Information Meeting on ZELBORAF® and cobas® BRAF V600 Mutation Test

CHUGAI PHAMACEUTICAL CO., LTD.
Roche Diagnostics K.K.

April 2, 2015

Forward-Looking Statements

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

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.

Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

at the Front Line
CHUGAI ONCOLOGY

Overview of ZELBORAF®

Takahiro Mizui
ZELBORAF Lifecycle Leader
CHUGAI PHARMACEUTICAL CO., LTD.

Zelboraf.
vemurafenib

Outline of ZELBORAF®

Innovation all for the patients

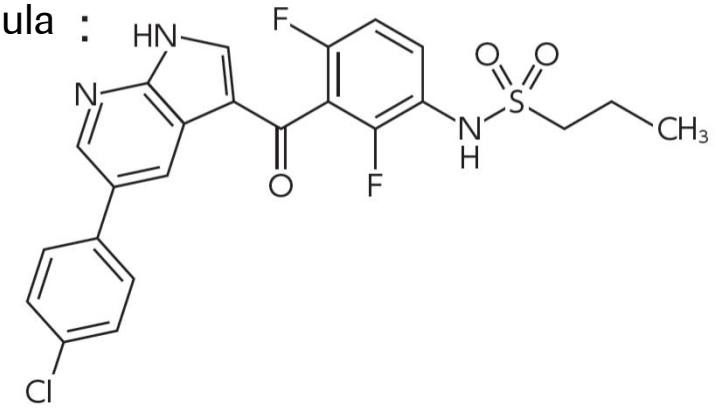
CHUGAI

Roche A member of the Roche group

ZELBORAF® is a small molecule compound that
selectively inhibits oncogenic BRAF kinase,
developed by F. Hoffmann-La Roche Ltd. and Plexxikon Inc.

- Nonproprietary name: Vemurafenib (JAN)

Structural formula :



- Molecular weight: 489.92

- Chemical name: *N*-{3-[5-(4-Chlorophenyl)
-1*H*-pyrrolo[2,3-*b*]pyridin-3-carbonyl]
-2,4-difluorophenyl}propane-1-sulfonamide

Development history of ZELBORAF®

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Month/Year	Global	Japan
Nov/2006	● Roche and Plexxikon Started Phase I study (PLX06-02 [BRIM1])	
Sep/2009	● Started Phase II study (NP22657 [BRIM2])	
Jan/2010	● Started Phase III study (NO25026 [BRIM3])	
Aug/2011	● Approval for the patients with unresectable or metastatic melanoma with BRAF V600E mutation in US	
Feb/2012	● Approval for the patients with unresectable or metastatic melanoma with BRAF V600 mutation in EU	
Sep/2012		● Chugai Started Phase I/II study (JO28178) ● Orphan drug designation
Apr/2014		● New drug application filed for vemurafenib
Dec/2014		● Approval for the patients with unresectable melanoma with BRAF mutation

BRAF mutation should be determined by cobas® 4800 BRAF V600 Mutation Test. The cobas® 4800 BRAF V600 Mutation Test has been approved as the companion diagnostics in the US (Aug. 2011), and CE-marked in the EU (Aug. 2011).

Selectivity against V600 mutated BRAF kinase (*in vitro*)

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

- Kinase inhibitory activity of vemurafenib against various kinases

Kinase	IC_{50} (nmol/L)
BRAF V600E	8
CRAF	16
ARAF	29
BRAF WT	39
SRMS	18
ACK1	19
MAP4K5 (KHS1)	51
FGR	63
BRK	202
LCK	218
NEK11	317
FYN	533
KIT	538
BLK	547
LYNB	599
KDR	723
YES1	800
WNK3	877
STK3 (MST2)	891
LYNA	995

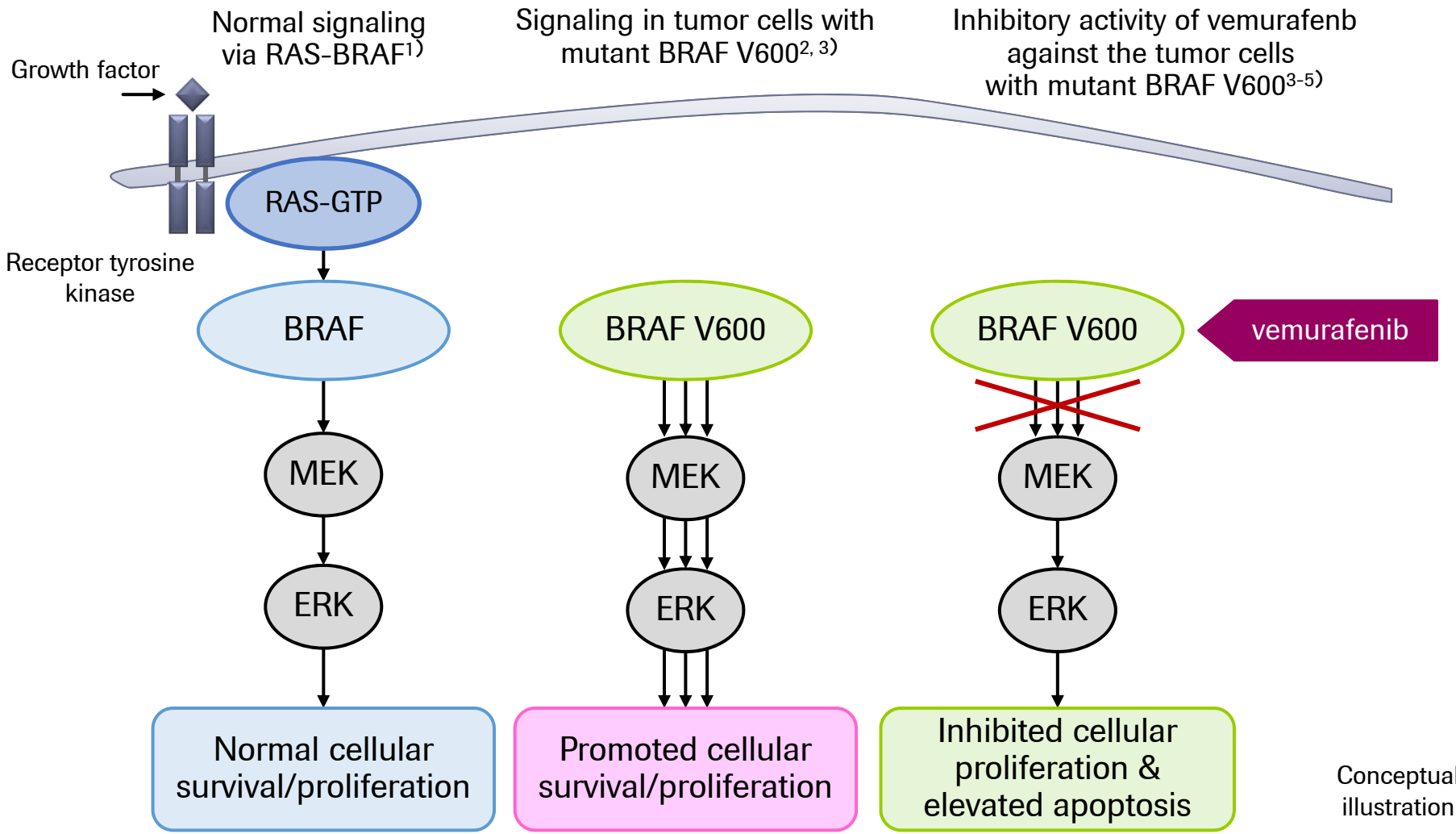
- Kinase inhibitory activity of vemurafenib against V600 mutated BRAF kinases

BRAF mutation	Source	ATP (μmol/L)	IC_{50} (nmol/L)
V600E*	*Baculo*	100	9, 9.9
V600A*	*Baculo*	100	27, 14
V600D	*E. coli*	100	5
V600G	*Baculo*	100	8
V600K	*E. coli*	10	110
V600K	*Baculo*	100	7
V600M	*E. coli*	100	13
V600M	*Baculo*	100	7
V600R	*E. coli*	10	34
V600R	*Baculo*	100	9
K601E	*E. coli*	10	68
K601E	*Baculo*	100	11
T599I	*Baculo*	100	31
F595L	*Baculo*	10	54
E586K	*Baculo*	10	46
G464V	*Baculo*	10	3
G469A	*Baculo*	10	7

*: Result from 2 *in vitro* studies

The mechanism of antitumor activity of vemurafenib in tumor cells with mutant BRAF V600

Innovation all for the patients
CHUGAI
Roche A member of the Roche group



Conceptual illustration

1) Garnett MJ, et al. Cancer Cell 2004, 6: 313-319 2) Wan PTC, et al. Cell 2004, 116: 855-867
3) Poulikakos PI, et al. Nature 2010, 464: 427-430 4) Bollag G, et al. Nature 2010, 467: 596-599
5) Yang H, et al. Cancer Res 2010, 70: 5518-5527

Description

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

- Regulatory classification

  Powerful drug, Prescription-only drug*

  * Caution - Use only pursuant to the prescription or directions of a physician, etc.

- Storage

  Store at room temperature; protect from moisture (ZELBORAF should be stored in its original PTP packaging)

- Expiration date

  2 years (Use before the expiration date indicated on the carton)

Long axis	approx. 19.1 mm
Short axis	approx. 9.7 mm
Thickness	approx. 7.4 mm
Weight	870 mg

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Indications

【INDICATIONS】

Unresectable melanoma with BRAF mutation

＜Precautions related to INDICATIONS＞

1. ZELBORAF should be administered only in patients confirmed to be *BRAF* mutation-positive through tests by an adequately experienced pathologist or test facility.
   The test should be conducted using an approved in vitro diagnostic.
2. Eligible patients should be selected after carefully reading the CLINICAL STUDIES section to gain a thorough understanding of the effectiveness and safety of ZELBORAF.
3. The effectiveness and safety of ZELBORAF as post-operative adjuvant chemotherapy have not been established.

Dosage and administration

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

【DOSAGE AND ADMINISTRATION】

The usual adult dosage of vemurafenib is 960 mg administered orally twice daily.

＜Precautions Related to DOSAGE AND ADMINISTRATION＞

1. If an adverse reaction occurs, the dose should be modified with reference to Table 1. However, if cutaneous squamous cell carcinoma or new primary melanoma occurs, treatment can continue without dose reduction or interruption after the patient receives appropriate intervention, such as surgical resection. In patients who develop QTc prolongation, the dose should be modified with reference to Table 2.
2. Increased C_{max} and AUC has been reported with postprandial administration of ZELBORAF. To avoid the food effect, dosing is preferable in a fasted state (fasting 2 hours before and 1 hour after dose) (see PHARMACOKINETICS).
3. The effectiveness and safety of ZELBORAF in combination therapy with other anti-cancer drugs have not been established.

Please refer to the package insert about “Table1” and “Table2.”

Conditions for approval

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

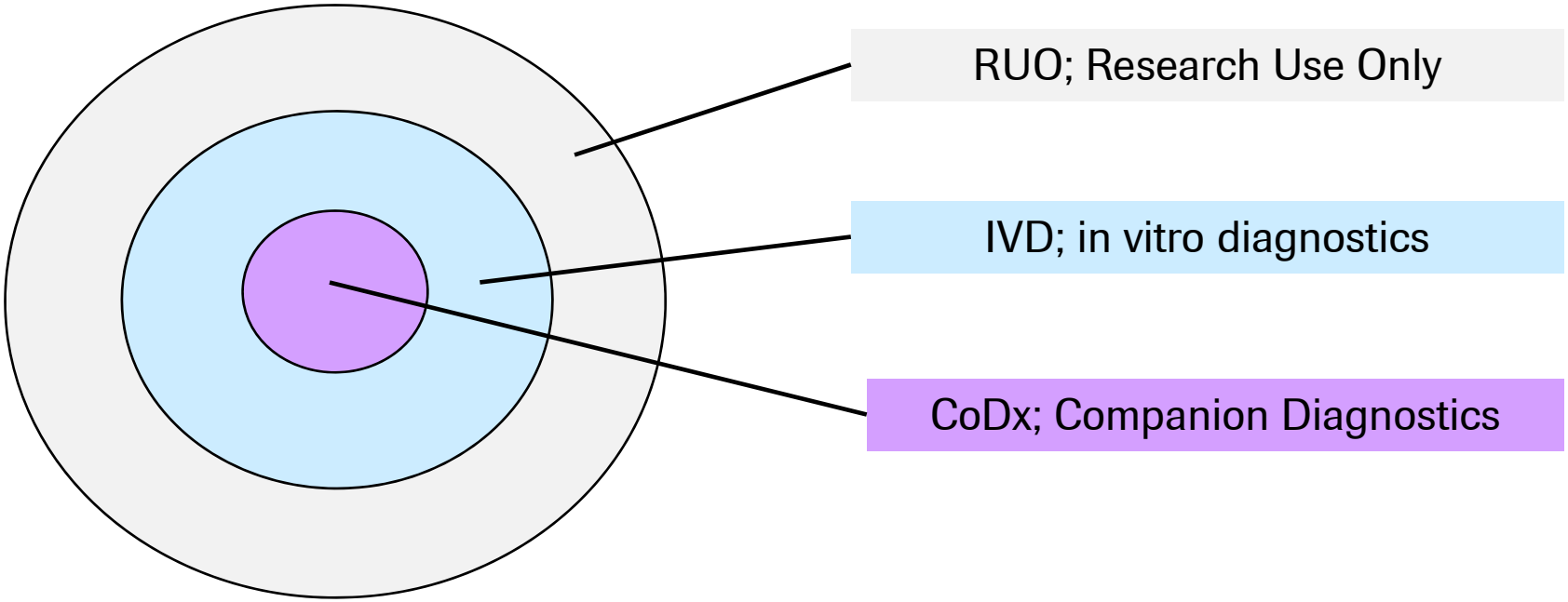
1. A drug risk management plan should be prepared and appropriately implemented.
2. Because the number of patients in Japanese clinical trials is very limited, postmarketing drug use surveillance of all patients receiving ZELBORAF should be conducted until data for a set number of patients are collected in order to identify the background characteristics of patients using ZELBORAF, collect early data on the safety and efficacy of ZELBORAF, and take necessary measures for appropriate use of ZELBORAF.

cobas® BRAF V600 Mutation Test

Toru Ogawa
Manager, Molecular Diagnostics
Roche Diagnostics K.K.

