# Japan Oncology Business


Taka Horii

Global Oncology Business Unit

Head of Japan Oncology Business Unit


February 25, 2021

Better Health, Brighter Future

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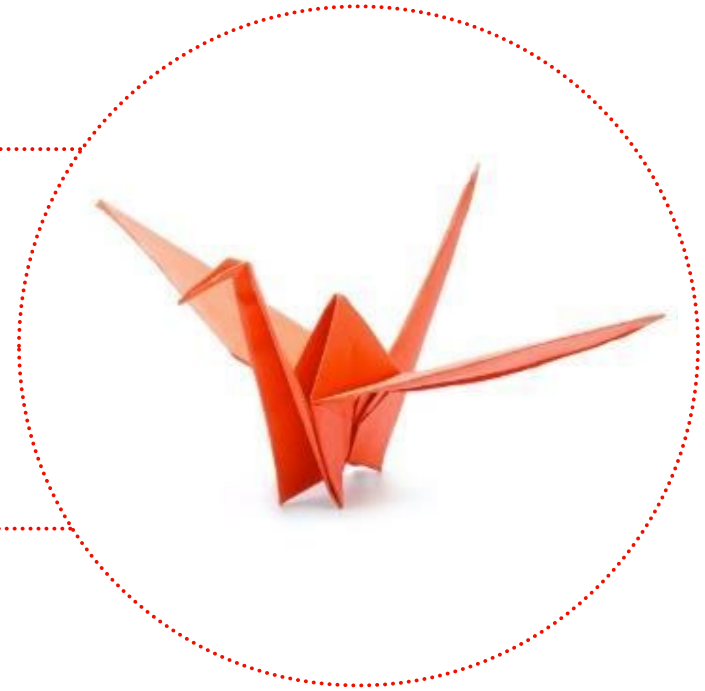
# VISION FOR TAKEDA ONCOLOGY

## VISION

"We aspire to cure cancer"

## AMBITION

Develop **transformative therapies,** built from **groundbreaking science, accelerated** by a **passionate team** united to **dramatically improve** the lives of people with cancer **around the globe**



# JAPAN ONCOLOGY BUSINESS

## We aspire to cure cancer for Japanese patients

### 1. Diverse Leadership Team

Experienced, diverse leadership team driving growth through innovation

### 2. Future Growth

Further growth acceleration by diverse and robust pipelines

### 3. Our Capability

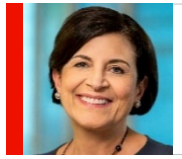
Track record on Clinical Development, Medical, Commercial and Digital

# 1. DIVERSE LEADERSHIP TEAM

## Takeda oncology is structured for agility in order to encourage innovation and market dynamism, our leaders have proven experience to drive future growth

**Christophe Weber**
President & CEO

**Teresa Bitetti**
President GOBU



**Rosa Notaroberto**
Chief of Staff

**Dion Warren**
Head of US OBU

**Takafumi Horii**
Head of Japan OBU

**Stefanie Granado**
Head of EUCAN OBU

**Sophie Opdyke**
Head of Global Commercial

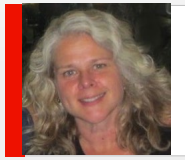
**Liz Lewis**
Head of Global Oncology Patient Value, Policy & Access

**Mauricio Silva de Lima**
Head of Global Oncology Medical Affairs

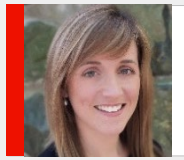
**Carrie Fernandez**
Head of Global Oncology Comms

**Fabien Dubois**
Head of Global Oncology Finance

**Ana Cardoso**
Head of Global Oncology HR

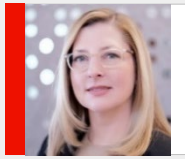


**Julie Dixon**
Head, Global Regulatory Affairs, Oncology



**Cristin McArdle**
Head, Global Oncology Legal Counsel

**Ana Paula Neves**
Head, E&C, OBU



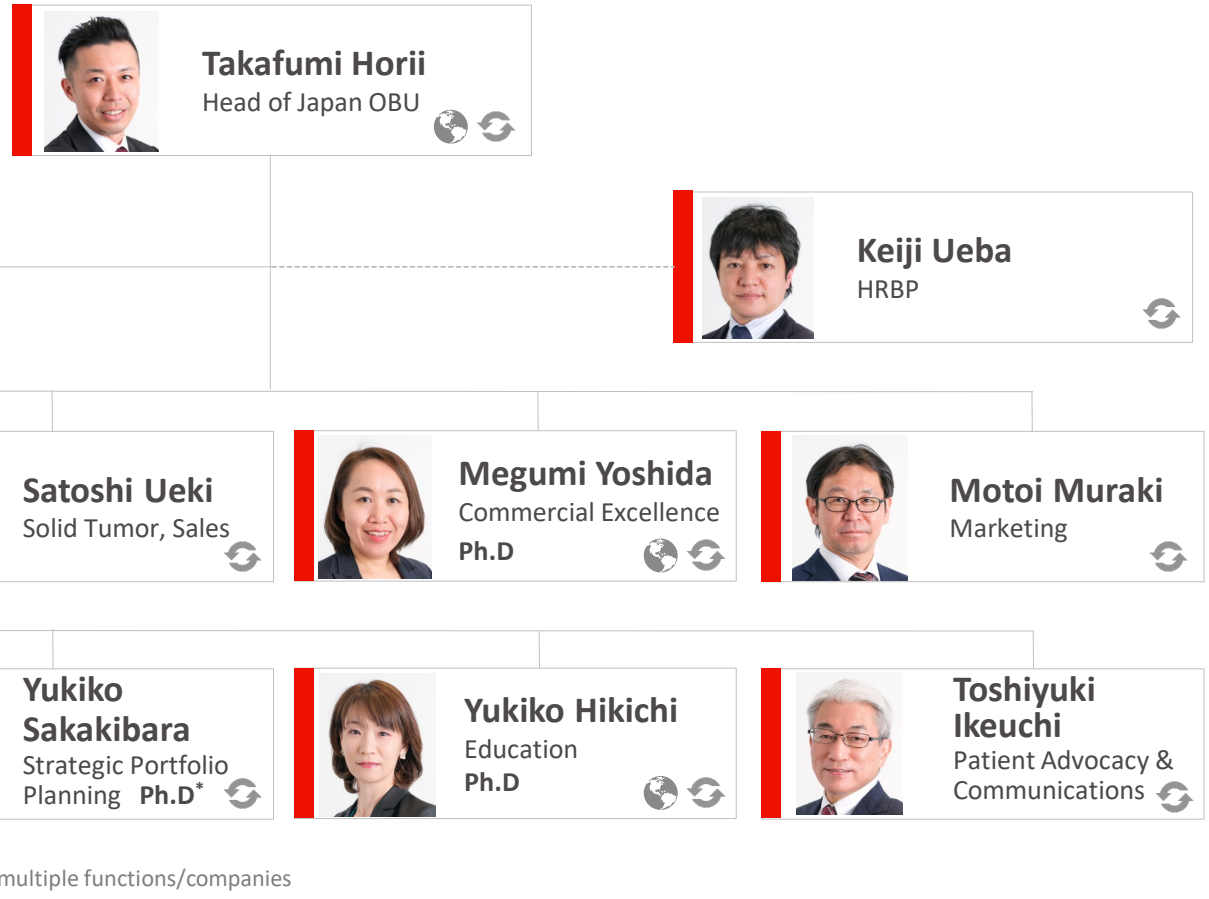
**Heather Huet**
Head of Oncology Strategic Operations

**Samer Ansari**
Head of IT & Digital


As of Dec. 2020

# 1. DIVERSE LEADERSHIP TEAM

## Our experienced and specialized leadership team is selected and supported to shepherd future growth




International experience  Experience in multiple functions/companies

**Masahiro Fujimaki**
Distribution & Regional Access

**Keiji Iwashita**
Market Access & Public Affairs

**Iwamoto Kenichi**
Regulatory Affairs

**Yukari Nishikata**
OTAU Japan & Asia

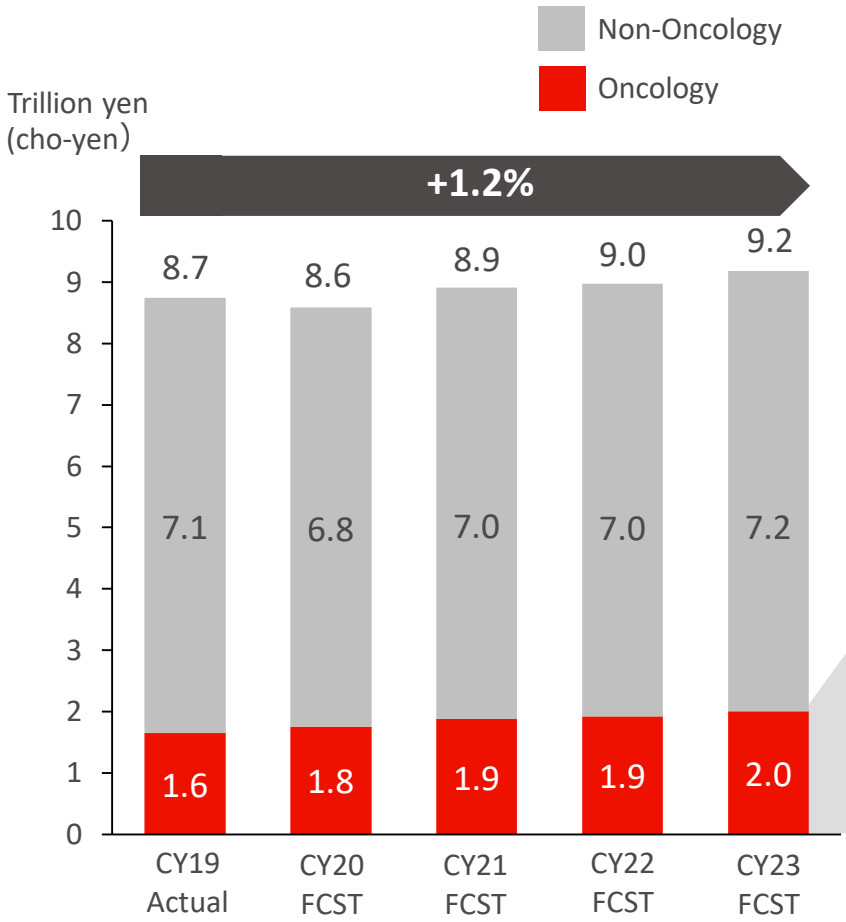
**Futoshi Yabuhana**
IT & Digital BP

**Ai Kokido**
Ethics & Compliance


* currently taking Ph.D. course

# 2. FUTURE GROWTH

## While total Japan market is expected to be flat, oncology market is expected to ＋5%




source: IQVIA Analytics Link Japan market by ATC code 20200819
Cancer Control and Information Service provided by National Cancer Center; 2019

**CAGR***
**CY19-23**

**+5.1%**

**JAPAN ONCOLOGY MARKET**

| Cancer type | CY23 (oku-yen) | CAGR* (18-23) |
|---|---|---|
| Lymphoma | 773 | 6.4% |
| Multiple myeloma | 1,179 | 5.7% |
| Leukemia | 1,146 | 9.2% |
| Lung | 3,422 | 3.6% |
| Colorectal | 1,285 | -2.2% |
| Renal Cell Carcinoma | 699 | 3.9% |
| Hepatocellular Carcinoma | 295 | 11.0% |
| Gynecologic (e.g. Ovarian) | 289 | 10.5% |
| Prostate | 1,693 | 0.3% |

source: Excerpt from Ethical drug data book, Fuji-Keizai; 2019

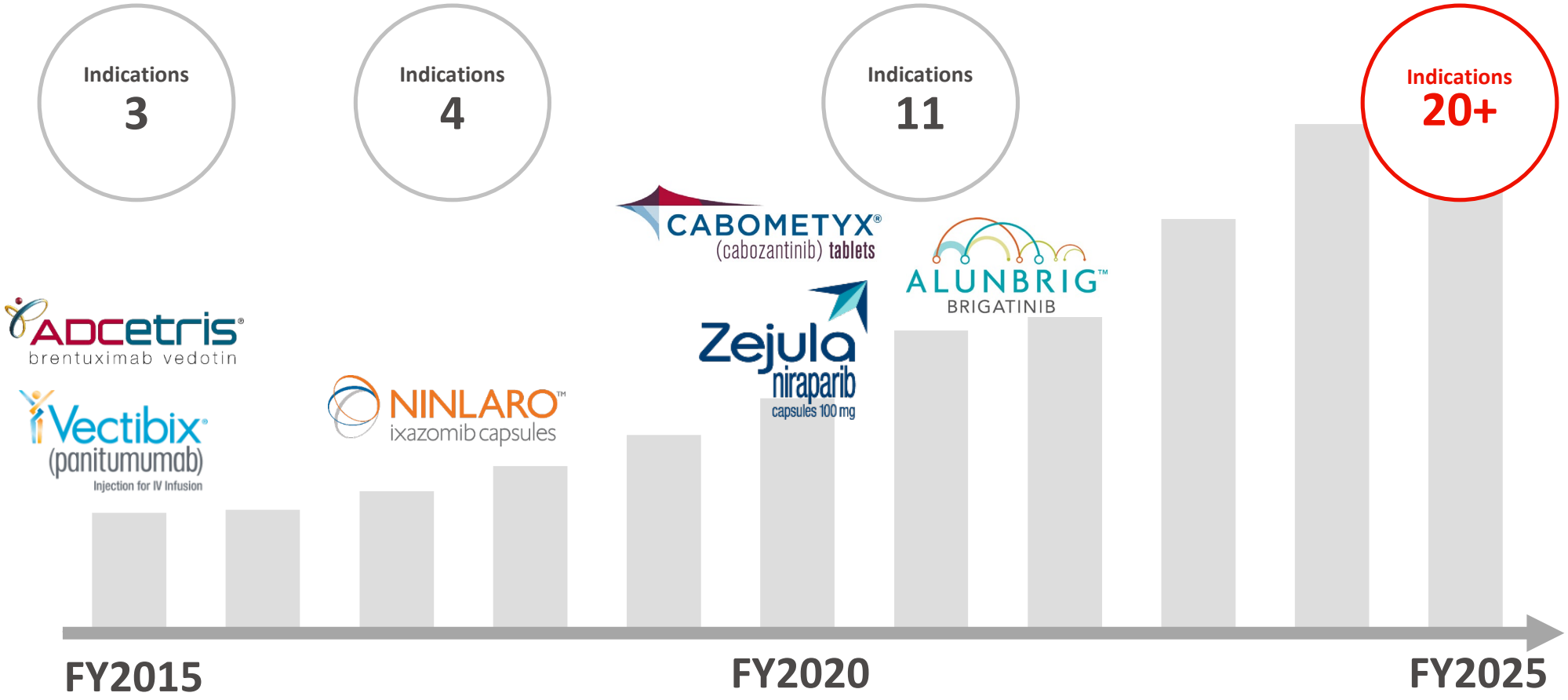
**(Reference)**
**JOBU related products**

| Product |
|---|
| Brentuximab vedotin |
| Ixazomib |
| Pevonedistat |
| Brigatinib Mobocertinib |
| Panitumumab |
| Cabozantinib |
| Cabozantinib |
| Niraparib |
| (Cabozantinib Niraparib) |

*CAGR: Compound Annual Growth Rate

# 2. FUTURE GROWTH

## Potential acceleration of future growth by providing patients with various treatment options by launching new products and adding new indications





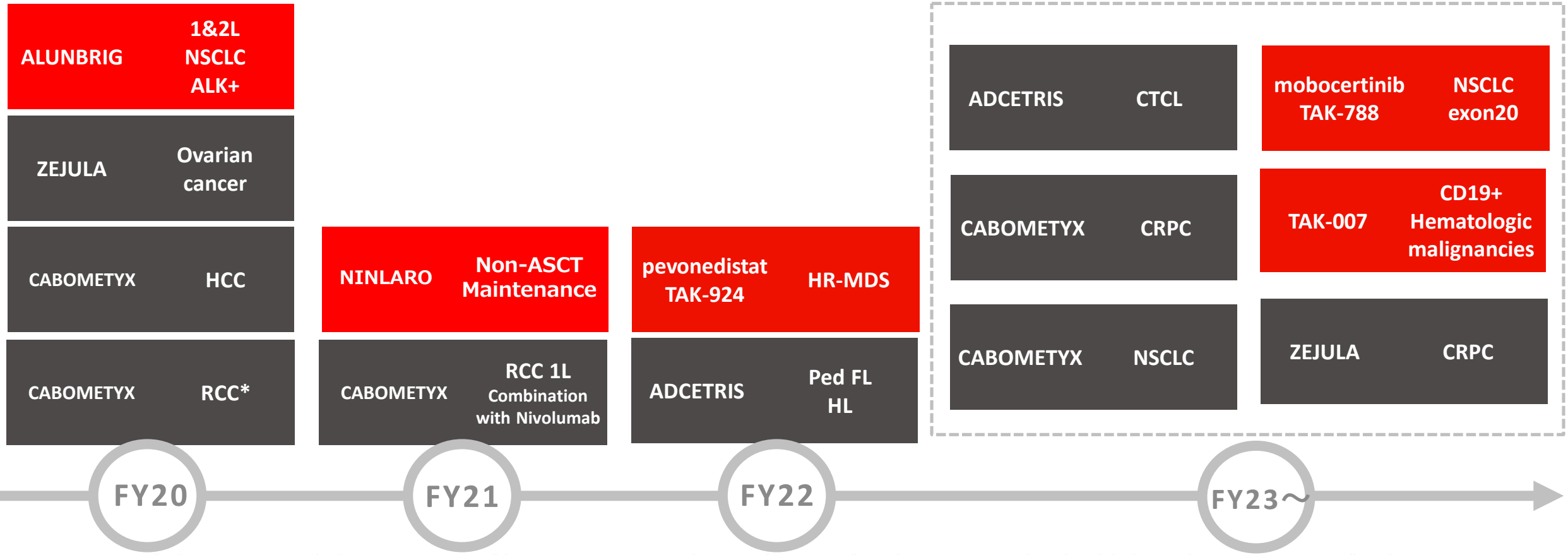

All timelines are approximate estimates as of February 25, 2021

# 2. FUTURE GROWTH

## Momentum in our diverse and robust pipelines contributing to unmet medical needs

Approval and additional indication of global brand

Approval and additional indication of Japan local brand






NSCLC: Non-Small Cell Lung Cancer, RCC: Renal Cell Carcinoma, HCC: Hepatocellular Carcinoma, Non-ASCT; Not Undergoing Autologous Stem Cell Transplantation, HR-MDS: Higher-Risk Myelodysplastic Syndromes, CTCL: Cutaneous T-cell Lymphoma, FL: Front Line, HL: Hodgkin Lymphoma, Ped: Pediatric, CRPC: Castration Resistant Prostate Cancer

Future indications after FY2021 are target approval dates and all timelines are approximate estimates as of February 25, 2021 *Approved in FY2019 (March 2020)

# 3. OUR CAPABILITY

## Track record on Clinical Development & Medical Affairs

### Innovative approach for providing cutting-edge treatments faster

- Bundle approach for multiple line application at the same time by leveraging global data
- Highly-innovative, unprecedented strategy characterized by complementary clinical data package
- Acceleration of the development from original development timeline

### Successful Partnership with key stakeholders

- Takeda-government-academia collaboration achieved;
  - New indication with investigator initiated study
  - Companion Diagnostics (CDx) development
  - POC study with investigators
- Talent exchange with key government offices*
- Strategic partnership agreement with National Cancer Center since 2015

