

# **FY2013 2Q Consolidated Financial Overview (IFRS based)**

CHUGAI PHARMACEUTICAL CO., LTD.  
Executive Vice President CFO  
Yoshio Itaya

July 25/26, 2013



# Forward-Looking Statements

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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.



# Summary

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## ■ Revenues: 201.0 billion JPY (+8.4% YoY)

- Domestic sales excl. TAM (+1.0%) : continued strong growth in oncology and new products more than offset the impact from termination of Evista and the NHI price revision
- Overseas sales: approx. 30% increase due to weak yen and growth in Actemra export
- Royalties and other operating income: more than doubled driven by milestone income

## ■ Expenses

- Double-digit increase results from negative foreign exchange impact on expenses of overseas sales subsidiaries and R&D expenses

## ■ Profits

- IFRS based profits: operating profit 38.1 billion JPY (+4.7%), net income 25.3 billion JPY (+15.0%)
- Core operating profit: 38.7billion JPY (+4.9%)
- Core EPS: 46.06 JPY (+14.4%)



# IFRS and Core Results Jan - Jun

Billions of JPY	2013 Jan - Jun	Non-core items		Core results 2013 Jan - Jun	<b>Non-Core items</b> 1. Intangible/Business combinations Amortization of intangible assets: +0.5bn JPY No impairment of intangible assets No business combinations 2. Other eliminated items Restructuring: +0.2bn JPY Environmental costs: -0.1 bn JPY Legal costs: immaterial (Billions of JPY) Core net income attributable to Chugai shareholders 25.1
		Intangible assets and Business combinations	Other eliminated items		
<b>Revenues</b>	<b>201.0</b>			<b>201.0</b>	
Sales	188.8			188.8	
Royalties and other operating income	12.2			12.2	
Cost of sales	-88.3	+0.4		-87.9	
<b>Gross profit</b>	<b>112.7</b>	<b>+0.4</b>		<b>113.1</b>	
<b>Operating expenses</b>	<b>-74.6</b>	<b>+0.0</b>	<b>+0.1</b>	<b>-74.4</b>	
Marketing and distribution	-34.1	+0.0	+0.1	-34.0	
Research and development	-34.9	+0.0	+0.1	-34.8	
General and administration	-5.6		-0.1	-5.7	
<b>Operating profit</b>	<b>38.1</b>	<b>+0.5</b>	<b>+0.1</b>	<b>38.7</b>	(Millions of shares)
Financing costs	-0.0			-0.0	
<b>Other financial income (expense)</b>	<b>-1.2</b>			<b>-1.2</b>	
<b>Profit before taxes</b>	<b>36.9</b>	<b>+0.5</b>	<b>+0.1</b>	<b>37.5</b>	
Income taxes	-11.7	-0.2	-0.0	-11.9	
<b>Net income</b>	<b>25.3</b>	<b>+0.3</b>	<b>+0.1</b>	<b>25.6</b>	
Chugai shareholders	24.7	+0.3	+0.1	25.1	(JPY)
Non-controlling interests	0.5			0.5	
					Core EPS 46.06

## Year on Year (Core)

## Financial Overview Jan - Jun



(Billion JPY)	2012 Jan - Jun vs. Rev*.		2013 Jan - Jun vs. Rev*.		Growth	
<b>Revenues</b>	<b>185.5</b>		<b>201.0</b>		<b>+15.5</b>	<b>+8.4%</b>
Sales	180.1		188.8		+8.7	+4.8%
excl. Tamiflu	171.9		179.8		+7.9	+4.6%
Domestic	150.5		152.0		+1.5	+1.0%
Export to Roche	13.4		18.4		+5.0	+37.3%
Other overseas	8.1		9.4		+1.3	+16.0%
Tamiflu	8.1		9.0		+0.9	+11.1%
Ordinary	7.8		8.2		+0.4	+5.1%
Stockpiling	0.4		0.8		+0.4	+100.0%
Royalties and other operating income	5.4		12.2		+6.8	+125.9%
Cost of sales	-81.3	43.8%	-87.9	43.7%	-6.6	+8.1%
<b>Gross profit</b>	<b>104.2</b>	<b>56.2%</b>	<b>113.1</b>	<b>56.3%</b>	<b>+8.9</b>	<b>+8.5%</b>
Operating expenses	-67.3	36.3%	-74.4	37.0%	-7.1	+10.5%
<b>Operating profit</b>	<b>36.9</b>	<b>19.9%</b>	<b>38.7</b>	<b>19.3%</b>	<b>+1.8</b>	<b>+4.9%</b>
Financing costs	-0.0		-0.0		+0.0	0.0%
Other financial income (expense)	-1.2		-1.2		+0.0	0.0%
Taxes	-13.3		-11.9		+1.4	-10.5%
<b>Net income</b>	<b>22.3</b>	<b>12.0%</b>	<b>25.6</b>	<b>12.7%</b>	<b>+3.3</b>	<b>14.8%</b>

(Billion JPY)

Royalties and other operating income

+6.8

Milestone income increased

Financing costs

+0.0

Other financial income (exp.)

+0.0

Exchange gains/losses

-3.0

Gains/Losses on derivatives

+3.0

Cost of sales ratio vs. Sales

	2012 Jan - Jun	2013 Jan - Jun
	45.1%	46.6%

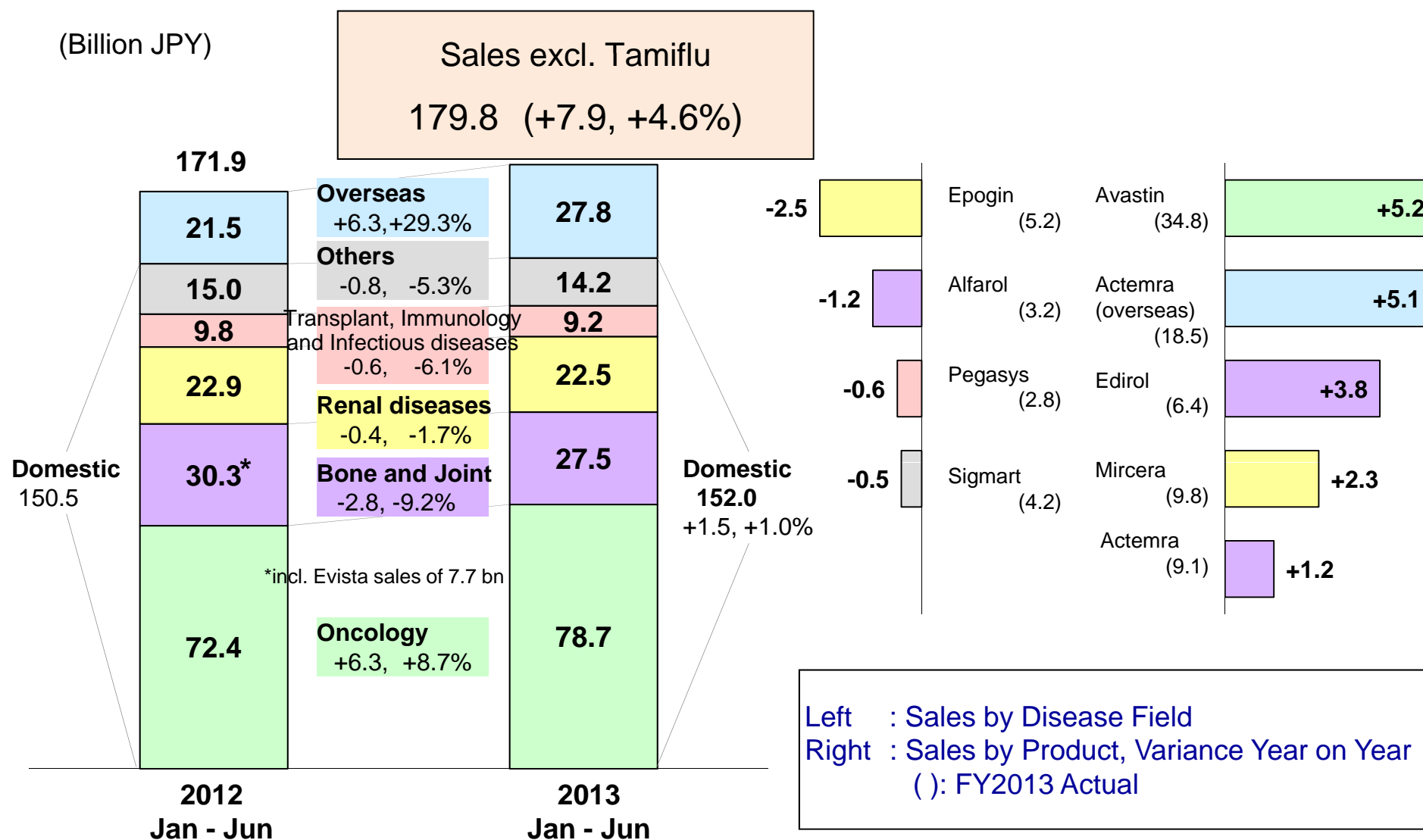
Average exchange rate (JPY)

