

#### **Oncology Development: Maximizing** the pipeline to deliver innovative treatments

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The following presentation includes discussions of investigational products and investigational indications for existing products. The efficacy and safety of such products and indications have not been established.



#### **Focus for today**

- Overview of the strong oncology development performance in 2012
- Update on selected priority compounds in full development
- Overview on newsflow projected through 2017



# Novartis Oncology Global Development:

Strong performance in 2012, anticipated to continue in coming years

- Oncology Development has industry-leading capabilities which culminated in 6 indications with regulatory approvals in 2012, including 2 new chemical entities
- Late stage pipeline is full with 14 targeted agents, and majority of the programs having companion diagnostics
- Dense newsflow projected through 2017
  - 13 pivotal study readouts planned in 2013-14
  - NDA<sup>1</sup>s and regulatory approvals expected to continue at a steady pace



3 | Novartis R&D Investor Day | Alessandro Riva | Boston, November 8, 2012

<sup>1</sup> New drug application

#### Six indications with regulatory approval in 2012 2 NCEs and 4 label extensions



<sup>1</sup> In combination with exemestane after progressing on an aromatase inhibitor

<sup>2</sup> Tuberous sclerosis complex

<sup>3</sup> Novartis licensed INC424/Jakavi® from Incyte for development and commercialization outside the US. Incyte has retained the rights in the US

<sup>4</sup> Gastro-intestinal stromal tumors

<sup>5</sup> Chronic myeloid leukemia





## **Broad & deep Development portfolio**

Sc	olid Tumor	Hematological Malignancies		
AFINITOR (everolimus) Tablets (mTOR inhibitor)	RCC <sup>1</sup> ; pNET <sup>2</sup> ; TSC <sup>3</sup> ; HR+ BC <sup>4, 5</sup> HER2+ BC <sup>5</sup> 1 <sup>st</sup> & 2 <sup>nd</sup> /3 <sup>rd line</sup> ; HCC <sup>6</sup> ; Non-functioning Carcinoid	(2 <sup>nd</sup> generation potent BCR-ABL inhibitor)	CML <sup>8</sup> – de novo; CML <sup>8</sup> Treatment Free Remission; c-KIT Melanoma	
(multi-receptor targeted	Signifor Cushing's Disease; Acromegaly Iti-receptor targeted Carcinoid		Myelofibrosis; Polycythemia Vera	
BKM120/BEZ235 (PI3K inhibitors)	NSCLC <sup>7</sup> ; Prostate; Glioblastoma multiforme; Breast	<b>EXJADE</b> deferasirox (Iron Chelator)	Non-Transfusion-Dependent Thalassemia	
TKI258 (FGFR & VEGFR inhibitor)	RCC <sup>1</sup> ; Breast; Endometrial; HCC <sup>6</sup>	AFINITOR (everolimus) Tablets	Lymphoma	
LDK378 (ALK inhibitor)	NSCLC <sup>7</sup>	(mTOR inhibitor)	Multiple Myclome	
LDE225	Basal cell carcinoma;	(Pan HDAC inhibitor)		
MEK162 <sup>9</sup> (MEK inhibitor)	NRAS-mutated Melanoma	PKC412 (FLT3; C-KIT; PDGFR inhibitor)	Acute Myeloid Leukemia Aggressive Systemic Mastocytosis)	
LGX818 (BRAF inhibitor)	BRAF-mutated Melanoma	CTL019 <sup>11</sup>	Chronic lymphocytic leukemia;	
<b>AUY922</b> <sup>10</sup> (HSP90 inhibitor)	ALK+ & EGFR-mutated NSCLC <sup>7</sup>	antigen receptor (CAR) immunotherapy)	other B-cell malignancies	

<sup>1</sup> Renal cell carcinoma; <sup>2</sup> Pancreatic neuroendocrine tumors; <sup>3</sup> Tuberous sclerosis complex incl SEGA, AML, seizures; <sup>4</sup> Advanced hormone-receptor positive; <sup>5</sup> Breast cancer;

<sup>6</sup> Hepatocellular carcinoma; <sup>7</sup> Non-small cell lung cancer; <sup>8</sup> Chronic myeloid leukemia; <sup>9</sup> MEK162 in-licensed from Array BioPharma; <sup>10</sup> Discovered under collaboration with Vernalis plc; <sup>11</sup> In-licensed from Univ. of Penn.