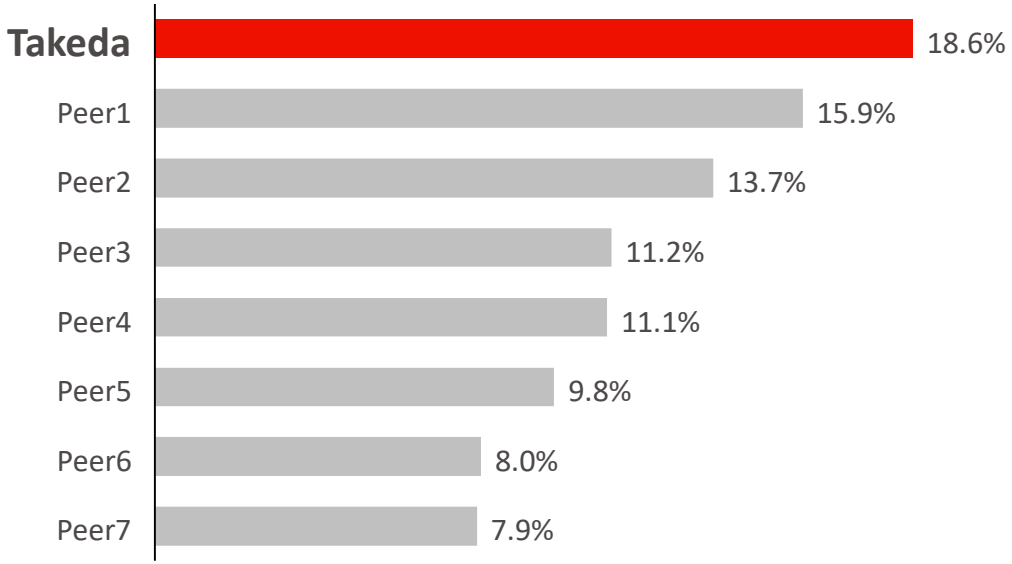

*Public-Private Exchange Program

# 3. OUR CAPABILITY

## Commercial's reputation

### Physicians' highest Reputation to MRs

**MR Reputation ranking (corporate power)**
Physicians market research (n=16,115)

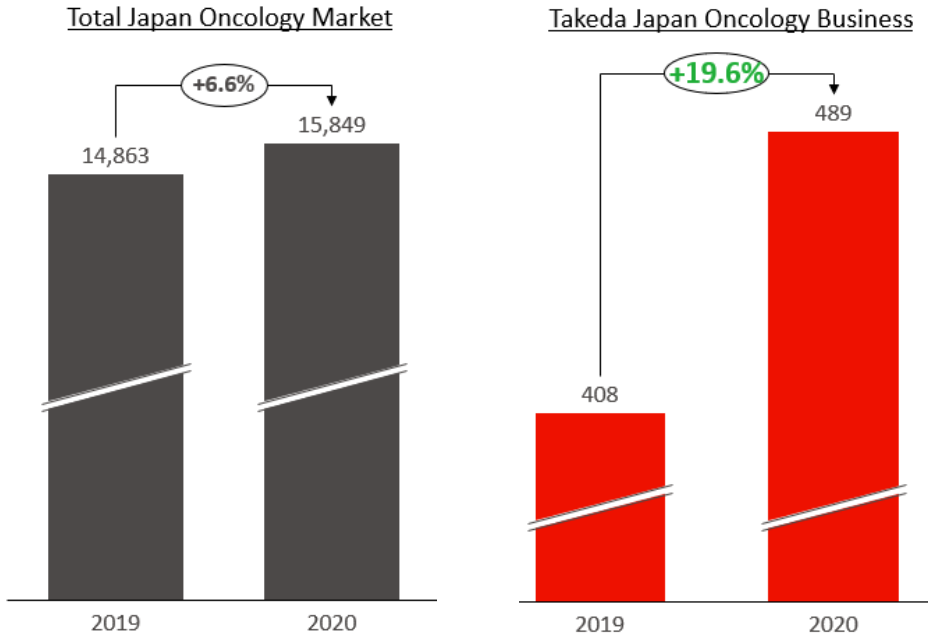



Source: Rep-i Aug 2020

### Japan Oncology Business outperformed against overall Japan oncology market

**Market growth comparison** (CY20 vs CY19)

Revenue, Unit:Oku-yen

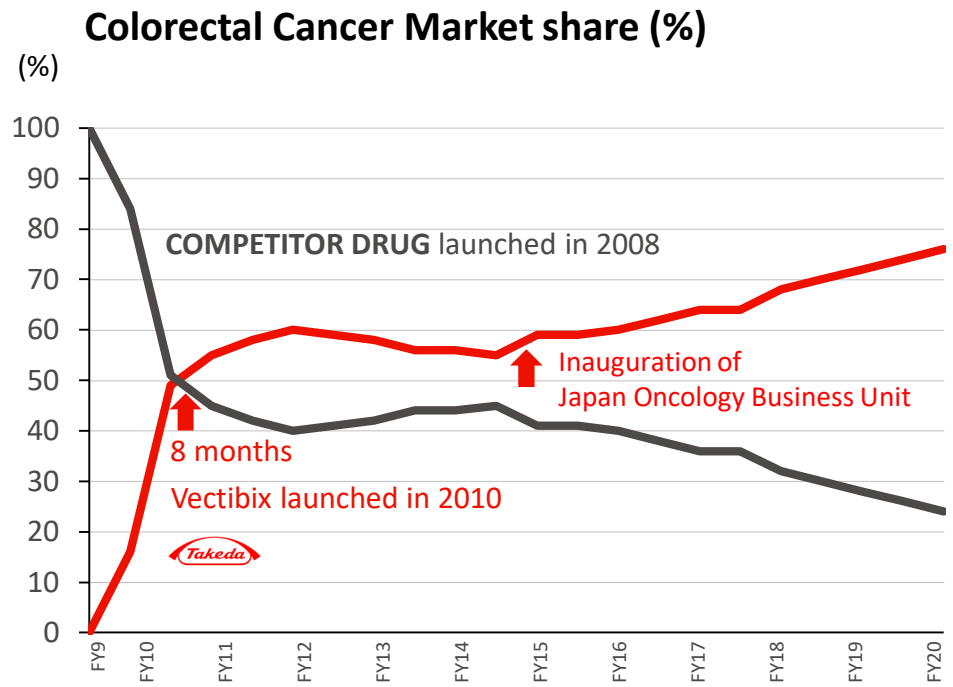



Source: IQVIA Market Prognosis, En-Cluster, NHI base

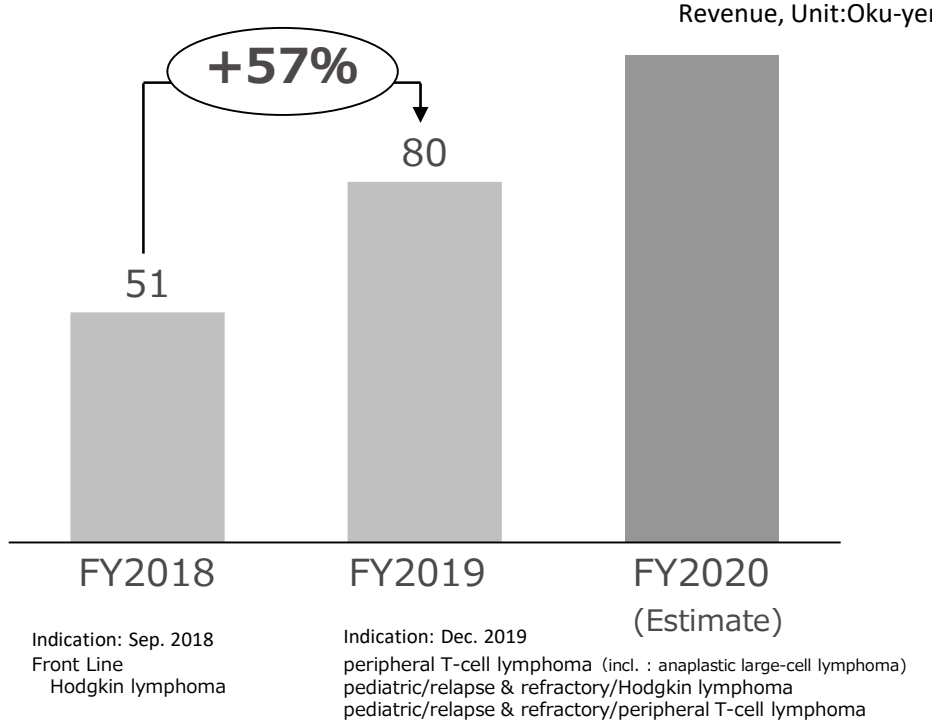
# 3. OUR CAPABILITY

## Commercial's reputation

### Track record of Vectibix in Japan




### Sustainable growth of Adcetris in Japan




Data Source : : JPM 2019.9/MDV analyzer , Brandscape (IQVIA), FY2018

# 3. OUR CAPABILITY

## Driving digital transformation

### NURTURE DIGITAL TALENT

43

**DIGITAL LEADS**

78

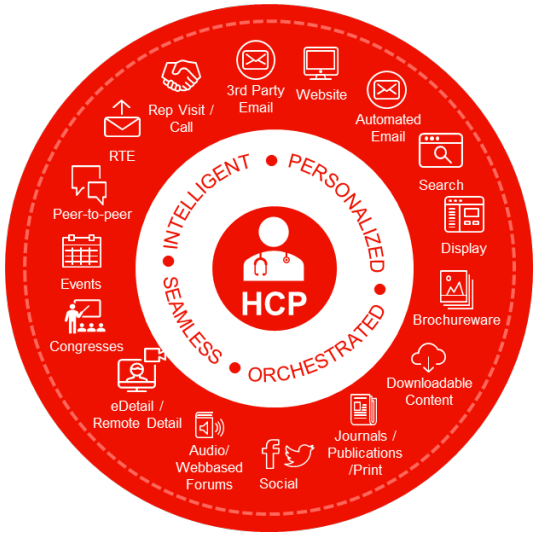
**IT PASSPORTS***
(as of January)

### OMNICHANNEL STRATEGY

Safety Dashboard

AI embedded
CRM system

Web Seminar




Electric Patient
Reported Outcome

Real World
Data/Evidence

 *National Certification

# 3. OUR CAPABILITY

## Transformation to a highly specialized organization for new products/indications, and a strategic focus of clinical research and talent resources

| | | FY2015 | | FY2020 |
|---|---|---|---|---|
| **Human Resource Investment** | Medical Affairs | 14 | ▶ | **42** |
| | Commercial* | 151 | ▶ | **379** |
| | | | | Number of employees |
| **Research from Japan** | Clinical research conducted/supported by Medical Affairs (Japan) | 6 | ▶ | **21** |
| | | | | Number of clinical researches |
| **Strengthening of MR expertise** | Sales Organization | Geographic Focus | ▶ | **Therapeutic Area Focus** |


*Commercial: Sales + Marketing + Commercial Excellence

# A VALUES-BASED AND R&D-DRIVEN BIOPHARMACEUTICAL LEADER

**PURPOSE**

Better health for people, brighter future for the world

**VISION**

Discover and deliver life-transforming treatments, guided by our commitment to patients, our people and the planet

**VALUES**

We are guided by our values of Takeda-ism which incorporate **Integrity, Fairness, Honesty,** and **Perseverance,** with Integrity at the core. They are brought to life through actions based on **Patient-Trust-Reputation-Business,** in that order

## IMPERATIVES

### PATIENT

- Responsibly translate science into highly innovative, life-changing medicines and vaccines
- Accelerate access to improve lives worldwide

### PEOPLE

- Create an exceptional people experience

### PLANET

- Protect our planet

### UNLEASH THE POWER OF DATA AND DIGITAL

- We strive to transform Takeda into the most trusted, data-driven, outcomes-based biopharmaceutical company

# Brigatinib

Kei Hiraoka, M.D., Ph.D., Medical Director
Japan Oncology Business Unit
February 25, 2021

Better Health, Brighter Future

# AGENDA

## Today's Topics

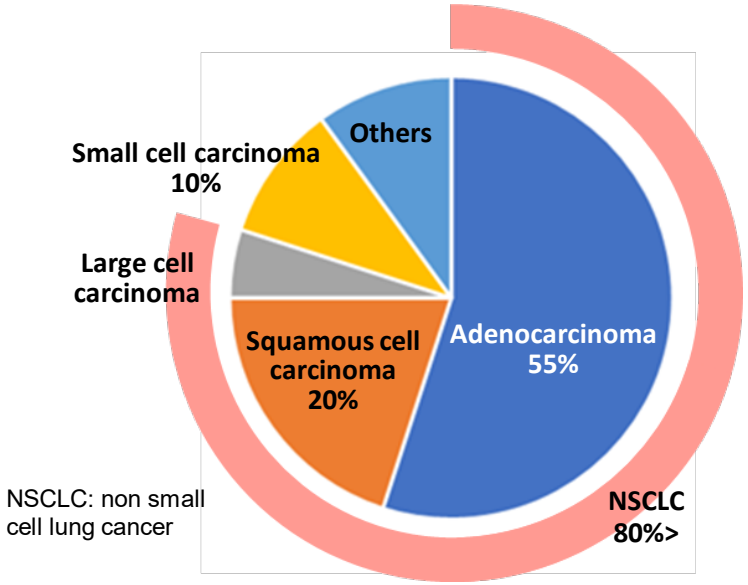
1. **Disease Epidemiology Information**
2. Overview and Mode of Action
3. Clinical Trials & Data
4. Product Positioning

# ALK+ NSCLC: DISEASE, EPIDEMIOLOGY INFORMATION

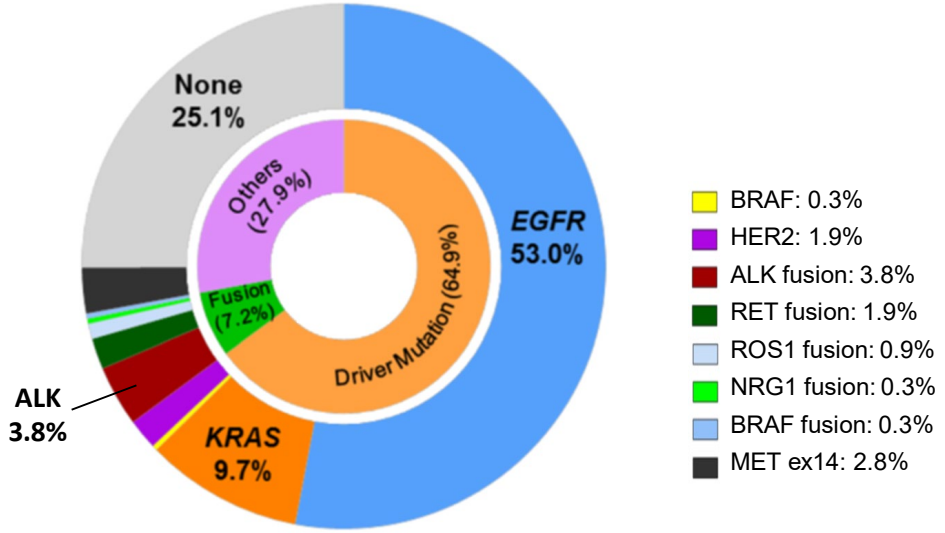
**ALK+ NSCLC Prevalence**

- Lung cancer is the leading cause of cancer death (**77,500**) and the number of cases is increasing (**125,100**) in Japan (2018).
- Non-small cell lung cancer (NSCLC) accounts for about 80-90% and lung adenocarcinoma accounts for about 55% of of all lung cancers.
- Approximately 2-5% of patients with NSCLC have a rearrangement in the ALK gene, identified specifically for adenocarcinoma.

## Lung Cancer




## Lung Adenocarcinoma




National Cancer Center (Japan)



National Cancer Center Council Membership Facility: Histologic Lung cancer Incidence (2006-2008).

Saito M, et al. Cancer S c i. 2016;107（6）:713-720.(modified)

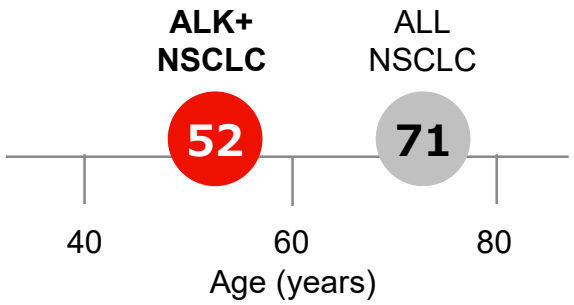
# ALK+ NSCLC: DISEASE, EPIDEMIOLOGY INFORMATION

## ALK+ NSCLC Disease Overview

- ALK+ NSCLC is a unique subset of lung cancer caused by a mutation in the anaplastic lymphoma kinase (ALK) gene.
- Histologically, adenocarcinoma is predominant. ALK-translocation is extremely rare in other histological types.
- ALK+ NSCLC on average affects younger people (median age at diagnosis is 52) and is not associated with a history of smoking.

## PATIENT CHARACTERISTICS

There are no apparent racial differences, unlike in EGFR gene mutations




Patients with ALK+ NSCLC are commonly still of **working age and contributing to society**

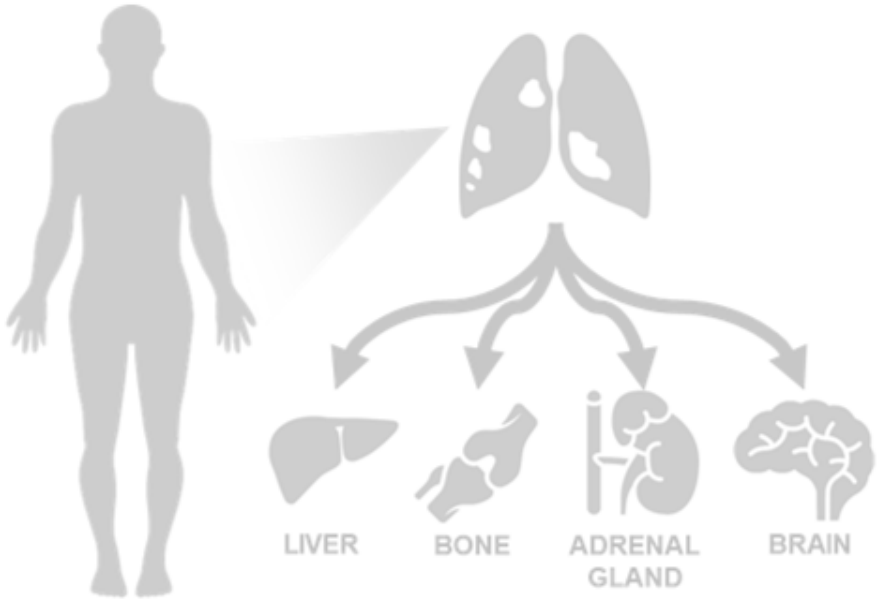
**ALK+ NSCLC is not associated with smoking**, as most patients have no or a light smoking history (<10 pack years)



1. Guidance for ALK Gene Testing in Lung Cancer Patients v3.1, 2/18/2019: Biomarker Committee, the Japan Lung Cancer Society. 2. Chia PL, et al. Clin Epidemiol. 2014;6:423-432. 3. Passaro A, et al. OncoTargets and therapy. 2016;9:6361-6376. 4. Subramanian J, et al. J Thorac Oncol. 2010;5(1):23-8.

# ALK+ NSCLC: DISEASE, EPIDEMIOLOGY INFORMATION

ALK+ NSCLC is a debilitating and progressive disease that is associated with poor survival rates

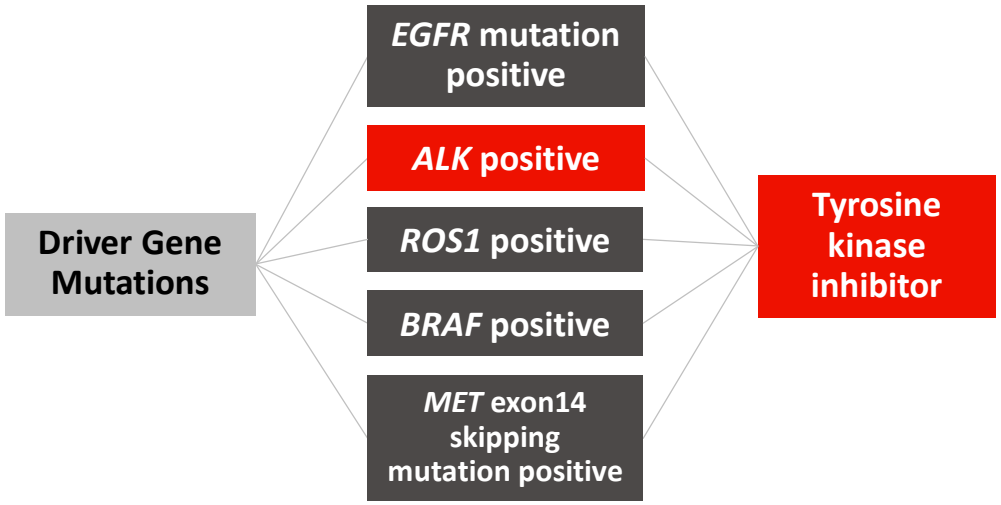



- ALK+ NSCLC patients face a **poor prognosis**, and almost all develop **tumor progression** and **eventually die** from their condition[1,2]
- Most patients who experience **systemic progression** will do so at **multiple sites**[3]
- Stage IV ALK+ NSCLC patients have a **median overall survival rate** of approximately **6.8 years in the U.S.**, and this rate is **associated with the number of organs with tumors at diagnosis**[4]
- The most **common sites** of NSCLC **metastases** are the **brain, bone, liver**, and **adrenal glands**, with **ALK+ NSCLC patients at higher risk** of developing **brain metastases** than patients of other subtypes[5,6]


. Notes: *Patients in this research were treated with crizotinib as their initial ALK inhibitor. Abbreviations: ALK, anaplastic lymphoma kinase. References: 1. Kayaniyil S. Current Oncology. 2016; 2. Du X. Thoracic Cancer. 2018; 3. Rothenstein J. Curr Onc. 2018; 4. Pacheco J. JTO. 2018; 5. West A. Case Rep Clin Pathol. 2014; 6. Petrelli F. PLoS One. 2018.

