DEUTSCHE GESELLSCHAFT FÜR REGULATORY AFFAIRS

Regulatory Affairs Meets HealthTechnology Assessment

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DGRA Jahreskongress 2021

Disclaimer

The views and opinions expressed in this presentation are those of the speaker and do not reflect official policies or positions of Daiichi Sankyo.

Agenda

- RA meets HTA or „quo vadis drug development?“

- Regulatory 2.0 meets HTA – how to bring promising medicines to patients faster AND get reimbursement

Traditional Drug Development (I)

Quality, Safety and Efficacy

- Requirements are standardised across regions due to ICH guidelines
- Regional differences are almost negligible
- Centralised Procedure (CP) – mandatory for many indications in the EU
- Many innovative drugs have a central MA in the EU
- Inter-regional collaboration of agencies is a possibility for further harmonisation (i.e. Project Orbis)

Traditional Drug Development (II)

- No added benefit compared to Standard of Care (SoC) necessary for receiving a Marketing Authorisation!
- Often no access components in clinical study design

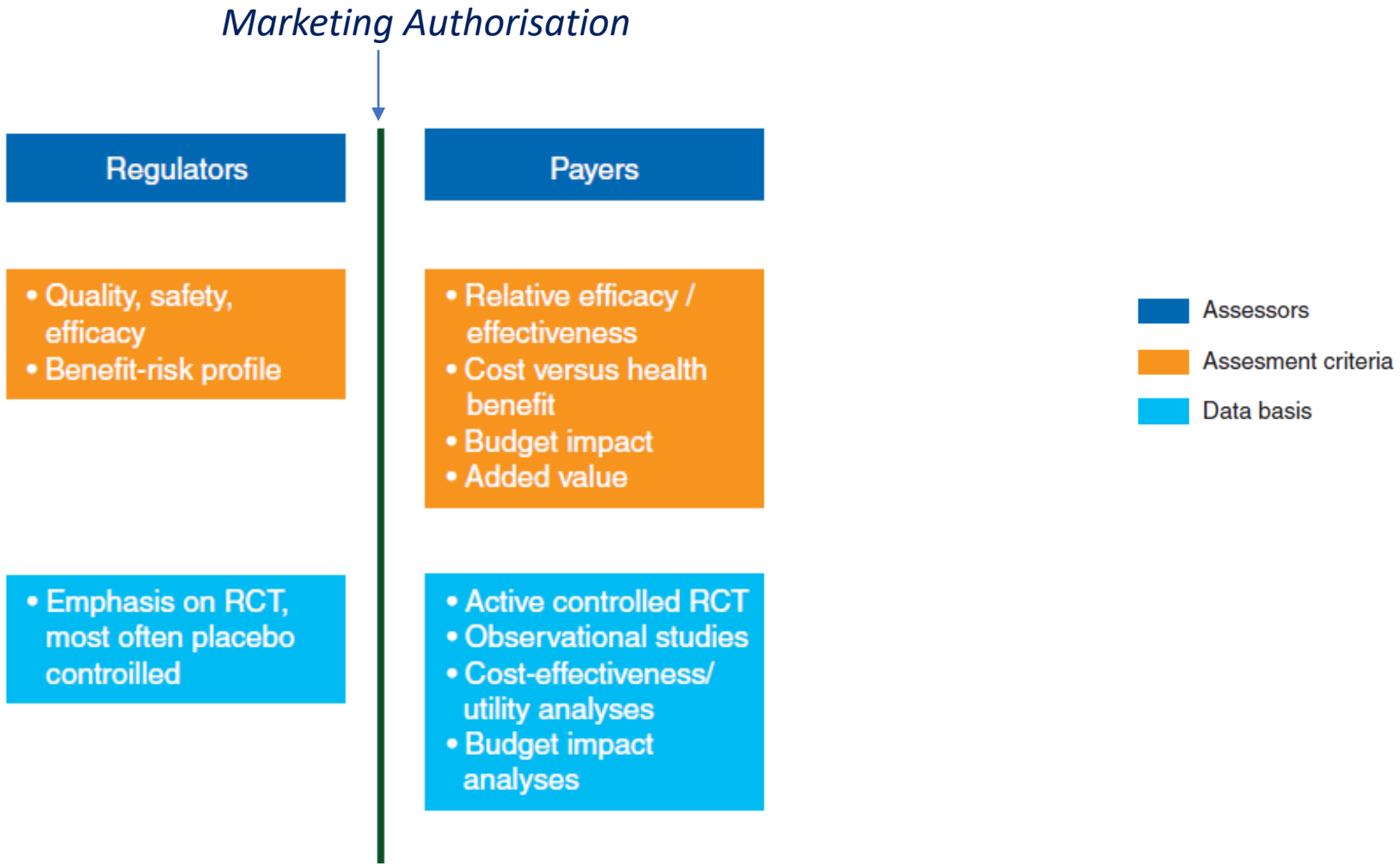
Current Chain of Drug Development:

