



## Novartis Oncology – Leadership in cancer and hematology that changes patients’ lives

December 13, 2011

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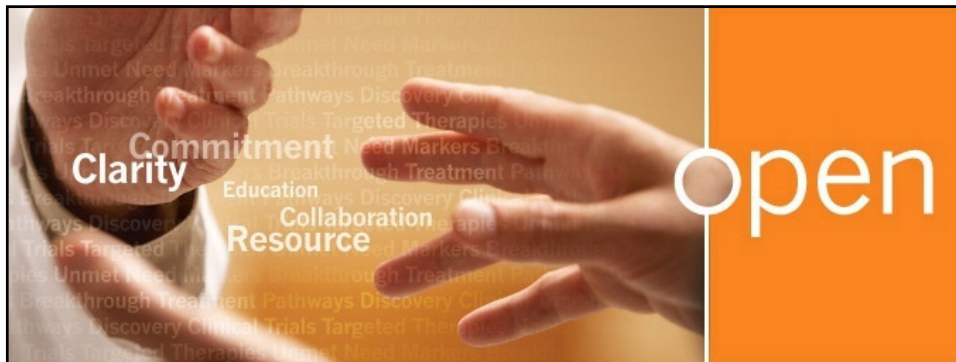
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## Today's agenda

- **Novartis strategy in oncology** H. Hoppenot
- **Key pipeline data from H2, 2011** A. Riva
- **Conclusion** H. Hoppenot
- **Q&A** H. Hoppenot  
A. Riva

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## Novartis strategy in oncology

Hervé Hoppenot  
President, Oncology

December 13, 2011

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## Key elements of the oncology strategy



### Following the science

- 4 first in human starts in 2011
  - LDK378 – Oral ALK inhibitor
  - AEB071 – PKC inhibitor
  - LGK974 – first in class WNT pathway inhibitor
  - LGX818 – selective BRAF inhibitor



### Translational Medicine

- 2 PoC declarations
  - AUJ922 – IV Non-geldanamycin-based HSP90 inhibitor
  - MEK162 – Oral MEK inhibitor
- 9+ new Phase Ib/II Studies this year
- 3 Novel combination studies with targeted agents



### Global Development

- On track to complete 4 major filings in 2011
- 20+ pivotal trials with 10 innovative compounds



### Commercial Solutions

- 2011 major approvals:
  - Afinitor® – pNET
  - Votubia® – TSC SEGA<sup>1</sup>
- 2012 expected approvals:
  - ER+HER2- Adv BC<sup>2</sup>
  - TSC-AML<sup>3</sup>
  - INC424 – MF<sup>4</sup> (EU)
  - Exjade®-NTDT<sup>5</sup>
  - SOM230 – Cushings
  - Glivec® – 3y Adj. GIST<sup>6</sup>

1. Tuberous Sclerosis Complex Subependymal Giant Cell Astrocytoma ; 2. Advanced Breast Cancer; 3. Tuberous Sclerosis Complex Angiomyolipoma; 4. Myelofibrosis; 5. Non transfusion dependent thalassemia; 6. Three-year adjuvant Gastrointestinal Stromal Tumor

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## In 2011, Oncology Development has Impacted Ten Disease Areas

