional or national) context	Production of ≥1 local (e.g. national or regional) report per REA

This rapid assessment addresses the research question whether the 1st line alectinib monotherapy in adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) is more effective and/or safer than crizotinib or ceritinib monotherapy.

Table 3. Project Scope: PICO (please see HTA Core Model for Rapid REA of pharmaceuticals)

Description	**Project scope**
Population	First line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). ICD-10: C34.xx Mesh-terms: Carcinoma, Non-Small-Cell Lung (C04.588.894.797.520.109.220.249; C08.381.540.140.500; C08.785.520.100.220.500) A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of alectinib therapy. Subgroup analysis: Patients with brain metastases at baseline
Intervention	The recommended dose of alectinib is 600 mg (four 150 mg capsules) taken twice daily with food (total daily dose of 1200 mg). Duration of treatment with alectinib should be continued until disease progression or unacceptable toxicity. Alectinib is a highly selective and potent ALK and RET tyrosine kinase inhibitor.
Comparison	• Crizotinib (Direct comparison), 250 mg twice daily (total daily dose 500 mg); Crizotinib is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK)

	and its oncogenic variants (i.e. ALK fusion events and selected ALK mutations). • Ceritinib (Indirect comparison, Network Meta Analysis (NMA), 750 mg once daily; Ceritinib is an orally highly selective and potent ALK inhibitor. According to approved 1st line indications Since direct study data of alectinib versus ceritinib is missing an indirect comparison is needed - Network Meta Analysis (NMA). Rationale: Comparators have been chosen based on information from Manufacturer submission file, relevant EPARs [1] and SmPCs [2], clinical guidelines [3] [4] and EUnetHTA guidelines [5].
Outcomes	**EFF Domain** **Primary end point:** Overall survival (OS), Progression-free survival (PFS) **Secondary end points:** Time to CNS progression, Objective response rate (ORR), Health-related quality of life (HRQoL), Other patient reported outcomes,CNS Objective response rate, CNS Duration of Response (DoR) **SAF Domain** Adverse events (AEs) Any AEs, Serious AE (SAE), most frequent AEs and SEAs, Death as SAE, discontinuation due to AEs, AE leading to dose reduction, AE of special interest/ grade≥3 AEs Rationale: Outcomes are selected based on the recommendations from the clinical guidelines [3] [4] and the EUnetHTA Guidelines [5].
Study design	**Effectiveness:** • Randomised controlled trials only **Safety:** • Randomised controlled trials • Non-randomised controlled trials (if applicable) • Prospective studies with or without a control group (if applicable) • Postmarketing surveillance data alectinib-related adverse events (if applicable) **Organisational, ethical, patient and social, legal aspects (if needed):** Qualitative and qualitative studies, reports or opinions according the EUnetHTA Core HTA Model 3.0 [6] Only English language studies will be included

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
Relevant EUnetHTA guidelines, such as the Guideline for Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness and the Guideline for Levels of evidence; Internal validity of randomised

controlled trials, will be considered in the assessment [5].

Assessment elements
The selection of assessment elements will be based on the EUnetHTA Model Application for Rapid Relative Effectiveness (REA) Assessments [7].

Information retrieval:
The information retrieval will primarily be based on the Manufacturer's submission file. In addition, the evidence included in the Manufacturer's submission file will be checked for completeness against published literature, EMA and FDA pages/databases. Further information sources include clinical experts and international Guidelines.
For registered ongoing clinical trials, clinical trials registries will be searched (ClinicalTrials.gov (U.S. National Institutes of Health registry.http://www.clinicaltrials.gov/), WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) and EU Clinical Trials Register https://www.clinicaltrialsregister.eu/)).

Quality assessment tools:
For TEC and CUR domains no quality assessment tool will be used, but multiple sources will be used in order to validate individual, possibly biased, sources.
The risk of bias of included RCTs on study and outcome level will be evaluated according to the EUnetHTA Guideline for Internal validity [5].
Indirect evidence on primary outcomes will be assessed according to the EUnetHTA Guideline on direct and indirect comparisons [5] and based on NICE Decision Support Unit Guidance [8].

Plan for synthesis:
The CUR and TEC domain will only be summarised descriptively.

EFF and SAF: a summary of findings table will be used for displaying the results and a NMA will be performed by the manufacturer and validated by the authoring team. In general, the completed part of EUnetHTA submission file from the manufacturer will be used as starting point.