*MAx: Market Access AND HT assessment
** RoI: Return of Investment

Regulatory Approval is no longer good enough!

- Costs for new medicines have risen in the past years
- Many countries have established reimbursement rules
- Health Technology Assessment (HTA) has become more and more important
- Different methods and standards of HTA across Europe
- HTA, followed by reimbursement negotiations, are purely national processes
- first attempts at harmonisation (EUnetHTA, EU-HTA Regulation)

Regulators vs Payers – Current Paradigm



Adapted from:
Eichler, H-G, Bloechl-Daum B, Abadie E, et al. Relative Efficacy of Drugs: An emerging issue between Regulatory Agencies and third-party payers. Nat Rev Drug Discovery 2010; 9: 277-291

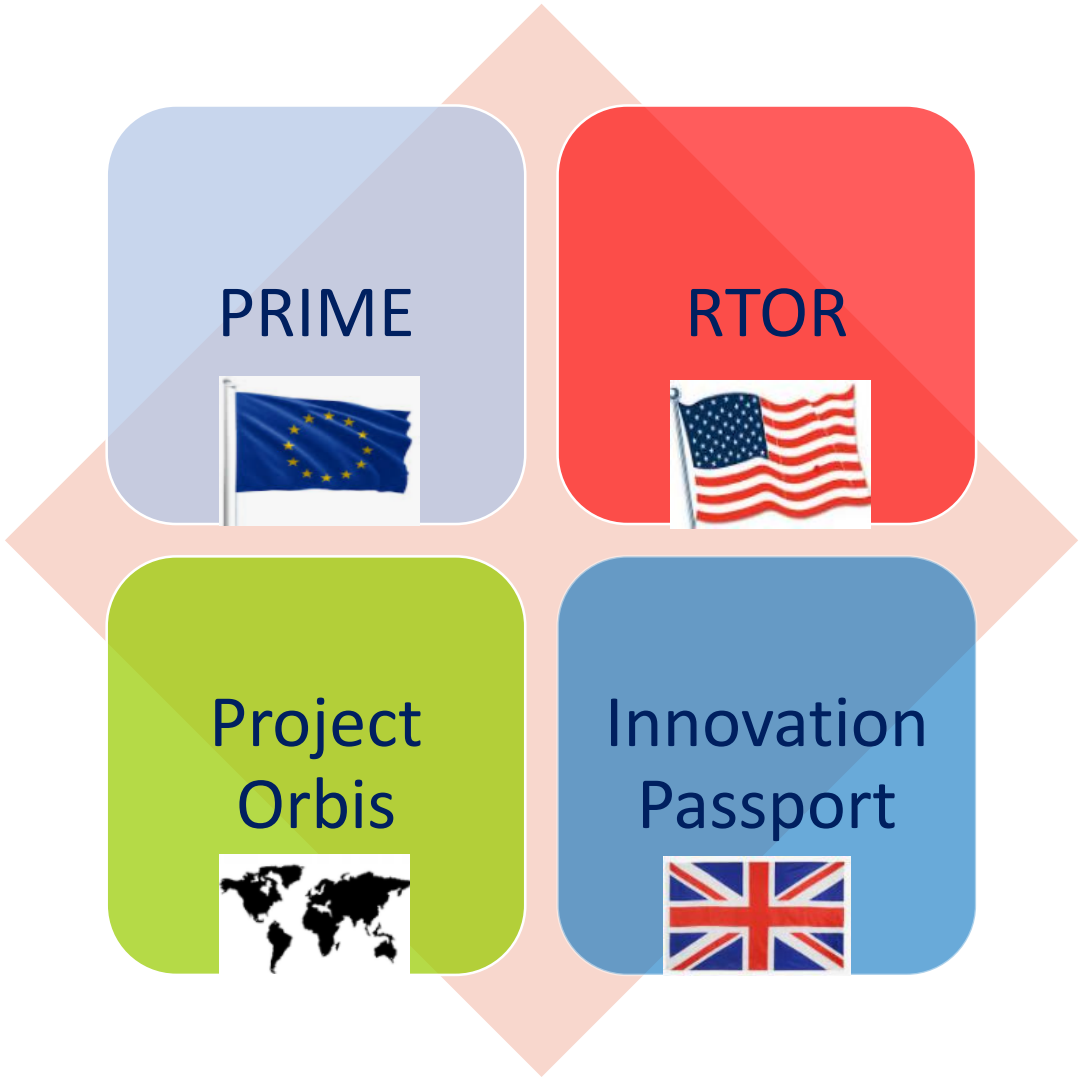
How does drug development work?