 <b>AFINITOR</b> (everolimus) Tablets	<b>pNET</b>	Pivotal Phase III trial RADIANT-3 vs. placebo	<ul style="list-style-type: none"> <li>Approved in US &amp; EU</li> </ul>
	<b>TSC SEGA</b>	Pivotal Phase III study vs. Placebo(EXIST-1)	<ul style="list-style-type: none"> <li>Approved in US, EU &amp; CH</li> </ul>
	<b>TSC AML</b>	Pivotal Phase III study vs. placebo (EXIST-2)	<ul style="list-style-type: none"> <li>Met primary endpoint</li> <li>Submission on-track for year-end</li> </ul>
	<b>Metastatic Breast</b>	Pivotal Phase III trial Exemestane vs. placebo (BOLERO-2)	<ul style="list-style-type: none"> <li>Met primary endpoint at interim analysis</li> <li>Submission on track for year-end</li> </ul>
 <b>glivec</b> imatinib	<b>Early GIST</b>	SSG adjuvant Pivotal Phase III study 1yr vs. 3 yrs	<ul style="list-style-type: none"> <li>Met primary &amp; secondary end points</li> <li>Dossier submitted in US &amp; EU Q3 2011</li> <li>US – priority review granted</li> </ul>
	<b>Acromegaly/Cushing's</b>	Pivotal Phase III studies	<ul style="list-style-type: none"> <li>Acromegaly study met primary endpoint</li> <li>Cushing's disease: EU under review</li> </ul>
 <b>Tasigna</b> nilotinib	<b>CML</b>	Studies vs. Glivec® : ENESTnd: in de novo CML ENESTcmr: switch to Tasigna® in pts <CMR @ 2y	<ul style="list-style-type: none"> <li>CMR: first data (12m) show twice as many deep molecular responses on Tasigna</li> <li>ND: 36m data: Confirmed superiority of nilotinib over imatinib in the primary &amp; secondary efficacy endpoints</li> </ul>
	<b>Myelofibrosis</b>	Pivotal Phase III trials (COMFORT I & II)	<ul style="list-style-type: none"> <li>Met primary endpoint</li> <li>EU – Dossier submitted in June 2011</li> <li>US- FDA Approved in Q4 (Incyte)</li> </ul>
 <b>EXJADE</b> deferasirox	<b>NTDT<sup>1</sup></b>	Pivotal Phase II trials	<ul style="list-style-type: none"> <li>Met primary endpoint</li> <li>Submission on-track for year-end</li> </ul>

1. Non transfusion dependent thalassemia 2. Incyte has rights INC424 in the US; Novartis has rights in the rest of the world. Incyte conducted COMFORT I and Novartis conducted COMFORT II. Incyte obtained FDA approval for INC424 under the name Jakafi(TM) (ruxitinib) in 2011.

## We Had a Strong Presence at ASH and SABCS 2011



125 Abstracts – 32  
Oral, 82 Posters

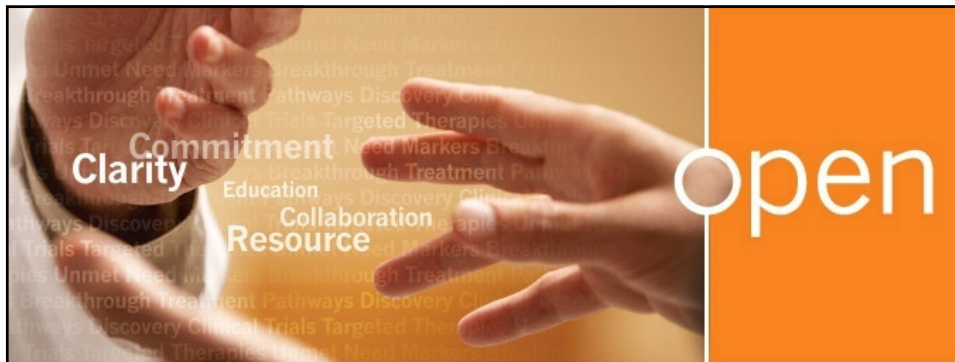


36 Abstracts – 6  
Oral, 33 Posters/  
Poster Discussions

### Highlights

- **Tasigna®**, CML
  - ENESTcmr, first results
  - ENESTnd 36 month update
- **INC424, Myelofibrosis : COMFORT I, II:** Long term follow up data
- **Exjade®**, NTD: Pivotal data in non-transfusion dependent thalassemia
- **Afinitor®**, ER+/ HER2- advanced breast cancer Updated Phase III BOLERO-2 data

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### Key pipeline data from H2 2011

Alessandro Riva, MD  
EVP and Global Head Development, Oncology

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## Focus for today

### Update at 2011 SABCS

Afinitor (Everolimus): Breast Cancer	BOLERO-2 (Pivotal Randomized trial) - 12 month Follow-up
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### Update at 2011 ASH