Companion Diagnostics

"cobas® BRAF V600 Mutation Test" is a companion diagnostic for "Zelboraf®"



- identify patients who are most likely to benefit from a particular therapeutic product
- identify patients who are likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product
- monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness

cobas® BRAF V600 Mutation Test

To aid in the selection of patients for therapy with Zelboraf®

Zelboraf®?

Unresectable Malignant Melanoma

cobas® BRAF V600 Mutation Test

Only cobas® BRAF Mutation Test can be used for the identification of patients for therapy with Zelboraf®.

Extracts from Package insert

■ cobas® BRAF V600 Mutation Test

【intended use】

Detection of BRAF V600 mutations
in DNA extracted from formalin-fixed,
paraffin-embedded human melanoma tissue（an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib)

■ Zelboraf® Tablets

【Precautions Related to INDICATIONS】

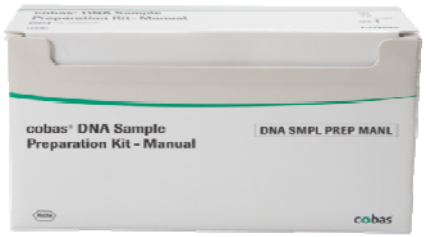
ZELBORAF should be administered only in patients confirmed to be *BRAF* mutation-positive through tests by an adequately experienced pathologist or test facility. The test should be conducted using an approved in vitro diagnostic.

【CLINICAL STUDIES】

Note 8: Tested using a cobas® BRAF V600 Mutation Test kit, the approved companion diagnostic.

Package insert “cobas BRAF V600 Mutation Test”
Package insert “Zelboraf”

Reagents and System for Diagnostics



cobas® DNA Sample Preparation Kit(FFPE)

DNA Extraction

cobas® BRAF V600 Mutation Test

Reagent for Amplification and Detection

cobas® 4800 System z480

System

cobas® BRAF V600 Mutation Test

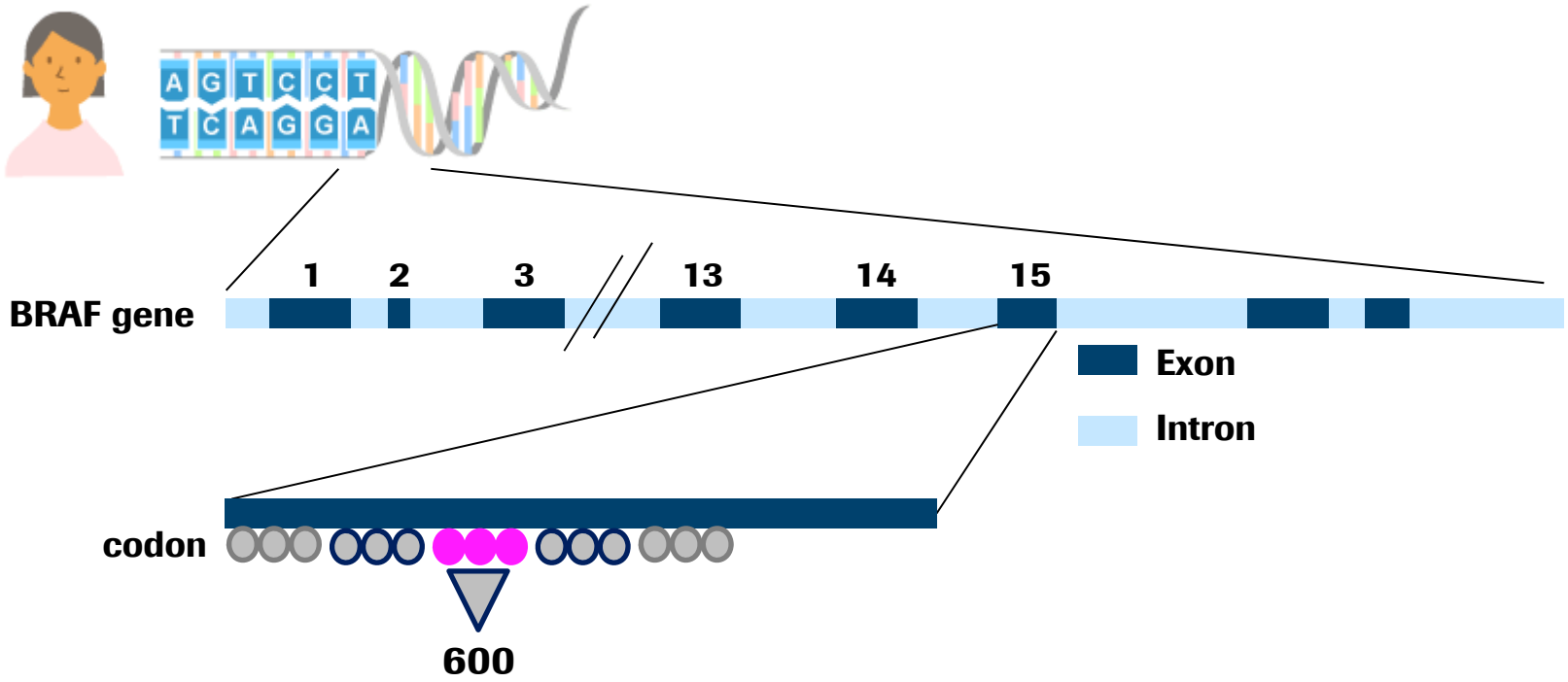
Specification

	cobas® BRAF V600 Mutation Test
Intended Use	Detection of BRAF V600 mutations in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue（an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib)
Mutation Coverage	Exon 15 codon 600
Specimen Type	formalin-fixed, paraffin-embedded tissue (FFPET)
DNA Volume	125 ng/Sample
Method	Real-time PCR
Sensitivity	**cobas**® 4800 BRAF V600 Mutation Test can detect the BRAF V600E mutation in actual clinical FFPET specimens at ≥5% mutation level
Instrument	**cobas**® 4800 z480 v2.1
Throughput/run	94 samples (8 batch/kit)

Package insert “cobas BRAF V600 Mutation Test”

Detection:

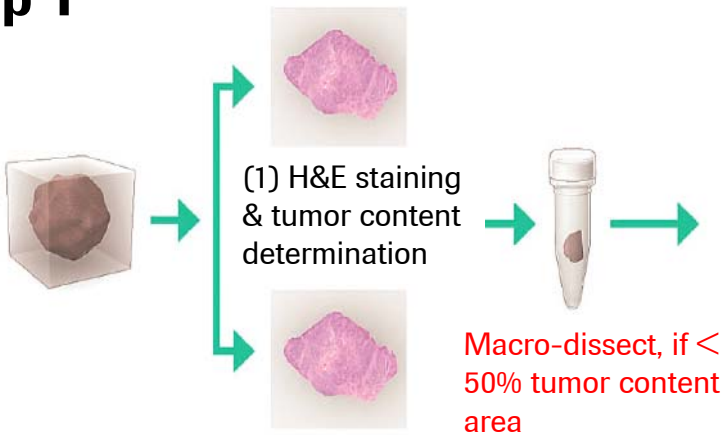
The detection of exon 15, codon 600 in BRAF gene



Most of malignant melanoma is the mutation of codon 600 V(Val) to E(Glu), D(Asp), and K(Lys).
cobas BRAF V600 mutation kit could cross react to D and K in addition to E.

4 key steps

Step 1



(1) H&E staining & tumor content determination

Macro-dissect, if < 50% tumor content by area

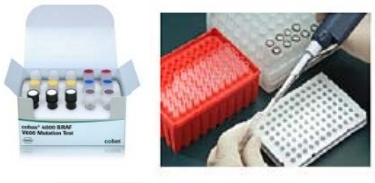
Step 2

Sample Preparation Kit

Genomic DNA isolation

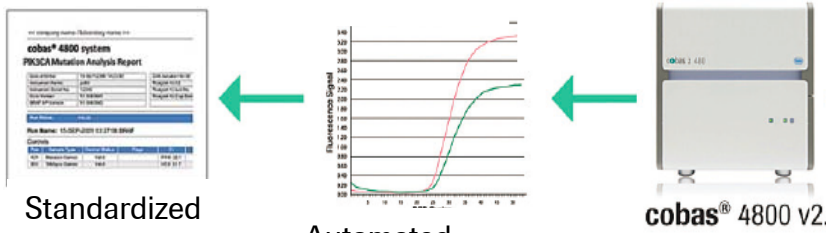
DNA quantification

Step 3



PCR setup

Step 4



Standardized reporting

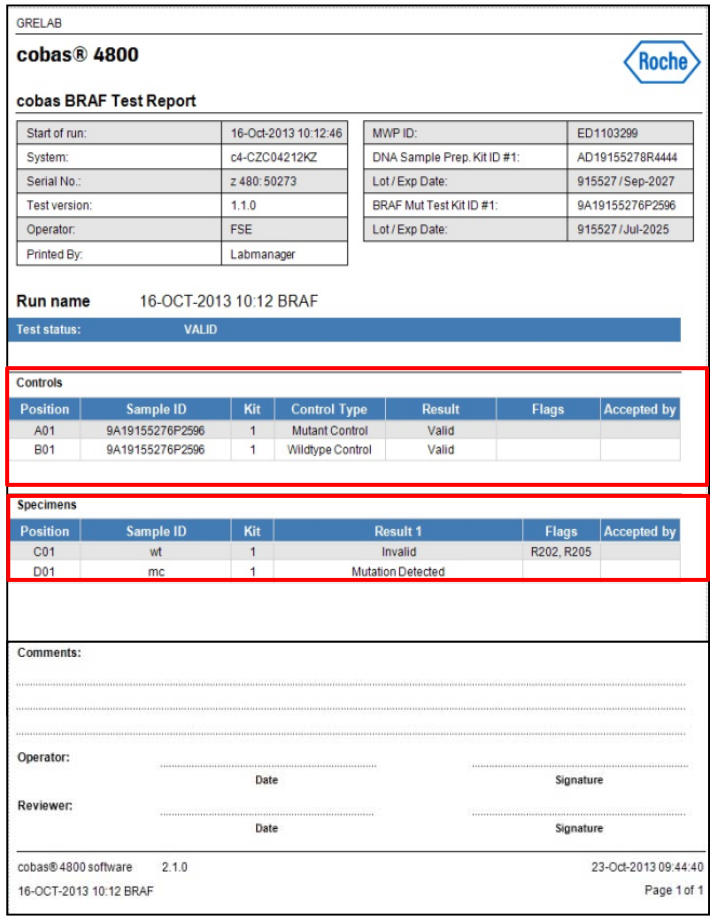
Automated analysis

cobas® 4800 v2.

Harkanwal Halait, et al, Diagn Mol Pathol Volume 21, Number 1, March 2012

Report

Test results are automatically reported.



GRELAB

cobas® 4800

cobas BRAF Test Report

Start of run:	16-Oct-2013 10:12:46	MWP ID:	ED1103299
System:	c4-CZC04212KZ	DNA Sample Prep. Kit ID #1:	AD19155278R4444
Serial No.:	z 480: 50273	Lot / Exp Date:	915527 / Sep-2027
Test version:	1.1.0	BRAF Mut Test Kit ID #1:	9A19155276P2596
Operator:	FSE	Lot / Exp Date:	915527 / Jul-2025
Printed By:	Labmanager		

Run name 16-OCT-2013 10:12 BRAF

Test status: VALID

Controls

Position	Sample ID	Kit	Control Type	Result	Flags	Accepted by
A01	9A19155276P2596	1	Mutant Control	Valid		
B01	9A19155276P2596	1	Wildtype Control	Valid		

Specimens

Position	Sample ID	Kit	Result 1	Flags	Accepted by
C01	wt	1	Invalid	R202, R205	
D01	mc	1	Mutation Detected		

Comments:

Operator: Date Signature

Reviewer: Date Signature

cobas® 4800 software 2.1.0 23-Oct-2013 09:44:40

16-OCT-2013 10:12 BRAF Page 1 of 1

Basic information
Date, Lot...

Control result

Measurement result

Doing now what patients need next

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

at the Front Line
CHUGAI ONCOLOGY

ZELBORAF® tablet

Postmarketing safety measures

Shin Yoshida

Pharmacovigilance Department

CHUGAI PHARMACEUTICAL CO., LTD.

Zelboraf.
vemurafenib

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Contents

1. Reasons for implementing safety measures
2. Safety measures based on post-approval commitments (PACs)
   - Implement safety measures on the basis of the risk management plan (RMP)
   - Implement postmarketing surveillance for all patients treated
3. Other approaches for safety measures
4. Summary

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

1. Reasons for implementing safety measures

- Only a very small number of patients were studied in Japanese clinical trials.
  - Only 11 patients received the clinical dose during the Japanese Phase I/II clinical trial. Therefore, it is necessary to identify demographic characteristics of patients given Zelboraf, collect data at an early stage on the safety and efficacy of Zelboraf, and take necessary measures for the appropriate use of Zelboraf.

- Serious adverse drug reactions (ADRs), such as squamous-cell carcinoma and QT interval prolongation, may occur.
  - It is necessary to reliably provide healthcare professionals and patients with information on the appropriate use of Zelboraf, such as ADR incidence and actions to take when ADRs occur.
  - It is necessary to set use requirements to ensure that Zelboraf will only be administered under the care of medical institutions and physicians who are thoroughly familiar with chemotherapy and can adequately control any risks associated with Zelboraf.

Strict postmarketing safety measures are necessary for the appropriate use of Zelboraf.