	2012 Jan - Jun	2013 Jan - Jun
CHF	85.82	101.94
EUR	103.39	125.33

\*Revenues

Year on Year

## Sales (excl. Tamiflu) Jan - Jun





# Tamiflu Sales Performance

(Billion JPY)		Fiscal Term Sales									Seasonal Sales	Cases per sentinel* (millions)
		FY2009.12		FY2010.12		FY2011.12		FY2012.12		FY2013.12		
		Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun		
Ordinary	2008-09	11.0									16.7	1.27
	2009-10		25.2	1.4							26.6	2.02
	2010-11				0.2	4.1					4.3	1.26
	2011-12						1.3	7.8			9.1	1.63
	2012-13								2.4	8.2	10.6	1.11
Ordinary		36.2	(+29.1)	1.6	(-34.6)	5.4	(+3.8)	10.2	(+4.8)			
Govt. Stockpile etc.	2008-09	14.4									15.5	
	2009-10		25.6	10.6							36.2	
	2010-11				5.9	0.5					6.4	
	2011-12						2.8	0.4			3.2	
	2012-13								1.5	0.8	2.3	
Govt. Stockpile etc.		40.0	(+38.7)	16.6	(-23.4)	3.3	(-13.3)	1.9	(-1.4)			
Total		25.4	50.8	12.0	6.1	4.6	4.1	8.1	3.9	9.0		
		76.2	(+67.8)	18.2	(-58.0)	8.7	(-9.5)	12.0	(+3.3)			

\*Total patient number of the controlled samples in the infectious Diseases Weekly Report, period between late October and mid-April (between early July 2009 and mid-March 2010 for 2009/2010), published by Japan's National Institute of Infectious Diseases.

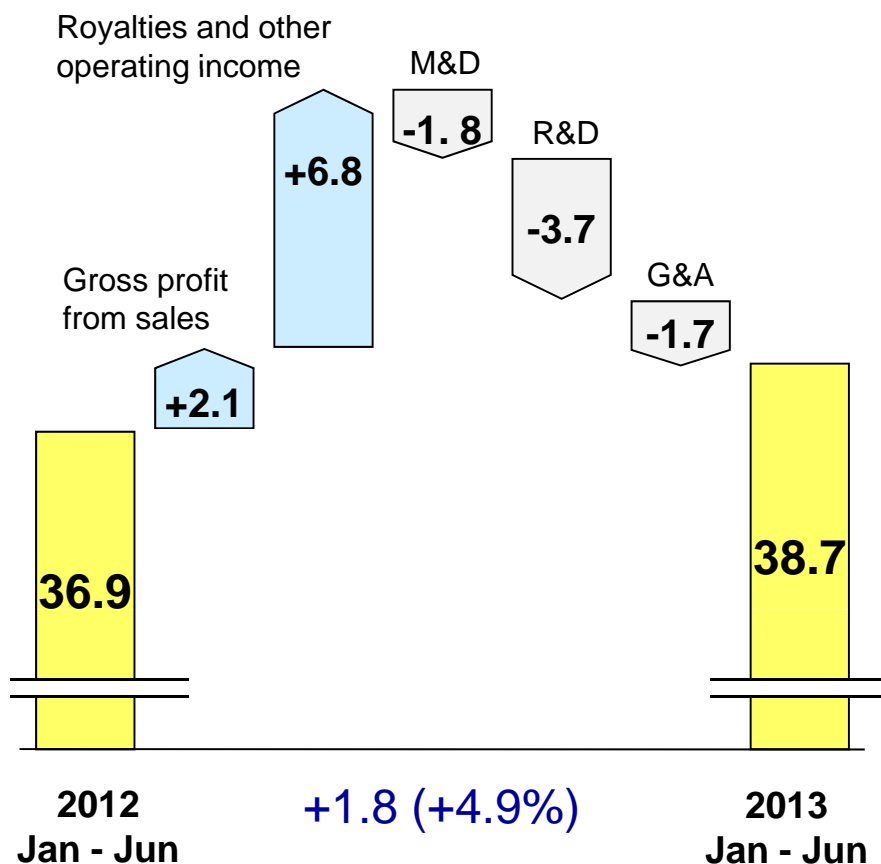
( ) Year on year

## Year on Year (Core)

## Operating Profit Jan - Jun



(Billion JPY)



(Billion JPY)	2012 Jan - Jun	2013 Jan - Jun	Growth
<b>Revenues</b>	<b>185.5</b>	<b>201.0</b>	<b>+15.5</b>
Cost of sales	-81.3	-87.9	-6.6
<b>Gross profit</b>	<b>104.2</b>	<b>113.1</b>	<b>+8.9</b>
Sales	98.8	100.9	+2.1
Royalties, etc.	5.4	12.2	+6.8
Marketing and distribution	-32.2	-34.0	-1.8
Research and development	-31.1	-34.8	-3.7
General and administration	-4.0	-5.7	-1.7
<b>Operating profit</b>	<b>36.9</b>	<b>38.7</b>	<b>+1.8</b>

Increase in gross profit from sales	+2.1
Increase in new products and Actemra overseas	
Increase in royalties and other operating income	+6.8
Increase in marketing and distribution	-1.8
Negative foreign exchange impact on expenses of overseas sales subsidiaries, etc	
Increase in research and development	-3.7
Negative foreign exchange impact and full-fledged operation of CPR*, etc	
Increase in general and administration	-1.7