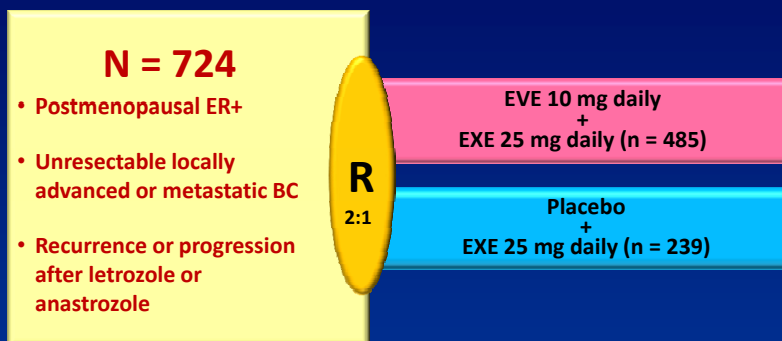
Tasigna (Nilotinib): CML	ENESTnd (Pivotal Randomized trial) - 36 month Follow-up ENESTcmr (Randomized trial) – 12 month Follow-up
INC424 (Ruxolitinib): Myelofibrosis	COMFORT I & II (Pivotal Randomized trials) : <ul style="list-style-type: none"> <li>• Efficacy of ruxolitinib across patient subgroups</li> <li>• Update on Overall survival (COMFORT-1)</li> </ul>
Exjade (Deferasirox): Non-transfusion dependent Thalassemia	THALASSA (Pivotal Randomized trial)

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## BOLERO-2 (Ph III): Everolimus in Advanced BC

**AFINITOR**  
(everolimus) Tablets

mTOR  
inhibitor



**Stratification:** Sensitivity to prior hormone therapy and presence of visceral metastases

### Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; EXE = exemestane; ORR, overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QOL = quality of life.  
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

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## BOLERO-2: Statistical Design

- Primary endpoint: PFS
  - Design: HR = 0.74, 528 events, 90% power
  - Interim analysis after 359 events, O'Brien-Fleming boundary

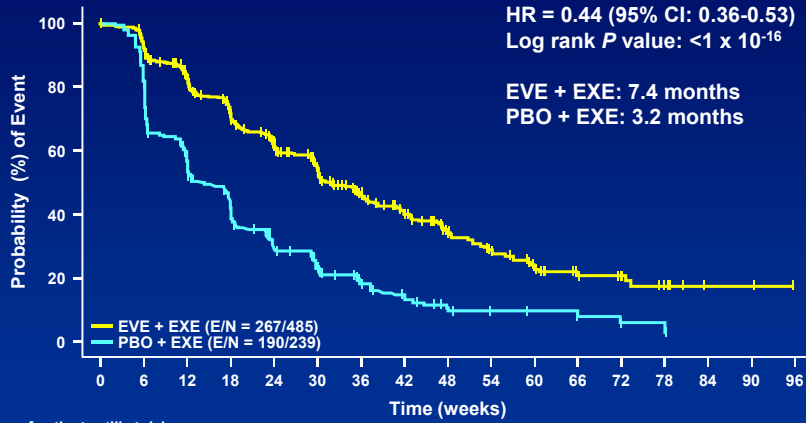
**PFS crossed boundary for efficacy at interim analysis (local & central)**

- Cut-off date for this update: July 8, 2011
  - Median duration of follow-up: 12.5 months
  - 457 PFS events based on local radiology review
  - 282 PFS events based on central radiology review

## BOLERO-2 (12 mo f/up): Patient Disposition

Disposition	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Protocol therapy ongoing	29	10
Discontinued	71	90
Disease progression	52	83
Adverse event	8	3
Subject withdrew consent	9	3
Death due to AE	1	<1
New cancer therapy	<1	<1
Protocol deviation	<1	0
Administrative problems	<1	0