- Clinical development needs are prioritised – globalised development
- Regulatory Affairs is usually a part of a global development team
- Market Access is often not a part of a global development team
- Market access input – if solicited – is often very regional and divergent

How does drug development *need* to work?

- Clinical development needs to take both regulatory and market access needs into account: Study designs need to satisfy both Regulators‘ and Payers‘ requirements!
- Regulatory and Market Access need to be part of a global development team
- Regional differences might need to be taken into account
- Early design of indication statements that take regulatory and HTA requirements into acocunt (broad vs limited indication statements)

Regulators: Flexible Approval Procedures



Different requirements of Regulators and Payers

Study design:

- Endpoints: Surrogate vs „hard“ endpoints
- Comparators: different Standard of Care (SoC), often more cost-based payers‘ choice
- Patient Populations: highly selected vs „real world“ populations
- Adaptive study designs vs Phase III RCT

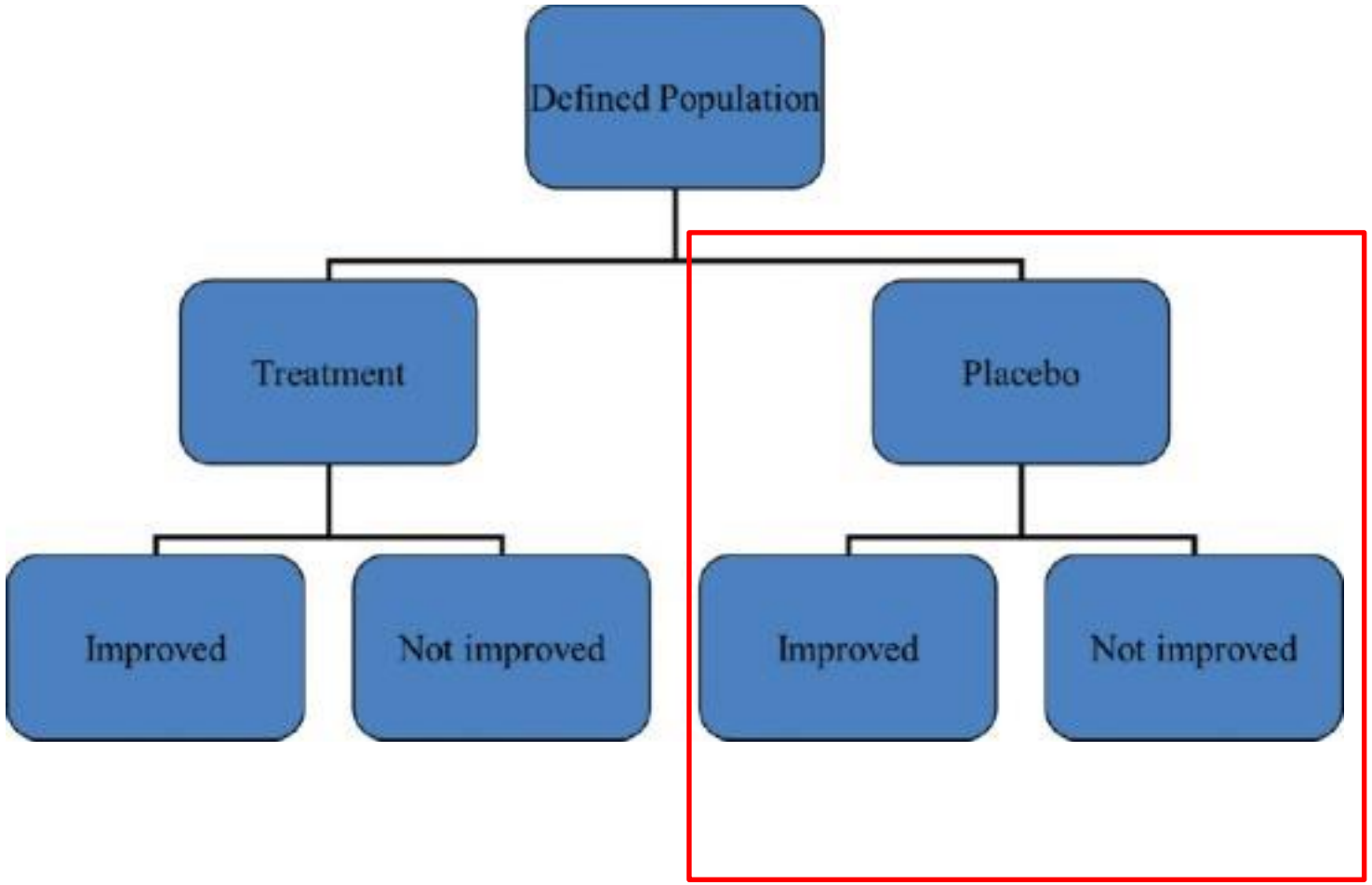
Procedural topics:

- Accelerated assessment – no payer equivalent
- conditional approval – temporary appraisals

Trends in Regulatory Affairs –

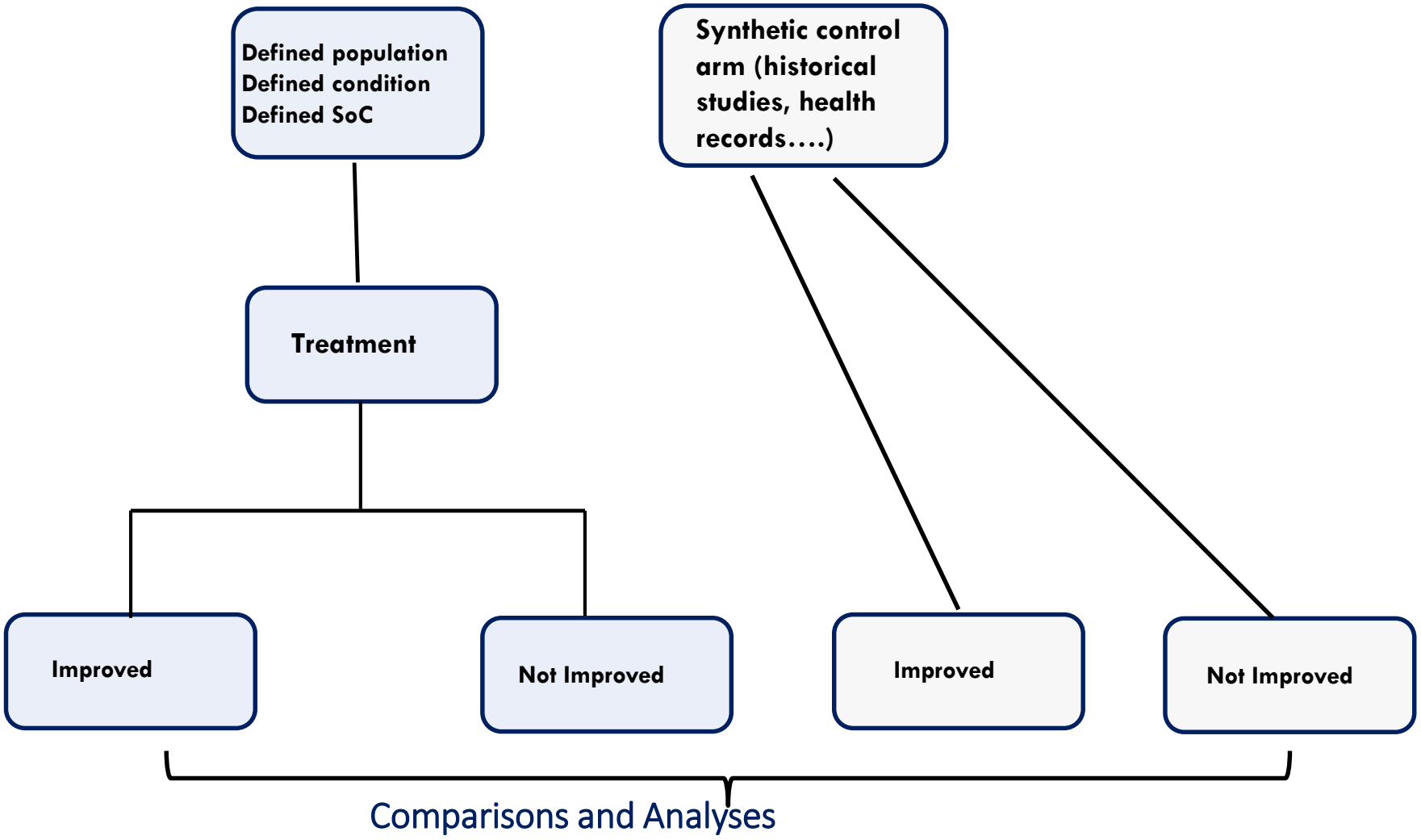
How to adapt for Market Access?

