Chugai R&D Meeting

CHUGAI PHARMACEUTICAL CO., LTD.

17 December, 2024

Important Reminders

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

Information regarding pharmaceuticals (including products under development) is included in this presentation, but is not intended as advertising or medical advice.

Agenda

01	Presence in the Oncology Area	**Tsukasa Kusano** Executive Vice President, Head of Project & Lifecycle Management Unit
02	Blood Cancer Pipeline	**Dr. Misato Hasizume** Franchise Lead for Hematological Malignancies
03	Giredestrant Tartrate, Inavolisib	**Yuji Habara** Giredestrant & Inavolisib & HER2 Franchise Lifecycle Leader
04	Divarasib	Divarasib Lifecycle Leader
05	Avutometinib	**Dr. Shunichiro Iwasawa** Avutometinib Lifecycle Leader

Presence in the Oncology Area

Tsukasa Kusano

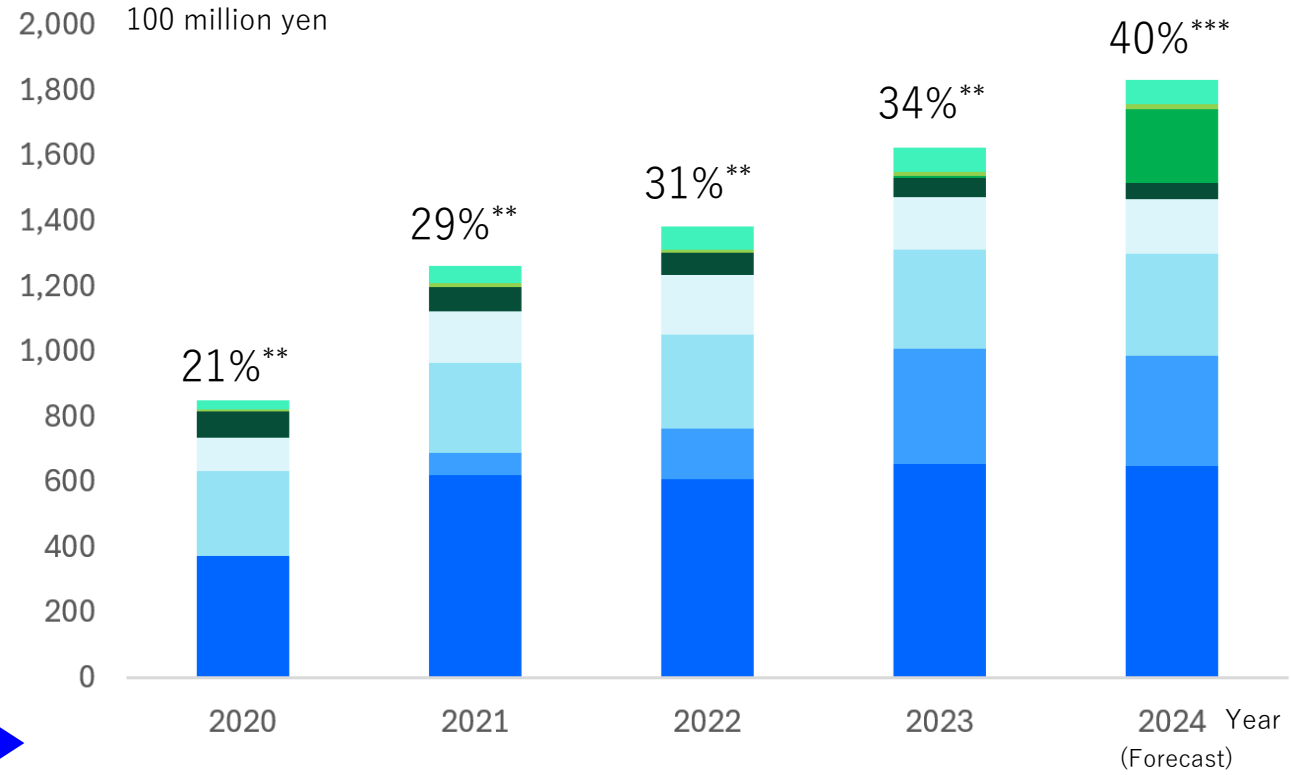
Executive Vice President, Head of Project & Lifecycle Management Unit

Presence in the Oncology Area

New Products and Mainstay Products to Drive Growth in the Short to Medium Term

- **Eight molecular targeted drugs** launched in Japan in the past 10 years
- Promoting the **advancement of personalized medicine** in conjunction with **cancer genome profiling**
- **Alecensa, a product developed in-house**, has been a blockbuster since 2020, achieving sales of over 230 billion yen worldwide last year.

- Oncology products launched over the past 10 years have shown **continuous growth, expanding to over 30% of domestic sales in 2023 (excluding Ronapreve).**



Tecentriq, Polivy, Alecensa, Kadcyla, Gazyva (including for agents), Phesgo, Rozlytrek + Zelboraf + Alaglio, Foundation Medicine

**Percentage of domestic product sales (excluding Ronaprive)

***Based on revised forecast

* An announcement was made in May 2021 regarding the termination of the license agreement and Chugai's sales activities based on the agreement (https://www.chugai-pharm.co.jp/english/news/detail/20210510113000_825.html?year=2021&category=)

Presence in the Oncology Area

Oncology Portfolio for Future Growth

A top-class portfolio with a wide variety of targets and technologies

Both research and early/late stage development are enhanced. Abundant development pipeline with 23 indications for 9 products in late-stage development

Selection of development candidates (7 items)
- Mid-size molecule (5 items)
- Small molecule (2 items)

Preclinical development (2 items)
- Mid-size molecule (1 item)
- Small molecule (1 item)

Before the start of development (already introduced)
- inavolisib: PI3K inhibitor

Announced today by Lifecycle leaders
(Alecensa, Tecentriq, Phesgo, and tiragolumab are in the Appendix)

Phase I (11 items)
- GC33 anti-GPC 3 antibody
- ALPS12 DLL3×CD3×CD137
- ERY974 GPC3×CD3
- LUNA18 RAS Inhibitor
- STA551 CD137 switch antibody
- SOF10 Anti-TGF-β1 antibody
- ROSE12
- SAIL66 CLDN6×CD3×CD137
- cobimetinib MEK Inhibitor
- cevostamab FcRH5×CD3
- runimotamab HER2×CD3

Phase II (1 item)
- avutometinib** NSCLC/PDAC

Phase III (8 items)
- Alecensa ALK+ NSCLC (Stage III)
- giredestrant HR+BC*
- tiragolumab multiple cancers
- Tecentriq multiple cancers
- Polivy NHL
- mosunetuzumab FL*/NHL*
- divarasib KRAS-G12C+NSCLC
- glofitamab Primary large B-cell lymphoma

Filed (3 items)
- Tecentriq ASPS/ENKL
- mosunetuzumab FL
- avutometinib** LGSOC

Research: as of February 1, 2024
Development: as of October 25, 2024

■ Monoclonal antibodies, ■ Switch antibodies, ■ Bispecific/trispecific antibodies, ■ Antibody-drug conjugates, ■ Mid-size molecules, ■ Small molecules
Orange: In-house developed products, **Blue**: Roche licensed products, *Planned lead-out in 2025: giredestrant (persevERA study, evERA study), mosunetuzumab (SUNMO study, CELESTIMO study)
Candidate selection: Screening is completed and candidates are selected from multiple candidates to proceed to preclinical trials. Preclinical development: After candidates are selected, animal testing takes place before clinical development begins. **Currently being developed by Verastem, the licensee.

Appendix

Presence in the Oncology Area

Domestic Market Sales: Oncology Area

As of April 24, 2024

- **Tecentriq**
  (lung cancer, breast cancer, hepatocellular carcinoma, urological cancer, etc.)
  Over 100 billion yen*
- **Polivy** (DLBCL, aNHL)
  Over 50 billion yen
- **Alecensa** (lung cancer, ALCL)
  Over 30 billion yen
- **Phesgo** (breast cancer, colon cancer)
  Over 20 billion yen
- **mosunetuzumab** (FL, aNHL)
  Over 20 billion yen
- **glofitamab**(LBCL)
  Over 20 billion yen
- **tiragolumab** (NSCLC, esophageal cancer)
  Over 15 billion yen*
- **giredestrant** (breast cancer)
  Over 10 billion yen

Orange: In-house developed products, **Blue**: Roche licensed products
*Projects with changes in development plan after April 24, 2024: Tecentriq (SKYSCRAPER-06 study and IMbrave050 study: development discontinued), tiragolumab (SKYSCRAPER-06 study: development discontinued), mosunetuzumab (phase III study in Japan: study initiated)

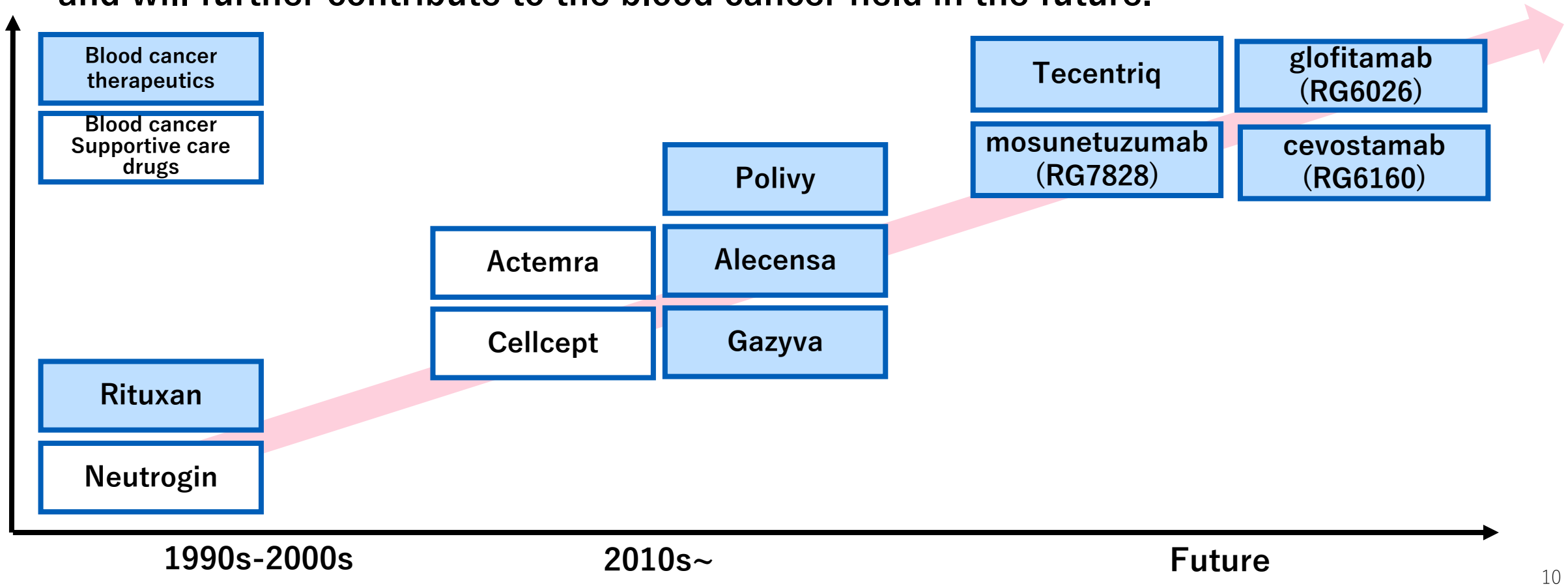
Blood Cancer Pipeline

Dr. Misato Hashizume

Franchise Lead for Hematological Malignancies

Our History in the Field of Blood Cancer

- For over 30 years, we have been delivering therapeutic and supportive care drugs to patients in the field of blood cancer.
- We are currently developing multiple candidate products for lymphoma and myeloma, and will further contribute to the blood cancer field in the future.



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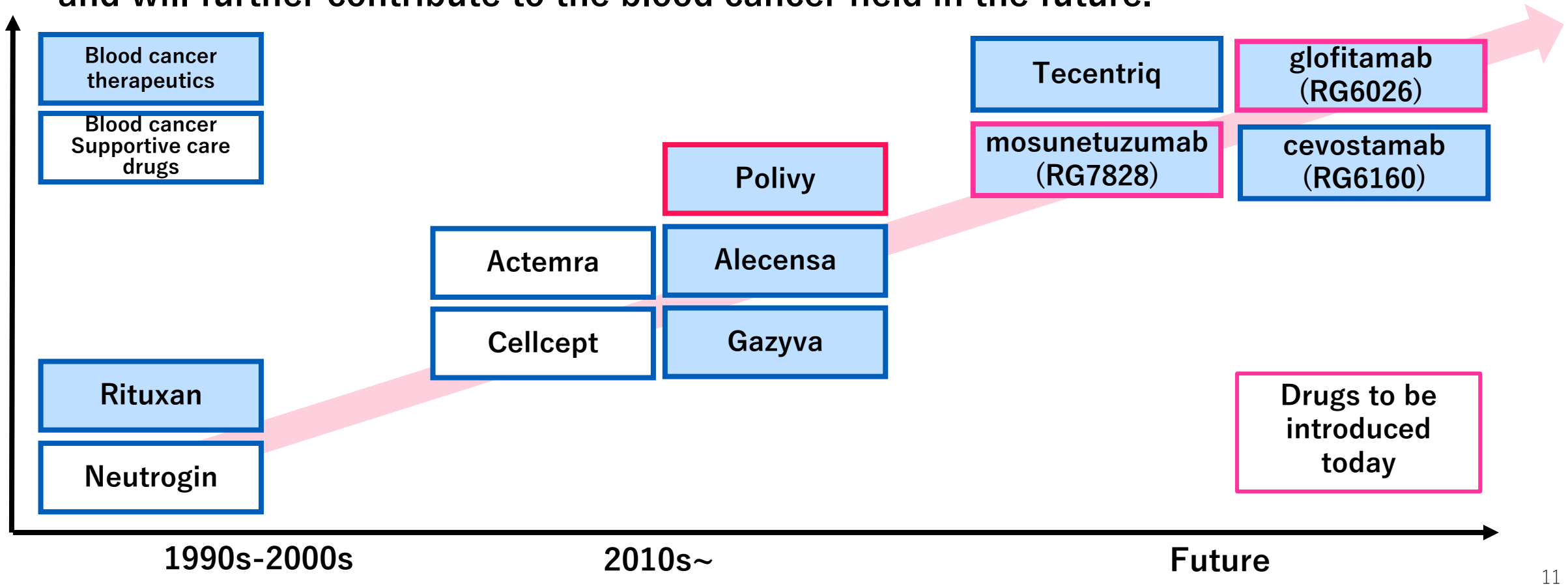
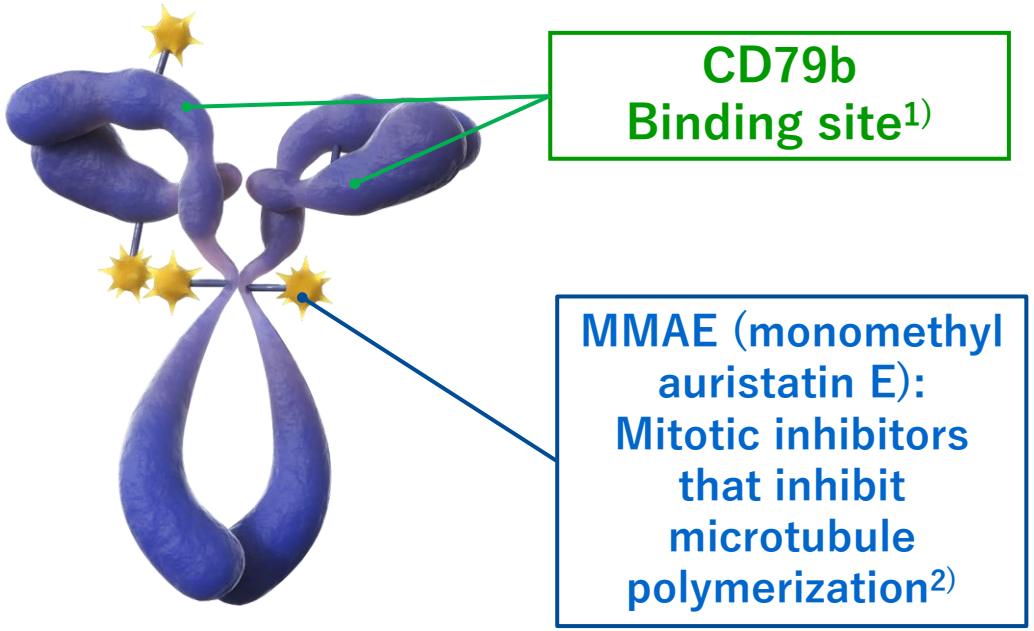


The Overview of Polivy

- Polivy is an antibody-drug conjugate (ADC) targeting CD79b expressed on B cells
- Launched in May 2021 for relapsed or refractory diffuse large B-cell lymphoma, followed by additional indication in August 2022 for untreated diffuse large B-cell lymphoma

Brand name	**Polivy® for Intravenous Infusion 30 mg** **Polivy® for Intravenous Infusion 140 mg**
Generic name	Polatuzumab vedotin (genetical recombination)
Launch	Initial: May 19, 2021 Additional indication: August 24, 2022
Indications	Diffuse large B-cell lymphoma

Structure of Polivy (image)



1) Polson AG, et al. Expert Opin Investig Drugs. 2011; 20(1): 75-85. (authors include Genentech employees), 2) Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784. (authors include Genentech employees)
ADC: anti-drug conjugate

Polivy: Mode of Action

- CD79b is a cell surface antigen expressed exclusively on all mature B cells except plasma cells, and is found in almost all B-cell lymphomas.
- Polivy binds to CD79b on tumor cells and releases MMAE intracellularly, thereby it is assumed to inhibit tumor cell growth and induce apoptosis.

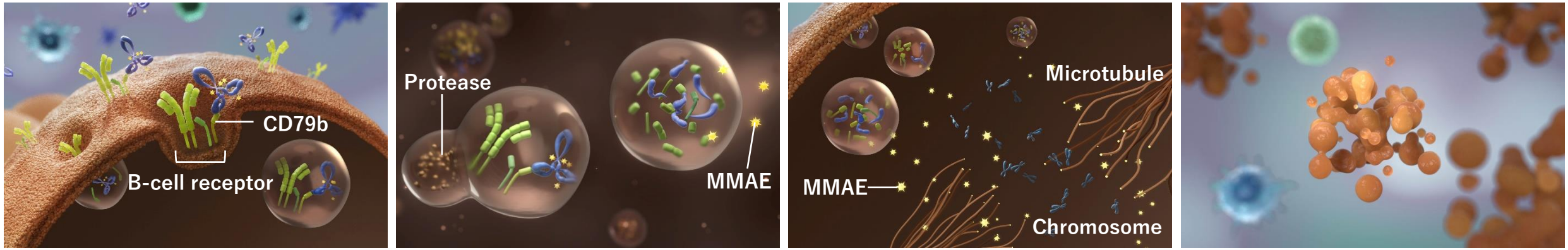
Mode of action of Polivy (conceptual image)

1 Binding of Polivy to CD79b on tumor cells, translocation into B cells

2 Degradation by lysosomal proteases, release of MMAE

3 Inhibition of microtubule polymerization

4 Inhibition of tumor cell proliferation, induction of apoptosis

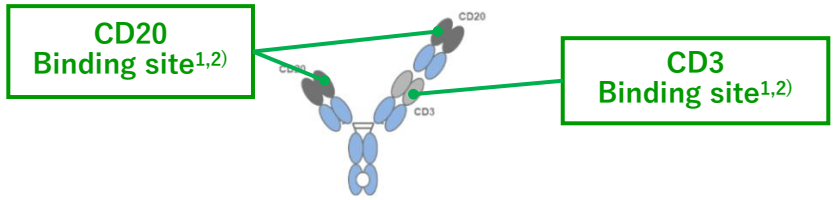
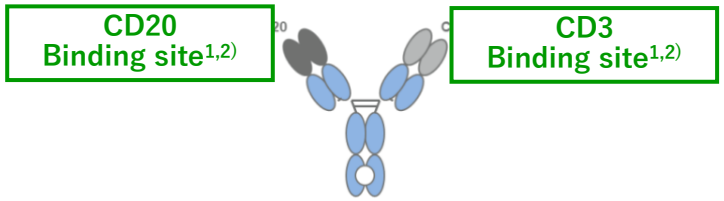


1) Polson AG, et al. Expert Opin Investig Drugs. 2011; 20(1): 75-85. (authors include Genentech emplyees) , 2) Doronina SO, et al. Nat Biotechnol. 2003; 21(7): 778-784. (authors include Genentech employees)

MMAE: monomethyl auristatin E

Overview of T-Cell Engaging Bispecific Antibody in Development

- **Glofitamab and mosunetuzumab are T-cell engaging bispecific antibodies targeting CD20/CD3, designed to target CD20 on B cells and CD3 on T cells**
- **Both drugs are being developed in parallel due to their different characteristics, leading to distinct indications under development and formulations in development**

Generic name	glofitamab	mosunetuzumab
Development code	RG6026	RG7828
Indications under development in Japan	• Untreated diffuse large B-cell lymphoma (Polivy + R-CHP combination)	• Relapsed or refractory follicular lymphoma (monotherapy) • Relapsed or refractory follicular lymphoma (combined with lenalidomide) • Untreated follicular lymphoma (combined with lenalidomide) • Relapsed or refractory aggressive non-Hodgkin's lymphoma (combined with Polivy)
Dosage form under development in Japan	• Intravenous injection	• Intravenous injection • Subcutaneous injection
Structure of mosunetuzumab (conceptual image)		

1) Bacac M, et al. Oncoimmunol 2016;5:e1203498 (authors include Roche employees), 2) Bacac M, et al. Clin Cancer Res 2018;24:4785–97 (authors include Roche employees), 3) Ferl GZ, et al. Clin Transl Sci 2018;11:296–304 (authors include Genentech employees), 4) Sun LL, et al. Sci Transl Med 2015;7:287ra70 (authors include Genentech employees), *Marketing authorization application submitted in Japan in March 2024, R-CHP: rituximab, cyclophosphamide, doxorubicin, prednisone

Mode of Action of Glofitamab and Mosunetuzumab

- CD20 is a cell surface antigen expressed exclusively on all B cells except pro-B cells and plasma cells, and is expressed in almost all B cell lymphomas.
- Glofitamab and mosunetuzumab bind to CD3 expressed on T cells and CD20 expressed on B cell tumors, and it is assumed to activate T cells and destroy CD20-positive tumor cells. [1,2)]

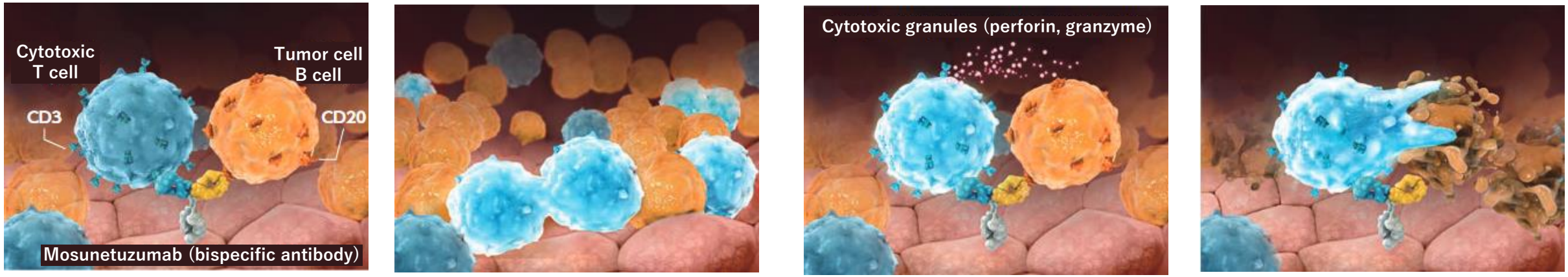
Mechanism of action of glofitamab and mosunetuzumab (conceptual image)

1 Glofitamab or mosunetuzumab bind to CD3 and CD20.

2 T cells are mobilized from the periphery via cytokines, and T cells proliferate at the tumor site.

3 T cell activation releases cytotoxic substances from T cells.

4 Collapse of tumor cells, induction of apoptosis

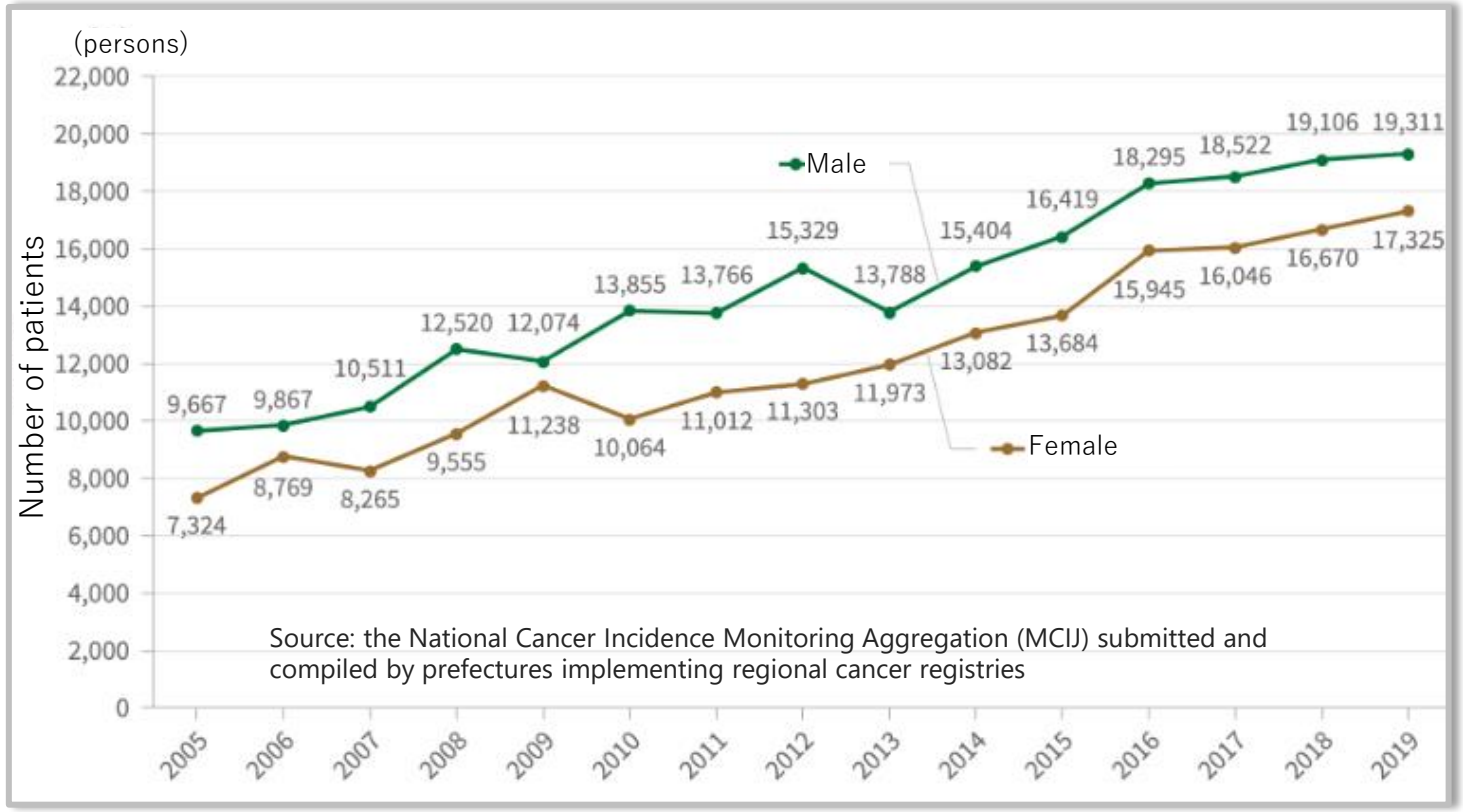


1) Bacac M, et al. Oncoimmunol 2016;5:e1203498, (authors include Roche employees) 2). Bacac M, et al. Clin Cancer Res 2018;24:4785–97. (authors include Roche employees)

What is Lymphoma?

- Lymphoma is a disease in which lymphocytes become cancerous and proliferate, with peak incidence in the 70-80 age group[1)]
- 36,638[2)] new cases of lymphoma diagnosed in 2019 Since 2000, the number of cases has been increasing.

Trends in Lymphoma Incidence in Japan (2005-2019)[3)]



Symptoms of lymphoma[1)]

- Painless lump in lymph node
- Fever
- Heavy night sweats
- Weight loss
- Fatigue, malaise
- Symptoms in organs other than lymph nodes

Examination and diagnosis of lymphoma[1)]

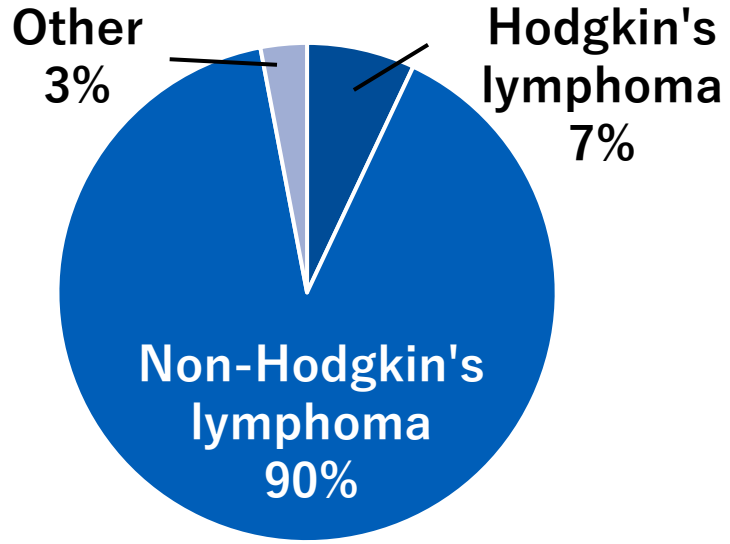
- Medical interview, blood test
- Ultrasonography, CT/MRI scan
- Pathological examination by lymph node biopsy

1) Practical Guidelines for Hematological Malignancies, 2023 Edition, 2) National Cancer Center Cancer Information Service "Cancer Registration and Statistics" (National Cancer Registry),
3) National Cancer Center Cancer Information Service "Cancer Registration and Statistics" (Monitoring of Cancer Incidence in Japan (MCIJ))

What is B-cell Non-Hodgkin's Lymphoma?

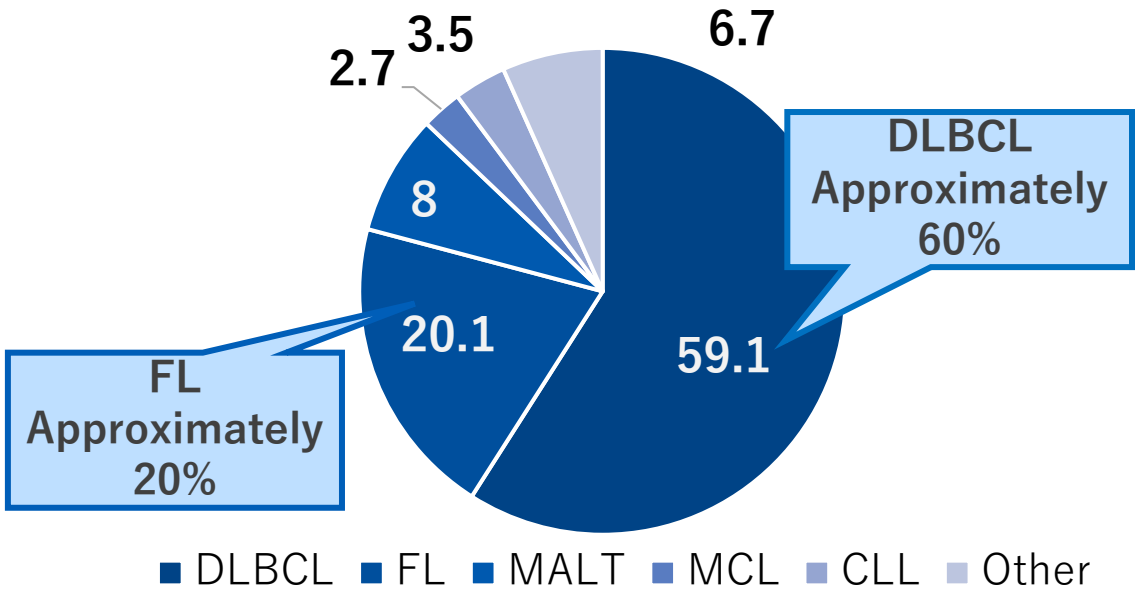
- 90% of lymphomas are non-Hodgkin's lymphomas, of which 85-90% are B-cell derived tumors[1, 2)]
- Among B-cell non-Hodgkin's lymphomas, diffuse large B-cell lymphoma (DLBCL) accounts for ~60%, follicular lymphoma (FL) for ~20%[3)], and aggressive non-Hodgkin's lymphoma (aNHL: including DLBCL, FL grade 3B, histrogically transformed FL, and high-grade B-cell lymphoma) for ~61%[3)].

Incidence rate of lymphoma in Japan (2001-2006)[2)]



Data Summary: Survey of 2,260 patients with lymphoid tumors referred to Fukuoka University and Kurume University from 2001 to 2006

Percentage of B-cell Non-Hodgkin's Lymphoma by Tissue in Japan[3)]



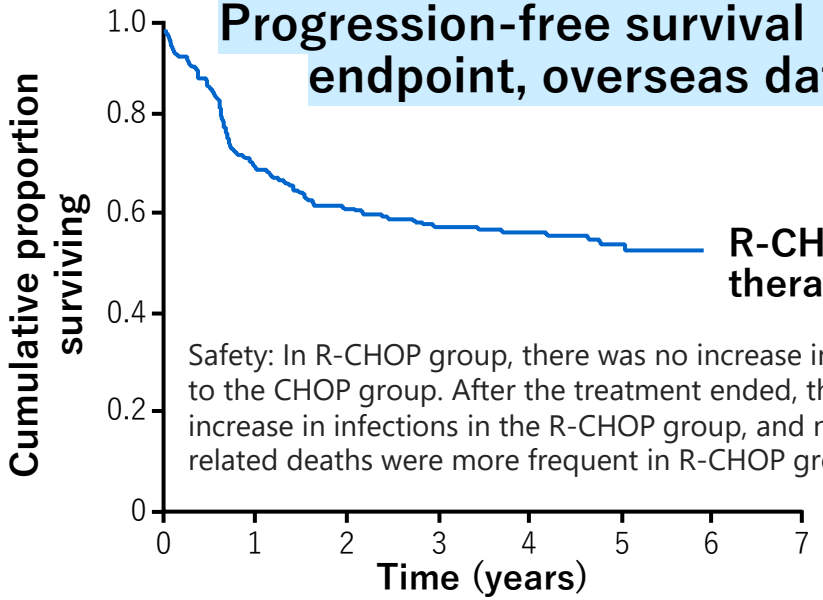
Data Summary: Analysis based on data obtained from 16 prefectures included in the Monitoring of Cancer Incidence in Japan (MCIJ) project (data from 1993 to 2008, N=125,418)

1) Elisabeth S et al, Lancet 2024; 403:1791-807, 2) Aoki R et al. Pathol Int. 2008; 58(3): Prepared from 174-82., 3) Chihara D, et al. Br J Haematol 2014; 164: prepared from 536-45
CLL: Chronic lymphocytic leukemia, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, MALT: mucosa-associated lymphoid tissue lymphoma, MCL: mantle cell lymphoma

What is Diffuse Large B-cell Lymphoma (DLBCL)?

- DLBCL is classified as an aggressive lymphoma, with an estimated 12,000-16,000 patients in Japan[1-3)]
- More effective treatment is needed for both initial treatment and relapsed or refractory treatment.

Therapeutic efficacy of R-CHOP therapy for untreated DLBCL Progression-free survival (primary endpoint, overseas data) [4)]

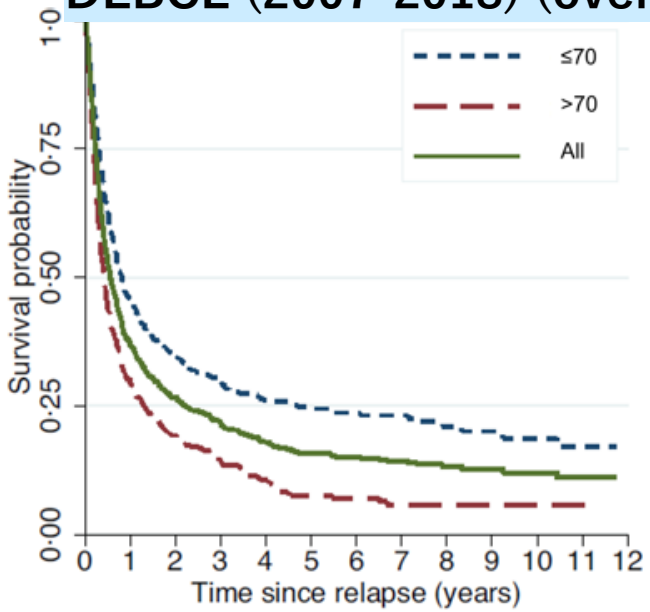


Safety: In R-CHOP group, there was no increase in adverse events compared to the CHOP group. After the treatment ended, there was a tendency for an increase in infections in the R-CHOP group, and non-disease progression-related deaths were more frequent in R-CHOP group.

Initial treatment is aimed at achieving remission, but with R-CHOP therapy, 40% of patients experience relapse or become refractory.

Data Summary: Results of an overseas clinical trial of R-CHOP therapy for untreated DLBCL (N=399) by the Lymphoma Study Group

Overall survival in relapsed or refractory DLBCL (2007-2018) (overseas data) [5)]



Median overall survival in relapsed or refractory disease is 6.6 months, a very poor prognosis.

Data Summary: Transcription study of 736 patients with R/R DLBCL who received curative treatment in Sweden between 2007 and 2014.

1) Foundation for Promotion of Cancer Research 'Cancer Statistics' 2018, 2) Aoki R et al. Pathol Int. 2008; 58(3): 174-82. 3) Chihara D, et al. Br J Haematol 2014; 164: 536-45, 4) Feugier P, et al. J Clin Oncol 2005;23:4117–26, 5) Harrysson S, et al. Br J Haematol 2022;198:267–77
DLBCL: Diffuse large B-cell lymphoma, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

Treatment for DLBCL in Japan

Untreated DLBCL

- Treatment algorithms for untreated patients are divided into limited-stage and advanced-stage
- The standard treatment for advanced stage disease is R-CHOP and Polivy-R-CHP.

Relapsed or refractory DLBCL

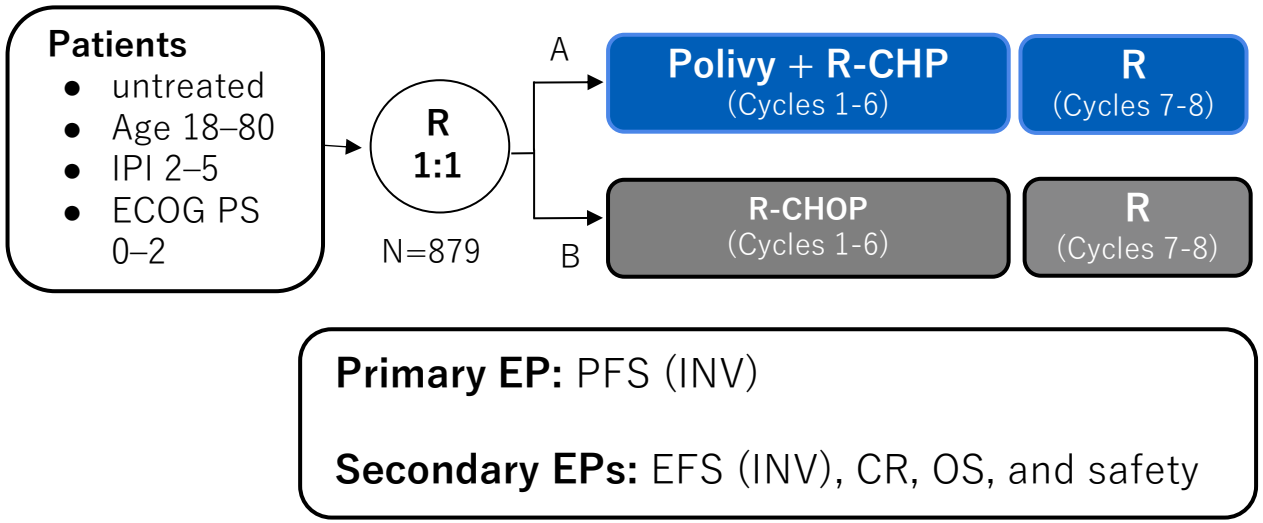
- Second-line and subsequent treatments include autologous transplantation, CAR-T therapy, and salvage chemotherapy.
- The superiority of salvage chemotherapy for relapsed or refractory DLBCL is unclear.

1) Practical Guidelines for Hematological Malignancies, 2023 edition
DLBCL: Diffuse large B-cell lymphoma, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-CHP: Rituximab, cyclophosphamide, doxorubicin, prednisolone

Efficacy of Polivy + R-CHP Therapy in Untreated DLBCL

- The POLARIX study is a global trial to verify the superiority of the Pola + R-CHP therapy in untreated DLBCL.
- The stratified hazard ratio for the Pola + R-CHP group compared to the R-CHOP group as the primary endpoint was 0.73 (95% CI: 0.57-0.95), demonstrating the superiority of the Pola + R-CHP group at a two-sided significance level of 0.05[1)].

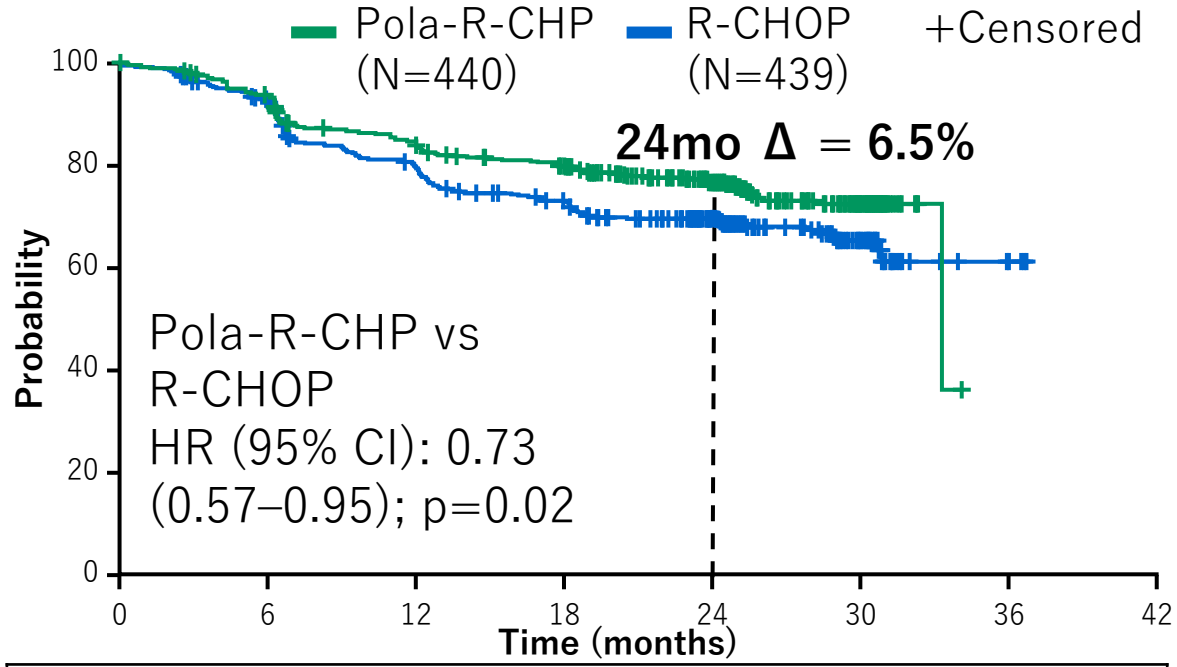
POLARIX study NCT03274492[1)]



Primary EP: PFS (INV)

Secondary EPs: EFS (INV), CR, OS, and safety

Primary endpoint: Progression-free survival[1)]



Number at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Safety

The main side effects are nausea, neutropenia, anemia, fatigue, alopecia, constipation, peripheral neuropathy, and diarrhea

1) Tilly H, et al. New Engl J Med 2022;386:351–63.(authors include Genentech employees)
DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, Pola: Polivy, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-CHP: Rituximab, cyclophosphamide, doxorubicin, prednisolone

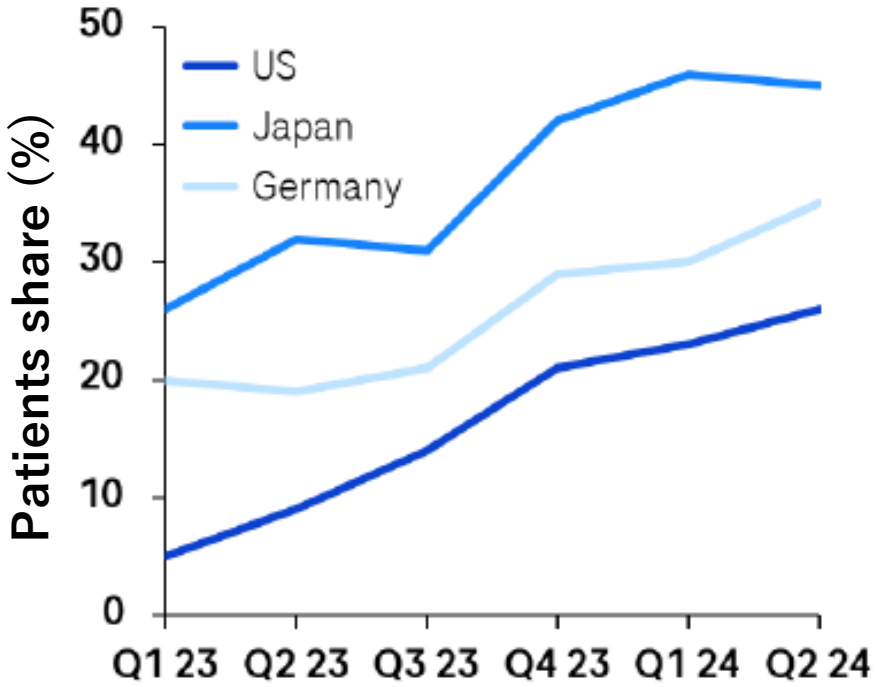
Penetration of Polivy + R-CHP Therapy in Untreated DLBCL

- Polivy + R-CHP therapy is one of the standard therapies in Japanese guidelines for untreated DLBCL* and is gaining popularity.

Positioning of Polivy + R-CHP therapy in untreated DLBCL

- Expanded domestic indications in August 2022
- Delivered to more than 33,000 untreated DLBCL patients worldwide
- The patient share of untreated DLBCL in major countries including Japan is increasing. Especially in Japan, just over 45%.
- Five-year follow-up data from the POLARIX study presented at ASH24

Patient share in 1L DLBCL and IPI 0-5[1)]

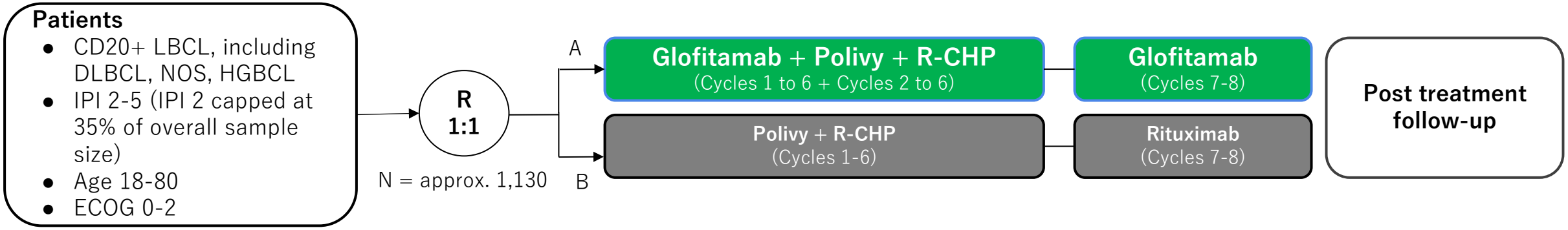


1) Roche Pharma Day 2024
DLBCL: Diffuse large B-cell lymphoma, IPI: International Prognostic Index, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-CHP: Rituximab, cyclophosphamide, doxorubicin, prednisolone
* Advanced stage, aged 18 to over 80, with an IPI score of 2 or higher

Examination of Glo-Pola-R-CHP Therapy in Untreated DLBCL

- The SKYGLO study is a global trial to verify the superiority of Glo-Pola-R-CHP therapy over Pola-R-CHP in untreated DLBCL.
- Case registration is ongoing at 17 sites in Japan.