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

1. Reasons for implementing safety measures

Package Insert: WARNINGS

【WARNINGS】

Zelboraf should be administered only in patients who are deemed suitable for treatment, in a medical facility adequately equipped to deal with emergencies, and under the supervision of a physician who is knowledgeable and experienced in cancer chemotherapy. Before treatment is started, patients or their families should be provided with a full explanation of the benefits and risks of Zelboraf. Zelboraf should be administered only after informed consent has been obtained.

Package Insert: CONTRAINDICATIONS

【CONTRAINDICATIONS (Zelboraf is contraindicated in the following patients.)】

Patients with a previous history of hypersensitivity to any of the ingredients of Zelboraf.

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

2. Safety measures based on PACs

- Implement safety measures on the basis of the RMP

  RMPs should be planned and appropriately implemented.

- Implement postmarketing surveillance for all patients treated

  Only a very small number of Japanese patients were treated during the clinical trials. Therefore, from product launch until data on a given number of patients have been accumulated, the MAH should conduct drug use surveillance in all patients, thereby identifying the background characteristics of patients given Zelboraf and collecting early data on the safety and efficacy of Zelboraf, and should take the measures necessary for the appropriate use of Zelboraf.

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

2. Safety measures based on PACs

RMP

Safety specification

Important identified risks	•Squamous-cell carcinoma •Secondary malignancies other than squamous-cell carcinoma •Liver disorder •Photosensitivity •QT interval prolongation •Skin disorder •Hypersensitivity •Eye disorder (Uveitis, etc.)
Important potential risks	•Progression of malignancies with *RAS* gene mutation •Facial nerve paralysis •Myelosuppression •Gastrointestinal polyp
Important missing information	•None

2. Safety measures based on PACs

-Implement safety measures on the basis of the RMP

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

RMP

	Pharmacovigilance activities		Risk minimization activities
Routine	1) Collection and evaluation of individual cases 2) Research report (literature, etc.) 3) Report on safety actions taken overseas 4) Periodic SAE signal detection and assessment	Routine	•JPI creation (revision) •Patient Guide creation (revision)
Additional	•Early postmarketing phase vigilance (EPPV) •Special drug use surveillance (all-patient) •Postmarketing clinical studies	Additional	•Provide information via EPPV •Provide healthcare professionals with information (Appropriate Use Guide) •Provide patients with information (Patient Handbook)

2. Safety measures based on PACs

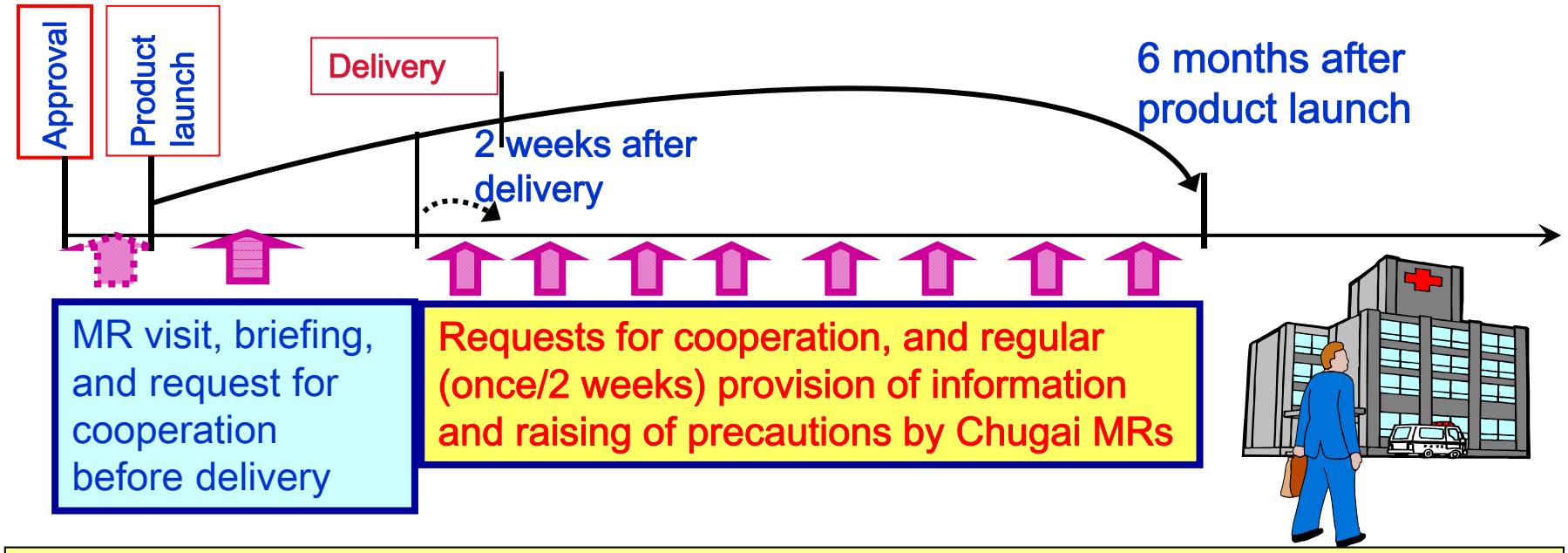
-Implement safety measures on the basis of the RMP

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Pharmacovigilance activities: EPPV



- Implement for 6 months after product launch
- MRs regularly visit medical institutions to collect information on ADRs and provide periodic information.

2. Safety measures based on PACs

-Implement safety measures on the basis of the RMP

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

Risk minimization activities: Information provision

Materials for healthcare professionals

Materials for patients

2. Safety measures based on PACs

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

-Implement postmarketing surveillance for all patients treated

Surveillance objectives	To determine the following items under the conditions of actual clinical use of Zelboraf during a long-term follow-up period (24 months) • Incidence of ADRs • Unlabeled ADRs • Overall survival • Factors thought to affect safety and effectiveness
Target patients	All patients who use Zelboraf during the enrollment period
Events of interest	Squamous-cell carcinoma, secondary malignancies other than squamous-cell carcinoma, QT interval prolongation, liver disorder, skin disorder, and hypersensitivity
Target Surveillance sample size	500 patients
Patient Enrollment period	For 72 months after product launch (Even after the target sample size is reached, patient enrollment will be continued until lifting of the PAC on all-patient surveillance.)

3. Other approaches for safety measures

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

- Confirmation of requirements for institutions/physicians planning to use Zelboraf
- Careful selection of patients for treatment
- Use of Zelboraf Emergency Contact Card

3. Other approaches for safety measures

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Confirmation of requirements for institutions/ physicians planning to use Zelboraf

Institution requirements

1. Understand and cooperate with the safety measures specified for Zelboraf.
2. Be able to appropriately provide urgent transportation and emergency treatment if a patient's condition suddenly deteriorates, etc.
3. Be able to perform ECG, provide cardiovascular diagnosis or evaluation, and provide appropriate emergency treatment on site or at an affiliated medical institution.
4. Be able to provide ophthalmologic diagnosis or evaluation and appropriate treatment on site or at an affiliated medical institution.
5. Be staffed by physicians belonging to the Japanese Skin Cancer Society or skin cancer specialists who can engage in treatment.
6. Be able to appropriately perform surgical resection or histopathological diagnosis on site or at an affiliated medical institution if cutaneous malignancies, including squamous-cell carcinoma, occur during Zelboraf treatment.
7. Be able to perform the BRAF gene mutation test approved as an in-vitro test, on site or at an affiliated medical institution.
8. Be able to perform the following tests, etc., for evaluation or diagnosis of secondary malignancies on site or at an affiliated medical institution.

(CT scan, radiography, MRI, gastrointestinal endoscopy, head and neck screening, and gynecological examination)

Physician requirements

1. Be able to accommodate routine visits from Chugai Pharmaceutical Co., Ltd. MRs.
2. Be able to cooperate with necessary safety measures for Zelboraf.
3. Possess adequate experience in surgery or chemotherapy for malignant melanoma.

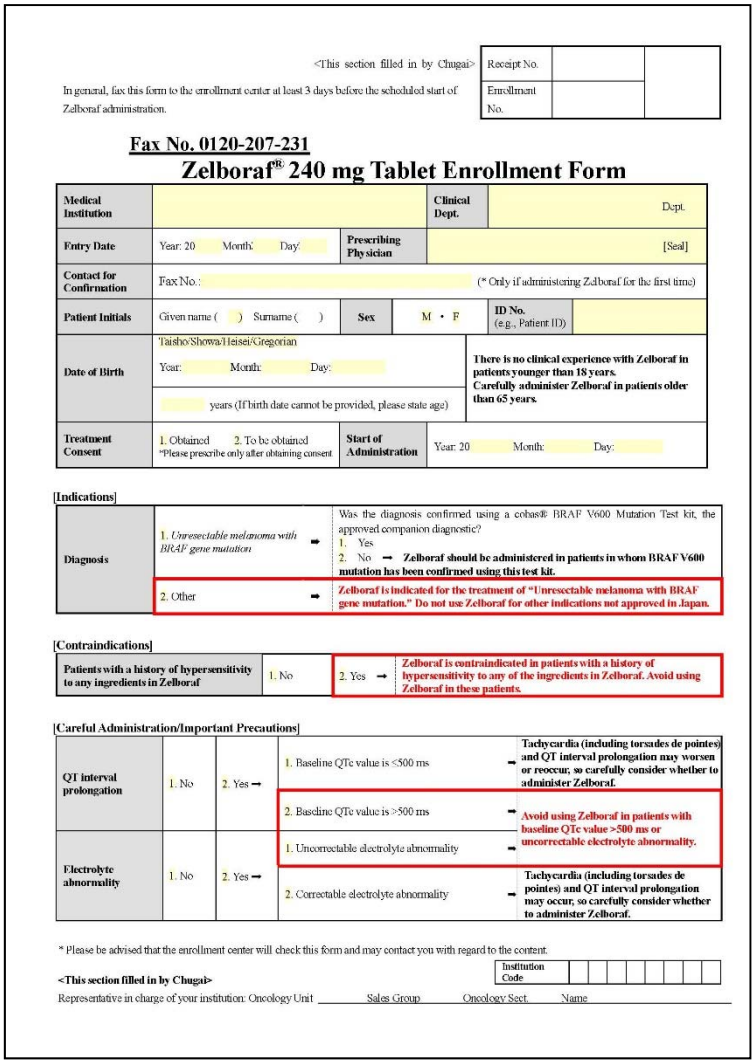
3. Other approaches for safety measures

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Careful selection of patients for treatment



<This section filled in by Chugai>

Receipt No.		
Enrollment No.		

In general, fax this form to the enrollment center at least 3 days before the scheduled start of Zelboraf administration.

Fax No. 0120-207-231

Zelboraf® 240 mg Tablet Enrollment Form

Medical Institution		**Clinical Dept.**	Dept.
Entry Date	Year: 20 Month: Day:	**Prescribing Physician**	[Seal]
Contact for Confirmation	Fax No.: (* Only if administering Zelboraf for the first time)		
Patient Initials	Given name ( ) Surname ( )	**Sex** M・F	**ID No.** (e.g., Patient ID)
Date of Birth	Taisho/Showa/Heisei/Gregorian Year: Month: Day: years (If birth date cannot be provided, please state age)	**There is no clinical experience with Zelboraf in patients younger than 18 years. Carefully administer Zelboraf in patients older than 65 years.**	
Treatment Consent	1. Obtained 2. To be obtained *Please prescribe only after obtaining consent	**Start of Administration**	Year: 20 Month: Day:

[Indications]

Diagnosis	1. *Unresectable melanoma with BRAF gene mutation* ➡	Was the diagnosis confirmed using a cobas® BRAF V600 Mutation Test kit, the approved companion diagnostic? 1. Yes 2. No ➡ **Zelboraf should be administered in patients in whom BRAF V600 mutation has been confirmed using this test kit.**
	2. Other ➡	**Zelboraf is indicated for the treatment of "Unresectable melanoma with BRAF gene mutation." Do not use Zelboraf for other indications not approved in Japan.**

[Contraindications]

Patients with a history of hypersensitivity to any ingredients in Zelboraf	1. No	2. Yes ➡	**Zelboraf is contraindicated in patients with a history of hypersensitivity to any of the ingredients in Zelboraf. Avoid using Zelboraf in these patients.**

[Careful Administration/Important Precautions]

QT interval prolongation	1. No	2. Yes ➡	1. Baseline QTc value is ≤500 ms ➡	**Tachycardia (including torsades de pointes) and QT interval prolongation may worsen or reoccur, so carefully consider whether to administer Zelboraf.**
			2. Baseline QTc value is >500 ms ➡	**Avoid using Zelboraf in patients with baseline QTc value >500 ms or uncorrectable electrolyte abnormality.**
Electrolyte abnormality	1. No	2. Yes ➡	1. Uncorrectable electrolyte abnormality ➡	
			2. Correctable electrolyte abnormality ➡	**Tachycardia (including torsades de pointes) and QT interval prolongation may occur, so carefully consider whether to administer Zelboraf.**

* Please be advised that the enrollment center will check this form and may contact you with regard to the content.

<This section filled in by Chugai> Institution Code

Representative in charge of your institution: Oncology Unit Sales Group Oncology Sect. Name

All patients who will use Zelboraf should be enrolled before drug administration

↓

Confirm patient eligibility

↓

Raise precautions by informing the prescribing physician about the package insert contents if necessary

↓

All-patient surveillance

3. Other approaches for safety measures

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Use of Zelboraf Emergency Contact Card

This card must be shown when Zelboraf is dispensed. Physicians are requested to provide patients with this card when Zelboraf is prescribed.

[Front: ADRs that need to be reported at onset]

Zelboraf Emergency Contact Card

Show this card to your pharmacist every time you fill a Zelboraf prescription.
Contact your hospital immediately if you develop any of the following symptoms.

- ☐ **Abnormally fast heartbeat, heart palpitations, dizziness, fainting**

These could be symptoms of an arrhythmia (abnormal ECG) called QT interval prolongation.