# ALK+ NSCLC: DISEASE, EPIDEMIOLOGY INFORMATION

Most diagnosed first-line ALK+ patients receive ALK inhibitors in Japan



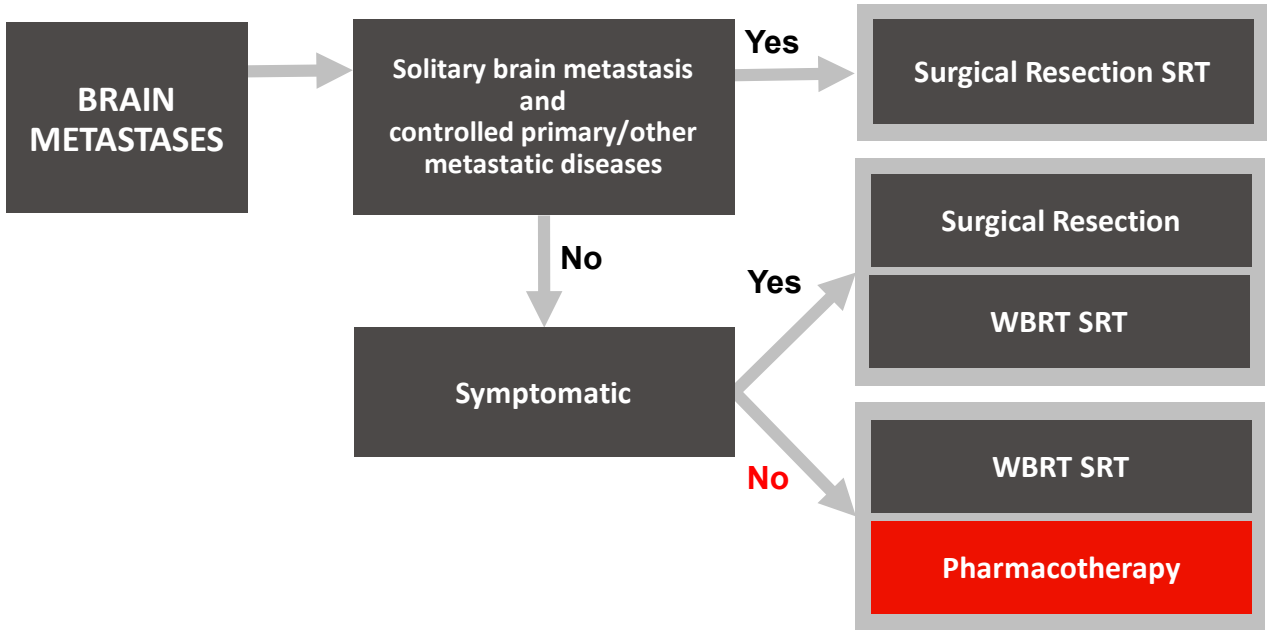

Approved agents in Japan, the United States and European Union that specifically target ALK rearrangements include:

- Crizotinib
- Ceritinib
- Alectinib
- Lorlatinib
- **Brigatinib**


Clinical Guidelines of Lung Cancer based on EBM (2020): the Japan Lung Cancer Society, https://www.haigan.gr.jp/modules/guideline/index.php?content_id=3 Accessed on 11/20/2020

# ALK+ NSCLC: DISEASE, EPIDEMIOLOGY INFORMATION

Current management of brain metastasis in Japan




**SRT, stereotactic radiation therapy; WBRT, whole-brain radiation therapy**

Pharmacotherapy is recommended for asymptomatic brain metastases in Japanese Clinical Guidelines of Lung Cancer based on EBM (evidence-based medicine)


Clinical Guidelines of Lung Cancer based on EBM (2020): the Japan Lung Cancer Society, https://www.haigan.gr.jp/modules/guideline/index.php?content_id=3 Accessed on 11/20/2020

# AGENDA

## Today's Topics

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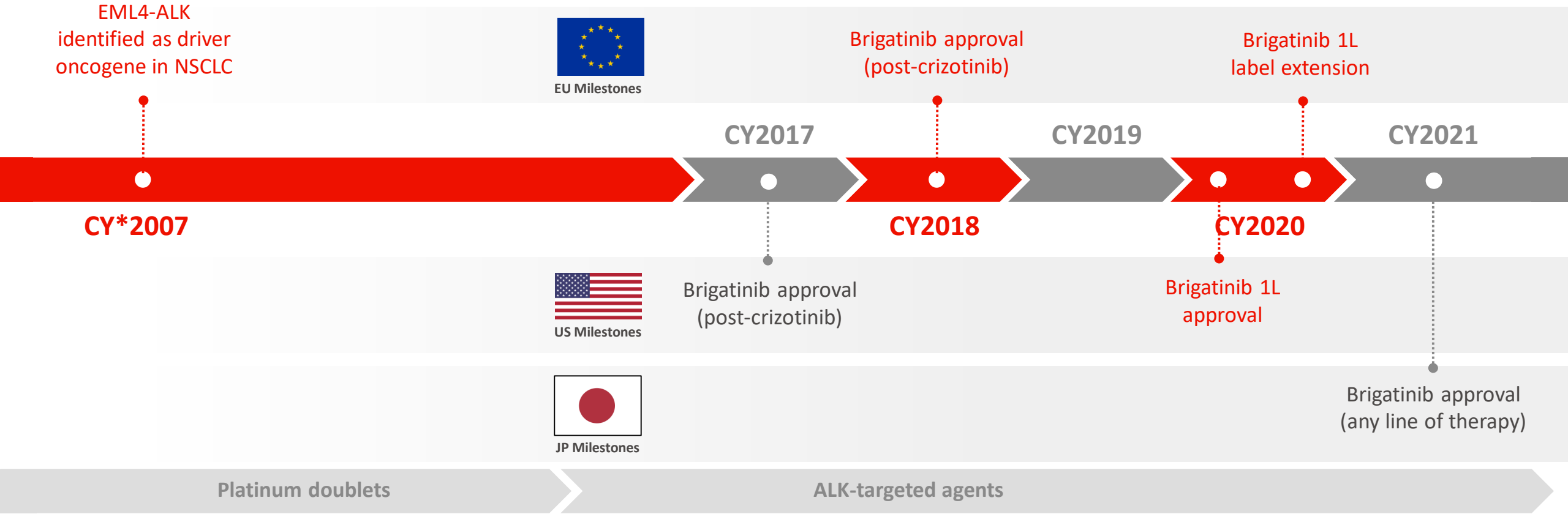
# HISTORICAL OVERVIEW OF BRIGATINIB

**In Japan, Brigatinib was approved for adult patients with ALK positive advanced/metastatic non-small cell lung cancer (NSCLC) for first- and second-line settings in Jan 2021**




Clinical Guidelines of Lung Cancer based on EBM (2020): the Japan Lung Cancer Society, https://www.haigan.gr.jp/modules/guideline/index.php?content_id=3 Accessed on 11/20/2020

*CY：Calendar Year

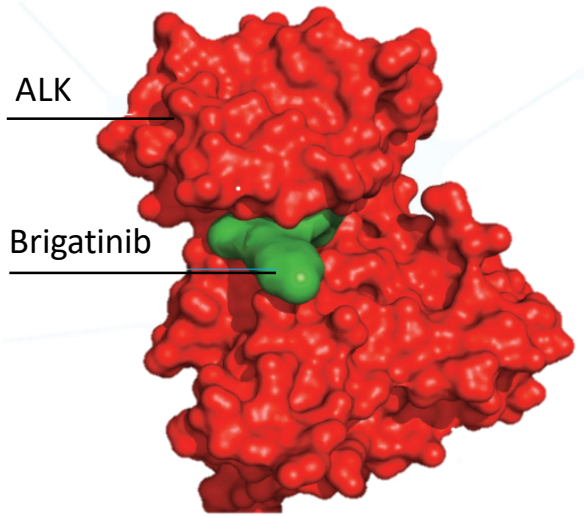
# MODE OF ACTION

Brigatinib is a small-molecule inhibitor that was designed to target ALK molecular alterations in NSCLC[1-3]

## BRIGATINIB OVERVIEW

| | |
|---|---|
| **Mode of Action** | • Brigatinib binds to the ATP-binding site of ALK[1,2]<br>• Key structural features of brigatinib contribute to its **potency** and **selectivity**<br>• Brigatinib demonstrated greater potency than crizotinib in ALK inhibition in vitro and in vivo[1]<br>• Brigatinib demonstrated greater CNS activity compared with crizotinib in an orthotopic mouse ALK+ brain tumor model[1] |

**Brigatinib-ALK Complex**




 CNS, central nervous system. 1. Zhang S, et al. Clin Cancer Res. 2016;22:5527-5538; 2. Huang WS, et al. J Med Chem. 2016;59:4948-4964; 5. Brigatinib investigator brochure 2015.

# BRIGATINIB PRECLINICAL INHIBITORY ACTIVITY AGAINST ALK AND OTHER KINASES

In preclinical studies, brigatinib was found to be a potent and selective inhibitor when screened against 289 kinases

- Potent against native ALK, with an IC50 of 0.6 nmol/L in a kinase assay
- Demonstrated activity against resistant ALK mutants, including L1196M, C1156Y, F1174L, and G1202R
- Overall selectivity, with only 8 other kinases (of > 250 tested) inhibited with IC50 < 10 nmol/L
  - ROS1, FLT3, FER, FES, FAK/PTK2, PTK6, TSSK1, and CHEK2
- Similar results were observed in cellular assays

**Brigatinib Preclinical Inhibitory Activity Against Native ALK, Resistant ALK Mutations, and Other Kinases**

| Kinase | Kinase Assay $IC_{50}$, nmol/L | Cellular Assay $IC_{50}$, nmol/L |
|---|---|---|
| ALK | 0.6 | 14 |
| ALK (C1156Y) | 0.6 | 45 |
| ALK (F1174L) | 1.4 | 55 |
| ALK (L1196M) | 1.7 | 41 |
| ALK (G1202R) | 4.9 | 184 |
| ALK (R1275Q) | 6.6 | ND |
| ROS1 | 1.9 | 18 |
| ROS1 (L2026M) | — | 17 |
| ROS1 (G2032R) | — | 1100 |
| FLT3 | 2.1 | 158 |
| FLT3 (D835Y) | 1.5 | 211 |
| EGFR | 67 | > 3000 |
| EGFR (L858R) | 1.5 | 397 |
| EGFR (L858R/T790M) | 29 | 489 |
| IGF-1R | 73 | 148 |
| INSR | 160 | 9331 |
| MET | > 1000 | ND |



The kinase assay was conducted in the presence of 10 µmol/L [33P]-ATP using brigatinib concentrations ranging from 0.05 nmol/L to 1 µmol/L. Zhang S, et al. Clin Cancer Res. 2016;22:5527-5538.

# AGENDA

## Today's Topics

1. Disease Epidemiology Information
2. Overview and Mode of Action
3. **Clinical Trials & Data**
4. Product Positioning

# CLINICAL TRIALS OF BRIGATINIB

| | First Line | Second Line+ |
|---|---|---|
| **Japan Trials** | | **Study 2001 (J-ALTA)**<br>Single arm Phase 2 study in Japanese patients with ALK+ NSCLC<br>***Met primary endpoint Jun 2020*** |
| **Global Trials** | | **ALTA**<br>Randomized Phase 2 study in Crizotinib-Refractory ALK+ NSCLC<br>***Met primary endpoint Jun 2016*** |
| | **ALTA-1L**<br>Randomized Phase 3 study in ALK+ NSCLC naive to ALK inhibitors<br>***Met primary endpoint Jul 2018*** | **ALTA 2**<br>Single-arm trial evaluating brigatinib in patients with advanced ALK+ NSCLC who have progressed on alectinib or ceritinib<br>***Data expected Jul 2021*** |
| | | **ALTA 3**<br>Randomized trial comparing the efficacy and safety of brigatinib versus alectinib in participants with ALK+ NSCLC who have progressed on crizotinib<br>***Data expected Dec 2022*** |

# ALTA-1L: open-label, multicenter, randomized, international, phase 3 trial conducted in 20 countries.

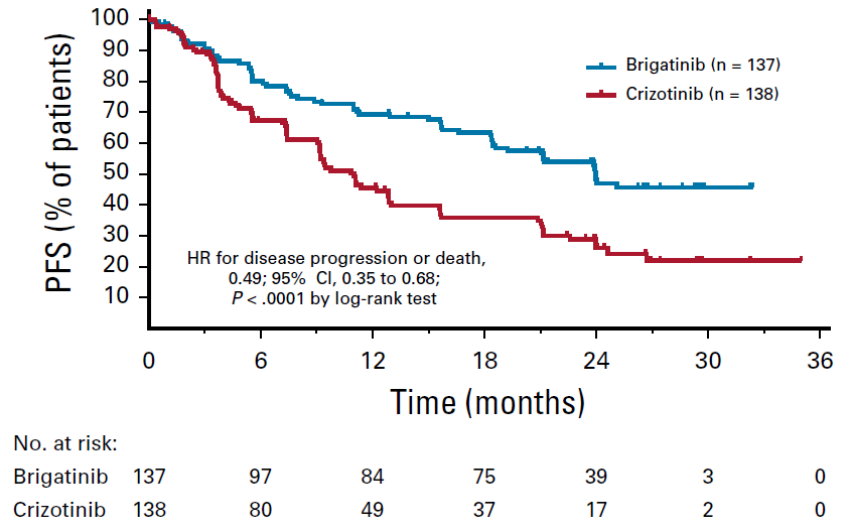
## BRIGATINIB OVERVIEW

In the Phase 3 ALTA 1L trial, brigatinib demonstrated*:

- Superior long-term efficacy compared to crizotinib with a median PFS of 24.0 months (95% CI: 18.5–NE) versus 11.0 months (95% CI: 9.2–12.9) for crizotinib.

*The primary end point was PFS as assessed by blind independent review committee (BIRC).

## PFS




| IRC-Assessed PFS | Median PFS (95% CI), months | HR (95% CI) | 2-Year PFS Rate (95% CI), % |
|---|---|---|---|
| Brigatinib (n = 137) | 24.0 (18.5-NR) | **0.49** (0.35-0.68) *P* < .0001 | 48 (39-57) |
| Crizotinib (n = 138) | 11.0 (9.2-12.9) | | 26 (18-35) |


PFS, progression-free survival; CI, confidence interval; HR, hazard ratio.

Camidge DR, et al. N Engl J Med. 2018;22:2027-2039.

# ALTA-1L: strong efficacy in patients with brain metastases

Brigatinib significantly improved PFS in patients with baseline brain metastases vs. crizotinib

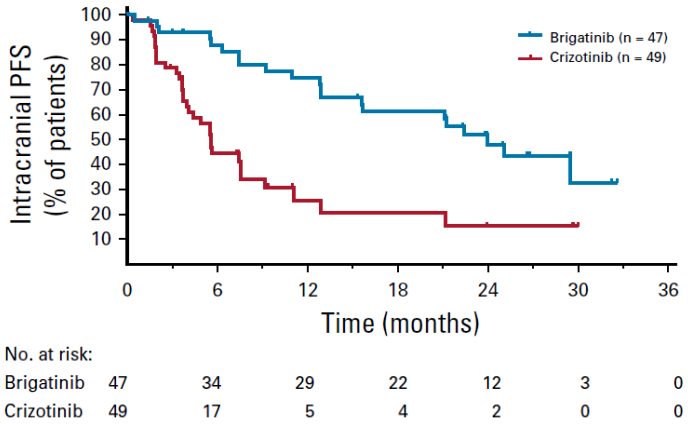
- The CNS is a known sanctuary site in advanced ALK+ NSCLC, with higher rates of brain metastases observed in patients with ALK+ NSCLC than in those with NSCLC with other driver mutations[1-5]
- Treatment options for patients with brain metastases include surgical resection, radiotherapy (SRS or WBRT), and ALK TKIs[1]

## BRIGATINIB OVERVIEW

Intracranial PFS rate at 2 years by BIRC assessment in patients with baseline brain metastases was 48% with brigatinib and 15% with crizotinib[6]

Intracranial **PFS**

**BIRC-Assessed Intracranial PFS: Patients With Brain Metastases at Baseline (ALTA-1L study)**




| BIRC-Assessed PFS | Median PFS (95% CI), months | HR (95% CI) | 2-Year PFS Rate (95% CI), % |
|---|---|---|---|
| Brigatinib (n = 47) | 24.0 (12.9-NR) | **0.31** (0.17-0.56) *P* < .0001 | 48 (30-63) |
| Crizotinib (n = 49) | 5.6 (3.7-7.5) | | 15 (5-32) |



BIRC, blind independent review committee; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; SRT, stereotactic radiation therapy; WBRT, whole-brain radiation therapy. 1. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. V3.2020; 2 Zhang I, et al. Lancet Oncol. 2015;16:e510-e521; 3. Johung KL, et al. J Clin Oncol. 2016;34:123-129; 4. Rangachari D, et al. Lung Cancer. 2015;88:108-111; 5. Drilon A, et al. J Thorac Oncol. 2018;13:1595-1601. 6. Camidge DR, et al. J Clin Oncol. 2020;38:3592-3603.

# ALTA-1L: Dose Reductions and Modifications

- Dose modifications for the brigatinib arm were required by protocol for any grade 3/4 nonhematologic toxicity, including laboratory abnormalities
  - Protocol-mandated dose modifications for crizotinib were less stringent
  - Dose reductions in the brigatinib arm were mainly due to protocol-mandated laboratory abnormalities
- 12% of patients in the brigatinib arm and 9% of patients in the crizotinib arm discontinued due to AEs
- No treatment-related deaths occurred in either arm

| TEAEs Leading to Dose Reduction, n (%) | Brigatinib (n = 136) | Crizotinib (n = 137) |
|---|---|---|
| ≥ 1 TEAE | 39 (28.7) | 29 (21.2) |
| Increased blood CPK | 14 (10.3) | 2 (1.5) |
| Increased ALT | 1 (0.7) | 8 (5.8) |
| Increased AST | 2 (1.5) | 1 (0.7) |
| Increased lipase | 7 (5.1) | 1 (0.7) |
| Increased amylase | 4 (2.9) | 0 |
| Nausea | 1 (0.7) | 6 (4.4) |
| Diarrhea | 0 | 3 (2.2) |
| Decreased appetite | 1 (0.7) | 2 (1.5) |
| Vomiting | 0 | 2 (1.5) |
| Peripheral edema | 0 | 3 (2.2) |
| Pneumonitis | 2 (1.5) | 1 (0.7) |
| Hypertension | 2 (1.5) | 0 |
| Pruritic rash | 2 (1.5) | 0 |


Data cutoff: February 19, 2018. Median follow up: 11.0 months in the brigatinib arm and 9.3 months in the crizotinib arm. Camidge DR, et al. J Clin Oncol. 2020;38:3592-3603.

# J-ALTA: single-arm, multicenter, phase 2, open-label study in Japanese patients

## BRIGATINIB OVERVIEW

In the Phase 2 J-ALTA trial, brigatinib demonstrated*:

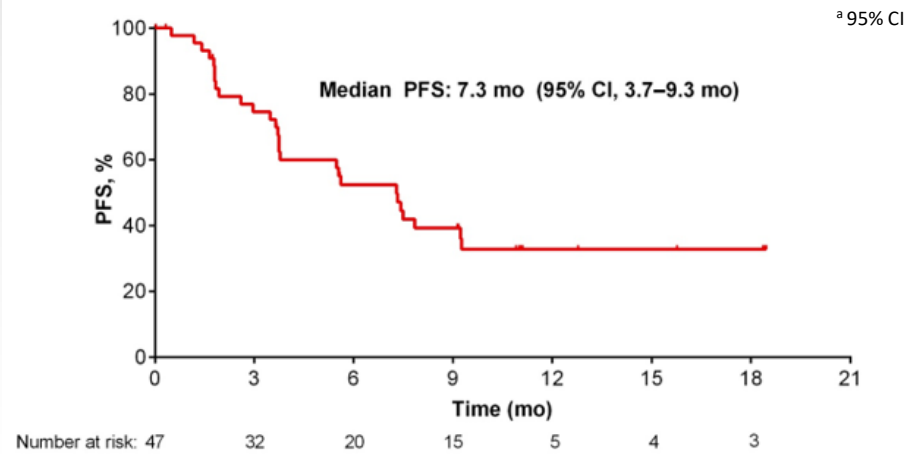
- Clinically meaningful efficacy, with IRC-assessed confirmed ORR of 31%, DCR of 79%, and median PFS of 7.3 months at the primary analysis in patients who had progressed on alectinib with or without prior crizotinib
- Brigatinib demonstrated intracranial objective responses (intracranial ORR, 25%) in alectinib-refractory patients with brain metastases

*The primary end point was confirmed ORR as assessed by independent review committee.