SKYGLO study NCT06047080[1)]



Primary EP: PFS (IRC)

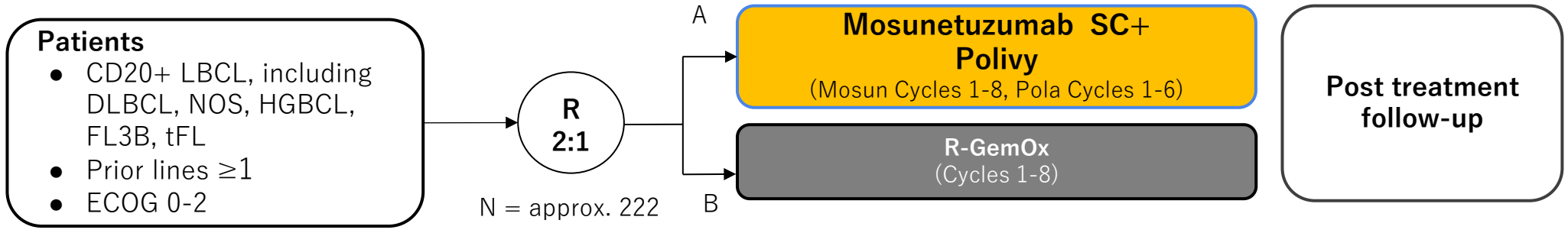
Secondary EPs: OS, PFS (INV), $EFS_{efficacy}$, DOR, DOCR, PFS in IPI 3-5 (IRC), safety, PK, PROs, ctDNA

1) NCT06047080 https://clinicaltrials.gov/study/NCT06047080?term=glofitamab&aggFilters=phase:3,status:rec&rank=2 (Accessed: November 2024)
DLBCL: Diffuse large B-cell lymphoma, Glo: glofitamab, IPI: International Prognostic Index, Pola: Polivy, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, R-CHP: Rituximab, cyclophosphamide, doxorubicin, prednisolone

Examination of Mosun+Polivy Therapy in 2L+aNHL

- The SUNMO study is a global trial to verify the superiority of mosunetuzumab + Polivy in 2L+ aggressive non-Hodgkin's lymphoma (aNHL).
- Domestic case registration has been completed, and lead-out is scheduled for 2025.

SUNMO study NCT05171647[1)]



Primary EP: PFS (IRC)

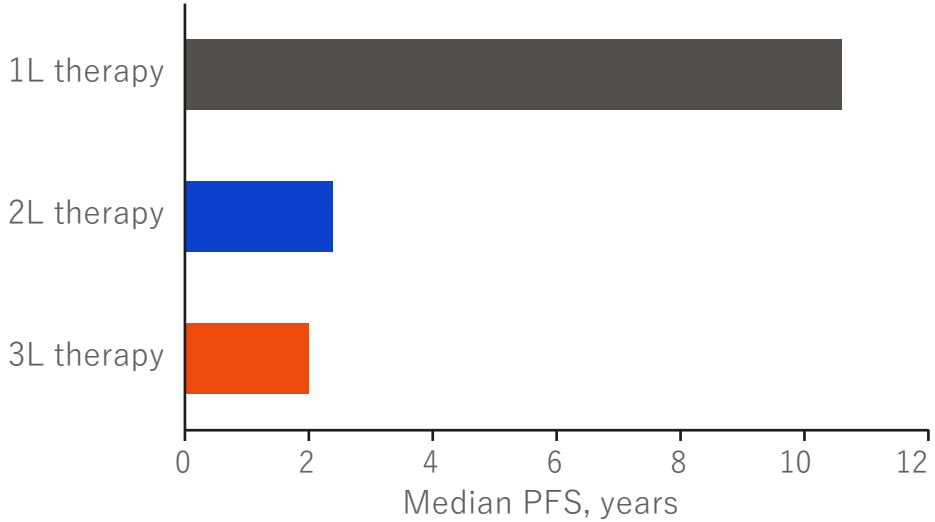
Secondary EPs: OS, ORR, CR rate, DOR, PROs, safety

1) NCT05171647 https://clinicaltrials.gov/study/NCT05171647?term=mosunetuzumab&aggFilters=phase:3&rank=5 (Accessed: November 2024)
aNHL: Aggressive non-Hodgkin's lymphoma (including diffuse large B-cell lymphoma, FL grade 3B, transformed FL, and aggressive B-cell lymphoma), IRC: Independent Review Committee, Mosun: Mosunetuzumab, SC: Subcutaneous formulation

What is Follicular Lymphoma (FL)?

- FL is classified as an indolent lymphoma, and the number of patients in Japan is estimated to be between 5,000 and 9,000.[1-3)]
- Although progression is slow, recurrences are common, and this tendency is particularly pronounced in the advanced stages.[4)]

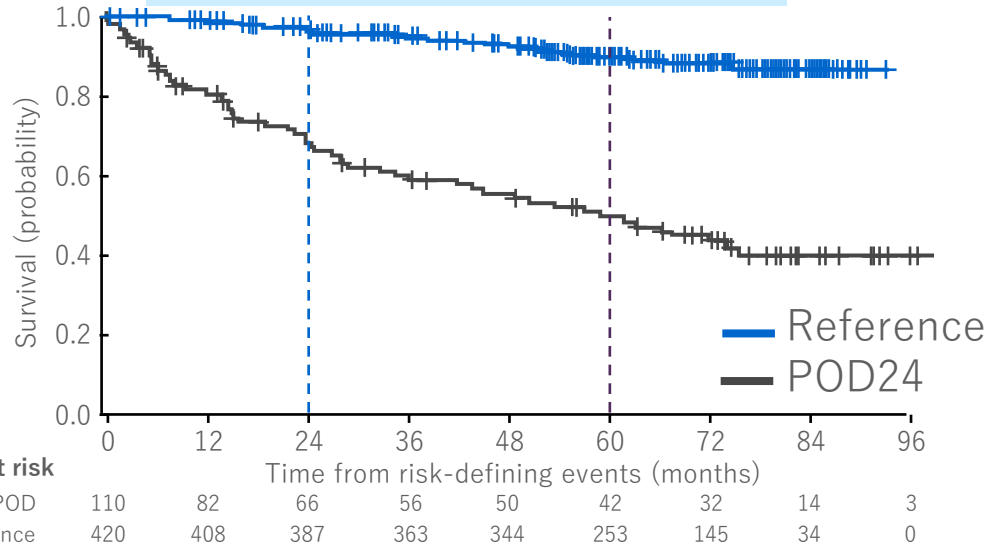
Progression-free survival by treatment line in FL(overseas data)[5)]



Data overview: analysis based on 348 patients diagnosed with FL and treated with chemoimmunotherapy at two institutions in Spain between 2001 and 2014.

Repeated recurrences are common, and progression-free survival is shorter the more advanced the treatment line.

Overall survival by response to first-line treatment (overseas data)[6)]



No. at risk									
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

Data overview: analysis of 588 patients diagnosed between 2001 and 2014 at a US institution who received R-CHOP as first-line treatment. Patients were divided (non-randomized) into two groups: those who relapsed within 2 years of diagnosis and those who did not relapse within 2 years of diagnosis.

The 5-year survival rate for first-line treatment was 50% in the group that relapsed within 2 years (POD24) . The rate in group with no relapse within 24 months (Reference) was 90%.

1) Foundation for Promotion of Cancer Research 'Cancer Statistics' 2018, 2) Aoki R et al. Pathol Int. 2008; 58(3): 174-82. 3) Chihara D, et al. Br J Haematol 2014; 164: 536-45, 4) Practical Guidelines for Hematological Malignancies, 2023 edition,
5) Rivas-Delgado A, et al. Br J Haematol 2019;184:753–59, 6) Casulo C, et al. J Clin Oncol 2015;33(23):2516–22. FL: follicular lymphoma, POD24: recurrence within 24 months

Treatment for FL in Japan

Untreated FL

- The treatment algorithm for untreated patients is classified into limited and advanced stages.
- For advanced high tumor burden patients, anti-CD20 antibody combination chemotherapy ± maintenance therapy is the standard treatment.

Relapse or refractory FL

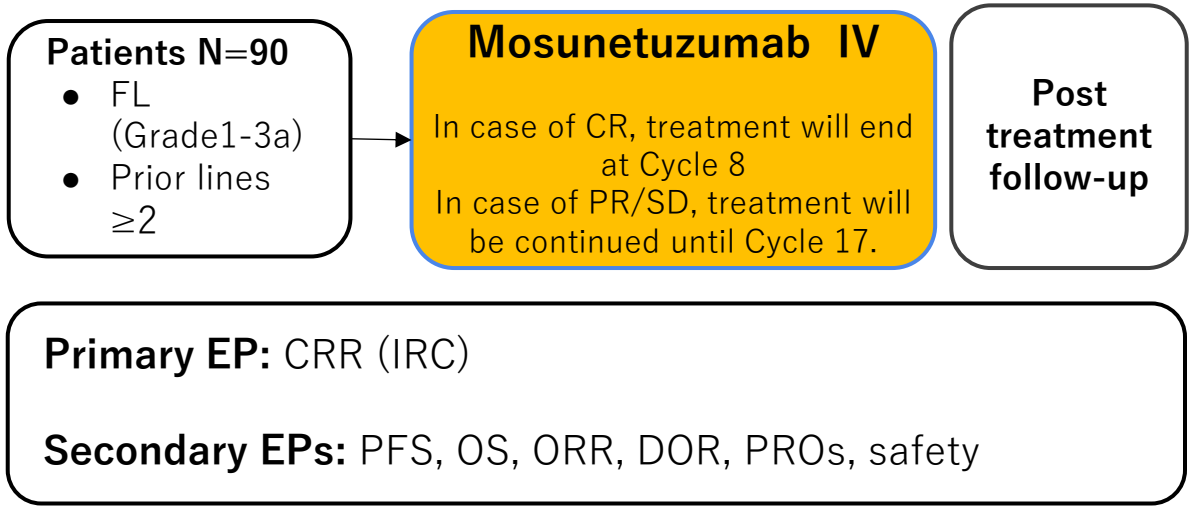
- Second-line and subsequent treatments include anti-CD20 antibody ± combination chemotherapy , CAR-T therapy, and salvage chemotherapy.
- Treatment at the time of recurrence is selected taking into consideration the details of previous treatment, the time until recurrence, the extent of the lesion, the presence or absence of histological transformation, the patient's condition (organ function, physical activity level, etc.), and the patient's wishes.

Reference: Practical Guidelines for Hematological Malignancies, 2023 edition （http://www.jshem.or.jp/gui-hemali/table.html）(Accessed on Nov 2024)
CAR-T: Chimeric Antigen Receptor-T cell

Development of Mosunetuzumab Monotherapy in 3L+FL

- **Efficacy and safety in 3L+ FL were evaluated in an overseas Phase I/II clinical trial (single-arm) and a domestic Phase I clinical trial (FLMOON-1) assessing mosunetuzumab monotherapy**
- **4-year data from the overseas Phase I/II clinical trial (monotherapy) and FLMOON-1 data have been presented at ASH24 and JSH24, respectively**

Overseas phase I/II clinical study (single-arm) [1)]



Primary EP: CRR (IRC)

Secondary EPs: PFS, OS, ORR, DOR, PROs, safety

3-year follow-up results of mosunetuzumab monotherapy in 3L+ FL (published in literature)[2)]

Safety

The main adverse events were CRS in 44.4% (40 patients, grade 1/2: 38 patients, grade 3/4: 2 patients). CRS occurred mainly in cycle 1. Neutropenia occurred in 28.9% (26 patients) and fever in 28.9% (26 patients). Safety was manageable, and no events of concern due to long-term administration were observed.

Efficacy

- CRR (IRC assessment, primary endpoint): 60.0% (95% CI: 49.1-70.2%)
- ORR (IRC assessment, secondary endpoint): 77.8% (95% CI: 67.8-85.9%)
- Median duration of CR (secondary endpoint): Not reached (95% CI: 33.0 months-not evaluable)

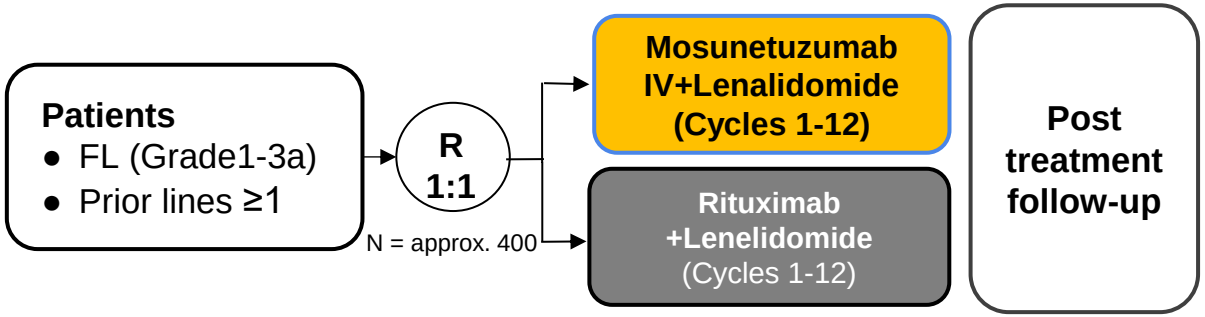
1) NCT02500407 https://clinicaltrials.gov/study/NCT02500407?term=GO29781&intr=mosunetuzumab&rank=1 (Accessed: November 2024)
2) Sehn L, 2024; Blood 2024025454 (The authors include employees from Genentech), CR: complete response, CRS: cytokine release syndrome, FL: follicular lymphoma, Gr: grade, NE: not estimated, ORR: response rate

Examination of Mosun + Lenalidomide Therapy in 2L+ Untreated FL

2L+FL

- The CELESTIMO study is a global trial to verify the superiority of mosunetuzumab + lenalidomide over rituximab + lenalidomide in 2L+FL patients.
- Domestic case registration has been completed, and lead-out is scheduled for 2025.

CELESTIMO study NCT04712097[1)]



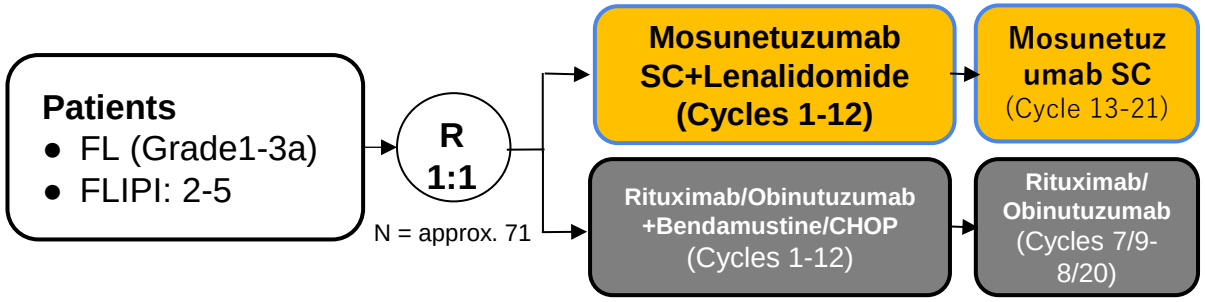
Primary EP: PFS (IRC)

Secondary EPs: OS, ORR, CR rate, DOR, PROs, safety

Untreated FL

- A domestic phase III clinical trial[1)] to verify the superiority of mosunetuzumab + lenalidomide therapy over rituximab + lenalidomide in untreated FL begins in November.
- Overseas, the Lymphoma Academic Research Organisation (LYSARC) in France, which is a collaborator in the domestic trial, is conducting the MorningLyte trial.[2)]

Japanese phase III clinical study jRCT2011240017[2)]



Primary EP: PFS (IRC)

Secondary EPs: OS, ORR, CR rate, DOR, PROs, safety

1) NCT04712097 https://clinicaltrials.gov/study/NCT04712097?term=mosunetuzumab&aggFilters=phase:3&rank=2 (Accessed: November 2024)
FL: Follicular lymphoma, IRC: Independent Review Committee, IV: Intravenous formulation, Mosun: Mosunetuzumab, PFS: Progression-free survival

Blood Cancer Portfolio

■ Contributing to the field of blood cancer through the development of Polivy, mosunetuzumab, and glofitamab

DLBCL	1L	Polivy + R-CHP POLARIX study	Expanded indications in August 2022
		glofitamab + Polivy + R-CHP SKYGLO study	Scheduled to file for approval in 2027 and beyond
aNHL	2L+	Mosunetuzumab + Polivy SUNMO study	Scheduled to file for approval in 2025
	1L	Mosunetuzumab + Len MorningLyte study	Scheduled to file for approval in 2027 and beyond
FL	2L+	Mosunetuzumab + Len CELESTIMO study	Scheduled to file for approval in 2026
	3L+	Mosunetuzumab monotherapy Overseas Phase I/II study / FLMOON-1 study	Filed for approval in March 2024

aNHL: Aggressive non-Hodgkin's lymphoma, DLBCL: diffuse large B-cell lymphoma, FL: follicular lymphoma, Len: lenalidomide, R-CHP: rituximab, cyclophosphamide, doxorubicin, prednisolone

Giredestrant Tartrate
Inavolisib

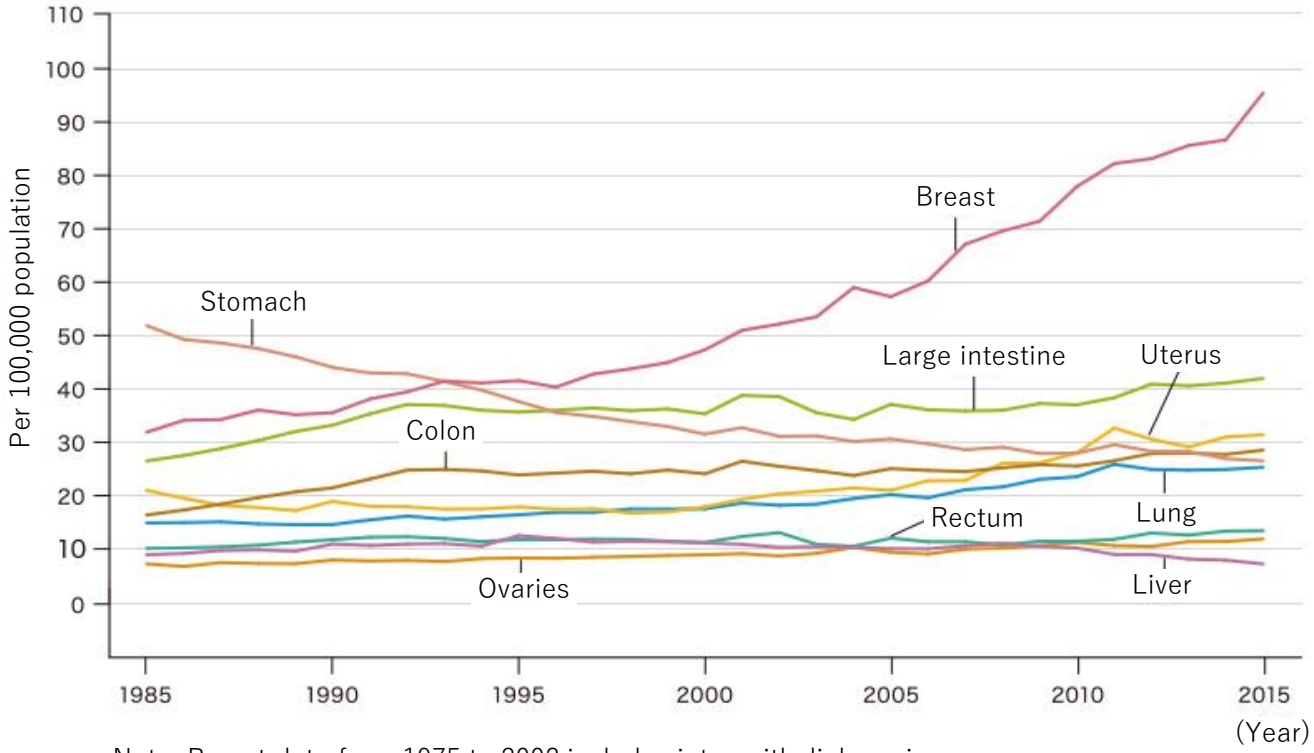
Yuji Habara

Giredestrant & Inavolisib & HER2 Franchise Lifecycle Leader

Disease and Epidemiological Information on Breast Cancer

■ Compared to the number of patients with cancer of various sites, the increase in breast cancer is particularly large, ranking first in the number of women with cancer by site (91,531 cases)[1].

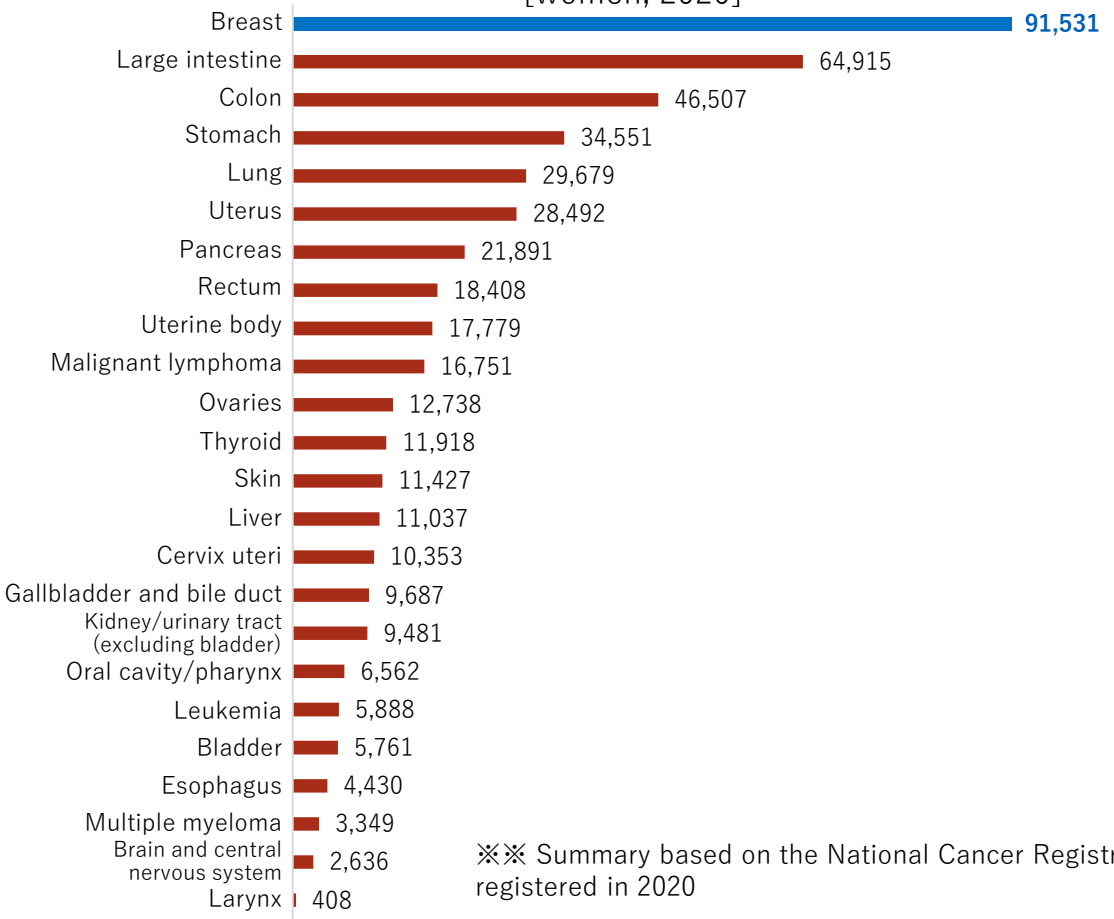
By site (main site)
Cancer Age-Adjusted Incidence Rates Yearly Trends: Women (1985-2015)[1]



Note: Breast data from 1975 to 2002 includes intraepithelial carcinoma.

※ Created based on cancer incidence data from 3 prefectural cancer registries since the 2015 edition
Actual incidence data from 3 prefectures: Yamagata, Fukui, and Nagasaki (regional cancer registries with long-term high accuracy and stability)

Number of patients with cancer by site [women, 2020]



※※ Summary based on the National Cancer Registry registered in 2020

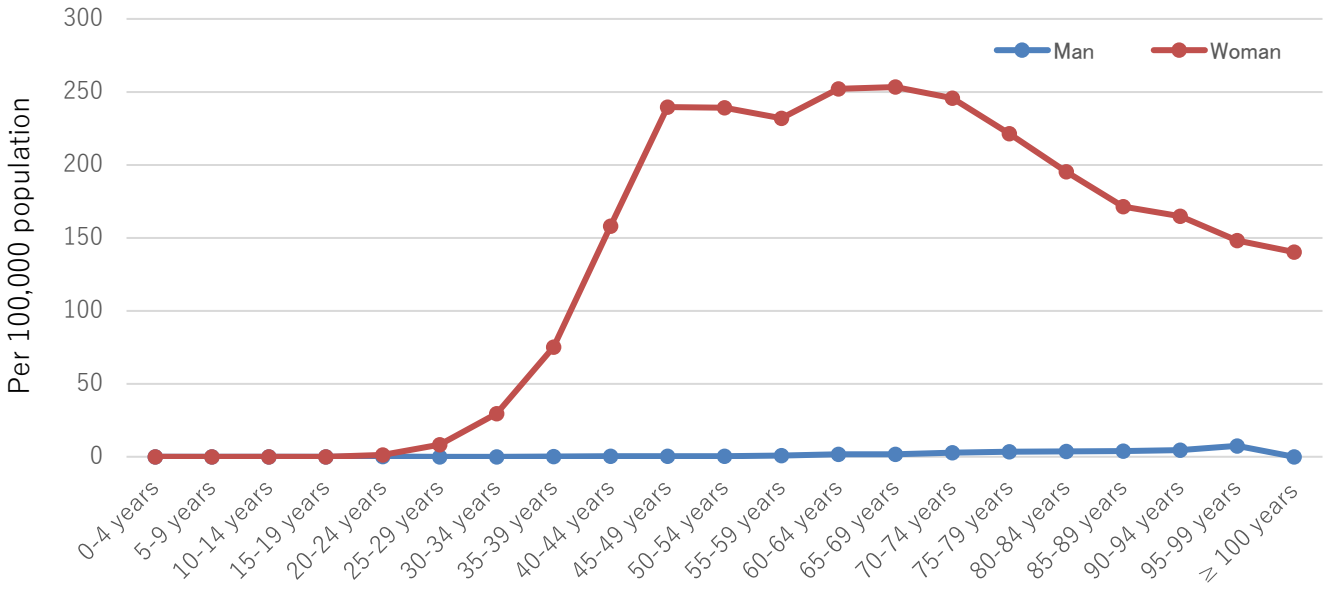
1) National Cancer Center Cancer Information Service "Cancer Statistics"

Disease and Epidemiological Information on Breast Cancer

- Breast cancer occurs frequently in women in their 40s and 50s[1)]
- Breast cancer is the most common cancer among Japanese women, but it ranks fourth in cancer deaths[1)]. Although the number of women who develop breast cancer is high, there are many women who overcome it.

Incidence rate by age group[1)]

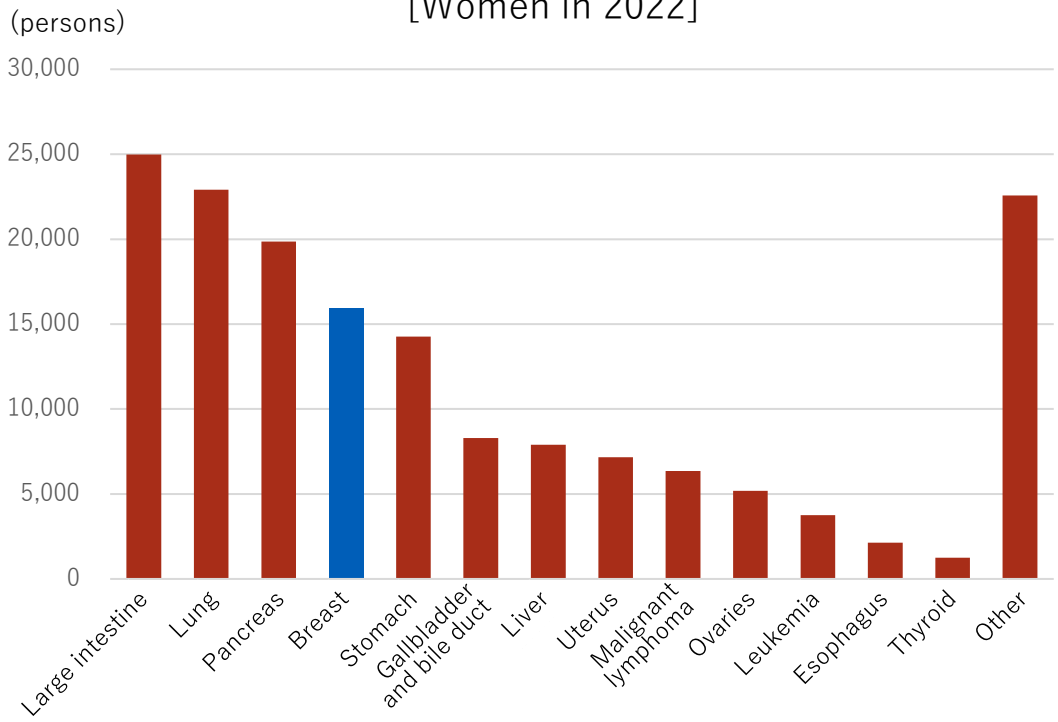
[Breast in 2020]



※ Summary based on the National Cancer Registry registered in 2020

Number of cancer deaths by site[1)]

[Women in 2022]



※※ Tabulated based on Vital Statistics (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare)

1) National Cancer Center Cancer Information Service "Cancer Statistics"

Main Therapeutic Agents Under the Guidelines for Breast Cancer Treatment

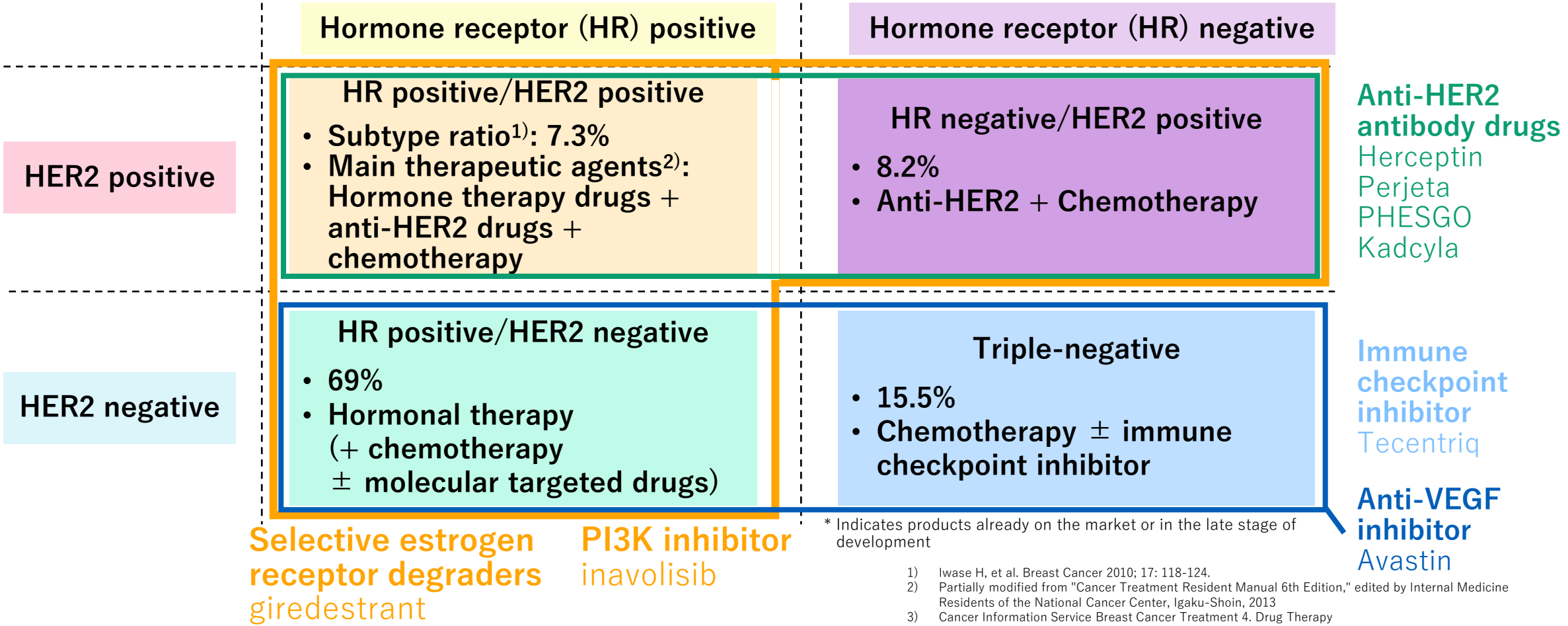
■ Breast cancer is classified into four main subtypes, and therapeutic agents are selected for each subtype.

	Hormone receptor (HR) positive	Hormone receptor (HR) negative
HER2 positive	**HR positive/HER2 positive** • Subtype ratio[1]: 7.3% • Main therapeutic agents[2]: Hormone therapy drugs + anti-HER2 drugs + chemotherapy	**HR negative/HER2 positive** • 8.2% • Anti-HER2 + Chemotherapy
HER2 negative	**HR positive/HER2 negative** • 69% • Hormonal therapy (+ chemotherapy ± molecular targeted drugs)	**Triple-negative** • 15.5% • Chemotherapy ± immune checkpoint inhibitor

1) Iwase H, et al. Breast Cancer 2010; 17: 118-124.
2) Partially modified from "Cancer Treatment Resident Manual 6th Edition," edited by Internal Medicine Residents of the National Cancer Center, Igaku-Shoin, 2013
3) Cancer Information Service Breast Cancer Treatment 4. Drug Therapy

Chugai Offers Comprehensive Treatments for Each Subtype of Breast Cancer

■ By strengthening our development pipeline for subtypes with high unmet needs, we will create synergies between products as part of our breast cancer strategy and contribute to improving patients' QoL.

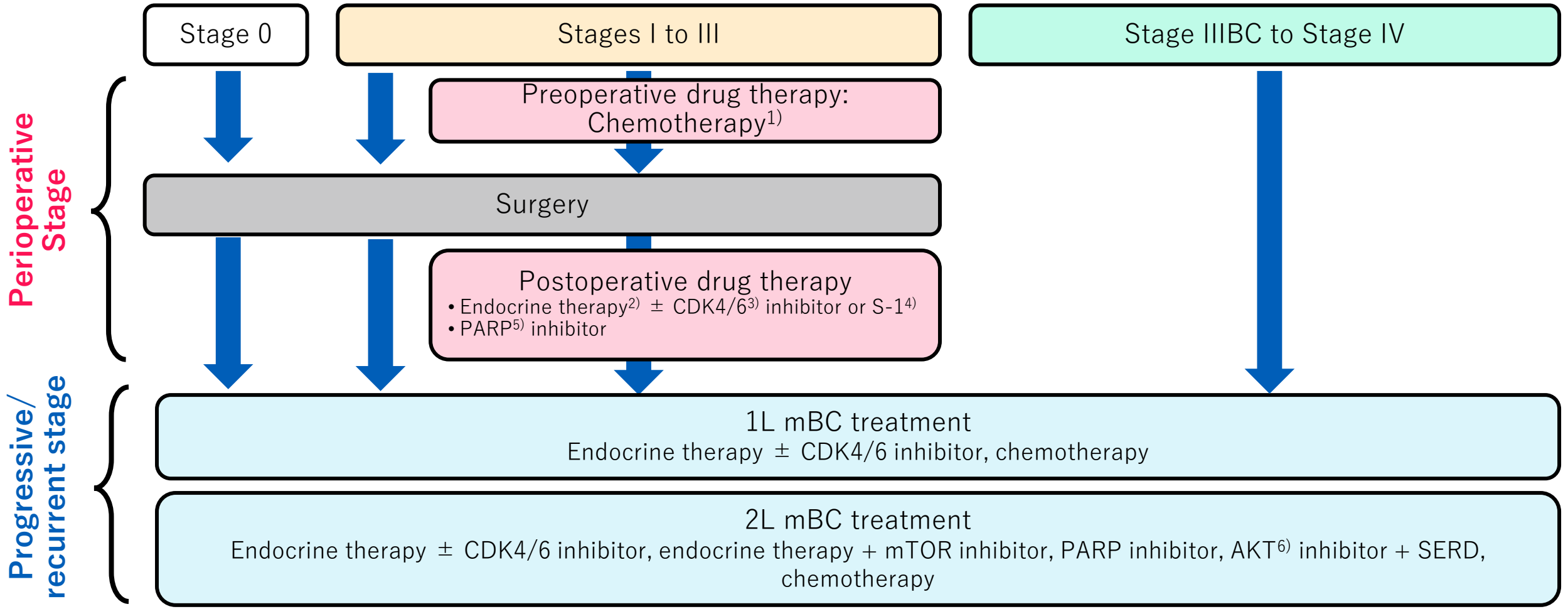


* Indicates products already on the market or in the late stage of development

1) Iwase H, et al. Breast Cancer 2010; 17: 118-124.
2) Partially modified from "Cancer Treatment Resident Manual 6th Edition," edited by Internal Medicine Residents of the National Cancer Center, Igaku-Shoin, 2013
3) Cancer Information Service Breast Cancer Treatment 4. Drug Therapy

Giredestrant Tartrate, Inavolisib

Chemotherapy Algorithm for HR-positive, HER2-Negative Breast Cancer



1) Anthracyclines, alkylating agents, taxanes, fluoropyrimidines, 2) LH-RH agonists, antiestrogens, aromatase inhibitors (AI), 3) cyclin-dependent kinases, 4) tegafur/gimeracil/oteracil potassium combination drugs, 5) poly ADP-ribose polymerase, 6) serine/threonine kinase AKT

Source: Clinical Practice Guidelines for Breast Cancer (1) Treatment Edition 2022 Edition compiled by the Japanese Breast Cancer Society, Breast Cancer Treatment Guidelines for Patients 2023 Edition compiled by the Japan Breast Cancer Society

Giredestrant Tartrate, Inavolisib

Overview of Pharmacotherapy Approaches for HR-Positive Breast Cancer

- Giredestrant is a selective estrogen receptor degrader (SERD), and inavolisib is a PI3K inhibitor under development.

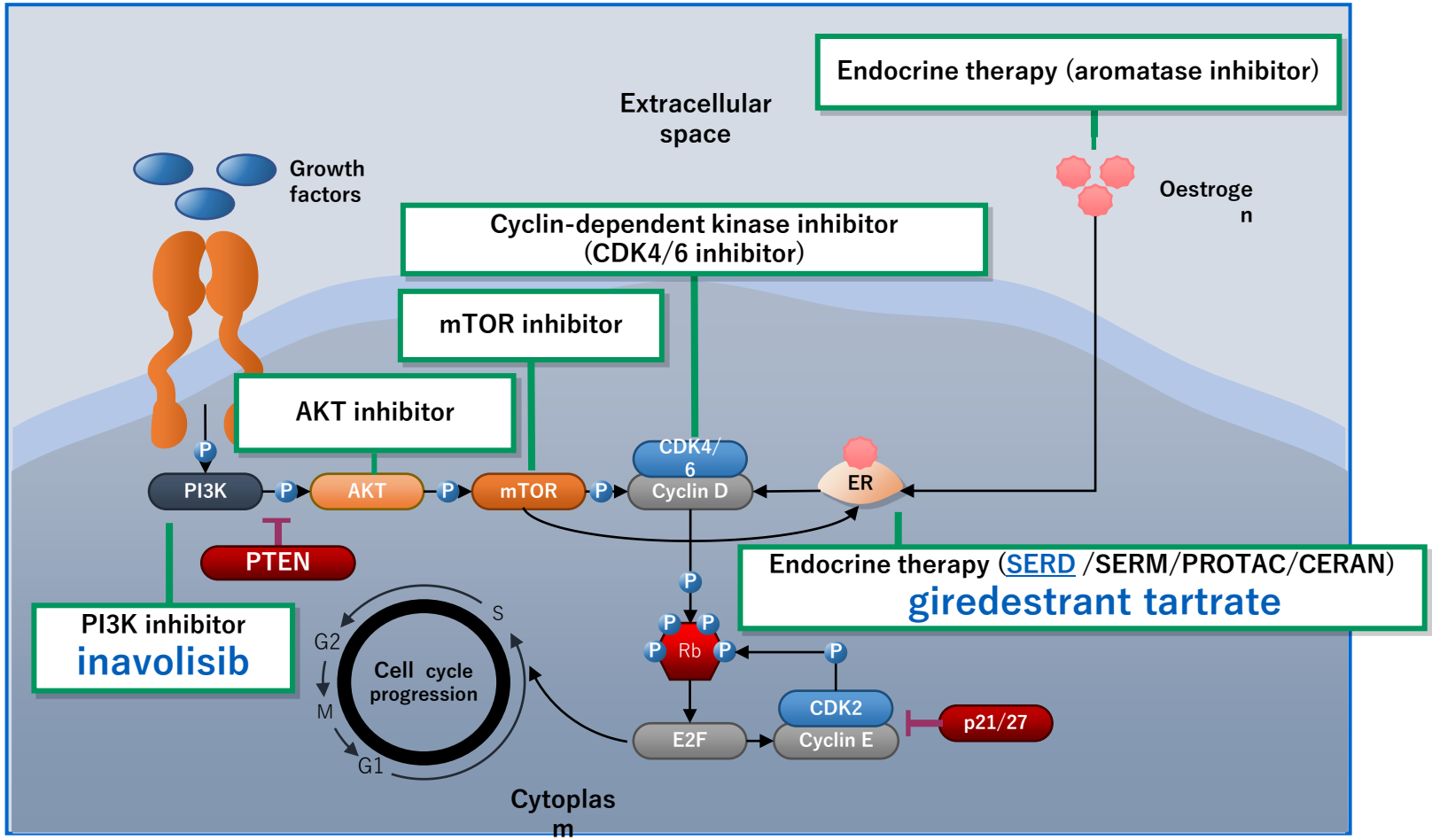
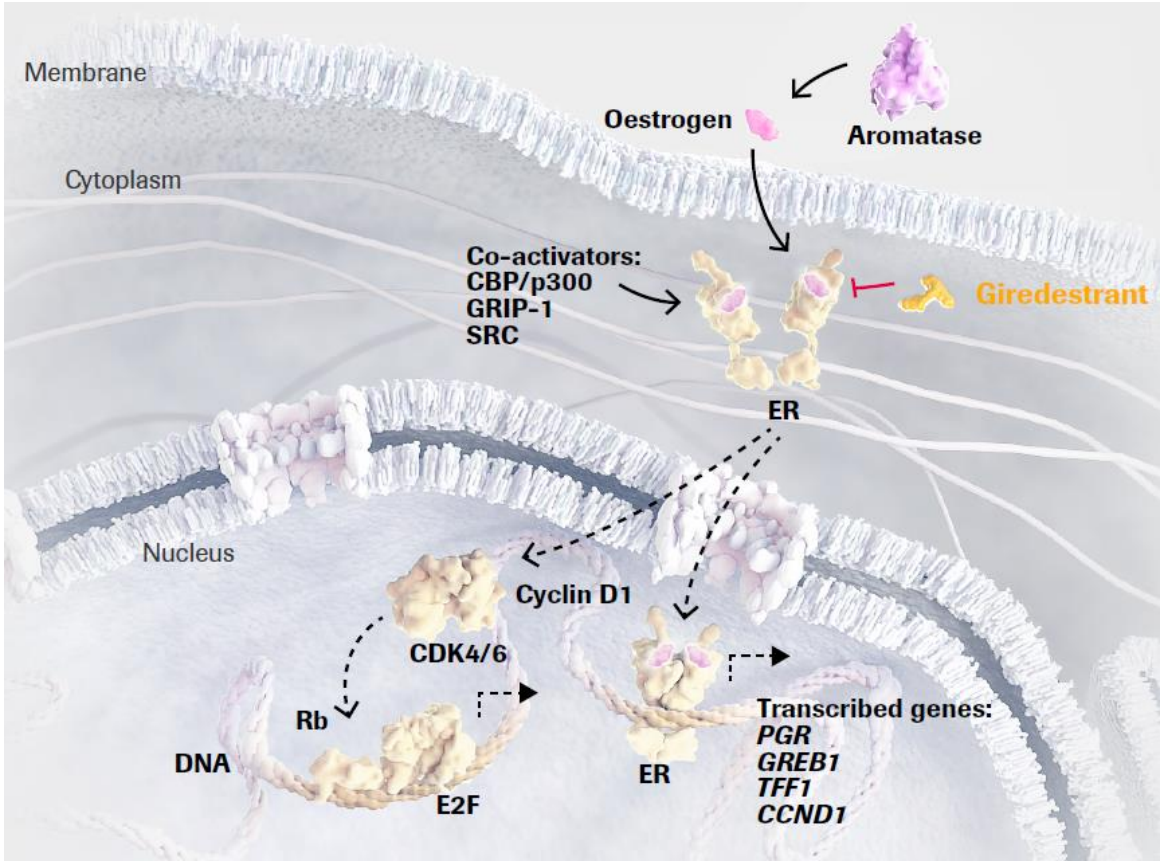


Figure taken from reference: Brufsky AM & Dickler MN. Oncologist 2018; 23:528－539.

Giredestrant (SERD)'s Mechanism of Action

- Giredestrant is a selective estrogen receptor degrader (SERD)
- It binds to estrogen receptors (ER) on the surface of breast cancer cells and inhibits the binding of estrogen. It also promotes the breakdown of estrogen receptors and reduces the number of estrogen receptors in cells[1)]. These mechanisms of action are thought to suppress cancer growth.



conceptual illustration

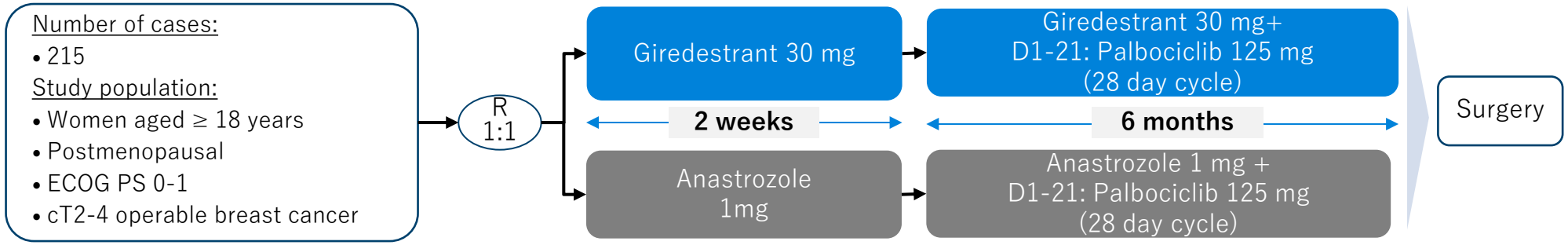
1) Metcalfe C. Presented at: Virtual Annual Meeting II of AACR. June 2020.

Giredestrant Tartrate

CoopERA Study (Overseas Phase II Clinical Study)

■ **Giredestrant showed a significantly greater relative geometric mean decrease in Ki67 from baseline to week 2 compared to anastrozole.**

Study design overview



Primary endpoint

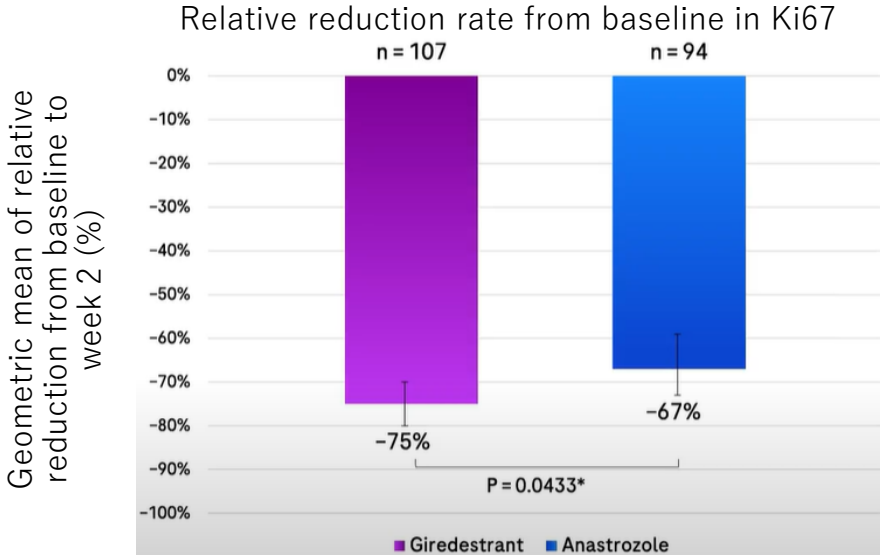
- Ki-67 reduction rate at 2 weeks
- Evaluation by a central laboratory using validated Ki-67 clinical trial assays

Secondary endpoints

- Ki-67 CCCA at 2 weeks and EOT, ORR at EOT, safety, PK and PRO
- RNAseq ER pathway activity and changes in ER and PR IHC H scores

Ki67: A nuclear protein present in proliferating cancer cells that is an indicator of the degree of cell proliferation, CCCA: complete cell cycle arrest, EOT: end of treatment, PK: pharmacokinetics, PRO: patient-reported outcome, RNAseq: RNA sequencing, ER: estrogen receptor, PR: progesterone receptor, IHC: immunohistochemical staining

Results (primary endpoint)



*P-value cutoff for superiority at primary analysis: 0.09687

Safety

Giredestrant demonstrated good tolerability both as monotherapy and in combination with palbociclib. The main side effects were neutropenia, decreased neutrophil count, asthenia, hot flush, and nausea.

- **Giredestrant: -75%**
- **Anastrozole: -67%**
- **P-value: 0.0433***

Hurvitz SA, et al. Lancet Oncol 2023; 24:1029–1041

Giredestrant Tartrate

AcelERA Study (Overseas Phase II Clinical Study)

■ **Although the primary endpoint of investigator-assessed median PFS was not statistically significant, giredestrant showed numerically superior results compared to physician's choice endocrine therapy, and suggested potential efficacy in patients with *ESR1* gene mutations.**

Study design overview

Number of cases: 303
Study population:
- ER positive/HER2 negative mBC
- Postmenopausal or premenopausal/perimenopausal women and men
- History of 1 or 2 lines of systemic therapy for LA/mBC: 1 line must be ET (>6 months), less than 1 targeted agent, less than 1 chemotherapy is acceptable.