Classical Clinical Trial Design



Nair B: Clinical Trial Designs; Indian Dermatol Online J 2019, 10(2)

Possible Clinical Trial Design



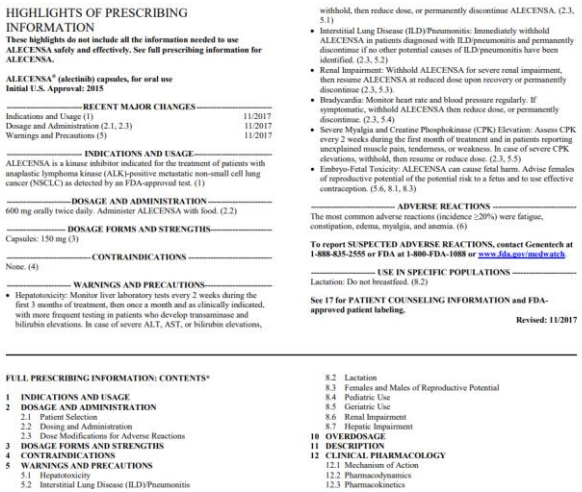
Example: Alectinib (Roche)

Approval based on 2 Phase II single arm studies (SAT)

Highly efficaceous drug – comparator arm with SoC?

Small populations/biomarker driven enrollment

Example: Alectinib (Roche)



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALECENSA safely and effectively. See full prescribing information for ALECENSA.

ALECENSA® (alectinib) capsules, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2017
Dosage and Administration (2.1, 2.3)	11/2017
Warnings and Precautions (5)	11/2017

INDICATIONS AND USAGE

ALECENSA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. (1)

DOSAGE AND ADMINISTRATION

600 mg orally twice daily. Administer ALECENSA with food. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Monitor liver laboratory tests every 2 weeks during the first 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. In case of severe ALT, AST, or bilirubin elevations, withhold, then reduce dose, or permanently discontinue ALECENSA. (2.3, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Immediately withhold ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified. (2.3, 5.2)
- Renal Impairment: Withhold ALECENSA for severe renal impairment, then resume ALECENSA at reduced dose upon recovery or permanently discontinue (2.3, 5.3).
- Bradycardia: Monitor heart rate and blood pressure regularly. If symptomatic, withhold ALECENSA then reduce dose, or permanently discontinue. (2.3, 5.4)
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation: Assess CPK every 2 weeks during the first month of treatment and in patients reporting unexplained muscle pain, tenderness, or weakness. In case of severe CPK elevations, withhold, then resume or reduce dose. (2.3, 5.5)
- Embryo-Fetal Toxicity: ALECENSA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) were fatigue, constipation, edema, myalgia, and anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