## ORR

| IRC-Assessed Systemic Objective Response | Post-Alectinib ± Crizotinib (Main Cohort) n=47 | All ALK TKI-Refrectory Patients n=72 |
|---|---|---|
| Confirmed ORR, % (n/N)<br>Confirmed CR, %<br>Confirmed PR, % | 30 (14/47)<br>0<br>30 | 31 (20-43)[a]<br>0<br>31 |
| DCR, % (95% CI) | 79 (64-89) | 74 (62-83) |

## PFS




[a] 95% CI



ORR, objective response ratio; DCR, disease control ratio; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio. Nishio M, et al. J Thorac Oncol. 2020;S1556-0864(20)31026-1.
a 95% CI

# J-ALTA: Treatment-Emergent Adverse Events (TEAEs) at Primary Analysis

- As of the primary analysis, one death due to TEAEs had been reported (respiratory failure due to disease progression; not drug related)
- Discontinuation of brigatinib due to TEAEs was reported in 4 (6%) of 72 patients
- Median dose intensity was 170 mg/day (range, 62–179 mg/day)
- ILD/pneumonitis
  - Six patients had at least one ILD/pneumonitis event Worst severity: Grade 1, n=1; grade 2, n=4; grade 3, n=1
  - Most ILD/pneumonitis cases improved after brigatinib discontinuation with or without steroid treatment

| TEAEs (Any Grade) in >15% of All Pateints or Grade ≥3 Reported in >2 Patients | Brigatinib 90 mg → 180 mg qd | |
|---|---|---|
| | Any Grade, % | Grade ≥3, % |
| Increased blood CPK[a] | 75 | 18 |
| Diarrhea | 43 | 0 |
| Hypertension | 39 | 11 |
| Nausea | 38 | 0 |
| Increased lipase[b] | 33 | 14 |
| Increased amylase[b] | 31 | 4 |
| Increased AST | 29 | 1 |
| Stomatitis | 26 | 1 |
| Headache | 18 | 1 |
| Increased ALT | 18 | 0 |
| Rash | 17 | 1 |
| Lung infection | 8 | 4 |
| Dyspnea | 6 | 4 |


a Neither myalgia nor musculoskeletal pain of any grade was reported in any patients; b No clinical cases of pancreatitis were reported. Nishio M, et al. J Thorac Oncol. 2020;S1556-0864(20)31026-1.

# ONGOING CLINICAL TRIALS IN JAPAN

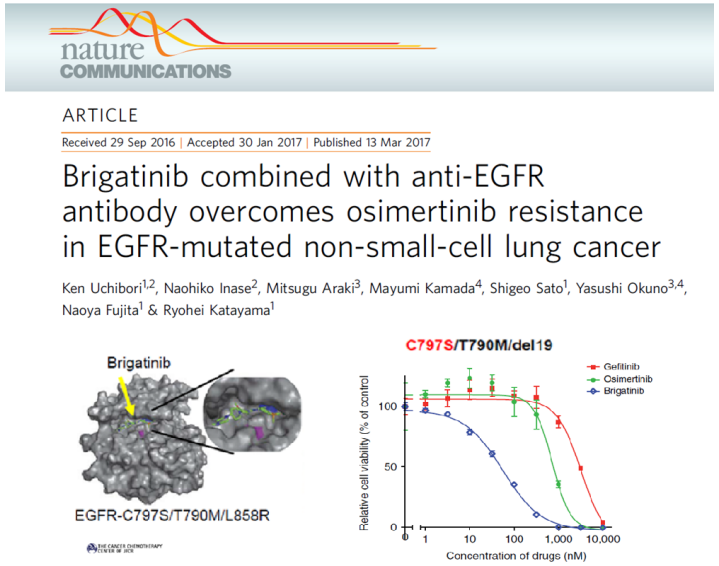
- Various investigator-initiated clinical trials are being conducted in Japan based on non-clinical data
- One study is currently ongoing and three studies are already approved for activation in 2021

## Brigatinib basket study in patients with advanced solid tumors with ROS1 rearrangement（JapicCTI-194851）

Multicenter, open-label, single-arm, basket study of oral brigatinib treatment consisting of 3 cohorts:

- Cohort 1: crizotinib-naive patients with ROS1-positive NSCLC
- Cohort 2: crizotinib-treated ROS1-positive NSCLC
- Cohort 3: patients with ROS1-positive solid tumors other than lung cancer

## Brigatinib combined with Panitumumab for EGFR C797S NSCLC (Phase1/2 study)



# AGENDA

## Today's Topics

1. Disease Epidemiology Information
2. Overview and Mode of Action
3. Clinical Trials & Data
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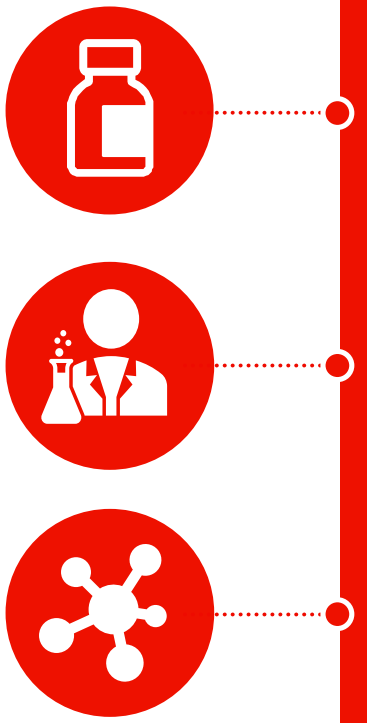
# PRODUCT POSITIONING IN JAPAN



- High unmet need in Japan with ALK positive NSCLC patients
  - ALK+ NSCLC is a progressive disease that is associated with poor survival rates
- Brigatinib offers a new option with unique profile of selectivity and safety
  - In preclinical studies, brigatinib was found to be a potent and selective inhibitor
  - Dose reductions were mainly due to laboratory abnormalities
  - No treatment-related deaths occurred in ALTA-1L and J-ALTA
- Compelling efficacy in patients with brain metastases
  - Brigatinib significantly improved PFS in patients with baseline brain metastases vs. crizotinib
- Takeda is preparing to launch brigatinib in Japan (FY21 Q1)

# Niraparib

Jumpei Soeda M.D., Ph.D.  Head Japan Medical Affairs
Japan Oncology Business Unit
February 25, 2021

Better Health, Brighter Future

# AGENDA

## Today's Topics

1. **Disease Epidemiology Information**
2. Overview and Mode of Action
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# OVARIAN CANCER AT A GLANCE…

## Japan epidemiology data

**9th** most common cause of cancer death in women[1]

*Majority diagnosed stage III–IV*

Approximately **13,400** women will be diagnosed with ovarian cancer in 2020[1]

- Median age at diagnosis: **63 years**[1]

Approximately **4,700** deaths will occur due to ovarian cancer in 2020[1,2]

- Median age at death: **70 years**[1,2]

**Ovarian cancer has the highest fatality-to-case ratio of all gynecologic cancers**[3,4]



1. National Cancer Center https://ganjoho.jp/reg-stat/statistics/stat/summary.html 2. NCI SEER Program: Cancer Stat Facts http://seer.cancer.gov/statfacts/html/ovary.html; 3. Siegel RL, et al. CA Cancer J Clin 2018;68:7–30; 4. Berek JS, Bast RC, Jr. Epithelial ovarian cancer. In: Holland-Frei Cancer Medicine. 6th ed. Hamilton (ON): BC Decker; 2003. All websites accessed February 13, 2020.

# CLINICAL PRESENTATION, WORKUP & DIAGNOSIS

## Japan epidemiology data

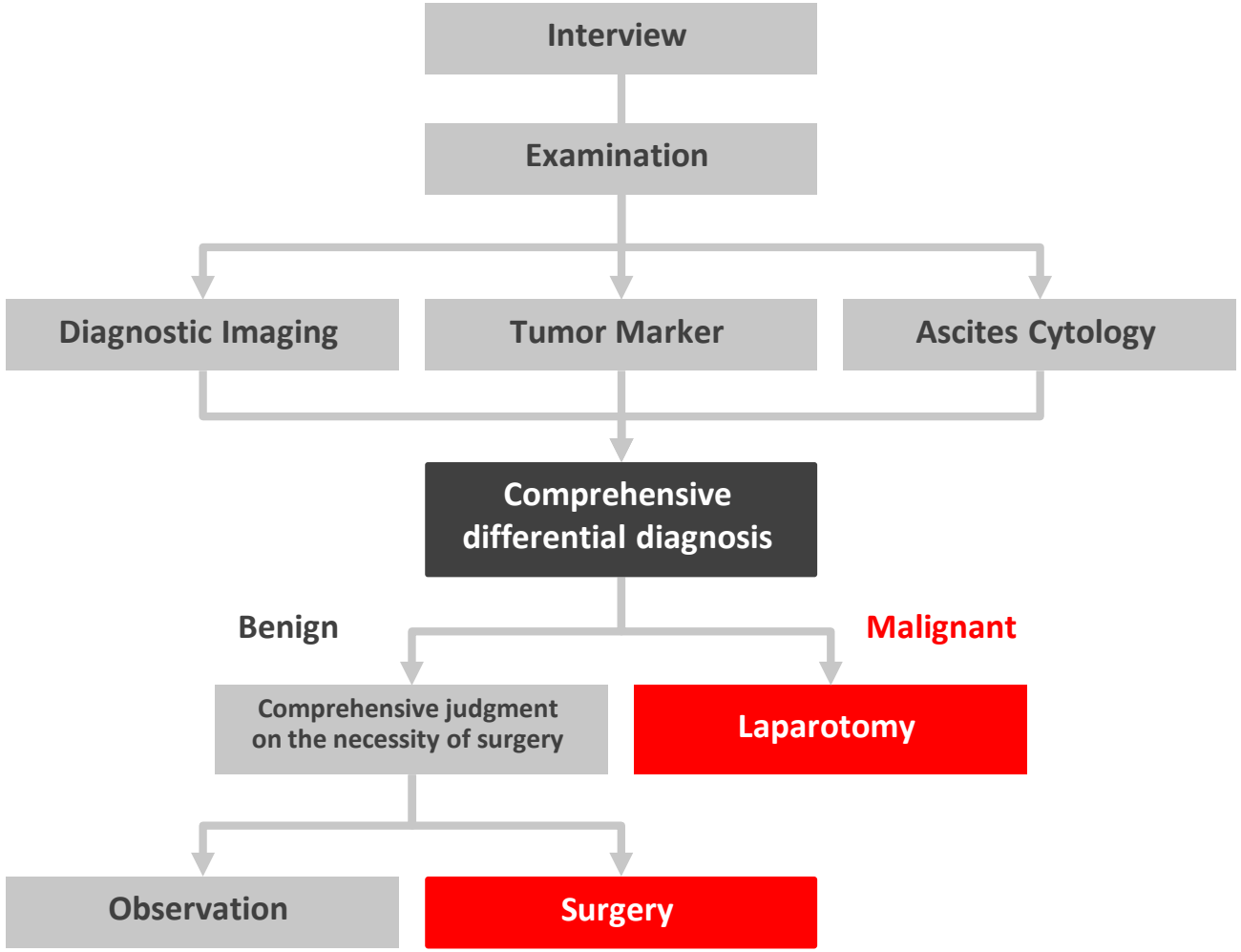
**Screening: Not recommended**

No screening tests have been validated[1,2]

**Early stages are often asymptomatic and difficult to detect**

### Most common symptoms

- Bloating
- Pelvic or abdominal pain or pressure
- Urinary symptoms (urgency or frequency)



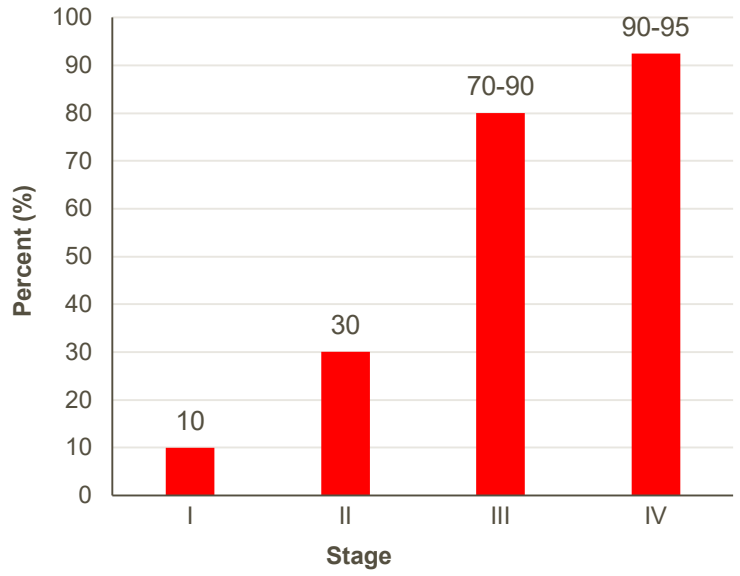



Signs and Symptoms of Ovarian Cancer. Atlanta, GA: American Cancer Society. Last revised April 11, 2018. https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/signs-and-symptoms.html. Accessed February 13, 2020. NCCN®, National Comprehensive Cancer Network®. 1. Grossman DC, et al. JAMA 2018;319:588–594. 2. American Congress of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 716 (https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/The-Role-of-the-Obstetrician-Gynecologist-in-the-Early-Detection-of-Epithelial-Ovarian-Cancer-in?). Accessed February 13, 2020.

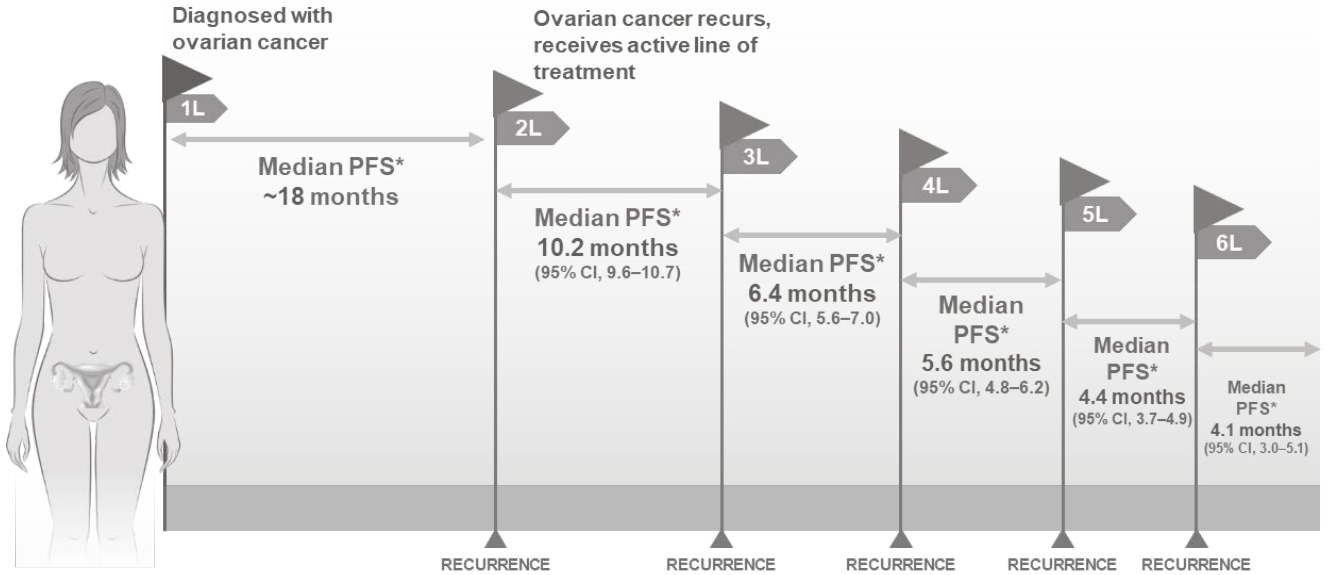
# SURVIVAL, STAGE AT DIAGNOSIS AND RECURRENCE

## 85% of women with advanced disease will recur after 1L therapy

**Recurrence rates by stage at diagnosis[1]**




## After each subsequent treatment, median PFS shortens without maintenance



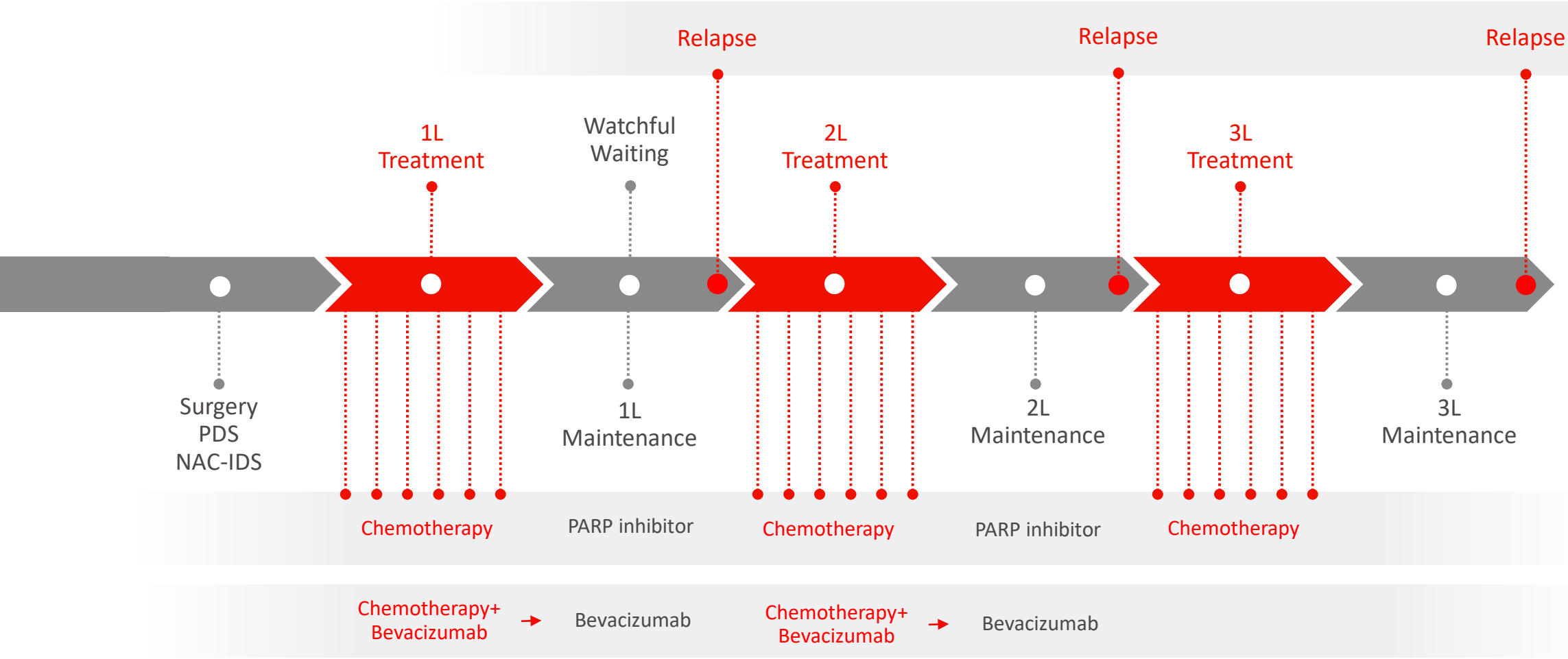

Recurrent ovarian cancer is

**treatable but not curable**

1L, first line.
1. https://ocrahope.org/patients/about-ovarian-cancer/recurrence/. Accessed February 13, 2020;
2. Ushijima K. J Oncol 2010:497429.

*PFS was calculated from the day of randomization (day of first cycle of chemotherapy) to the first disease progression.
PFS, progression-free survival; L, line.
Hanker LC, et al. Ann Oncol 2012;23:2605–12.