R 1:1

- Giredestrant 30 mg
- Endocrine therapy (monotherapy) at the doctor's choice (AI or fulvestrant)

→ Survival follow-up

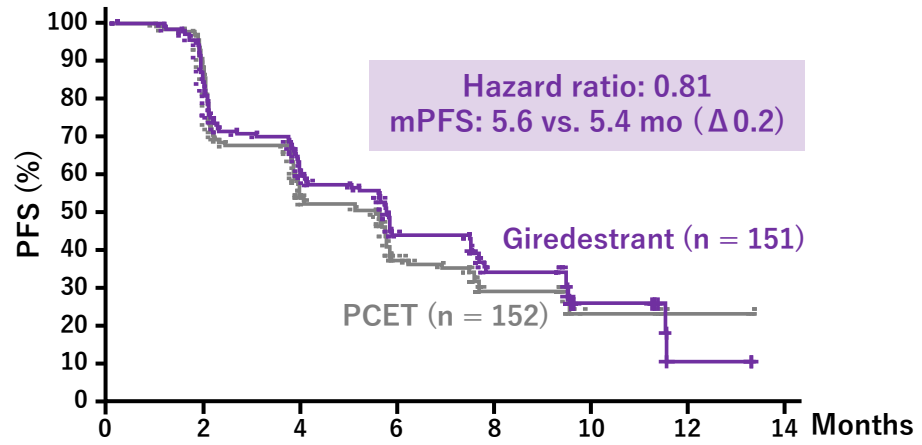
Primary endpoint

- Investigator-assessed PFS (RECIST v1.1)

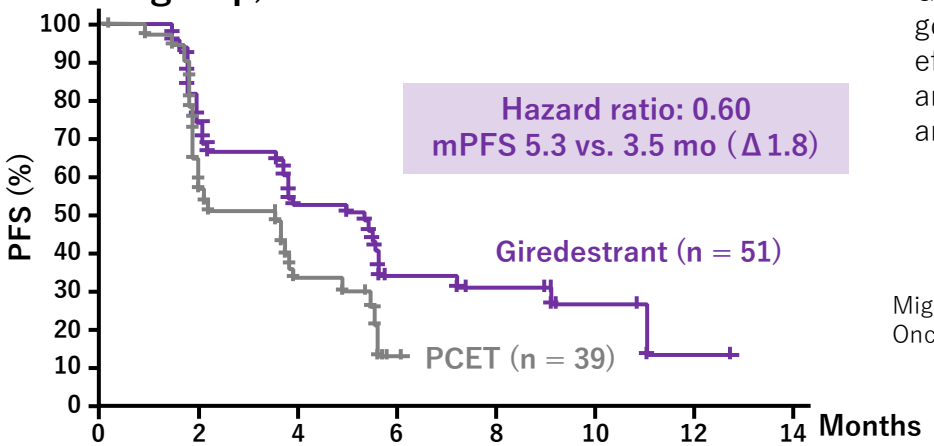
Secondary endpoints

- OS, CBR, ORR, DoR, PFS in *ESR1* gene mutation group by ctDNA, safety, PROs

Results (primary endpoint)



Results (Secondary endpoint: PFS in *ESR1* gene mutation group)



Safety

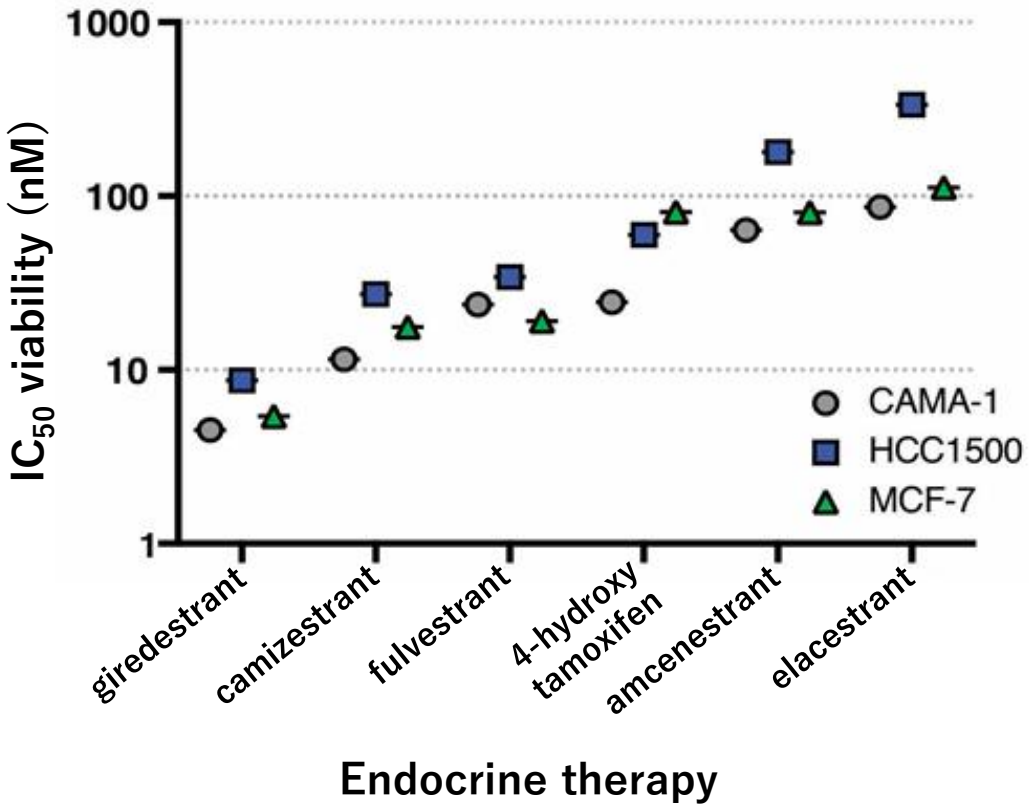
Giredestrant demonstrated good tolerability. The main Side effects were increased AST, arthralgia, increased ALT, anemia, and nausea.

Miguel Martín, et al. J Clin Oncol. 2024;42:2149-2160.

ESR1: Estrogen receptor 1, ER: estrogen receptor, HER2: human epidermal growth factor receptor 2, mBC: inoperable or recurrent breast cancer, LA: luminal A, ET: endocrine therapy, PFS: progression-free survival, OS: overall survival, CBR: clinical benefit rate, ORR: response rate, DoR: duration of response, ctDNA: DNA derived from cancer circulating in the blood, PRO: patient-reported outcome

Giredestrant is a Highly Potent Oral SERD Aiming to be Best-In-Class

Viability assay: Potency of ER antagonists in three types of ER-positive cell lines[1)]



Endocrine therapy	Potency (IC_{50}) of ER antagonists in three types of ER-positive cell lines[1)]
giredestrant	**4.5–8.7 nM**
camizestrant	11.5–27.2 nM
fulvestrant	19.1–34.1 nM
4-hydroxy tamoxifen	24.5–80.7 nM
amcenestrant	63.7–179 nM
elacestrant	86.3–334.8 nM

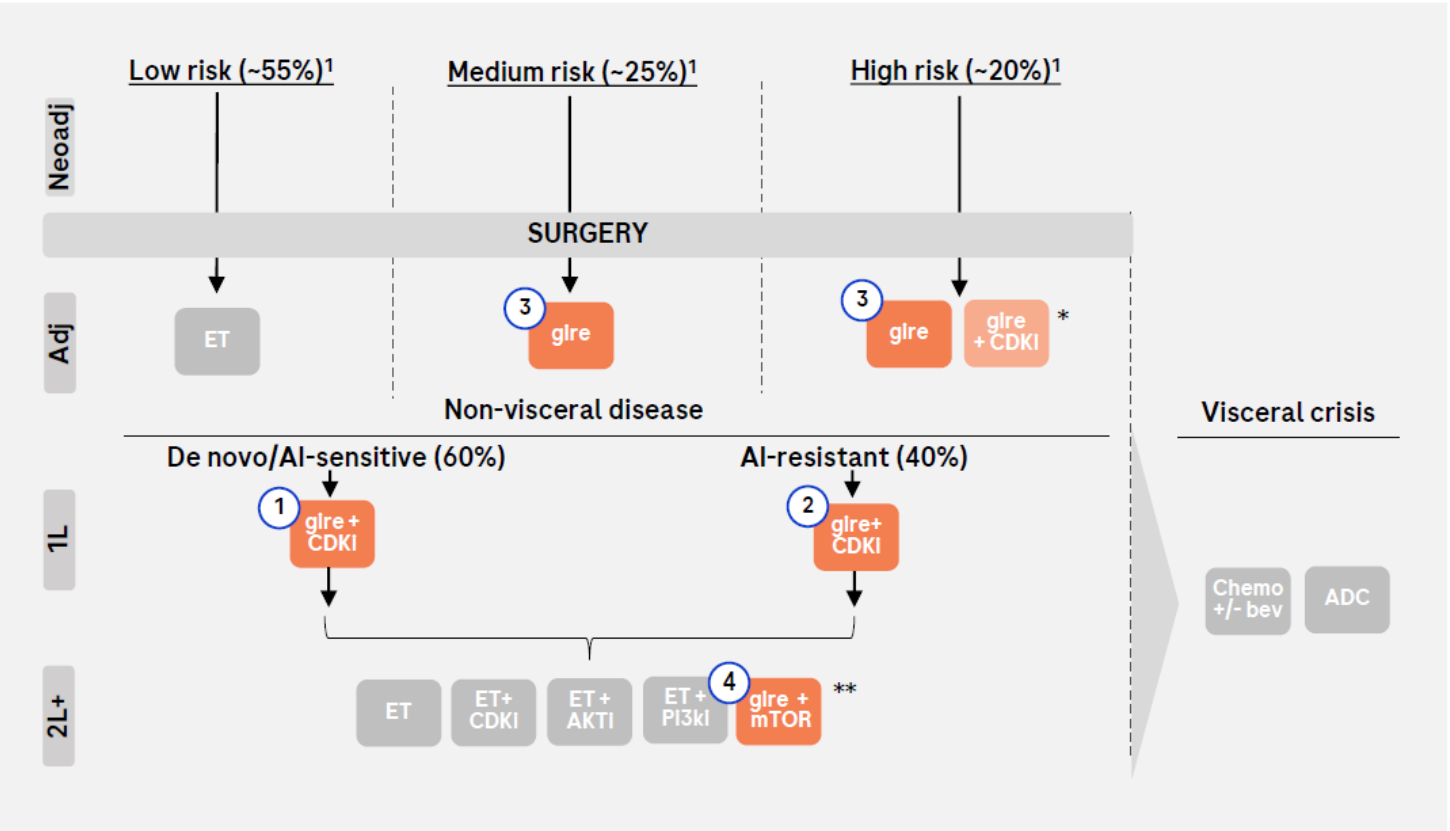
ER: Estrogen receptor, IC_{50}, half maximal inhibitory concentration, SERD: Selective estrogen receptor degrader

1) Liang J, et al. J Med Chem 2021; 64:11841–11856 (Incl. suppl.)

Giredestrant Tartrate

Overview of Clinical Trials, Treatment Lines, etc. for Giredestrant

Giredestrant aims to replace standard of care ET across eBC & mBC



gire giredestrant

1	gire + palbociclib (persevERA)	1L ER+/HER2-mBC (Endocrine therapy sensitivity)
2	gire + CDK4/6 inhibitor (pionERA)	1L ER+/HER2-mBC (Endocrine therapy resistant)
3	giredestrant (lidERA)	Postoperative ER+/HER2-eBC
4	gire + everolimus (evERA)	2L ER+/HER2-mBC
	gire + PHESGO (heredERA)	1L ER+/HER2+mBC

1 4 Test results will be available in 2025.

1 3 4 Studies in which Japan is participating.

1 Risk definitions vary according to guidelines and tools used: stage at diagnosis based on internal estimates using SEER data *giredestrant + CDK4/6i in adjuvant HR+ BC being evaluated as single arm substudy as part of Ph 3 lidERA **giredestrant + everolimus in 2L+ HR+ BC is being investigated as Medical Affairs study; AI=aromatase inhibitor, ET=endocrine therapy , eBC=early breast cancer, mBC=metastatic breast cancer, neoadj=neoadjuvant , adj=adjuvant , SERD=selective estrogen receptor degrader

Quoted from the presentation slides of Roche Pharma Day 2024

Current Understanding of the Main Status of Endocrine Therapy

[Improvement of convenience]

- Existing SERDs are intramuscular injectable formulations, which may cause pain associated with administration[1)] and patient burden for administration at medical facilities.

[New treatment options for resistance/recurrence]

- In metastatic breast cancer, there are cases of resistance to aromatase inhibitors.[2-4)] *ESR1* mutations are thought to be one of the mechanisms by which such resistance is acquired[5-7)], and the prevalence of *ESR1* mutations after treatment with aromatase inhibitors is thought to be less than 40%.[6)]
- Fewer than one-third of patients treated with tamoxifen as postoperative adjuvant therapy will relapse within 15 years[8)].

[Improvement of adherence]

- Adherence is often not followed due to adverse events, belief that clinical benefits do not outweigh risks, etc[9-13)] .

1) Fulvestrant IM 250mg package insert, 2) Miller WR & Larionov AA. Breast Cancer Res 2012; 14:201, 3) Lopez-Knowles E, et al. Br J Cancer 2019; 120:247–255, 4) Arnedos M, et al. Ann Oncol 2014; 25:605–610, 5) Schiavon G, et al. Sci Transl Med 2015; 7:313ra182, 6) Chandarlapaty S, et al. JAMA Oncol 2016; 2:1310–1315, 7) Fribbens C, et al. J Clin Oncol 2016; 34:2961– 2968;, 8) Musgrove EA & Sutherland RL. Nat Rev Cancer 2009; 9:631–643, 9) Partrige A, et al. J Clin Oncol 2008; 6:556-562, 10) Sawesi S, et al. Clin J Oncol Nursing 2014; 18:E50–57, 11) Schulz M, et al. Can Pharm J (Ott) 2019; 152:28–34 , 12) Moon Z, et al. Br J Health Psychol 2017; 22:978–997 , 13) Lin JH, Zhang SM, Manson JE. Cancer Prev Res (Phila) 2011; 4:1360–1365;

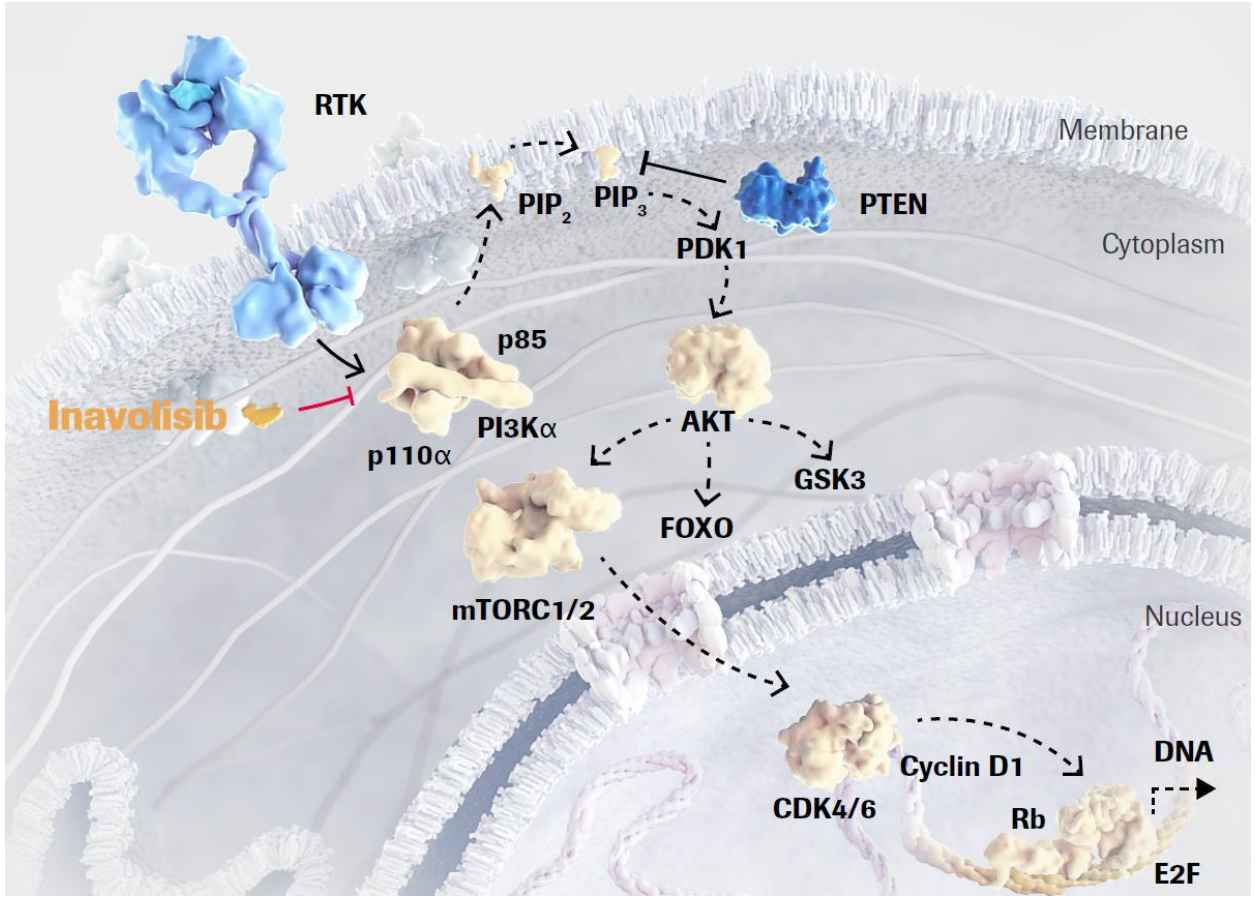
Expected Clinical Positioning of Giredestrant

- **It is the backbone of endocrine therapy for HR-positive breast cancer.**
  - Selective estrogen receptor degraders (SERDs) that inhibit estrogen binding to estrogen receptors and promote estrogen receptor degradation, and can inactivate estrogen receptors more potently than conventional anti-estrogen drugs.
  - It is thought to be effective in cases of *ESR1* mutations as a mechanism of resistance after aromatase inhibitor administration.
  - Clinical benefits are expected to outweigh the risks, and patient adherence and convenience will be improved because giredestrant is an oral drug, whereas existing SERDs are intramuscular injections.

- **Aiming to be the best-in-class SERD**
  - The potency (IC_{50}) of estrogen receptor antagonists in estrogen receptor-positive cell lines has been shown to be higher than that of other endocrine therapies, including SERD.

Inavolisib (PI3K Inhibitor): Mode of Action

- Inavolisib is a highly potent, selective inhibitor of p110α, the catalytic subunit of PI3Kα. In addition, inavolisib promotes the degradation of mutated p110α (mutant degrader)



- Inavolisib is a new targeted molecular agent that specifically inhibits PI3Kα [1)], a key molecule involved in oncogenesis and tumor progression.
- PI3Kα is composed of 2 subunits, p110α and p85, and p110α, called the catalytic subunit, is responsible for the main function of PI3Kα. On the other hand, p85 is called a regulatory subunit and plays a role in controlling the activity of p110α.
- A key feature of inavolisib is that it acts on both of these two subunits, thereby dual inhibiting PI3Kα function. The effect on p110α inhibits PI3Kα and promotes the degradation of mutated p110α (mutant degrader). These effects result in potent and sustained blockade of the PI3Kα pathway.
- In addition, inavolisib selectively inhibits PI3Kα, expected to result in less impact on other PI3K molecules and a reduced risk of side effects.

1) Multiple PI3K isoforms (α, β, γ, δ) exist, with the PI3Kα isoform playing a pivotal role in cellular proliferation and survival, exerting its oncogenic effects from the earliest stages of tumorigenesis. In contrast, the other PI3K isoforms are implicated in distinct physiological processes such as immune function and metabolic regulation, distinct from their roles in oncogenesis. Consequently, it is hypothesized that selective inhibition of the PI3Kα isoform could suppress tumor cell proliferation while minimizing disruption of normal physiological functions mediated by the other PI3K isoforms.

Status of *PIK3CA* Gene Mutations in Breast Cancer

- Mechanisms that lead to resistance to CDK4/6 inhibitors include upregulation of growth factor signaling pathways such as the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway[1-2)]
- It has been reported that approximately 40% of HR-positive breast cancer patients have tumors with *PIK3CA* gene mutations that lead to upregulation of the PI3K pathway[3-4)]
- Activation of the PI3K pathway has been shown to predict poor prognosis after adjuvant endocrine therapy[5)]

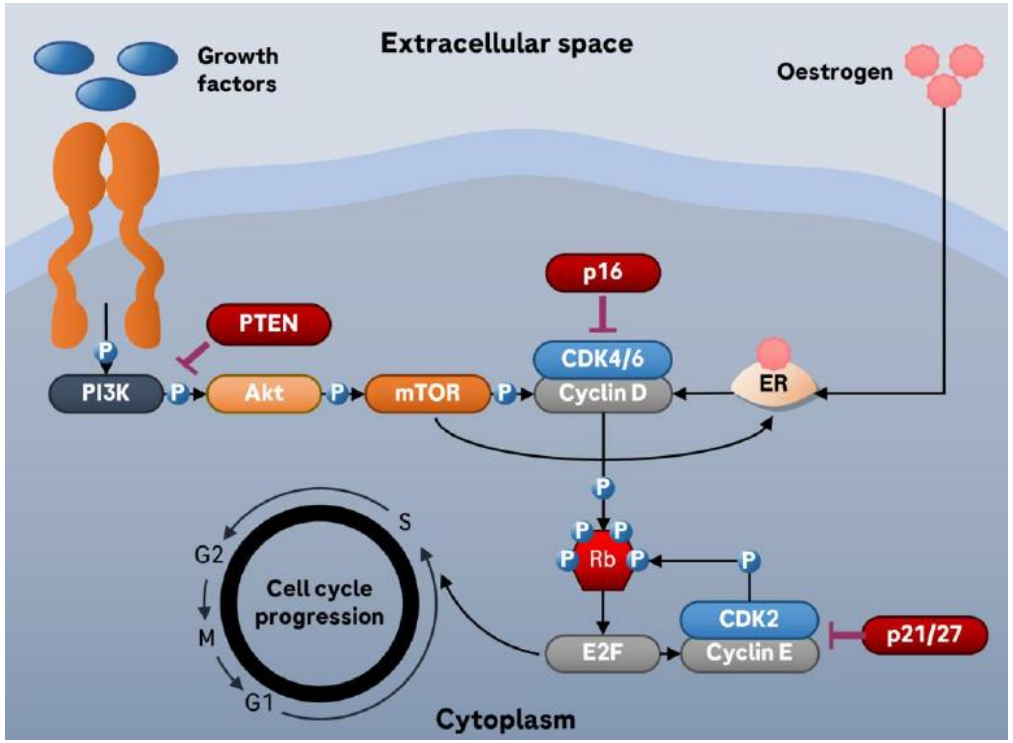


Figure taken from reference: Brufsky AM & Dickler MN. Oncologist 2018; 23:528－539.

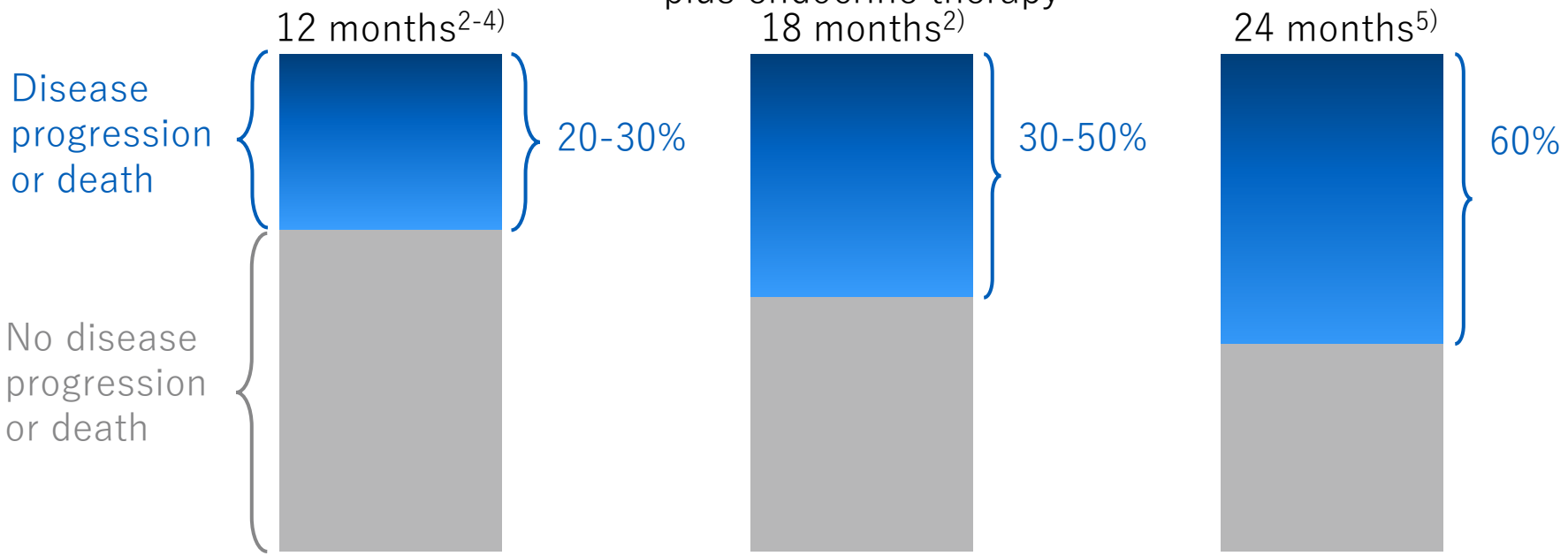
Breast cancer subtype[6-8)]	*PIK3CA* mutation rate
HR+	Approximately 35-40%
HER2＋	Approximately 23-31%
Triple-negative	<16%

1) O'Leary B, et al. Cancer Discov. 2018;8(11):1390-403, 2) Portman N, et al. Endocr Relat Cancer. 2019;26(1):R15-R30. 3) Saal LH, Holm K, Maurer M, et al. Cancer Res 2005;65:2554－9., 4) Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. Cancer Res 2008;68:6084–91., 5) Miller TW, Hennessy BT, González-Angulo AM, et al. J Clin Invest 2010;120:2406–13., 6) Anderson EJ, et al. Int J Breast Cancer 2020; 2020:3759179, 7) LoRusso PM, et al. J Clin Oncol 2016; 34:3803－3815, 8) Martínez-Sáez O, et al. Breast Cancer Res 2020; 22:45.

Rate of Disease Progression etc. with CDK4/6 Inhibitors + Endocrine Therapy

- CDK4/6 inhibitors plus endocrine therapy is one of the standard 1L treatments for HR-positive, HER2-negative mBC[1)]
- It has been shown that approximately 20%-30% of patients treated with CDK4/6 inhibitors plus endocrine therapy in 1L mBC experience disease progression or death after 12 months,[2-4)] with this increasing to approximately 30%-50% after 18 months.[2)]

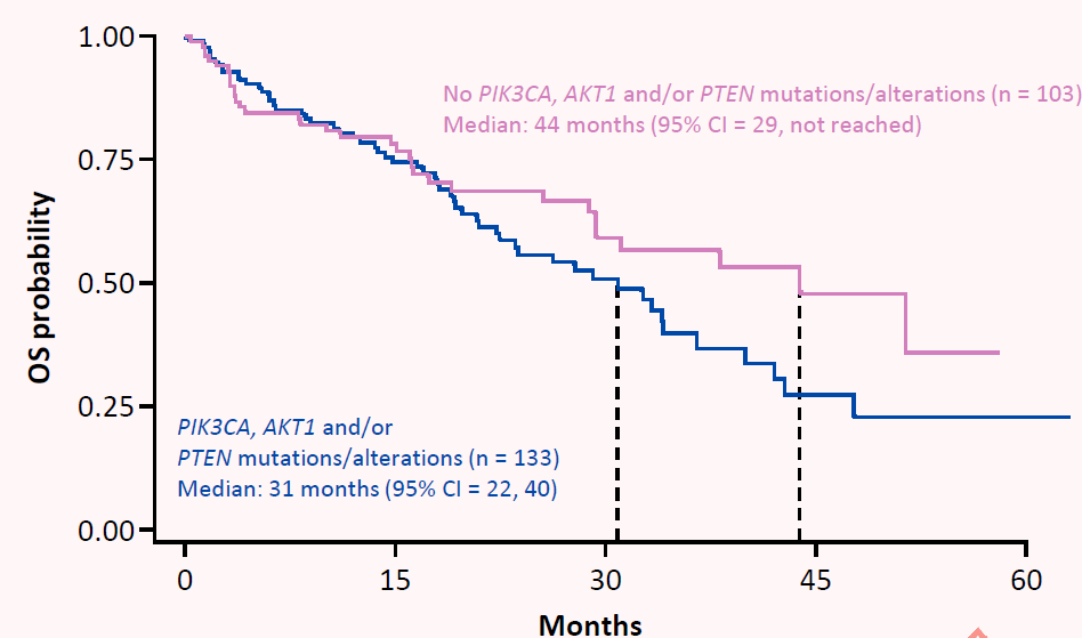
Proportion of disease progression or death with 1L mBC CDK4/6 inhibitor plus endocrine therapy



1) Breast Cancer Treatment Guidelines 2022 Edition, 2) De Laurentiis M, et al. SABCS 2019 (Poster P3-11-25), 3) Suzuki DA, et al. JCO Glob Oncol 2024; 10:e2300484, 4) Nozawa K, et al. Breast Cancer 2023; 30:657–665, 5) Brufsky A, et al. Clin Breast Cancer 2019; 19:317－325.

PIK3CA Gene Mutation-Positive Breast Cancer Has a Poorer Prognosis

- A meta-analysis of 11 clinical trials targeting HR-positive, HER2-negative mBC found that patients with *PIK3CA* gene mutations had shorter overall survival (OS) by 8.4 months (95% CI: -13.4, -3.5) compared to patients without mutations[1)*]
- In HR-positive, HER2-negative mBC, patients with *PIK3CA/AKT/PTEN* gene mutations were suggested to have a shorter median OS from the start of 1L treatment compared to patients without mutations (31 months vs. 44 months) (US)[2)]



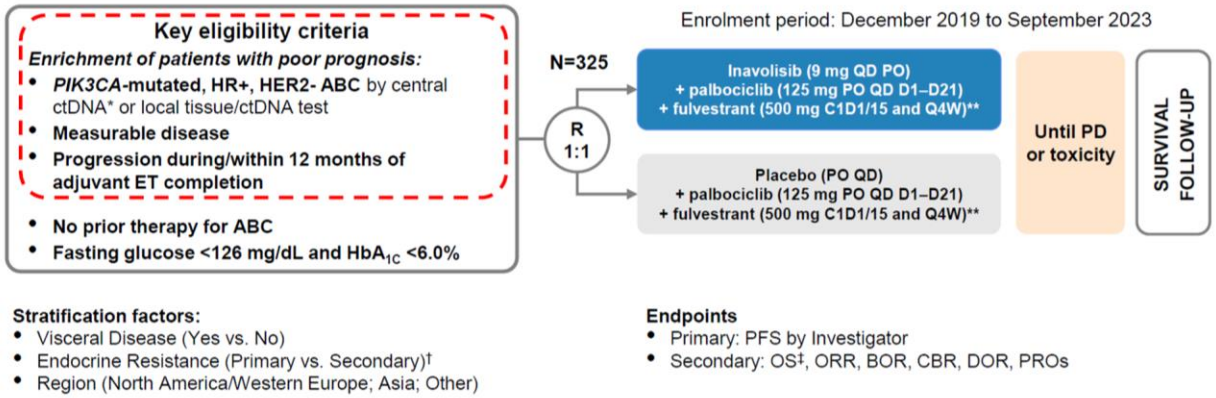
* Unadjusted meta-regression model, HR: Hormone receptor, HER2: human epidermal growth factor receptor 2, mBC: inoperable or recurrent breast cancer, OS: overall survival
1) Fillbrunn M, et al. BMC Cancer 2022; 22:1002, 2) Park L, et al. ASCO 2024 (Poster 1041).

Inavolisib

Global Phase 3 Study (INAVO120) of Inavolisib

- Expected to become a new standard molecular-targeted drug by combining CDK4/6 inhibitors and anti-estrogen drugs in hormone receptor-positive, HER2-negative advanced breast cancer with a *PIK3CA* mutation

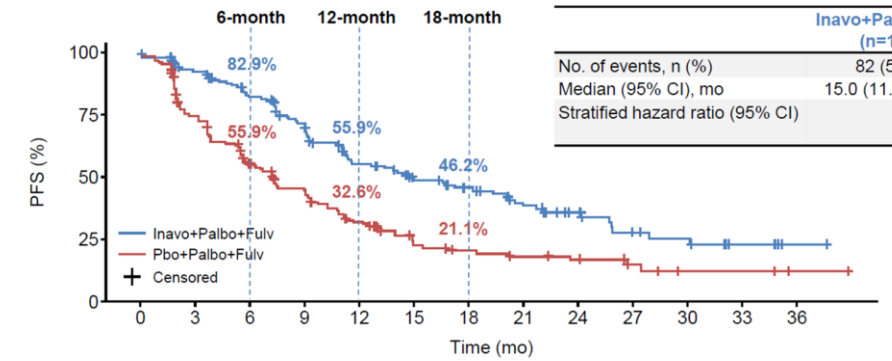
【Study design】



* Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; ** Pre-menopausal women received ovarian suppression. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, *et al. Ann Oncol* 2018;**29**:1634–1657.

【Results】

Primary endpoint: PFS (investigator-assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up: **21.3 months**

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Jhaveri et al. SABCS 2023

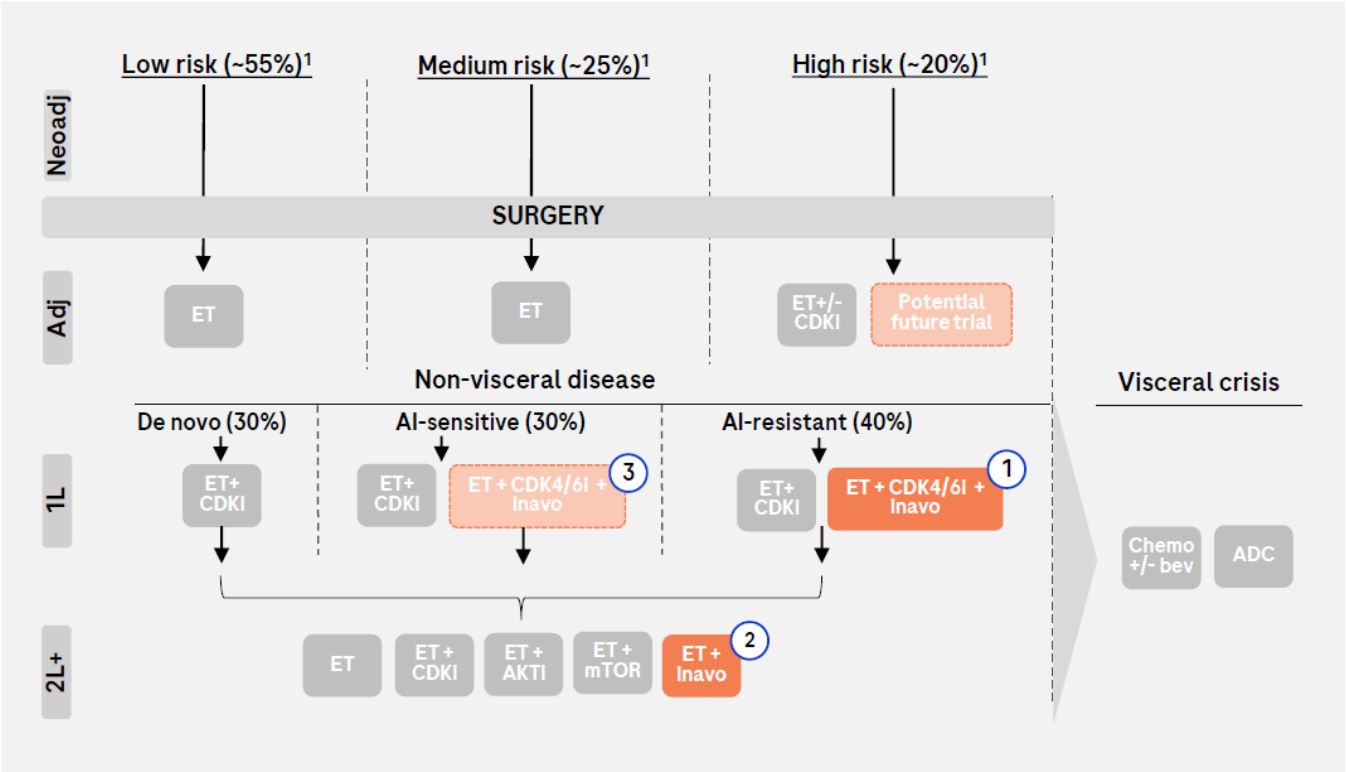
- Patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer
  - ✓ relapsed during/within 12 months of adjuvant endocrine therapy completion in 1st line
- Palbociclib + fulvestrant (one of the standard of care) with inavolisib/placebo on the above segment

- The study met its primary endpoint, with a statistically significant and clinically meaningful improvement in PFS (15.0 months vs 7.3 months; hazard ratio, 0.43 [95% CI = 0.32, 0.59]; p<0.0001)
- Overall survival was immature, but with clear positive trend (HR=0.64, [95% CI=0.43, 0.97]; p=0.0338)
- The safety and tolerability profile of inavolisib + palbociclib + fulvestrant was confirmed to be manageable. The major adverse events were neutropenia, stomatitis or mucositis, hyperglycemia, diarrhea, and rash.

Turner N., et al. N Engl J Med 2024;391:1584-1596

Overview of Clinical Trials and Treatment Lines, etc. for Inavolisib

Potential for inavolisib based regimen in *PIK3CA*m HR+ BC



Ongoing clinical trials

Under development consideration

inavo inavolisib

1	inavolisib (INAVO120)	1L *PIK3CA*m HR+/HER2- mBC (Endocrine therapy resistant)
2	inavolisib (INAVO121)	CDK4/6 inhibitor pre-treated *PIK3CA*m HR+/HER2- BC
3	inavolisib (INAVO123)	1L *PIK3CA*m HR+/HER2- mBC (Endocrine therapy sensitivity)
	inavolisib (INAVO122)	1L *PIK3CA*m HER2+ mBC

(1) Approved in the U.S. / Filed in Europe

1 Risk definitions vary according to guidelines and tools used: stage at diagnosis based on internal estimates using SEER data; AI=aromatase inhibitor, ET=endocrine therapy, eBC=early breast cancer, mBC=metastatic breast cancer, neoadj=neoadjuvant , adj=adjuvant

Quoted from the presentation slides of Roche Pharma day 2024

Expected Clinical Positioning of Inavolisib

- **Inavolisib in combination with CDK4/6 inhibitors and SERDs could become a new standard molecular targeted drug for *PIK3CA* gene mutation-positive, HR-positive, HER2-negative, inoperable or recurrent breast cancer.**
  - In an overseas Phase III clinical trial (WO41554), inavolisib demonstrated a more than two-fold improvement in PFS compared to standard treatment. The triple combination therapy with palbociclib and fulvestrant showed a manageable safety profile, demonstrating an excellent risk-benefit balance for inavolisib.[1)]

- **Potential to become a new treatment option for *PIK3CA* gene mutation-positive breast cancer**
  - Patients with *PIK3CA/AKT/PTEN* gene mutations have a worse prognosis than those without these mutations, and there is a need for new treatment options.[2-3)]
  - PI3K is the most frequently altered protein in the PI3K/AKT/mTOR signaling pathway, and inhibiting PI3K, which is located further upstream, suppresses AKT/mTOR and other downstream signaling pathways expected to be involved in tumor growth, exerting an antitumor effect. [4-9)]
  - In addition to the overseas Phase III clinical trial (WO41554), multiple overseas Phase III clinical trials targeting *PIK3CA* gene mutation-positive breast cancer are underway, and it is expected that this will become a new treatment option.
  - It has two mechanisms of action: selectively inhibiting p110α kinase activity, the catalytic subunit of PI3Kα, and promoting the degradation of p110α mutant proteins. As a result, it is expected to be more effective than other PI3K inhibitors in cancers with *PIK3CA* gene mutations.

1) Turner N., et al. N Engl J Med 2024;391:1584-1596、2) Fillbrunn M, et al. BMC Cancer 2022; 22:1002, 3) Park L, et al. ASCO 2024 (Poster 1041), 4) Burke JE, et al. Proc Natl Acad Sci U S A 2012; 109:15259–15264, 5) Wang N, et al. Cancers 2022, 14:811, 6) Gasser JA, et al. Mol Cell 2014; 56:595–607, 7) Wang W, et al. Curr Med Chem 2015; 22:264–289, 8) Xu J, et al . Genes Cancer 2010; 1:629–640, 9) Vasudevan KM, et al. Cancer Cell 2009; 16:21–32

Divarasib (RG6330)

Divarasib Lifecycle Leader

Epidemiological Information on *KRAS G12C* Mutation-positive Cancers

■ *KRAS G12C* mutation-positive cancers are a rare group of driver mutations

Information on Morbidity and Mortality

- Lung cancer is one of the most common cancers in the world and in Japan, there are approximately estimated 169,000 lung cancer patients[1], and approximately 76,000 deaths per year.[2] Approximately 85-90% of lung cancer patients are classified as NSCLC.[3] NSCLC is a serious, life-threatening disease with a poor prognosis. The five-year survival rate of stage IV NSCLC patients in Japan is 8.0% for adenocarcinoma and 3.5% for squamous cell carcinoma.[4]
- *KRAS G12C* mutation is one of the driver mutations observed in NSCLC and gastrointestinal cancers. It has been suggested that the incidence of *KRAS G12C* mutations is lower in Japan than in other countries and it is estimated that *KRAS G12C* mutations are present in approximately 4% of non-squamous NSCLC patients and approximately 3% of colorectal cancer patients.[5,6]

Disease Characteristics

- There is no consistency in opinion regarding *KRAS G12C* mutation-positive NSCLC. Some claim that the prognosis and chemotherapy sensitivity of *KRAS G12C* mutation-positive NSCLC are poorer, others suggest that the presence or absence of a mutation makes no difference, and there are also reports that differences exist among subtypes.[7,8,9]
- PD-L1 expression tends to be higher in *KRAS G12C* mutation-positive NSCLC compared to mutation-negative NSCLC,[10] and the effectiveness of immune checkpoint inhibitors has been demonstrated.[11]

1. Ministry of Health, Labour and Welfare, Health Statistics Office. Overview of the Patient Survey 2017. https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/dl/toukei.pdf. (Accessed: November 2024), 2. National Cancer Center Japan, Center for Cancer Control and Information Services, 2020, 3. Japanese Society of Medical Oncology, 2018, 4. Japanese Association of Clinical Cancer Centers, 2020, 5. Tamiya Y, et al. J Clin Oncol 2020, 6. Chida K, et al. Oncologist 2021, 7. Ghimessy A et al. Cancer Metastasis Rev. 2020;39(4):1159-1177., 8. Izar B, Zhou H, et al. J Thorac Oncol. 2014;9(9):1363-1369., 9. Mellema WW, et al. Lung Cancer. 2015;90(2):249-254., 10. Schoenfeld AJ, et al. Ann Oncol. 2020;31(5):599-608., 11. Borghaei H, et al. N Engl J Med. 2015;373(17):1627-1639.

Position in the Guidelines

- **The KRAS G12C inhibitor sotorasib (approved in 2022) is recommended as a second-line or later treatment for stage IV non-small cell lung cancer in the Japanese Guidelines for Diagnosis and Treatment of Lung Cancer. No KRAS G12C inhibitors have been approved for first-line treatment. For first-line treatment, it is recommended to follow the guidelines for patients without driver gene mutations/translocations**

Source: The Japanese Guidelines for Diagnosis and Treatment of Lung Cancer 2024

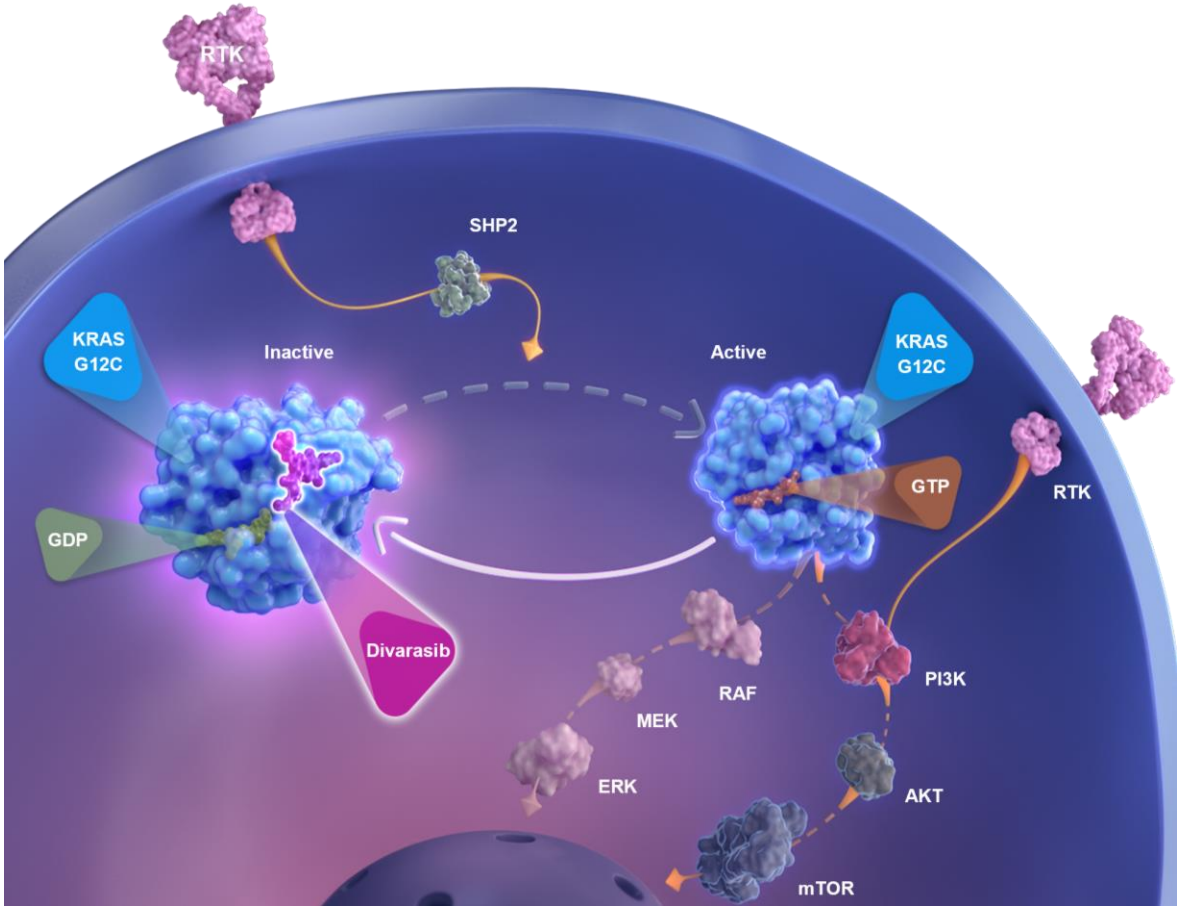
- **No KRAS G12C inhibitors have been approved for colorectal cancer in Japan. The Japanese Guidelines for the Treatment of Colorectal Cancer do not make a distinction between treatments based on the presence or absence of *KRAS G12C* mutations.**

Source: The Japanese Guidelines for the Treatment of Colorectal Cancer 2024

Overview and Mechanism of Action of KRAS G12C Inhibitor Divarasib

Indications under development	Unresectable, advanced and/or recurrent non-small cell lung cancer with *KRAS G12C* mutation

(Image)



- GTP-bound KRAS activates downstream signaling pathways involved in cell proliferation, migration and survival, including the MAPK and PI3K pathways. The KRAS G12C mutant protein is constitutively active and enhances oncogenic signaling, leading to uncontrolled cancer cell proliferation and tumor formation.
- divarasib is an orally bioavailable, KRAS G12C- selective small molecule compound. In non-clinical models, it irreversibly binds to the KRAS G12C protein, fixing it in an inactive state, thereby selectively inhibiting its function in non-clinical models.
- In non-clinical models, it suggests to have stronger cell proliferation inhibitory activity and higher selectivity for *KRAS G12C* mutant cells than sotorasib and adagrasib.

Purkey, H., AACR, 2022, ND11
GTP: guanosine triphosphate, KRAS: Kirsten rat sarcoma viral oncogene homolog, MAPK: mitogen-activated protein kinase, PI3K: phosphatidyl inositol 3-kinase, G12C: glycine 12 to cysteine

Divarasib

Overseas Phase I Clinical Study Results (GO42144)

■ **The study suggested that divarasib is well tolerated and has favorable efficacy.**

[Study overview]

An overseas Phase Ia/Ib clinical trial to evaluate the safety, pharmacokinetics, and efficacy of divarasib monotherapy and in combination with other anti-tumor drugs in patients with advanced/metastatic solid tumors that harbor a *KRAS G12C* mutation. The primary endpoint is safety, and the secondary endpoint is pharmacokinetics and efficacy. The study consisted of a dose escalation part (50 mg to 400 mg) and an expansion cohort part. A total of 137 patients were enrolled (60 with non-small cell lung cancer, 55 with colorectal cancer, and 22 with other solid tumors).