# **19 active registration trials in 2012:**

7 Trials completed enrollment, 9 ongoing, 3 to be initiated

<b>Afinitor</b> <sup>®</sup>	<b>BKM120</b>	<b>Tasigna</b> ®	SOM230
Diffuse Large B-Cell Lymphoma	mBC <sup>1</sup> ER+: Fulvestrant mTOR naive	C-KIT Melanoma	Cushing's Disease (LAR) <sup>2</sup>
non-functioning Carcinoid	mBC <sup>1</sup> HER2-: Fulvestrant post-mTOR	Path to Cure (Treatment Free Remission)	Acromegaly
HER2+ Breast Cancer 1 <sup>st</sup> line			
HER2+ Breast Cancer – 2 <sup>nd</sup> /3 <sup>rd</sup> line	INC424	LBH589	<b>TKI258</b>
Hepatocellular Carcinoma	Polycythemia Vera	Multiple Myeloma	Renal Cell Carcinoma
PKC412		LDE225	LDK378
	Acute Myeloid Leukemia	Basal Cell Carcinoma	NSCLC <sup>3</sup> – chemotherapy & crizotinib refractory
	Aggressive Systemic Mastocytosis	Medulloblastoma	
New Trials to be initiated	<ol> <li><sup>1</sup> Metastatic breast cancer</li> <li><sup>2</sup> Long-acting release form</li> <li><sup>3</sup> Non-small cell lung cancer</li> </ol>		

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#### Patient selection strategies in multiple programs 10 Companion diagnostics in development

Program	Companion diagnostics	Potential indications	
Tasigna®	BCR/ABL (Version 2)	<ul> <li>Treatment-free remission in CML<sup>1</sup></li> </ul>	
BKM120 BEZ235 BYL719	PIK3CA mutations, PTEN mutations or PTEN loss of expression	<ul> <li>Breast, NSCLC<sup>2</sup>, prostate cancer</li> </ul>	
PKC412	FLT3 mutation	Newly diagnosed AML <sup>3</sup>	
LDE225	Hh 5 gene signature	<ul> <li>Medulloblastoma</li> </ul>	
TKI258	FGFR amplification & mutation	<ul> <li>Breast cancer (FGFR amplification)</li> <li>Endometrial Cancer (FGFR mutation)</li> </ul>	
MEK162	NRAS mutation	<ul> <li>NRAS mutated melanoma</li> </ul>	
LGX818	BRAF mutation	<ul> <li>BRAF mutated melanoma (combination with MEK162)</li> </ul>	
LDK378	ALK translocation	<ul> <li>ALK-translocated NSCLC<sup>2</sup> patients</li> </ul>	

<sup>1</sup> Chronic myeloid leukemia

<sup>2</sup> Non-small cell lung cancer

<sup>3</sup> Acute myeloid leukemia



#### **Focus for today**





#### Large parallel Phase III program ongoing; Critical role of mTOR pathway across tumor types (everolimus) tablets 5 Indications approved to date

the WID PR©gr/	
Kidnr F Breast	ORD RADIANT BOLERO
TSC Liver	PILLAF EXIST VOLVE

		<b>Registration Studies</b>	Recruitment Status	Expect to File/ Regulatory Status
	1.	Kidney Cancer	Complete	Approved
	2.	Pancreatic NET <sup>2</sup> s	Complete	Approved
	3.	TSC <sup>3</sup> SEGA <sup>4</sup>	Complete	Approved
	4.	TSC AML⁵	Complete	Approved
) R	5.	ER+ Breast Cancer (BOLERO-2)	Complete	Approved
	6.	HER2+ Breast Cancer (BOLERO-1 & 3)	Complete	2013 / 2014
	7.	Liver Cancer	Complete	2013
	8.	Non-functioning Carcinoid	Enrolling	2015
	9.	Lymphoma	Enrolling	2015