# OVARIAN CANCER TREATMENT






Japan Society of Gynecologic Oncology Guidelines 2020 for Treatment Ovarian Cancer
Prescribing Information: Olaparib, Niraparib, Bevacizumab

# AGENDA

## Today's Topics

1. Disease Epidemiology Information
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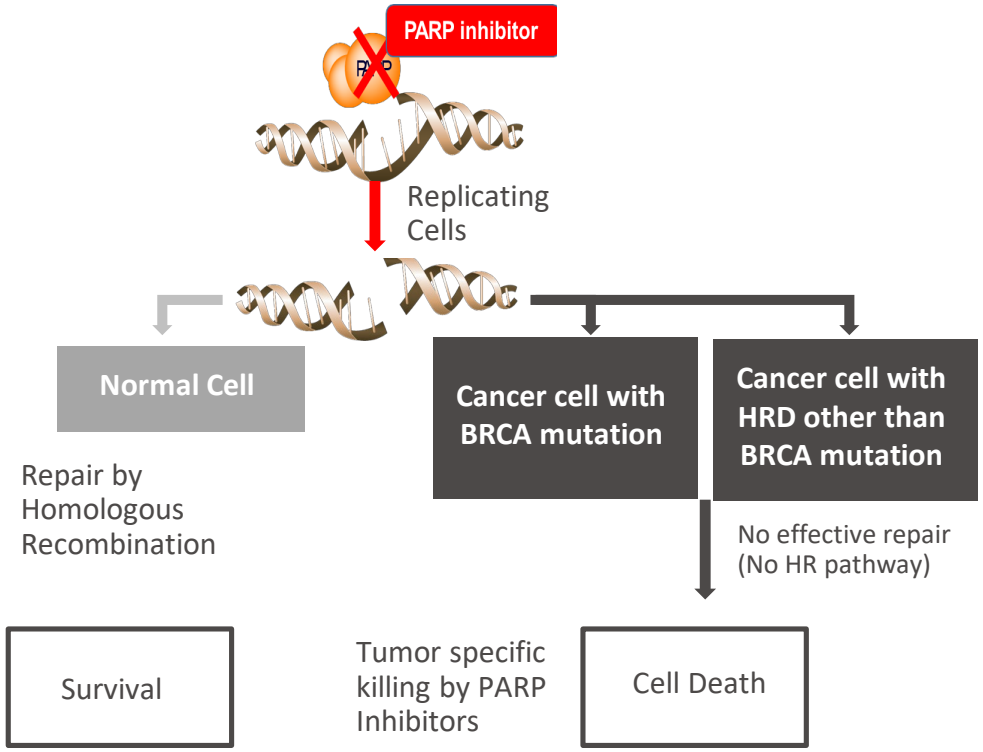
# NIRAPARIB OVERVIEW

Approved in Japan on 25, September 2020 for 1L maintenance treatment in platinum-sensitive relapsed ovarian cancer, and a treatment of homologous recombination deficient platinum-sensitive relapsed ovarian cancer

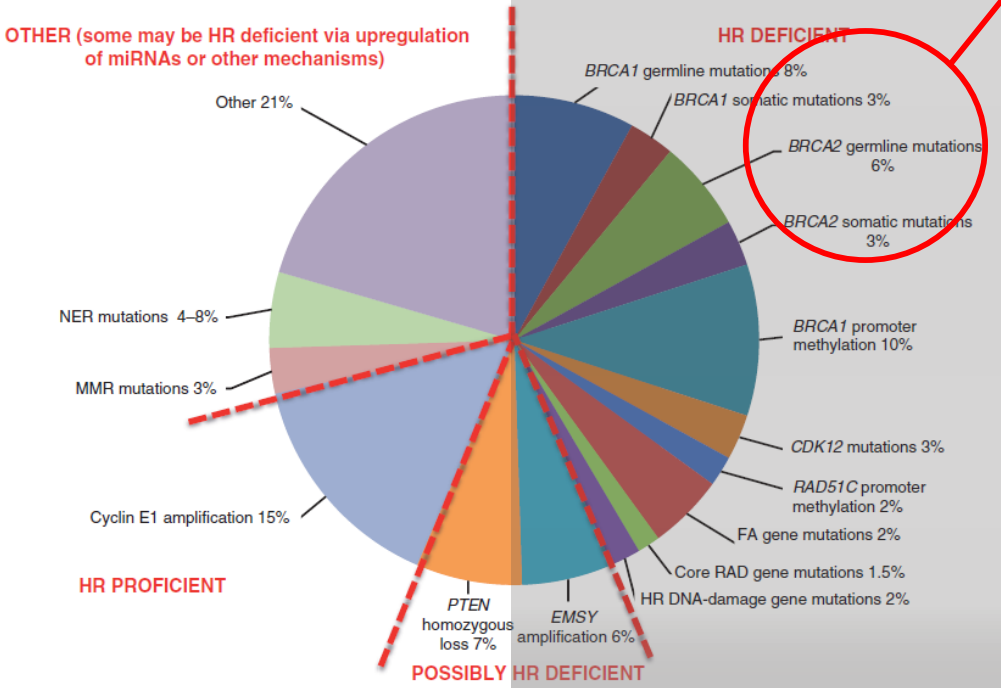
| NIRAPARIB OVERVIEW | |
|---|---|
| **Mode of Action** | • Niraparib is highly selective PARP1/2 inhibitor to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. |
| **Indications** | • 1L maintenance treatment in platinum-sensitive ovarian cancer<br>• Maintenance treatment in platinum-sensitive recurrent ovarian cancer<br>• Treatment of homologous recombination deficient platinum-sensitive relapsed ovarian cancer |
| **Dosage and administration** | • Once a day orally<br>• Body weight and platelet count adjusted |

# MECHANISM OF ACTIONS: EFFICACY BEYOND BRCA MUTATION




Modified from
Cancer Res Treat. 2012;44(1):1-10

**Approximately 20%–22% harbor a BRCA mutation at diagnosis**




**Approximately 50% of high-grade serous EOCs have alterations in HR repair genes (HRD)**

Adopted from
Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. Cancer Discovery 2015;5(11):3570-3576. DOI: 10.1200/JCO.2009.27.2997

# PARP INHIBITORS: NOT THE SAME

| | Absorption | Distribution | | Metabolism | Elimination |
|---|---|---|---|---|---|
| | F (%) | $P_{app}$ (10-6 cm/s) | $V_d$/F (L) | Major enzyme | $t_{1/2}$ (h) |
| Niraparib | 73[1] | 12-18[2] | 1,074[1] | CE[1] | 48-51[1] |
| Olaparib | NA[3] | 46-4[4] | 167[5] | CYP3A4[5] | 11.9[5] |
| Rucaparib | 36[6] | 6-8[7] | 113-262[6] | CYP2D6[6] | 17-19[6] |

Niraparib is characterised by:

- High tumour penetration – largest volume of distribution
- No relevant drug-drug interaction
- Once daily dosing with or without food[1]

| | Competitive binding to the NAD+ site | | |
|---|---|---|---|
| | Catalytic inhibition (IC50 nM) | Cytotoxicity (IC90 ÂµM) | PARP-trapping potency (relative to olaparib set as 1) |
| Olaparib | 6 | 4.5 | 1 |
| Rucaparib | 21 | 3 | 1 |
| Niraparib | 60 | 2.3 | ~2 |
| Talazoparib | 4 | 0.04 | ~100 |

1. ZEJULA® Summary of Product Characteristics, Nov 2017; 2. TESARO Inc., Data on File; 3. CHMP Assessment Report: Lynparza (EMA/CHMP/789139/2014). Available at: http://www.ema.europe.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003726/WC500180154.pdf. Accessed Jan 2018.4.Clinical and biopharmaceutics review: Lynparza. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206162Orig1s000ClinPharmR.pdf. Accessed Jan 2018; 5. Lynparza Summary of Product Characteristics, July 2017; 6. Rubraca package leaflet, Dec 2016; 7. Durmus S, et al. Pharm Res 2015;32(1):37-46. Zhang ZY, et al. Oral presentation at ISSX 2015, Oct 18-22, 2015, Orlando, USA. Murai J, et al. *Mol Cancer Ther* 2014;13(2):433-443.

# AGENDA

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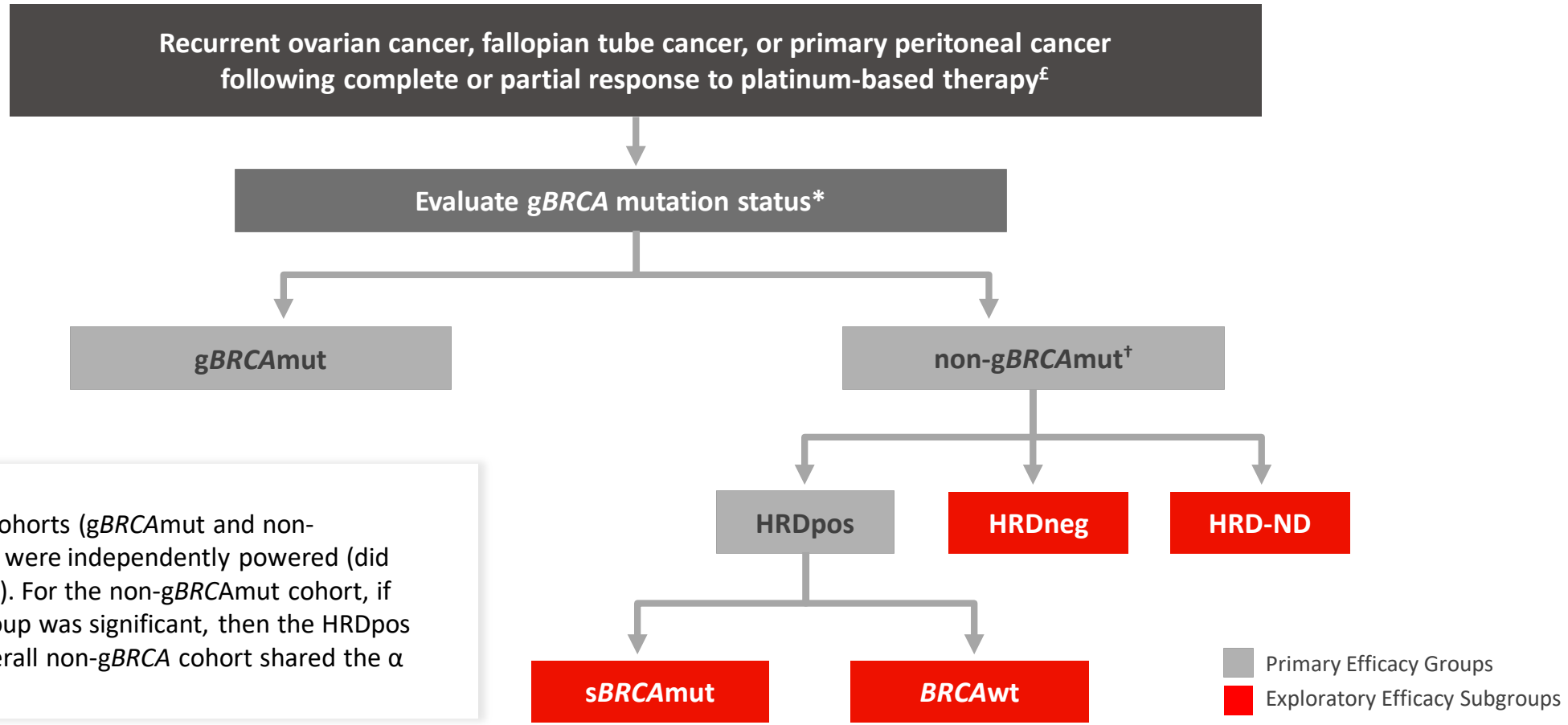
# NOVA STUDY DESIGN




Two main cohorts (g*BRCA*mut and non-g*BRCA*mut) were independently powered (did not share α). For the non-g*BRCA*mut cohort, if HRDpos group was significant, then the HRDpos and the overall non-g*BRCA* cohort shared the α

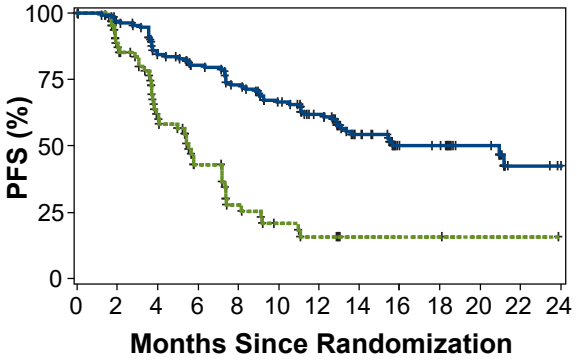


£ Patients who had a complete or partial response to penultimate platinum-based therapy lasting ≥ 6 months ; *gBRCA mutation status defined by BRACAnalysis® (Myriad Genetics); †in the non-gBRCAmut cohort, tumors were retrospectively defined as HRD by the myChoice® HRD test (Myriad Genetics). HRD=homologous recombination deficiency; HRDpos=HRD positive; HRDneg=HRD negative; HRD-ND=HRD status not determined; sBRCAmut=somatic BRCA mutation; wt=wild-type. Mirza MR et al. N Engl J Med. 2016;375:2154-2164.

# NIRAPARIB SIGNIFICANTLY IMPROVED PFS FOR ALL PATIENT POPULATIONS

## PRIMARY EFFICACY POPULATIONS

### g*BRCA*mut

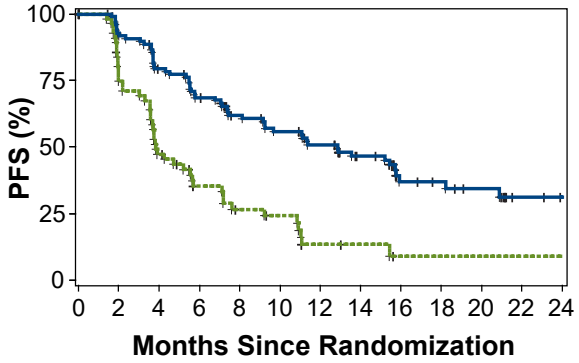



HR=0.27 *p*<0.0001

Median PFS (months)

| | |
|---|---|
| Niraparib: | 21.0 |
| Placebo: | 5.5 |

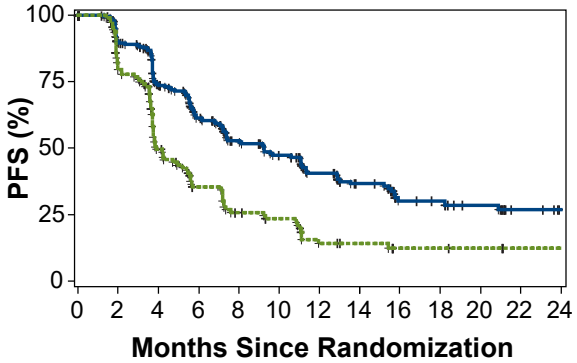
### Non-g*BRCA*mut HRD positive




HR=0.38 *p*<0.0001

| | |
|---|---|
| Niraparib: | 12.9 |
| Placebo: | 3.8 |

### Non-g*BRCA*mut Overall




HR=0.45 *p*<0.0001

| | |
|---|---|
| Niraparib: | 9.3 |
| Placebo: | 3.9 |



Mirza MR et al. N Engl J Med. 2016;375:2154-2164.

# SUMMARY OF ADVERSE EVENTS IN NOVA

| Reported — n (%) | Niraparib (n=367) | Placebo (n=179) |
|---|---|---|
| Any TEAE | 367 (100.0) | 171 (95.5) |
| Any related TEAE | 358 (97.5) | 127 (70.9) |
| Any CTCAE grade ≥3 TEAE | 272 (74.1) | 41 (22.9) |
| Any related CTCAE grade ≥3 TEAE | 237 (64.6) | 8 (4.5) |
| Any serious TEAE | 110 (30.0) | 27 (15.1) |
| Any related serious TEAE | 62 (16.9) | 2 (1.1) |
| Any TEAE leading to treatment interruption | 253 (68.9) | 9 (5.0) |
| Any TEAE leading to dose reduction | 244 (66.5) | 26 (14.5) |
| Any TEAE leading to treatment discontinuation | 54 (14.7) | 4 (2.2) |

– **Less than 15% of patients discontinued niraparib due to TEAEs**

**NOVA Treatment-Emergent Adverse Events:**
Grade 3/4 Occurring in ≥5% of Patients
(as presented in Mirza MR et al. N Engl J Med)

| Events— n (%) | Niraparib (n=367) | Placebo (n=179) |
|---|---|---|
| Thrombocytopenia[a] | 124 (33.8) | 1 (0.6) |
| Anemia[b] | 93 (25.3) | 0 |
| Neutropenia[c] | 72 (19.6) | 3(1.7) |
| Fatigue[d] | 30 (8.2) | 1 (0.6) |
| Hypertension | 30 (8.2) | 4(2.2) |

MDS/AML occurred in 1.4% of patients who received niraparib and 1.1% of patients who received placebo



TEAE=treatment-emergent adverse event.
Mirza MR et al. N Engl J Med. 2016;375:2154-2164. Supplementary Material

[a]Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count. No Grade 3 or 4 bleeding events were associated with thrombocytopenia; [b]anemia includes reports of anemia and decreased hemoglobin counts; [c]neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [d]fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
MDS/AML=myelodysplastic syndrome/acute myeloid leukemia. Mirza MR et al. N Engl J Med. 2016;375:2154-2164.

# QUADRA: STUDY DESIGN AND PATIENT ELIGIBILITY

## Evaluate the efficacy of niraparib in a broad, late-line recurrent ovarian cancer population

**Patients with histologically diagnosed advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 3 or more prior chemotherapy**

↓

**Niraparib 300 mg orally once daily, 28-day cycles**

↓

**Endpoint assessment**

| | |
|---|---|
| **Primary Endpoint** | ORR by RECIST in HRD-positive patients who have received 3 or 4 lines of previous chemotherapy, platinum-sensitive, and PARPi-naïve |

### Key Eligibility Criteria

- Serous epithelial ovarian, fallopian tube or primary peritoneal cancer
- Tumor HRD testing and blood g*BRCA*mut status testing
- Completed >3 prior chemotherapy regimens
- Following enrollment of 292 patients, study amendment:
  - Limited to 3 or 4 previous chemotherapy regimens
  - Patients must have experienced a response lasting at least 6 months to first line platinum-based therapy



ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors; HRD=homologous recombination deficiency; PARPi=poly (ADP-ribose) polymerase inhibitor; gBRCAmut=germline breast cancer susceptibility gene mutant;
Moore KN, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicenter, open-label, single-arm phase 2 trial. Lancet Oncol. April 1, 2019. http://dx.doi.org/10.1016/ S1470-2045(19)30087-7.

# QUADRA MET ITS PRIMARY ENDPOINT WITH AN ORR OF 28%

## (p = 0.0005) in platinum-sensitive, HRD-positive, PARPi-naïve patients

| Response Rate in the Primary Endpoint Population (n=47) | | |
|---|---|---|
| **ORR%** | 28% | • Patients in the primary outcome group had received three or four prior anti-cancer therapies<br>• They were also platinum-sensitive to the last platinum therapy<br>• All were PARPi-naive<br>• This population was chosen as the primary endpoint population following the NOVA study results that demonstrated niraparib activity beyond the gBRCA$^{mut}$ cohort |
| **95% Confidence Interval** | 15.6 – 42.6 | |
| ***One-Sided P Value** | P = 0.00053 | |

**Additional assessments in primary endpoint population**

- Median PFS 5.5 months
- Median Duration of Response 9.2 months



* The p value reflects the very high likelihood that the true response rate actually falls between 15.6 and 42.6 months. Because this is an open label trial without a comparator arm, we cannot use this statistical analysis to infer that this is better/worse than other treatment regimens. Source: Moore et al, *Lancet Oncol* 2019.