- ☐ **Generalized red blotchiness; fever; chills; swollen lips, tongue, or mouth; fragile blisters; increased blood flow to eyelids or eyes**

These could be early symptoms of hypersensitivity or serious drug rash.

- ☐ **Suddenly occurring and growing nodules (that look like warts), bleeding or (seeping) ulceration on the lesion surface**

These could be skin cancers (such as squamous-cell carcinoma).

Chugai Pharmaceutical.

[Back : Emergency contact details]

Emergency contact details

Medical institution:

Telephone No.:

Clinical Department:

Prescribing physician:

Patient registration card No.:

Patient name:

Telephone No.:

December 2014
ZEL 0008-01

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

4. Summary

- Reasons for implementing safety assurance measures
  - Only a very small number of patients were studied in clinical trials in Japan.
  - Serious ADRs may occur.
- Approaches for safety assurance
  - Safety measures based on PACs
    - ✓Implement safety measures on the basis of the RMP
    - ✓Implement postmarketing surveillance for all patients treated
  - Other approaches for safety measures

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

at the Front Line
CHUGAI ONCOLOGY

Overview of melanoma and clinical trials of vemurafenib

Naoya Yamazaki, M.D., Ph.D.
Chief, Dept. of Dermatologic Oncology
National Cancer Center Hospital, Japan

Zelboraf.
vemurafenib

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

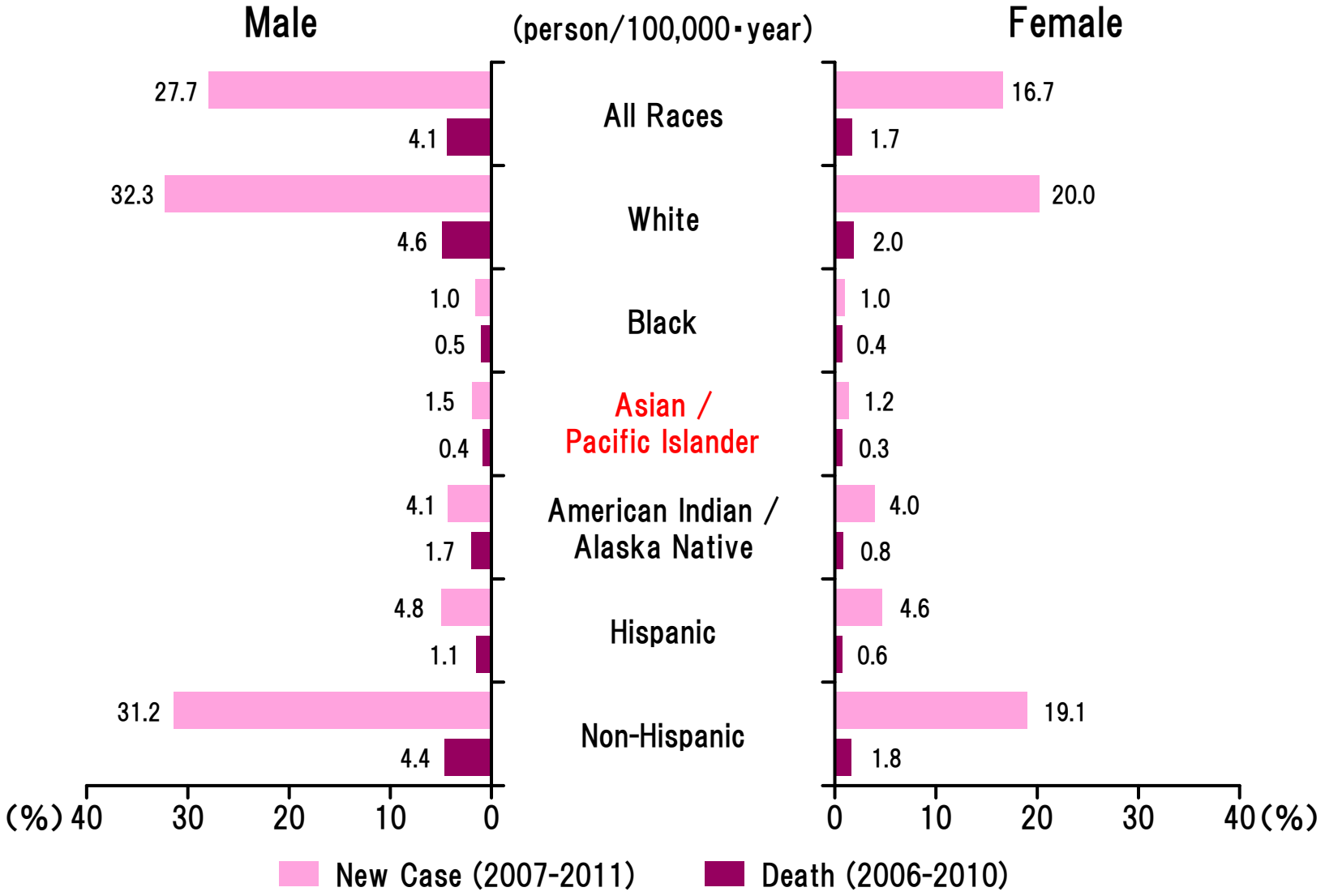
Characteristics of main skin cancer

Basal cell carcinoma	● Usually caused by UV ray exposure and occur frequently on the face in the elderly ● Rarely spread to other parts of the body and become life-threatening ● Generally treated by surgical excision
Squamous cell carcinoma	● Malignant growth of epidermal keratinocytes ● Occur frequently on the sun-exposed area ● Necrosis and ulceration accompanying malodor in hard node ● Treatment options are surgical excision, lymph node dissection, radiation therapy and chemotherapy ● Solar keratosis or Bowen's disease is popular genesis
Malignant melanoma	● Lymphogenic metastasis, hematogenous metastasis ● Although melanoma accounts for only 4% of all skin cancers, 80% of the patients who die from skin cancers have melanoma, thus it is a highly malignant form of carcinoma ● Treatment options are surgical excision, radiation therapy, chemotherapy, molecular-targeted therapy and immunotherapy
Paget disease excl. breast	● Intraepidermal carcinoma derived from apocrine gland ● Occur frequently on the vulva, anal region and axilla ● Generally treated by surgical excision

Atarashii hifukagaku version2 (Nakayama shoten) 2011, p422-430, 433-436, 457, tabularisation

Number of New Cases/Deaths of Melanoma by Race/Ethnicity

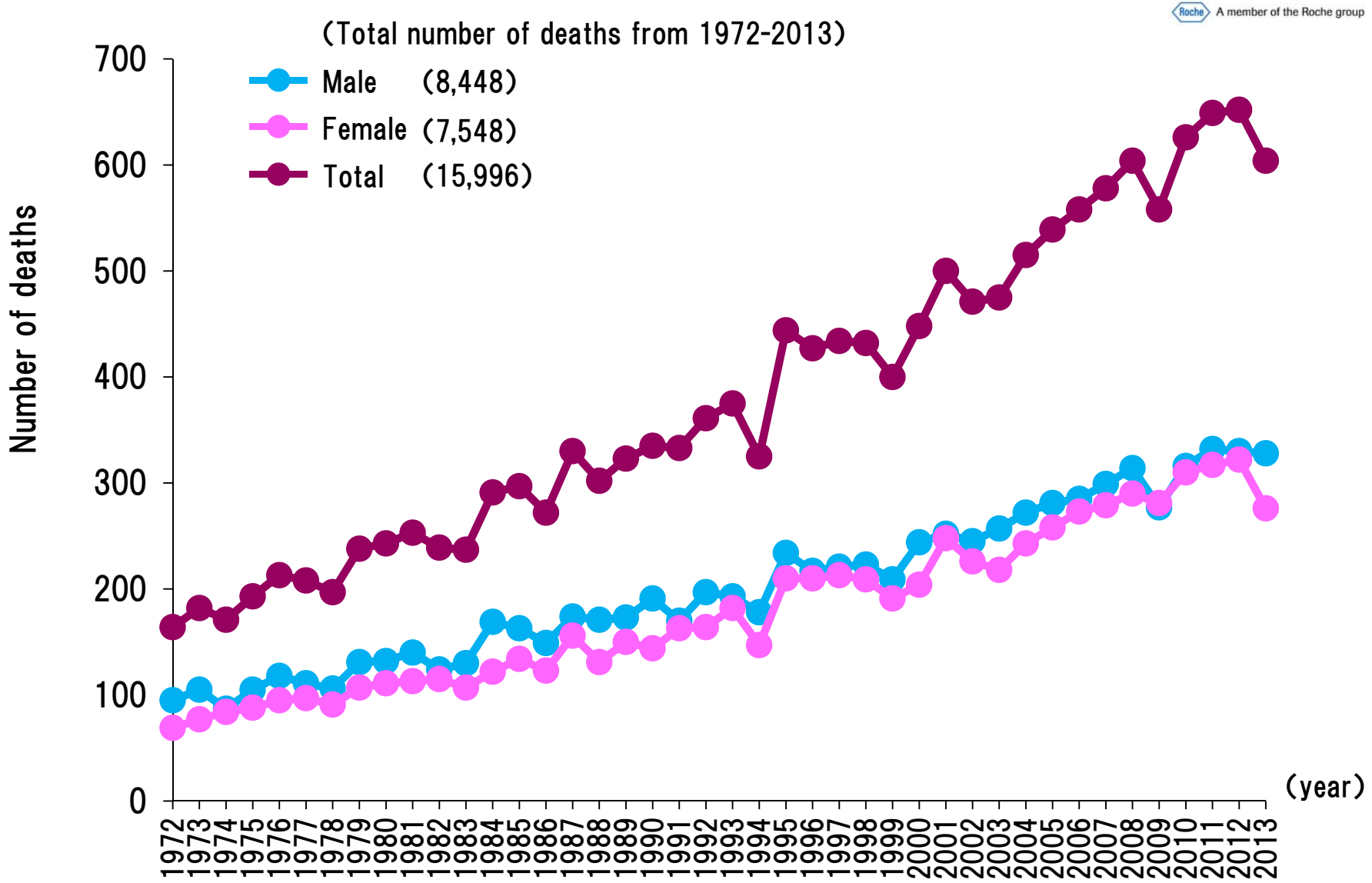
Innovation all for the patients
CHUGAI
Roche A member of the Roche group



SEER18 Registry data set analyzed by SEER Stat ver8.0.1
SEER Stat Fact Sheets: Melanoma of the Skin (http://seer.cancer.gov/statfacts/html/melan.html)

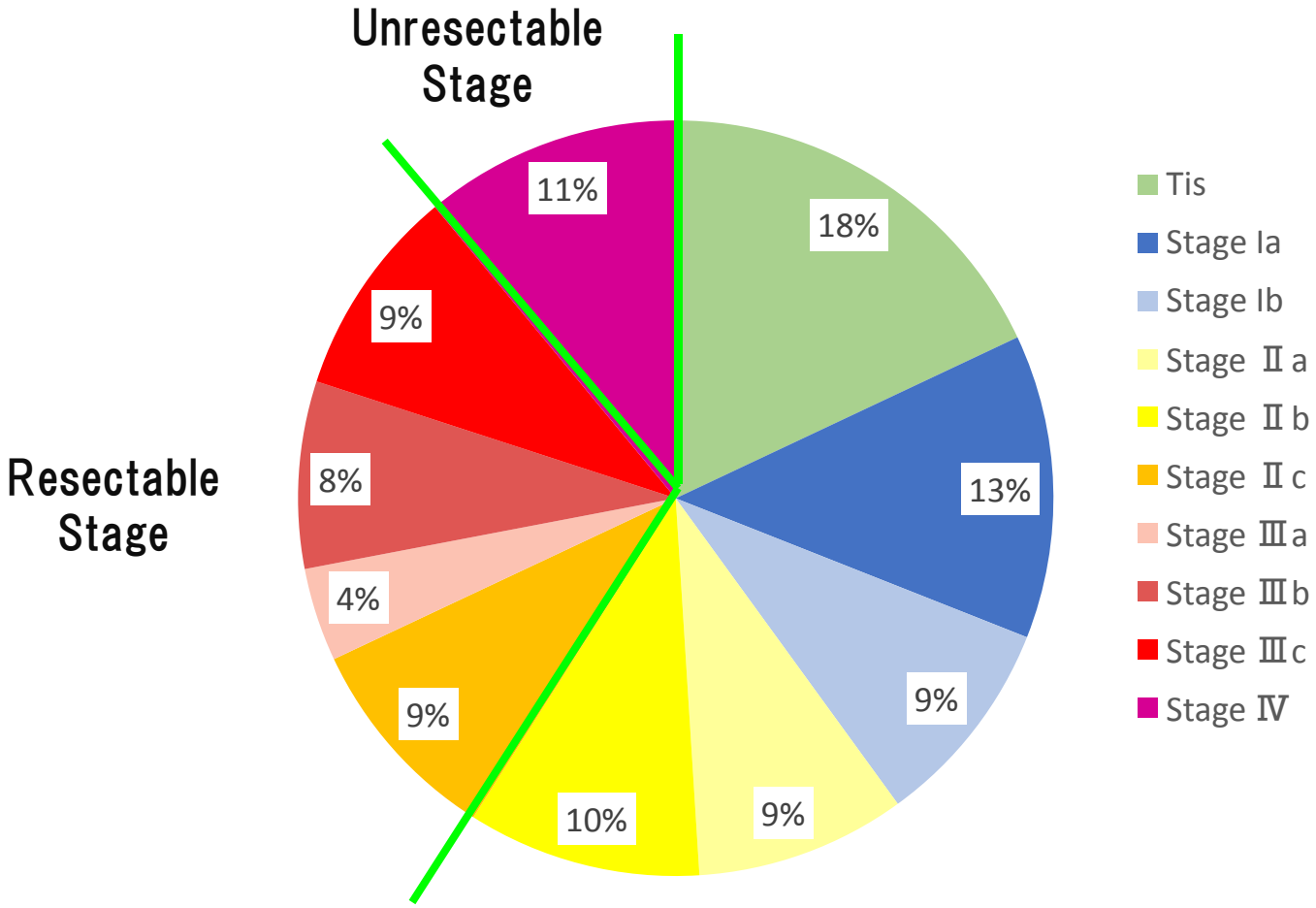
Number of deaths of melanoma patients in Japan