Appendix:
There will be a general discussion about the long term relative effectiveness of Alecensa compared to its comparators. For example through extrapolated efficacy outcomes.

Table 4b. Preliminary Evidence

Preliminary evidence table Please provide an overview of the most relevant studies included
ALEX, Peters et al. 2017 [9] In a randomized, open-label, phase 3 trial, 303 patients with previously untreated, advanced *ALK*-positive NSCLC were randomly assigned to receive either alectinib (600 mg twice daily) or crizotinib (250 mg twice daily).
ASCEND-4, Soria et al. 2017 [10] First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study.
PROFILE 1014, Solomon et al. 2016 [11] First-line crizotinib versus chemotherapy in ALK-positive lung cancer

PROFILE 1029, Lu et al. 2016b [12] Phase 3 study of first-line crizotinib vs pemetrexed−cisplatin/carboplatin (PCC) in East Asian patients (pts) with ALK+ advanced non-squamous non-small cell lung cancer (NSCLC).

Selected assessment elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessments elements contained in the document “Model for Rapid Relative Effectiveness Assessment”.

Table 5. Assessment elements and translating research questions

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Description and technical characteristics of technology				
B0001 Critical element	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	What are alectinib and the comparators – crizotinib and ceritinib?
A0020 Critical element	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	What are the approved indications of alectinib ?
B0002 Critical element	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparators?	Yes	What is the claimed benefit of alectinib in relation to the comparator(s)?
B0003 *Optional element*	*Features of the technology*	*What is the phase of development and implementation of the technology and the comparator(s)?*	Yes	What is the phase of development and implementation of alectinib and the comparator(s)?
B0004 *Optional element*	*Features of the technology*	*Who administers the technology and the comparators and in what context and level of care are they provided?*	Yes	Who administers alectinib and the comparator(s) and in what context and level of care are they provided?
B0008	*Investments and tools required to*	*What kind of special premises are needed for the*	Yes	What kind of special premises are needed for alectinib and the

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Optional element	*use the technology*	*technology and the comparator (s)?*		comparator (s)?
B0009 *Optional element*	*Investments and tools required to use the technology*	*What supplies are needed for the technology and the comparator (s)?*	No	
A0021 *Optional element*	*Regulatory Status*	*What is the reimbursement status of the technology?*	Yes	What is the reimbursement status of alectinib?
Health problem and current use of technology				
A0002 Critical element	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is NSCLC in the scope of this assessment?
A0003 *Optional element*	Target Condition	*What are the known risk factors for the condition?*	Yes	What are the known risk factors for NSCLC? (briefly)
A0004 *Optional element*	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of (advanced) NSCLC? (briefly)

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
A0005 Critical element	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	What are the symptoms and the burden of advanced NSCLC for the patient?
A0006 *Optional element*	Target Condition	*What is the burden of disease for society?*	No	
A0024 *Optional element*	Current Management of the Condition	*How is the disease or health condition currently diagnosed according to published guidelines and in practice?*	Yes	How is (ALK+ advanced) NSCLC currently diagnosed according to published guidelines? (briefly)
A0025 Critical element	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	How is ALK+ advanced NSCLC in adults currently managed according to published guidelines and in practice?
A0007 Critical element	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?
A0023 Critical element	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population?

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
A0011 *Optional element*	Utilisation	*How much are the technologies utilised?*	No	
Clinical effectiveness				
D0001 Critical element	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	What is the effect on overall survival for alectinib compared to other approved treatments in the 1st line therapy?
D0005 Critical element	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition or disease?	Yes	How does alectinib affect symptoms and findings (e.g. time to CNS progression, objective response rate (ORR), overall survival (OS), health-related quality of life (HRQoL))) of adults with ALK+ advanced NSCLC?
D0006 Critical element	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	How does alectinib affect progression free-survival of adults with ALK+ advanced NSCLC, compared to other approved treatments in the 1st line therapy?
D0011 *Optional*	*Function*	*What is the effect of the technology on patients' body functions?*	No	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
element				
D0016 *Optional element*	*Function*	*How does the use of technology affect activities of daily living?*	Yes	How does alectinib affect activities of daily living?
D0012 Critical element	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	What is the effect of alectinib on generic health-related quality of life?
D0013 Critical element	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of alectinib on disease-specific quality of life?
D0017 *Optional element*	*Patient satisfaction*	*Was the use of the technology worthwhile?*	No	
Safety				
C0008 Critical element	Patient safety	How safe is the technology in relation to (the) comparator(s)?	Yes	What is the frequency of any adverse events of alectinib compared to other approved treatments in the 1st line therapy? What are the most frequent AEs of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of discontinuation of treatment due to adverse