# THE OCCURRENCE OF TREATMENT-EMERGENT ADVERSE EVENTS IN QUADRA WAS CONSISTENT WITH THE PRIOR CLINICAL EXPERIENCE

| Most common all causality AEs ≥30% in the each arm was: | N, (%) | | |
|---|---|---|---|
| | Grade 1-2 | Grade 3 | Grade 4 |
| Any drug-related treatment-emergent adverse event | 416 (90) | 257 (56) | 93 (20) |
| Nausea | 261 (56) | 20 (4) | 0 |
| Fatigue | 185 (40) | 20 (4) | 1 (<1) |
| Anaemia | 176 (38) | 112 (24) | 1 (<1) |
| Vomiting | 139 (30) | 19 (4) | 0 |
| Thrombocytopenia | 136 (29) | 76 (16) | 58 (13) |
| Decreased platelet count* | 91 (20) | 35 (8) | 22 (5) |
| Decreased appetite | 85 (18) | 4 (1) | 0 |
| Constipation | 76 (16) | 5 (1) | 0 |
| Insomnia | 55 (12) | 3 (1) | 0 |
| Headache | 52 (11) | 1 (<1) | 0 |
| Decreased white blood cell count | 48 (10) | 17 (4) | 2 (<1) |

## KEY TAKEAWAYS

- TEAEs Grade 3 in 56% of Patients (Safety Population, N=463)
- TEAEs, including Grade ≥3, were consistent with prior clinical experience
- Percentage of patients who experienced a TEAE resulting in:
  - Dose interruption (62%)
  - Dose reduction (47%)
  - Study withdrawal (21%)
- Nine patients (1.9%) experienced a TEAE which led to death, 1 of which was considered related to study treatment

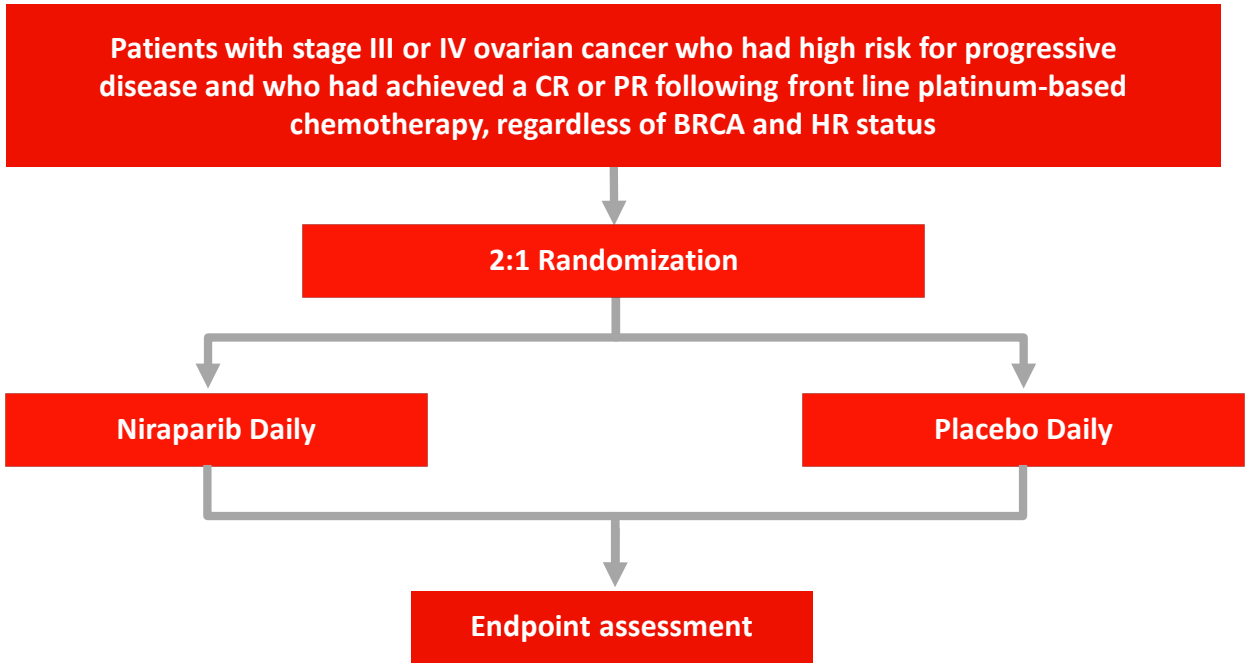


Only events with a rate of at least 10% at any grade are listed. 1 patient out of 463 (0.2%) with MDS/AML and 1 patient with related grade 5 gastric hemorrhage. *Events are not mutually exclusive

Moore K., et al. Presented at 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. Poster #241. CTCAE=common terminology criteria of adverse events; TEAE=treatment-emergent adverse events; MDS=myelodysplastic syndrome; AML=acute myeloid leukemia.

# PRIMA TRIAL DESIGN

## Once-daily oral maintenance therapy evaluated in patients with newly diagnosed advanced ovarian cancer




| | |
|---|---|
| **Primary Endpoint** | **Hierarchical Testing for PFS (radiologic, central review)**<br>• PFS in HR-deficient population<br>• PFS in ITT population |
| **Key Secondary Endpoints** | • Overall Survival<br>• Safety & Tolerability<br>• Patient Reported Outcomes (FOSI, EQ-5D-5L, EORTC-QLQ-30 & -OV28)<br>PFS2 · Time to CA-125 Progression |
| **Exploratory** | • Population PK<br>• PK parameters for niraparib and major metabolite<br>• HR Diagnostic Test |

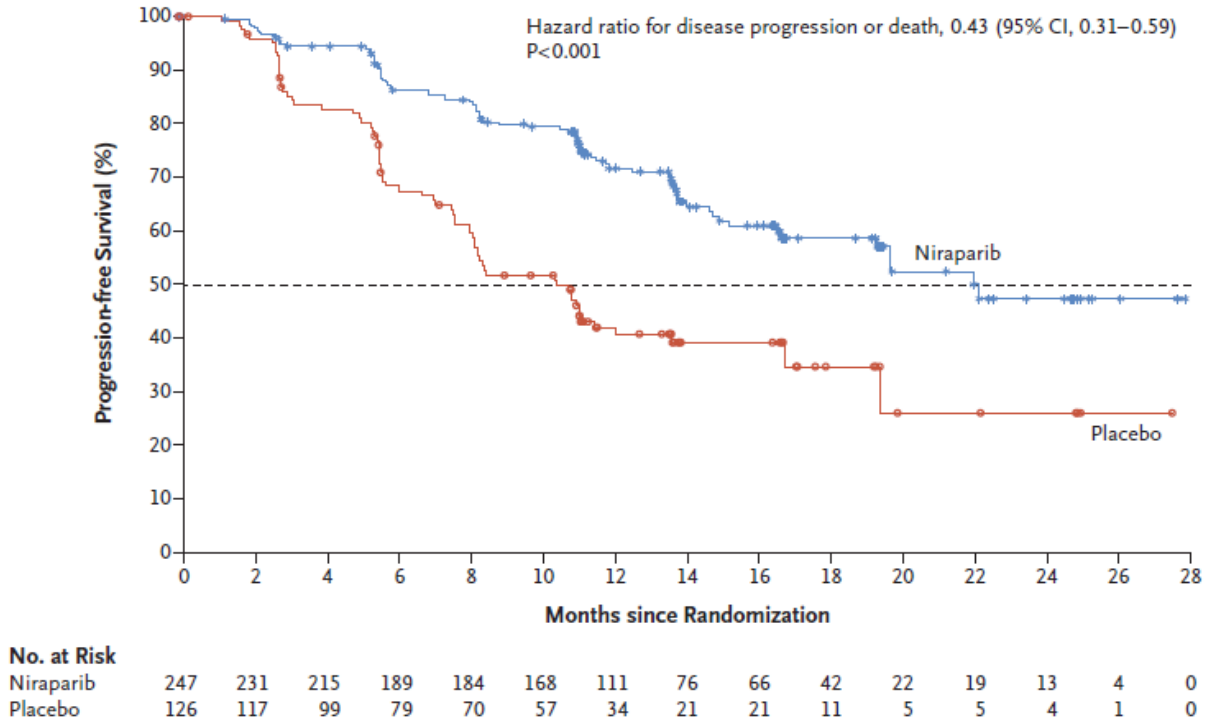
**The PRIMA study protocol was modified to prospectively investigate a starting dose of either 300 mg or 200 mg of niraparib (or placebo) based on baseline body weight and platelet counts (individualized starting dose).**



CR = complete response; PR = partial response; HR = homologous recombination;; PFS = progression-free survival; ITT = intent to treat; FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptom Index; EQ-5D-5L = European Quality of Life 5-Dimensions 5-Level Scale; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire; EORTC-QLQ-OV28 = EORTC Quality of Life Questionnaire Ovarian Cancer Module; PFS2 = Progression-free survival 2; PK = pharmacokinetics. Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402.

# PRIMARY ENDPOINT: PFS IN THE HR-DEFICIENT POPULATION

## Niraparib significantly reduced the risk of progression or death by 57% in women in the PRIMA study with newly diagnosed HR-deficient advanced ovarian cancer




**HR (95% CI) for disease progression or death: 0.43 (0.31–0.59; P<0.0001)**

| | Niraparib (n = 247) | Placebo (n = 126) |
|---|---|---|
| **Median PFS** | | |
| **Months (95% CI)** | 21.9 (19.3 – NE) | 10.4 (8.1 – 12.1) |
| **Patients without PD or death (%)** | | |
| **6 months** | 86% | 68% |
| **12 months** | 72% | 42% |
| **18 months** | 59% | 35% |

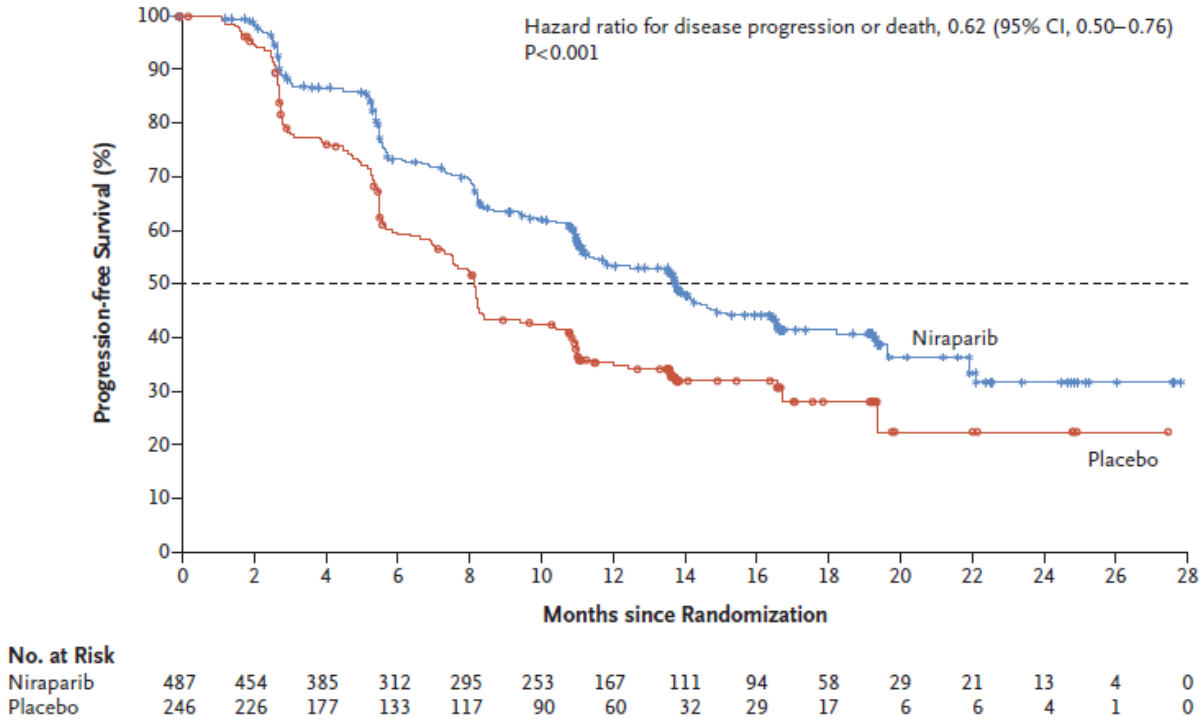


CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; NE = not estimable; PD = progressive disease; PFS = progression-free survival

Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

# PRIMARY ENDPOINT: PFS IN THE OVERALL POPULATION

## Niraparib significantly reduced the risk of progression or death by 38% in women in the PRIMA study with newly diagnosed HR-deficient advanced ovarian cancer




**HR (95% CI) for disease progression or death: 0.62 (0.50–0.76; P<0.001)**

| | Niraparib (n = 487) | Placebo (n = 246) |
|---|---|---|
| **Median PFS** | | |
| **Months (95% CI)** | 13.8 (11.5 – 14.9) | 8.2 (7.3 – 8.5) |
| **Patients without PD or death (%)** | | |
| **6 months** | 73% | 60% |
| **12 months** | 53% | 35% |
| **18 months** | 42% | 28% |



CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; NE = not estimable; PD = progressive disease; PFS = progression-free survival

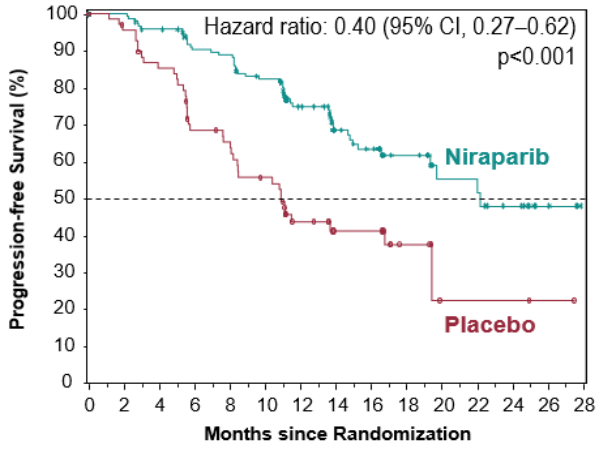
Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

# PFS IN BIOMARKER SUBGROUPS

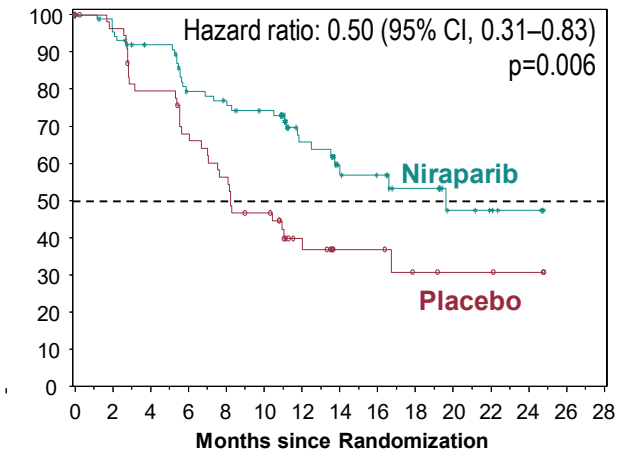
## Niraparib reduced the risk of progression or death regardless of BRCA status and HR-deficiency or HR-proficiency

**Homologous Recombination Deficient (HRd)**

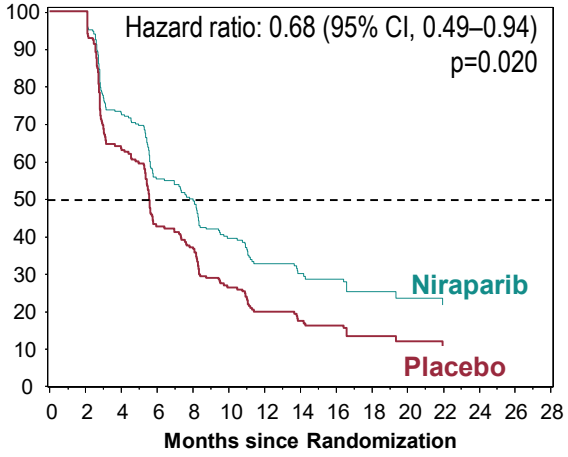
### HRD/*BRCA*mut




### HRD/*BRCA*wt HRD positive




### HR-proficient*




**While HR testing was implemented in PRIMA, all subgroups benefited regardless of HRd status**



*There was not stratification in the HR-proficient subgroup; as a result, in this exploratory analysis, imbalances were observed. To account for these imbalances within the subgroup, statistical adjustments were made to the Kaplan-Meier curve in accordance with accepted statistical methods. CI = confidence interval; HRd = homologous recombination deficient; mut = mutation; PFS = Progression-free survival; wt = wild-type. Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402; Gonzalez-Martin A, et al. Presented at ESMO 2019. Barcelona, Spain.

# PRIMA SAFETY OVERVIEW

| Adverse Event, n (%) | Niraparib (n=484) | Placebo (n=244) |
|---|---|---|
| **Any TEAE** | 478 (98.8) | 224 (91.8) |
| Grade ≥3 | 341 (70.5) | 46 (18.9) |
| **Led to treatment discontinuation** | 58 (12.0) | 6 (2.5) |
| **Led to dose reduction** | 343 (70.9) | 20 (8.2) |
| **Led to dose interruption** | 385 (79.5) | 44 (18.0) |
| **TEAEs leading to death** | 2 (0.4) | 1 (0.4) |

- TEAEs were consistent with the PARP inhibitor class
- Dose interruptions were similar to those in the previous niraparib trials
- Treatment discontinuation due to thrombocytopenia was 4.3%
- TEAEs leading to death were determined to be non treatment-related



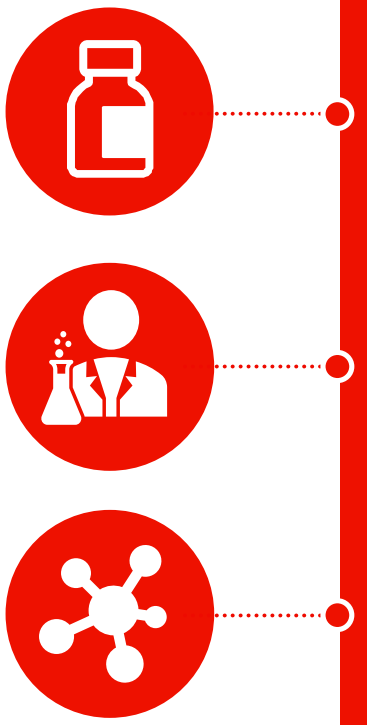
PARP, poly(ADP-ribose) polymerase; TEAE, treatment-emergent adverse event.
Gonzalez-Martin et al. N Engl J Med. 2019, 381:2391-2402.

# AGENDA

## Today's Topics

1. Disease Epidemiology Information
2. Overview and Mode of Action
3. Clinical Trials & Data
4. **Product Positioning**

# PRODUCT POSITIONING IN JAPAN



- NOVA shows significant clinical benefit in BRCAmt and non-BRCAmt population in maintenance therapy for platinum-sensitive recurrent ovarian cancer
- QUADRA shows clinical meaningful benefit in 4th line or later platinum sensitive HRD+ve population beyond BRCAmt
- PRIMA shows clinically meaningful benefit across all biomarker groups in 1L maintenance treatment in platinum-sensitive ovarian cancer
  - Presently, niraparib is the only PARP inhibitor with data showing benefit in HR-proficient ovarian cancer (exploratory analysis)

# Cabozantinib

Akiko Kimura M.D., Ph.D., Senior Medical Director
Oncology Therapeutic Area Unit for Japan & Asia, Oncology Clinical Science
February 25, 2021

Better Health, Brighter Future

# AGENDA

## Today's Topics

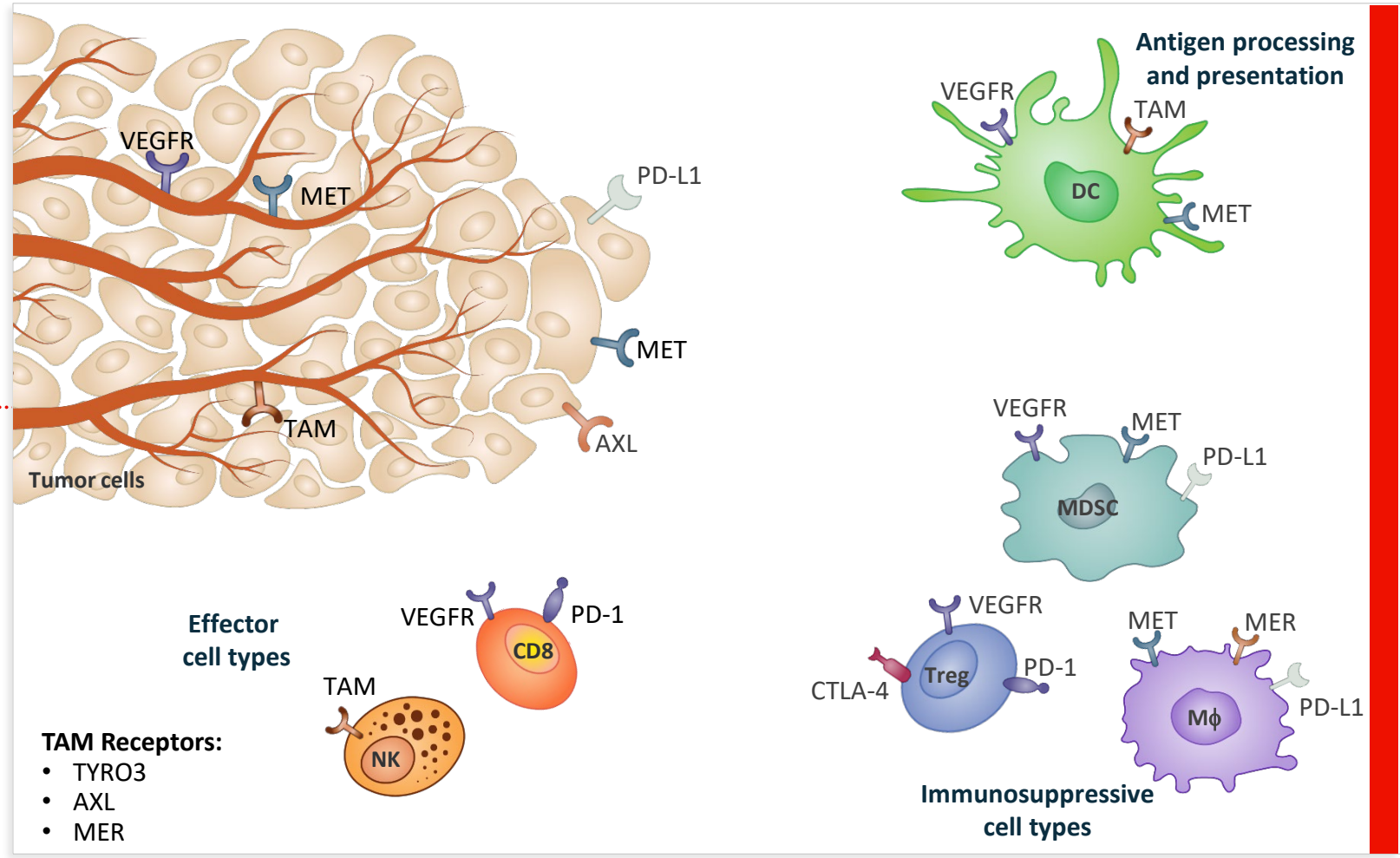
1. **Mode of Action & Product Information**
2. Disease Epidemiology Information
3. Clinical Trials and Data, Life Cycle Management
4. Product Positioning