<sup>1</sup> <u>W</u>orldwide <u>Initiative to Develop Everolimus;</u>

<sup>4</sup> Sub-ependymal giant cell astrocytoma;
 <sup>5</sup> Angiomyolipoma

<sup>2</sup> Neuro-endocrine tumors;

<sup>3</sup> Tuberous sclerosis complex;



# Bolero-2 Rationale: Resistance to endocrine (everolimus) tablets therapy is associated with PI3K/mTOR activation

- mTOR is a protein that regulates cell growth, cellular metabolism and the creation of new blood vessels through angiogenesis
- In advanced breast cancer, overactivation of the PI3K/Akt/mTOR pathway promotes estrogenindependent cell proliferation
- Inhibiting certain cellular pathways, such as mTOR, PI3K and, potentially, FGFR, is critical to overcoming resistance to endocrine therapy<sup>3,4</sup>



<sup>&</sup>lt;sup>1</sup> Inhibiting the PI3K/Akt/mTOR signaling Pathway. National Cancer Institute. Available at

<sup>&</sup>lt;sup>3</sup> Normanno N, et al. Endocr Relat Cancer. 2005;12:721-747. <sup>4</sup> Di Cosimo S, Baselga J. Nat Rev Clin Oncol. 2010;7:139-147.





http://www.cancer.gov/cancertopics/understandingcancer/targetedtherapies/breastcancer\_htmlcourse/page6. Accessed May 2012.

<sup>&</sup>lt;sup>2</sup> Baselga J. 2011 European Multidisciplinary Cancer Congress. Presentation of late breaking abstract No. 9LBA. September 26, 2011.

# **BOLERO-2: Updated 18-month follow-up<sup>1</sup>** Paradigm shift in the treatment for women with HR+





#### **Overall Survival (EVE<sup>3</sup> versus PBO<sup>4</sup>)**

- 2<sup>nd</sup> Interim Analysis Results
  - 182 events, hazard ratio: 0.77 (0.57-1.04) in favor of Afinitor<sup>®</sup>
- Final analysis in late 2013 / early 2014 (total of 398 deaths)

<sup>1</sup> ASCO 2012 – Abstract #559 <sup>2</sup> Non-steroidal aromatase inhibitor <sup>3</sup> Everolimus=Afinitor

<sup>₄</sup> Placebo



#### Afinitor<sup>®</sup> in advanced HER2+ Breast Cancer strong rationale



Preclinical<sup>1</sup> & early clinical<sup>2</sup> : combination of Afinitor<sup>®</sup> with anti-HER2+ treatment (e.g trastuzumab) is synergistic and has the potential to overcome trastuzumab resistance



<sup>1</sup> Lu C-H (2007) Clin Cancer Res ; 13 : 5883-8 <sup>2</sup> Andre F (2010) J Clin Oncol; 28: 5110-5 and Jerusalem G (2011) Breast Cancer Research and Treatment; 125: 447-455



## **PI3K inhibitors in development**



<sup>1</sup> Voliva et al. AACR, 2010. Abstract 4498

<sup>2</sup> Maira et al. AACR, 2010. Abstract 4497

<sup>3</sup> Maira et al. Mol Cancer Ther. 2008;7:1851

13 | Novartis R&D Investor Day | Alessandro Riva | Boston, November 8, 2012

#### <u>BKM120</u>

Oral pan-class I PI3K inhibitor of all four class I PI3K isoforms (α, β, γ, δ)<sup>1,2</sup>