## BOLERO-2 (12-month f/up): PFS Local



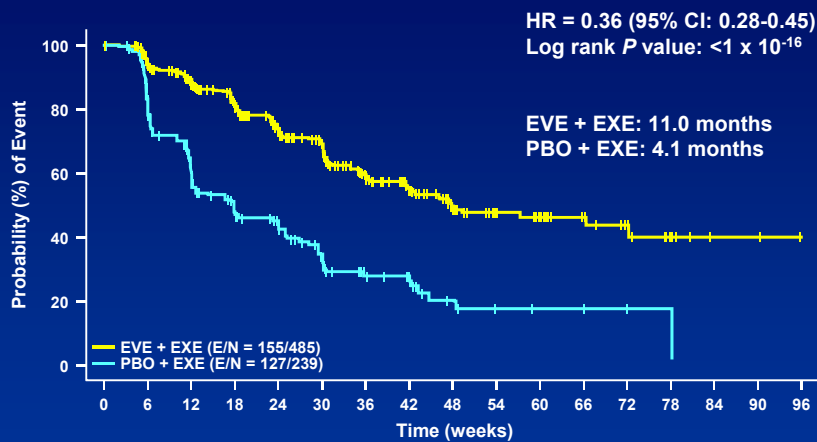
Number of patients still at risk

Everolimus	485	436	365	303	246	188	136	96	64	45	34	21	13	9	2	2	0
Placebo	239	190	131	95	63	45	29	19	12	8	6	6	4	2	0	0	0

CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free survival.  
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

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## BOLERO-2 (12 mo f/up): PFS Central



Number of patients still at risk

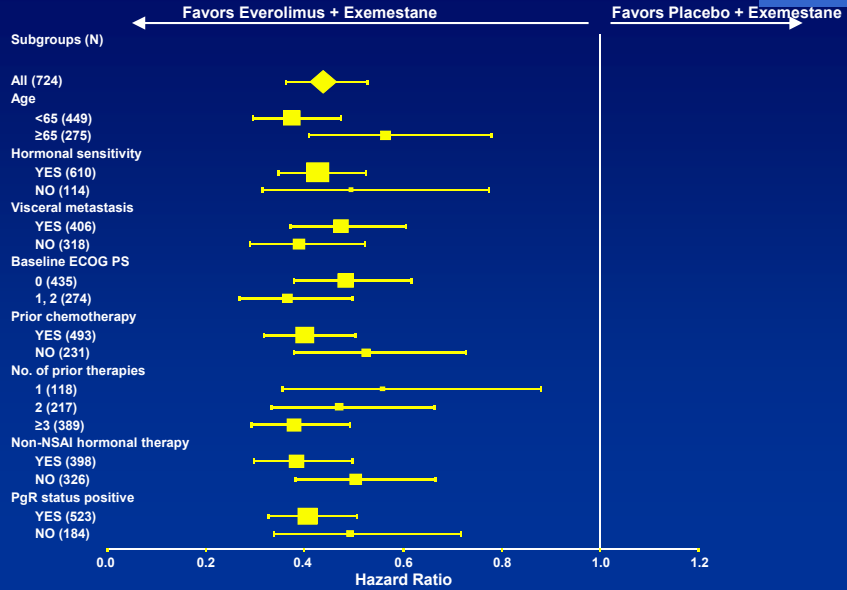
Everolimus	485	422	351	284	224	176	119	86	57	38	32	22	12	7	2	2	0
Placebo	239	179	112	74	56	36	23	18	8	5	4	4	3	1	0	0	0

CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free survival.  
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

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## BOLERO-2 (12 mo f/up): PFS in Subgroups

**AFINITOR**  
(everolimus) Tablets  
mTOR  
inhibitor



PFS = progression-free survival; PgR = progesterone receptor; NSAI = nonsteroidal aromatase inhibitor; ECOG PS = Eastern Cooperative Oncology Group performance status. Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

## BOLERO-2 (12 mo f/up): Overall Survival

**AFINITOR**  
(everolimus) Tablets  
mTOR  
inhibitor

- As of July 8, 2011: 137 deaths
  - 17.2% in everolimus arm
  - 22.7% in placebo arm
- OS final analysis at 392 events
  - 80% power to detect 26% reduction in risk

OS = overall survival; PFS = progression-free survival. Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

## BOLERO-2 (12 mo f/up): Most Common Adverse Events



	Everolimus + Exemestane (n = 482), %			Placebo + Exemestane (n = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	59	8	0	11	<1	0
Rash	39	1	0	6	0	0
Fatigue	36	4	<1	27	1	0
Diarrhea	33	2	<1	19	<1	0
Appetite decreased	30	1	0	12	<1	0
Nausea	29	<1	<1	28	1	0
Non-infectious Pneumonitis*	15	3	0	0	0	0
Hyperglycemia*	14	5	<1	2	<1	0

\*Adverse Events of clinical interest  
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

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## BOLERO-2 (12 mo f/up): Summary & Conclusions