Innovation all for the patients
CHUGAI
Roche A member of the Roche group



Statistics and Information Department, MHLW, Vital Statistics, 1972～2013

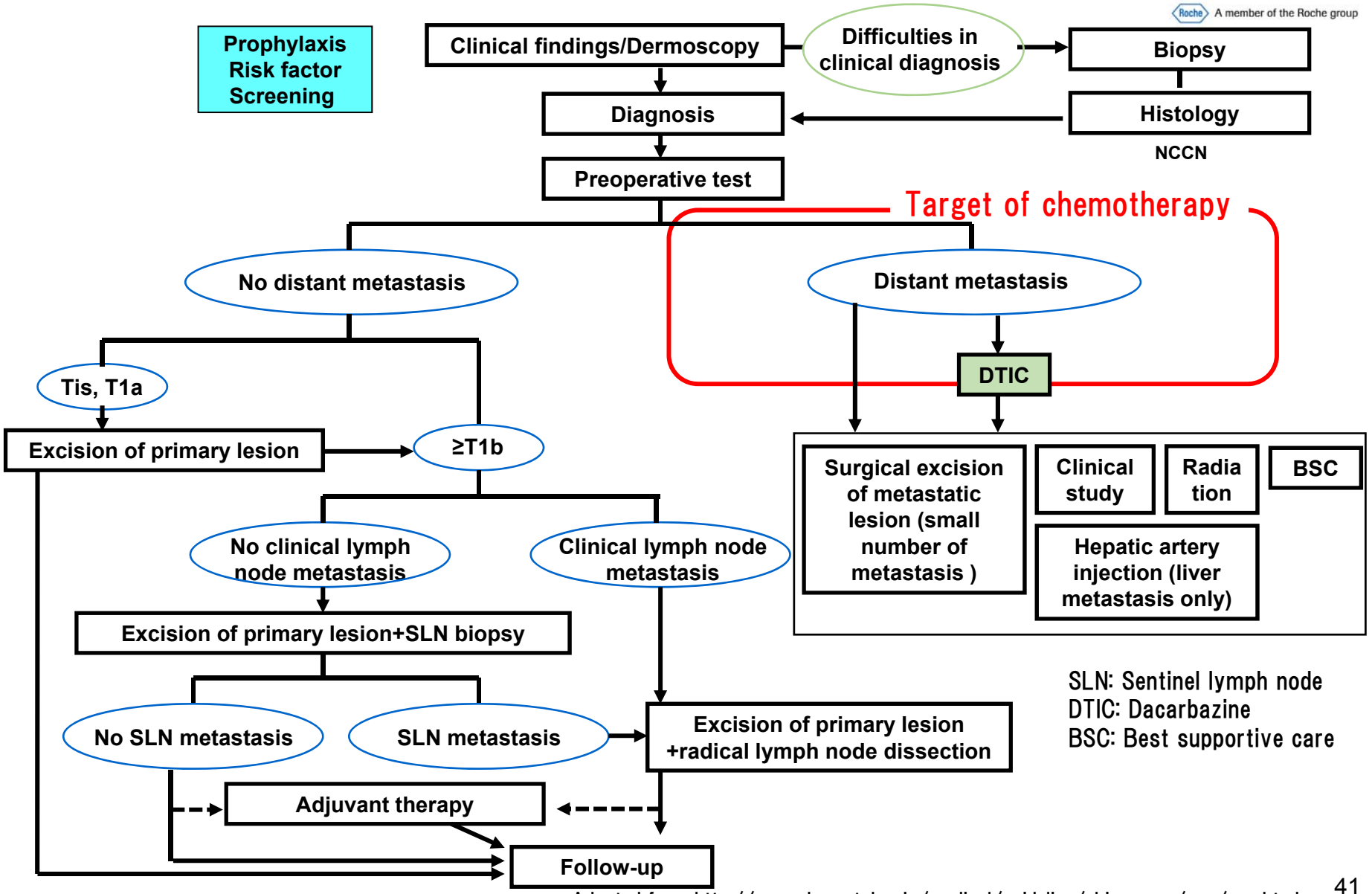
Incidence rates of melanoma by Stage (UICC, 2002)



Fujisawa Y. et al., Skin Cancer 2008;195-204

Treatment algorithm for melanoma : Clinical practice guideline for skin cancer (Japan)

Innovation all for the patients
CHUGAI
Roche A member of the Roche group



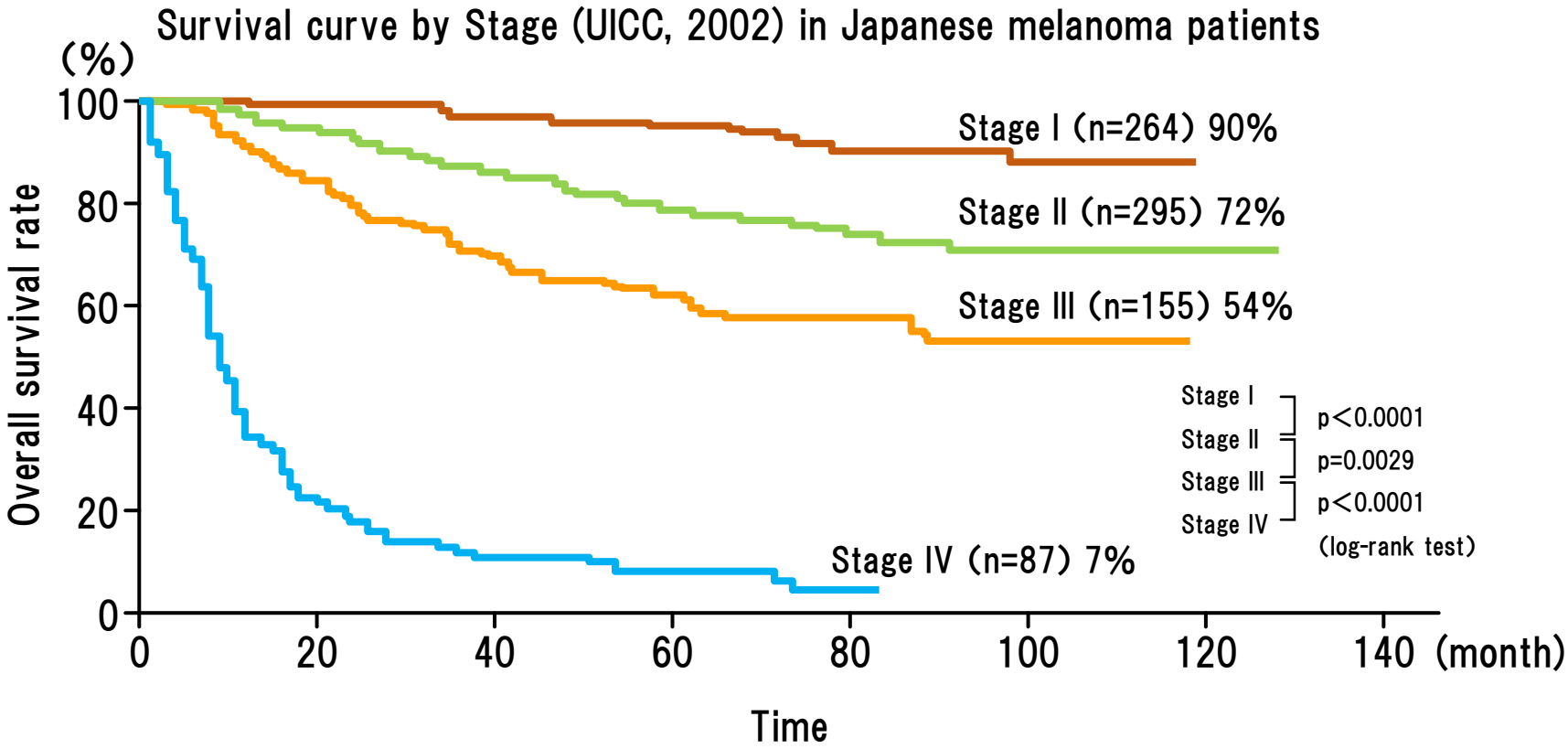
SLN: Sentinel lymph node
DTIC: Dacarbazine
BSC: Best supportive care

Adapted from http://www.dermatol.or.jp/medical/guideline/skincancer/mm/mm.html

Overall survival rate of melanoma by Stage

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

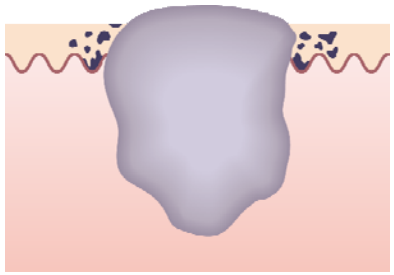
- Melanoma is extremely resistant to chemotherapy. The response rate of DTIC (Dacarbazine), standard treatment for progressive melanoma, is 10-20%.
- Melanoma is resistant to radiotherapy in general.

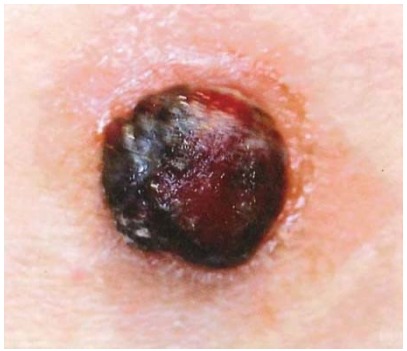


Ishihara K, et al. Int J Clin Oncol 2008, 13: 33-41
Saida T. et al. Issatsu de wakaru hifu gan (Bunkodo) 2011, p234-237

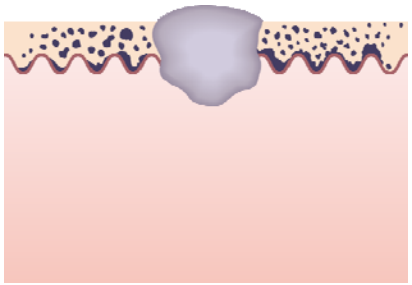
Histological subtypes of melanoma (Clark's classification)