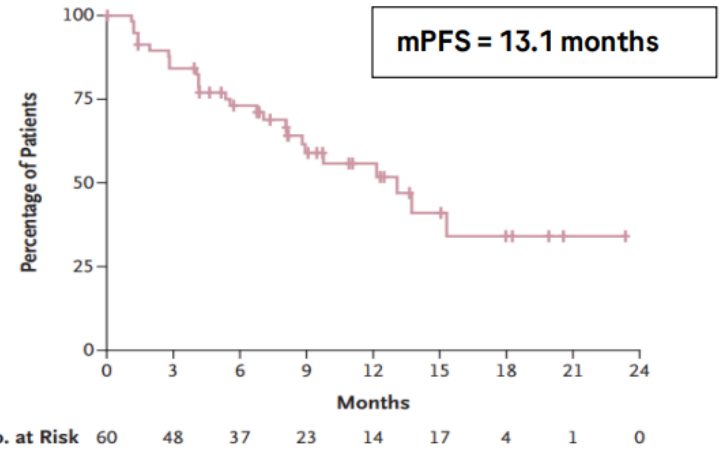
[Study results]

Efficacy

Overall response rates

Indication Regimen	Confirmed ORR
2L+ NSCLC Monotherapy	53% (all doses) 56% (400mg dose)
2L+ CRC Monotherapy	29% (all doses) 36% (400mg dose)
2L+ CRC Divarasib + cetuximab	62%

PFS (all doses) in 2L+ NSCLC monotherapy



Safety

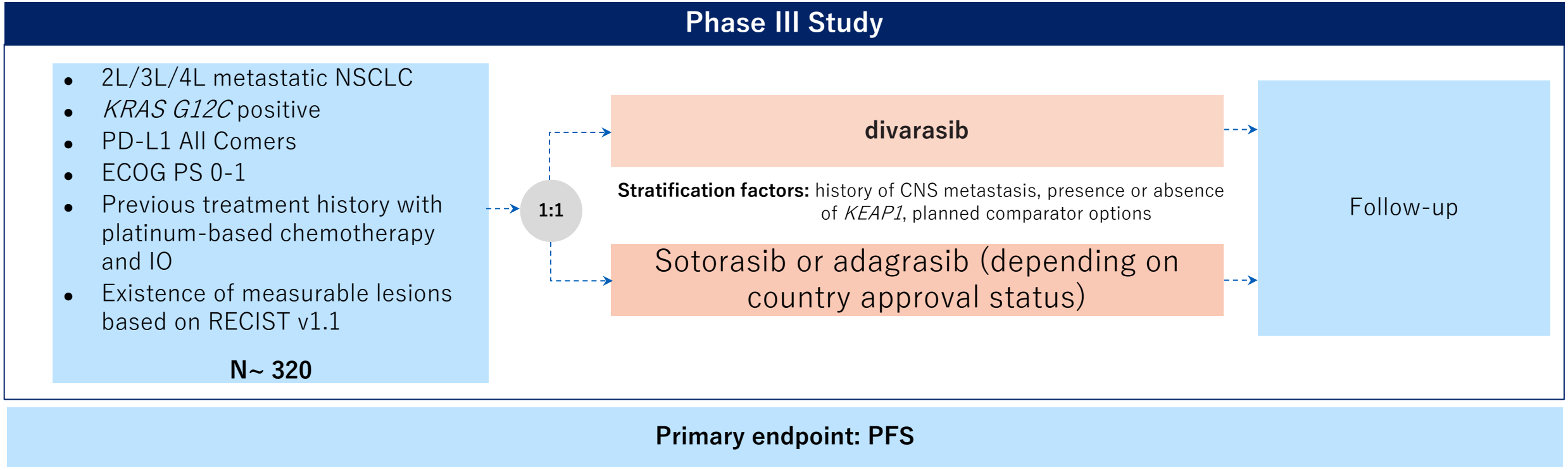
No dose-limiting toxicity was observed. Adverse events occurred in 127 patients (93%), and the major adverse events were nausea (74%), diarrhea (61%), vomiting (58%), and fatigue (22%), loss of appetite (13%).

Sacher A. et al., NEJM Aug 2023

Divarasib

Krascendo 1 Study Design

■ **Based on the expectation of superior antitumor effects, a Phase III clinical trial to verify the superior efficacy of divarasib versus sotorasib/adagrasib in 2L mNSCLC started in Japan in October 2024.**



Divarasib

Clinical Studies Under Development

Name of study	Target	Projected submission
Krascendo 1 Study	Unresectable, advanced and/or recurrent non-small cell lung cancer with *KRAS G12C* mutation	2027 or later
–	Solid tumors	–

Avutometinib

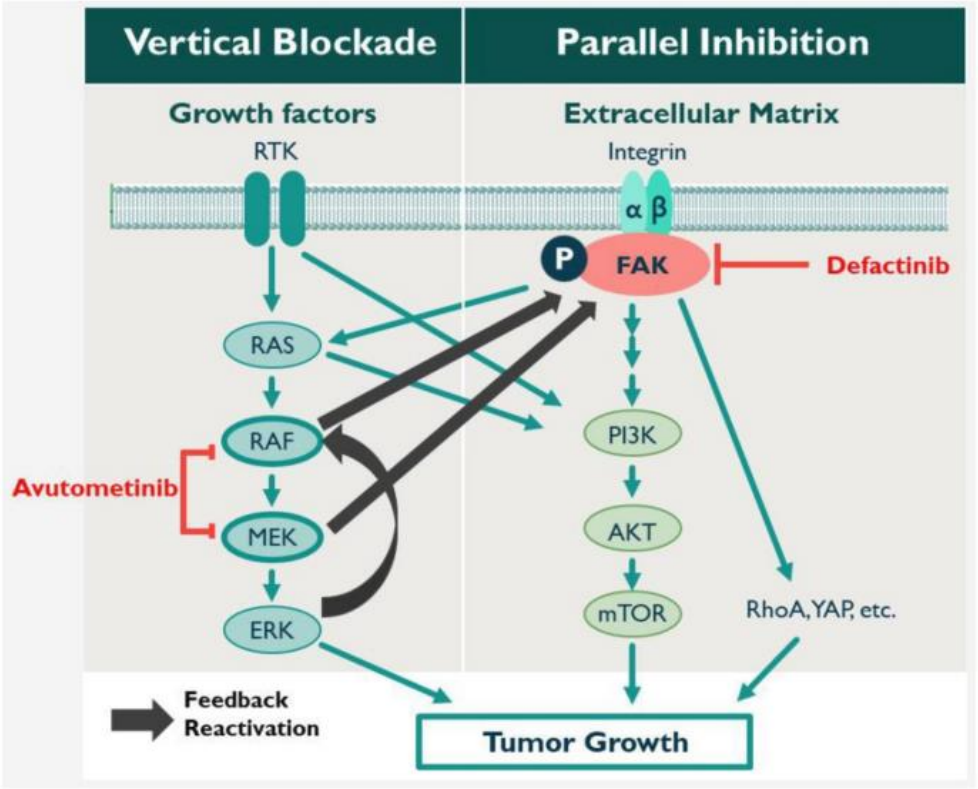
Dr. Shunichiro Iwasawa

Avutometinib Lifecyle Leader

RAS/MAPK Pathway Inhibition by Avutometinib

■ Avutometinib + Defactinib Aims to Inhibit Multiple Resistance Mechanisms in the RAS/MAPK Pathway

- Avutometinib is an oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF[1-3]
- FAK is activated in response to MAPK pathway inhibition by avutometinib as well as by RAF inhibitors and MEK-only inhibitors[4,5]
- Defactinib is an oral selective FAK inhibitor that inhibits parallel pathway signaling and FAK inhibition has been demonstrated to enhance the antitumor efficacy of avutometinib[6-8]
- Together, avutometinib and defactinib have the potential to offer more complete blockade of the signaling that drives the growth of RAS/MAPK pathway-dependent tumors with the objective of deeper and more durable responses



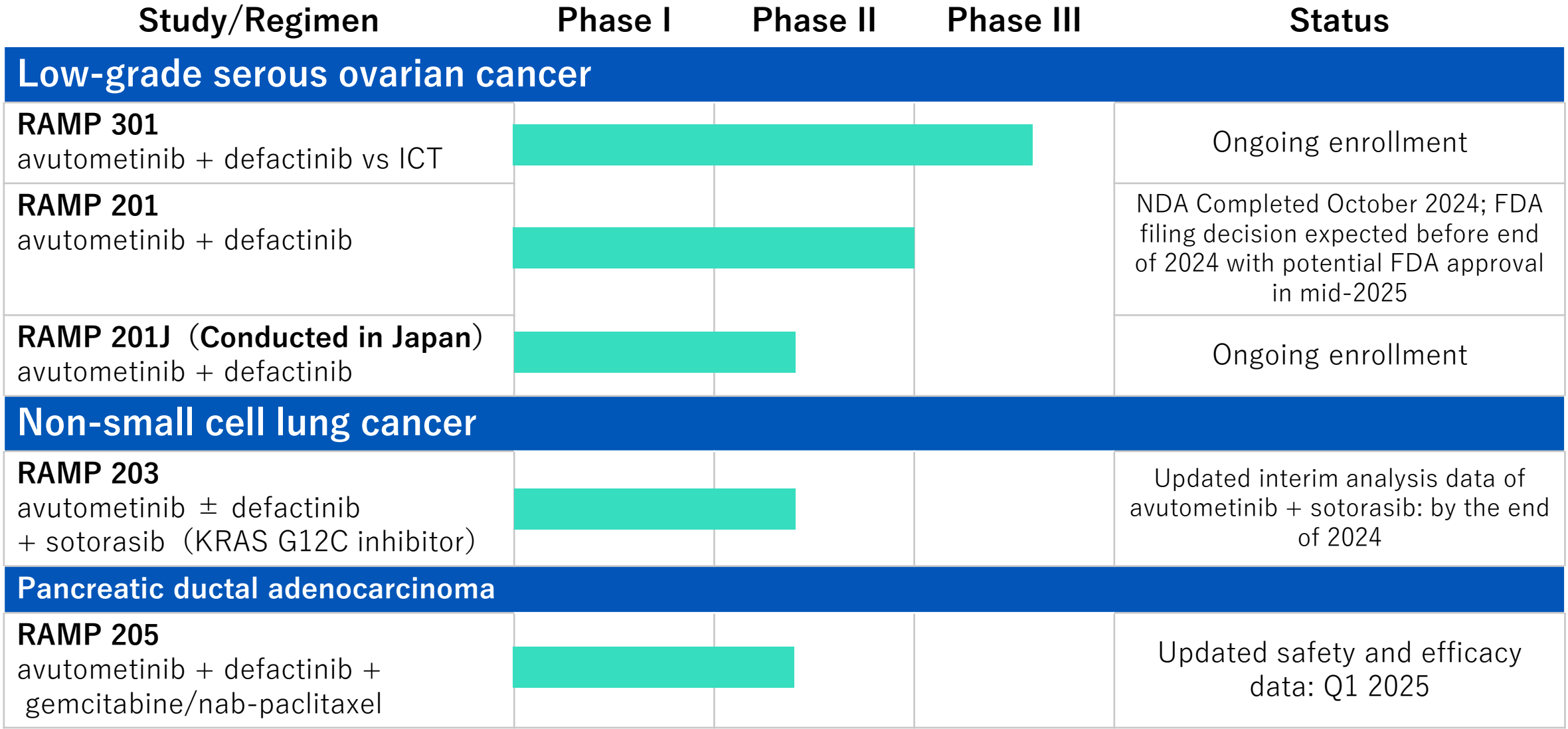
Grisham R, et al. Int J Gynecol Cancer 2024;0:1–7.

1. Coma et al., AACR 2022; 2. Ishiiet al., CancerRes, 2013; 3. Lito et al., CancerCell, 2014; 4. Lubranoet al., AACR 2024; 5 Banerjiet al., AACR 2020; 6. Jones et al., Invest New Drugs 2015; 7. McNamara et al., GynecolOncol 2024; 8. Banerjee et al., ASCO 2023 (1,4,5,8 includes employees of Verastem oncology; 2,3 includes employees of Chugai Pharmaceutical)

ERK; extracellular signal-regulated kinase; FAK, focal adhesion kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, Yes-associated protein.

Avutometinib

Development Pipeline



Low-grade Serous Ovarian Cancer (LGSOC)

- LGSOC is one of two types of serous ovarian cancer, the other being high-grade. Compared to high-grade, LGSOC is rare (less than 10% of cases) but not uncommon in advanced stages.
- An estimated 1,000-2,000 cases are diagnosed annually in the United States, and 15,000-30,000 worldwide. The prevalence is estimated at 6,000-8,000 patients in the U.S. and 80,000 globally.
- Due to its low proliferative activity, LGSOC generally has a longer survival period. However, it is highly resistant to chemotherapy . While many patients progress to second-line and subsequent treatments, therapeutic options are limited, and new drugs are needed.
- Currently, treatment is primarily based on therapies for high-grade serous ovarian cancer (HGSOC), including chemotherapy, and anti-angiogenic drugs. MEK inhibitors are also considered for LGSOC, but their efficacy is limited (overseas data) often due to high rates of discontinuation due to adverse events.
- In recurrent cases, LGSOC is resistant to chemotherapy, and there are no FDA-approved drugs specifically for this condition in the United States.

Reference: Monk, Randall, Grisham, The Evolving Landscape of Chemotherapy in Newly Diagnosed Advanced Epithelial Ovarian Cancer, Am Soc Clin Oncol Educ Book; 2019; Slomovitz, Gourley, Carey, Malpica, Shih, Huntsman, Fader., Grisham et al, Low-Grade serous ovarian cancer: State of the Science; Gynecol Oncol; 2020. Grisham, Iyer, Low-Grade Serous Ovarian Cancer: Current Treatment Paradigms and Future Directions; Curr Treat Options Oncology; 2018.

Avutometinib

Overseas Phase II Study (RAMP 201) Result

RAMP 201 study design

RAMP 201 study is a multicenter Phase II study conducted in the U.S., EU, UK, Canada, to evaluate the efficacy and safety of avutometinib alone and in combination with defactinib in patients with recurrent low-grade serous ovarian cancer. The first part of the study (Part A) determined the selection of the go forward regimen, which was the combination of avutometinib and defactinib versus avutometinib alone, based on overall response rates. The expansion phases of the trial (Parts B and C) are evaluating the safety and efficacy of the go forward regimen of avutometinib 3.2 mg twice weekly and defactinib 200 mg twice daily as a recommended dose.

Primary endpoint: confirmed overall response rate assessed by blinded independent central review

[Result of go forward regimen in Part A-C]

Efficacy

Endpoint	**All (N=109)***	**KRASmt (N=57)***	**KRASwt (N=52)***
Primary endpoint			
Confirmed ORR (95%CI)	31% (23, 41)	44% (31, 58)	17% (8, 30)
Secondary endpoints			
Median DoR (95%CI)	31.1 month (14.8, 31.1)	31.1 month (14.8, 31.1)	9.2 month (5.5, NE)
Median PFS (95%CI)	12.9 month (10.9, 20.2)	22 month (11.1, 36.6)	12.8 month (7.4 18.4)

*patients with measurable disease by RECISTv1.1, ORR: overall response rate, DoR: duration of response, PFS: progression-free survival, NE: could not be estimated based on number of patients with loss of response

Safety

Major treatment-related AEs (N=115)	All	≥Grade 3
Nausea	77 (67.0%)	3 (2.6%)
Increased blood CPK	69 (60.0%)	28 (24.3%)
Diarrhea	67 (58.3%)	9 (7.8%)
Edema peripheral	61 (53.0%)	1 (0.9%)
Fatigue	50 (43.5%)	3 (2.6%)
Vomiting	49 (42.6%)	3 (2.6%)
Vision blurred	47 (40.9%)	0

- Discontinuation due to AEs: 12 patients (10%)
- Severe adverse events were typically managed by a treatment pause
- Combination of avutometinib and defactinib was well tolerated

Susana Banerjee etc., IGSC 2024 (LB007 / #1548) (includes employees of Verastem oncology)

Avutometinib

Overseas Phase III Study (RAMP 301) Design

Inclusion Criteria

- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented KRAS mutation status(wt or mt)
- Measurable disease per RECIST v1.1
- Prior MEKi allowed
- Prior Bevacizumab allowed

This study is being conducted in the U.S., EU, UK, AUS, CAN and KOR.

1:1 Randomization
n = ~270

Stratification Factors:
- KRAS mutation status (wt vs. mt)
- Number of prior lines of therapy (1-3 vs. ≥4)
- Geography (North America/Europe vs. rest of world)

Avutometinib + Defactinib
n = ~135

Avutometinib 3.2 mg PO BIW
Defactinib 200 mg BID
3weeks on, 1 week off

May crossover upon BICR-confirmed PD

Investigator's Choice
n = ~135

Pegylated Liposomal Doxorubicin
Paclitaxel
Letrozole
Anastrozole

Primary Endpoint:
PFS (BICR by RECIST v1.1)
Hierarchical Evaluation of PFS:
1) KRAS mutant LGSOC only
2) All recurrent LGSOC

Secondary Endpoints
OS
PFS by RECIST v1.1 per INV assessment
ORR
DoR
DCR
Safety
Pharmacokinetics
PROs

Unless otherwise specified, all tumor response-based endpoints will be analyzed using both BICR and INV assessments

BICR: blinded independent central review, BID: twice a day; BIW: twice a week, DCR: disease control rate, DoR: duration of response, INV: investigator, KRAS: kirsten rat sarcoma virus, MEKi: MEK inhibitor, mt: mutant, PO: per oral, pts, patients, ORR: objective response rate, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PROs: patient-reported outcomes, RECIST: response evaluation criteria in solid tumors, wt: wild type.

Grisham R, et al. Int J Gynecol Cancer 2024;0:1–7. (includes employees of Verastem Oncology)

Avutometinib

Development Status for LGSOC

- **Verastem Oncology, the licensee, has completed the rolling submission of a New Drug Application (NDA) to the U.S. FDA for avutometinib and defactinib for recurrent KRAS-mutant LGSOC. They are seeking priority review.**
  - FDA filing decision is expected before the end of 2024 with potential FDA approval in mid-2025
  - The NDA submission is based on one-year data from the RAMP 201 study.
  - The FDA has granted Breakthrough Therapy Designation for the combination of avutometinib and defactinib for the treatment of patients with recurrent LGSOC after one or more prior lines of therapy, including platinum-based chemotherapy. Additionally, this combination has ~~already~~ received Orphan Drug Designation from the FDA.
- **The ongoing RAMP 301 study for recurrent LGSOC (including both KRAS-mutant and wild-type) is positioned as a confirmatory trial for the initial indication. It aims to expand the indication to low-grade serous ovarian cancer regardless of KRAS mutation status.**
- **RAMP 201J has initiated in Japan to test the combination in Japanese patients with recurrent LGSOC**

Appendix

Alecensa

Alecensa

Disease Information

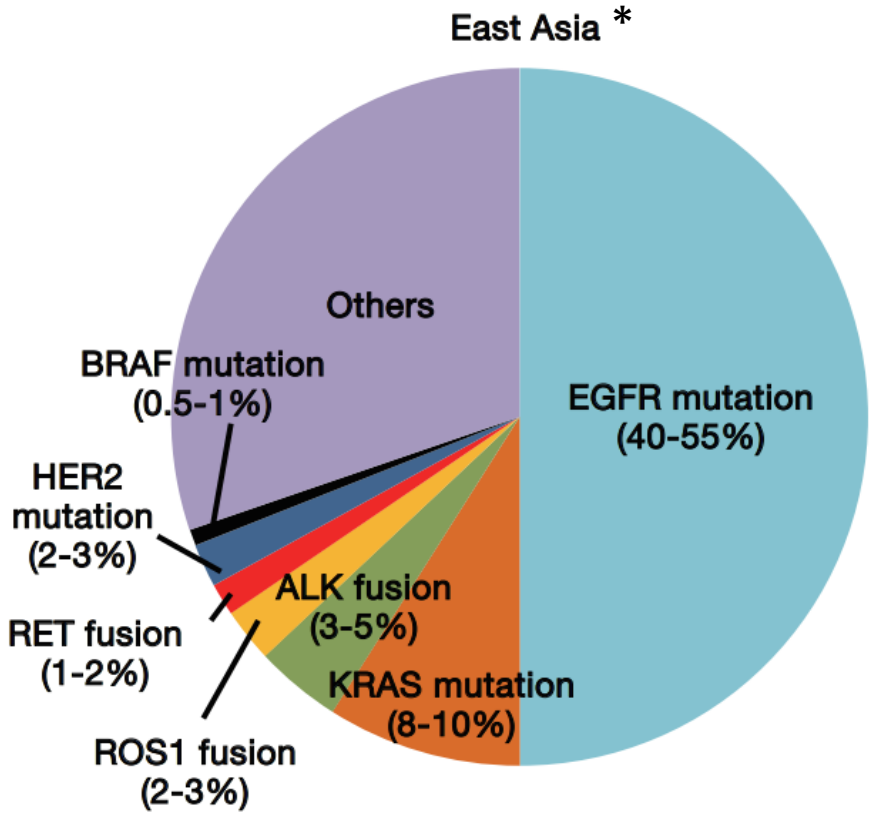
Number of lung cancer diagnoses	[Japan] 120,759 cases (2020) (Male: 81,080, Female: 39,679) [Global*] 2,480,675 cases (2022) (Male: 1,572,045, Female: 908,630)
Number of lung cancer deaths	[Japan] 76,663 (2022) (Male: 53,750, Female: 22,913) [Global*] 1,817,469 cases (2022) (Male: 1,233,241, Female: 584,228)
5-year relative survival rate	[Japan] 34.9% (2009 - 2011) (Male: 29.5%, Female: 46.8%)

*Global includes Japan

National Cancer Center Cancer Information Service "Cancer Statistics" (National Cancer Registry) https://ganjoho.jp/reg_stat/statistics/stat/cancer/12_lung.html) (Accessed: November 2024)

World Cancer Research Fund International, Lung cancer statistics https://www.wcrf.org/cancer-trends/lung-cancer-statistics/ (Accessed: November 2024)

Frequency of *ALK* fusion gene expression in surgical specimens from non-small cell lung cancers



* Pie charts showing the proportion of lung adenocarcinoma harboring aberrations in driver oncogenes. Data from patients in East Asia (Japan, Korea, and China) were generated by summarizing the results from previous reports (1-3).
1. Kohno T, et al.: Cancer Sci 2013;104:1396-400.
2. Pao W, et al.: Nat Med 2012;18:349-51.
3. Li T, et al.: J Clin Oncol 2013;31:1039-49.

Kohno T, et al.: Transl Lung Cancer Res. 2015; 4(2): 156-164.

Position in the Guidelines

■ **Alecensa is recommended as follows in the Japanese Guidelines for Diagnosis and Treatment of Lung Cancer.**

[Stage IV non-small cell lung cancer] Strongly recommended for first-line treatment

Referenced from: Guidelines for Diagnosis and Treatment of Lung Cancer 2024 Stage IV Non-Small Cell Lung Cancer 7-1-2. *ALK* fusion gene-positive

[Perioperative non-small cell lung cancer] Weakly recommended for postoperative adjuvant therapy in stages II-IIIB

Referenced from: Guidelines for Diagnosis and Treatment of Lung Cancer 2024 Perioperative period 4-2. Postoperative adjuvant drug therapy

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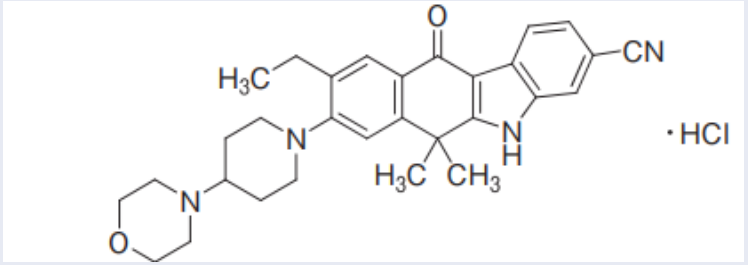
Product Overview

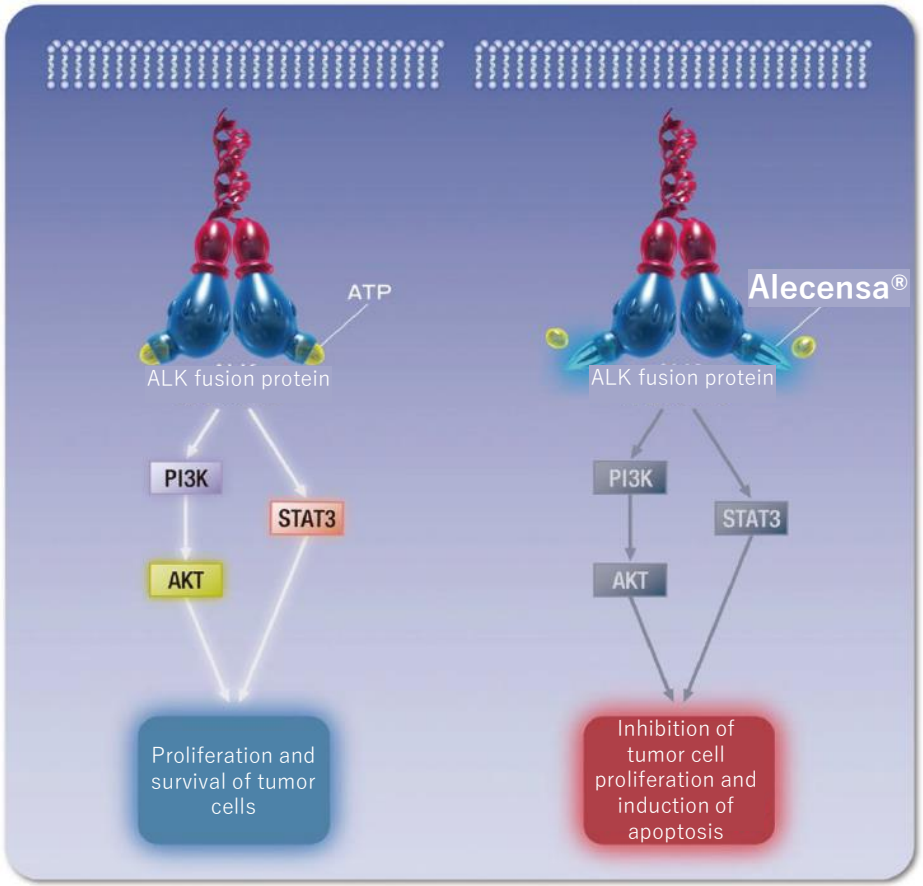
Compound	■ Nonproprietary name: Alectinib hydrochloride (JAN) ■ Chemical name: 9-Ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6, 11-dihydro-5H-benzo[b]carbazole -3carbonitrile Hydrochloride ■ Molecular formula: $C_{30}H_{34}N_4O_2$ ・HCl ■ Molecular weight: 519.08 ■ Structure: Selective ALK inhibitor with a benzo[b]carbazole skeleton 
Dosage Form	■ 150 mg capsule (# 1 capsule) 
Indications Dosage and Administration	■ *ALK* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer □ The usual adult dose of alectinib is 300 mg, taken orally twice daily. ■ Postoperative adjuvant therapy for *ALK* fusion gene-positive non-small cell lung cancer □ The usual adult dose of alectinib is 600 mg, taken orally after meals twice daily. However, the administration period is restricted to 24 months. The dosage should be reduced according to the patient's condition. ■ Relapsed or refractory *ALK* fusion gene-positive anaplastic large cell lymphoma □ The usual dose of alectinib is 300 mg, taken orally twice daily. However, a single dose of 150 mg is administered to patients weighing 35 kg or less.

Created based on the electronic package insert for Alecensa® Capsule 150 mg (Chugai Pharmaceutical Co., Ltd.)

Mechanism of Action

- **Alecensa is an ALK (Anaplastic Lymphoma Kinase) tyrosine kinase inhibitor developed by Chugai Pharmaceuticals. It's highly selective inhibition of EML4-ALK fusion kinase and is expected to suppress the proliferation of tumor cells and induce apoptosis.**

Illustration



Modified from Sasaki T, et al. Clin Cancer Res 2011;17(23):7213-8 [COI] Some of the authors have received consulting fees from Chugai Pharmaceutical Co., Ltd.

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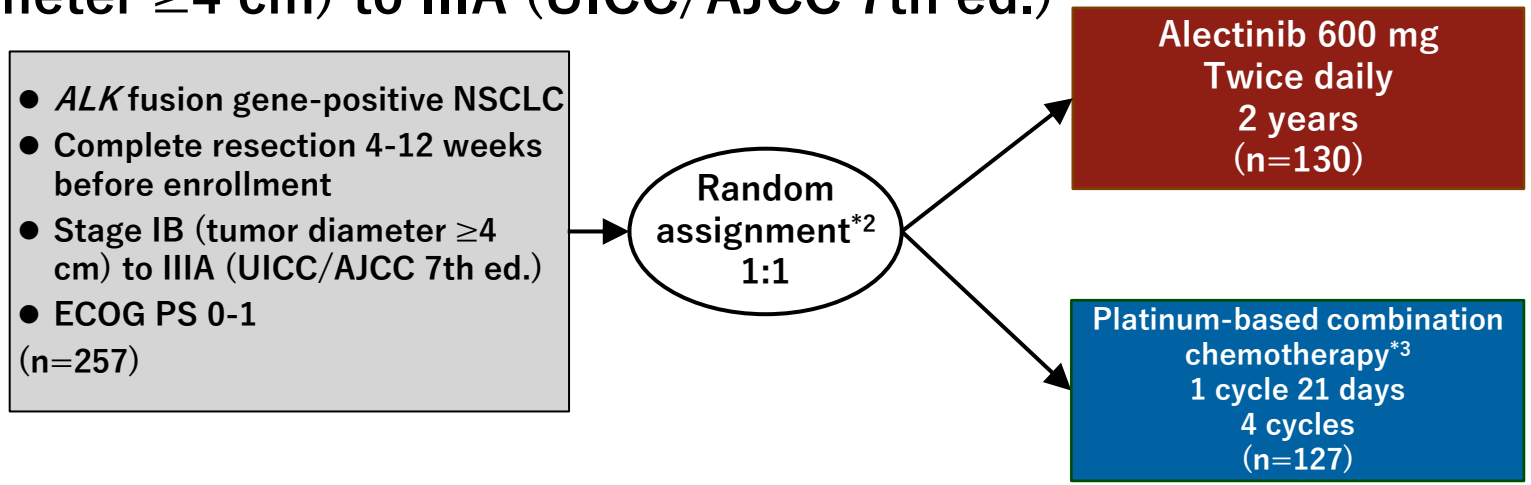
Major Clinical Trials for Non-Small Cell Lung Cancer

	Postoperative adjuvant therapy	Locally advanced unresectable stage III	Advanced or recurrent unresectable
Global studies (including Japan)/ Domestic studies	ALINA - Global phase III study - Primary endpoint (disease-free survival)	HORIZON-01 - Global phase I - III study - Study currently underway	J-ALEX - Domestic phase III Study - Primary endpoint (progression-free survival)
Global studies (excluding Japan)	–		ALEX - Global phase III study - Primary endpoint (progression-free survival)
			ALESIA - Global phase III study - Primary endpoint (progression-free survival)

ALINA (1/4)

■ **ALINA was a randomized positive control multicenter open-label global phase III study comparing the efficacy and safety of postoperative adjuvant alectinib versus platinum-based combination chemotherapy in *ALK* fusion gene-positive non-small cell lung cancer (NSCLC) patients with completely resected stage IB (tumor diameter ≥4 cm) to IIIA (UICC/AJCC 7th ed.)**



*1 Equivalent to stage II-IIIB (excluding N3) (9th edition)
*2 Stratification factors: disease stage (stage IB [tumor diameter ≥4 cm] vs. stage II vs. stage IIIA) and race (Asian vs. non-Asian)
*3 One of the following platinum-based combination chemotherapy regimens was selected by the investigator (sub-investigator):
- Cisplatin 75 mg/m^2 (Day 1) + Vinorelbine 25 mg/m^2 (Days 1, 8)
- Cisplatin 75 mg/m^2 (Day 1) + Gemcitabine 1,250 mg/m^2 (Days 1, 8)
- Cisplatin 75 mg/m^2 (Day 1) + Pemetrexed 500 mg/m^2 (Day 1)

If cisplatin was not tolerated, it was possible to change to carboplatin AUC5 or 6 mg･min/mL.

*Indication and Dosage approved in Japan based on this clinical trial:
<**Postoperative adjuvant therapy for *ALK* fusion gene-positive non-small cell lung cancer**>
The usual adult dose of alectinib is 600 mg, taken orally after meals twice daily. However, the administration period is restricted to 24 months. The dosage should be reduced according to the patient's condition.

NCT03456076 https://clinicaltrials.gov/study/NCT03456076 (Accessed: November 2024)

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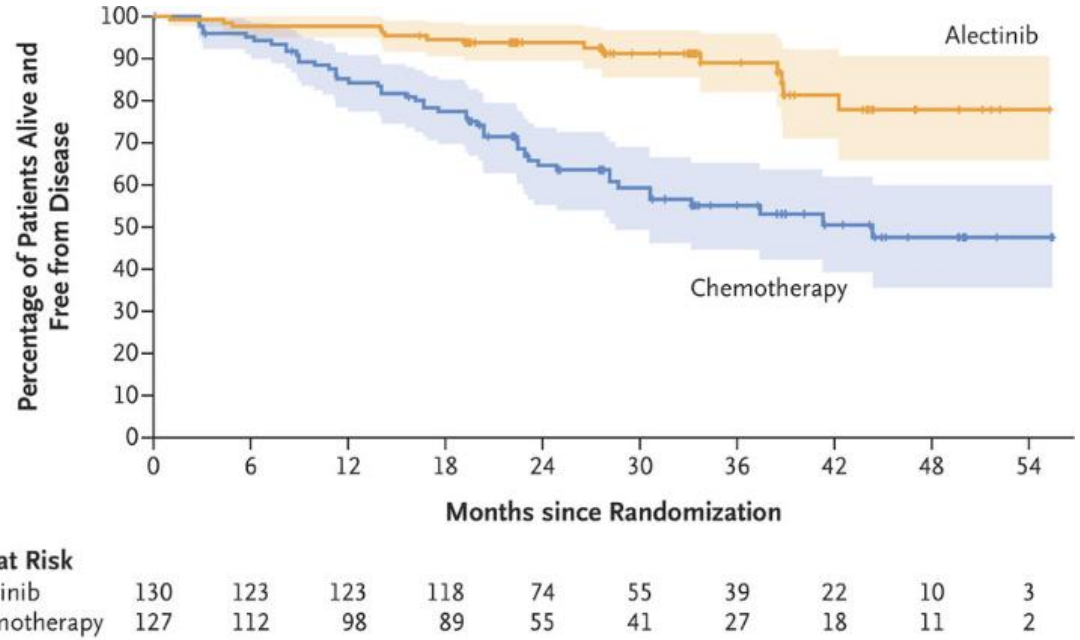
ALINA (2/4)

- **Primary endpoint (disease-free survival [DFS]): At the time of the interim analysis (data cutoff: June 26, 2023), alectinib was shown to have significantly reduced the risk of recurrence or death by 76% compared with platinum-based chemotherapy in all randomized subjects (ITT population) with stage IB (tumor diameter ≥ 4 cm) to IIIA (UICC/AJCC 7th edition), verifying the superiority of alectinib over chemotherapy.**

	Alectinib group (n=130)	Chemotherapy group (n=127)
Number of subjects who experienced events, n (%)	15 (11.5%)	50 (39.4%)
Death	0	1
Recurrence	15	49
DFS median (months) (95%CI)	NE (NE, NE)	41.3 (28.5, NE)
Stratification*1 HR (95%CI)	0.24 (0.13, 0.43)	
P value (stratification*2 log-rank test)	p<0.0001	



*1 Estimated value using stratified Cox regression model
Stratification factors: disease stage (stage IB [tumor diameter ≥4 cm] vs. stage II vs. stage IIIA) and race (Asian vs. non-Asian)
*2 Two-sided significance level: 0.0077

Wu YL, et al. N Engl J Med. 2024 Apr 11;390(14):1265-1276
[COI] This study was supported by F. Hoffmann-La Roche Ltd. Some of the authors have received funding from F. Hoffmann-La Roche Ltd. and Chugai Pharmaceutical Co., Ltd. Five of the authors are employees of F. Hoffmann-La Roche Ltd.

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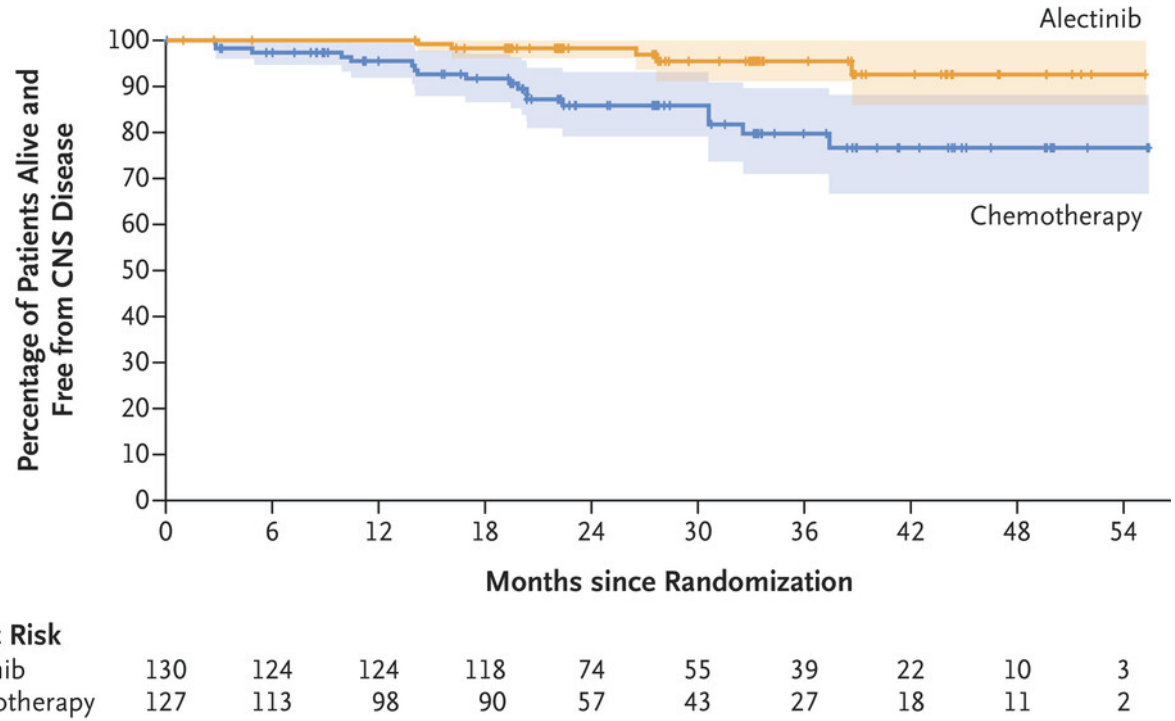
ALINA (3/4)

- **Exploratory endpoint (central nervous system disease-free survival [CNS-DFS]): At the time of the interim analysis, the hazard ratio for CNS-DFS in the ITT population with stage IB (tumor diameter ≥4 cm) to IIIA (UICC/AJCC 7th ed.) was 0.22 (95% CI: 0.08-0.58) for alectinib versus chemotherapy.**

	Alectinib group (n=130)	Chemotherapy group (n=127)
Number of subjects who experienced events, n (%)	5 (3.8%)	18 (14.2%)
Death	1	4
CNS recurrence	4	14
CNS - DFS median (months) (95%CI)	NE (NE, NE)	NE (NE, NE)
Stratification*1 HR (95%CI)	0.22 (0.08, 0.58)	



*1 Estimated value using stratified Cox regression model
Stratification factors: disease stage (stage IB [tumor diameter ≥4 cm] vs. stage II vs. stage IIIA) and race (Asian vs. non-Asian)

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ALINA (4/4)

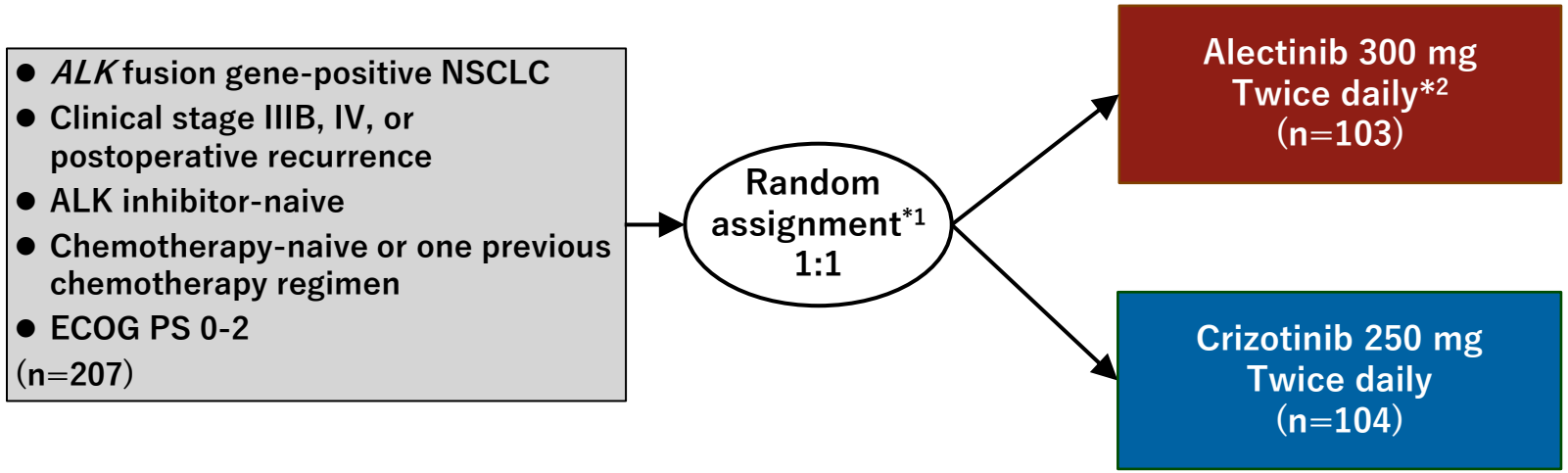
- The median follow-up period for the safety analysis set was 24.84 months (range: 1.1-26.2 months) in the alectinib group and 3.71 months (range: 1.6-5.3 months) in the chemotherapy group, reflecting the difference in treatment duration with the investigational drug. The proportion of subjects who experienced at least one adverse event was similar to that of the chemotherapy group.
- The most common adverse events were increased creatine kinase levels (43.0%) and constipation (42.2%) in the alectinib group, and nausea (72.5%) and decreased appetite (29.2%) in the chemotherapy group.

	Alectinib group (n=128)	Chemotherapy group (n=120)
Number of cases (%)		
All adverse events	126 (98.4%)	112 (93.3%)
Adverse events ≥ grade 3	38 (29.7%)	37 (30.8%)
Adverse events that resulted in death	0	0
Serious adverse events	17 (13.3%)	10 (8.3%)
Adverse events that resulted in discontinuation	7 (5.5%)	15 (12.5%)
Adverse events that resulted in drug interruption	35 (27.3%)	22 (18.3%)
Adverse events that resulted in dose reduction	33 (25.8%)	12 (10.0%)

Wu YL, et al. N Engl J Med. 2024 Apr 11;390(14):1265-1276
[COI] This study was supported by F. Hoffmann-La Roche Ltd. Some of the authors have received funding from F. Hoffmann-La Roche Ltd. and Chugai Pharmaceutical Co., Ltd. Five of the authors are employees of F. Hoffmann-La Roche Ltd.

J-ALEX (1/4)

■ J-ALEX was a multicenter open-label randomized phase III study in Japan comparing the efficacy and safety of alectinib with crizotinib in patients with *ALK* fusion gene-positive advanced or recurrent non-small cell lung cancer (NSCLC)



*1 Stratification factors: ECOG PS (0/1 vs. 2), prior chemotherapy history (0 vs. 1), clinical stage (stage IIIB/stage IV vs. postoperative recurrence)
*2 The dose administered in the ALEX study was alectinib 600 mg twice daily

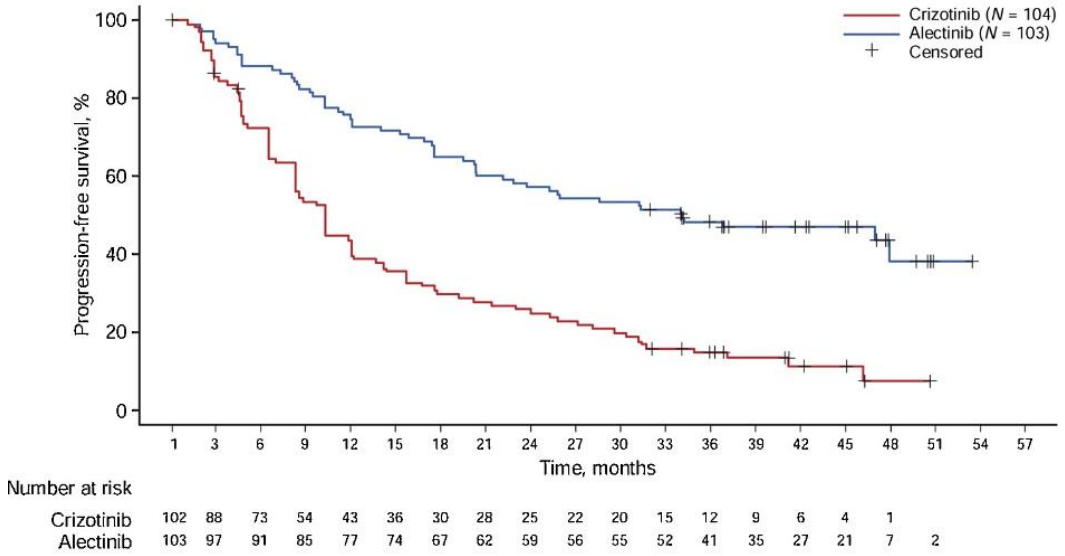
*Indication and Dosage approved in Japan based on this clinical trial:
<***ALK* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer**>
The usual adult dose of alectinib is 300 mg, taken orally twice daily.

JapicCTI-132316 https://jrct.niph.go.jp/latest-detail/jRCT2080222267 (Accessed: November 2024)

Alecensa

J-ALEX (2/4)

- At final analysis of progression-free survival (PFS) (data cutoff: June 30, 2018), the median follow-up periods were 42.4 months in the alectinib group and 42.2 months in the crizotinib group.(Primary endpoint)
- There were 56 events of progression or death in the alectinib group and 89 in the crizotinib group. The PFS hazard ratio*1 was 0.37 (95% CI: 0.26-0.52) for alectinib compared with crizotinib.
- Median PFS was 34.1 months (95% CI: 22.1 months-not estimable) in the alectinib group and 10.2 months (95% CI: 8.3-12.0 months) in the crizotinib group.



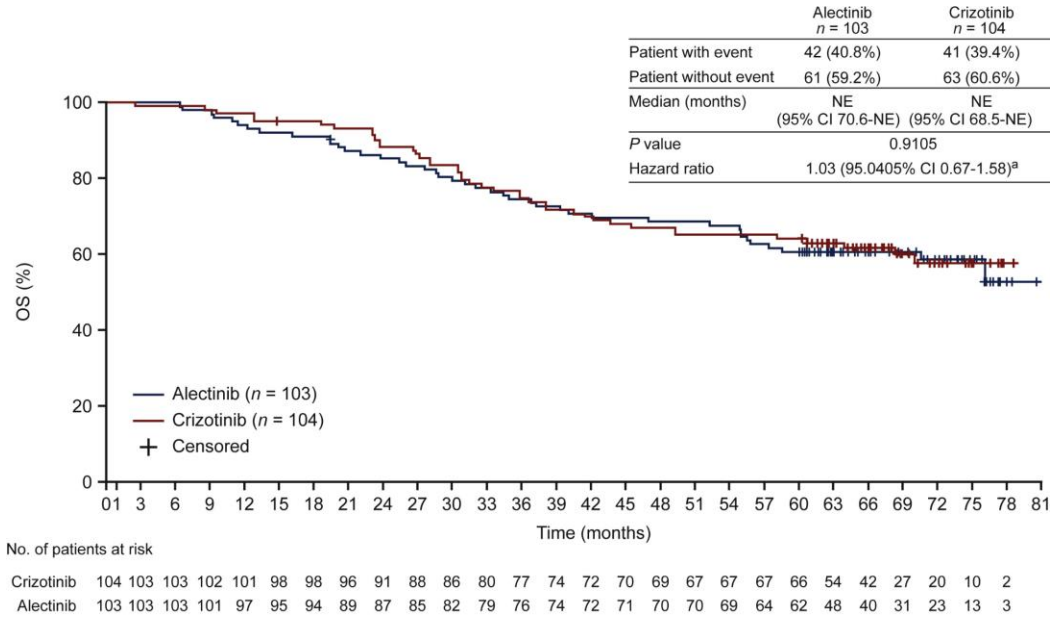
*1 Estimated value using stratified Cox proportional hazards model
Stratification factors: ECOG PS (0/1 vs. 2), prior chemotherapy history (0 vs. 1), clinical stage (stage IIIB/stage IV vs. postoperative recurrence)

Nakagawa K, et al. Lung Cancer. 2020 Jan;139:195-199.