#### **BEZ235**

Oral pan-class I inhibitor of PI3K, mTORC1 and mTORC2<sup>3</sup>

#### <u>BYL719</u>

Oral alpha-selective (p110α) PI3K inhibitor



#### PRISM: A broad development program with BKM120



![](_page_14_Picture_3.jpeg)

# **BKM120 – Ongoing studies in Breast Cancer**

Encouraging activity seen in heavily pre-treated patients

HR+	Combination Partner	Population	Number of Patients Enrolled	Clinical Benefit (CR/PR/SD <sup>1</sup> )
Phase I <sup>2</sup> (Solid tumors)	single agent	BKM120 dose escalation; prior endocrine and chemotherapy allowed (Phase I)	N=21	47.6% (2 PR [1 unconfirmed], 8 SD)
Phase lb <sup>3</sup>	letrozole	Prior AI, anti-estrogen and chemotherapy allowed	N=51	47% (1 CR, 1 PR, 22 SD)
HER2+	HER2+ Combination Population		Number of Patients enrolled	Clinical Benefit (CR/PR/SD)
Progression on or with Ib/II <sup>4</sup> trastuzumab 4 weeks after last dos of trastuzumab		Progression on or within 4 weeks after last dose of trastuzumab	N=50	52% (1 CR, 4 PR, 21 SD)

<sup>1</sup> CR=complete response; PR=partial response; SD=stable disease

<sup>2</sup> Grana, B. et. al. ASCO 2011

<sup>3</sup> Meyer, I et. al. ASCO 2012

<sup>4</sup> Pistillil, B et.al, ESMO 2012

![](_page_15_Picture_8.jpeg)

#### **BKM120 – 2 Phase III in HR+ Breast Cancer initiated** *Work in progress in other Breast Cancer sub-groups*

![](_page_16_Figure_1.jpeg)

![](_page_16_Picture_3.jpeg)

# 2012 innovative key combinations with PI3 kinase inhibitors

![](_page_17_Figure_1.jpeg)

![](_page_17_Picture_2.jpeg)

#### LDK378: Outstanding data from ALK+ NSCLC<sup>1</sup> Patients – Refractory to Crizotinib (Phase I study)

	LDK378 versus crizotinib:	
Preclinical Data*	More potent and selective ALK inhibitor	
	<ul> <li>Longer responses in EML4-ALK crizotinib-resistant and crizotinib- sensitive xenografts</li> </ul>	
	Phase I study in advanced solid tumors is ongoing:	
Clinical Data*	<ul> <li>LDK378 exhibits potent anti-tumor activity in patients with ALK+ NSCLC, including those who have progressed following crizotinib</li> </ul>	
	<ul> <li>LDK378 is active in brain metastases</li> </ul>	
	<ul> <li>Response rate observed in NSCLC patients treated at ≥ 400 mg who progressed following crizotinib:</li> </ul>	
	• Response Rate with $PR^2 + CR^3 + uPR^4 = 80\%$ (36/45)	
	<ul> <li>Response Rate with PR +CR = 47% (21/45)</li> </ul>	

<sup>1</sup> NSCLC: Non-small cell lung cancer <sup>2</sup> PR=partial response <sup>3</sup> CR=complete response <sup>4</sup> uPR=unconfirmed partial response <sup>\*</sup> Shaw , et al. ESMO Congress, Vienna 2012

![](_page_18_Picture_3.jpeg)

#### LDK378: Clinical Development Plan

Planned Pivotal Studies	<ul> <li>Initiate 1 pivotal study in Dec, 2012:</li> <li>In chemotherapy- and crizotinib-refractory non-small cell lung cancer</li> <li>Other pivotal trials planned for 2013</li> </ul>
Regulatory Filing	Planned in 2014

![](_page_19_Picture_2.jpeg)

## Jakavi<sup>®</sup> (JAK1/JAK2 inhibitor): Myelofibrosis & Polycythemia Vera

![](_page_20_Picture_1.jpeg)