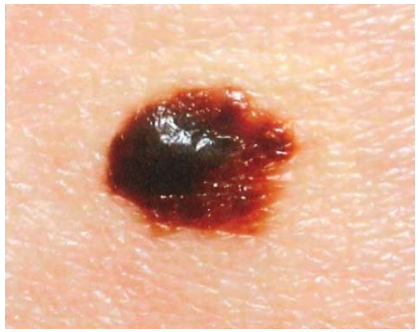
Nodular melanoma:NM



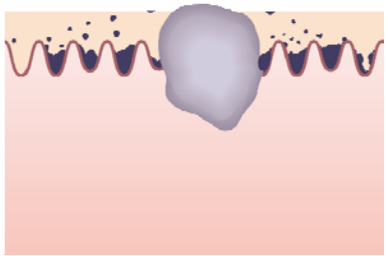


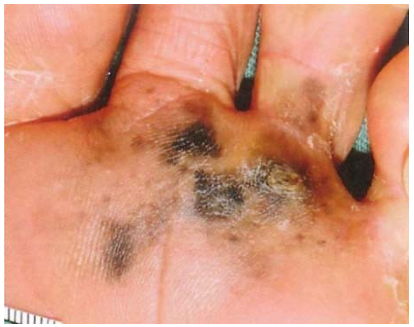
Superficial spreading melanoma:SSM



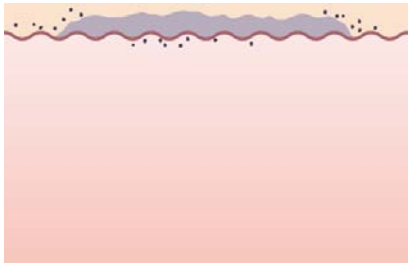


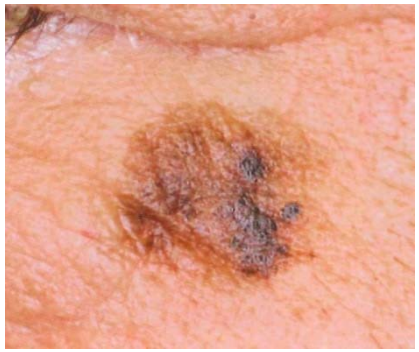
Acral lentiginous melanoma:ALM





Lentigo maligna melanoma:LMM



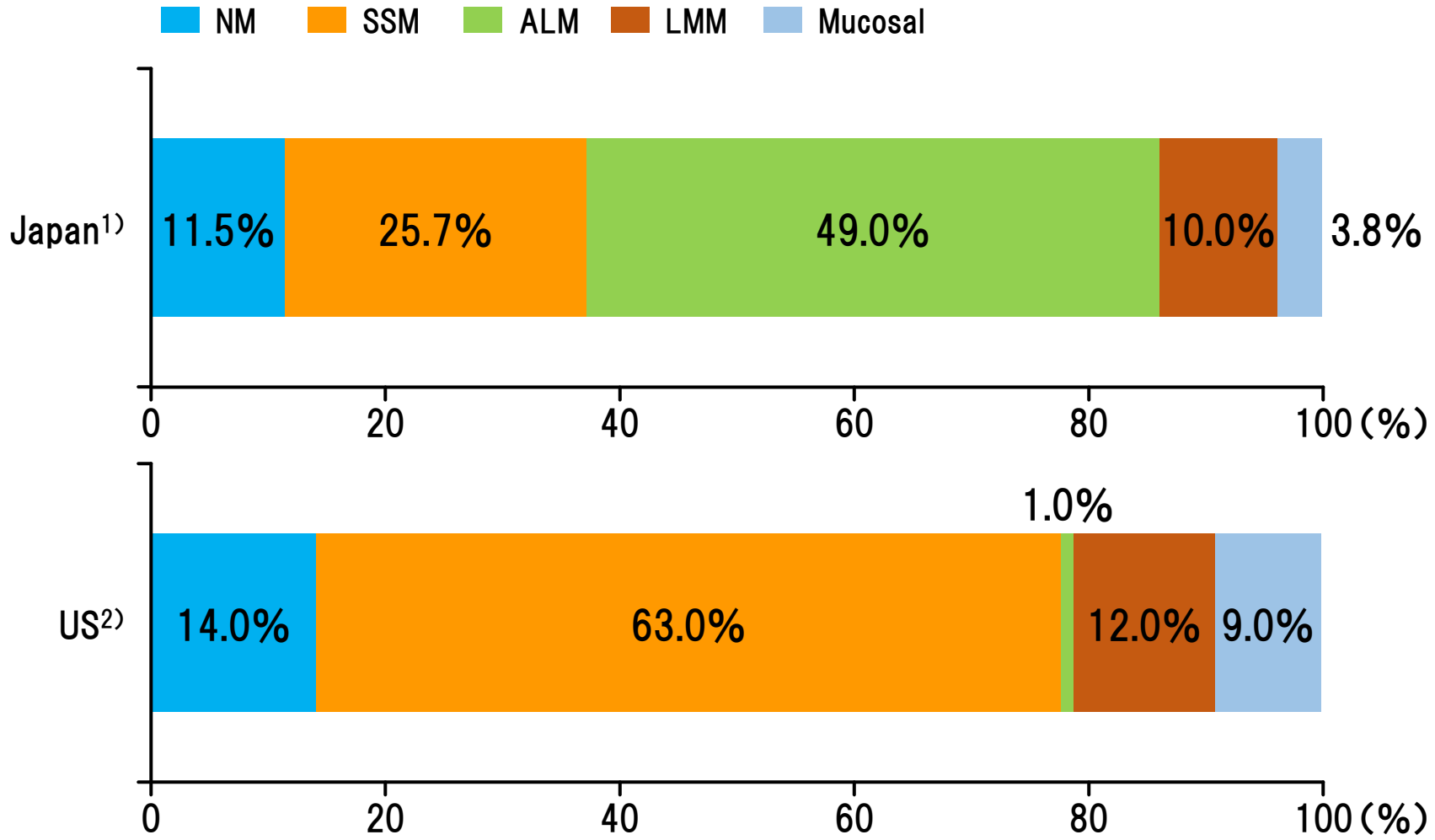


∴ Atypical melanocyte (individuality) ○ Alveolar of atypical melanocyte

Atarashii hifukagaku version 2 (Nakayama shoten) 2011, p457-458
Saida T. et al. Issatsu de wakaru hifu gan (Bunkodo) 2011, p222, 229

Incidence rate according to types of melanoma

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

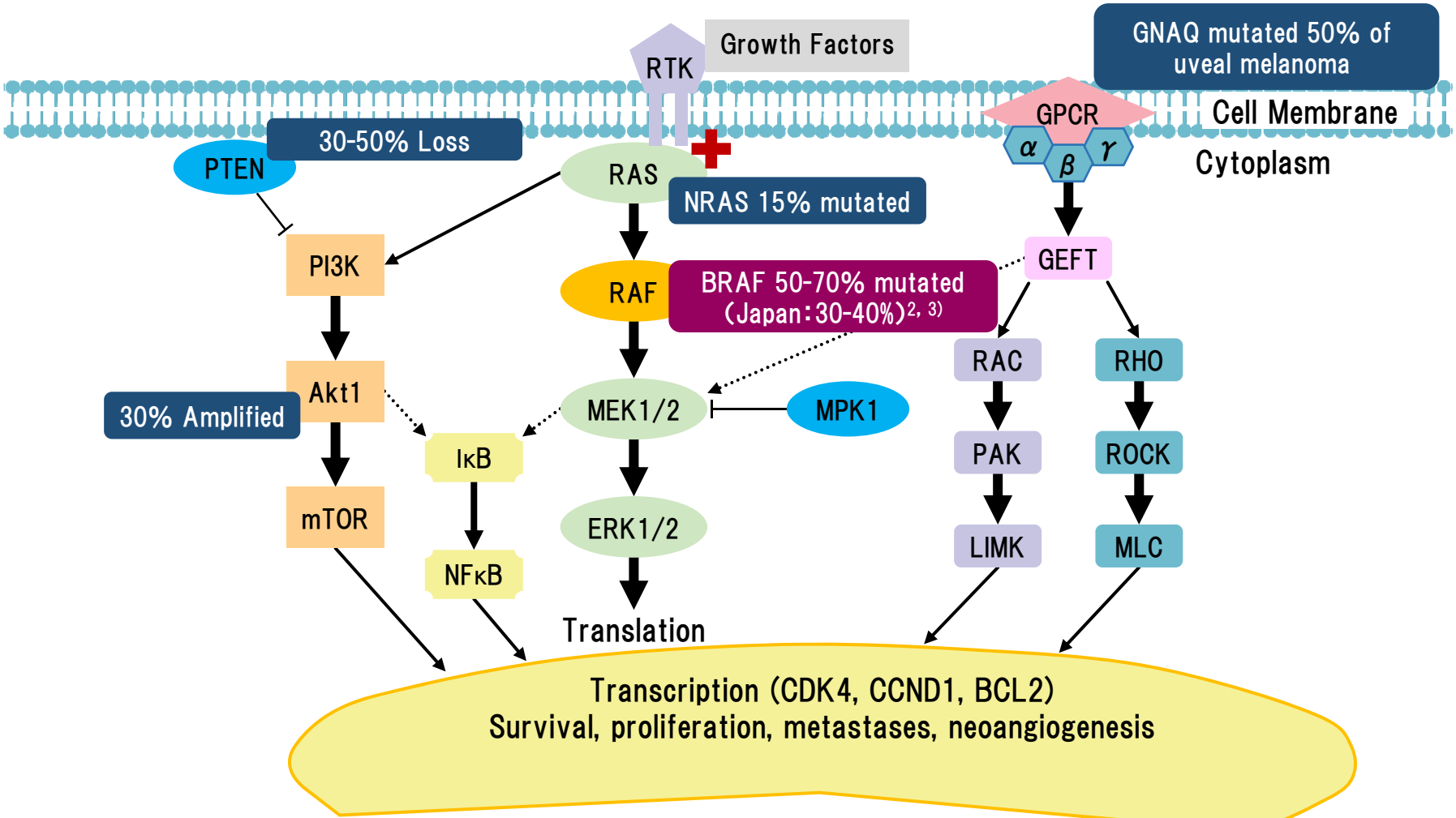


1) Japanese Classification of Skin Cancer version 2 (KANEHARA & Co., LTD) 2010, p178-179
2) Fujisawa Y. et al. Nihon Rinsho 2013, 71 (Suppl 4): 7-12

Oncogenic mutation of melanoma

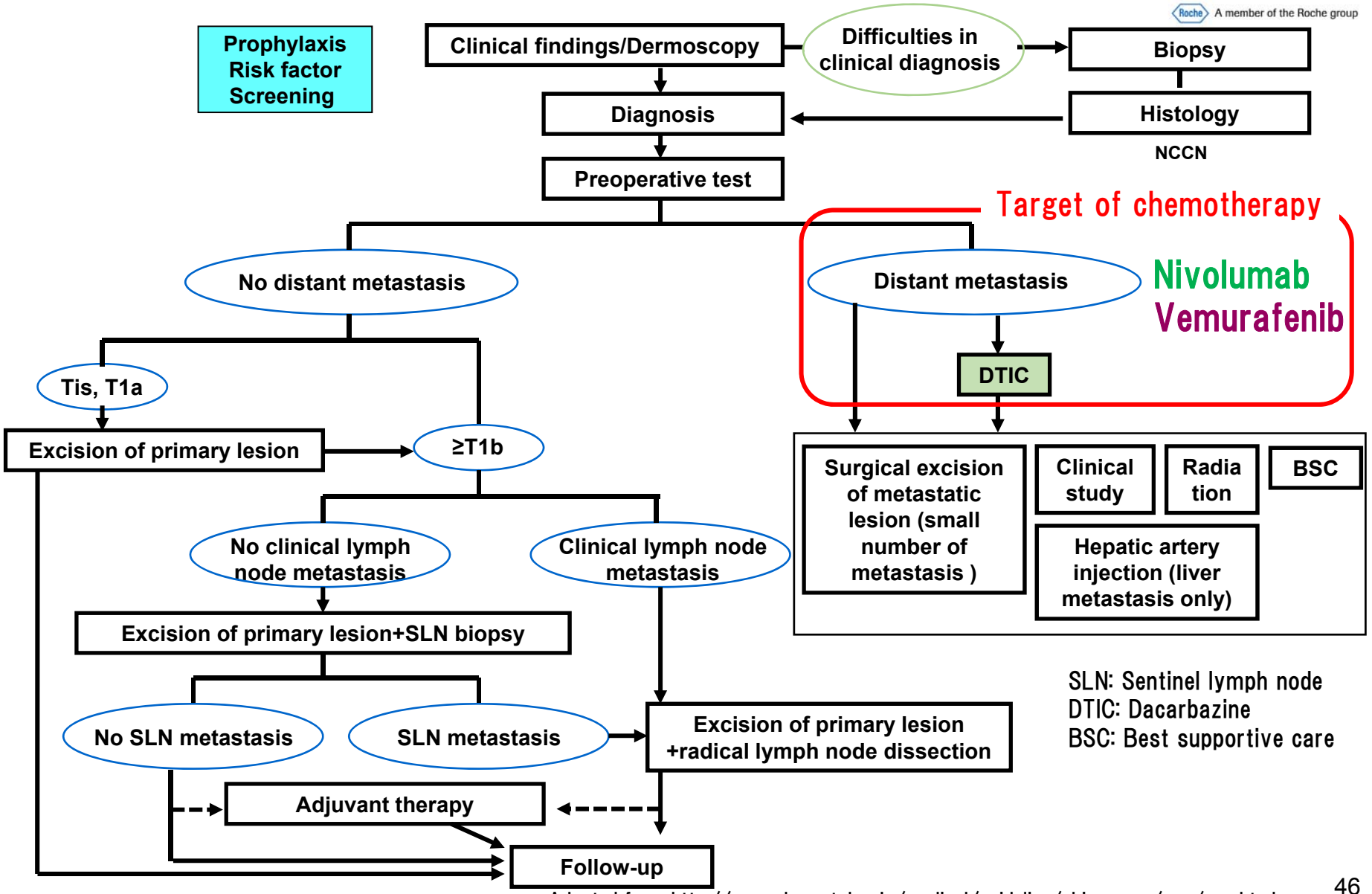
Innovation all for the patients
CHUGAI
Roche A member of the Roche group

- Major signaling pathways in melanoma and oncogenic mutation frequency[1)]



1) Bello DM, et al: Cancer Control 20: 261-281, 2013
2) Ashida A., et al.: J Dermatol Sci. 66 (3): 240-242, 2012
3) Yamazaki N., et al.: Melanoma Res. 25 (1): 9-14, 2015

Treatment algorithm for melanoma: Clinical practice guideline for skin cancer (Japan)



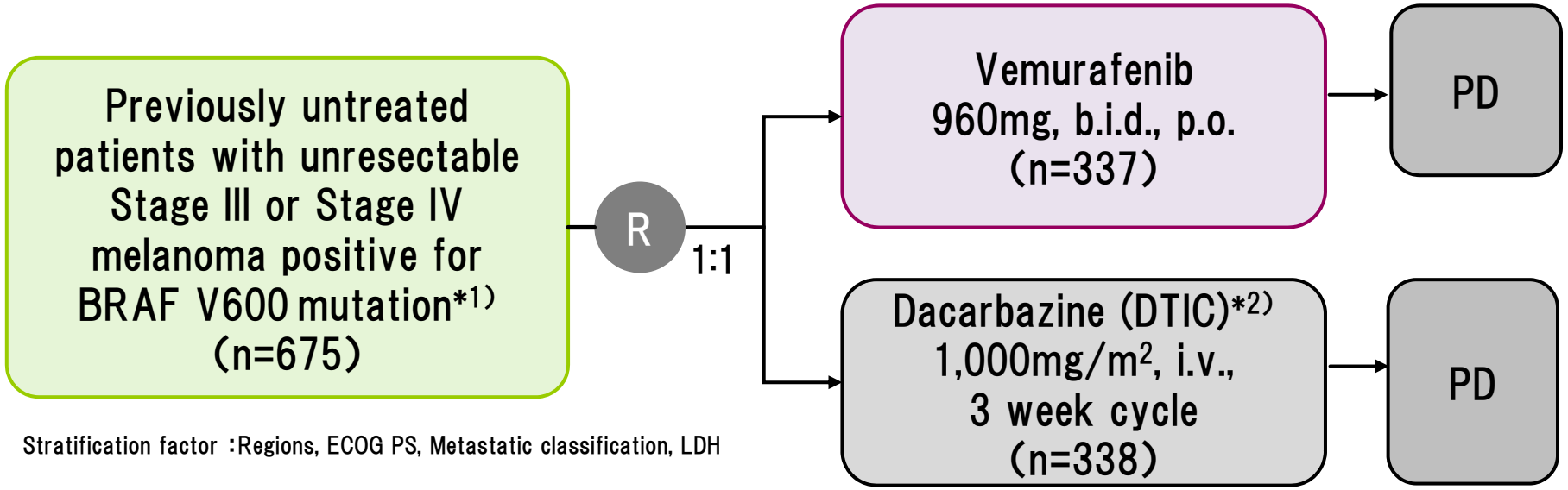
SLN: Sentinel lymph node
DTIC: Dacarbazine
BSC: Best supportive care

Adapted from http://www.dermatol.or.jp/medical/guideline/skincancer/mm/mm.html

Innovation all for the patients
CHUGAI
Roche A member of the Roche group

Overseas Phase III study (NO25026[BRIM3])

- Study design



Stratification factor :Regions, ECOG PS, Metastatic classification, LDH

*1) Determined by cobas® 4800 BRAF V600 Mutation Test approved as the companion diagnostics.
*2) This dosage and administration of DTIC is not approved in Japan.