\*Chugai Pharmabody Research: antibody research center in Singapore



## Year on Year (Core)



# Financial Overview Apr - Jun

(Billion JPY)	2012 Apr - Jun <small>vs. Rev*</small>		2013 Apr - Jun <small>vs. Rev*</small>		Growth	
<b>Revenues</b>	<b>95.2</b>		<b>110.6</b>		<b>+15.4</b>	<b>+16.2%</b>
Sales	93.3		101.8		+8.5	+9.1%
excl. Tamiflu	93.0		101.1		+8.1	+8.7%
Domestic	82.4		83.2		+0.8	+1.0%
Export to Roche	6.6		13.3		+6.7	+101.5%
Other overseas	4.1		4.6		+0.5	+12.2%
Tamiflu	0.3		0.7		+0.4	+133.3%
Ordinary	0.3		0.7		+0.4	+133.3%
Stockpiling	-		-		-	-
Royalties and other operating income	1.9		8.8		+6.9	+363.2%
Cost of sales	-41.9	44.0%	-47.3	42.8%	-5.4	+12.9%
<b>Gross profit</b>	<b>53.2</b>	<b>55.9%</b>	<b>63.3</b>	<b>57.2%</b>	<b>+10.1</b>	<b>+19.0%</b>
Operating expenses	-34.5	36.2%	-39.6	35.8%	-5.1	+14.8%
<b>Operating profit</b>	<b>18.8</b>	<b>19.7%</b>	<b>23.6</b>	<b>21.3%</b>	<b>+4.8</b>	<b>+25.5%</b>
Financing costs	-0.0		-0.0		+0.0	-
Other financial income (expense)	-0.9		-0.2		+0.7	-77.8%
Taxes	-6.6		-7.3		-0.7	+10.6%
<b>Net income</b>	<b>11.3</b>	<b>11.9%</b>	<b>16.2</b>	<b>14.6%</b>	<b>+4.9</b>	<b>43.4%</b>

(Billion JPY)

Royalties and other operating income

+6.9

Milestone income increased

Expenses

-5.1

M&amp;D

-1.2

FX impact, promotions for new products, etc

R&amp;D

-3.0

FX impact, CPR, facility-related expenses, etc

G&amp;A

-1.0

Increase in activities

Cost of sales ratio vs. Sales

2012 Apr - Jun	2013 Apr - Jun
44.9%	46.5%

\*Revenues

vs. Forecast (Core)



# Financial Overview Jan - Jun

(Billion JPY)	Actual	Forecast on Jan 30		2012
	2013 Jan - Jun	2013 Jan - Dec	Progress	Progress*
<b>Revenues</b>	<b>201.0</b>	<b>416.0</b>	<b>48.3%</b>	<b>48.0%</b>
Sales	188.8	394.3	47.9%	48.0%
excl. Tamiflu	179.8	385.5	46.6%	47.3%
Domestic	152.0	329.3	46.2%	46.9%
Export to Roche	18.4	40.6	45.3%	52.3%
Other overseas	9.4	15.6	60.3%	48.5%
Tamiflu	9.0	8.8	102.3%	67.5%
Royalties and other operating income	12.2	21.7	56.2%	47.8%
Cost of sales	-87.9	-183.2	48.0%	48.6%
<b>Gross profit</b>	<b>113.1</b>	<b>232.8</b>	<b>48.6%</b>	<b>47.5%</b>
Operating expenses	-74.4	-155.3	47.9%	46.8%
<b>Operating profit</b>	<b>38.7</b>	<b>77.5</b>	<b>49.9%</b>	<b>48.8%</b>
EPS (JPY)	46.06	92.57	49.8%	47.0%

\*Jan - Jun progress versus Jan - Dec

vs. Forecast



# Domestic Sales (excl. Tamiflu) Jan - Jun

(Billion JPY)	Actual 2013 Jan - Jun	Forecast on Jan 30 2013 Jan - Dec	Progress	2012 Progress*
<b>Domestic sales excl. Tamiflu</b>	<b>152.0</b>	<b>329.3</b>	<b>46.2%</b>	<b>46.9%</b>
<b>Oncology</b>	<b>78.7</b>	<b>175.4</b>	<b>44.9%</b>	<b>46.4%</b>
Avastin	34.8	76.6	45.4%	45.2%
Herceptin	14.4	30.4	47.4%	47.0%
Xeloda	5.5	13.9	39.6%	47.7%
Tarceva	4.6	11.0	41.8%	47.4%
<b>Bone and Joint</b>	<b>27.5</b>	<b>54.3</b>	<b>50.6%</b>	<b>45.7%</b>
Actemra	9.1	19.1	47.6%	46.2%
Edirol	6.4	11.0	58.2%	32.9%
<b>Renal</b>	<b>22.5</b>	<b>52.0</b>	<b>43.3%</b>	<b>47.6%</b>
Mircera	9.8	28.2	34.8%	42.1%
Epogin	5.2	8.6	60.5%	53.1%
<b>Transp., Immun., Infectious</b>	<b>9.2</b>	<b>18.1</b>	<b>50.8%</b>	<b>48.3%</b>
Pegasys	2.8	5.7	49.1%	49.3%
Copegus	0.7	1.2	58.3%	50.0%
<b>Others</b>	<b>14.2</b>	<b>29.6</b>	<b>48.0%</b>	<b>49.8%</b>

\* Jan - Jun progress versus Jan - Dec

vs. Forecast (Core)

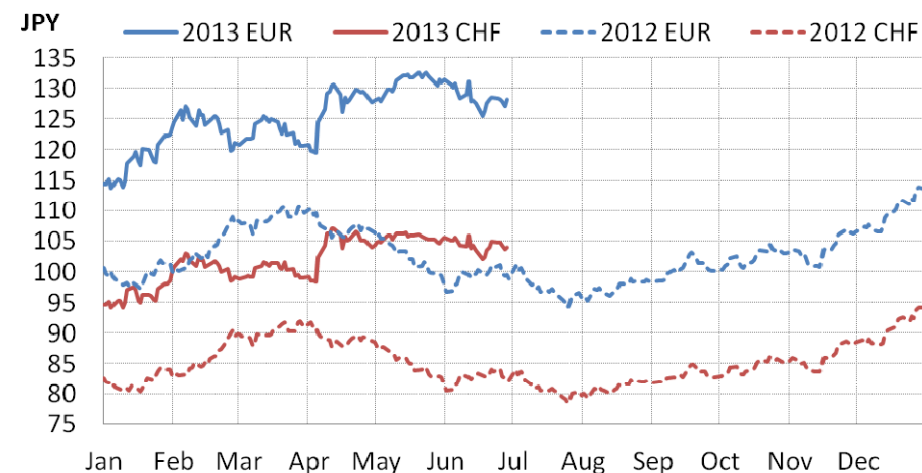


# Impact from Foreign Exchange

(Billion JPY)	FX impact Jan - Jun (vs. Forecast on Jan. 30)	
Revenues	<b>+2.4</b>	
	Actemra (Export)	+1.3
	Neutrogin (Overseas)	+0.6
	Other products, royalties, etc	+0.5
Cost of sales	Cost of sales	-2.2
Operating expenses	Expenses	-0.7
<b>Operating Profit</b>	<b>-0.5</b>	

FX rate to the JPY	1CHF	1EUR
Assumption Jan – Dec (as of Jan. 30)	95.00	115.00
Actual Jan – Jun avg.	101.94	125.33
Reference Actual Jan – Jun avg. (2012)	85.82	103.39

[Reference]  
Historical exchange rates to the JPY (Jan - Jun)



vs. 2012 Year End



# Balance Sheet Items

(Billion JPY)	2013 Dec	2013 Jun	Change
Trade accounts receivable	115.7	109.2	- 6.5
Inventories	108.4	114.1	+ 5.7
Trade accounts payable	-41.8	-33.6	+ 8.2
Other net working capital	-24.4	-18.6	+ 5.8
<b>Net working capital</b>	<b>157.9</b>	<b>171.1</b>	<b>+ 13.2</b>
Property, plant and equipment	143.1	139.9	- 3.2
Intangible assets	6.5	7.2	+ 0.7
Other long-term assets -net	0.4	-2.1	- 2.5
<b>Long-term net operating assets</b>	<b>150.0</b>	<b>145.0</b>	<b>- 5.0</b>
<b>Net operating assets</b>	<b>307.9</b>	<b>316.1</b>	<b>+ 8.2</b>
Debt	-0.3	-0.3	0.0
Marketable securities	116.5	122.9	+ 6.4
Cash and cash equivalents	95.4	100.5	+ 5.1
<b>Net cash</b>	<b>211.7</b>	<b>223.2</b>	<b>+ 11.5</b>
Other non-operating assets - net	9.6	9.6	0.0
<b>Net non-operating assets</b>	<b>221.3</b>	<b>232.7</b>	<b>+ 11.4</b>
<b>Total net assets</b>	<b>529.2</b>	<b>548.8</b>	<b>+ 19.6</b>
<b>Total net assets</b>	<b>529.2</b>	<b>548.8</b>	<b>+ 19.6</b>
Total assets	645.3	654.5	+ 9.2
Total liabilities	-116.2	-105.7	+ 10.5

Other net working capital: accrued payable, accrued expenses etc

Other long-term assets: long term prepaid expenses, deferred income etc.