**Polycythemia Vera** 

Pivotal Phase III trial vs. best available care

> Enrollment ongoing

**Myelofibrosis: Combination Studies** 

+ LBH589

 Mouse model combination with ruxolitinib shows significant reduction of bone marrow fibrosis and allele burden<sup>1</sup>

Other combinations planned with compounds in our portfolio

![](_page_20_Picture_11.jpeg)

## Tasigna<sup>®</sup>: Paradigm shift in the management of CML<sup>1</sup>

**ENESTnd:** Randomized pivotal trial (nilotinib vs. imatinib) in untreated Ph+ CML-CP<sup>2</sup>

- 3 years of follow-up confirms the superiority of nilotinib
- Faster and deeper molecular response 4-log Reduction (MR<sup>4.0</sup>) and 4.5-log Reduction (MR<sup>4.5</sup>)
- Decreased risk of progression to AP/BC<sup>3</sup> and death following progression

ENESTnd: Saglio G. et al, ASH 2011 (Abstract #452)

#### **ENESTcmr**:

Randomized trial (nilotinib vs. continuation of imatinib) in Ph+ CML-CP patients who did not achieve a complete molecular response after treatment with imatinib for at least ≥2 years

- 12 months of follow-up shows nilotinib more than doubled in comparison to imatinib the rate of:
  - Confirmed Complete Molecular Response
  - Complete Molecular response 4-log Reduction (MR <sup>4.0</sup>)
  - Complete Molecular response 4.5-log Reduction (MR <sup>4.5</sup>)
- 5 year follow up is planned

ENESTcmr: Hughes et al. ASH 2011 (Abstract #606)

![](_page_21_Picture_18.jpeg)

<sup>&</sup>lt;sup>1</sup> Chronic myeloid leukemia

<sup>&</sup>lt;sup>2</sup> Chronic phase

<sup>&</sup>lt;sup>3</sup> Acute phase / blast crisis

## **Rationale for treatment-free remission strategy** Deeper & faster molecular response with Tasigna®

#### **ENESTnd 36 month follow-up cumulative incidence of MR4.5**

![](_page_22_Figure_2.jpeg)

![](_page_22_Picture_4.jpeg)

## Treatment free remission: 2 international trials expected to start recruitment in Q1 2013

![](_page_23_Figure_1.jpeg)

![](_page_23_Figure_2.jpeg)

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#### **Oncology Portfolio: Planning for expected key** activities in 2013-2014

- Target Regulatory Approvals expected in 4 NCEs
- **Exjade**<sup>®</sup>: Expected approval in non-transfusion-dependent thalassemia
- Signifor<sup>®</sup>: Expected approval in acromegaly
- Afinitor<sup>®</sup>: Further expand label
- Accelerate development in:
  - Tasigna®: Treatment-Free Remission strategy for CML
  - PI3 Kinase Programs: BKM120, BEZ235 & BYL719
  - ALK Inhibitor: LDK389
  - HSP90 Inhibitor: AUY922
  - MEK Inhibitor: MEK162
  - BRAF Inhibitor: LGX818
- Pivotal Trials: Results expected from 13 trials

![](_page_24_Picture_13.jpeg)