- Primary endpoints:PFS, OS
- Secondary endpoints:Best overall response rate (BORR), Duration of response, Time to response, Safety etc.
  *Efficacy endpoints by investigator assessment

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Patient Characteristics

	DTIC (n=338)	Vemurafenib (n=337)
Male	181 (54%)	200 (59%)
Median age (range)	52.5 (17-86)	56.0 (21-86)
Metastatic Classification		
IV:M1a	40 (12%)	34 (10%)
IV:M1b	65 (19%)	62 (18%)
IV:M1c	220 (65%)	221 (66%)
Unresectable StageIIIC	13 (4%)	20 (6%)
Histological Subtypes		
SSM	109 (32%)	104 (31%)
LMM	5 (1%)	1 (<1%)
ALM	3 (<1%)	1 (<1%)
NM	78 (23%)	78 (23%)
Other	143 (42%)	153 (45%)
ECOG PS		
0	230 (68%)	229 (68%)
1	108 (32%)	108 (32%)
Serum LDH		
Normal range	196 (58%)	195 (58%)
Elevated	142 (42%)	142 (42%)

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

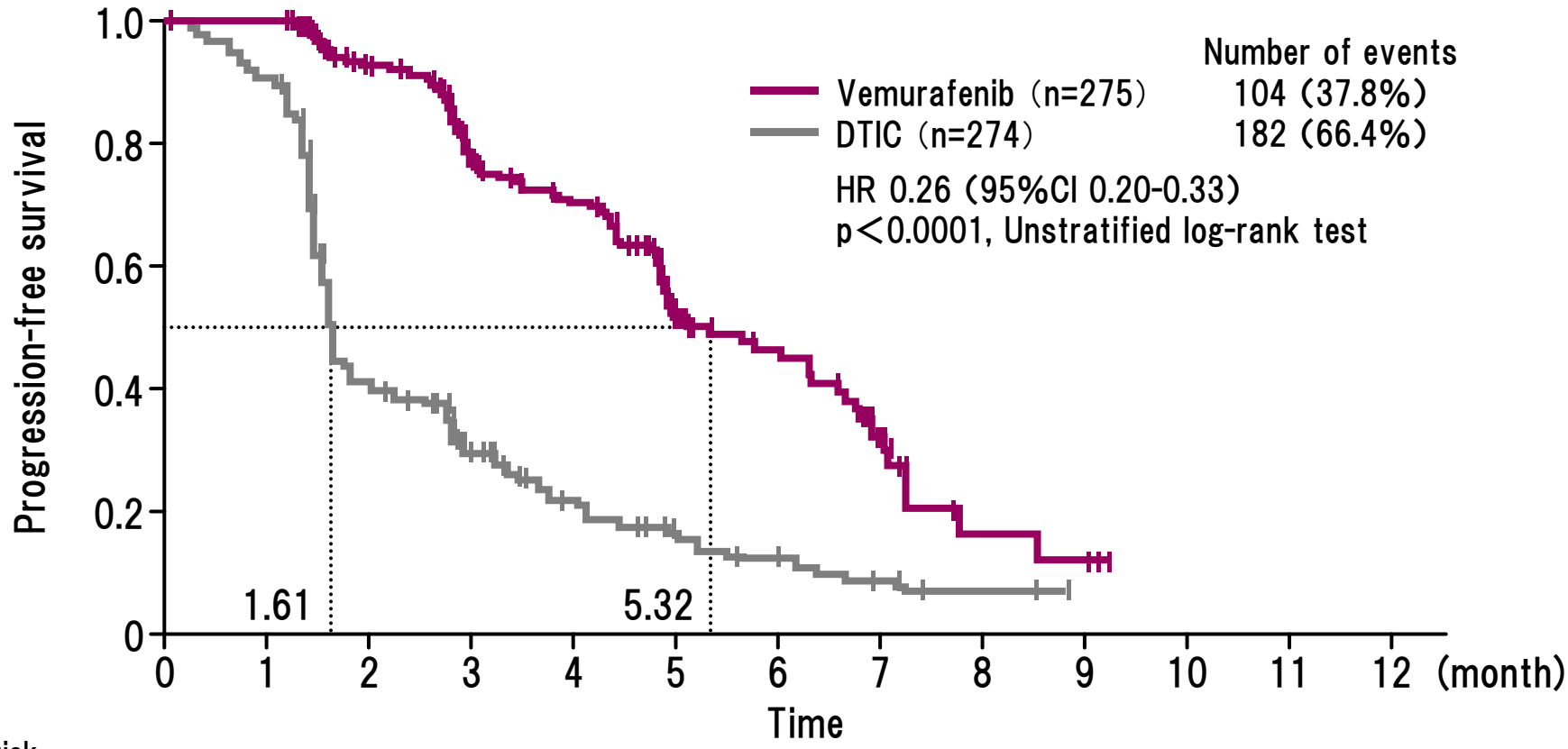
Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

PFS (at the time of primary analysis)



n at risk													
DTIC	274	213	85	48	28	16	10	6	3	0	0	0	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3	0	0	0

Investigators assessment, RECIST ver. 1.1
Data cut-off:2010/12/30

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

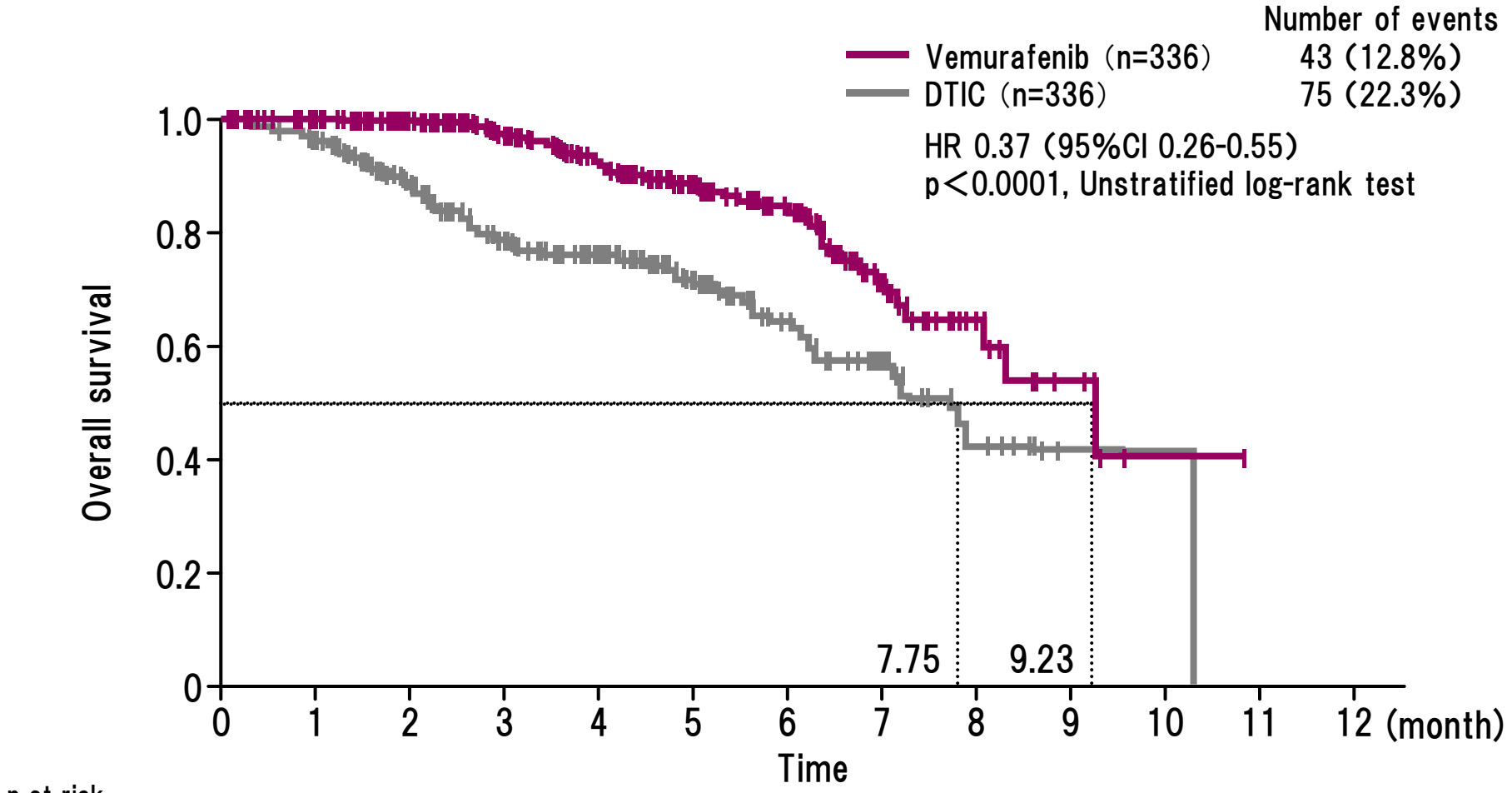
Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

OS (at the time of primary analysis)



n at risk													
DTIC	336	283	192	137	98	64	39	20	9	1	1	0	0
Vemurafenib	336	320	266	210	162	111	80	35	14	6	1	0	0

Data cut-off:2010/12/30

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Best overall response rate, Duration of response (at the time of primary analysis)

	DTIC (n=220)	Vemurafenib (n=219)	p-value (Schouten χ^2 test)
Responders Response rate (95%CI)	12 5.5% (2.8-9.3)	106 48.4% (41.6-55.2)	<0.0001
CR PR SD PD	0 (0.0%) 12 (5.5%) 53 (24.1%) 103 (46.8%)	2 (0.9%) 104 (47.5%) 81 (37.0%) 23 (10.5%)	
Median Duration of response (95%CI)	NR (4.60-NR)	5.49 month (3.98-5.72)	

NR:Not reached

Data cut-off:2010/12/30

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Phase III study (NO25026[BRIM3])

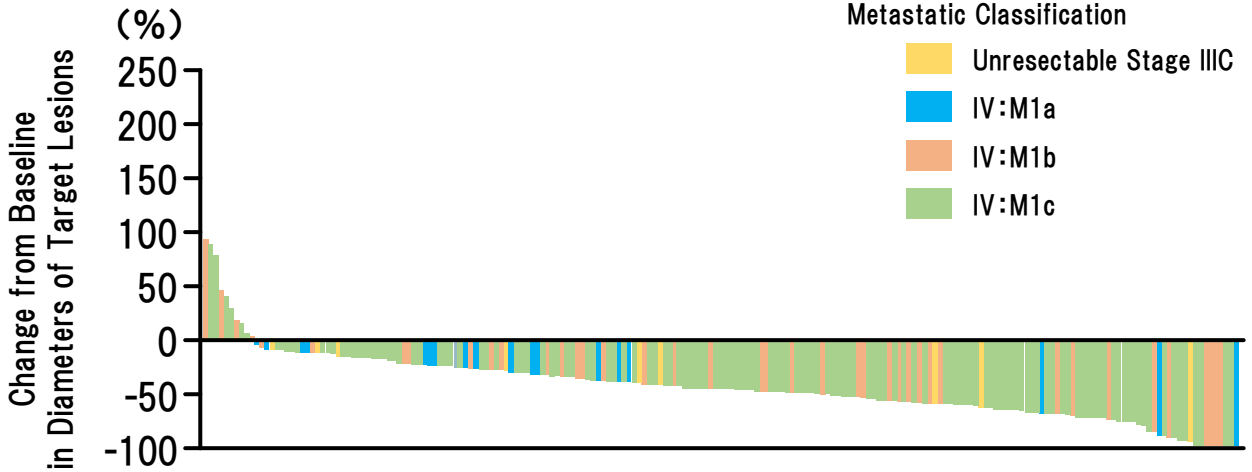
Innovation all for the patients

CHUGAI

Roche A member of the Roche group

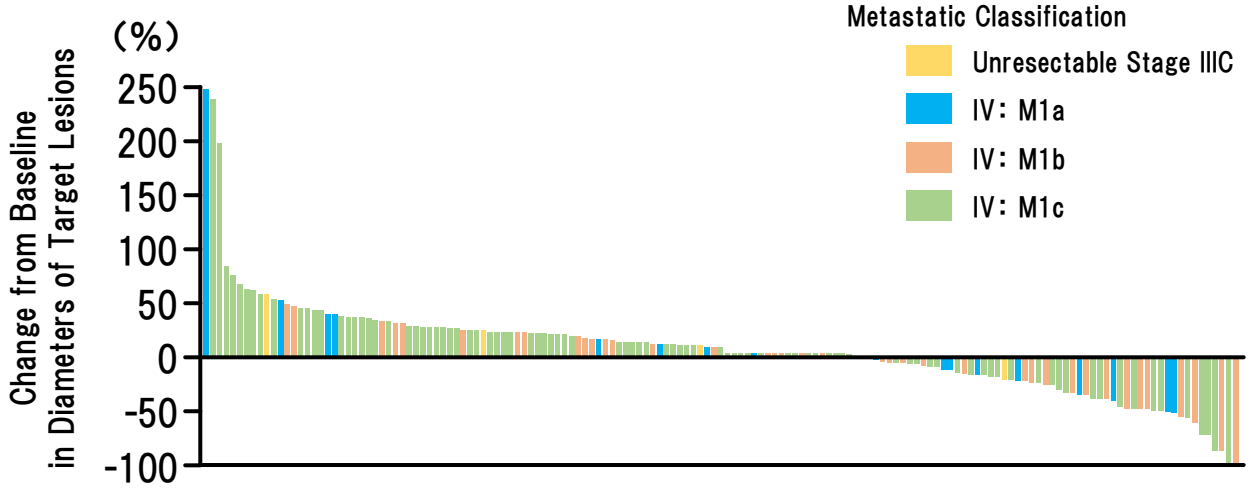
Best tumor response (at the time of primary analysis)