### Summary

- Addition of everolimus to exemestane prolongs PFS in patients with ER+ HER2- breast cancer refractory to nonsteroidal aromatase inhibitors
  - Local: median 7.4 vs. 3.2 months, HR = 0.44,  $P < 1 \times 10^{-16}$
  - Central: median 11.0 vs. 4.1 months, HR = 0.36,  $P < 1 \times 10^{-16}$
- Benefit is observed in all subgroups
- Adverse events are consistent with previous experience with everolimus

### Conclusions

- Everolimus is the first agent to significantly enhance the efficacy of hormonal therapy in patients with ER+ HER2- breast cancer
- The addition of everolimus in advanced Breast cancer could represent a paradigm shift in the management of this patient population

Hortobagyi G. et al, SABCS 2011 (Abstract #S3-7)

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## Breast Program Update



- BOLERO-2**
  - Pivotal Phase III Trial - Evaluating everolimus in combination with exemestane was conducted in post-menopausal women with ER positive refractory ABC
  - Submission on-track for Dec 2011

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- BOLERO-1**
  - Pivotal Phase III trial - Everolimus (RAD001) in combination with trastuzumab and paclitaxel in first-line treatment of women with HER2+ locally recurrent or metastatic breast cancer
  - Enrollment completed

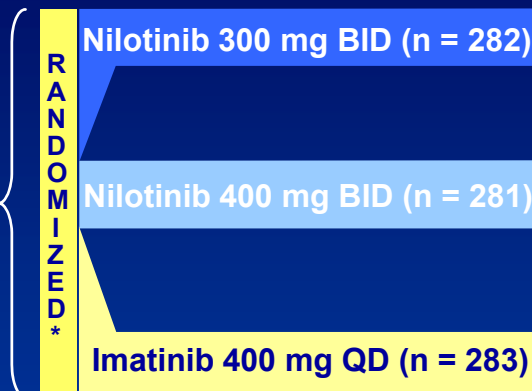
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- BOLERO-3**
  - Pivotal Phase III trial –Everolimus (RAD001) in combination with trastuzumab and vinorelbine in the treatment of women with HER2+ locally-advanced or metastatic breast cancer previously treated with taxanes and resistant to trastuzumab.
  - Enrollment ongoing

## ENESTnd 36 month follow-up Study Design



- N = 846
- 217 centers
- 35 countries



\*Stratification by Sokal risk score

Follow-up 5 years

## ENESTnd 36 month follow-up: Nilotinib superior to Imatinib in all major efficacy endpoints



BCR-ABL,  
cKIT

	Nilotinib 300 mg BID (N=282)	Nilotinib 400 mg BID (N=281)	Imatinib 400 mg QD (N=283)	P-value (Nilotinib 300 mg BID vs Imatinib 400 mg QD)	P-value (Nilotinib 400 mg BID vs Imatinib 400 mg QD)
Major Molecular Response (MMR#)	73.4%	70.5%	53.0%	<0.0001	<0.0001
Complete Molecular Response 4-log Reduction (MR <sup>4.0</sup> )	50.0%	43.8%	26.1%	<0.0001	<0.0001
Complete Molecular Response 4.5-log Reduction (MR <sup>4.5</sup> )	31.9%	27.8%	15.2%	<0.0001	0.0003
Progression to AP/BC	2 pts	5 pts	17 pts	0.0003*	0.0085*
Progression Free Survival (AP/BC) on Core Treatment	96.7%	98.1%	93.5%	0.0496	0.0076