Other long-term non-operating assets: deferred income tax assets, accrued corporate tax.

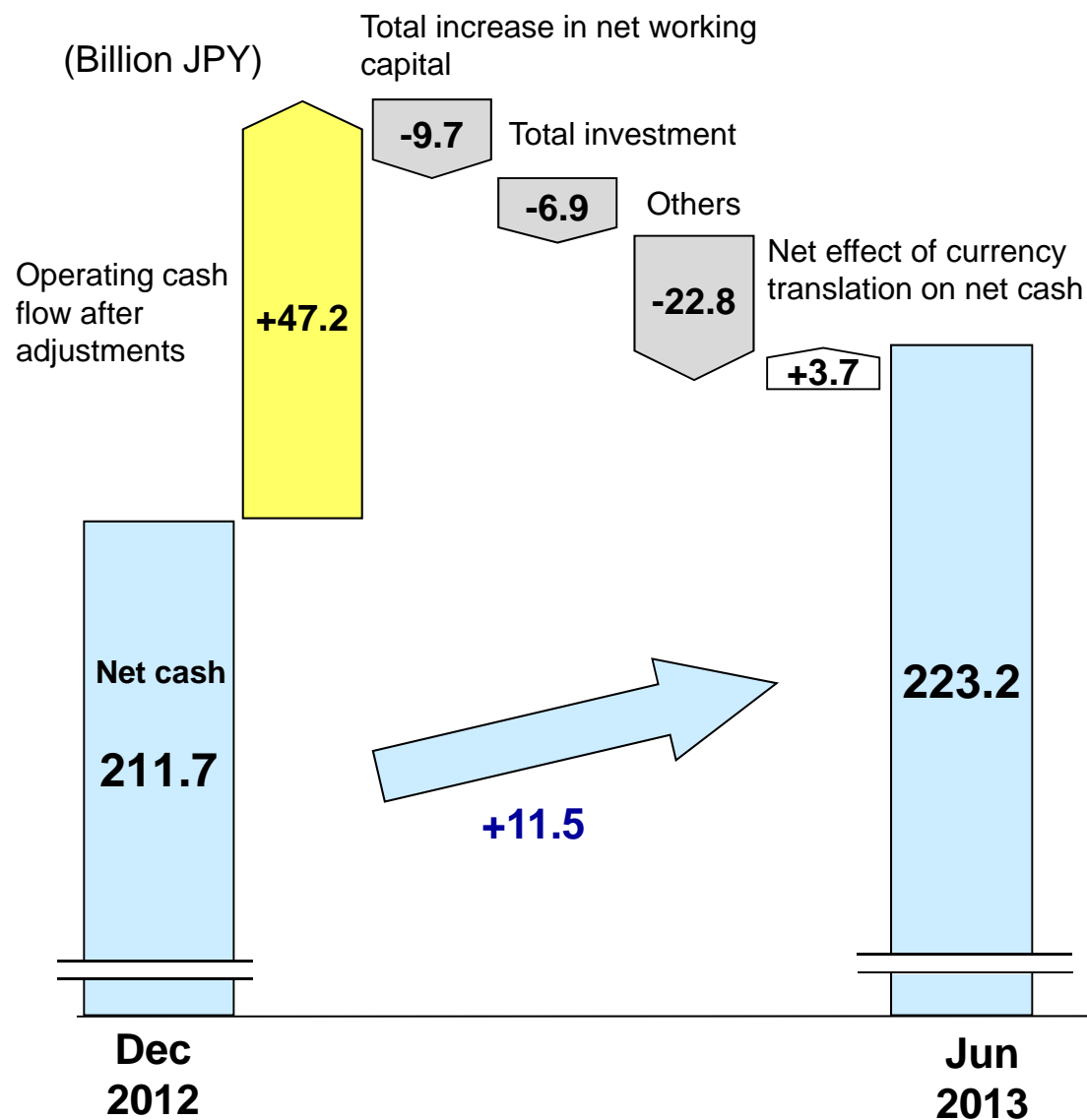
Net working capital	+13.2
Trade accounts receivable	
Seasonal change	-6.5
Inventories	+5.7
Increase in demand and in safety stocks to ensure stable supply, and FX impact	
Trade accounts payable	+8.2
Procurement timing	
Long-term net operating assets -	5.0
Property, plant and equipment	-3.2
Net cash	+11.5

Equity ratio attributable to Chugai shareholders	+1.8%pts
2013 Jun	83.6%
2012 Dec	81.8%

Actual 2013



# Net Cash Jan - Jun



Operating cash flow after adjustments  
+47.2

Total increase in net working capital -9.7  
Seasonal change for AR and increase in  
procurement payments

Decrease in trade accounts receivable  
+6.8

Increase in inventories  
-6.1

Decrease in trade accounts payable  
-8.4

Total investment -6.9  
Investment in PPE -6.5

Mainly maintenance expenditures for R&D  
equipment and plant production machinery

Others -22.8  
Tax paid -11.9  
Dividends paid -11.4



Year on Year

# Free Cash Flow Jan - Jun

(Billion JPY)	2012 Jan-Jun	2013 Jan-Jun	Change
<b>Operating profit - IFRS basis</b>	36.4	38.1	+1.7
Depreciation and impairment of PPE	6.4	7.2	+0.8
Amortization and impairment of intangible assets	0.4	0.5	+0.1
Other cash adjustment on operating profit	-1.7	1.3	+3.0
<b>Operating cash flow after adjustments</b>	41.5	47.2	+5.7
Increase (-) / decrease in trade accounts receivable	11.7	6.8	-4.9
Increase (-) / decrease in inventories	4.7	-6.1	-10.8
Increase / decrease (-) in trade accounts payable	9.4	-8.4	-17.8
Other change in net working capitals	-3.0	-1.9	+1.1
<b>Total increase (-) / decrease in net working capital</b>	22.8	-9.7	-32.5
Investment in PPE*	-7.1	-6.5	+0.6
Investment in intangible assets	-0.3	-0.4	-0.1
<b>Total investment</b>	-7.4	-6.9	+0.5
<b>Operating free cash flow</b>	56.9	30.6	-26.3
<b>as % of revenues</b>	30.7%	15.2%	-15.5%pts
Treasury activities	-0.1	0.5	+0.6
Tax paid	-13.9	-11.9	+2.0
Dividends paid	-11.3	-11.4	-0.1
<b>Free cash flow</b>	31.5	7.8	-23.7
Transaction in own equity instruments	-0.0	0.6	+0.6
Net effect of currency translationactions on net cash	-0.3	3.1	+3.4
<b>Net change in net cash</b>	31.2	11.5	-19.7

Treasury activities: interest income/expenses, foreign exchange gains/losses etc.