[COI] This study was supported by Chugai Pharmaceutical Co., Ltd. Some of the authors have received consultant fees and other compensation from Chugai Pharmaceutical. Three of the authors are employees of Chugai Pharmaceutical.

J-ALEX (3/4)

- At final analysis of overall survival (OS), the median follow-up was 68.6 months in the alectinib group and 68.0 months in the crizotinib group.(Secondary endpoint)
- There were 42 events of death in the alectinib group and 41 in the crizotinib group. The OS hazard ratio*1 was 1.03 (95.0405% CI: 0.67-1.58) for alectinib compared with crizotinib. No statistically significant difference was observed. (End of testing procedure)
- Median OS was not reached in the alectinib group (95% CI: 70.6 months-not estimable) or in the crizotinib group (95% CI: 68.5 months-not estimable).



*1 O'Brien–Fleming critical value: P < 0.049595

Hotta K, et aConflict of Interest] This study was supported by Chugai Pharmaceutical Co., Ltd. Some of the I. ESMO Open. 2022 Aug;7(4):100527.
[authors have received consultant fees and other compensation from Chugai Pharmaceutical. Three of the authors are employees of Chugai Pharmaceutical.

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J-ALEX (4/4)

- **The most common adverse events of Grade 3 or higher were creatine phosphokinase increased and interstitial lung disease (5 cases each, 4.9%) in the alectinib group, and neutrophil count decreased [20 cases (19.2%)] and alanine aminotransferase increased [14 patients (13.5%)] in the crizotinib group.**

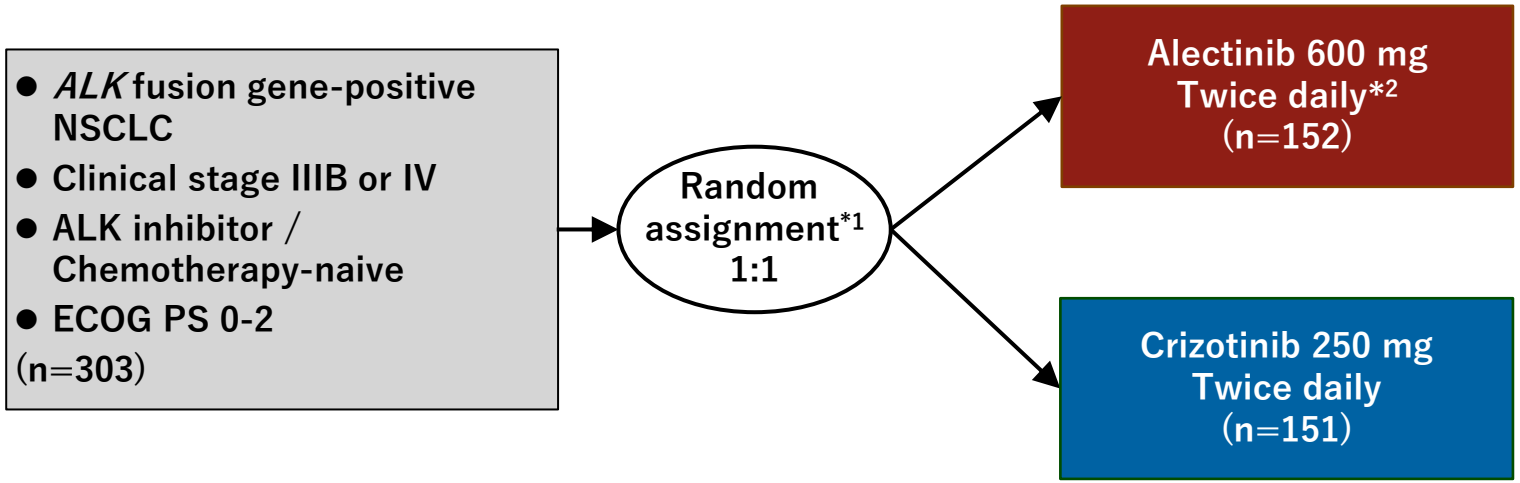
Safety summary at final PFS analysis

	Alectinib group (n=103)	Crizotinib group (n=104)
Number of cases (%)		
All adverse events	101 (98.1%)	104 (100.0%)
Adverse events ≥ grade 3	38 (36.9%)	63 (60.6%)
Adverse events that resulted in death	0	0
Serious adverse events	28 (27.2%)	30 (28.8%)
Adverse events that resulted in discontinuation	12 (11.7%)	24 (23.1%)
Adverse events that resulted in drug interruption	35 (34.0%)	70 (67.3%)

Nakagawa K, et al. Lung Cancer. 2020 Jan;139:195-199.
[COI] This study was supported by Chugai Pharmaceutical Co., Ltd. Some of the authors have received consultant fees and other compensation from Chugai Pharmaceutical. Three of the authors are employees of Chugai Pharmaceutical.

ALEX (1/4)

■ ALEX was a multicenter open-label randomized phase III study comparing the efficacy and safety of alectinib with crizotinib in patients with *ALK* fusion gene-positive non-small cell lung cancer (NSCLC)



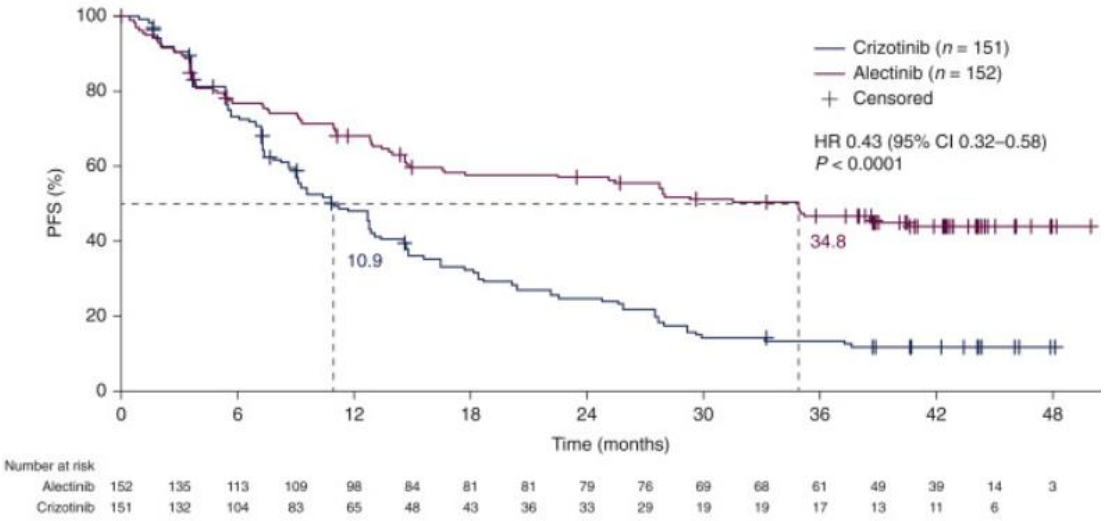
*1 Stratification factors: baseline central nervous system metastasis (present vs. absent), race (Asian vs. non-Asian), ECOG PS (0/1 vs. 2)
*2 The dosage approved overseas based on this study has not been approved in Japan.

NCT02075840 https://clinicaltrials.gov/study/NCT02075840 (Accessed: November 2024)

Alecensa

ALEX (2/4)

- At final analysis of progression-free survival (PFS) (data cutoff: November 30, 2018), the median follow-up periods were 37.8 months in the alectinib group and 23.0 months in the crizotinib group. (Primary endpoint)
- There were 81 events of progression or death in the alectinib group and 122 in the crizotinib group. The PFS hazard ratio was 0.43 (95% CI: 0.32-0.58) for alectinib compared with crizotinib.
- Median PFS was 34.8 months (95% CI: 17.7 months-not estimable) in the alectinib group and 10.9 months (95% CI: 9.1-12.9 months) in the crizotinib group.

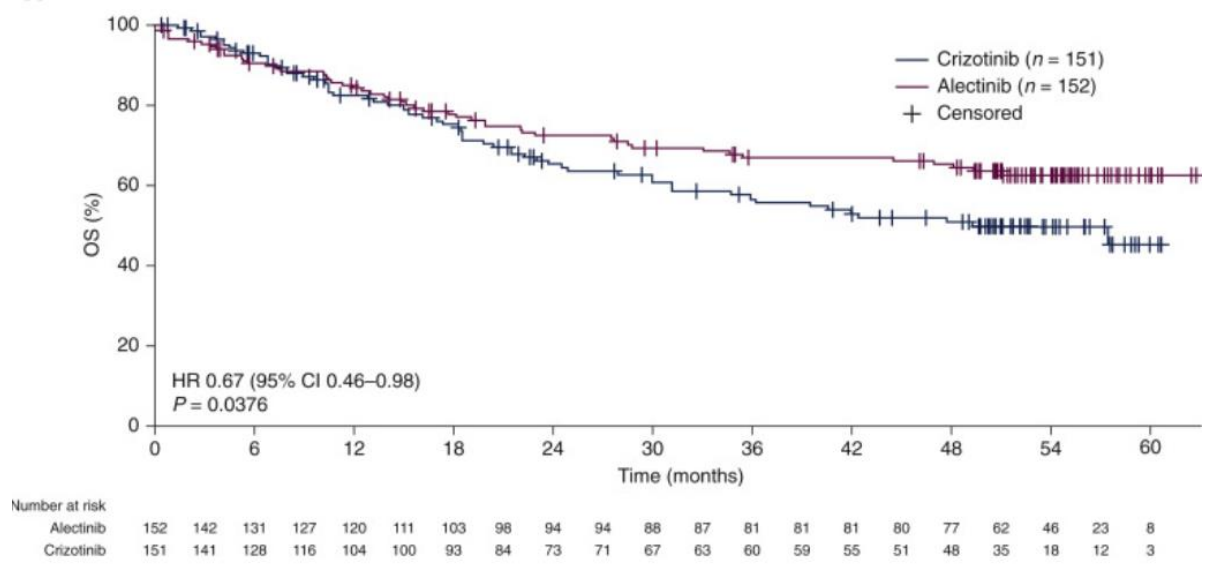


Mok T, et al. Ann Oncol. 2020 Aug;31(8):1056-1064.

[COI] This study was supported by F. Hoffmann-La Roche Ltd. Some of the authors have received funding from F. Hoffmann-La Roche Ltd., Genentech, Inc., and Chugai Pharmaceutical Co., Ltd. Five of the authors are employees of F. Hoffmann-La Roche Ltd.

ALEX (3/4)

- At the time of the updated analysis of overall survival (OS) (data cutoff: November 29, 2019), the median follow-up periods were 48.2 months in the alectinib group and 23.3 months in the crizotinib group. (Secondary endpoint)
- There were 51 events of death in the alectinib group and 62 in the crizotinib group. The OS hazard ratio was 0.67 (95% CI: 0.46-0.98) for alectinib compared with crizotinib.
- Median OS was not reached in the alectinib group and was 57.4 months (95% CI: 34.6 months -not estimable) in the crizotinib group.



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ALEX (4/4)

- **The proportion of patients who experienced Grade 3 or higher adverse events or adverse events resulting in treatment discontinuation/interruption/reduction was similar in each group.**
- **The most common adverse events of Grade 3 or higher were anemia (5.9%), aspartate aminotransferase increased (5.3%), alanine aminotransferase increased (4.6%), and pneumonia (4.6%) in the alectinib group, and alanine aminotransferase increased (15.9%), aspartate aminotransferase increased (10.6%), neutropenia (5.3%), and blood creatine phosphokinase increased (4.0%) in the crizotinib group.**

Safety summary at OS update analysis

	Alectinib group (n=103)	Crizotinib group (n=104)
Number of cases (%)		
All adverse events	147 (96.7%)	147 (97.4%)
Adverse events ≥ grade 3	79 (52.0%)	85 (56.3%)
Adverse events that resulted in death	7 (4.6%)	7 (4.6%)
Serious adverse events	59 (38.8%)	48 (31.8%)
Adverse events that resulted in discontinuation	22 (14.5%)	22 (14.6%)
Adverse events that resulted in drug interruption	40 (26.3%)	40 (26.5%)
Adverse events that resulted in dose reduction	31 (20.4%)	30 (19.9%)

Mok T, et al. Ann Oncol. 2020 Aug;31(8):1056-1064.
[COI] This study was supported by F. Hoffmann-La Roche Ltd. Some of the authors have received funding from F. Hoffmann-La Roche Ltd., Genentech, Inc., and Chugai Pharmaceutical Co., Ltd. Five of the authors are employees of F. Hoffmann-La Roche Ltd.

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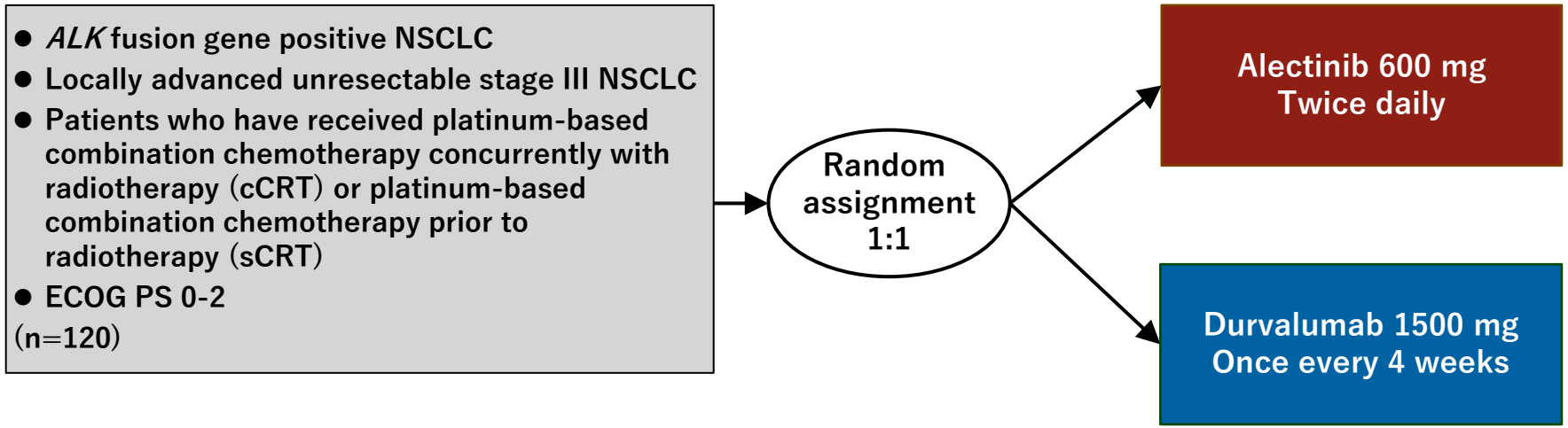
HORIZON-01

■ **The HORIZON study evaluated the efficacy and safety of multiple treatments in each cohort of patients with locally advanced unresectable stage III NSCLC**

A1 cohort



NCT05170204 https://www.clinicaltrials.gov/study/NCT05170204 (Accessed: November 2024)

Clinical Positioning

- **_ALK_ fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer**
  - Results from the J-ALEX study demonstrate the clinical usefulness of alectinib in patients with _ALK_ fusion gene-positive, unresectable, advanced or recurrent NSCLC. Alectinib can be considered as a treatment option for such patients.

- **Postoperative adjuvant therapy for _ALK_ fusion gene-positive non-small cell lung cancer**
  - Results from the ALINA study demonstrate the clinical benefit of alectinib in postoperative patients with stage IB (tumor diameter ≥ 4 cm) to IIIA _ALK_ fusion gene-positive NSCLC. Alectinib can be considered as a treatment option for such patients.

Tecentriq

Product Overview

Anti-cancer agent / humanized anti-PD-L1 monoclonal antibody atezolizumab (genetical recombination) injection

Tecentriq Intravenous Infusion 840 mg / Tecentriq Intravenous Infusion 1200 mg

Indications

<Tecentriq Intravenous Infusion 1200 mg>

○ Unresectable, advanced, or recurrent non-small cell lung cancer (NSCLC)

○ Adjuvant treatment of PD-L1-positive non-small cell lung cancer

○ Extensive-stage small cell lung cancer (SCLC)

○ Unresectable hepatocellular carcinoma (HCC)

<Tecentriq Intravenous Infusion 840 mg>

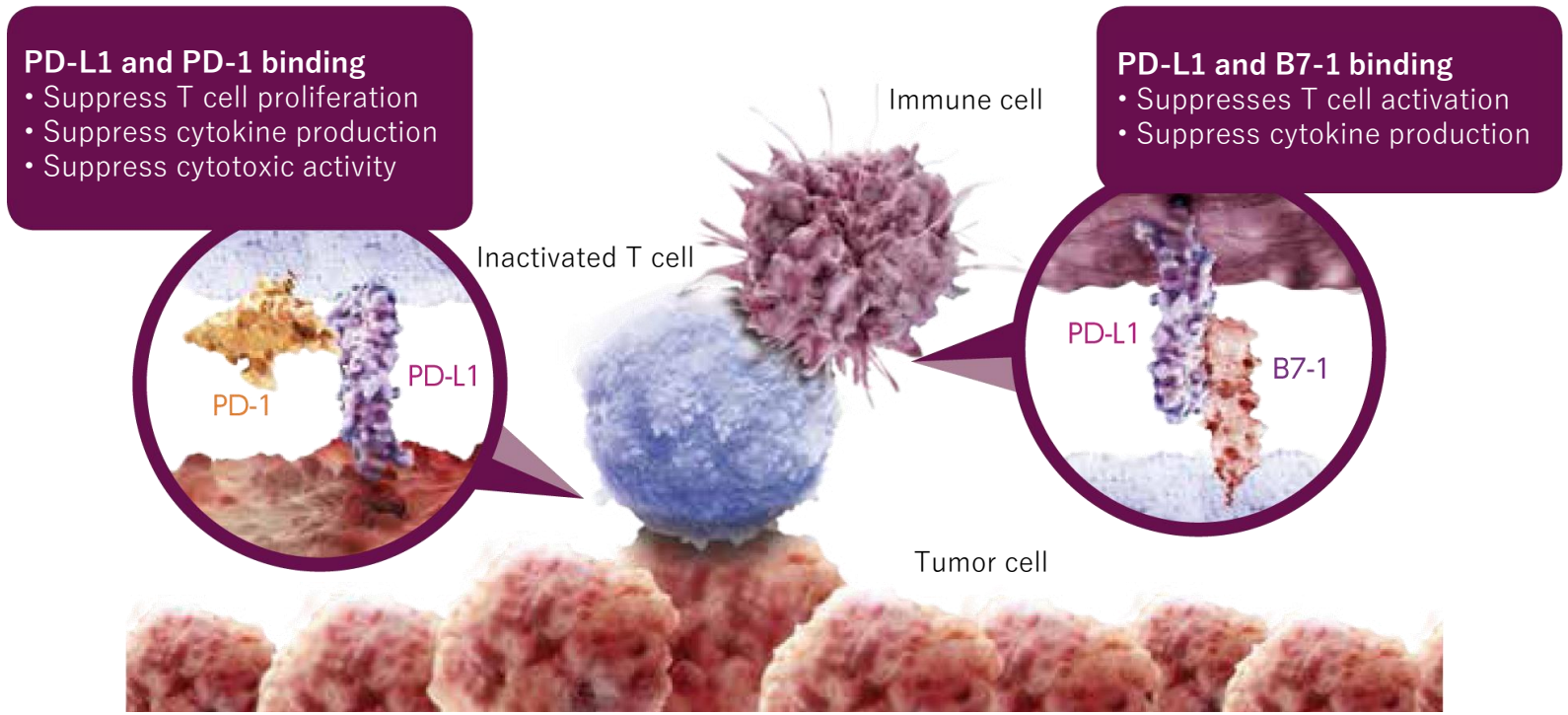
○ PD-L1-positive, hormone receptor-negative, and HER2-negative inoperable or metastatic breast cancer

PD-L1: Programmed Death-Ligand 1

Mode of Action (1/2)

PD-L1 is primarily expressed on tumor cells or immune cells. By binding to PD-1 or B7-1 on T cells, it transmits inhibitory signals and regulates T cell activation. Tumor cells are reported to evade immune system attacks by suppressing T cell activation through PD-L1 expression.[1,2)]

Diagram



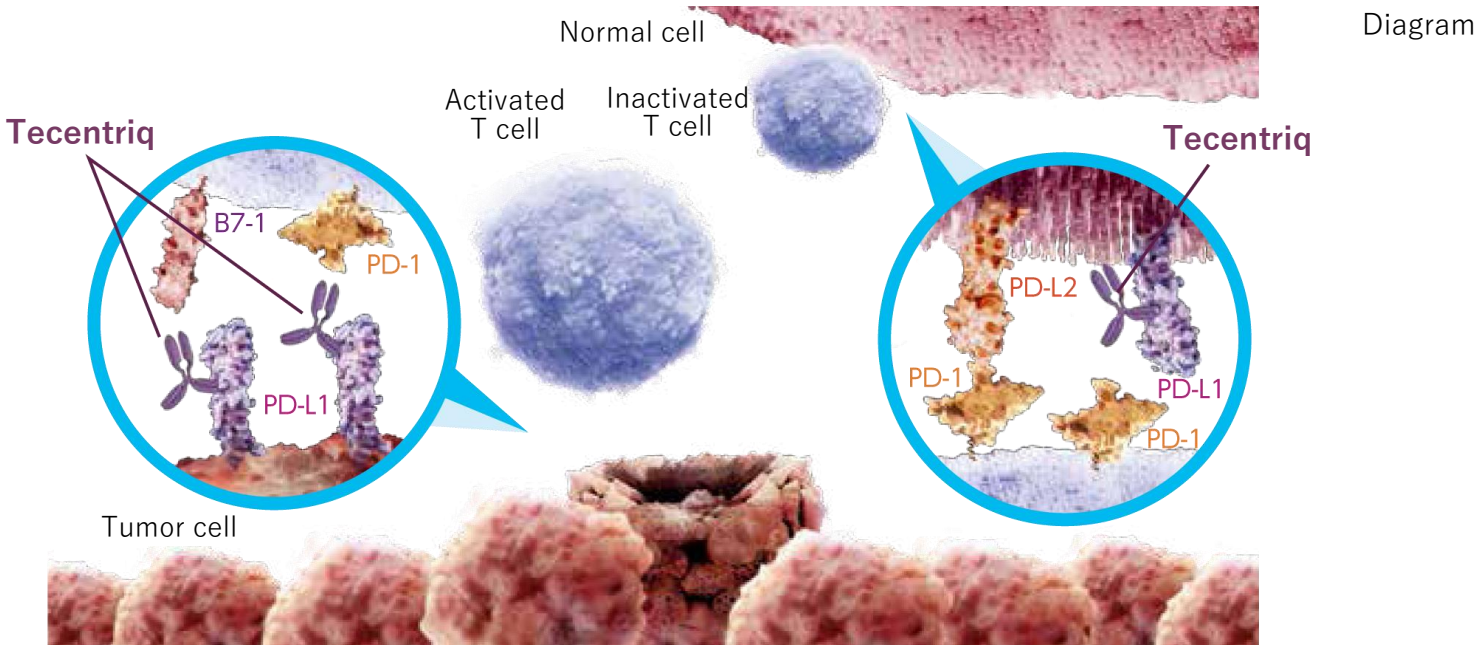
Blank C, et al.: Cancer Immunol Immunother, 2007; 56(5): 739-45. [Illustration adapted]
Chen DS, et al.: Clin Cancer Res, 2012; 18(24): 6580-7. [Illustration adapted]

1) Blank C, et al.: Cancer Immunol Immunother, 2007; 56(5): 739-45.
2) Chen DS, et al.: Clin Cancer Res, 2012; 18(24): 6580-7.
[COI] The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of Genentech.
3) Cha E, et al.: Semin Oncol, 2015; 42(3): 484-7.
[COI] The study was supported by Genentech. The authors include employees of Genentech.

Mode of Action (2/2)

Tecentriq is a humanized IgG1 monoclonal antibody targeting PD-L1. By binding to PD-L1, it blocks inhibitory signals derived from the PD-L1/PD-1 and PD-L1/B7-1 pathways, thereby reactivating T cells, inducing anti-tumor immune responses, and promoting T cell-mediated tumor cell attack.[2)]

Tecentriq does not bind to PD-L2, another ligand of PD-1, and is therefore believed to preserve the suppression of Th2-type immune responses mediated by the PD-L2/PD-1 pathway.[2,3)]



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3) Cha E, et al.: Semin Oncol, 2015; 42(3): 484-7.
[COI] The study was supported by Genentech. The authors include employees of Genentech.

Tecentriq

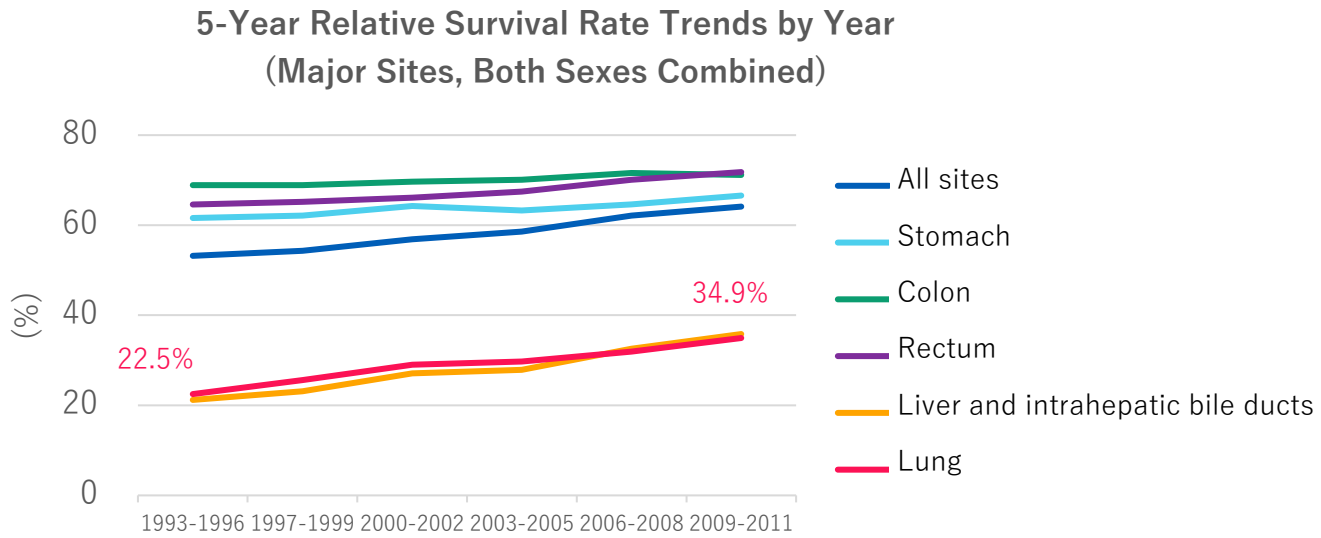
Development Pipeline

Launched		Launch Year
OAK	Unresectable, advanced, or recurrent non-small cell lung cancer previously treated with chemotherapy	2018
IMpower150	Unresectable, advanced, or recurrent non-small cell lung cancer	2018
IMpower133	Extensive-stage small cell lung cancer	2019
IMpower130/132	Unresectable, advanced, or recurrent non-small cell lung cancer	2019
IMpower110	PD-L1-positive, unresectable, advanced, or recurrent non-small cell lung cancer	2020
IMpower010	Adjuvant treatment of PD-L1-positive non-small cell lung	2022
IMpassion130	PD-L1-positive, hormone receptor-negative, and HER2-negative inoperable or metastatic breast cancer	2019
IMbrave150	Unresectable hepatocellular carcinoma	2020

Under development		Application schedule
Investigator-initiated trial (ALBERT), etc.	Alveolar soft part sarcoma	March 14, 2024
Investigator-initiated trial (ATTACK)	Extranodal NK/T-cell lymphoma, nasal type	October 31, 2024
IMpower030	Perioperative non-small cell lung cancer	2026
IMvigor011	Adjuvant therapy for ctDNA-positive muscle-invasive bladder cancer after surgery	2025

NSCLC: Disease and Epidemiological Information

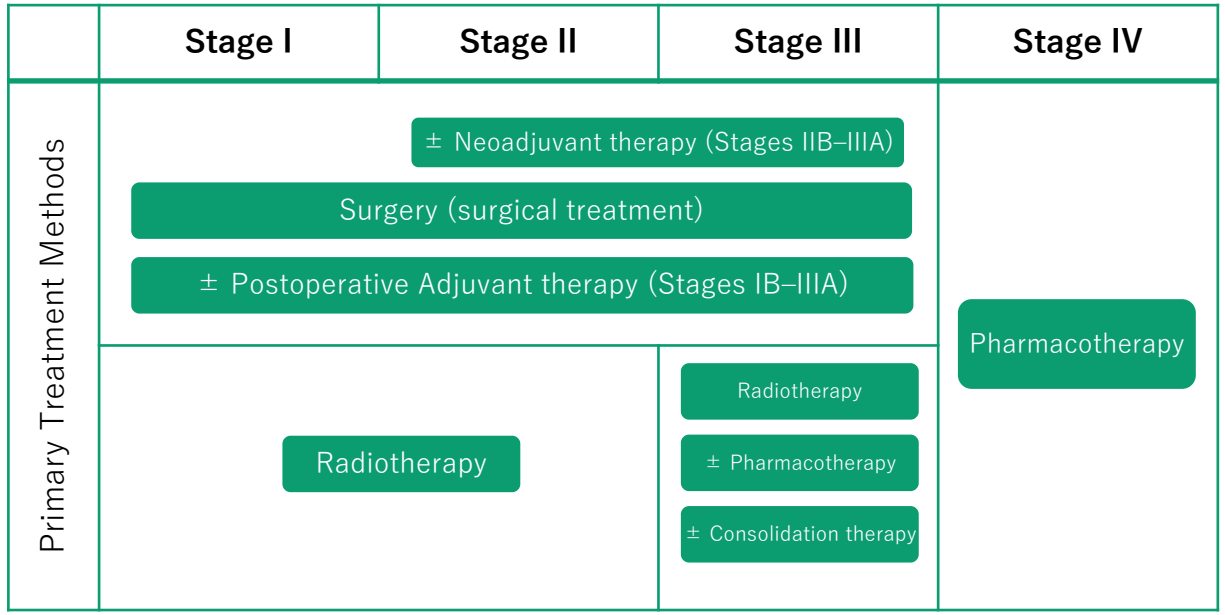
- **Lung cancer ranks as the leading cause of cancer-related deaths (2022, approximately 77,000 deaths), with over 120,000 new diagnoses each year.**
- **Advances in treatment have led to an upward trend in lung cancer survival rates, though these rates remain lower compared to other cancer types.**
- **Based on histological classification, non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases.**



Monitoring of Cancer Incidence in Japan - Survival 2009–2011 (Center for Cancer Control and Information Services, National Cancer Center, 2020).
FY 2010 Report: “Research on Improving the Accuracy and Utilization of Regional Cancer Registries,” supported by the National Cancer Center Cancer Research and Development Expenses grant.

NSCLC: Primary Treatment Methods

- **Lung cancer treatments include surgery, radiotherapy, and pharmacotherapy, with the choice of treatment depending on the stage of cancer, the patient's age, and overall health status.**
- **For stage IV lung cancer, pharmacotherapy primarily involves cytotoxic anticancer drugs, molecular targeted therapies, and immune checkpoint inhibitors.**
- **As the cancer stage advances, survival rates tend to decrease. Progress in treatment options for advanced stages is highly anticipated.**



Created based on the Guidelines for Diagnosis and Treatment of Lung Cancer, 2023 Edition.

5-Year Survival Rates for NSCLC by Stage (Diagnosed in 2014–2015)

Stage	Observed SurvivalRate
Overall	43.2%
Stage I	74.6%
Stage II	47.7%
Stage III	28.2%
Stage IV	8.4%

*Observed survival rate: Includes all-cause mortality, regardless of cause of death.

Data summary: Collected from 555 facilities nationwide, including designated cancer care hospitals (Sample size: 106,783 cases).

Hospital-Based Cancer Registry 2014-2015, 5-Year Survival Rate Compilation (March 2023, National Cancer Center, Institute for Cancer Control, Center for Cancer Registries).

SCLC: Disease and Epidemiological Information

- **Small Cell Lung Cancer (SCLC) accounts for 10% to 15% of all lung cancer cases and is the third most common histological type of lung cancer.**
- **It is one of the cancers strongly associated with smoking.**
- **SCLC is a highly malignant tumor characterized by rapid growth and early lymph node and distant metastasis.**
- **While it is highly sensitive to radiotherapy and pharmacotherapy, it has a high recurrence rate, with only around 10% of cases achieving a cure through treatment.**

5-Year Survival Rates for SCLC by Stage (Diagnosed in 2014–2015)

Stage	Observed Survival Rate
Overall	10.6%
Stage I	38.9%
Stage II	26.1%
Stage III	16.3%
Stage IV	2.0%

Hospital-Based Cancer Registry 2014-2015, 5-Year Survival Rate Compilation (March 2023, National Cancer Center, Institute for Cancer Control, Center for Cancer Registries).

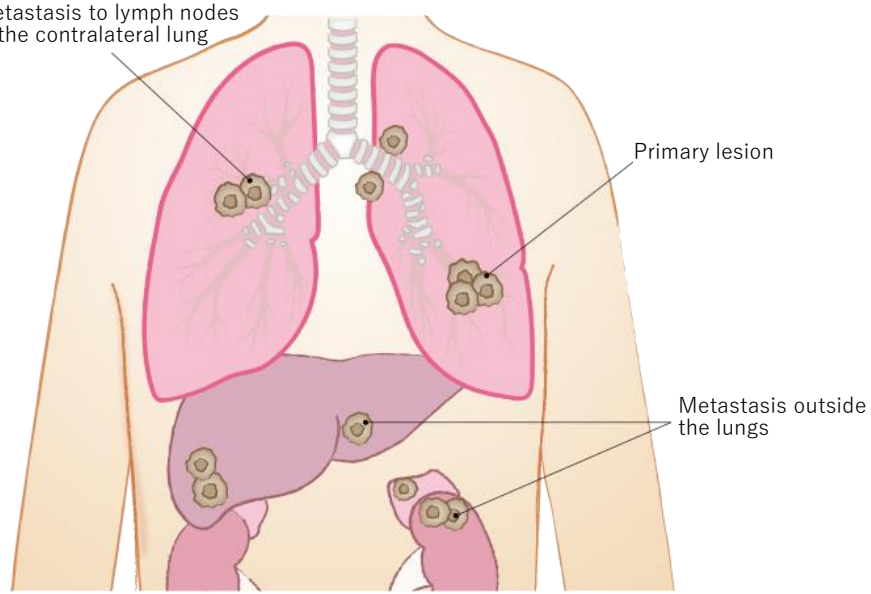
*Observed survival rate: Includes all-cause mortality, regardless of cause of death.
Data summary: Collected from 555 facilities nationwide, including designated cancer care hospitals (Sample size: 9,937 cases).

The Japan Lung Cancer Society. Guidelines for Diagnosis and Treatment of the Lung Cancer, Malignant Pleural Mesothelioma, Thymic Tumors, 2023 Edition.

SCLC: Primary Treatment Methods

- In SCLC, the UICC-TNM classification is important for determining the eligibility for surgical resection. However, for selecting medical treatments (chemoradiotherapy or pharmacotherapy), the limited disease (LD) and extensive disease (ED) classifications are widely used.
- The primary treatment for limited-stage SCLC is a combination of pharmacotherapy and radiotherapy. However, in clinical stages I/IIA (8th edition), multimodal therapy including surgical treatment is also applied.
- Extensive-stage SCLC accounts for approximately 70% to 80% of cases. It often involves distant metastases, such as brain metastases, and has a poor prognosis.
- The primary treatment for extensive-stage SCLC is pharmacotherapy. Initial treatment involves platinum-based combination chemotherapy along with immune checkpoint inhibitors.

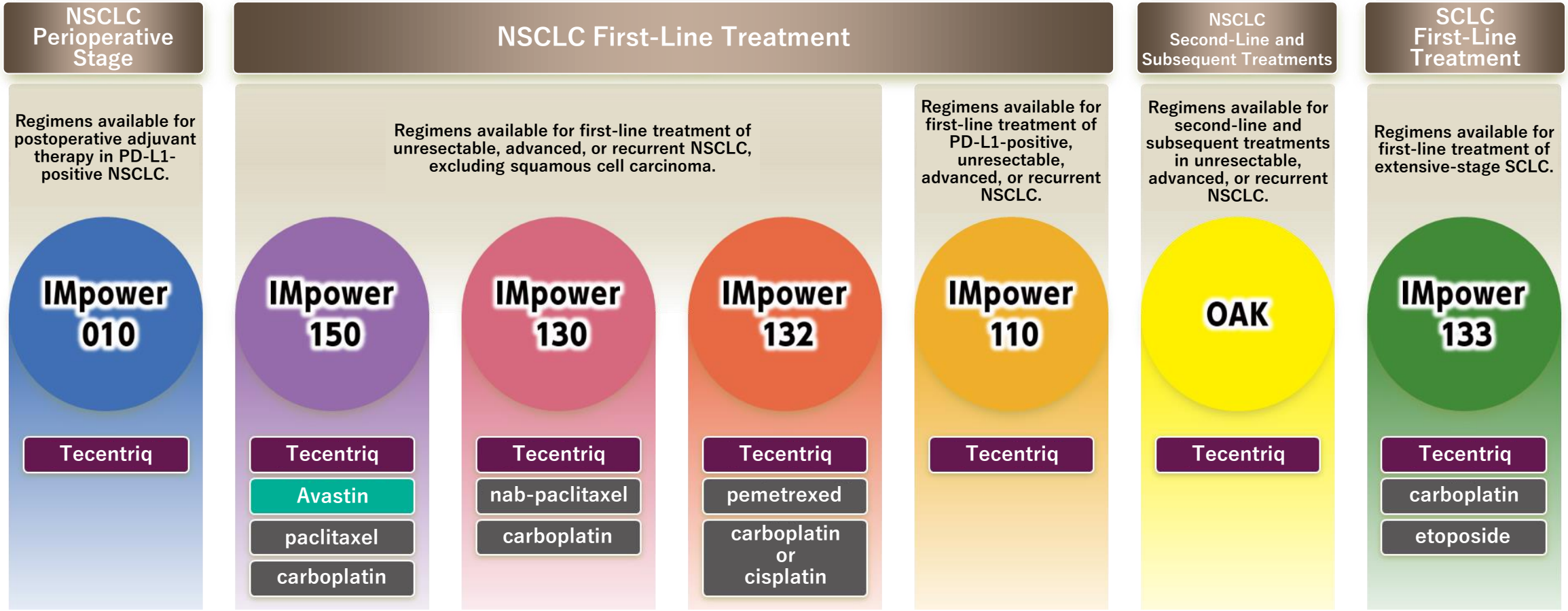
[Overview of Extensive-Stage SCLC]



The cancer has spread beyond the range treatable by radiotherapy.

The Japan Lung Cancer Society. Guidelines for Diagnosis and Treatment of the Lung Cancer, Malignant Pleural Mesothelioma, Thymic Tumors, 2023 Edition.
Simon GR, et al. Chest. 2003;123(1 Suppl):259s–271s.

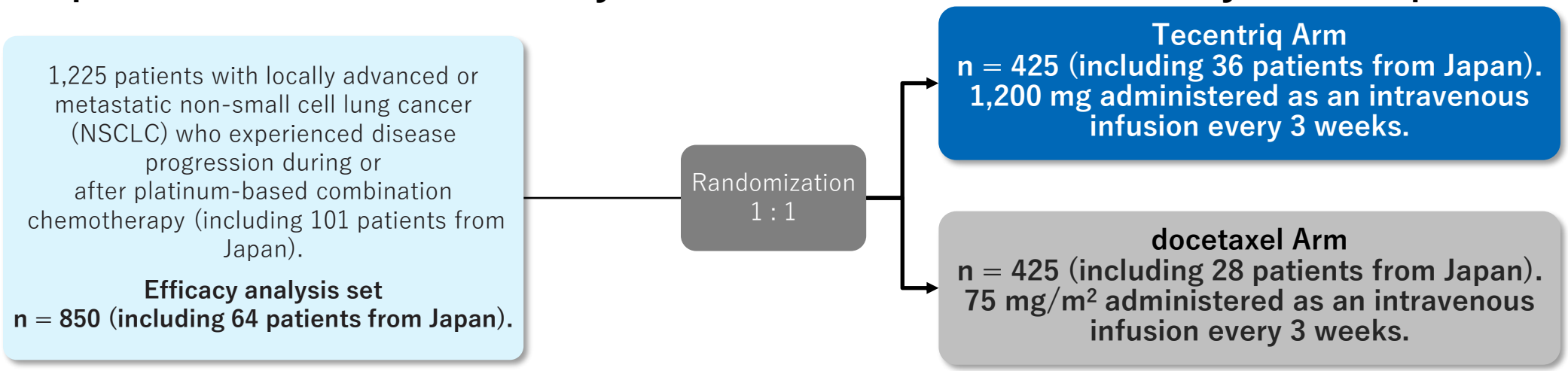
List of Studies Related to Lung Cancer Indications



Felip E, et al.: Lancet, 2021; 398(10308): 1344-57. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of Roche (China) or Genentech.
Data evaluated at the time of approval: Global Phase III Clinical Trial (IMpower010).
Socinski MA, et al.: N Engl J Med, 2018; 378(24): 2288-301. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of Genentech.
Data evaluated at the time of approval: Global Phase III Clinical Trial (IMpower150).
West H, et al.: Lancet Oncol, 2019; 20(7): 924-37. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of F. Hoffmann-La Roche.
Data evaluated at the time of approval: Overseas Phase III Clinical Trial (IMpower130).
Data evaluated at the time of approval: Global Phase III Clinical Trial (IMpower132).
Herbst RS, et al.: N Engl J Med, 2020; 383(14): 1328-39. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche, Genentech, and Chugai Pharmaceutical Co., Ltd. The authors include employees of F. Hoffmann-La Roche, Genentech, and Chugai Pharmaceutical Co., Ltd.
Data evaluated at the time of approval: Global Phase III Clinical Trial (IMpower110).
Rittmeyer A, et al.: Lancet, 2017; 389(10066): 255-65. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of Genentech.
Data evaluated at the time of approval: Global Phase III Clinical Trial (OAK trial).
Horn L, et al.: N Engl J Med, 2018; 379(23): 2220-9. [COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche and Genentech. The authors include employees of Genentech.
Data evaluated at the time of approval: Global Phase I/III Clinical Trial (IMpower133).

NSCLC Second-Line and Subsequent Treatments for Non-Small cell lung cancer: OAK Study

- **The first positive Phase III clinical study results for the anti-PD-L1 antibody Tecentriq.**



Stratification factors:
- PD-L1 expression (IC0, IC1, IC2, IC3)
- Number of prior chemotherapy regimens (1 or 2).
- Histology (non-squamous vs. squamous)

Primary endpoint: Overall survival (OS) (efficacy analysis set irrespective of PD-L1 expression, efficacy analysis set expressing PD-L1)

Secondary endpoints: Progression-free survival (PFS), response rate, duration of response (DOR) (all based on RECIST v1.1, investigator assessment)

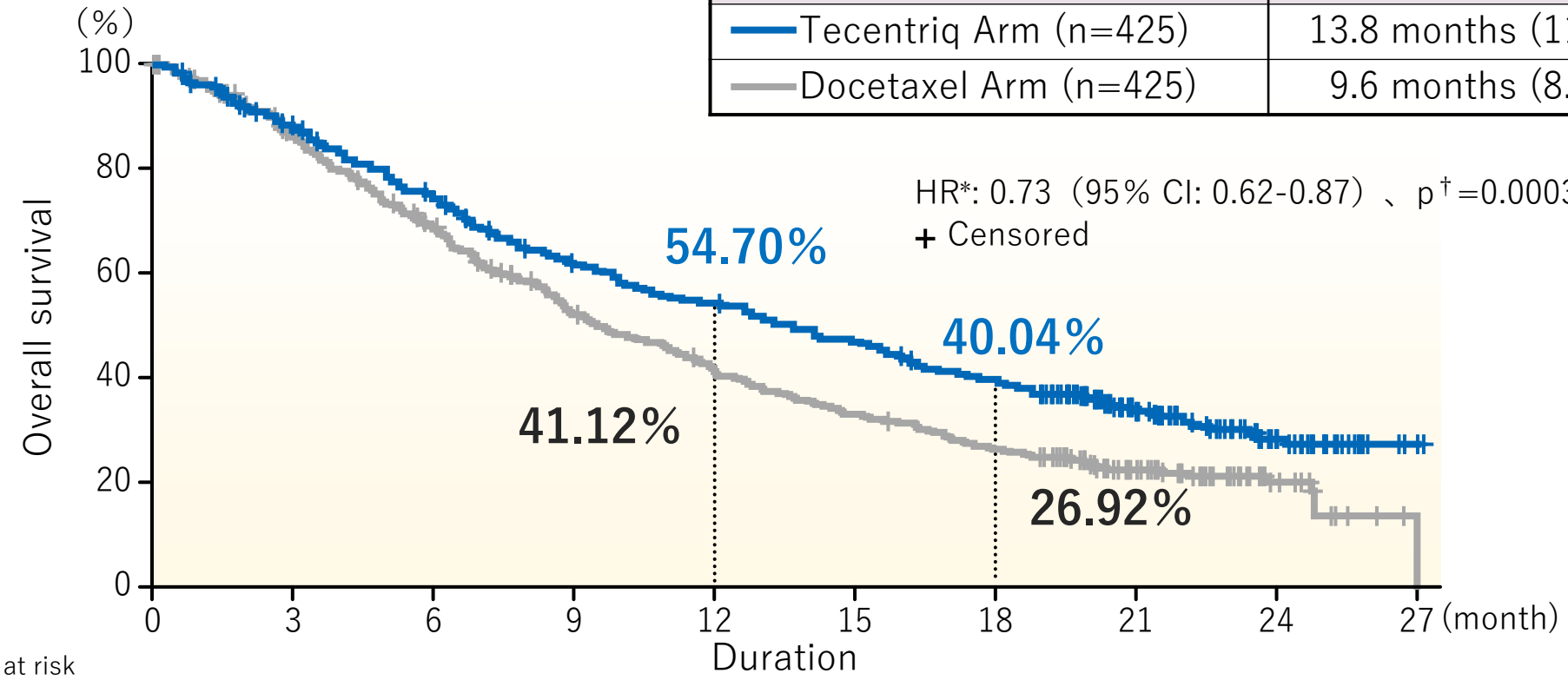
Analysis plan: The first 850 randomized patients were included in the efficacy analysis set for the primary endpoint evaluation. Subgroup analyses based on PD-L1 expression assessed by the IHC method and histological type were conducted according to the pre-specified plan.

Rittmeyer A, et al.: Lancet 2017; 389(10066): 255-65. (The authors include employees of Genentech.)

OAK Study: Second-Line and Subsequent Treatments for NSCLC

Overall Survival (OS) in the Efficacy Analysis Set Irrespective of PD-L1 Expression (Primary Endpoint)

	Median OS (95% CI)
Tecentriq Arm (n=425)	13.8 months (11.8–15.7)
Docetaxel Arm (n=425)	9.6 months (8.6–11.2)



No. at risk										
Tecentriq Arm	425	363	305	248	218	188	157	74	28	1
Docetaxel Arm	425	336	263	195	151	123	98	51	16	–

*Stratified HR
† Stratified log-rank test

Rittmeyer A, et al.: Lancet 2017; 389(10066): 255-65. (The authors include employees of Genentech.)

OAK Study: Second-Line and Subsequent Treatments for NSCLC

Safety Overview

	Tecentriq Arm (n=609)	Docetaxel Arm (n=578)
All adverse events (AEs)	573 (94.1%)	555 (96.0%)
Treatment-related AEs	390 (64.0%)	496 (85.8%)
Grade 3–4 AEs	227 (37.3%)	310 (53.6%)
Grade 3–4 treatment-related AEs	90 (14.8%)	247 (42.7%)
All deaths	10 (1.6%)	14 (2.4%)
Treatment-related deaths	0	1 (0.2%)
Serious AEs	194 (31.9%)	181(31.3%)
AEs leading to treatment discontinuation	46 (7.6%)	108 (18.7%)
Dose modification, delayed dosing, or interruptions	152 (25.0%)	210 (36.3%)

Immune-related Adverse Events

	Tecentriq Arm (n=609)	
	All Grades	Grade 3 or Higher
Interstitial lung disease	14 (2.3%)	5 (0.8%)
Hepatic function disorder, hepatitis	67 (11.0%)	18 (3.0%)
Colitis	2 (0.3%)	0
Diarrhea	94 (15.4%)	4 (0.7%)
Pancreatitis	1 (0.2%)	1 (0.2%)
Type 1 diabetes mellitus	1 (0.2%)	0
Thyroid dysfunction	34 (5.6%)	0
Adrenal dysfunction	3 (0.5%)	0
Pituitary disorder	1 (0.2%)	0
Encephalitis, meningitis	5 (0.8%)	3 (0.5%)
Neurological disorders	39 (6.4%)	5 (0.8%)
Myasthenia gravis	0	0

Rittmeyer A, et al.: Lancet 2017; 389(10066): 255-65. (The authors include employees of Genentech.)