### 2013 – 2014 Expected newsflow: Results from 13 pivotal trials

2013	2014
<ul> <li>Afinitor<sup>®</sup> Hepatocellular carcinoma – 2<sup>nd</sup> line</li> </ul>	<ul> <li>Afinitor<sup>®</sup> HER2+ breast cancer 1<sup>st</sup> line</li> </ul>
<ul> <li>Afinitor<sup>®</sup> HER2+ breast cancer – 2<sup>nd</sup>/3<sup>rd</sup> line</li> </ul>	<ul> <li>Afinitor<sup>®</sup></li> <li>Diffuse large B-cell lymphoma -</li> </ul>
<ul> <li>LBH589 Multiple myeloma – 2<sup>nd</sup> line</li> </ul>	<ul> <li>Afinitor<sup>®</sup></li> <li>Non-functioning carcinoid</li> </ul>
<ul> <li>PKC412</li> <li>FLT3+ Acute myeloid leukemia – 1<sup>st</sup> line</li> <li>Taginge<sup>®</sup></li> </ul>	<ul> <li>Jakavi<sup>®</sup></li> <li>Polycythemia vera</li> </ul>
<ul> <li>Iasigna<sup>®</sup></li> <li>cKIT mutated melanoma – 1<sup>st</sup> line</li> <li>TKI258</li> </ul>	<ul> <li>LDK378         ALK+ Non-small cell lung cancer     </li> </ul>
<ul> <li>Renal cell carcinoma – after mTOR</li> <li>PKC412</li> </ul>	<ul> <li>LDE225</li> <li>Basal cell carcinoma – 1<sup>st</sup> line</li> </ul>
Aggressive systemic mastocytosis	

![](_page_25_Picture_2.jpeg)

#### **One of the largest regulatory filing charts in the industry** *Planned filings 2013 to 2 2016*

![](_page_26_Figure_1.jpeg)

![](_page_26_Picture_2.jpeg)

![](_page_26_Picture_4.jpeg)

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# **Back-Up**

![](_page_27_Picture_2.jpeg)

## **Key Oncology and Hematology Projects**

Exploratory Trials	Confirmatory Trials (Phase I/II)	Registration Trials (Phase III or pivotal)		Filed (in Registration)
BGJ398 Solid tumors	AUY922 Solid tumors	LBH589 PKC412 Multiple Myeloma AML <sup>2</sup>		Signifor <sup>®</sup> Cushing's disease
BHQ880 Myeloma	BEZ235 Solid tumors	LDE225 Basal Cell Carcinoma	<b>TKI258</b> RCC <sup>3</sup>	Exjade <sup>®</sup> NTDT <sup>6</sup>
INC280 Solid tumors	RAF265 Melanoma	BKM120 Breast Cancer	INC424 Polycythemia Vera	<b>Afinitor<sup>®</sup></b> TSC AML⁵
LCL161 Solid tumors	MEK162 Solid tumors	Afinitor® HER2+ Breast Cancer 1st	<b>PKC412</b> ASM <sup>4</sup>	
LEE011 Solid tumors	LCI699 Cushing's Syndrome	HER2+ Breast Cancer 2 <sup>nd</sup>	<b>Signifor®</b> Acromegaly	
LEQ506 Solid tumors	LGX818 Solid tumors	Afinitor <sup>®</sup> HCC <sup>1</sup>	Afinitor® Non-functional carcinoid	
LFA102 Solid tumors	LDK378 NSCLC	<b>Afinitor</b> ® Lymphoma	tanior	
AEB071 Solid tumors	CTL019 Leukemia			
LGK974 Solid tumors	BYL719 Solid tumors			
<b>LGH477</b> Hemat. Tumors	BKM120 Solid tumors	<sup>1</sup> Hepatocellular carcinoma New mo		New molecule
TAS266 Solid tumors	LDE225 Solid tumors	<ul> <li><sup>2</sup> Acute myeloid leukemia</li> <li><sup>3</sup> Renal Cell Carcinoma</li> <li><sup>4</sup> Agressive systemic mastocytosis</li> <li><sup>5</sup> Tuberous sclerosis complex angiomyolipomas</li> <li><sup>6</sup> Non-Transfusion-Dependent Thalassemia</li> </ul>		
LJM716 Solid tumors	Signifor <sup>®</sup> Rare neuroendocrine tumors			
VAY736 Leukemia	LBH589 Hemat. tumors			
	<b>Tasigna<sup>®</sup></b> cKIT Melanoma			
	TKI258 Solid & Hemat. tumors			
	Afinitor <sup>®</sup> Solid tumors			

![](_page_28_Picture_2.jpeg)