\*Property, plant and equipment

Operating cash flow after adjustments

+5.7

Milestone income increased

Total increase (-) / decrease in net working capital

-32.5

Increase in procurement payments

Increase (-) / decrease in inventories

-10.8

Increase / decrease (-) in trade accounts payable

-17.8

Total investment

+0.5

Operating free cash flow

-26.3

Increase in procurement payment due to increase in demand and in safety stocks to ensure stable supply, and FX impact

Operating free cash flow as % of revenues

-15.5%pts

Revenues

+15.5

# Overview of Development Pipeline

CHUGAI PHARMACEUTICAL CO., LTD.

Senior Vice President

Head of Project & Lifecycle Management Unit

Yutaka Tanaka

July 25/26, 2013





# Projects under Development (as of 25 July, 2013)

	Phase I	Phase II	Phase III	Filed
Oncology	<b>CIF/RG7167 (Japan/overseas)</b> - solid tumors <b>CKI27/RG7304 (Japan/overseas)</b> - solid tumors <b>PA799 (overseas)</b> - solid tumors RG7414/parsatuzumab - solid tumors RG7321/pictilisib - solid tumors★	RG3502 /trastuzumab emtansine - GC (PII/III) <b>GC33/RG7686</b> - LC RG340/Xeloda - aGC <b>AF802/RG7853 (Japan/overseas)</b> - NSCLC (PI/II) RG7204/vemurafenib - melanoma (PI/II)★	RG1273/Perjeta - aBC - GC★ RG435/Avastin - aBC RG3638/onartuzumab - NSCLC GA101 (RG7159) /obinutuzumab - NHL	RG435/Avastin - OC RG3502 /trastuzumab emtansine - BC

Letters in orange: in-house projects ★: Projects with advances in stages since 25 April, 2013



# Projects under Development (as of 25 July, 2013)

	Phase I	Phase II	Phase III	Filed
Bone & Joint			RG484/Bonviva (oral) - osteoporosis NRD101/Suvenyl - enthesopathy	
Autoimmune	SA237 - RA RG7415/rontalizumab - SLE	MRA/Actemra (overseas) - systemic sclerosis★	MRA/Actemra (overseas) - giant cell arteritis★	MRA/Actemra (overseas) - RA (sc)
CNS	RG1450/gantenerumab - alzheimer's disease RG1577 - alzheimer's disease★	RG7090 - major depressive disorder	RG1678/bitopertin - schizophrenia	
Others	RG3637/lebrikizumab (overseas) - asthma CIM331 - atopic dermatitis ACE910 - hemophilia A RG7652 (overseas) - hyperlipidemia URC102 (South Korea) - gout★			CSG452/tofogliflozin - Type 2 diabetes★

Letters in orange: in-house projects ★: Projects with advances in stages since 25 April, 2013

★: The applications for approval were filed by Sanofi K.K. and Kowa Company, Ltd., respectively.



# Development Status - Oncology Field

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In-  
licensed

## RG1415 / Tarceva® :

- Indication: Chemotherapy-Naïve, Unresectable, Recurrent/Advanced Non-Small Cell Lung Cancer (NSCLC) with *EGFR* Mutations  
Approved in June 2013

In-  
licensed

## RG1273 / Perjeta® :

- Indication: HER2-Positive Inoperable or Recurrent Breast Cancer  
Approved in June 2013
- Expected Indication: Gastric Cancer  
Started Global P3 in July 2013

In-  
licensed

## RG435 / Avastin® :

- Indication: Malignant Glioma  
Approved in June 2013



## Development Status - Oncology Field

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In-  
licensed

### **RG597 / Herceptin® :**

Indication: Weekly Dosage with Chemo-Therapy for HER2  
Positive Adjuvant Breast Cancer

Approved in June 2013

In-  
licensed

### **RG7321 / GDC-0941 / pictilisib (PI3K inhibitor) :**

Expected Indication: Solid Tumors

Started P1 in June 2013

In-  
licensed

### **RG7446 / MPDL3280A (anti-PD-L1 MAb) :**

Expected Indication: Solid Tumors

In preparation to start P1 in the second half of 2013



# Development Status - Primary Field

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In-  
licensed

## RG484 / Bonviva® Injection :

- Indication: Osteoporosis  
Approved in June 2013

In-  
house

## MRA / Actemra® :

- Indication: Polyarticular Juvenile Idiopathic Arthritis (pJIA)  
Approved in April 2013 (FDA)  
Approved in June 2013 (EMA)
- Subcutaneous Injection Formulation  
Indication: Rheumatoid Arthritis  
Launched in May 2013 (Japan)
- Expected Indication: Giant Cell Arteritis  
Started P3 in July 2013 (overseas)
- Expected Indication: Systemic Sclerosis  
Started P2 in March 2012 (overseas)



## Development Status - Primary Field

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In-house

### CSG452 / tofogliflozin :

Expected indication: Type 2 diabetes

The applications for approval were filed by Sanofi K.K. and Kowa Company, Ltd., respectively in April 2013

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### RG1577 (MAO-B inhibitor) :

Expected indication: Alzheimer's disease

Started P1 in May 2013

In-house

### URC102 (URAT1 inhibitor) :

Expected Indication: Gout

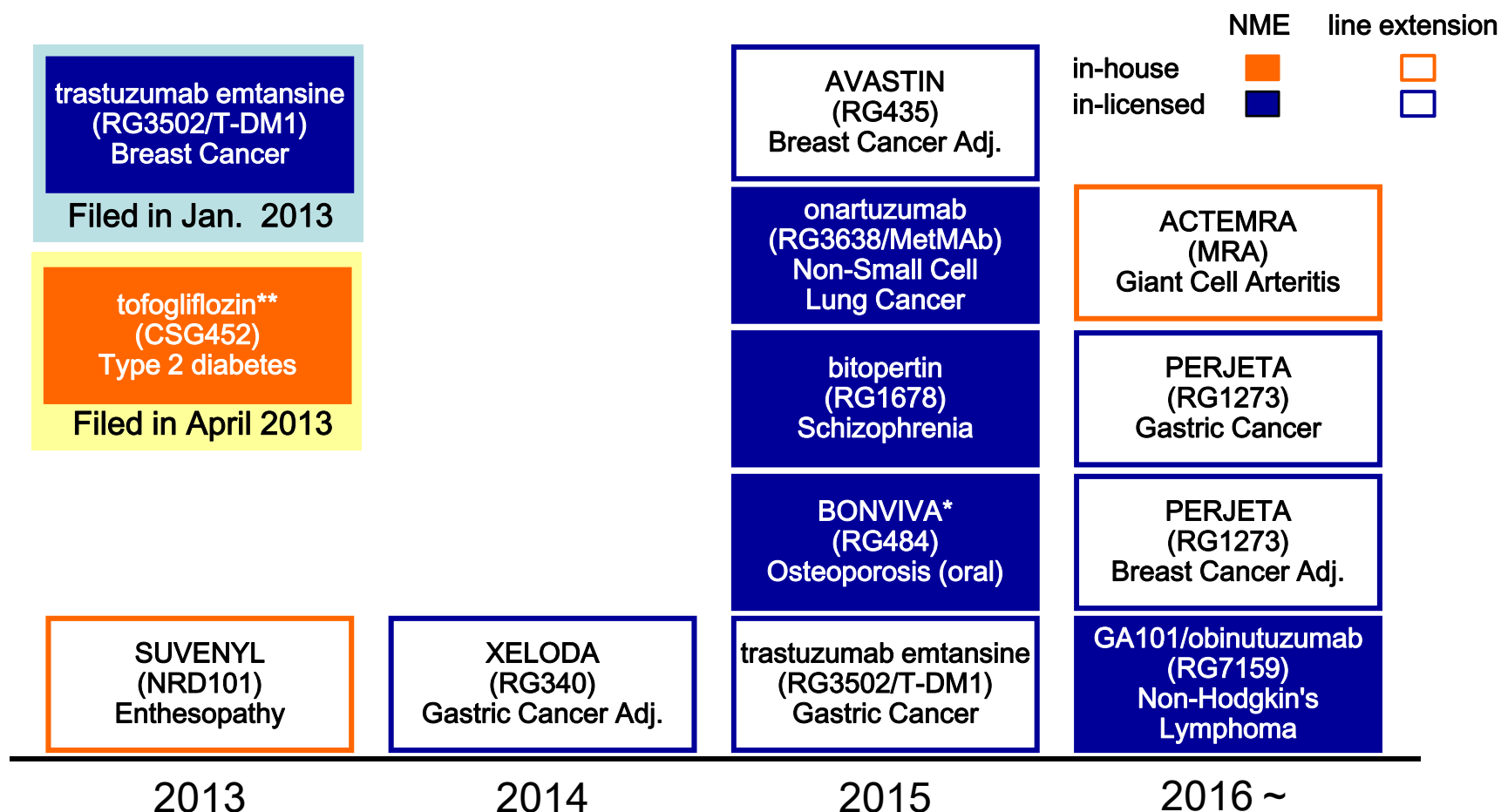
Started P1 in June 2013 (South Korea)