NSCLC First-Line Treatment: 4 Global Clinical Studies

- **In chemotherapy-naïve NSCLC, 3 combination therapies and 1 monotherapy contribute to treatment for patients.**

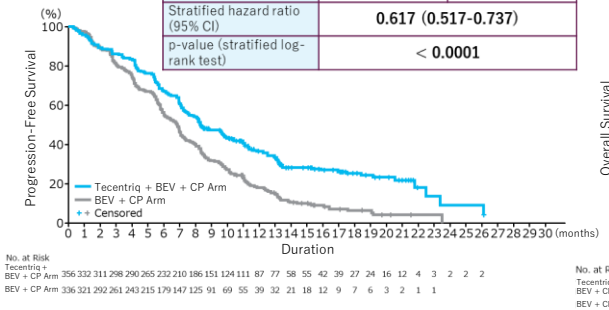
Avastin + Paclitaxel + Carboplatin Combination Therapy

A multicenter, randomized, open-label, overseas Phase III clinical study comparing Tecentriq ± Avastin + chemotherapy (paclitaxel and carboplatin) versus chemotherapy alone in patients with chemotherapy-naïve, non-squamous NSCLC (IMpower150)

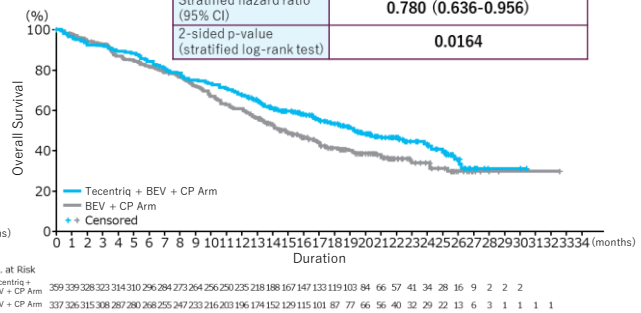
Primary Endpoints: progression-free survival (PFS), overall survival (OS).

Efficacy:

PFS	Tecentriq + BEV + CP Arm (n=356)	BEV + CP Arm (n=336)
Median PFS	8.3 months	6.8 months
Stratified hazard ratio (95% CI)	0.617 (0.517-0.737)	
p-value (stratified log-rank test)	< 0.0001	



OS	Tecentriq + BEV + CP Arm (n=359)	BEV + CP Arm (n=337)
Median OS	19.2 months	14.7 months
Stratified hazard ratio (95% CI)	0.780 (0.636-0.956)	
2-sided p-value (stratified log-rank test)	0.0164	



Safety:

The main side effects in the combination group were alopecia, nausea, fatigue, anemia, decreased appetite, peripheral neuropathy, and diarrhea.

Data evaluated at the time of approval

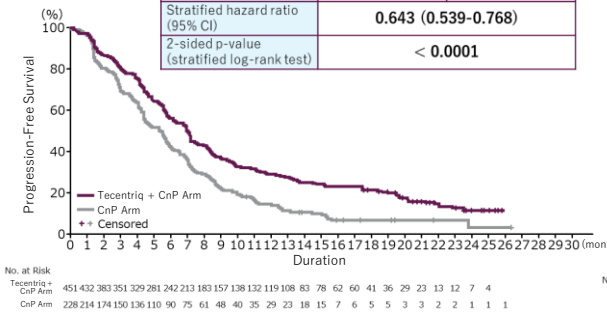
Nab-Paclitaxel + Carboplatin Combination Therapy

A multicenter, randomized, open-label, overseas Phase III clinical study comparing Tecentriq + carboplatin + nab-paclitaxel versus carboplatin + nab-paclitaxel in chemotherapy-naïve patients with non-squamous NSCLC (IMpower130)

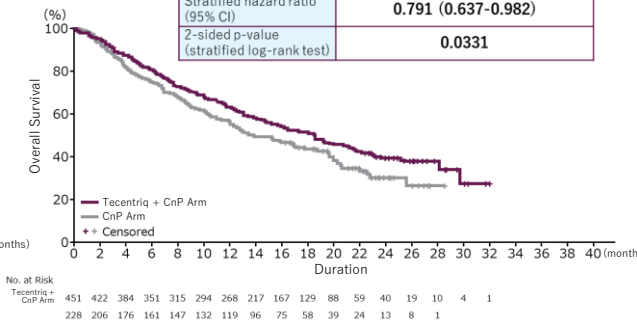
Primary Endpoints: progression-free survival (PFS), overall survival (OS).

Efficacy:

PFS	Tecentriq + CnP Arm (n=451)	CnP Arm (n=228)
Median PFS	7.0 months	5.5 months
Stratified hazard ratio (95% CI)	0.643 (0.539-0.768)	
2-sided p-value (stratified log-rank test)	< 0.0001	



OS	Tecentriq + CnP Arm (n=451)	CnP Arm (n=228)
Median OS	18.6 months	13.9 months
Stratified hazard ratio (95% CI)	0.791 (0.637-0.982)	
2-sided p-value (stratified log-rank test)	0.0331	



Safety:

The main side effects in the combination group were anemia, neutropenia, nausea, fatigue, diarrhea, alopecia, thrombocytopenia, decreased appetite, platelet count decreased, and vomiting.

Data evaluated at the time of approval

NSCLC First-Line Treatment: 4 Global Clinical Studies

- **In chemotherapy-naïve NSCLC, 3 combination therapies and 1 monotherapy contribute to treatment for patients.**

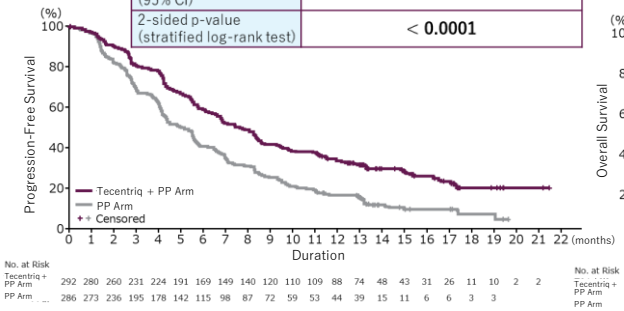
Pemetrexed + Platinum-Based Combination Therapy

A multicenter, randomized, open-label, global Phase III clinical study comparing Tecentriq combined with chemotherapy (carboplatin or cisplatin + pemetrexed) versus chemotherapy alone in chemotherapy-naïve patients with non-squamous NSCLC (IMpower132)

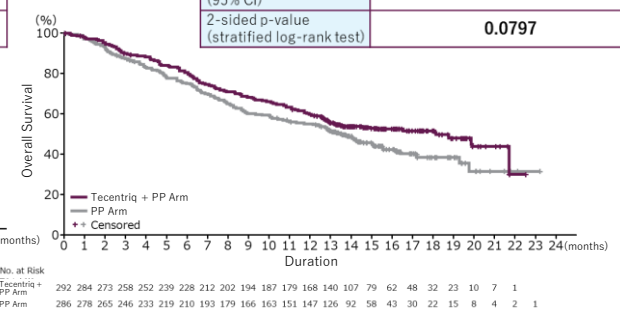
Primary Endpoints: progression-free survival (PFS), overall survival (OS).

Efficacy:

PFS	Tecentriq + PP Arm (n=292)	PP Arm (n=286)
Median PFS	7.6 months	5.2 months
Stratified hazard ratio (95% CI)	0.596 (0.494-0.719)	
2-sided p-value (stratified log-rank test)	< 0.0001	



OS	Tecentriq + PP Arm (n=292)	PP Arm (n=286)
Median OS	18.1 months	13.6 months
Stratified hazard ratio (95% CI)	0.813 (0.644-1.025)	
2-sided p-value (stratified log-rank test)	0.0797	



Safety:

The main side effects in the combination group were anemia, nausea, and asthenia.

Data evaluated at the time of approval

Tecentriq Monotherapy (PD-L1 Strongly Positive)

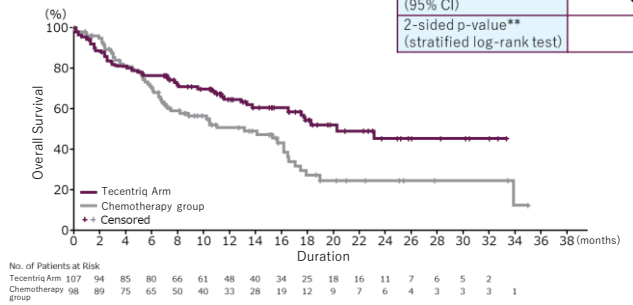
A multicenter, randomized, open-label, global Phase III clinical study comparing Tecentriq combined with chemotherapy (cisplatin or carboplatin + pemetrexed or gemcitabine) versus chemotherapy alone in chemotherapy-naïve patients with PD-L1-positive NSCLC (IMpower110).

Primary endpoint: overall survival (PD-L1 strongly positive, PD-L1 positive)

Efficacy:

PD-L1 Strongly Positive

OS	Tecentriq Arm (n=107)	Chemotherapy group (n=98)
Median OS	20.2 months	13.1 months
Stratified hazard ratio* (95% CI)	0.595 (0.398-0.890)	
2-sided p-value** (stratified log-rank test)	0.0106	



Safety:

The main side effects in the combination group were fatigue, asthenia, nausea, decreased appetite, hypothyroidism, rash, ALT increased, and diarrhea.

Data evaluated at the time of approval

NSCLC Postoperative Adjuvant Therapy: IMpower010

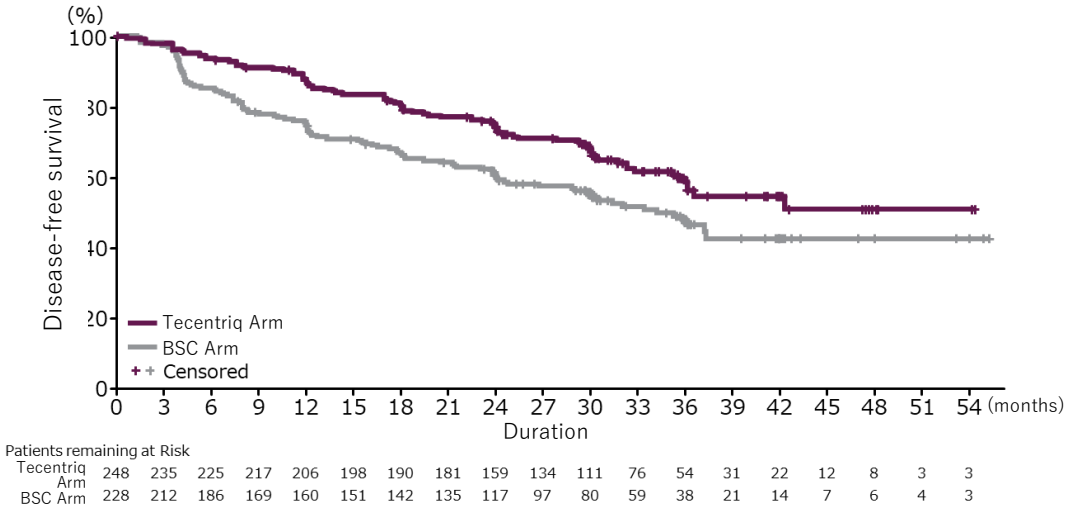
- **The first immune checkpoint inhibitor to demonstrate efficacy in PD-L1-positive early-stage NSCLC.**

A multicenter, randomized, open-label, global Phase III clinical study comparing Tecentriq versus best supportive care (BSC) in patients with completely resected stage IB-IIIA (UICC classification) NSCLC (IMpower010).

Primary Endpoint: Disease-free survival (DFS) ([1] PD-L1-positive population in stages II–IIIA, [2] overall population in stages II–IIIA, [3] ITT population in stages IB–IIIA; assessed by the investigator).

Efficacy:

DFS: PD-L1-positive



DFS	Tecentriq Arm (n=248)	BSC Arm (n=228)
Median DFS	**Not reached**	**35.3 months**
Stratified hazard ratio (95% CI)	**0.659 (0.495-0.877)**	
2-sided p-value (stratified log-rank test)	**0.0039**	
3-year DFS rate (95% CI)	**59.96% (52.82-67.10)**	**48.22% (40.73-55.71)**

Safety:

The main side effects in the combination group were hypothyroidism, pruritus, rash, AST increased, ALT increased, hyperthyroidism, pyrexia, and arthralgia.

Data evaluated at the time of approval

First-Line Treatment for Extensive-Stage Small Cell Lung Cancer: IMpower133

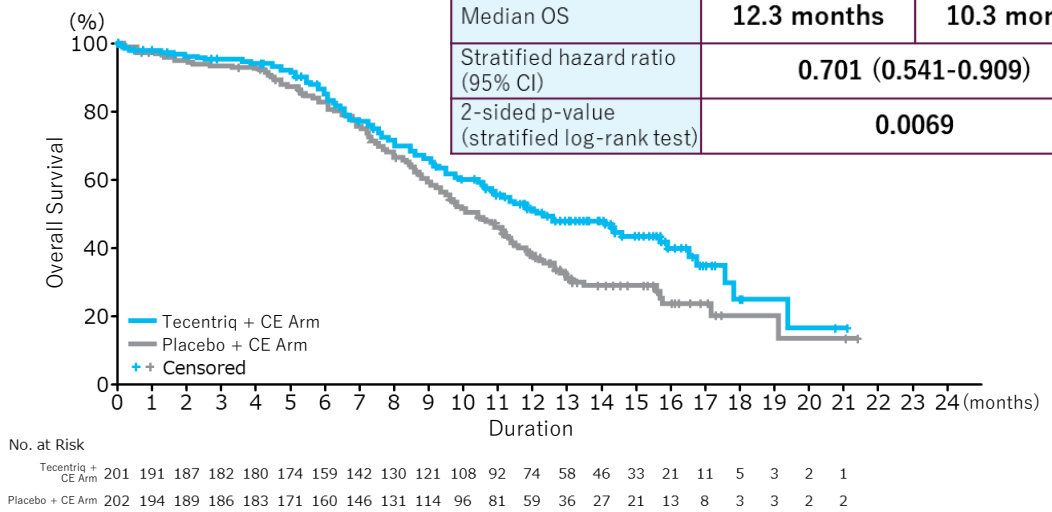
- **The first immune checkpoint inhibitor to demonstrate efficacy in extensive-stage small cell lung cancer. A therapy approved for the first time in 17 years.**

A multicenter, randomized, open-label, global Phase III clinical study comparing Tecentriq in combination with chemotherapy (carboplatin and etoposide) versus chemotherapy alone in chemotherapy-naïve patients with extensive-stage small cell lung cancer (IMpower133).

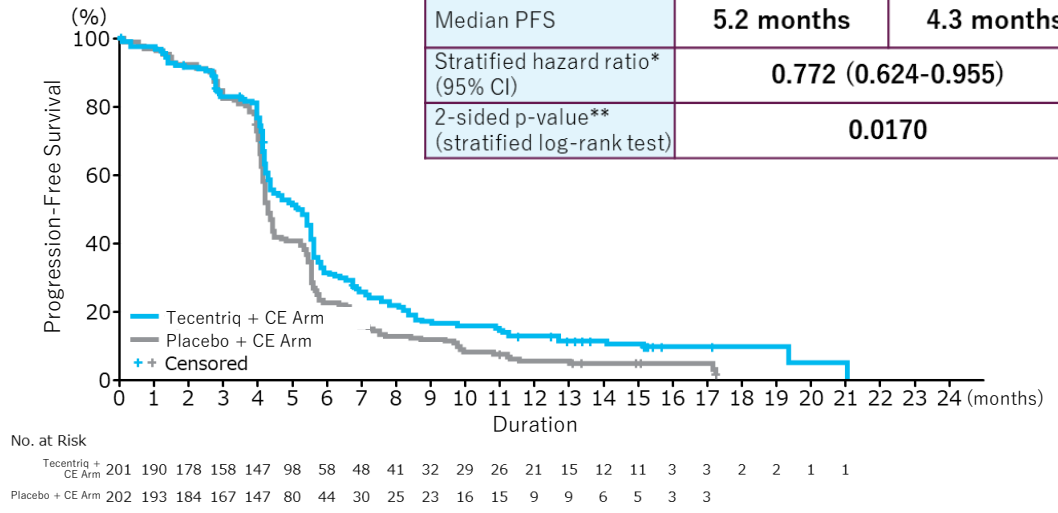
Primary endpoints: Overall survival, progression-free survival

Efficacy:

OS	Tecentriq + CE Arm (n=201)	Placebo + CE Arm (n=202)
Median OS	12.3 months	10.3 months
Stratified hazard ratio (95% CI)	0.701 (0.541-0.909)	
2-sided p-value (stratified log-rank test)	0.0069	



PFS	Tecentriq + CE Arm (n=201)	Placebo + CE Arm (n=202)
Median PFS	5.2 months	4.3 months
Stratified hazard ratio* (95% CI)	0.772 (0.624-0.955)	
2-sided p-value** (stratified log-rank test)	0.0170	



Safety:

The main side effects in the combination group were anemia, neutropenia, alopecia, nausea, fatigue, and decreased appetite.

Data evaluated at the time of approval

Positioning in Lung Cancer Treatment Guidelines

Postoperative pathological stages IIB–IIIB for non-small cell lung cancer

For tumor cells exhibit PD-L1 expression ≥ 50%, the addition of atezolizumab monotherapy following cisplatin-based chemotherapy is weakly recommended.（For tumor cells exhibit PD-L1 expression ≥ 1% but < 50%, 、 there is insufficient evidence to clearly support.）

Non-small cell lung cancer first-line treatment

- Monotherapy: Recommended as one of the first-line treatment for patients with high PD-L1 expression.
- Combination therapies: Recommended as one of the first-line treatment for non-squamous NSCLC regardless of PD-L1 expression level.

Non-small cell lung cancer: second-line and subsequent treatments

- Monotherapy is recommended as one of the immune checkpoint inhibitors for second-line and subsequent treatments.

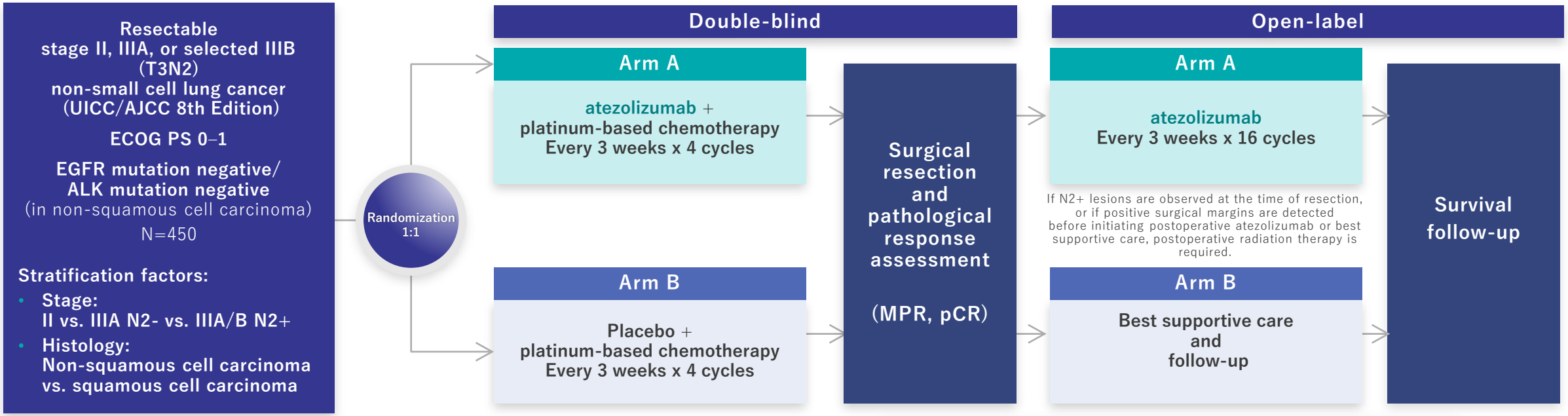
Extensive-stage small cell lung cancer

- Combination therapy with platinum agents and etoposide is recommended as part of first-line treatment with PD-L1 inhibitors.

The Japan Lung Cancer Society. Guidelines for Diagnosis and Treatment of the Lung Cancer, Malignant Pleural Mesothelioma, Thymic Tumors, 2024 Edition.

Ongoing Clinical Study IMpower030: Study Design

■ **A global Phase III clinical study evaluating the efficacy and safety of neoadjuvant atezolizumab in combination with chemotherapy in patients with resectable stage II, stage IIIA, or certain cases of stage IIIB non-small cell lung cancer.**



Primary Endpoint:

- **Centrally assessed event free survival (EFS)**
  Investigator-assessed Event Free Survival (EFS)

Key Secondary Endpoints:

- Major pathological response (MPR) assessed centrally
- Overall survival (OS)
- Objective response rate (ORR)
- Pathological complete response (pCR)
- Disease-free survival (DFS)
- Health-related quality of life (HRQOL)
- Safety

Ongoing Clinical Study BEAT-SC: Study Design

■ A Phase III Japan-China joint study of platinum-based therapy + atezolizumab ± bevacizumab for treatment-naïve patients with extensive-stage small cell lung cancer

Inclusion criteria:
- Confirmed diagnosis of ES-SCLC
- ECOG PS 0-1
- Aged 20 years or older
- No prior systemic treatment for ES-SCLC

N=330

Stratification factors:
- Sex
- ECOG PS (0 vs 1)
- Platinum agent (cisplatin vs. carboplatin)

R 1:1

Induction phase 4 cycles of 21 days	Maintenance phase
Arm A **bevacizumab 15 mg/kg** atezolizumab 1200 mg Carboplatin AUC 5 or Cisplatin 80 mg/m^2 (75–80 mg/m^2 in China) Etoposide 100 mg/m^2	bevacizumab atezolizumab
Arm B **Placebo** atezolizumab 1200 mg Carboplatin AUC 5 or Cisplatin 80 mg/m^2 (75–80 mg/m^2 in China) Etoposide 100 mg/m^2	Placebo atezolizumab

Etoposide is administered on Days 1, 2, and 3.

Treat until disease progression or loss of clinical benefit.

Survival follow-up

Primary Endpoint:
- Investigator-assessed progression-free survival (INV-PFS)

Key Secondary Endpoints:
- PFS assessed by an independent review committee (IRC-PFS)
- Overall survival (OS)
- Overall response rate (ORR), duration of response (DoR), safety, and patient-reported outcomes (PRO) assessed by the investigator
- Subgroup analysis

*For the latest updates, please refer to the following link: https://www.annalsofoncology.org/article/S0923-7534(24)03399-4/fulltext (Accessed: November 2024)

Breast Cancer Subtypes and Their Proportion in Japan

Breast cancer is classified into subtypes based on hormone receptor (positive/negative) and HER2 (positive/negative) status.

			Hormone Receptor: Positive	Hormone Receptor: Negative
HER2	Positive		Hormone receptor(+) HER2 (+) **7.3%**	Hormone receptor(-) HER2 (+) **8.2%**
	Negative	High proliferation potential	Luminal B-like **69%**	**Triple-negative** **15.5%**
		Low proliferation potential	Luminal A-like	

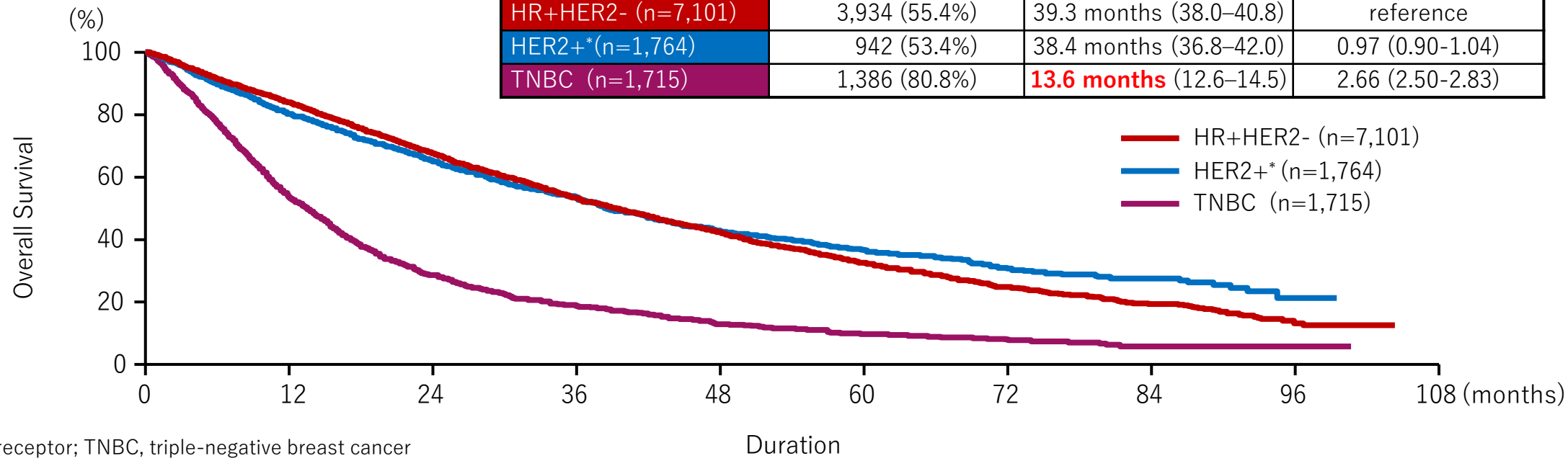
Iwase H, et al. Breast Cancer 2010; 17: 118-124 (Limitation: There are no strict criteria set for the determination of ER, PgR, and HER2, and each facility applies its own standards)
Partially adapted from the National Cancer Center's "Cancer Treatment Resident Manual, 6th Edition," Igaku-Shoin, 2013

Overall Survival in Patients with Metastatic Breast Cancer

[By breast cancer subtype: Subgroup analysis] (ESME MBC database, overseas data)

The prognosis was 13.6 months for triple-negative breast cancer, compared to 39.3 months and 38.4 months for other breast cancer subtypes (hormone receptor-positive and HER2-positive, respectively).

Breast cancer subtypes	Number of events (%)	Median (95% CI)	Hazard ratio (95% CI)
HR+HER2- (n=7,101)	3,934 (55.4%)	39.3 months (38.0–40.8)	reference
HER2+*(n=1,764)	942 (53.4%)	38.4 months (36.8–42.0)	0.97 (0.90-1.04)
TNBC (n=1,715)	1,386 (80.8%)	**13.6 months** (12.6–14.5)	2.66 (2.50-2.83)



HR, hormone receptor; TNBC, triple-negative breast cancer
*: Includes both hormone receptor (HR)-positive and HR-negative cases.

Overview

Using the French Epidémio-Stratégie Médico-Economique (ESME) metastatic breast cancer (MBC) database, 10,595 patients with known hormone receptor and HER2 expression status were extracted from16,702 patients who received first-line treatment for metastatic breast cancer between 2008 and 2014. The study examined the impact of breast cancer subtypes, the time to metastatic recurrence, age at the time of metastatic recurrence, and other factors on prognosis.

Gougis P, et al. Breast. 2019; 49: 17–24 (COI: ESME MBC database is sponsored by Roche.)
(Limitation: This is a retrospective study. Stage data at disease onset was missing for 50% of patients.)

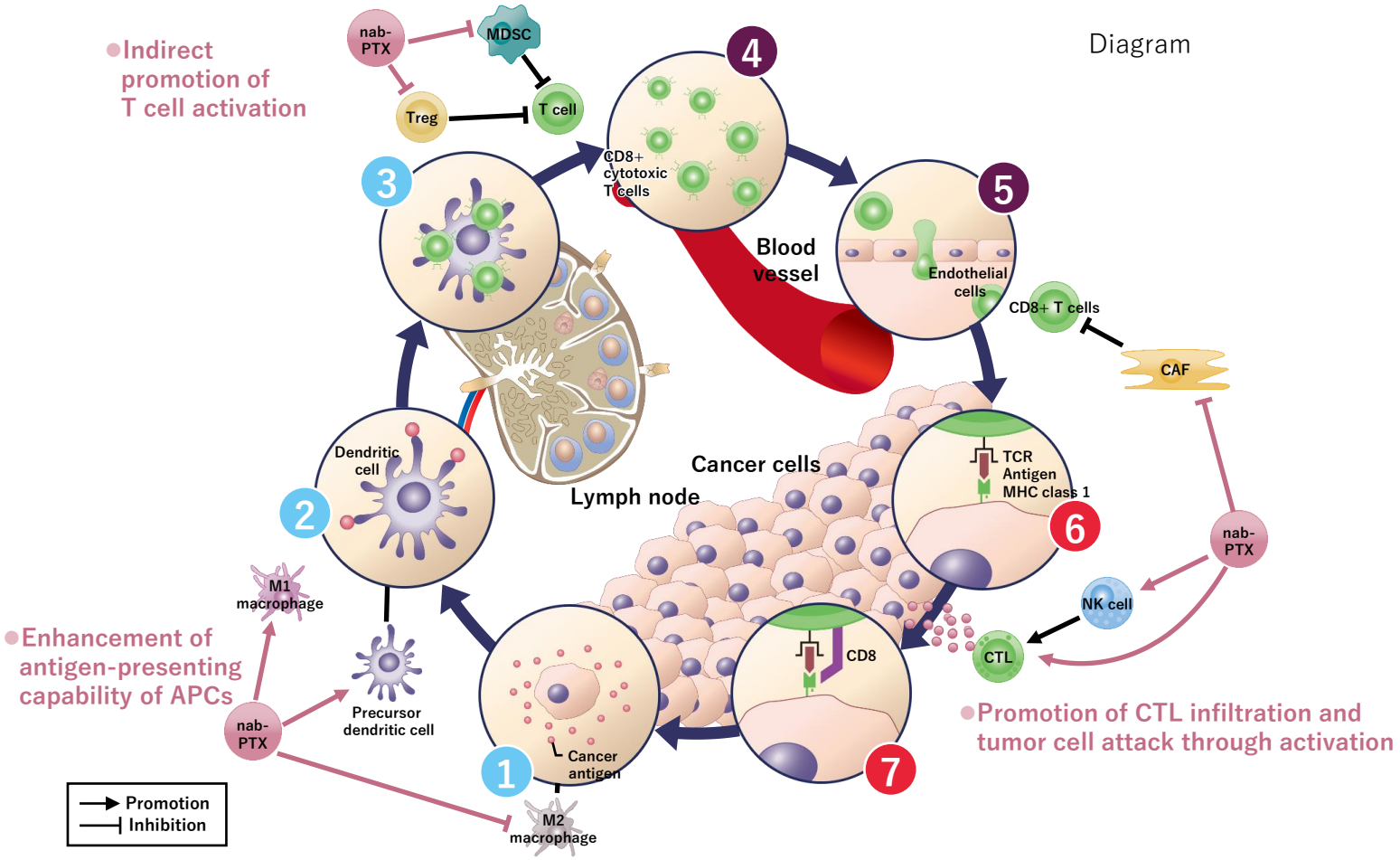
Tecentriq + nab-Paclitaxel: Positioning in Clinical Practice Guidelines

The combination of albumin-bound paclitaxel and atezolizumab is strongly recommended for PD-L1-positive triple-negative metastatic or recurrent breast cancer.

Breast Cancer. 2023 Nov;30(6):872-884

Involvement of nab-Paclitaxel in the Cancer-Immunity Cycle

Nab-paclitaxel has been shown to potentially enhance antitumor immunity by immunomodulation within the cancer-immunity cycle.



Diagram

Enhancement of Antigen-Presenting Capability of Antigen-Presenting Cells (APCs):

APCs, primarily dendritic cells, are thought to stimulate antitumor responses by promoting their maturation and polarizing macrophages toward the M1 phenotype.

Indirect Promotion of T Cell Activation:

Regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) both promote tumor progression. However, by acting to inhibit these cells, antitumor T cell activation is indirectly enhanced.

Promotion of Cytotoxic T Cell (CTL) Infiltration and Tumor Cell Attack through Activation:

By inhibiting the proliferation of cancer-associated fibroblasts (CAFs), stromal cells that promote tumor immune evasion, nab-paclitaxel is believed to facilitate the infiltration of immune cells and therapeutic agents into the tumor microenvironment.
It is also believed to play a role in activating natural killer (NK) cells, which kill tumor cells and release cancer antigens.

APC: antigen presenting cell; MDSC: myeloid derived suppressor cells; CTL: Cytotoxic T lymphocyte; CAF: cancer-associated fibroblast; NK: natural killer

Chen Y, et al.: Am J Cancer Res 2021; 11(7): 3445-60. [Illustration adapted]

Supervised by: Dr. Tomoharu Sugie, Professor, Department of Breast Surgery, Kansai Medical University Hospital

IMpassion 130: Study Design

Patients with metastatic, recurrent, or locally advanced hormone receptor-negative and HER2-negative breast cancer who have no history of prior systemic treatment for metastatic or recurrent breast cancer.

Efficacy analysis set n=902

- ECOG PS: 0-1
- Patients with measurable lesions (RECIST v1.1)
- Known PD-L1 expression status

Randomization Factors:
- Presence of liver metastases (Yes/No)
- Prior treatment with taxane-based therapy (Yes/No)
- PD-L1expression status (IC0 or IC1/2/3)

Randomization 1:1

Tecentriq + nab-PTX Arm
n = 451 (including 34 patients from Japan)

Tecentriq 840 mg: Days 1 and 15
nab-PTX100mg/m^2: Day1, 8, 15

Placebo + nab-PTX Arm
n = 451 (including 31 patients from Japan)

Placebo: Days 1 and 15
nab-PTX100mg/m^2: Day1, 8, 15

28 days per cycle

[Objective]

To evaluate the efficacy and safety of the combination therapy of Tecentriq + nab-PTX compared to placebo + nab-PTX in patients with metastatic, recurrent, or locally advanced hormone receptor-negative and HER2-negative breast cancer who have no history of prior systemic treatment for metastatic or recurrent breast cancer.

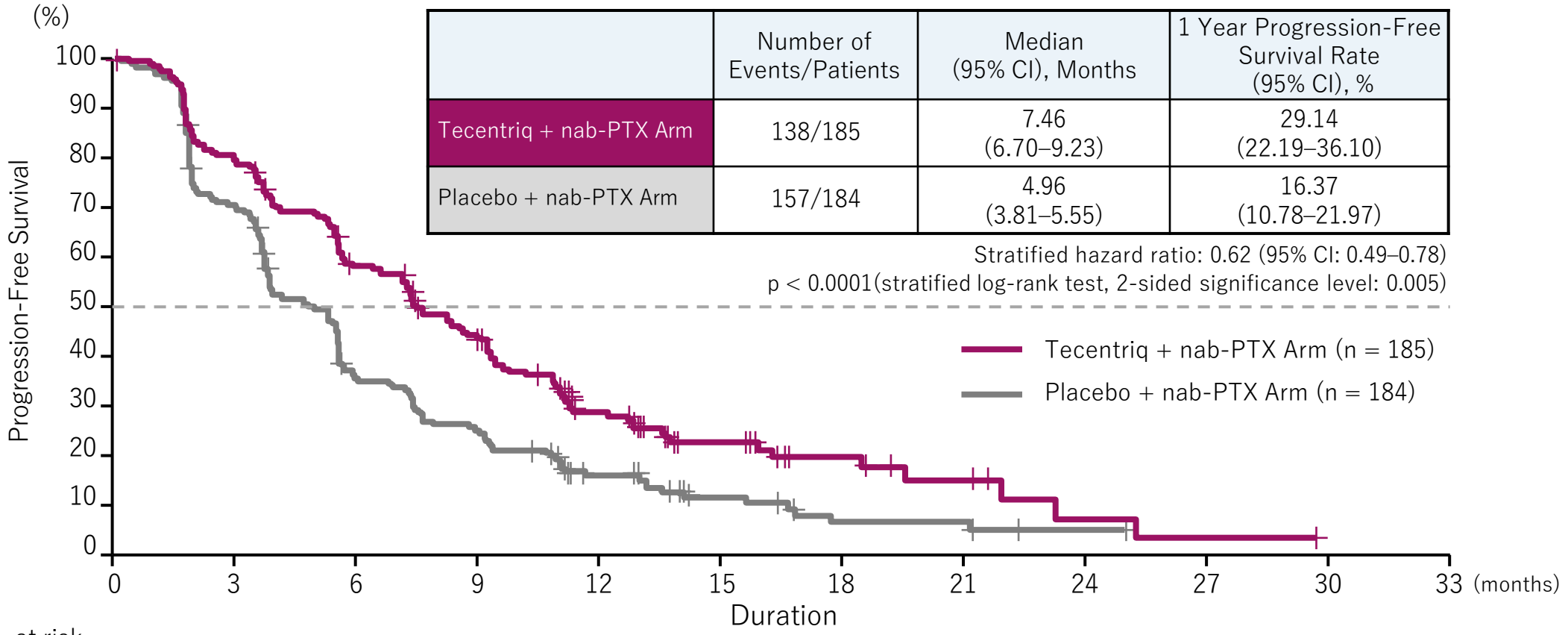
[Primary endpoint] The following items assessed by the investigator based on RECIST v1.1.
- Progression-free survival (PFS) in the ITT population and PD-L1-positive population
- Overall survival (OS) in the ITT population and PD-L1-positive population

Figure created based on data evaluated at the time of approval: A global Phase III clinical study (IMpassion130) and Schmid P, et al., N Engl J Med 2018; 379: 2108–2121. (COI: This study was supported by Genentech and F. Hoffmann-La Roche, involved individuals receiving consultancy fees or other compensation from these companies, and included employees of F. Hoffmann-La Roche and Genentech).

Primary PFS analysis: PD-L1+ Population (Primary Endpoint)

	Number of Events/Patients	Median (95% CI), Months	1 Year Progression-Free Survival Rate (95% CI), %
Tecentriq + nab-PTX Arm	138/185	7.46 (6.70–9.23)	29.14 (22.19–36.10)
Placebo + nab-PTX Arm	157/184	4.96 (3.81–5.55)	16.37 (10.78–21.97)

Stratified hazard ratio: 0.62 (95% CI: 0.49–0.78)
p < 0.0001(stratified log-rank test, 2-sided significance level: 0.005)



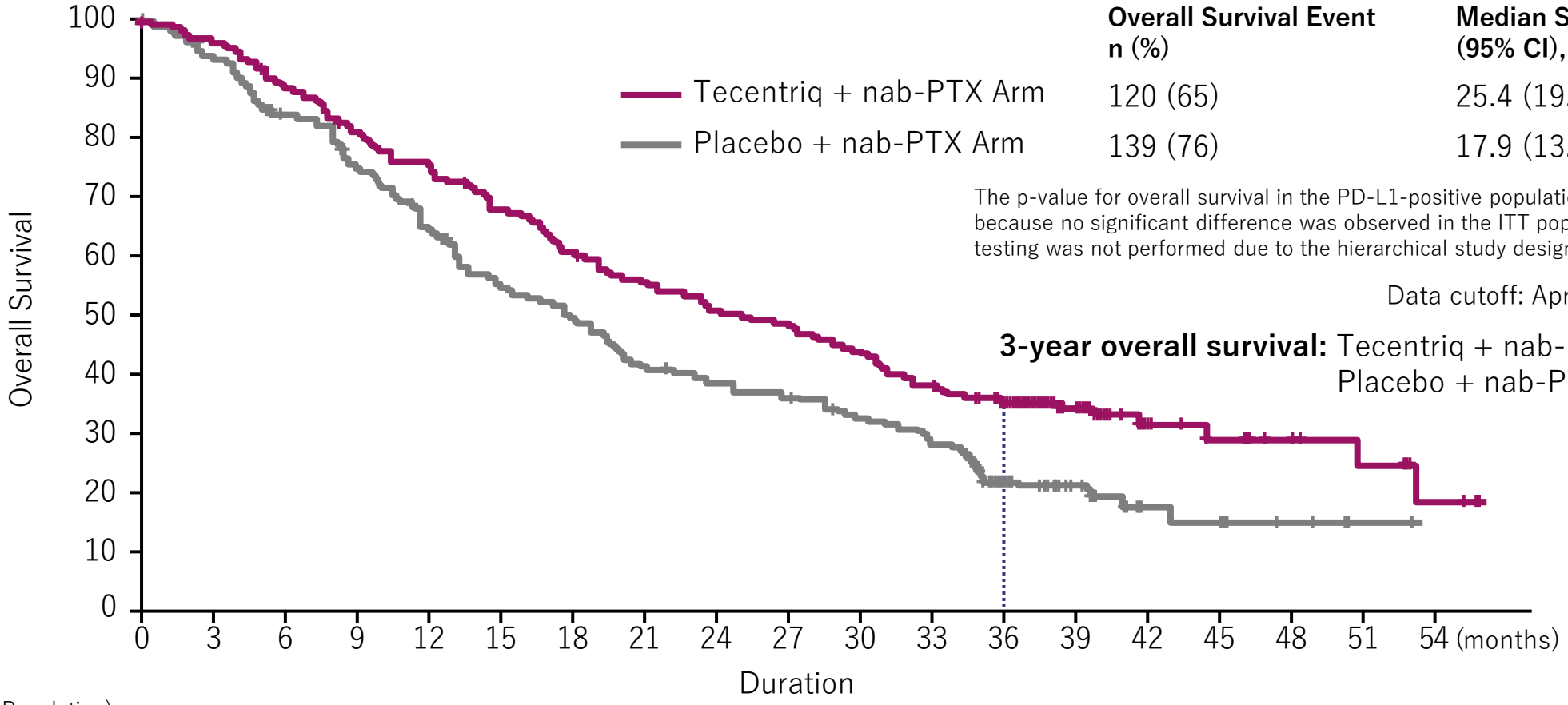
No. at risk												
Tecentriq + nab-PTX Arm	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo + nab-PTX Arm	184	127	62	44	22	11	5	5	1	NE	NE	NE

Investigator assessment (RECIST v1.1)
Stratification factors: Presence of liver metastases (Yes/No), prior treatment with taxane-based therapy (Yes/No), NE: Not estimable

Median follow-up: 12.9 months Data cutoff: April 17, 2018

Data evaluated at the time of approval: A global Phase III clinical study (IMpassion130) and Schmid P, et al. N Engl J Med 2018; 379: 2108-2121

Final OS analysis: PD-L1+ Population (Primary Endpoint)



	Overall Survival Event n (%)	Median Survival (95% CI), Months
Tecentriq + nab-PTX Arm	120 (65)	25.4 (19.6–30.7)
Placebo + nab-PTX Arm	139 (76)	17.9 (13.6–20.3)

The p-value for overall survival in the PD-L1-positive population was not presented because no significant difference was observed in the ITT population, and formal testing was not performed due to the hierarchical study design.

Data cutoff: April 14, 2020.

3-year overall survival: Tecentriq + nab-PTX: 36%
Placebo + nab-PTX: 22%

No. at Risk (ITT Population):

Tecentriq + nab-PTX Arm	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
Placebo + nab-PTX Arm	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

Emens LA, et al. Ann Oncol. 2021; 32(8): 983–993. (COI: This study was supported by Genentech and F. Hoffmann-La Roche. The authors include those who have received consultancy fees or other compensation from Genentech and F. Hoffmann-La Roche, as well as employees of F. Hoffmann-La Roche and Genentech.)

Safety Evaluation

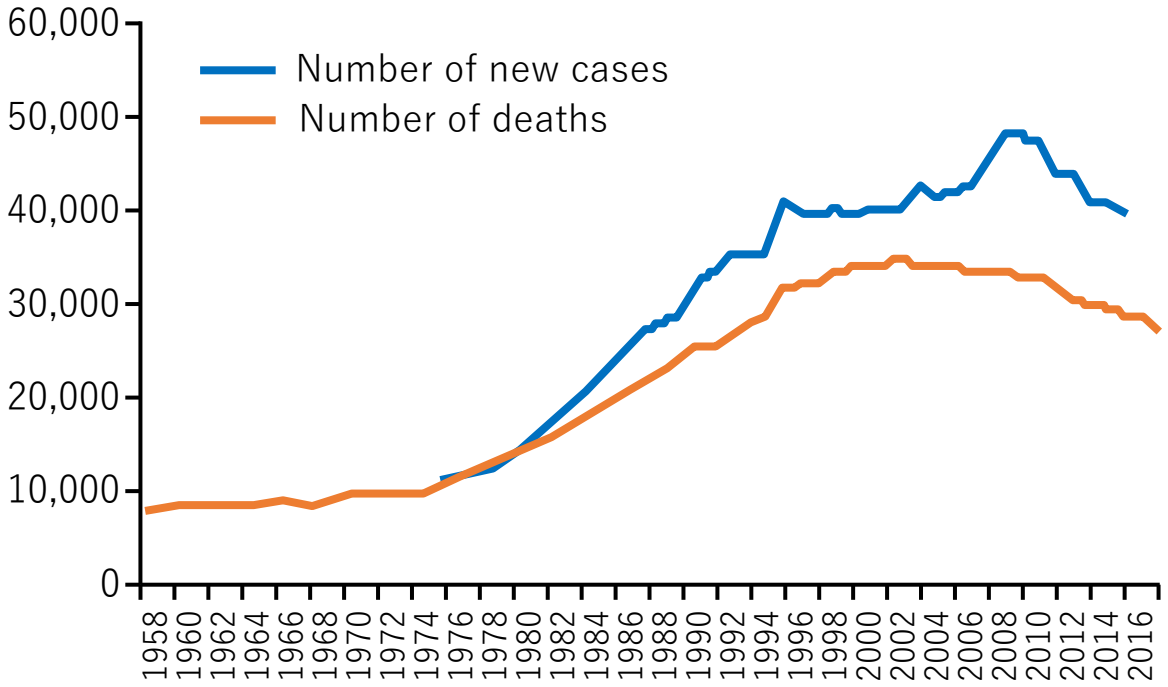
- In the PD-L1-positive patient population treated with Tecentriq and paclitaxel (albumin-bound formulation), the main side effects were alopecia, fatigue, nausea, anemia, diarrhea, neutropenia, and peripheral neuropathy.

Emens LA, et al. Ann Oncol. 2021; 32(8): 983–993. (COI: This study was supported by Genentech and F. Hoffmann-La Roche. The authors include those who have received consultancy fees or other compensation from Genentech and F. Hoffmann-La Roche, as well as employees of F. Hoffmann-La Roche and Genentech.)

Trends in Hepatocellular Carcinoma in Japan

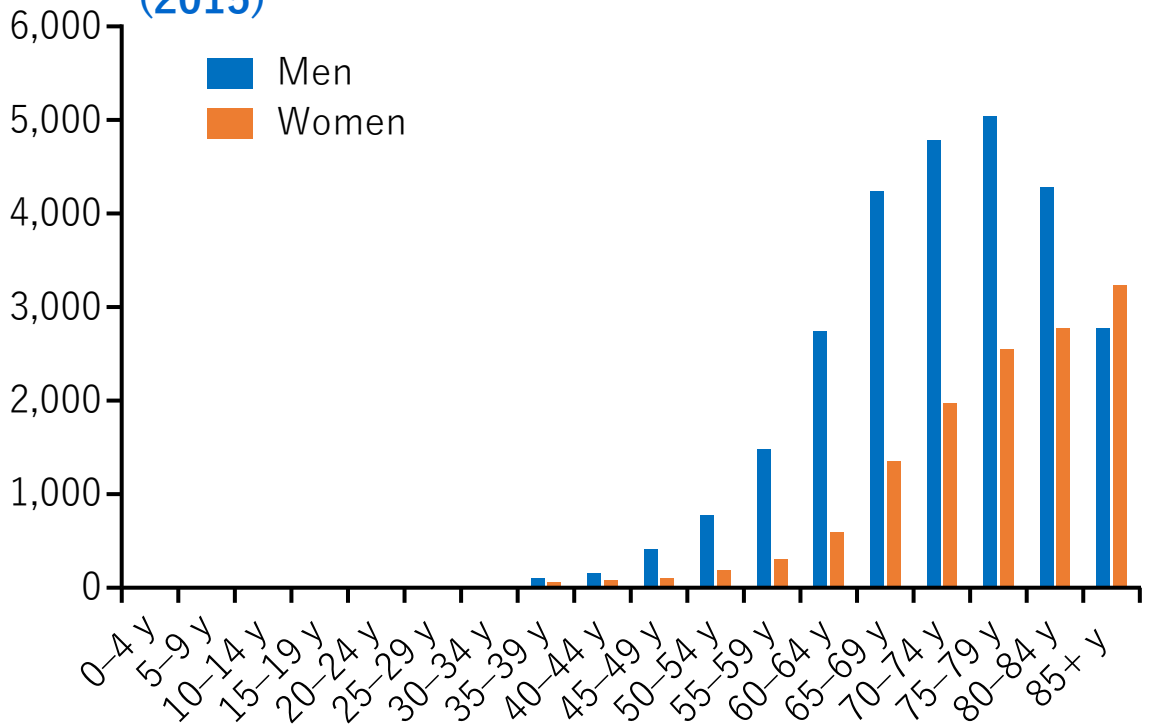
- Over the years, the number of deaths remains high, exceeding approximately 30,000 (around 20,000 men and 10,000 women).
- By sex, the number of deaths in men is about twice that of women. In terms of incidence, the number of cases in women increases with age.
- Advances in treatment improving prognosis, along with a reduction in high-risk populations for liver cancer, have contributed to a declining trend in mortality and incidence rates.

▼ Trends in the Incidence and Mortality of Liver Cancer



Data Summary: Based on Vital Statistics (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare) and National Cancer Registry.