- Vemurafenib (n=209)



	n=219
Responders (n)	106
Response rate (%)	48.4
CR (n)	2
PR (n)	104
Median Time to response (month)	1.45

- DTIC (n=158)



	n=220
Responders (n)	12
Response rate (%)	5.5
CR (n)	0
PR (n)	12
Median Time to response (month)	2.72

Data cut-off:2010/12/30

Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Summary of safety (at the time of primary analysis)

	DTIC (n=282)	Vemurafenib (n=336)
Any AEs	253 (89.7%)	326 (97.0%)
AEs of Grade 3 and above	86 (30.5%)	168 (50.0%)
AEs of Grade 4	22 (7.8%)	13 (3.9%)
AEs of Grade 5	6 (2.1%)	6 (1.8%)
Serious AEs	45 (16.0%)	110 (32.7%)
AEs that led to discontinuation	12 (4.3%)	19 (5.7%)
AEs that led to dose modification/interruption	44 (15.6%)	129 (38.4%)
Deaths*	16 (5.5%)†	22 (6.5%)
Due to other causes besides disease progression	1 (0.3%) †	4 (1.2%)
Typical AEs associated with vemurafenib		
Cutaneous squamous cell carcinoma	1 (0.4%)	62 (18.5%)
Rash	10 (3.5%)	202 (60.1%)
Photosensitivity	10 (3.5%)	124 (36.9%)
Arthralgia	9 (3.2%)	165 (49.1%)
Fatigue	108 (38.3%)	138 (41.1%)
Abnormal liver function test	13 (4.6%)	59 (17.6%)
QT prolongation	16 (5.7%)	28 (8.3%)

* Deaths within 28 days of last dosing
† DTIC (n=289)

Data cut-off:2010/12/30

Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Phase III study (NO25026[BRIM3])

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Adverse events (incidence: ≥10%)

	DTIC (n=282)		Vemurafenib (n=336)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Total Pts with at Least one AE	253 (89.7%)	86 (30.5%)	326 (97.0%)	168 (50.0%)
Nausea	115 (40.8%)	5 (1.8%)	101 (30.1%)	4 (1.2%)
Fatigue	87 (30.9%)	5 (1.8%)	112 (33.3%)	6 (1.8%)
Arthralgia	9 (3.2%)	2 (0.7%)	165 (49.1%)	11 (3.3%)
Rash	3 (1.1%)	—	121 (36.0%)	28 (8.3%)
Alopecia	6 (2.1%)	—	117 (34.8%)	1 (0.3%)
Diarrhea	34 (12.1%)	1 (0.4%)	84 (25.0%)	2 (0.6%)
Vomiting	67 (23.8%)	3 (1.1%)	50 (14.9%)	4 (1.2%)
Photosensitivity reaction	10 (3.5%)	—	101 (30.1%)	9 (2.7%)
Headache	26 (9.2%)	—	72 (21.4%)	2 (0.6%)
Constipation	65 (23.0%)	—	32 (9.5%)	—
Pyrexia	25 (8.9%)	2 (0.7%)	59 (17.6%)	2 (0.6%)
Pruritus	4 (1.4%)	—	74 (22.0%)	5 (1.5%)
Decreased appetite	20 (7.1%)	—	53 (15.8%)	—
Hyperkeratosis	—	—	67 (19.9%)	4 (1.2%)
Edema peripheral	13 (4.6%)	—	50 (14.9%)	1 (0.3%)
Pain in extremity	17 (6.0%)	5 (1.8%)	45 (13.4%)	1 (0.3%)
Skin papilloma	—	—	62 (18.5%)	1 (0.3%)
Dry skin	3 (1.1%)	—	54 (16.1%)	—
Dysgeusia	9 (3.2%)	—	44 (13.1%)	—
Myalgia	4 (1.4%)	—	39 (11.6%)	—
Erythema	4 (1.4%)	—	38 (11.3%)	—
Cutaneous squamous cell carcinoma	1 (0.4%)	1 (0.4%)	40 (11.9%)	38 (11.3%)
Neutropenia	32 (11.3%)	24 (8.5%)	2 (0.6%)	1 (0.3%)

MedDRA ver. 13.1, NCI-CTCAE ver. 4.0 Data cut-off:2010/12/30 Chugai Internal Document; Chapman PB, et al. N Engl J Med 2011, 364: 2507-2516

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Conclusions : NO25026[BRIM3]

- Vemurafenib demonstrated superior benefit across the clinically relevant efficacy endpoints of OS, PFS and BORR compared with dacarbazine in previously untreated patients with unresectable Stage III or Stage IV melanoma positive for BRAF V600 mutation.
  - Patients who received vemurafenib had a 74 percent reduced risk of the disease progression or death, with significant prolongation of PFS compared to those who received dacarbazine.
  - The risk of death was reduced by 63 percent for people who received vemurafenib compared to those who received dacarbazine, with significant prolongation of OS.
  - There was a statistically significant improvement in BORR with vemurafenib (48.4%) compared to dacarbazine (5.5%).
- The tolerability of vemurafenib was confirmed, based on the fact that for most adverse events, patients were able to continue the treatment with vemurafenib by temporarily halting the administration of vemurafenib or changing of the dose.

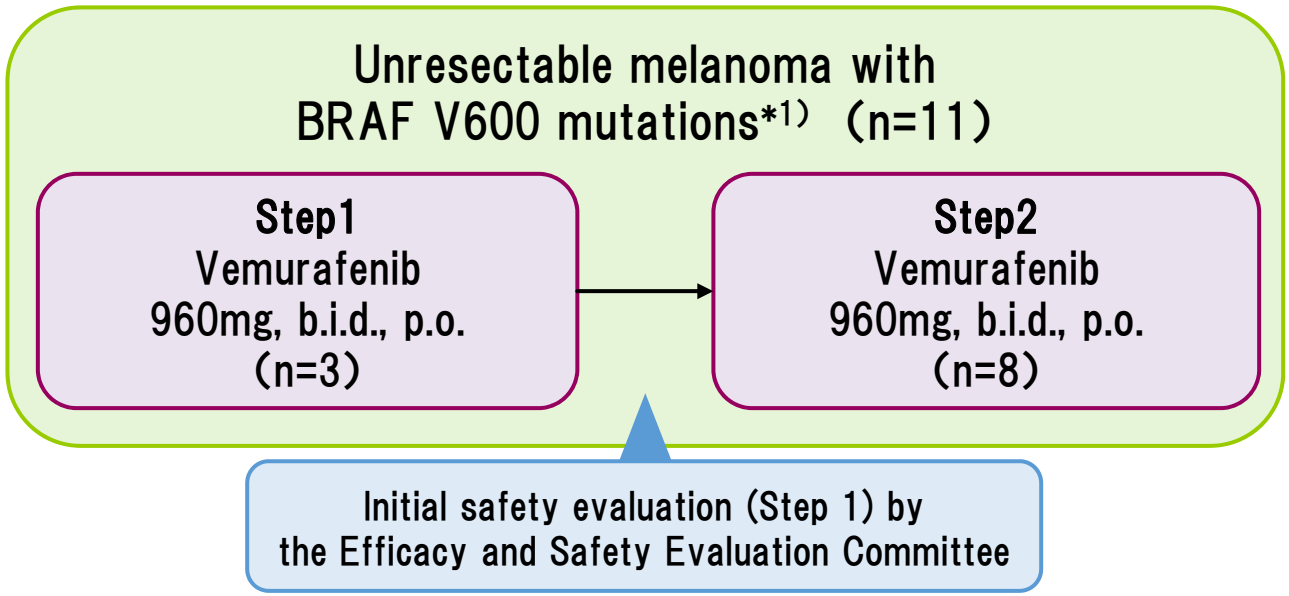
Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Japanese phase I/II study (JO28178)

- Study design



Efficacy analysis populations: 8 pts in Step2

Safety analysis populations: 11 pts in Step 1 and 2

*1) Determined by cobas® 4800 BRAF V600 Mutation Test approved as the companion diagnostics.

- Step1 (n=3)
  - Primary endpoint: Initial safety
  - Secondary endpoints: Response rate, Safety, PK, Dose intensity
- Step2 (n=8)
  - Primary endpoint: Response rate (IRC* assessment)
  - Secondary endpoints: Duration of response (IRC), Disease control rate (IRC), PFS (IRC), OS, Safety etc.

* IRC: Independent review committee

JPN Phase I/II study (JO28178)

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Patient characteristics (Steps1, 2)

		Step1 (n=3)	Step2 (n=8)
Male		2 (66.7%)	1 (12.5%)
Median age (range)		51.0 (38-68)	45.0 (23-62)
Disease Stage at relapse		n=2	n=7
	III	—	1 (14.3%)
	IV	2 (100.0%)	6 (85.7%)
Histological subtypes	SSM	1 (33.3%)	2 (25.0%)
	LMM	—	1 (12.5%)
	ALM	1 (33.3%)	1 (12.5%)
	NM	—	1 (12.5%)
	Other	1 (33.3%)	3 (37.5%)
ECOG PS	0	3 (100.0%)	6 (75.0%)
	1	—	2 (25.0%)
Serum LDH	Normal range	3 (100.0%)	5 (62.5%)
	Elevated	—	3 (37.5%)
Prior systemic treatment		3 (100.0%)	7 (87.5%)
DTIC containing treatment		3 (100.0%)	6 (75.0%)

JPN Phase I/II study (JO28178)

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Summary of efficacy (Steps1, 2)

		IRC assessment
Efficacy analysis population (n)		8
Responders (n)		6
Best overall response (n)	CR PR SD NE	0 6 1 1
Duration of response	Median* (day) [95%CI]**	59.0 [56.0-NR]
Time to response	Median* (day) [95%CI]	29.0 [27.0-29.0]
PFS	Median* (day) [95%CI]**	NR [84.0-NR]
OS	Median* (day) [95%CI]**	NR [116.0-NR]

NR:Not reached
* Kaplan-Meier estimate
** 95%CI was calculated by Brookmeyer and Crowley method

RECIST ver. 1.1
Data cut-off: 2013/8/29

JPN Phase I/II study (JO28178)

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Summary of safety (Steps1, 2)

	Vemurafenib (n=11)
Patients experience any AEs	11 (100%)
AEs of Grade 1	11 (100%)
AEs of Grade 2	7 (63.6%)
AEs of Grade 3	3 (27.3%)
AEs of Grade 4 and above	—
Serious AEs	1 (9.1%)
AEs that led to discontinuation	—
AEs that led to dose modification/interruption	6 (54.5%)
Deaths*	1 (9.1%)
Due to other causes besides disease progression	—
Typical AEs associated with vemurafenib	
Cutaneous squamous cell carcinoma	—
Rash	10 (90.9%)
Photosensitivity	3 (27.3%)
Arthralgia	10 (90.9%)
Fatigue	6 (54.5%)
Hepatic function disorder	5 (45.5%)
QT prolongation	3 (27.3%)

* Deaths within 28 days of last dosing

Data cut-off: 2013/8/29

JPN Phase I/II study (JO28178)

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Adverse events (incidence: ≥10%) (Steps1, 2)

	All Grades	≥ Grade 3
Number of patients experiencing AEs	11 (100.0%)	3 (27.3%)
Arthralgia	10 (90.9%)	—
Myalgia	7 (63.6%)	—
Alopecia	7 (63.6%)	—
Rash	5 (45.5%)	—
Maculopapular rash	5 (45.5%)	1 (9.1%)
Decreased appetite	4 (36.4%)	—
Fatigue	4 (36.4%)	—
Liver disorder	3 (27.3%)	1 (9.1%)
Malaise	3 (27.3%)	—
Photosensitivity reaction	3 (27.3%)	—
Oropharyngeal pain	3 (27.3%)	—
Erythema	3 (27.3%)	—
Headache	3 (27.3%)	—

	All Grades	≥ Grade 3
Pyrexia	3 (27.3%)	—
Nasopharyngitis	3 (27.3%)	—
Milium	3 (27.3%)	—
Insomnia	3 (27.3%)	—
Dysgeusia	3 (27.3%)	—
Nausea	2 (18.2%)	—
Hyperkeratosis	2 (18.2%)	—
Purpura	2 (18.2%)	—
Hand-foot syndrome	2 (18.2%)	—
Palmoplantar keratoderma	2 (18.2%)	—
QT prolongation	2 (18.2%)	—
Skin papilloma	2 (18.2%)	—
Edema peripheral	2 (18.2%)	—
Vomiting	2 (18.2%)	—

MedDRA ver. 15.1, NCI-CTCAE ver. 4.03

Data cut-off: 2013/8/29

Innovation all for the patients

CHUGAI

Roche A member of the Roche group

Conclusions : JO28178

- This study investigated the efficacy and safety of vemurafenib 960 mg orally administered twice daily to Japanese patients with unresectable melanoma with BRAF V600 mutations.
- An objective response was confirmed by the IRC in 6 patients in Step 2, demonstrating clinical significance.
- Vemurafenib is expected to show efficacy in Japanese melanoma patients.
- No patients in the safety analysis (Steps1 and 2) discontinued treatment due to AE, demonstrating tolerability.

Contacts

CHUGAI PHARMACEUTICAL CO., LTD.

Corporate Communications Dept.

Media Relations Group

Tel: +81 (0)3-3273-0881 Fax: +81 (0)3-3281-6607
e-mail: pr@chugai-pharm.co.jp
Koki Harada, Hiroshi Araki, Sachiyo Yoshimura, Chisato Miyoshi

Investor Relations Group

Tel: +81 (0)3-3273-0554 Fax: +81 (0)3-3281-6607
e-mail: ir@chugai-pharm.co.jp
Toshiya Sasai, Takayuki Sakurai, Tomoko Shimizu, Yusuke Tokita

Roche Diagnostics K.K.

Corporate Planning & Administration
Communications

Tel: +81 (0)3-5443-7040 Fax: +81 (0)3-5443-7113
e-mail: tokyo.pr@roche.com
Michi Arakawa, Tomomi Kawaguchi