Co-development with JW Pharmaceutical Corporation



# Projected Submissions (Post PoC products and NMEs)

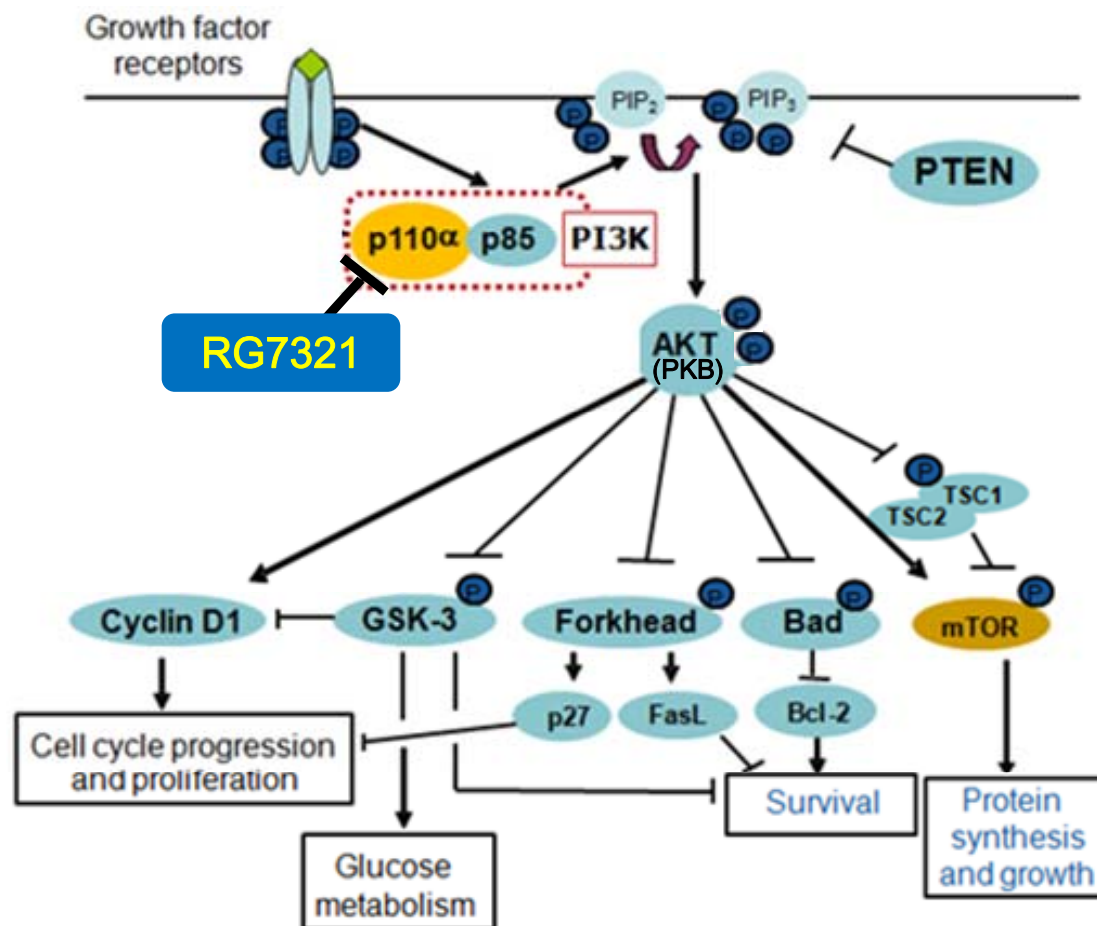
## ■ Seamless filings every year



\* Overseas brand name

\*\* The applications for approval were filed by Sanofi K.K. and Kowa Company, Ltd., respectively.

# RG7321 (PI3K inhibitor) - Mode of Action



- PI3K transmits intracellular signaling from the receptor through the PI3K-AKT-mTOR pathway
- PI3K participates in growth and invasion of cancer cells, and acquisition of resistance to anti-cancer drugs<sup>1, 2)</sup>
- RG7321 is a novel small-molecule anti-cancer agent with potent and selective PI3K inhibitory activity.

1) Liu P et al., Nat Rev Drug Discov 2009

2) Berns K et al., Cancer Cell 2007

PI3K: Phosphoinositide 3-kinase

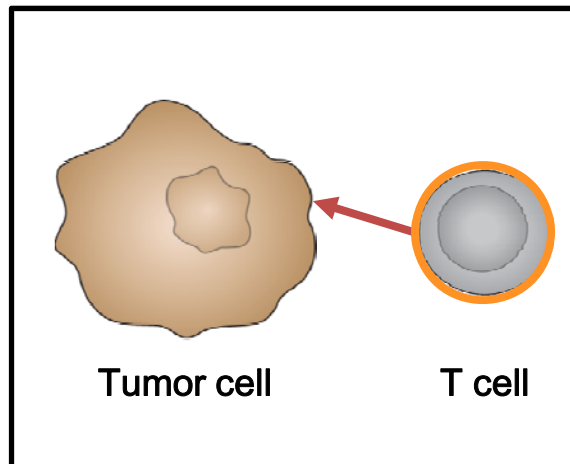
AKT (PKB): Protein kinase B

mTOR: mammalian target of rapamycin

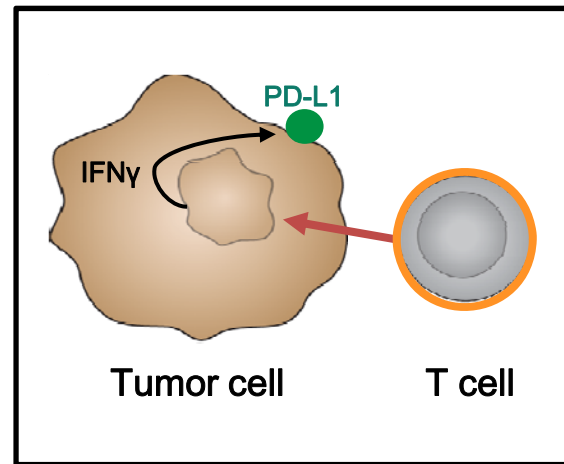




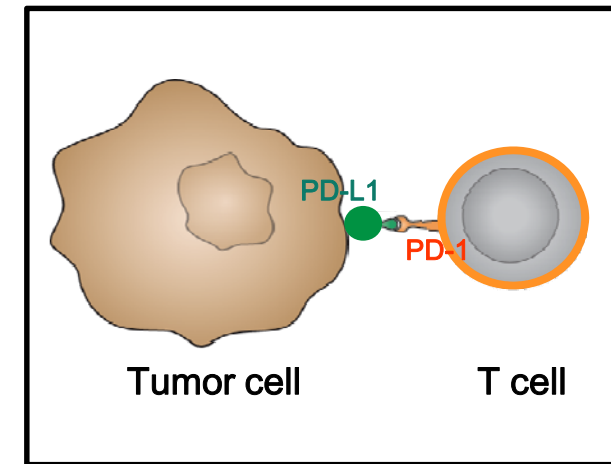
## RG7446/MPDL3280A (anti-PD-L1 MAb) - Mode of Action



T cell attacks tumor cells as non-self antigens.