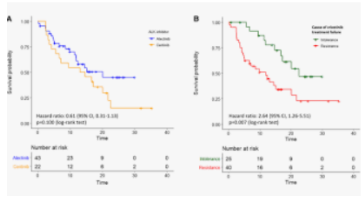
USE IN SPECIFIC POPULATIONS

Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2017

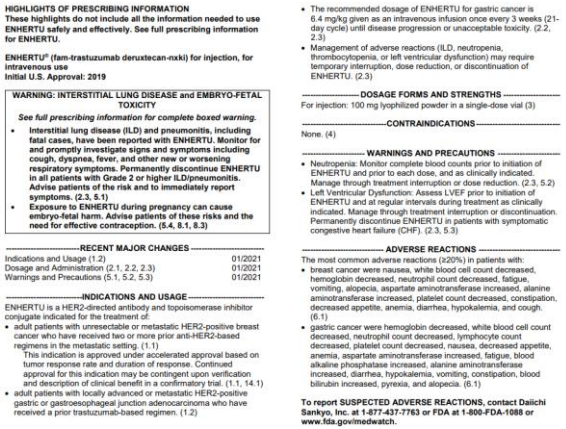
FULL PRESCRIBING INFORMATION: CONTENTS*



FDA approved Alectinib based on 2 SAT (accelerated approval) plus RWE (included public health records)

EMA approved Alectinib based on 2 SAT and emerging data from a Phase III trial with comparator arm (conditional approval) plus RWE

Example: Enhertu (Daiichi Sankyo)



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENHERTU safely and effectively. See full prescribing information for ENHERTU.

ENHERTU® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use
Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms. (2.3, 5.1)**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	01/2021
Dosage and Administration (2.1, 2.2, 2.3)	01/2021
Warnings and Precautions (5.1, 5.2, 5.3)	01/2021

----------INDICATIONS AND USAGE----------

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. (1.1)
  This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1.1, 14.1)
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. (1.2)

- The recommended dosage of ENHERTU for gastric cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 100 mg lyophilized powder in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia: Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Manage through treatment interruption or dose reduction. (2.3, 5.2)
- Left Ventricular Dysfunction: Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF). (2.3, 5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) in patients with:

- breast cancer were nausea, white blood cell count decreased, hemoglobin decreased, neutrophil count decreased, fatigue, vomiting, alopecia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, constipation, decreased appetite, anemia, diarrhea, hypokalemia, and cough. (6.1)
- gastric cancer were hemoglobin decreased, white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, platelet count decreased, nausea, decreased appetite, anemia, aspartate aminotransferase increased, fatigue, blood alkaline phosphatase increased, alanine aminotransferase increased, diarrhea, hypokalemia, vomiting, constipation, blood bilirubin increased, pyrexia, and alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

EMA approved Enhertu based on 1 SAT and RWE (conditional approval)

FDA approved Enhertu based on 1 SAT plus RWE (accelerated approval)

Methodology to Create a Synthetic Control Arm

- Clearly define condition
- Establish Standard of Care
- Design Single Arm Clinical Trial
- Select Partner for RWE evaluation and SCA design