\* Log Rank Test

# MMR is defined as value of  $\leq 0.1\%$  of BCR-ABL/ABL ratio on the International Scale (IS)

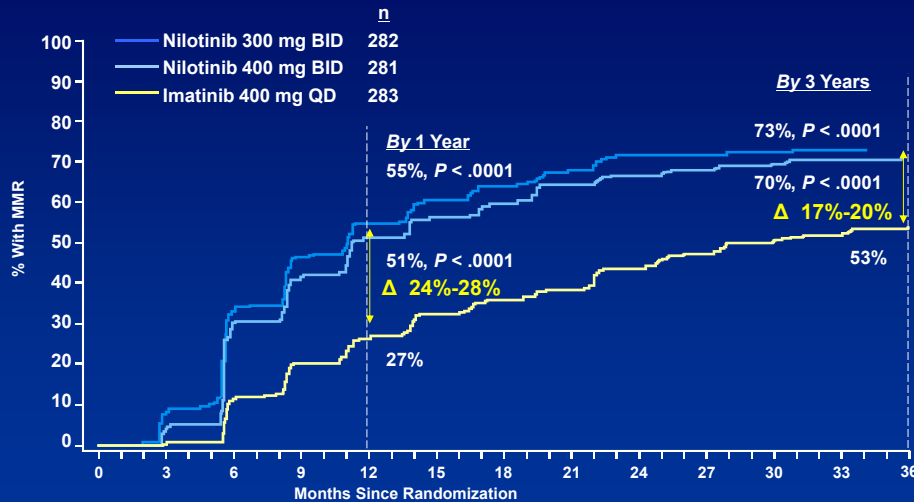
Saglio G. et al, ASH 2011 (Abstract #452)

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## ENESTnd 36 month follow-up Cumulative Incidence of MMR\*



BCR-ABL,  
cKIT



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

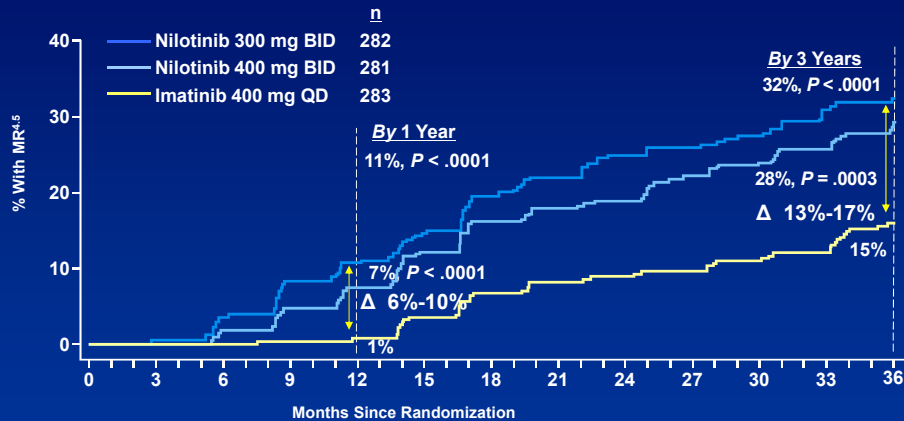
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Data cut-off: 27 Jul 2011.

## ENESTnd 36 month follow-up Cumulative Incidence of MR<sup>4.5</sup>\*



BCR-ABL,  
cKIT



\* Equivalent to BCR-ABL transcript levels of  $\leq 0.0032\%$  (IS).  
Saglio G. et al, ASH 2011 (Abstract #452)

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Data cut-off: 27 Jul 2011.

## ENESTnd 36 month follow-up Overall Survival



BCR-ABL,  
cKIT

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Total number of deaths	13	8	17
Estimated 3-year overall survival (OS)	95.1%	97.0%	94.0%
Hazard ratio (95% CI)	0.8 (0.4, 1.6)	0.5 (0.2, 1.1)	—
P value (OS)	.4413	.0639	—

- Of 38 total deaths on study, 23 were following progression to AP/BC

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

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Data cut-off: 27 Jul 2011.

## ENESTnd 36 month follow-up Deaths Following Progression to AP/BC



BCR-ABL,  
cKIT

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Deaths following progression	5	4	14
Estimated 3-year OS (Deaths following progression to AP/BC)	98.1%	98.5%	95.2%
Hazard ratio (95% CI)	0.4 (0.1, 1.0)	0.3 (0.1, 0.8)	—
P value	.0356	.0159	—

- OS considering only deaths following progression to AP/BC was significantly higher for nilotinib 300 mg BID and nilotinib 400 mg BID vs imatinib

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

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Data cut-off: 27 Jul 2011.

## ENESTnd 36 month follow-up Patient Disposition

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Still on active follow-up* or died, %	95	95	94
Still on core treatment, %	71	74	62
Discontinued core treatment and entered extension study†, %	7	1	12
Discontinued core treatment without entering extension study, %	22	25	26
Disease progression	< 1	1	4
Suboptimal response / treatment failure	2	3	4
Adverse events / lab abnormalities	10	14	11
Death	1	< 1	< 1
Other reason	8	6	7

- Few patients discontinued treatment since the 2-year follow-up
  - 4% on nilotinib 300 mg BID; 5% on nilotinib 400 mg BID; 6% on imatinib

\* Patients are either on study drug or in follow-up after discontinuation of study drug.