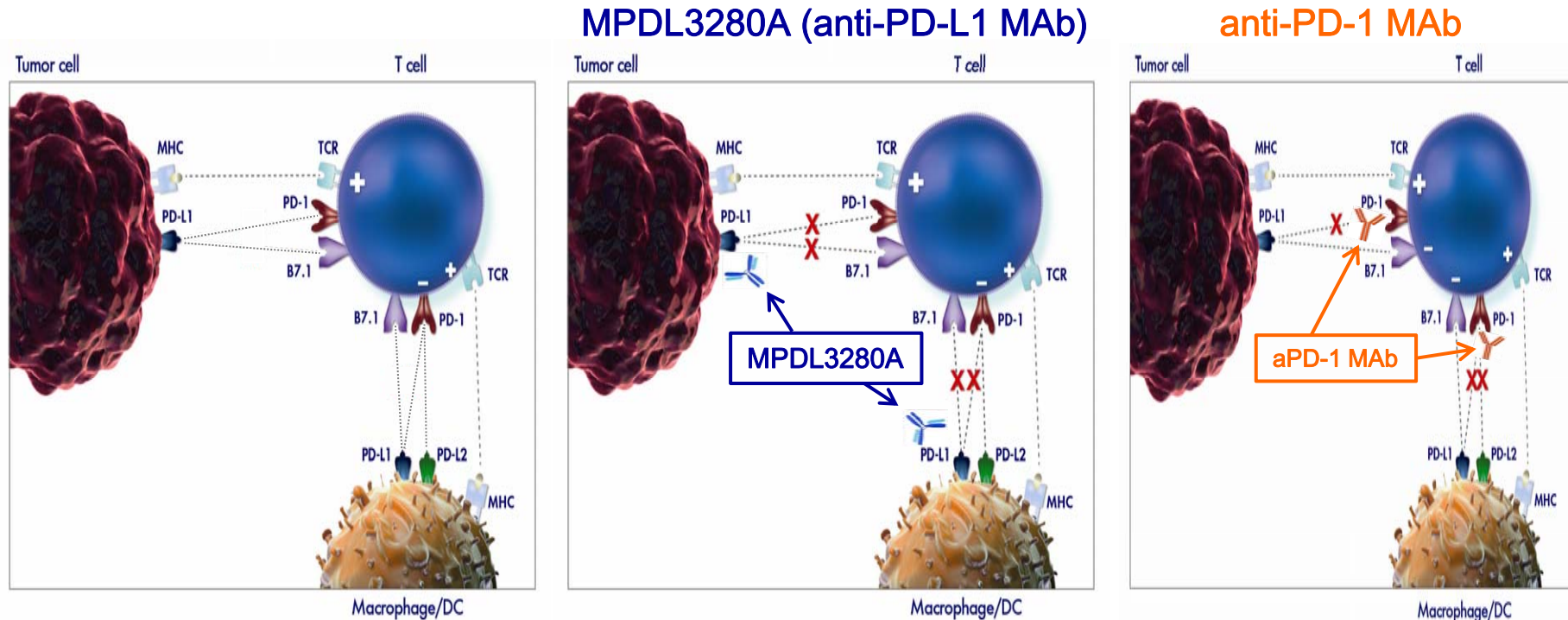
PD-L1 expression is induced by stimulation of IFN $\gamma$ , or expressed by activation of oncogenic pathway of the tumor itself.



T cell will not attack the tumor cell due to induced immune tolerance by negative signal of PD-1/PD-L1 pathway.



## RG7446/MPDL3280A (anti-PD-L1 MAb) - Mode of Action



Binding of PD-L1 to PD-1 and B7.1 induces suppressive signals and negatively regulates T cell immune responses.

Binding of MPDL3280A to PD-L1 exerts anti-tumor effects through inhibition of the PD-L1 pathway, thereby enabling anti-tumor T cell responses.

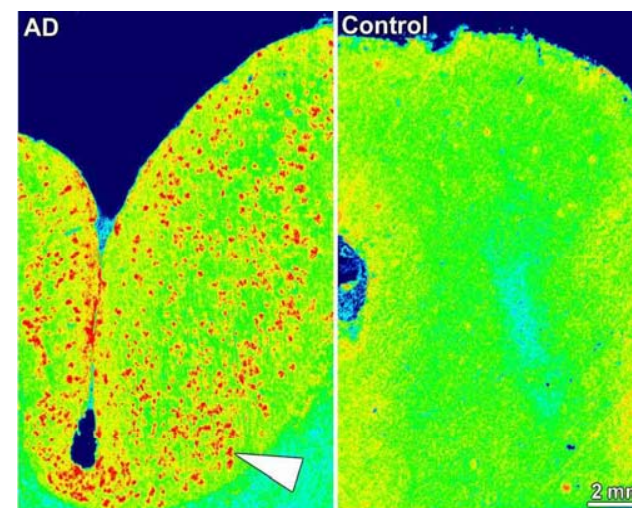
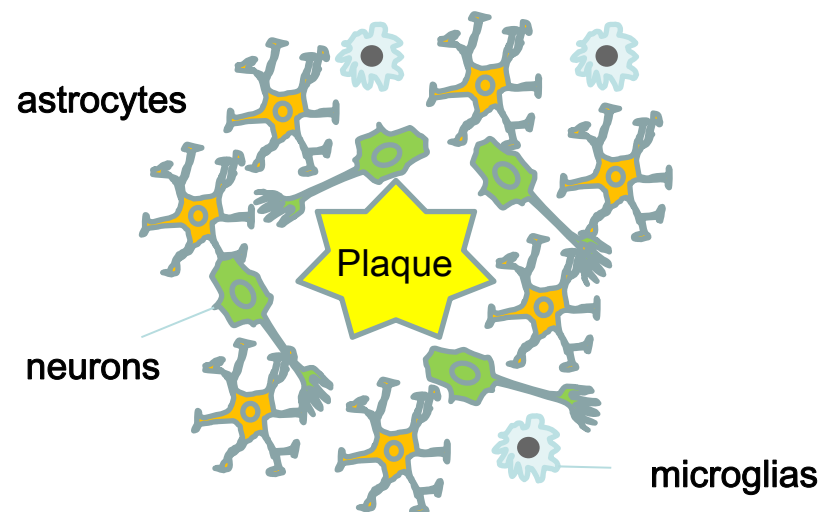
Binding of aPD-1 MAb to PD-1 on T cells inhibits PD-1 inhibition, but not B7.1 inhibition. Normal immune homeostasis mediated by PD-L2 is also disrupted.

## RG1577 (MAO-B inhibitor) - Mode of Action

- MAO-B is abundant in astrocytes and some neurons in human brain
- MAO-B produces reactive oxygen species associated with breakdown of the substrates
- Expression of MAO-B is increased in patients with Alzheimer's disease (AD) compared to healthy adults (Control).

MAO-B: monoamine oxidase B  
substrate: phenylethylamine, dopamine

Inhibition of MAO-B in AD is expected to have therapeutic effects on cognition through neuroprotection by reducing reactive oxygen species, and improvement on motivation (reduced apathy) and mood due to increased substrate levels.