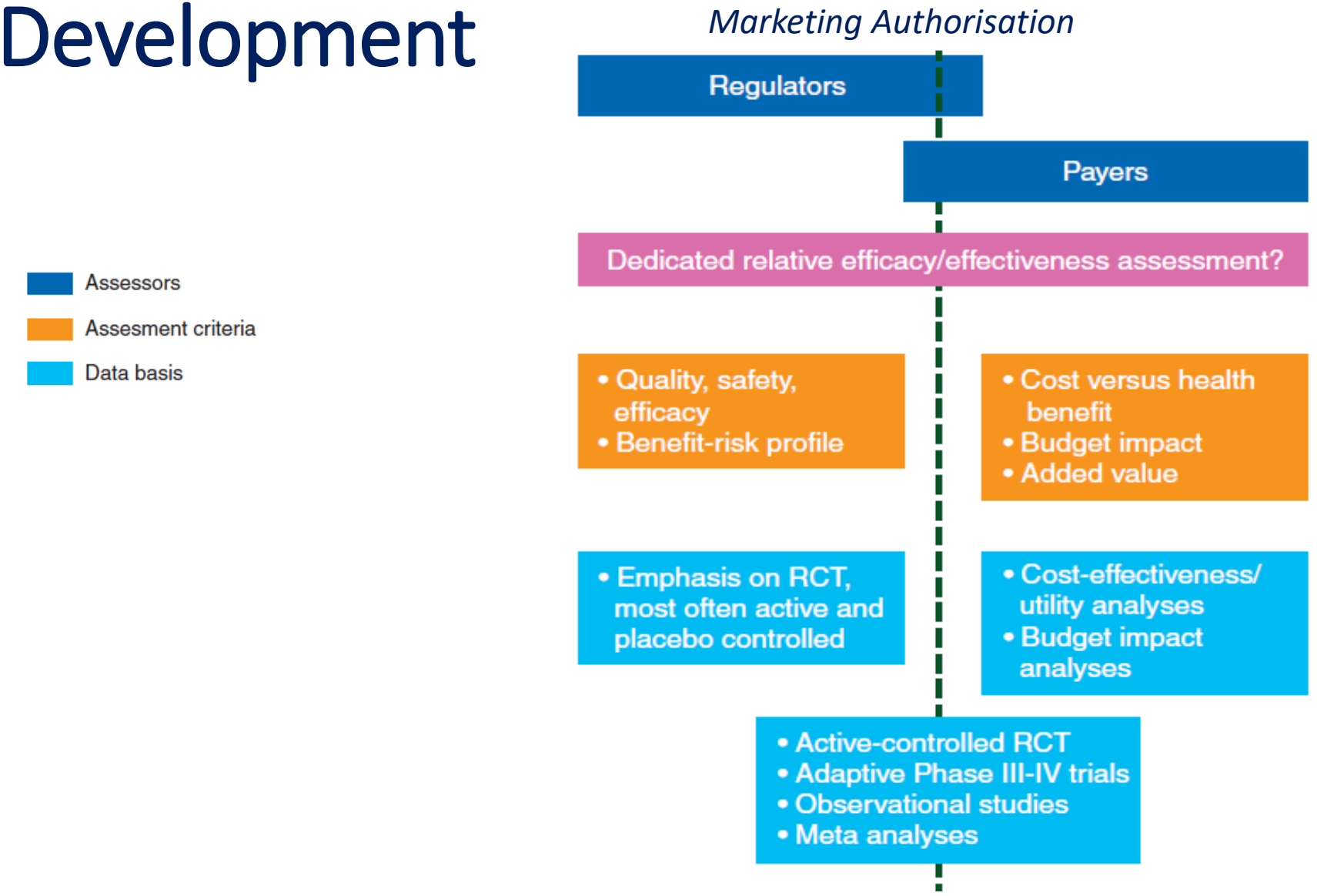
→

- Run SAT
- Run RWE Analyses

Issues with HTA/Reimbursement

- Single arm clinical trials are not widely accepted with HTAAs
- Endpoints such as ORR and PFS are also not widely accepted
- Real world evidence accepted under certain conditions
- Patient Populations are highly scrutinised
- Synthetic control arms not accepted
- Conditional approvals lead to difficult HTA/Pricing negotiations

How to Prevent HTA Issues already during Drug Development



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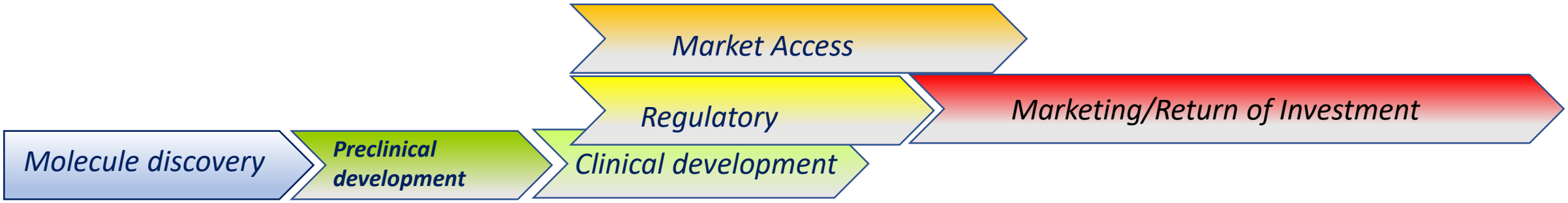
Future Chain of Drug Development



- Bringing promising drugs to patients in need faster
- Fulfilling regulatory and HTA requirements
- Possibly earlier marketing of drug

For your attention

Backup Slides

Regulators: Conditional Approval

- the medicine fulfils an unmet medical need;
- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.