▼ Age Distribution of Liver Cancer Diagnoses by Sex (2015)



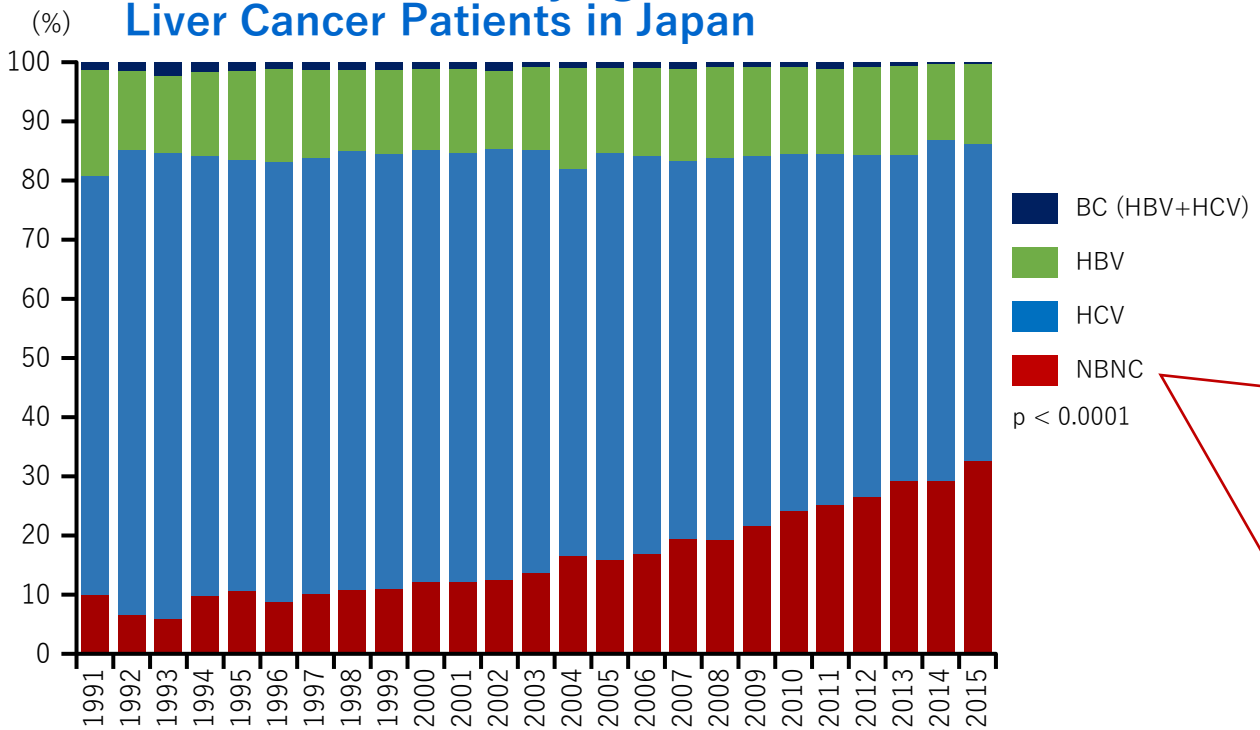
Data Summary: Based on National Cancer Registry.

National Cancer Center, Cancer Information Service, "Cancer Registry and Statistics" (https://ganjoho.jp/reg_stat/statistics/dl/index.html), accessed April 2020.
The Japan Society of Hepatology, Liver Cancer White Paper (2015 Edition).

Causes of Liver Cancer in Japan

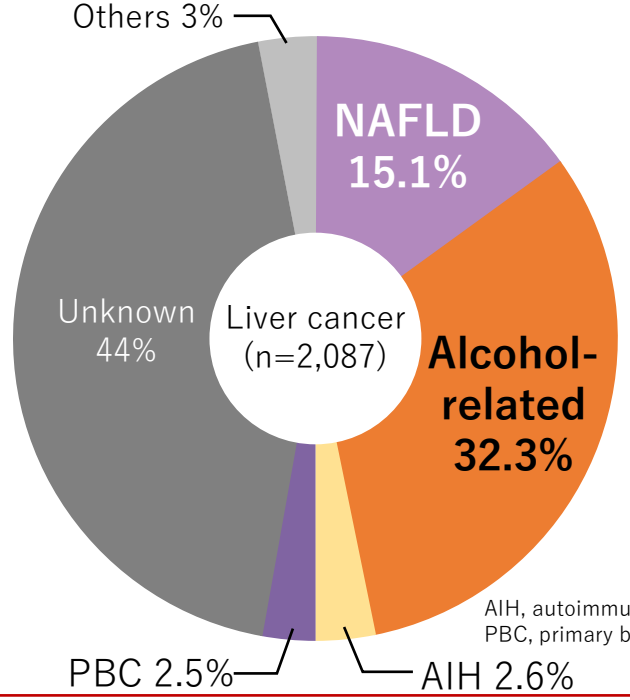
- In 1991, HCV infection was the primary cause of liver cancer, accounting for approximately 70%, but this proportion has gradually decreased.
- Liver cancer caused by HBV infection has remained relatively stable over time. However, non-B, non-C virus-related liver cancer has been steadily increasing.
- In Japan, the causes of non-B, non-C liver cancer include NAFLD (approximately 15%) and alcohol-related factors (approximately 32%).

▼ Trends in the Underlying Diseases of Liver Cancer Patients in Japan



NBNC-HCC: non-B, non-C hepatocellular carcinoma
NAFLD: Nonalcoholic fatty liver disease

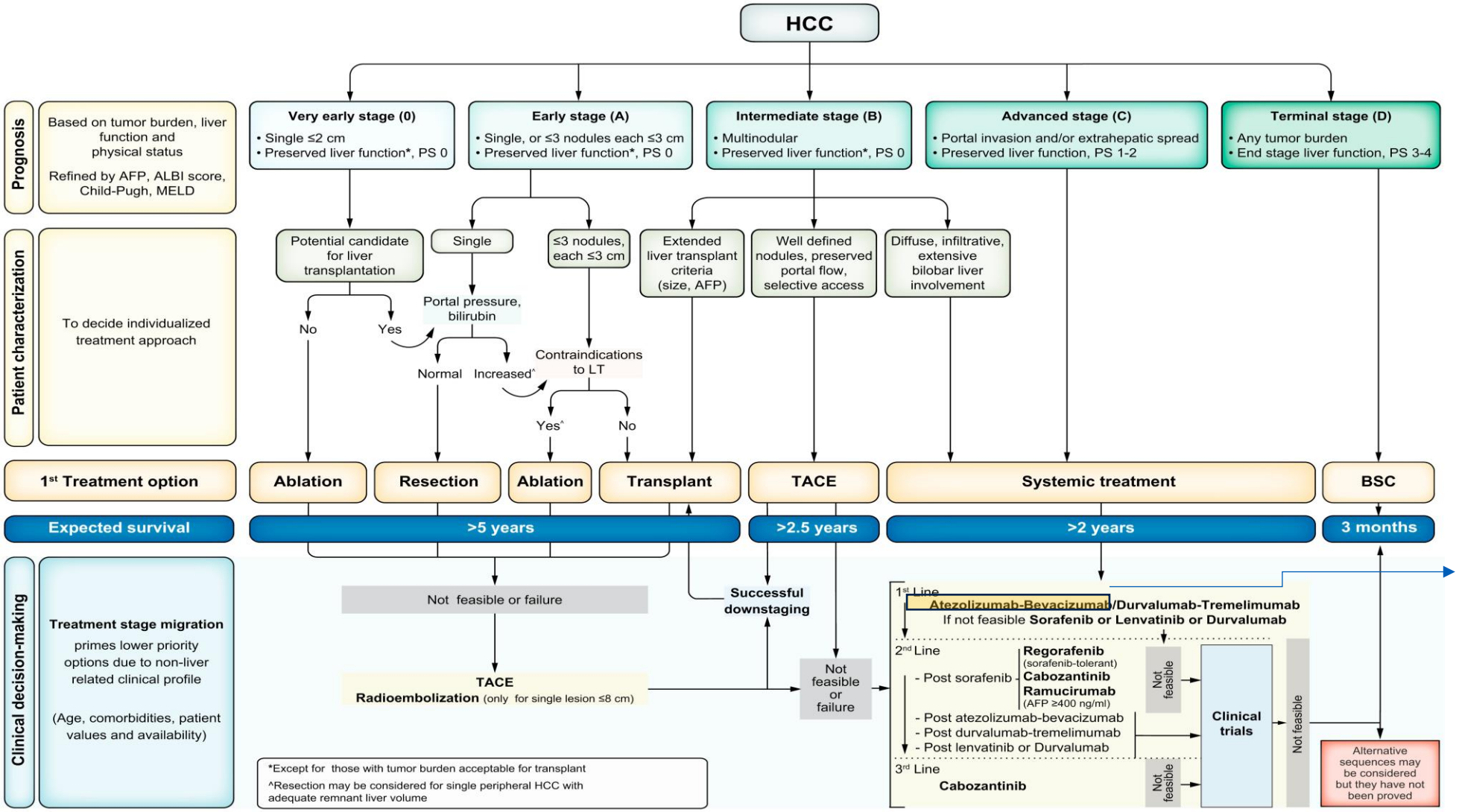
▼ Causes of Non-B, Non-C Hepatocellular Carcinoma



Data summary: A study based on data of patients diagnosed with non-B, non-C HCC at 34 hospitals in Japan between 2011 and 2015.

Tateishi R, et al. J Gastroenterol 2019, 54(4): 367-376. Limitations: Unable to estimate the influence of lifestyle-related risk factors due to the lack of a control group consisting of viral hepatitis patients. Also, as this is an observational study, it cannot prove a causal relationship between the increase in the proportion of non-viral hepatocellular carcinoma and the increase in obesity prevalence in Japan

Hepatocellular Carcinoma Treatment Algorithm



Atezo + Bev is recommended as the 1st-line treatment.

Reig et al. J Hepatol. 2022 Vol76, Issue 681-693

The Significance of Tecentriq + Avastin Combination Therapy from the Perspective of the Tumor Microenvironment

It is thought that by inhibiting VEGF and improving the immunosuppressive tumor environment, the inherent anti-tumor immunity of cells can take effect.

STEP③

Tecentriq is thought to block the inhibitory signal by the PD-L1/PD-1 pathway and promote the priming of T cells (mouse, *in vitro*).[3-5)]

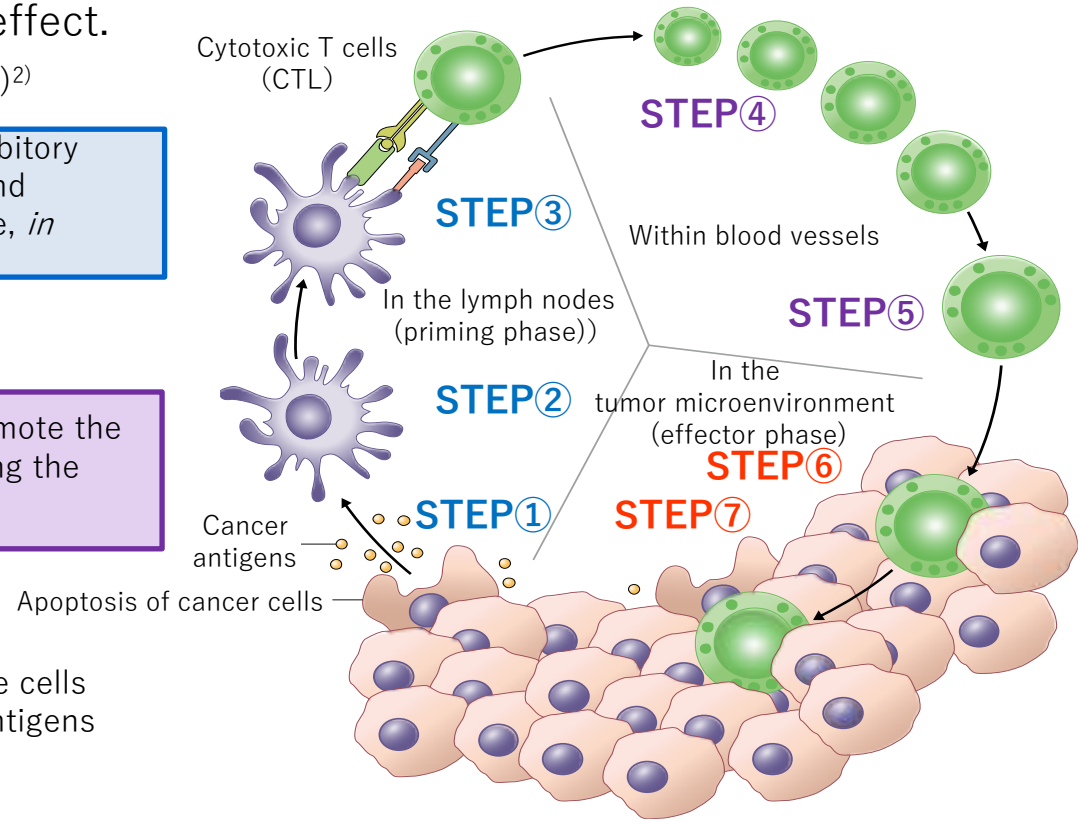
STEP②

Anti-VEGF agents are thought to promote the maturation of dendritic cells, enhancing the priming of T cells (*in vitro*).[6-8)]

STEP①

Cancer cells are destroyed by immune cells and other factors, releasing cancer antigens

(Diagram)[2)]



STEP④⑤

Anti-VEGF agents are thought to normalize the tumor vasculature, increasing the infiltration of cytotoxic T cells (CTL) into tumors (mouse, non-Japanese).[6,9-12)]

STEP⑥

Anti-VEGF agents are thought to reduce MDSCs and Tregs, removing immunosuppression in the tumor microenvironment (*in vitro,* mouse, non-Japanese).[6,12,13-16)]

STEP⑦

Tecentriq is thought to block the inhibitory signal via the PD-L1/PD-1 pathway and reactivate T cells (mouse, *in vitro*).[3-5)]

1) Voron T, et al.: Front Oncol 2014; 4: 70. (This study was supported by F. Hoffmann-La Roche. The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche.) 2) Chen DS, Mellman I: Immunity 2013; 39(1): 1-10. Figure adapted from this source (authors are employees of Genentech) 3) Data evaluated at the time of approval: Mechanism of action (internal document) 4) Blank C, et al.: Cancer Immunol Immunother 2007; 56 (5) : 739-745. 5) Chen DS, et al.: Clin Cancer Res 2012; 18 (24) : 6580-6587. (The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche or Genentech. Authors also include employees of Genentech) 6)Hegde PS, et al.: Semin Cancer Biol 2018; 52 (Pt 2) : 117-124. (Authors are employees of Genentech) 7)Gabrilovich DI, et al.: Nat Med 1996; 2 (10) : 1096-1103 8)Oyama T, et al.: J Immunol 1998; 160 (3) : 1224-1232. 9)Goel S, et al.: Physiol Rev 2011; 91 (3) : 1071-1121. (The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche.) 10) Motz GT, et al.: Nat Med 2014; 20 (6) : 607-615. 11)Hodi FS, et al.: Cancer Immunol Res 2014; 2 (7) : 632-642. (The authors include those who have received consultancy fees or other compensation from F. Hoffmann-La Roche or Genentech.) 12) Wallin JJ, et al.: Nat Commun 2016; 7: 12624. (Authors are employees of Genentech) 13) Gabrilovich DI, Nagaraj S: Nat Rev Immunol 2009; 9 (3) : 162-174. 14) Roland CL, et al.: PLoS One 2009; 4 (11) : e7669. 15)Facciabene A, et al.: Nature 2011; 475 (7355) : 226-230. 16) Voron T, et al.: J Exp Med 2015; 212 (2) : 139-148. Supervised by Professor Hironori Koga, Department of Medicine, Division of Gastroenterology, Research Center for Innovative Cancer Therapy, Kurume University School of Medicine

Global Phase III Clinical Study (IMbrave150): Study Overview

Patients with unresectable hepatocellular carcinoma classified as Child-Pugh A and no prior systemic therapy

Efficacy analysis set
n = 501 (including 61 patients from Japan)

Randomization 2:1

Tecentriq + Avastin Arm
n=336
Tecentriq 1200 mg
Avastin 15 mg/kg, administered via intravenous infusion every 3 weeks

Sorafenib Arm
n=165
Sorafenib 400 mg, administered orally twice daily

Stratification factors:
- Region (Asia excluding Japan vs. other countries/regions)
- Macrovascular invasion (MVI) and/or extrahepatic spread (EHS) (present vs. absent)
- Baseline alpha-fetoprotein (AFP) level (< 400 vs. ≥ 400 ng/mL)
- ECOG PS (0 vs. 1)

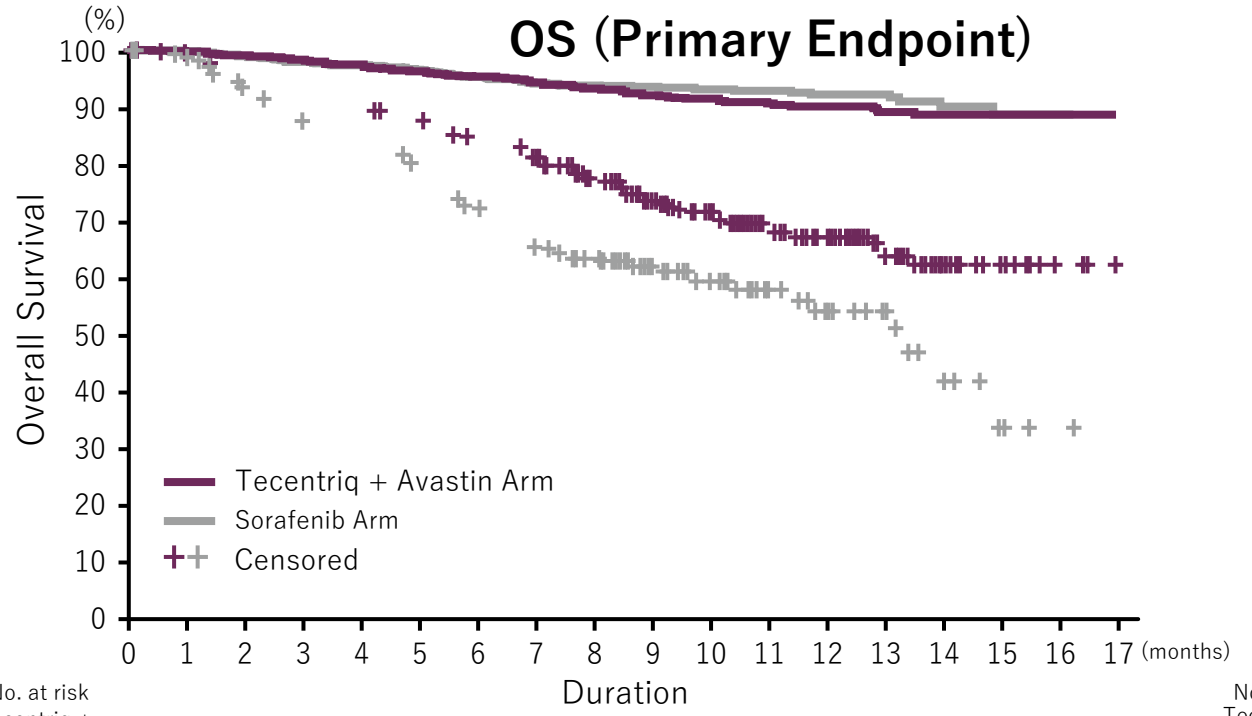
- Treatment was continued in both groups as long as the attending physician determined there was clinical benefit (i.e., no unacceptable toxicity or worsening of symptoms caused by disease progression).

Analysis Population	Efficacy analysis set (ITT population): n=501 (including 61 patients from Japan) Safety analysis set (participants who received at least 1 dose of the investigational drug): n=485 (including 58 patients from Japan)	
Endpoints	Efficacy endpoints	Primary endpoints: Overall survival (OS) and progression-free survival (PFS) [assessed by an independent review facility (IRF) based on RECIST v1.1] Secondary Endpoints: PFS (assessed by IRF using HCCmRECIST and by the investigator using RECIST v1.1), response rate (assessed by IRF using RECIST v1.1/HCCmRECIST and by the investigator using RECIST v1.1), time to progression (TTP), and others. PFS, response rate, and TTP were evaluated based on 3 criteria: RECIST v1.1 assessed by IRF and investigator, and HCCmRECIST assessed by IRF. Exploratory endpoints: Time to decrease in symptom scores assessed using scales related to anorexia, fatigue, and others.
	Safety endpoints	Adverse events, etc.

Finn RS, et al.: N Engl J Med. 2020;382(20): 1894-1905, Data evaluated at the time of approval: Global Phase III Clinical Trial (IMbrave150)
[COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or honoraria from F. Hoffmann-La Roche or Genentech.
The Phase III clinical trial of the combination therapy of Tecentriq and bevacizumab, one of the first-line treatments recommended in the Clinical Practice Guidelines for Hepatocellular Carcinoma, 2021 Edition (Revised 2023).

Study Results: OS/PFS (RECIST v1.1 IRF Assessment) ITT Population

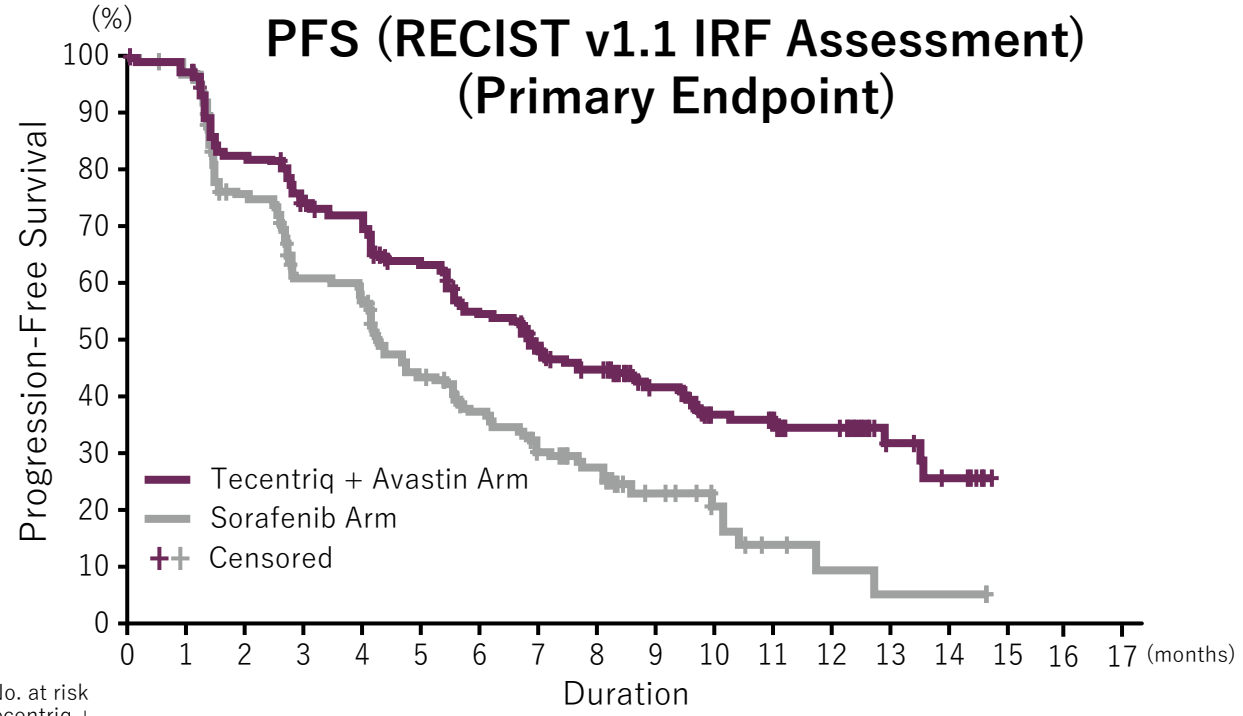
OS (Primary Endpoint)



No. at risk																		
Tecentriq + Avastin Arm	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib Arm	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

	Tecentriq + Avastin Arm (n=336)	Sorafenib Arm (n = 165)
Number of events (%)	96 (28.6)	65 (39.4)
Median OS (95% CI)	Not reached (NE)	13.2 months (10.4–NE)
Stratified hazard ratio (95% CI)	0.58 (0.42–0.79)	
2-sided p-value (stratified log-rank test)	0.0006	

PFS (RECIST v1.1 IRF Assessment) (Primary Endpoint)



No. at risk																		
Tecentriq + Avastin Arm	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE		
Sorafenib Arm	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE		

	Tecentriq + Avastin Arm (n=336)	Sorafenib Arm (n = 165)
Number of events (%)	197 (58.6)	109 (66.1)
Median PFS (95% CI)	6.8 months (5.7–8.3)	4.3 months (4.0–5.6)
Stratified hazard ratio (95% CI)	0.59 (0.47–0.76)	
2-sided p-value (stratified log-rank test)	< 0.0001	

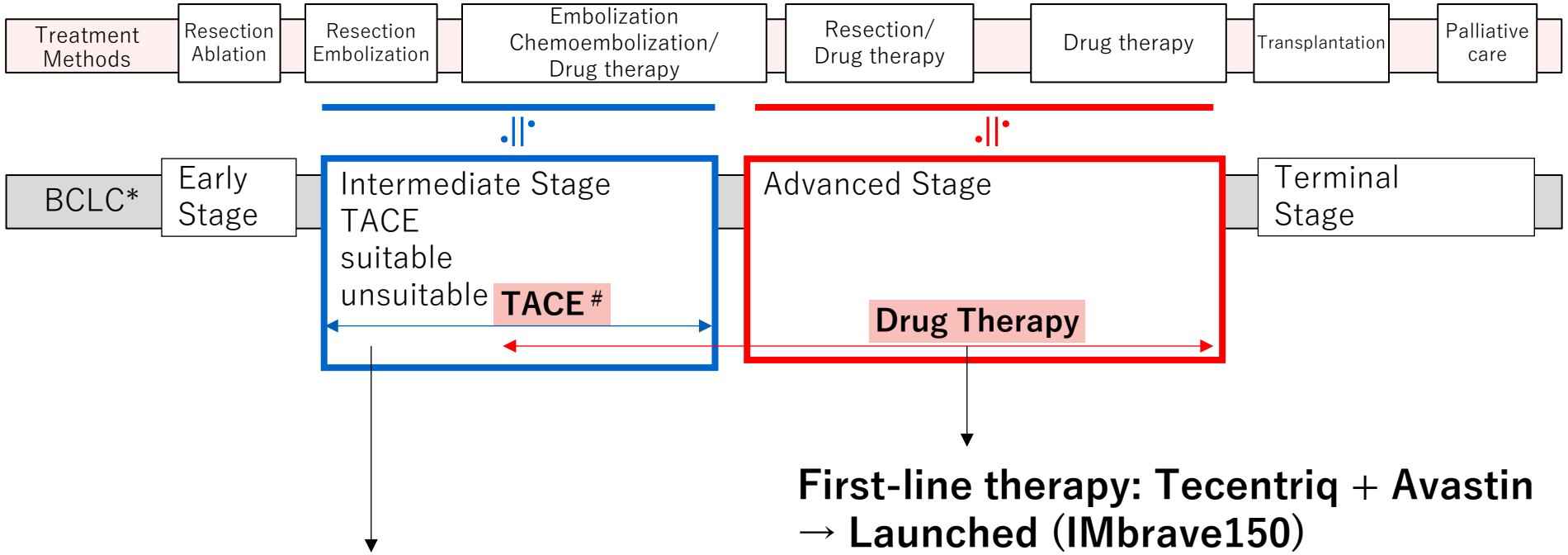
As of the data cutoff on August 29, 2019, the median follow-up was 8.9 months in the Tecentriq + Avastin arm and 8.1 months in the sorafenib arm.
NE: not estimable

Finn RS, et al.:N Engl J Med. 2020;382(20): 1894-1905, Data evaluated at the time of approval: Global Phase III Clinical Trial (IMbrave150)
[COI] This study was supported by F. Hoffmann-La Roche and Genentech. The authors include those who have received consultancy fees or honoraria from F. Hoffmann-La Roche or Genentech.

Safety Evaluation

- The main side effects were hypertension, proteinuria, fatigue, AST increased, pruritus, infusion-related reactions, diarrhea, ALT increased, and decreased appetite.

Hepatocellular Carcinoma – Overview of Launch and Development Status



TACE + Tecentriq + Avastin
→ Under clinical study (TALENTACE)

First-line therapy: Tecentriq + Avastin
→ Launched (IMbrave150)

First-line therapy: Tecentriq + Avastin + tiragolumab
→ Under clinical study (IMbrave152)

Second-line treatment: Tecentriq + lenvatinib/sorafenib
→ Under clinical study (IMbrave251)

TACE, transarterial chemoembolization
*BCLC (Barcelona Clinic Liver Cancer) classification

Global Phase III Clinical Study (TALENTACE): Study Overview

- **An open-label, randomized Phase III clinical study comparing the combination therapy of atezolizumab and bevacizumab with on-demand TACE versus on-demand TACE monotherapy in untreated hepatocellular carcinoma (HCC).**
- **Participating countries: China and Japan**

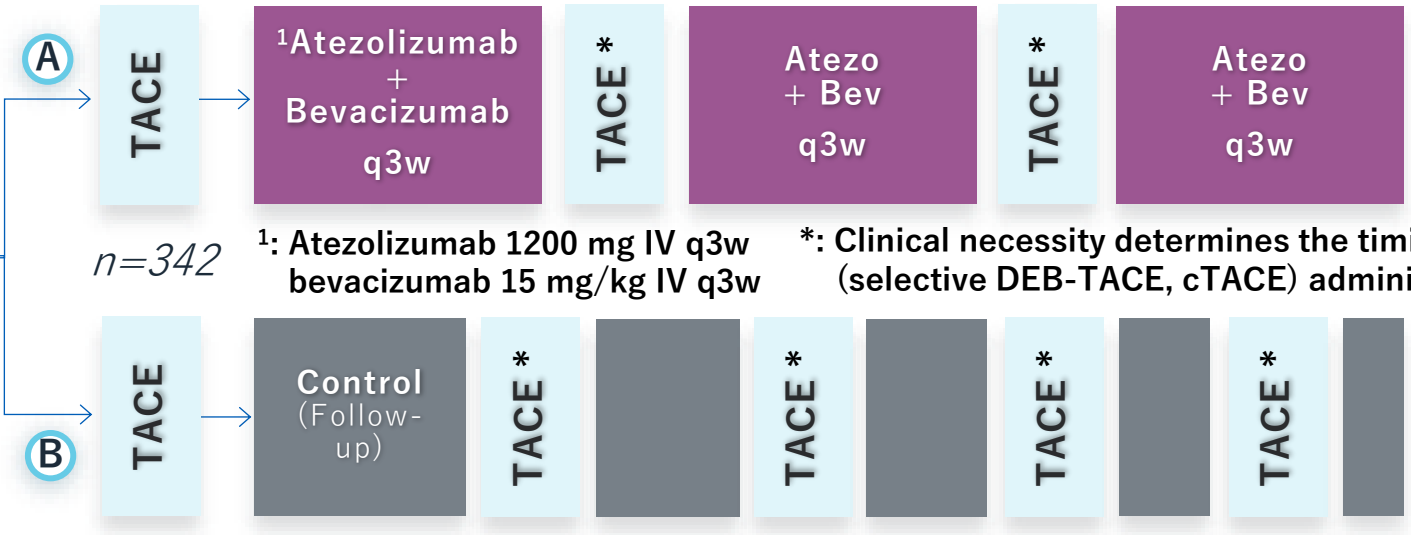
- Confirmed HCC diagnosis
- Eligibility for TACE treatment, including:

Unresectable BCLC-A, BCLC-B, or BCLC-C (ECOG PS1 and VP1-2 only)

- Total of tumor maximum diameter + number of tumors ≥ 6
- No prior systemic therapy or local therapy for target lesions
- Child-Pugh Class A
- No extrahepatic metastasis
- No VP3 or VP4
- ECOG Performance Status: 0–1

R 1:1

n=342



[1]: Atezolizumab 1200 mg IV q3w bevacizumab 15 mg/kg IV q3w

*: Clinical necessity determines the timing of TACE (selective DEB-TACE, cTACE) administration.

Stratification factors:

- Baseline alpha-fetoprotein (AFP: <400 vs. ≥ 400 ng/mL)
- History of local therapy for HCC (excluding curative resection and RFA) [TACE vs. other local therapies vs. none]
- Vascular invasion (Vp1/2 present vs. absent)

Primary endpoint	TACE PFS (INV), OS
Secondary endpoints	Time to unTACEable progression (TTUP) (INV), time to progression (TTP) (INV), time to extrahepatic spread (EHS) (INV), objective response rate (ORR) (INV), duration of response (DOR) (INV)

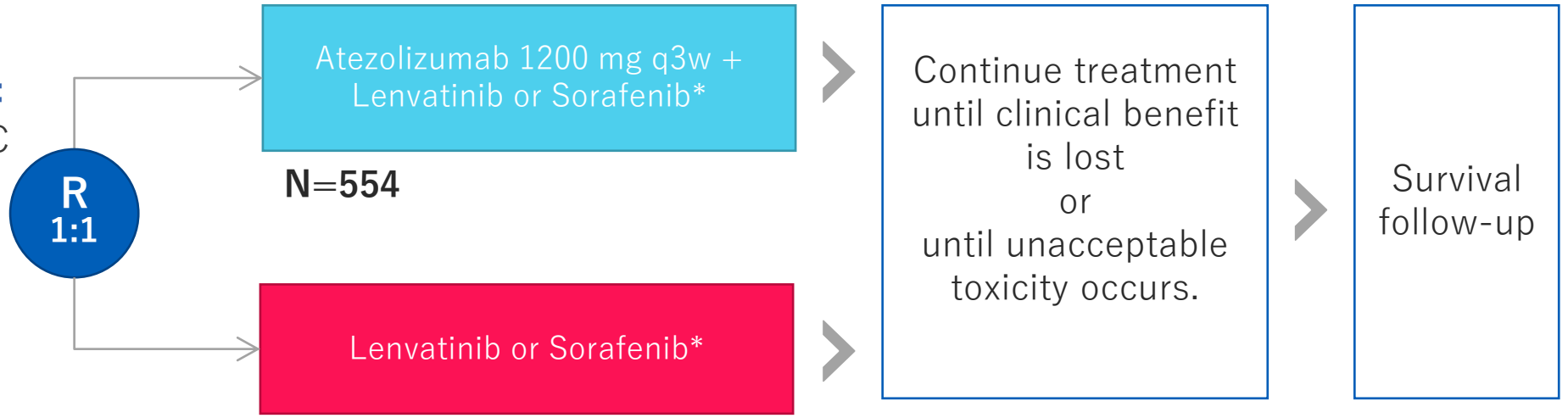
- Atezolizumab/bevacizumab administration will continue until the investigator determines that no clinical benefit can be achieved, unacceptable toxicity occurs, or consent is withdrawn.
- Atezolizumab/bevacizumab administration begins **2 to 8 weeks after** TACE is performed.

Global Phase III Clinical Study (IMbrave251): Study Overview

■ **To evaluate the efficacy and safety of combination therapy with atezolizumab and lenvatinib or sorafenib compared to lenvatinib or sorafenib monotherapy in HCC patients previously treated with atezolizumab and bevacizumab.**

Patient population:

- Unresectable HCC
- Disease progression after combination therapy with atezolizumab + bevacizumab



*: Selection of lenvatinib or sorafenib is determined by the participating medical institution.

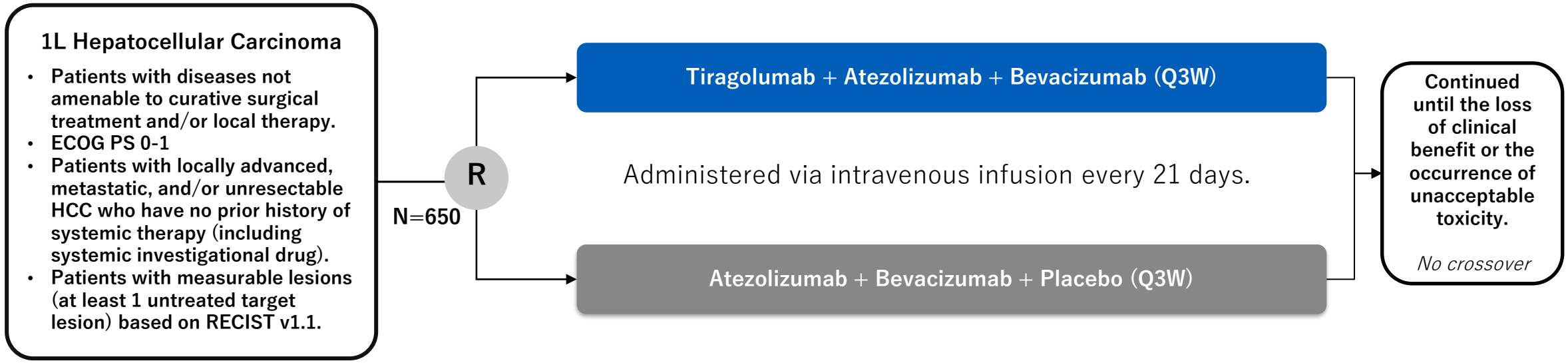
Stratification factors:

- **Selected TKI (lenvatinib vs. sorafenib)**
- **AFP (< 400 ng/mL vs. ≥ 400 ng/mL)**
- **Etiology (HBV/HCV infection vs. non-viral causes)**
- **Baseline ALBI score (Grade 1 vs. Grade 2 and Grade 3)**

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; TKI, tyrosine kinase inhibitor

Global Phase III Clinical Study (IMbrave152): Study Design

■ A randomized, double-blind, placebo-controlled phase III clinical study investigating the combination of atezolizumab, bevacizumab, and tiragolumab versus atezolizumab, bevacizumab, and placebo in patients with untreated locally advanced or metastatic hepatocellular carcinoma (HCC).



Stratification Factors:
- Geographic region (Asia, excl Japan vs. RoW)
- MVI and/or EHS (presence vs. absence)
- Baseline AFP (<400 vs. ≥400 ng/mL)
- Etiology (viral vs. non viral)

Primary Endpoints:
- PFS (investigator)
- Overall survival

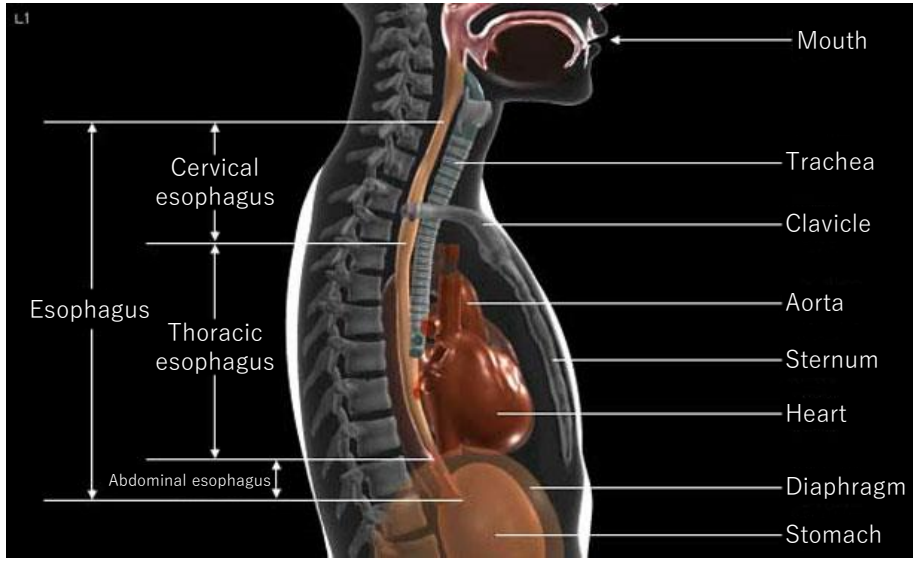
Other Key Endpoints:

Secondary endpoints
- ORR, DoR, landmark PFS/OS, Safety, QoL/PRO

Exploratory endpoints
- Biomarkers, PD-L1, others TBD

Esophageal Cancer: Overview

- The esophagus is a tubular organ connecting the pharynx and the stomach, located at the center of the body and surrounded by critical organs such as the trachea, heart, aorta, and lungs.
- Esophageal cancer ranks as the 11th most common cancer in Japan, predominantly affecting men, with the majority of cases occurring in individuals around the age of 70. Approximately 11,000 people die annually from esophageal cancer in Japan.



Cited from the National Cancer Center website.

Ranking	Site	Number of Cases (2019)
1	Large intestine	155,625
2	Lung	126,548
3	Stomach	124,319
4	Breast	97,812
5	Prostate	94,749
6	Pancreas	43,865
7	Liver	37,296
8	Malignant lymphoma	36,638
9	Kidney/urinary tract (excluding bladder)	30,458
10	Uterus	29,136
11	Esophagus	26,382
12	Skin	25,247
13	Oral cavity/pharynx	23,671
14	Bladder	23,383
15	Gallbladder/bile duct	22,159
16	Thyroid	18,780
17	Uterine corpus	17,880
18	Leukemia	14,318
19	Ovaries	13,388
20	Cervix uteri	10,879
21	Multiple myeloma	7,591

	Number of cases			Death	
Fiscal year	Men	Women	Fiscal year	Men	Women
2010	18,145	3,282	2010	9,992	1,875
2015	19,305	3,838	2015	9,774	1,965
2019	21,719	4,663	2019	9,571	2,048

Data Summary: Based on Vital Statistics (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare) and National Cancer Registry.

Source: National Cancer Center, Cancer Information Service, "Cancer Statistics" https://ganjoho.jp/reg_stat/index.html (Accessed November 2024).

Esophageal Cancer: Overview

- Esophageal cancer tends to show higher incidence rates in East Asia when viewed on a global scale.
- In East Asia, including Japan, approximately 90% of esophageal cancers are squamous cell carcinomas.
- The standard treatment for Stage II and III involves assessing the patient's physical condition before treatment, with surgery being the first choice if the patient is deemed physically fit for the procedure.
- On the other hand, if the patient is deemed physically unfit for surgery but capable of undergoing chemoradiotherapy, or if the patient does not wish to undergo surgery, definitive chemoradiotherapy is performed as a curative treatment.

CA Cancer J Clin. 2021;71:209-249.,Esophagus. 2022;19:1-26., Gut. 2020;69:1564-1571. (Limitation: The study is limited by the range of histological and topographical information available from each cancer registry; difficulty in distinguishing between cardia and non-cardia gastric cancers; cases where it's challenging to differentiate between gastric and esophageal origin of tumors; and the data obtained are estimates, so caution is necessary in their interpretation), Gut. 2021;70:234-242., Cureus. 2018;10:e3709., Website for general information on esophageal cancer (https://www.esophagus.jp/public/cancer/05_stage.html) (Accessed: November 2024), Cancer Information Service (https://ganjoho.jp/public/cancer/esophagus/treatment.html) (Accessed: November 2024)

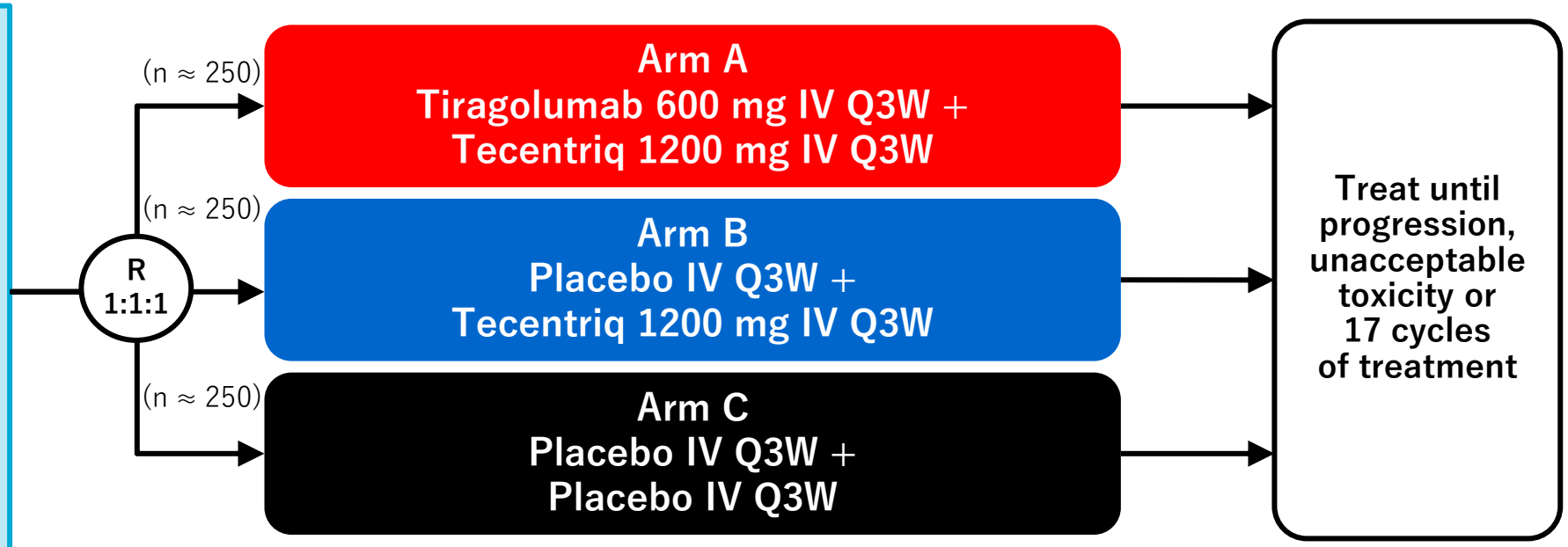
SKYSCRAPER-07/YO42137

■ A randomized, double-blind, placebo-controlled Phase III clinical study evaluating the combination therapy of Tecentriq + tiragolumab (anti-TIGIT antibody) versus Tecentriq monotherapy in patients with unresectable esophageal squamous cell carcinoma who have not progressed after definitive concurrent chemoradiotherapy.

Unresectable Locally Advanced Esophageal Squamous Cell Carcinoma

- ECOG PS 0 or 1
- Histologically or cytologically confirmed diagnosis of esophageal squamous cell carcinoma
- Determined to be ineligible for curative surgery based on the opinion of a medical oncologist, surgical oncologist, or radiation oncologist
- Must have undergone definitive concurrent chemoradiotherapy

N≈750



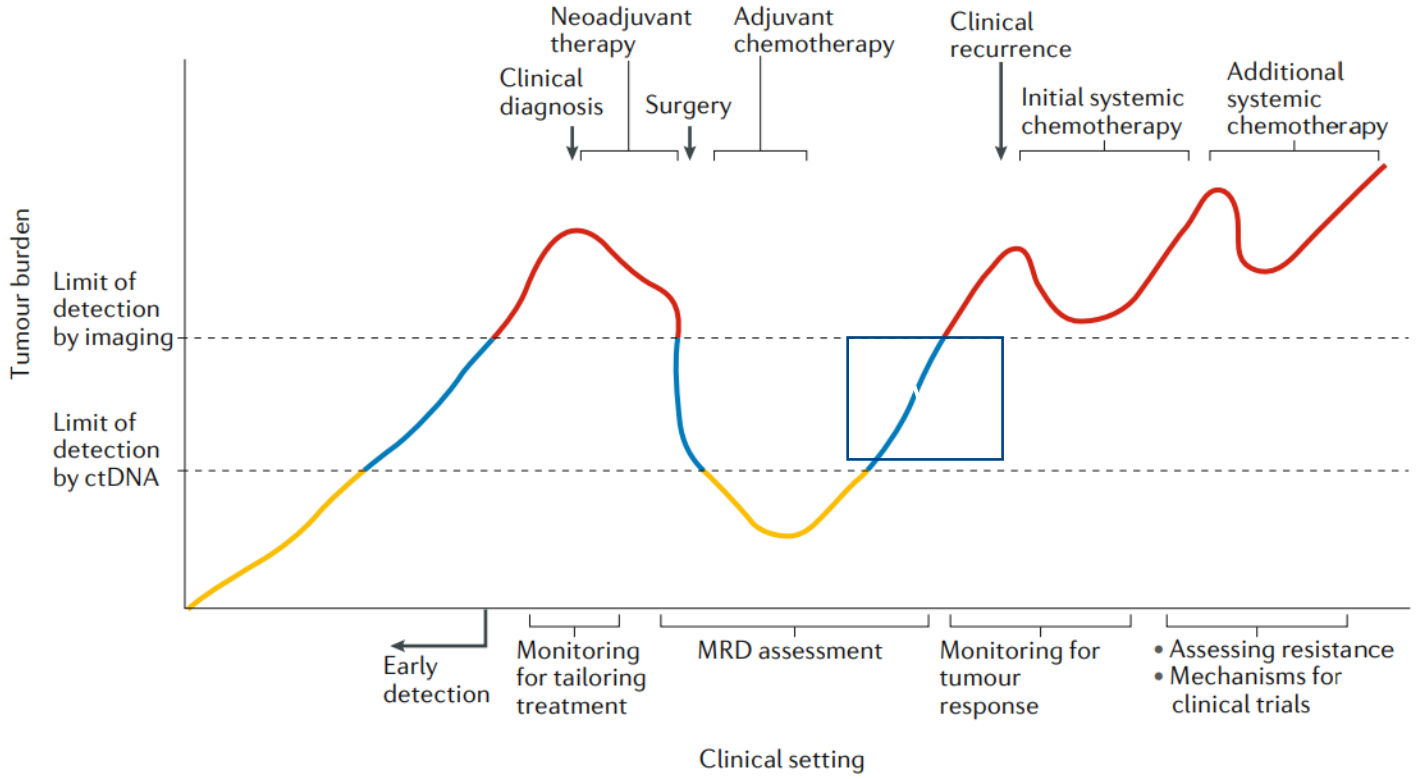
Stratification: geographic region (Asia vs Rest of World); PD-L1 status‡ (TIC score <10% vs ≥10%); staging (II vs III vs IVA)

Co-primary endpoints

- Arm A vs Arm C: PFS by INV assessment; OS
- Arm B vs Arm C: OS

ctDNA Testing Prior to Postoperative Adjuvant Therapy for Muscle-Invasive Bladder Cancer

- **Detection of tumor-derived DNA circulating in the blood allows minimally invasive acquisition of tumor DNA information from a blood sample.**
- **It has high detection sensitivity, and its clinical application is anticipated for early cancer diagnosis, prognosis prediction, and recurrence prediction.**



ctDNA levels are known to rise before recurrence is detectable via imaging, and its application in early detection of recurrence is anticipated.