# CABOZANTINIB TARGETS MULTIPLE RECEPTORS THAT CONTRIBUTE TO TUMOR CELL GROWTH, SURVIVAL AND METASTASIS

**These receptors contribute to:**

- Angiogenesis
- Proliferation
- Survival
- Migration and Invasion
- Resistance to VEGFR TKI

➢ Combining cabozantinib and an immune checkpoint inhibitor (such as nivolumab or atezolizumab) may promote a synergistic anti-tumor immune response

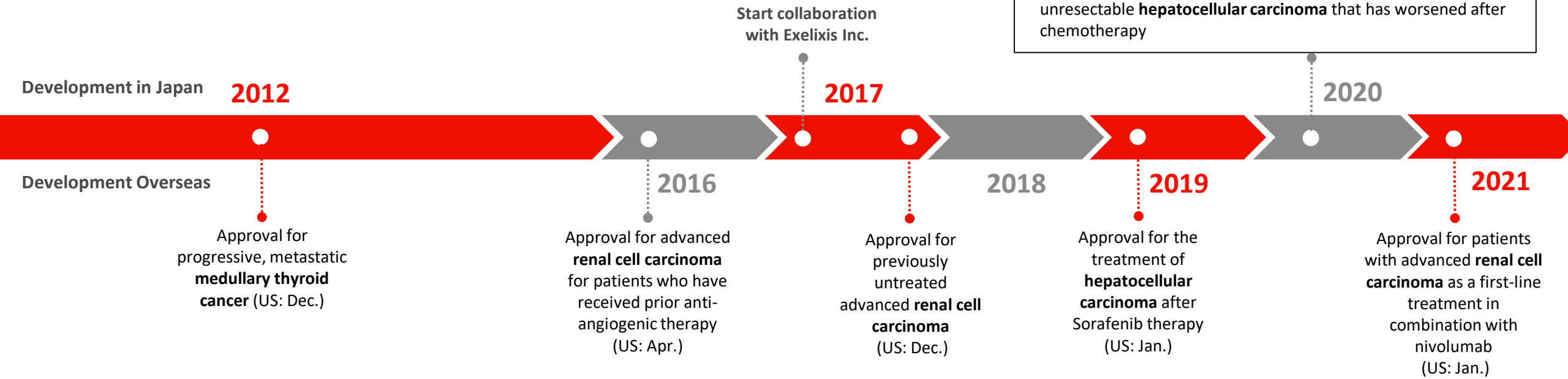



1. McKay RR et al JCO 2018; 36(36): 3615-3623, 2. Zhou L, et al. Oncogene. 2015. Epub, 3. Gustafsson A, et al. Clin Cancer Res. 2009;15(14):4742-4749, 4. Chang K, et al. Oncotarget. 2015;6(6):3507-3518, 5. Gibney GT, et al. Ann Oncol. 2013;24(2):343-349, 6. Capitanio U et al. Lancet. 2015;Epub [Figure adaptation], 7. Holland SJ, et al. Cancer Res. 2005;65(20):9294-9303.

# CLINICAL DEVELOPMENT OF CABOZANTINIB

➢ **Cabozantinib is one of multiple TKIs, those targets includes VEGFR, MET and AXL, that Exelixis, Inc. has originally developed**

- **March:** Received approval to manufacture and market cabozantinib for the indication of unresectable or metastatic **renal cell carcinoma**
- Began multiple global Phase III clinical trials to evaluate cabozantinib as a combo with atezolizumab (Roche/Chugai) (Clinical Trial Notification **NSCLC:** July, **CRPC:** August)
- **October:** Applied for unresectable or metastatic **renal cell carcinoma** as a combo with Nivolumab
- **November:** Received approval for partial change to the manufacturing and marketing approval for the indication of unresectable **hepatocellular carcinoma** that has worsened after chemotherapy






NSCLC: non-small cell lung cancer, CRPC: castration resistant prostate cancer.

# AGENDA

## Today's Topics

1. Mode of Action & Product Information
2. **Disease Epidemiology Information**
3. Clinical Trials and Data, Life Cycle Management
4. Product Positioning

# EPIDEMIOLOGY OF RENAL CELL CARCINOMA (RCC): Japanese data

- Renal carcinoma: A malignant tumor arising in the renal parenchyma (epithelial tumor), including cancer (epithelial tumor), sarcoma (mesenchymal tumor) and lymphoma
  - Estimated number of cases of renal cancer in Japan: 29,572 (2017)
  - Estimated number of deaths from renal cancer in Japan: 4,531 (2018)
- Approximately **90%** of renal cancer takes the form of **RCC**[1]
- The morbidity and mortality of RCC are on the rise worldwide
- Histological types of RCC[2]:
  - **Clear cell RCC (about 65% to 75%)**
  - Type 1 and type 2 papillary RCC (about 15% to 20%)
  - Chromophobe RCC (about 5% to 7%)
  - Other types include collecting duct carcinoma, renal medullary carcinoma and translocated renal carcinoma

  Each histological type is associated with a different genetic abnormality and has a different clinical course


[1] Znaor A, et al. Eur Urol. 2015;67(3):519-30, [2] Inamura et al. Int J Mol Sci. 2017;18(10).

# WHAT IS RENAL CELL CARCINOMA?

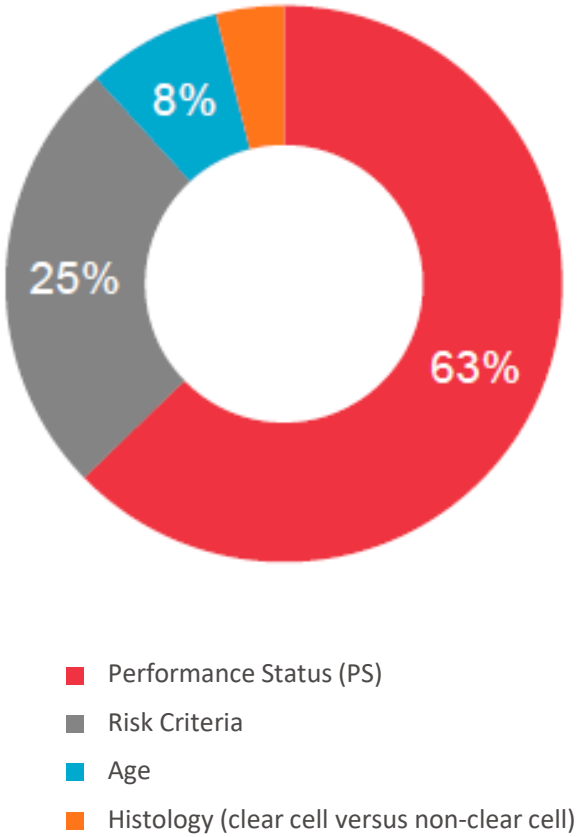
## Major symptoms of Renal Cell Carcinoma

- RCC itself is often **asymptomatic**
- **Symptoms by metastases** are often detected incidentally: bone pain, enlarged lymph nodes or masses, respiratory symptoms, paraneoplastic syndromes (e.g., fever with unknown cause, night sweats, anorexia, weight loss)
- Clinical findings: macro- or microscopic hematuria, hypertension, anemia, red blood cell hyperplasia, hypercalcemia, etc.

## Treatment of Renal Cell Carcinoma

- Diagnostic imaging: Determines the **clinical stage (Stage I-IV)** according to the size of the primary RCC, anatomical location, presence and number of lymph node metastases and presence of distal metastases
- Biopsy: For diagnosis of **histological type**
- Treatment plan is determined according to the **histological type, clinical stage, risk classification and general condition**
- Unlike other malignant diseases, surgical resection is recommended even if metastasis has taken place
- If completely unresectable, **systemic administration of anticancer drugs** is a treatment option

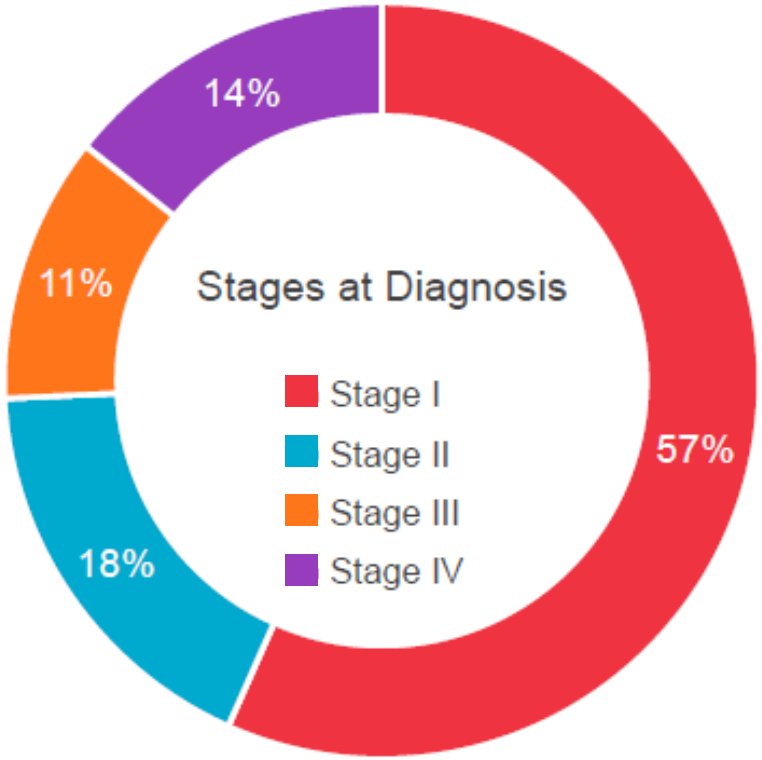
**Factors Influencing Treatment Decisions, RCC, Japan, 2020**



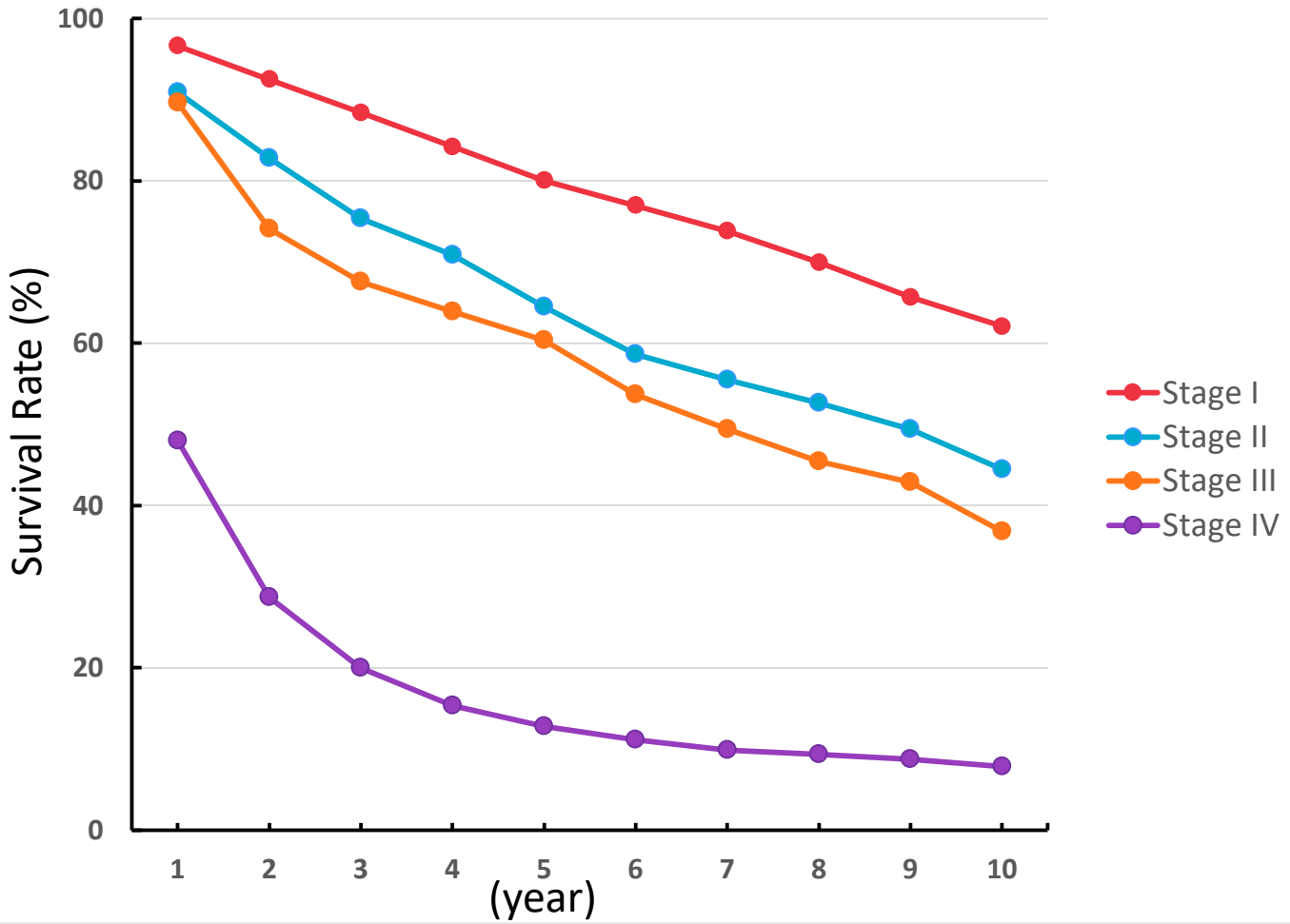

 

# CLINICAL STAGING OF RENAL CELL CARCINOMA (JAPAN 2020)

## Clinical Staging Distribution of renal cell carcinoma



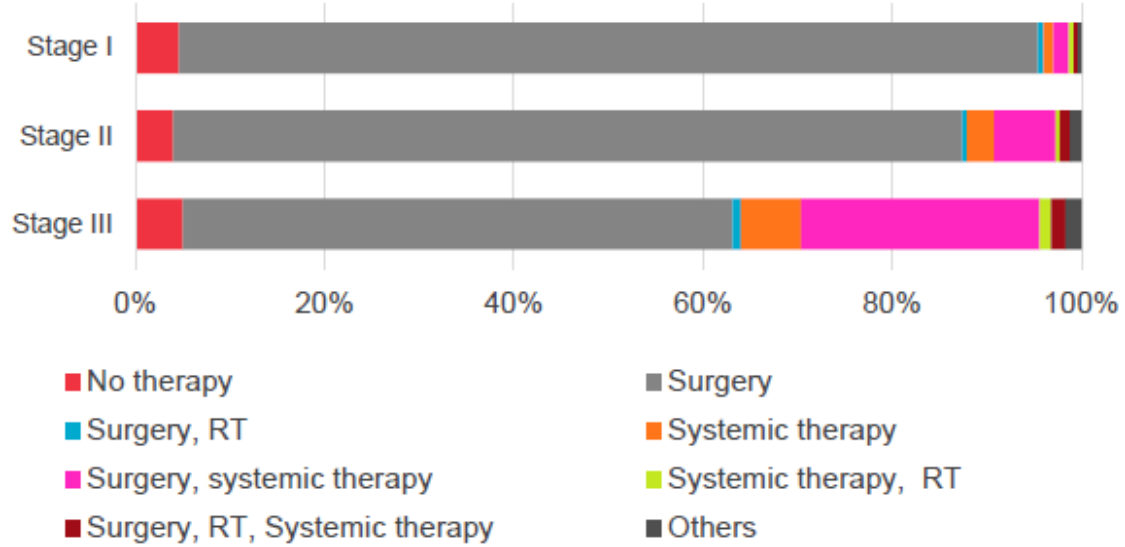

## Survival Rate by Staging of Kidney cancer



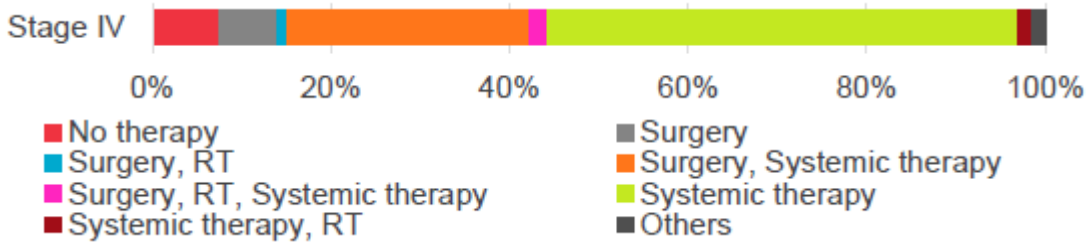

 

# TREATMENT MODALITY OF RENAL CELL CARCINOMA (Japan 2020)

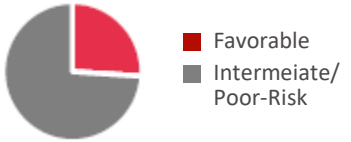
## Initial Treatment Modality Distribution (%)




## Metastatic Treatment Modality Distribution (%)




## Patient Risk Status




## Top 3 Initial Systemic Regimens

| Neoadjuvant | Adjuvant |
|---|---|
| Sunitinib<br>Pazopanib | Sunitinib<br>Pazopanib |

## Top 3 Metastatic Systemic Regimens

| | Favorable Risk | Intermediate/ Poor Risk |
|---|---|---|
| First-line | Sunitinib<br>Pazopanib<br>Pembrolizumab/Axitinib | Nivolimab / Ipilimumab<br>Pazopanib<br>Sunitinib |
| Second-line | Axitinib<br>Nivolumab<br>Sunitinib | |
| Third-line | Nivolumab<br>Axitinib<br>Pazopanib | |

# AGENDA

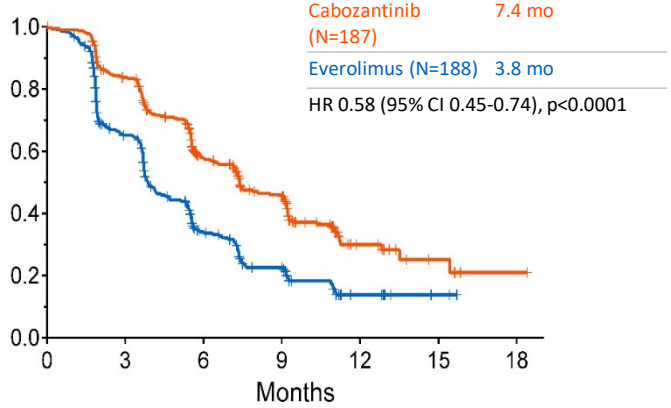
## Today's Topics

1. Product Information & Mode of Action
2. Disease Epidemiology Information
3. **Clinical Trials & Data, Life Cycle Management**
4. Product Positioning

# METEOR STUDY (PH3, MONOTHERAPY, 2L~) EFFICACY

- Cabozantinib significantly improved all of PFS, OS and ORR
- The clinical benefits of cabozantinib consistent across all subgroups evaluated, including subgroups by risk classification and bone/liver metastases
- Cabozantinib is a standard of care for patients with advanced RCC after prior antiangiogenic therapy

## Progression-Free Survival (PFS) [1]

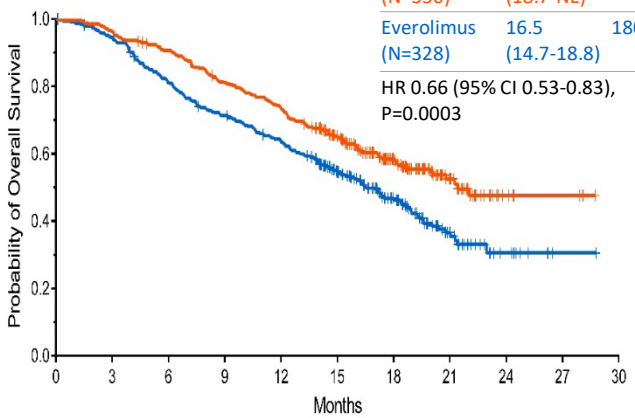



| | Median PFS |
|---|---|
| Cabozantinib (N=187) | 7.4 mo |
| Everolimus (N=188) | 3.8 mo |

HR 0.58 (95% CI 0.45-0.74), p<0.0001

Cut-off : May 22, 2015

## Overall Survival (OS)




| | Median OS mo (95% CI) | No. of Deaths |
|---|---|---|
| Cabozantinib (N=330) | 21.4 (18.7-NE) | 140 |
| Everolimus (N=328) | 16.5 (14.7-18.8) | 180 |

HR 0.66 (95% CI 0.53-0.83), P=0.0003

Cut-off: Dec 31, 2015

## Objective Response Rate (ORR)[1]

| | Cabozantinib N=330 | Everolimus N=328 |
|---|---|---|
| **ORR, % (95% CI)** | 17 (13, 22) | 3 (2, 6) |
| Stratified CMH test p-valued[2] | | <0.001 |
| Unstratified CMH test p-valued | | <0.001 |
| **Best overall response, N (%)** | 57 (17) | 11 (3) |
| Confirmed complete response | 0 | 0 |
| Confirmed partial response | 57 (17) | 11 (3) |
| Stable disease | 216 (65) | 203 (62) |
| Progressive disease | 41 (12) | 88 (27) |
| Unable to determine | 16 (5) | 26 (8) |

Cut-off: May 22, 2015


Prescribing information for CABOMETYX (USA), [1] Per RECIST version 1.1., by IRC, [2] p-value from CMH test with stratification factors of prior VEGFR-targeting TKI therapy (1 vs 2 or more), and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3), IRC: independent radiology review committee, RECIST: Response Evaluation Criteria in Solid Tumors.