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
				events of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of AE leading to dose reduction of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency and what are serious adverse events (SAE) of alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of serious adverse events (SAE) leading to death for alectinib compared to other approved treatments in the 1st line therapy? What is the frequency of AE of special interest for alectinib?
C0002 *Optional element*	*Patient safety*	*Are the harms related to dosage or frequency of applying the technology?*	No	
C0004 *Optional element*	*Patient safety*	*How does the frequency or severity of harms change over time or in different settings?*	No	
C0005 Critical element	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	What are the susceptible patient groups that are more likely to be harmed through the use of alectinib?
C0007	*Patient safety*	*Are the technology and comparator(s) associated*	No	

ID	Topic	Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'Critical' elements
Optional element		*with user-dependent harms?*		
B0010 *Optional element*	*Investments and tools required to use the technology*	*What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?*	Yes	*What kind of data/records and/or registry is needed to monitor the use of the alectinib and the comparator?*

Checklist for potential ethical, organisational, social and legal aspects

The following checklist is a short list of questions in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the medicine to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new medicine will lead to changes.
If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further. Examples are provided for clarification (for more details please see also Model for rapid REA).

Table 6. Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	No
3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Please note that the timeline for the assessment phase was updated, in order to consider the Christmas break

Table 7. Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**04/07/2017**	**31/01/2018**
Expression of interest of manufacturer	04/07/2017	

Pilot's team building (including possible external experts)	04/07/2017	25/07/2017
Scoping phase duration	**25/07/2017**	**20/10/2017**
Receive the Draft Submission File from MAH	17/07/2017	
Draft Project Plan	17/08/2017	22/08/2017
Review Draft Project Plan by dedicated reviewers and experts	23/08/2017	05/09/2017
Feedback on draft submission file	23/08/2017	05/09/2017
Receive Final Submission File from MAH	~ 20/10/2017	
Final Project Plan	25/09/2017	20/10/2017
Assessment phase duration	**23/10/2017**	**23/01/2018**
First draft of the pilot assessment	23/10/2017	24/11/2017
Review of the first draft of the pilot assessment by dedicated reviewers	24/11/2017	04/12/2017
Second draft of the pilot assessment	05/12/2017	18/12/2017
Editorial version of the second draft	18/12/2017	04/01/2018
Consultation of the editorial version of the pilot assessment by external experts and MAH	04/01/2018	14/01/2018
Final version of the pilot assessment	15/01/2018	22/01/2018
Final technical editing and publication	22/01/2018	23/01/2018
Local Reports (if applicable)	[DD/MM/YYYY]	[DD/MM/YYYY]

5.2 MEETINGS

A face-to-face scoping meeting will be planned with the manufacturer, authors and co-authors (see table 8). In addition, several e-meetings or teleconferences may be scheduled by the REA team, if considered necessary (see table 8).

6.0 COMMUNICATION

Table 8. Communication

Communication Type	Description	Date (if known)	Format	Participants/ Distribution
Kick-off	Informal kick-off meeting in which procedures are explained	09/08/2017	e-meeting	Author(s), co-author(s),

Communication Type	Description	Date (if known)	Format	Participants/ Distribution
authoring team	to involved parties			dedicated reviewers, CT
Kick-off MAH	Informal kick-off meeting in which procedures are explained to involved parties	TBD	e-meeting	MAH, CT
Scoping	To discuss draft submission file and reach consensus on the scoping (draft project plan)	~08/09/2017	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
	To discuss scoping and draft submission file with MAH	15/09/2017	Face-to-face meeting	MAH, author(s), co-author(s), CT
Feedback on draft submission file	To point out the requirements for the final submission file by MAH	~11/09/2017	E-mail	MAH
Final Project Plan with timelines	Information on timelines, scoping, methods and assessment elements	20/10/2017	E-mail	Review by DR. Distribution to MAH, WP4 members
First draft of the assessment	To be reviewed by DR	24/11/2017	E-mail	DR
	To discuss comments of DR and reach consensus on adaptations	TBD, if needed	e-meeting	Author(s), co-author(s), dedicated reviewers, CT
Consultation MAH and external experts of the assessment	To be consulted with MAH and external experts	05/01/2017	E-mail	MAH, external experts
	To discuss comments of MAH (optional)	TBD	e-meeting	Author(s), co-author(s), (dedicated reviewers)

6.1 DISSEMINATION PLAN

The final pilot rapid assessment will be distributed as laid-out in the Work Plan of WP4.