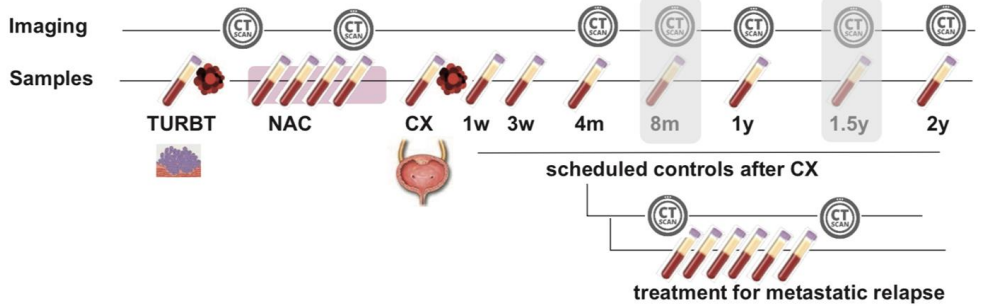
Clinical applications of ctDNA

Dasari et al. 2020, Nat Rev Clin Oncol. 17, pages757–770 (2020)

ctDNA and Prognosis After Cystectomy

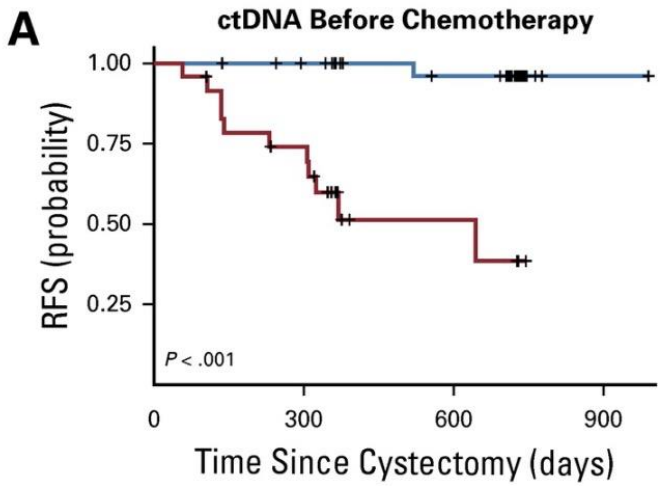
■ **Patients who are ctDNA-positive after cystectomy exhibit higher recurrence rates, suggesting that ctDNA may serve as a prognostic factor. (overseas data)**

Diagram

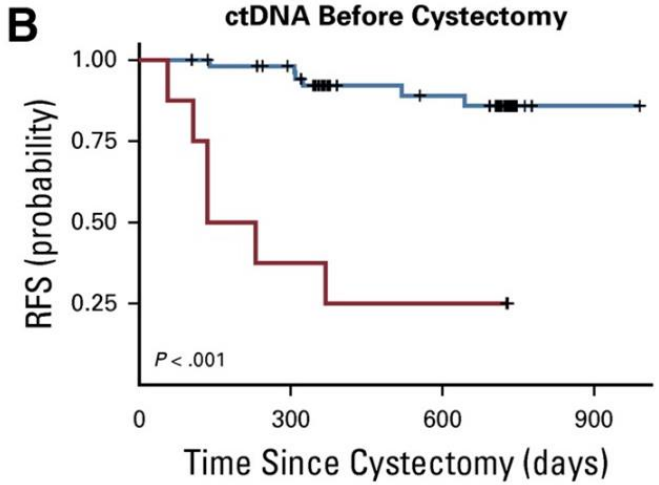


Data overview: Circulating tumor DNA (ctDNA) was evaluated using blood samples collected from 68 patients with locally advanced bladder cancer at the time of diagnosis, during chemotherapy, before cystectomy, and during surveillance.

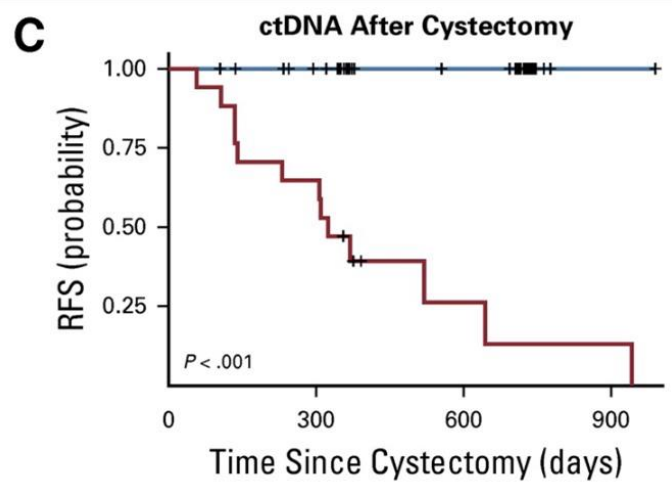
Fig A1. Protocols for treatment, surveillance and blood sampling.
Detailed overview of time points for CT scans, treatment and blood sample procurement for patients with localized MIBC. Grey shaded areas indicate extraordinary CT scans offered to high-risk patients (pT>2 and/or N+ at diagnosis).



No. at risk				
Negative	35	32	23	1
Positive	24	16	4	0



No. at risk				
Negative	55	49	28	1
Positive	8	3	2	0



No. at risk				
Negative	47	42	29	1
Positive	17	11	2	1

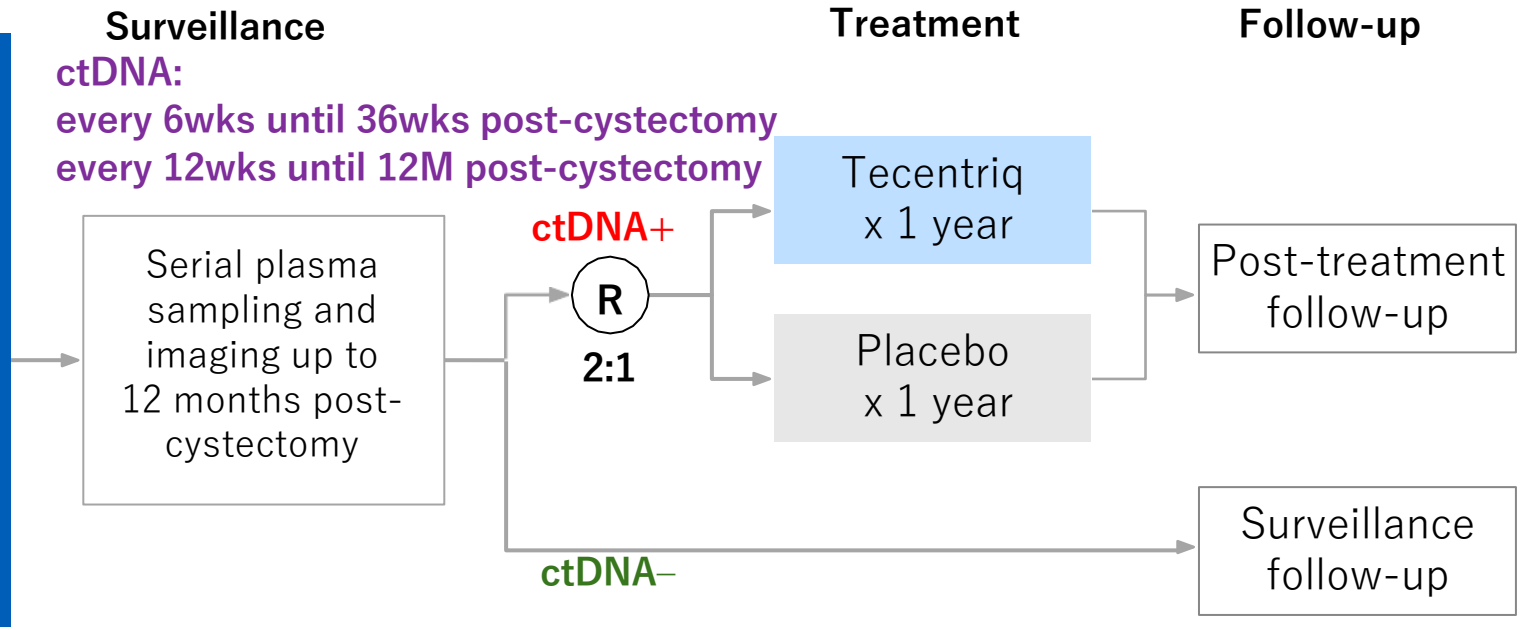
Christensen et. al. 2019, JCO.

IMvigor011 Study Design

■ A Phase III, double-blind, multicenter randomized study comparing atezolizumab (anti-PD-L1 antibody) with placebo as postoperative adjuvant therapy for high-risk muscle-invasive bladder cancer (MIBC) patients with circulating tumor DNA (ctDNA)-positive status after cystectomy.

Screening

- High-risk MIBC at the time of cystectomy: (y)pT2-T4a N0 M0 or (y)pT0-T4a N+ M0-
- With or without prior neoadjuvant chemotherapy
- Eligible or not eligible for postoperative adjuvant chemotherapy.
- Within 6 to 24 weeks post-cystectomy



Stratification factors

Nodal status (positive vs negative)	Tumour stage after cystectomy (≤(y)pT2 vs (y)pT3/(y)pT4)	PD-L1 IHC status (IHC score of IC0/1 vs IC2/3)	Time from cystectomy to first ctDNA(+) sample (≤ 20 weeks vs > 20 weeks)

- Primary endpoint: DFS (overall population)
- Secondary endpoints: OS, disease-specific survival, distant metastasis-free survival (overall population), etc.

Alveolar Soft Part Sarcoma (ASPS) Disease Overview

■ ASPS Epidemiology

- A very rare soft tissue sarcoma, accounting for approximately 1% of malignant soft tissue tumors.
- Japan: Between 2006 and 2015, 128 ASPS cases were registered in the Malignant Soft Tissue Tumor Registry in Japan (2015).
- US: Between 1973 and 2012, 251 ASPS cases were registered in the SEER database.
- It occurs predominantly in young individuals (median age: 28 years), commonly in the so-called AYA (Adolescent and Young Adult) generation, with the limbs being the most frequent site.

■ ASPS Treatment

- ASPS generally does not respond to cytotoxic chemotherapy, and there is no established standard treatment for unresectable cases.
- In the U.S., the NCCN guidelines list the angiogenesis inhibitor sunitinib as a treatment option; however, it is not approved for ASPS in Japan. Instead, pazopanib, a similar drug approved for sarcomas, is sometimes used.
- Tecentriq is approved for ASPS in the US, but no immune checkpoint inhibitors are currently approved for ASPS in Japan.

SEER: Surveillance Epidemiology and End Results, NCCN: National Comprehensive Cancer Network
ASPS: Alveolar Soft Part Tissue Sarcoma

Paoluzzi L, et al. JAMA Oncol. 2019 Feb 1;5(2): 254-260.
Eisuke Kobayashi, et al. Journal of the Japanese Orthopaedic Association, 2015, Vol. 89, No. 6: p.1287.

Development Status for Alveolar Soft Part Sarcoma (ASPS)

- **On March 14, 2024, an application for indication expansion for ASPS was submitted.**
- **The application is based on results from the ALBERT trial, a Japanese Phase II investigator-initiated clinical trial led by the National Cancer Center Hospital, evaluating the efficacy and safety of Tecentriq for unresectable ASPS, as well as results from an overseas Phase II clinical trial led by the US National Cancer Institute (NCI).**
  - The ALBERT trial was conducted as a sub-study of the MASTER KEY Project, promoting the development of treatments for rare cancers through industry-academia collaboration with the National Cancer Center Hospital.
- **If approved, Tecentriq is expected to become the first immune checkpoint inhibitor for ASPS in Japan.**

Extranodal NK/T-cell Lymphoma, Nasal Type (ENKL): Disease Overview

■ ENKL Epidemiology

- A tumor associated with Epstein-Barr Virus (EBV).
- More prevalent in East Asian countries, with rare cases reported in Caucasians in Western countries.
- In Japan, it accounts for 0.68% of malignant lymphomas and has a relatively early onset, with a median patient age in their 50s.
- Advanced cases are treated with multi-agent chemotherapy; however, the prognosis remains poor.

■ ENKL Treatment

- Treatment strategies differ between limited and advanced stages.
- For the limited stage, the Japanese guidelines recommend concurrent chemoradiotherapy, specifically RT-2/3 DeVIC therapy (dexamethasone, etoposide, ifosfamide, carboplatin). However, no consensus exists on the best treatment, and participation in clinical trials is also encouraged.
- For the advanced stage, initial treatment includes SMILE therapy or chemotherapy containing L-asparaginase. If remission is not achieved, options include salvage therapy and subsequent autologous or allogeneic transplantation. Nevertheless, the prognosis remains poor, and no standard therapy has been established.

ENKL: extranodal natural killer/T-cell lymphoma, nasal type

Reiji M, et al. Cancer Med. 2018;7(11):5843-5858.
Ritsuro Suzuki. Journal of the Japanese Society of Internal Medicine. Vol. 104, No. 9: 1878-1884.
The Japanese Society of Hematology. Practical Guidelines for Hematological Malignancies, 2023 Edition.

Development Status for Extranodal NK/T-cell Lymphoma, Nasal Type (ENKL)

- **On October 31, 2024, an application for indication expansion for relapsed or refractory ENKL was submitted.**
- **The application is based on the results of the ATTACK trial, a Japanese Phase II investigator-initiated clinical trial led by the National Cancer Center Hospital, evaluating the efficacy and safety of Tecentriq for relapsed or refractory ENKL.**
  - The ATTACK trial was conducted as a sub-study of the MASTER KEY Project, promoting the development of treatments for rare cancers through industry-academia collaboration with the National Cancer Center Hospital.
- **If approved, Tecentriq is expected to become the first immune checkpoint inhibitor for ENKL in Japan.**

Development Status for Flexible Dosing

- On October 31, 2024, an application was submitted for the addition of every-4-week regimen.
- The application is based on results from Japanese Phase I/II clinical trials and overseas clinical trials.
- If approved, this will provide patients and healthcare providers with more convenient dosing intervals.
- In the US and Europe, flexible dosing for monotherapy was approved in 2019, while for combination therapy, it was approved in 2021.

“PHESGO® combination for subcutaneous injection MA / IN”

pertuzumab (genetical recombination), trastuzumab (genetical recombination), and vorhyaluronidase alfa (genetical recombination) injection

IN: Initial dose, MA: Maintenance dose

History of Development of PHESGO

[Conventional treatment]
- Combination therapy with pertuzumab and trastuzumab is the standard treatment for HER2-positive breast cancer
- The time required for administration is approximately 150 minutes for the initial dose, and 60 to 150 minutes for the second and subsequent doses*

* If the initial dose is well-tolerated, the duration can be shortened to 30 minutes for both drugs

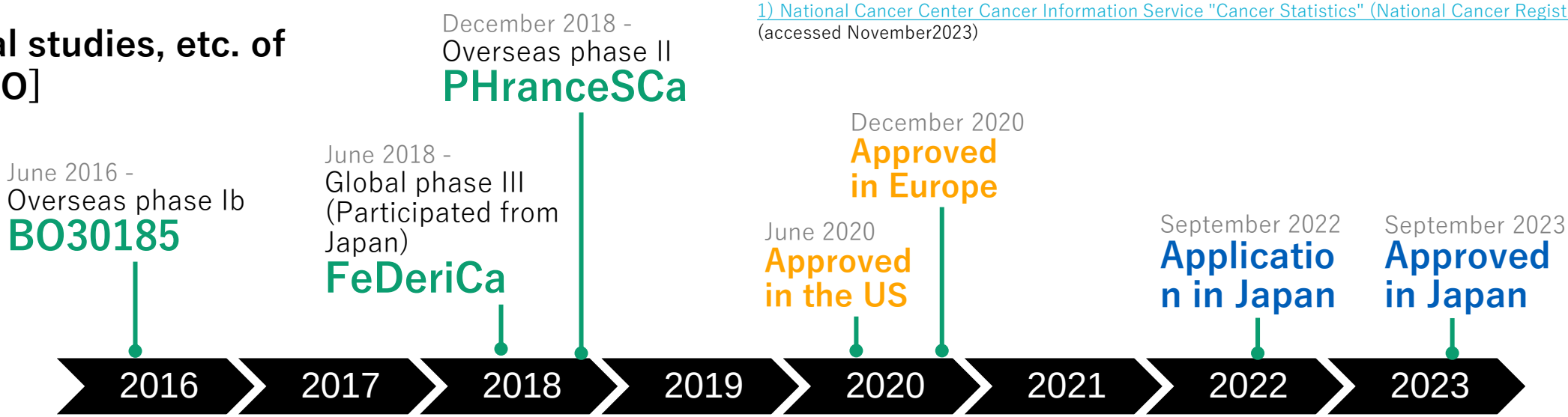
[Patient's perspective (needs)]
- Breast cancer is common among working-age women, so balancing work with childcare, nursing care, etc. is important[1)]

[Medical institution's perspective (needs)]
- Efficient management of time is important as new drugs are introduced, treatment regimens increase, and chemotherapy rooms, etc. are crowded

PHESGO contributes to improved patient convenience and the efficiency of medical resources

1) National Cancer Center Cancer Information Service "Cancer Statistics" (National Cancer Registry) (accessed November2023)

[Clinical studies, etc. of PHESGO]



Active Pharmaceutical Ingredients of PHESGO

Inhibitory effect on HER2 signaling ADCC (antibody-dependent cellular cytotoxicity)

pertuzumab (genetical recombination)

trastuzumab (genetical recombination)

Tissue permeability-increasing action

vorhyaluronidase alfa (genetical recombination)

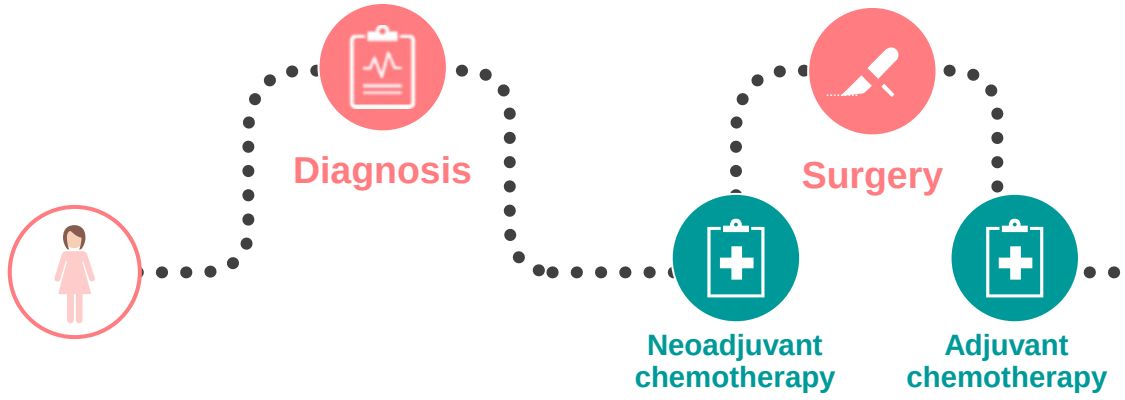
conceptual illustration

Phesgo

Overview of HER2-Positive Breast Cancer Treatment (PHESGO Prescription Segment)

The segments for which Herceptin + Perjeta combination therapy is recommended in the Japanese guidelines are preoperative/postoperative therapy and first-line therapy for advanced/recurrent breast cancer. These are expected to be replaced by PHESGO

Early breast cancer



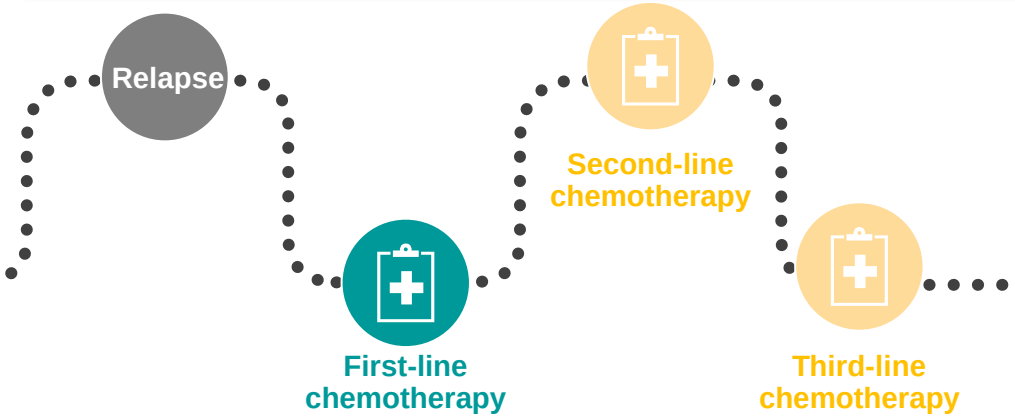
Neoadjuvant chemotherapy

The addition of pertuzumab to trastuzumab is strongly recommended.

Adjuvant chemotherapy

Adding pertuzumab to trastuzumab is strongly recommended in patients at a high risk of recurrence.

Advanced/recurrent breast cancer



First-line chemotherapy

The combination of trastuzumab + pertuzumab + docetaxel is strongly recommended.
Combination therapy with trastuzumab + pertuzumab + paclitaxel is weakly recommended.

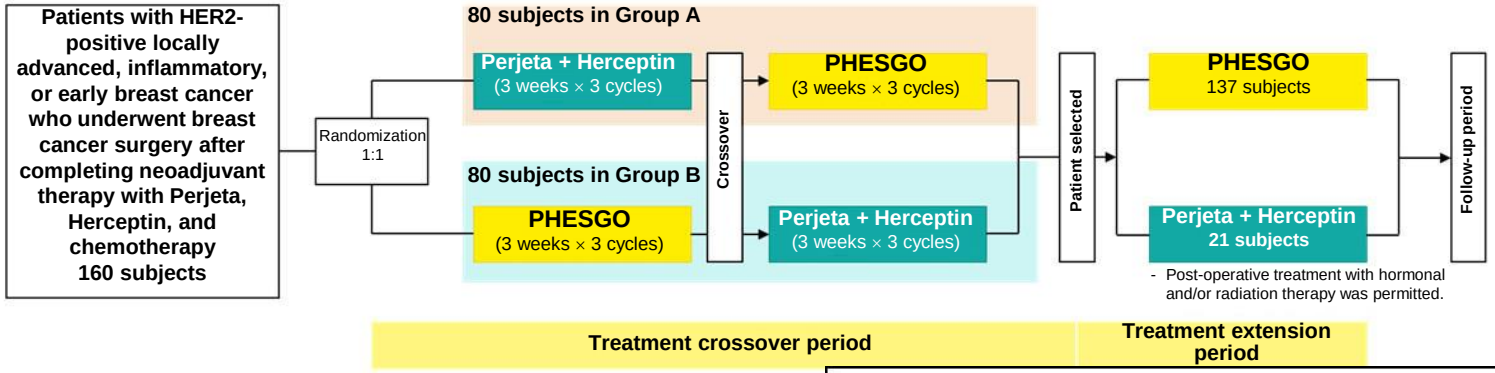
Breast Cancer Treatment Guidelines https://jbcs.xsrv.jp/guideline/2022/y_index/ (Japanese only) (accessed November 2024)

Phesgo

Overseas Phase II Clinical Study [PHranceSCa Study]

85% of Patients Preferred PHESGO

[Objective] To evaluate patient preference and satisfaction for treatment, by intravenously administering PHESGO or Perjeta and Herceptin (Perjeta + Herceptin [IV]) as a postoperative therapy in patients with HER2-positive early breast cancer.



Stratification factor
- Type of neoadjuvant chemotherapy (anthracycline + taxane, carboplatin + taxane, or taxane only)
- Response to preoperative therapy: pCR or non-pCR
- Hormone receptor expression status (ER and/or PgR positive, or ER and PgR negative)

pCR: pathological complete response
ER, estrogen receptor; PgR, progesterone receptor

[Endpoints]

Primary endpoint: Patient preference for PHESGO (based on responses to PPQ Question 1) [reference information]

Secondary endpoints: The strength of preference for the method of administration preferred in PPQ Question 1 and main reasons for the preference (PPQ Questions 2 and 3) [reference information], patient satisfaction with PHESGO and Perjeta + Herceptin (IV) (based on responses to TASQ-SC and TASQ-IV Question 1) [reference information], selection rate of PHESGO for the treatment extension period [reference information], and healthcare professional perception of time/resource use and convenience with PHESGO (based on healthcare professional's responses to HCPQ) [reference information], etc.

■ Patient preference for PHESGO (based on responses to PPQ Question 1) [reference information]

85.0% of patients (95% CI: 78.5 - 90.2) preferred PHESGO, while 13.8% of patients preferred Perjeta + Herceptin (IV).

Number of patients (%)	Group A (n = 80) Perjeta + Herceptin (IV) → PHESGO	Group B (n = 80) PHESGO → Perjeta + Herceptin (IV)	All patients (n = 160)
PHESGO	70 (87.5%)	66 (82.5%)	136 (85.0%)
Perjeta + Herceptin (IV)	10 (12.5%)	12 (15.0%)	22 (13.8%)
No particular preference	0	2 (2.5%)	2 (1.3%)

Data cutoff date for the primary analysis: February 24, 2020

Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa Study), O'Shaughnessy J, *et al.* Eur J Cancer. 2021; 152: 223 -232.

This publication includes employees of F. Hoffmann-La Roche and Genentech, as well as authors funded by F. Hoffmann-La Roche and Genentech.

Overseas Phase II Clinical Study (PHranceSCa Study) Common Adverse Events During the Treatment Crossover Period

- **The major adverse events during the treatment crossover period included radiation skin injury [Group A: at the time of administration of Perjeta + Herceptin (IV) (Cycle 1-3) 21.3%, Group A: at the time of administration of PHESGO (Cycle 4-6) 8.8%, Group B: at the time of administration of PHESGO (Cycle 1-3) 12.5%, Group B: at the time of administration of Perjeta + Herceptin (IV) (Cycle 4-6) 12.5%; the same order, hereinafter], injection site reaction (Group A: 0%, 15.0%, Group B: 30.0%, 0%), and diarrhea (Group A: 15.0%, 8.8%, Group B: 7.5%, 5.0%).**

n (%)	Group A (n = 80) Perjeta + Herceptin (IV) → PHESGO		Group B (n = 80): PHESGO → Perjeta + Herceptin (IV)	
	At the time of administration of Perjeta + Herceptin (IV) Cycle 1-3	At the time of administration of PHESGO Cycle 4-6	At the time of administration of PHESGO Cycle 1-3	At the time of administration of Perjeta + Herceptin (IV) Cycle 4-6
All adverse events	62 (77.5%)	58 (72.5%)	62 (77.5%)	51 (63.8%)
Radiation skin injury*	17 (21.3%)	7 (8.8%)	10 (12.5%)	10 (12.5%)
Injection site reactions	0	12 (15.0%)	24 (30.0%)	0
Diarrhoea	12 (15.0%)	7 (8.8%)	6 (7.5%)	4 (5.0%)
Hot flush	6 (7.5%)	4 (5.0%)	5 (6.3%)	0
Pruritus	6 (7.5%)	3 (3.8%)	0	1 (1.3%)
Erythema	6 (7.5%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Fatigue	5 (6.3%)	4 (5.0%)	5 (6.3%)	4 (5.0%)
Infusion reaction	5 (6.3%)	0	0	1 (1.3%)
Arthralgia	4 (5.0%)	3 (3.8%)	5 (6.3%)	2 (2.5%)
Upper respiratory infection	1 (1.3%)	2 (2.5%)	5 (6.3%)	4 (5.0%)

* During the treatment crossover period in this study, concomitant radiotherapy was used in 23 patients (28.8%) in Group A and 21 patients (26.3%) in Group B.

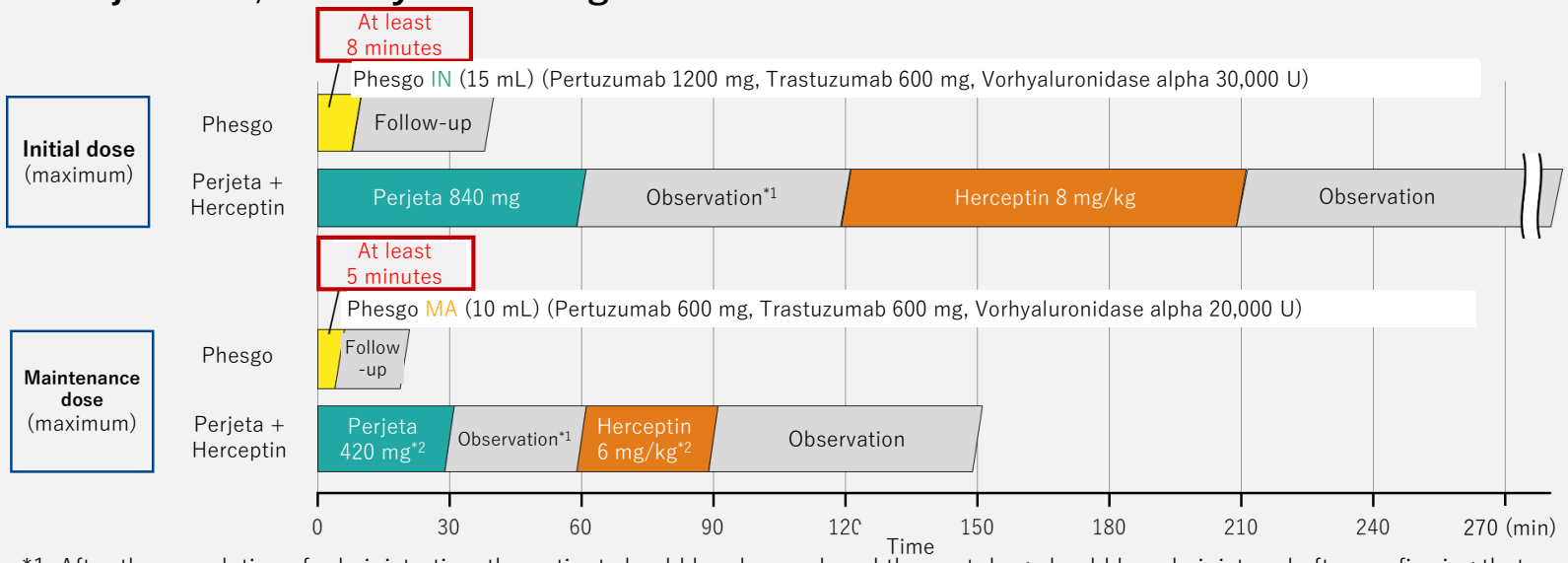
MedDRA ver.22.1

Data evaluated at the time of approval: Overseas phase II clinical study (PHranceSCa Study), O'Shaughnessy J, *et al.* Eur J Cancer. 2021; 152: 223 -232.
This publication includes employees of F. Hoffmann-La Roche and Genentech, as well as authors funded by F. Hoffmann-La Roche and Genentech.

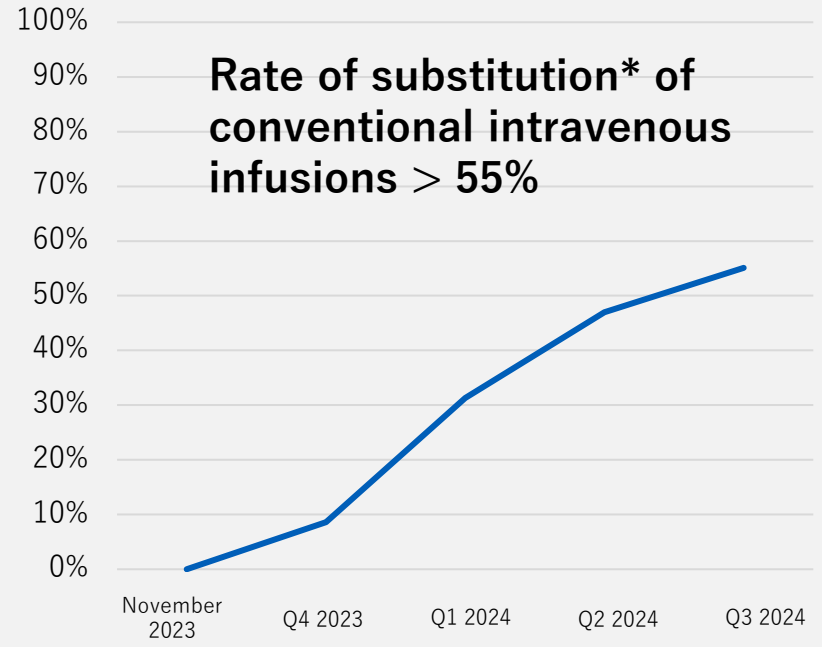
Steady Market Penetration of Phesgo Since its Launch in November 2023

- Early market penetration has been achieved due to increased convenience through shorter administration times than conventional intravenous injections

Phesgo can be administered in a shorter time than conventional intravenous injections, thereby enhancing convenience



*1: After the completion of administration, the patient should be observed, and the next drug should be administered after confirming that no infusion reaction symptoms are observed.
In clinical studies, subjects were observed for 60 minutes at the initial administration, and if there were no problems such as infusion reaction and the drug was well-tolerated in Cycle 2 and subsequent cycles, the monitoring period could be shortened to 30 minutes.
*2: If the initial dose is well-tolerated, the duration of the second and subsequent doses can be shortened to 30 minutes.



Internal calculated data
*The rate of decline in Chugai's quarterly Perjeta sales volume from before the launch of Phesgo is shown as the substitution rate.

- When administered intravenously in succession, Perjeta and Herceptin are administered over approximately 150 minutes in the case of the first dose and between 60 and 150 minutes for the second and subsequent doses [1]. In contrast, infusions of Phesgo are administered over at least 8 minutes for the first dose and at least 5 minutes for the second and subsequent doses [2].
- The substitution rate of conventional intravenous infusions exceeded 50% around 10 months after its launch.

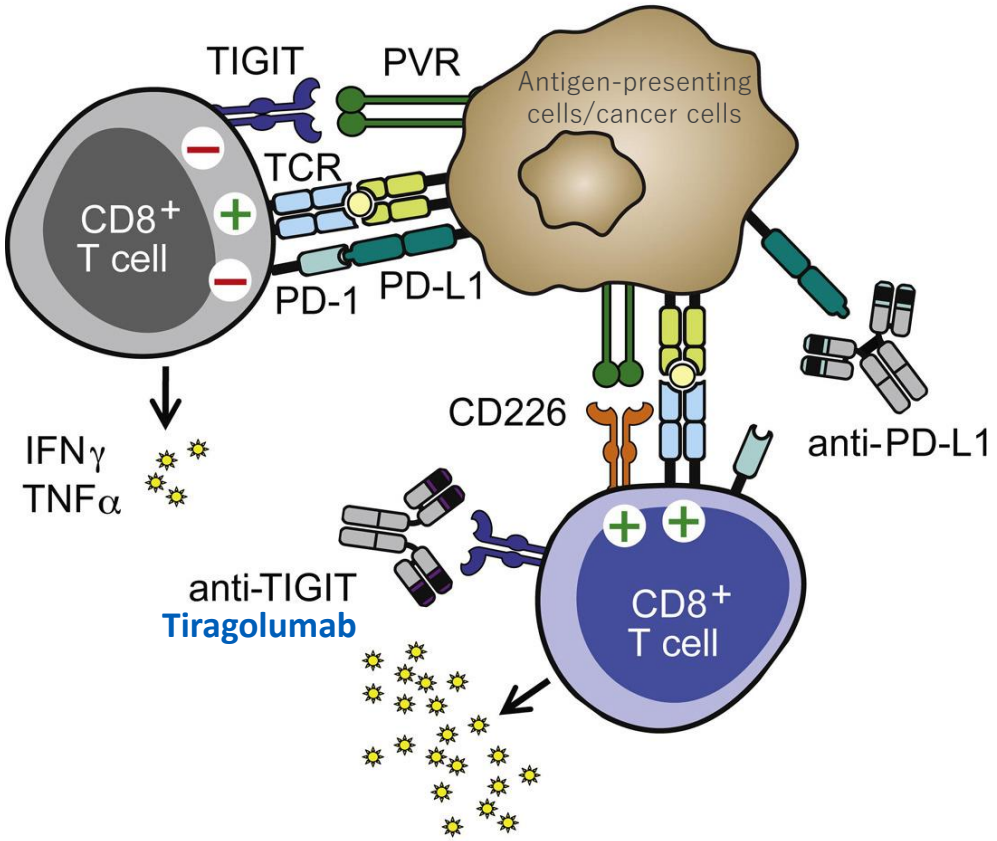
[1] Perjeta® Appropriate Use Guide (Chugai Pharmaceutical Co., Ltd.) p.13 Administration schedule, [2] Phesgo® Appropriate Use Guide (Chugai Pharmaceutical Co., Ltd.) p.18 Administration schedule

Tiragolumab (RG6058)

Tiragolumab (RG6058)

Anti-TIGIT Fully Human Monoclonal Antibody

(Image)



Johnston RJ et al. *Cancer Cell*. 2014;26(6):923-937.
(authors include employees of Genentech)

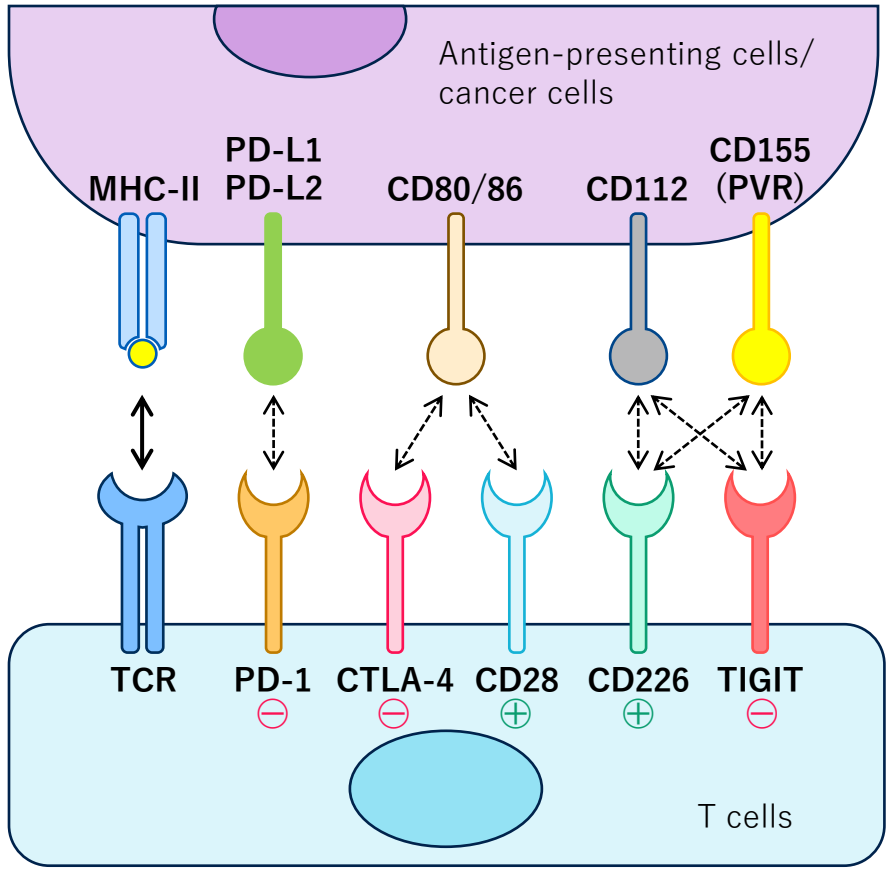
CD226: Cluster of Differentiation 226, IFN γ : Interferon gamma, PD-1: Programmed Cell Death Protein 1, PD-L1: Programmed Cell Death Ligand 1, PVR: Poliovirus Receptor, TCR: T Cell Receptor, TIGIT: T Cell Immunoreceptor with Ig and ITIM domains, TNF α : Tumor Necrosis Factor Alpha

- **Immune checkpoint inhibitor with a new mechanism of action**
- **Anti-tumor effects are expected to improve when used in combination with other immune checkpoint inhibitors**
- **Four global phase III clinical trials are ongoing, including for non-small cell lung cancer**

	Expected Indications
SKYSCRAPER-01	PD-L1-positive locally advanced or metastatic non-small cell lung cancer (first-line treatment)
SKYSCRAPER-03	Unresectable, locally advanced, stage III non-small cell lung cancer
SKYSCRAPER-07	Locally advanced esophageal squamous cell carcinoma
IMbrave152/SKYSCRAPER-14	Locally advanced or metastatic hepatocellular carcinoma (first-line treatment)

Immune Checkpoint Molecules

- The activation of T cells, one of the vital cells in the immune system, is controlled by two different signals, that of primary stimulatory and co-stimulatory signals.
- There are two types of co-stimulatory signals: inhibitory (brake) and stimulatory (accelerator) signals. Immune checkpoint molecules are co-inhibitory.
- Immune checkpoint molecules include PD-1, CTLA-4, and TIGIT.
- The proliferation and function of T cells are suppressed when physiological ligands bind to these immune checkpoint molecules.
- Cancer cells utilize this inhibitory mechanism to avoid attacks from the immune system.

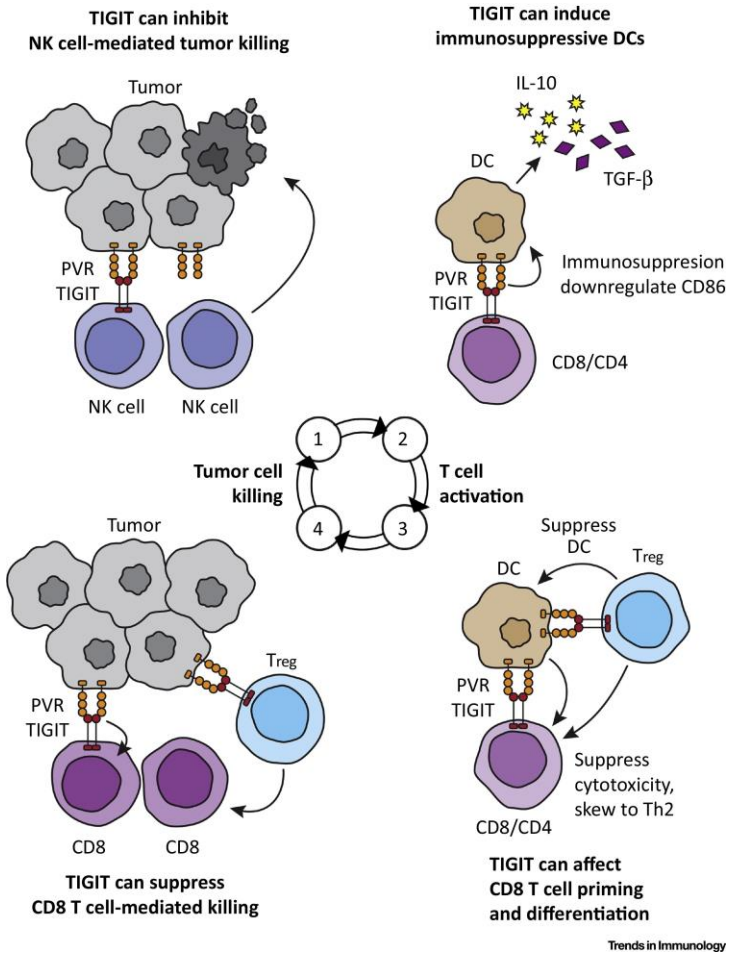


CTLA-4: Cytotoxic T lymphocyte-associated antigen-4, MHC: Major histocompatibility complex, PD-1: Programmed cell death protein-1, PD-L1: Programmed cell death ligand 1, TCR: T cell receptor, TIGIT: T cell immunoglobulin and ITIM domain

Figure taken from Qin S. et al. *Mol Cancer*. 2019;18(1):155

Novel Immune Checkpoint Inhibitor: Anti-TIGIT Antibody Tiragolumab

■ TIGIT blocks immune cells at multiple stages



■ TIGIT and PD-L1/PD-1 pathways have a complementary relationship

The TIGIT and the PD-1/PD-L1 pathways suppress the co-stimulatory molecule CD226 by way of different mechanisms

Combination therapy with tiragolumab and atezolizumab may be useful in enhancing anti-tumor immunity by activating both CD28 and CD226 co-stimulatory molecules through derepression.

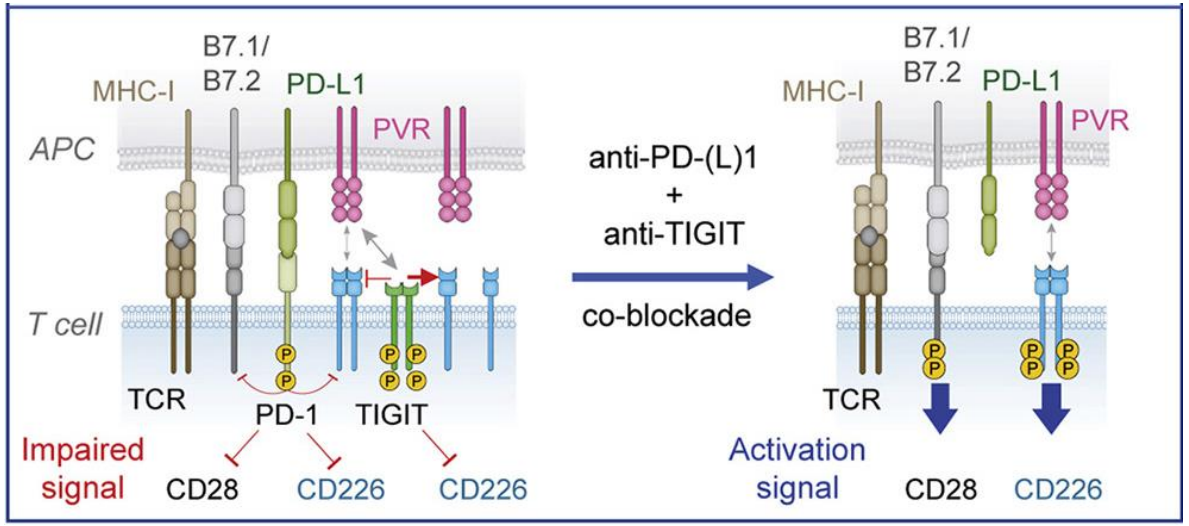


Figure based on Manieri NA, et al. *Trends Immunol*. 2017;38(1):20-28 (authors include employees of Genentech)
Banta KL, Xu X, Chitre AS, et al. *Immunity*. 2022;55(3):512-526.e9. (authors include employees of Genentech)

Study Design: Non-Small Cell Lung Cancer

SKYSCRAPER-01[1]

- Previously untreated, locally advanced, unresectable or metastatic non-small cell lung cancer
- No *EGFR* mutation or *ALK* fusion gene
- ECOG PS 0–1
- PD-L1 TPS ≥50% (22C3 assay) or TC ≥50% (SP263 assay) or TC3 or IC3 (SP142 assay)

R 1:1

- **Tiragolumab + Atezolizumab**
- **Placebo + Atezolizumab**

Primary endpoint
- Overall survival
- Progression-free survival (Investigator-assessed)

SKYSCRAPER-03

- Unresectable, locally advanced, stage III non-small cell lung cancer without disease progression after cCRT
- No *EGFR* mutation or *ALK* fusion gene
- ECOG PS 0–1
- PD-L1 status known

R 1:1

- **Tiragolumab + Atezolizumab**
- **Durvalumab**

Primary endpoint
- Progression-free survival (Independent review facility-assessed)

1. NCT04294810, 2. NCT04543617
TPS: Tumor Proportion Score, TC: Tumor Cells, IC: Immune Cells, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase
ECOG PS: Eastern Cooperative Oncology Group Performance Status, cCRT: Concurrent Chemoradiotherapy

Study Design: Esophageal Cancer, Liver Cancer

SKYSCRAPER-07[1]

- Unresectable, locally advanced, esophageal squamous cell carcinoma without disease progression after dCRT
- ECOG PS 0–1
- PD-L1 all-comer

R 1:1:1

- Tiragolumab + Atezolizumab
- Placebo + Atezolizumab
- Placebo + Placebo

Primary endpoint
- Progression-free survival (Investigator-assessed)
- Overall survival

IMbrave152/SKYSCRAPER-14[2]

- Locally advanced or metastatic and/or unresectable hepatocellular carcinoma
- ECOG PS 0-1

R 1:1

- Tiragolumab + Atezolizumab + Bevacizumab
- Atezolizumab + Bevacizumab + Placebo

Primary endpoint
- Progression-free survival (Investigator-assessed)
- Overall survival

dCRT: definitive Chemoradiotherapy、1. NCT04543617, 2. NCT05904886, Badhrinarayanan S et al. Future Oncol. 2024;20(28):2049-2057. (authors include employees of Genentech)

Notes and Contacts

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Corporate Communications Dept.

For Media: Media Relations Group	
Tel :	+81 (0)3-3273-0881
E-mail :	pr@chugai-pharm.co.jp
Person in charge :	Hideki Sato, Shumpei Yokoyama, Naoki Kouzai, Ikue Miyazawa, Mari Otsuka

For Investors: Investor Relations Group	
Tel :	+81 (0)3-3273-0554
E-mail :	ir@chugai-pharm.co.jp
Person in charge :	Takayuki Sakurai, Tomoyuki Shimamura, Shumpei Yokoyama, Sachiyo Yoshimura, Yayoi Yamada, Yuri Ikegaya

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