# METEOR STUDY (PH3, MONOTHERAPY, 2L~) SAFETY

- The overall incidence of all-causality AEs was similar, 100% in the cabozantinib arm and 99.7% in the everolimus arm
- Treatment-emergent AEs were effectively managed with supportive care and/or dose modifications
- Discontinuations due to AEs were 12% in the cabozantinib arm and 11% in the everolimus arm

**Most common all causality AEs ≥30% in the each arm were:**

| Cabozantinib arm | Everolimus arm |
|---|---|
| • diarrhea (75%)<br>• fatigue (60%)<br>• nausea (53%)<br>• decreased appetite (49%)<br>• palmar-plantar erythrodysaesthesia (PPE) syndrome (44%)<br>• hypertension (37%)<br>• weight decreased (35%)<br>• vomiting (35%) | • fatigue (48%)<br>• anemia (40%)<br>• decreased appetite (36%)<br>• cough (35%)<br>• dyspnea (30%) |



PMDA Review Report (Mar. 25. 2020).

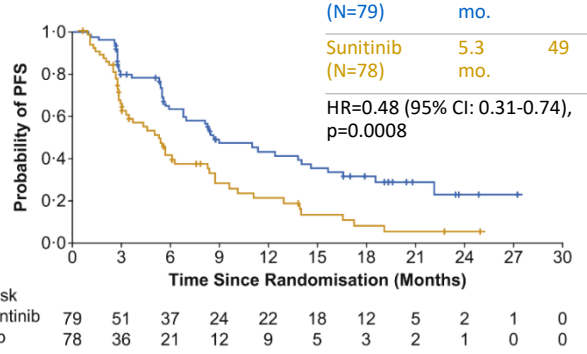
# CABOSUN STUDY (PH2, MONOTHERAPY, 1L) EFFICACY

- Cabozantinib improved PFS and ORR compared to sunitinib in intermediate/poor risk groups
- PFS and ORR, consistently favorable for cabozantinib in the subgroups (≥ 20 subjects per treatment arm), including subgroups by risk classification and bone metastases
- Cabozantinib is a treatment option for untreated advanced RCC
- USA: Cabozantinib has been approved for RCC without line limitation (METEOR & CABOSUN)

## Progression-Free Survival (PFS) [1]

| | Median PFS | No. of Events |
|---|---|---|
| Cabozantinib (N=79) | 8.6 mo. | 43 |
| Sunitinib (N=78) | 5.3 mo. | 49 |

HR=0.48 (95% CI: 0.31-0.74), p=0.0008

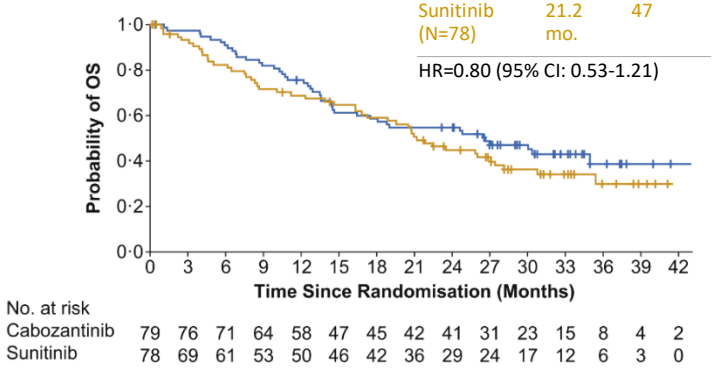



Cut-off : Sep 15, 2016

## Overall Survival (OS)

| | Median OS | No. of Deaths |
|---|---|---|
| Cabozantinib (N=79) | 26.6 mo. | 43 |
| Sunitinib (N=78) | 21.2 mo. | 47 |

HR=0.80 (95% CI: 0.53-1.21)




Cut-off: Jul 01, 2017

## Objective Response Rate (ORR) [1]

| | Cabozantinib N=79 | Sunitinib N=78 |
|---|---|---|
| **ORR, % (95% CI)** | 20 (12, 31) | 9 (4, 18) |
| Stratified CMH test p-valued[2] | 0.0406 | |
| **Best overall response, N (%)** | 16 (20) | 7 (9) |
| Confirmed complete response | 0 | 0 |
| Confirmed partial response | 16 (20) | 7 (9) |
| Stable disease | 43 (54) | 30 (38) |
| Progressive disease | 14 (18) | 23 (29) |
| Unevaluable or missing[2] | 6 (8) | 18 (23) |

Cut-off: Sep 15, 2016


Prescribing information for CABOMETYX (USA), [1] Per RECIST version 1.1., by IRC, [2] Unevaluable or missing for the following reasons, Cabozantinib arm: adverse event (5), withdrew consent (1); Sunitinib arm: adverse event (6), death (2), disease progression (1), withdrew consent (9), IRC: independent radiology review committee, , RECIST: Response Evaluation Criteria in Solid Tumors.

# CABOSUN STUDY (PH2, MONOTHERAPY, 1L) SAFETY

- The overall incidence of all-causality AEs was similar, 96.2% in the cabozantinib arm and 98.6% in the sunitinib arm
- Safety profile of cabozantinib similar to METEOR result was shown
- Treatment-emergent AEs were effectively managed with supportive care and/or dose modifications
- Discontinuations due to AEs were 21% in the cabozantinib arm and 22% in the sunitinib arm

**Most common all causality AEs ≥30% in the each arm were:**

| Cabozantinib arm | Sunitinib arm |
|---|---|
| • diarrhea (73%)<br>• hypertension (67%)<br>• fatigue (64%)<br>• AST increased (60%)<br>• ALT increased (55%)<br>• decreased appetite (47%)<br>• palmar-plantar erythrodysaesthesia (PPE) syndrome (42%)<br>• dysgeusia (41%)<br>• platelet count decreased (38%)<br>• stomatitis (37%)<br>• anemia (33%)<br>• nausea (32%)<br>• weight decreased (32%) | • fatigue (68%)<br>• platelet count decreased (61%)<br>• diarrhea (54%)<br>• anemia (46%)<br>• hypertension (44%)<br>• nausea (39%)<br>• neutrophil count decreased (35%)<br>• white blood cell count decreased (35%)<br>• palmar-plantar erythrodysaesthesia (PPE) syndrome (33%)<br>• decreased appetite (32%)<br>• AST increased (31%) |


PMDA Review Report (Mar. 25. 2020).

# C2001 STUDY (PH2, MONOTHERAPY, 2L~) EFFICACY

- METEOR and C2001: Cabozantinib has shown comparable ORR in Japanese patients
- Similar effects by ORR were demonstrated by cabozantinib in the subgroups (≥ 10 subjects), including subgroups by risk classification, previous treatment regimens/ numbers and lung metastases
- METEOR, CABOSUN and C2001: Cabozantinib is considered effective for Japanese RCC without line limitation

## Bridging strategy to METEOR study per ORR: similar target population with METEOR study

| Objective Response Rate (ORR) per IRC[1] Overall N=35 | |
|---|---|
| **ORR, % (95% CI)** | **20 (10, 34)** |
| **Best overall response, N (%)** | |
| • Confirmed complete response (CR) | 0 |
| • Confirmed partial response (PR) | 7 (20) |
| • Stable disease (SD) | 23 (66) |
| • Progressive disease (PD) | 4 (11) |
| • Not evaluable | 0 |
| • Missing | 1 (3) |

Data Cut-off: Oct 23, 2018

6 months-PFSR by IRC[1] was 72.3% (95%CI, 53.3 to 84.), better than the cabozantinib data in METEOR study



PMDA Review Report (Mar. 25. 2020), [1] Per RECIST version 1.1, by IRC, CI: confidence interval, IRC: independent radiology committee, RECIST: Response Evaluation Criteria in Solid Tumors.

# C2001 STUDY (PH2 MONOTHERAPY, 2L~) SAFETY

- The overall incidence of all-causality AEs was, 100% in the cabozantinib arm and 99.7% in the sunitinib arm
- Similar safety profile of cabozantinib was shown in Japanese patients compared to METEOR study
- All patients experienced adverse events (AEs), all of which were effectively managed with supportive care and/or dose modifications
- Discontinuations due to AEs were 5.7%, lower than that in the cabozantinib arm of METEOR study (13.0%)

**The most common all causality AEs (≥30%)**

**Cabozantinib arm**

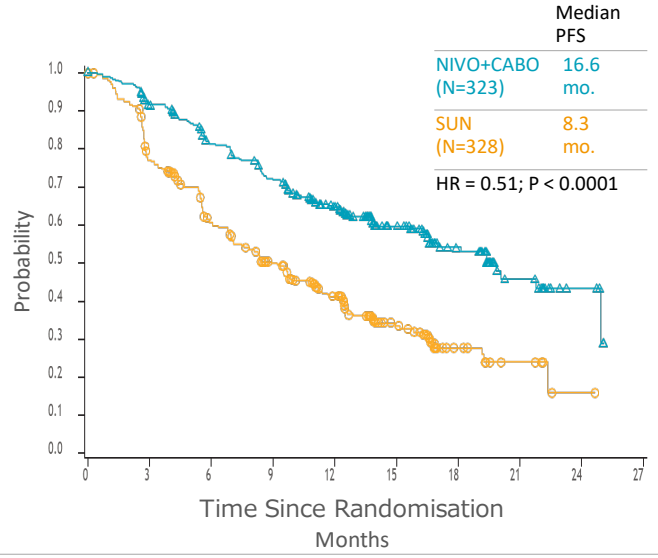
- palmar-plantar erythrodysaesthesia (PPE) syndrome (63%),
- diarrhoea (60%),
- hypertension, proteinuria and stomatitis (each 40%),
- dysgeusia and hepatic function abnormal (each 34%)


PMDA Review Report (Mar. 25. 2020).

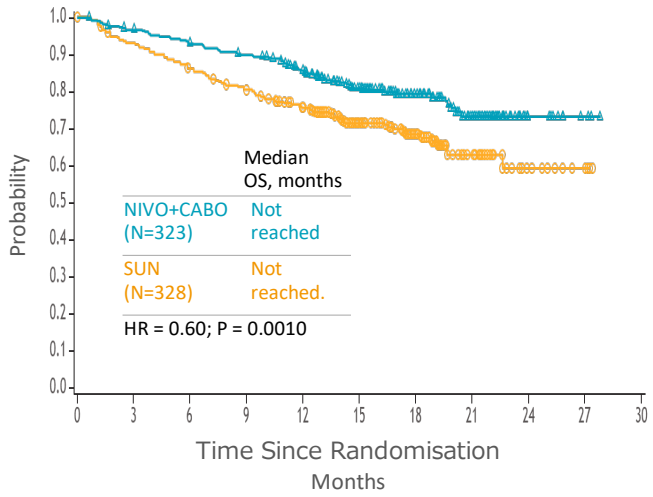
# CHECKMATE-9ER STUDY (PH3, COMBO WITH NIVO, 1L) EFFICACY

- Nivo/Cabo significantly improved all of PFS, OS and ORR in previously untreated patients with advanced or metastatic RCC
- The observed clinical benefits were consistent across almost of subgroups evaluated, including subgroups by PD-L1 status at baseline, risk classification, bone metastases
- Nivo/Cabo can be a standard of care for patients with advanced or metastatic untreated RCC

## Progression-Free Survival (PFS)[1]




## Overall Survival (OS)




## Objective Response Rate (ORR)[1]

| | NIVO+CAVO N=323 | SUN N=328 |
|---|---|---|
| **ORR, % (95% CI)** | 55.7 (51, 61) | 27.1 (22, 32) |
| | P < 0.0001 | |
| **Best overall response, N (%)** | 180 (55.7) | 89 (27.1) |
| Complete response | 26 (8.0) | 15 (4.6) |
| Partial response | 154 (47.7) | 74 (22.6 |
| Stable disease | 104 (32.2) | 138 |
| Progressive disease | 18 (5.6) | (42.1) |
| Not evaluable/not assessed[2] | 21 (6.5) | 45 (13.7) |
| | | 56 (17.1) |

Data Cut-off: Feb.12, 2020


ESMO presentation #6960, 2020, [1] Per RECIST version 1.1., by IRC, [2] Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per IRC, or other reason not reported/specified, IRC:: independent radiology review committee, , RECIST: Response Evaluation Criteria in Solid Tumors.

# PH3 CHECKMATE-9ER STUDY (COMBO WITH NIVO, 1L) SAFETY

- The overall incidence of all-causality AEs was similar, 99.7% in the cabozantinib/nivolumab arm and 99.1% in the sunitinib arm
- Most AEs were recovered or recovering by treatment and/or dose modifications, and thus manageable.
- Discontinuations due to AEs were 19.7% and 16.9% in the cabozantinib/nivolumab arm and the sunitinib arm[1]

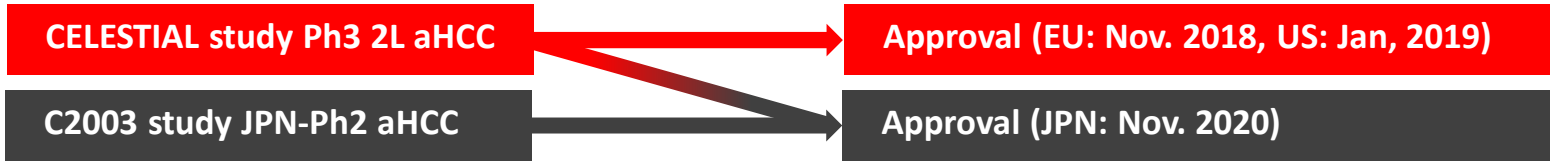
**Most common all causality TEAEs ≥30% in the each arm were:**

| Nivo/Cabo arm | Sunitinib arm |
|---|---|
| • diarrhea (63.8%)<br>• palmar-plantar erythrodysaesthesia syndrome (40.0%),<br>• hypertension (34.7%),<br>• hypothyroidism (34.1%)<br>• fatigue (32.2%) | • diarrhea (47.2%)<br>• palmar-plantar erythrodysaesthesia syndrome (40.6%),<br>• hypertension (37.2%)<br>• fatigue (34.7%)<br>• nausea (30.6%) |

 ESMO presentation #6960, 2020 , [1] Discontinuation includes events leading to discontinuation of either NIVO or CABO at any time; the assessment for discontinuation of NIVO and CABO were made separately for each drug, it was acceptable to continue treatment with only the study drug that was not related to the observed toxicity.

# LIFE CYCLE MANAGEMENT

## Monotherapy




## Combination with Atezolizumab (JPN: CONTACT-01, -02 and -03)

| Study | Setting | Status Update | Next Milestone(s) |
|---|---|---|---|
| COSMIC 311 Cabozantinib | **DTC** RAI refractory, up to 2 prior VEGFR TKIs | Analysis in Q4 2020: Trial met primary endpoint of PFS, cabozantinib reduced the risk of death or PD by 78% (HR 0.22, p<0.0001) | File sNDA in 2021; Present detailed data at an upcoming medical meeting |
| COSMIC 312 Cabozantinib + Atezolizumab | **1L aHCC** | Global enrollment complete | Event-driven, top-line analysis of PFS and OS in 1H 2021; File sNDA in 2021, data-dependent |
| COSMIC 313 Cabozantinib + Nivolumab + Ipilimumab | **1L aRCC** IMDC intermediate and poor risk | Expanded enrollment to 840 patients to provide additional power to assess secondary endpoint OS | Event-driven analysis 2022 |
| COSMIC 021 Cabozantinib + Atezolizumab | **Multiple Tumors** | Expanded cohorts in mCRPC (Cohort 6) and ICI pretreated NSCLC (Cohort 7) fully enrolled | Final analysis of ORR by BIRC of Cohort 6 (mCRPC) in mid-2021; File sNDA in 2021, data-dependent |
| CONTACT-01 Cabozantinib + Atezolizumab | **Metastatic NSCLC**, after ICI and platinum chemo | Actively enrolling globally | Study enrollment ongoing |
| CONTACT-02 Cabozantinib + Atezolizumab | **mCRPC**, after one NHT | Actively enrolling globally | Study enrollment ongoing |
| CONTACT-03 Cabozantinib + Atezolizumab | **aRCC**, w/progression during or following ICI | Actively enrolling globally | Study enrollment ongoing |

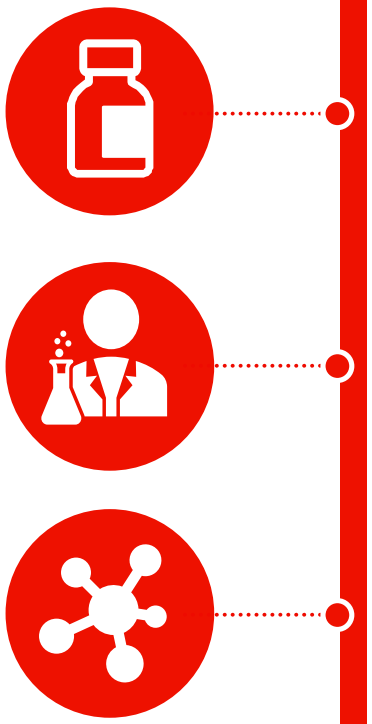
DTC: differentiated thyroid cancer
aHCC: advanced hepatocellular carcinoma
ORR: objective response rate
mCRPC: metastatic castration-resistant prostate cancer
ICI: immune checkpoint inhibitor
IMDC: International Metastatic RCC Database Consortium
NSCLC: non-small cell lung cancer
NHT: novel hormonal therapy

# AGENDA

## Today's Topics

1. Product Information & Mode of Action
2. Disease Epidemiology Information
3. Clinical Trials & Data, Life Cycle Management
4. **Product Positioning**

# PRODUCT POSITIONING IN JAPAN



- High unmet needs in Japan for **RCC**, **HCC**, **NSCLC** and **CRPC** patients, with limited therapies available
  - Limited number of treatment options
  - Limited efficacy
- Cabozantinib offers a new option with unique profile of VEGFR, MET and AXL inhibition
- Combination with ICI, addition to monotherapy, offers broader indications and target populations
  - RCC 1L: Combination therapy with ICI is expected to have higher efficacy, but may not be an option in some cases, such as in patients with autoimmune diseases
  - Combination with atezolizumab may expand target indications
- Launch projection
  - RCC combo with nivolumab: Dec.2021
  - Combo with atezolizumab
    - NSCLC: 1Q 2024
    - CRPC: 1Q 2024
    - RCC: 2Q 2024 (conducted by Chugai in Japan)

 NSCLC: non-small cell lung cancer, CRPC: castration-resistant prostate cancer, RCC: renal cell carcinoma.


Takeda Pharmaceutical Company Limited