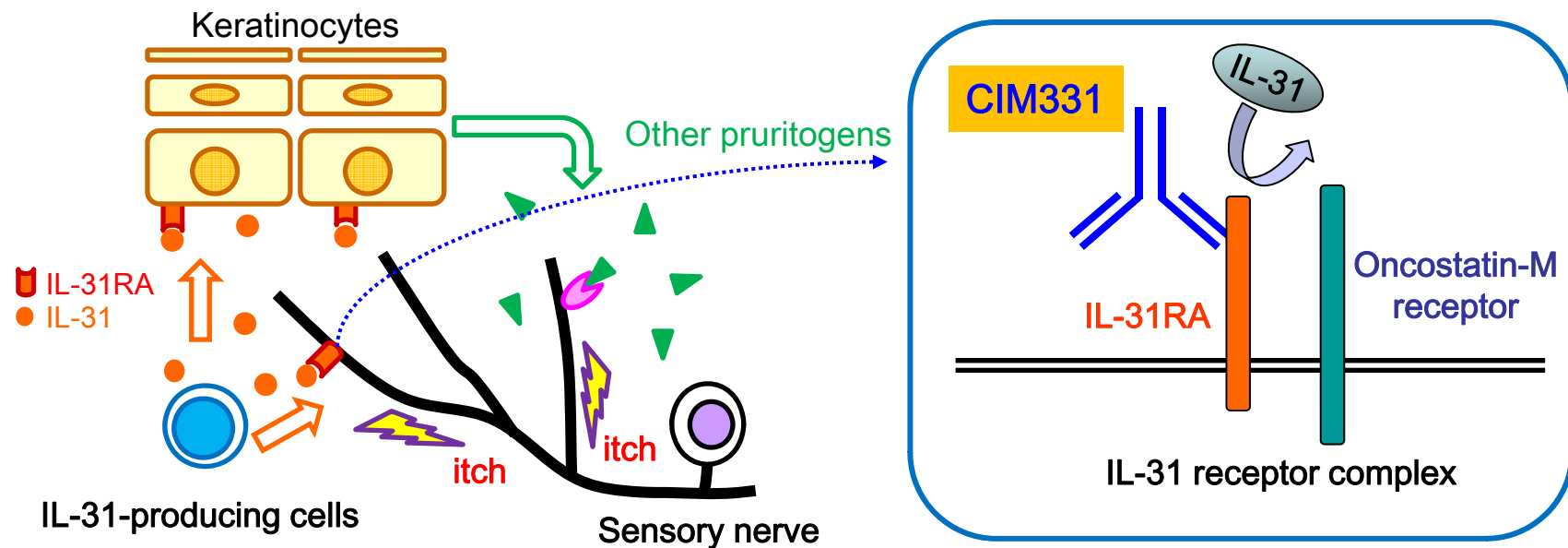


Neuroscience (1994) 62, 15 - 30

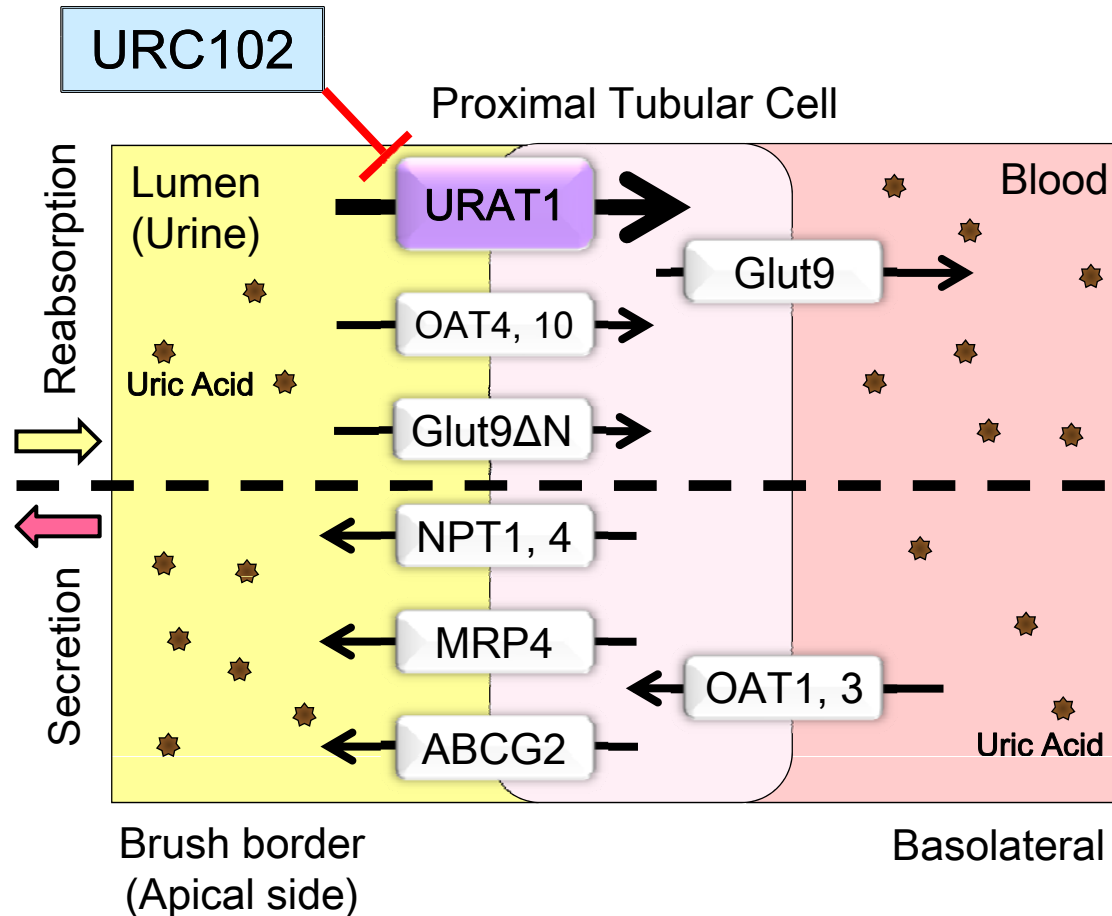
# CIM331 (anti-IL-31R MAb) - Mode of Action

To be presented at EADV (European Academy of Dermatology and Venereology) in October 2013

- Interleukin-31 (IL-31) is involved in pruritus in atopic dermatitis (AD)
- CIM331 inhibits IL-31 from binding to the receptor, and is expected to suppress the itching and to improve dermatitis by blocking the itch-scratch-cycle



# URC102 (URAT1 inhibitor) - Mode of Action



URAT1: urate transporter 1

- URAT1 is an essential molecule that mediates the reabsorption of uric acid on the lumen side of the proximal tubule
- URC102 promotes the excretion of uric acid by selectively inhibiting URAT1
- Consequently, URC102 potently decreases serum uric acid



# Update on the Development Requests for Unapproved Drugs/Indications

- Review Committee of Development Request for Unapproved Drugs/Indication
  - Nine indications of 8 products have been approved, out of 10 indications (including additional dosages and administrations) of 8 products officially requested by MHLW to develop at the 1st round
  - Status of products remaining from the 1st round (Avastin) and 3 indications of the 3 products are shown below

	Product	Indication	Current Situation
1st round requests	Avastin	Ovarian cancer	Filed on 5 Oct. 2012
2nd round requests	Avastin	Recurrent glioblastoma	Approved for malignant glioma on 14 June 2013
	Herceptin	Weekly dosage with chemotherapy for HER2 positive adjuvant breast cancer	Approved on 14 June 2013
	Cellcept	Lupus nephritis	Submitted company opinion and waiting for its evaluation by the committee

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