7.0 COLLABORATION WITH STAKEHOLDERS

Collaboration with Market Authorisation Holder or prospective Market Authorisation Holder

Manufacturers can indicate their willingness to participate by submitting an expression of interest. The draft REA submission file provided by the company applying for market authorisation is the basic documentation for a rapid assessment and (in most cases) is received by authors before the positive opinion of the CHMP. Therefore the company applying for market authorisation is asked to provide the scientific discussion section of the CHMP report.

There will be a face-to-face scoping meeting of author(s)/co-author(s)/coordinators with the manufacturer. Within one week after face-to-face scoping meeting authors will send their feedback on the draft submission file to the manufacturer. The final

submission file from the company is expected not later than by further four weeks, during which time the authors finalise the project plan and plan the timelines.

In general, the consultation with the manufacturer includes the project plan (especially timelines) and the second draft of the pilot assessment. However, if necessary, it is possible to send queries to the manufacturer during the assessment phase.

Collaboration with other stakeholders

Payers organization at EU level will be contacted related to reimbursement status of alectinib and the comparators for the first-line indication and to reply on editorial version of the pilot assessment, as well as Patient organization, during the collaborative process (reply to editorial version of the pilot assessment).

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual pilot rapid assessment, some collaboration with other WPs is planned. WP7 [Implementation] will be informed in time of the project plan and timelines, in order to prepare activities to improve national uptake of the final report. Feedback on the WP4 REA process will be asked from the involved parties, this information will be discussed with WP6 [Quality Management] to improve the quality of the process and output.

9.0 RESOURCE PLANNING

9.1 HUMAN RESOURCES

Table 9. Human resources

Role	Total number of person days	Source	
		Staff of participating organisations	Subcontracting
Author	60 person days	60 person days	-
Co-Author	40 person days	40 person days	-
Reviewer	5 person days each	5 person days each	-
Editor/Medical writer	5 person days	-	5 person days

The individuals participating in the production of the assessment will be asked to collect actual person days invested through a timesheet template.

10.0 CONFLICT OF INTEREST MANAGEMENT

All individuals participating in this project will sign the standardized “Conflict of Interest” Statement.

Authors and reviewers who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other pilots.

For external experts involved, conflict of interest declarations are collected from them regarding the topic. External experts who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other pilots.

All individuals involved will also sign a Confidentiality waver.

11.0 EXPECTED OUTCOME(S)

Project outcome(s)
The capacity of national or regional HTA bodies to collaboratively produce structured rapid core HTA has been proven.

Translation into local reports will take place, reducing redundancies and therefore efficiency gains will be achieved.

C. REFERENCES

[1] EPAR Alecensa
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004164/human_med_002068.jsp&mid=WC0b01ac058001d124

EPAR Xalkori
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124

EPAR Zykadia
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003819/human_med_001860.jsp&mid=WC0b01ac058001d124

[2]. SmPC Alecensa
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004164/human_med_002068.jsp&mid=WC0b01ac058001d124

SmPC Xalkori
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124

SmPC Zykadia
Available from:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003819/human_med_001860.jsp&mid=WC0b01ac058001d124

[3]. NCCN Guidelines 2017; Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

[4]. ESMO Guidelines 2016; Available from: http://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer

[5]. European network for Health Technology Assessment (EUnetHTA). Updated EUnetHTA methodological Guidelines. EUnetHTA; 2015. Available from: http://www.eunethta.eu/eunethta-guidelines.

[6]. HTA Core Model. EUnetHTA; 2016.
Available from: http://www.eunethta.eu/outputs/hta-core-model-30

[7]. HTA Core Model for Rapid Relative Effectiveness (REA) Assessments (4.2) 2015. Available from http://meka.thl.fi/htacore/model/HTACoreModel_ForRapidREAs4.2.pdf

[8]. NICE Decision Support Unit Guidance
Available from: http://scharr.dept.shef.ac.uk/nicedsu/

[9] ALEX, Peters et al. 2017

Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1704795

[10] ASCEND-4, Soria et al. 2017
Avalable from: https://www.ncbi.nlm.nih.gov/pubmed/28126333

[11] PROFILE 1014, Solomon et al. 2016
Available from: https://www.ncbi.nlm.nih.gov/pubmed/25470694

[12] PROFILE 1029, Lu et al. 2016b
Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.9058