† Patients with suboptimal response or treatment failure were allowed to discontinue core study and enter into extension study (allowed only for treatment failure in nilotinib 400 mg BID arm).

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Data cut-off: 27 Jul 2011.

## ENESTnd 36 month follow-up 3-Year Safety Update



BCR-ABL,  
cKIT

- Minimal change in myelosuppression since the 2-year analysis
- Minimal change in biochemical abnormalities since the 2-year analysis
  - < 1% increase in lipase or bilirubin elevations, or hyperglycemia in both nilotinib arms
  - No new cases of pancreatitis or hepatic events
  - No patient discontinued due to hyperglycemia
- No QTcF > 500 msec or LVEF < 45% reported in any treatment arm during the study

## ENESTnd 36 month follow-up Conclusions



BCR-ABL,  
cKIT

- 3 years of follow-up confirms the superiority of nilotinib over imatinib, and an acceptable tolerability profile, for the treatment of patients with newly diagnosed CML-CP
- Nilotinib continues to demonstrate
  - Significantly faster and higher rates of MMR, MR<sup>4</sup>, and MR<sup>4.5</sup>
  - Significantly decreased risk of progression to AP/BC and death following progression

- Benefit-Risk ratio is significantly in favor of Nilotinib
- Nilotinib is continuing to emerge as the best option for de-novo CML patients

# ENESTcmr: Study Design and Endpoints



BCR-ABL,  
cKIT

CML-CP  
Imatinib ≥ 2 years (stable dose for ≥ 6 mos prior to study entry)

Documented CCyR by standard cytogenetics or peripheral blood BCR-ABL<sup>IS</sup> < 1%

No major toxicity on imatinib

RANDOMIZE

Nilotinib 400 mg BID

N = 207

1:1 randomization stratified by:

1. Prior imatinib (≤ 36 mos, > 36 mos) AND
2. Prior interferon (None, ≤ 12 mos, > 12 mos)

Imatinib continue same dose

4 year study

## END POINTS

### Primary

Confirmed CMR (undetectable BCR-ABL) by 12 months

### Secondary

- Kinetics of molecular response (undetectable BCR-ABL levels, MR<sup>4</sup> and MR<sup>4.5</sup> over time
  - RQ-PCR for primary and secondary endpoints was performed every 3 months and assessed at a central laboratory in Adelaide, Australia
- Safety profile

RQ-PCR, real-time quantitative polymerase chain reaction; CCyR, complete cytogenetic response

Hughes et al. ASH 2011 (Abstract #606)

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# ENESTcmr: Definition of Molecular Response



BCR-ABL,  
cKIT

Test Sensitivity > 4.5 logs reduction of BCR-ABL transcripts from standardized baseline

MR4.0	Detectable BCR-ABL transcripts ≤ 0.01% IS (≥4.0 logs) <b>or</b> Undetectable BCR-ABL
MR4.5	Detectable BCR-ABL transcripts ≤ 0.0032% IS (≥4.5 logs) <b>or</b> Undetectable BCR-ABL
CMR	Undetectable BCR-ABL: <ul style="list-style-type: none"> <li>• Unconfirmed</li> <li>• Confirmed 3 months apart (Primary endpoint)</li> </ul>

Hughes et al. ASH 2011 (Abstract #606)

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# ENESTcmr: Baseline Demographics (N = 207)



BCR-ABL, cKIT

	Nilotinib 400 mg BID n = 104	Imatinib 400-600 mg QD n = 103
Median age, years (range)	46 (23 – 82)	52 (19 – 76)
Prior duration of imatinib > 36 months, %	83	80
Prior duration of interferon, %		
None	57	55
≤ 12 months	20	21
> 12 months	23	23
Responses at baseline, %		
Missing	1	1
BCR-ABL <sup>IS</sup> > 0.1%	23	27
BCR-ABL <sup>IS</sup> > 0.01 - ≤ 0.1%	48	49
BCR-ABL <sup>IS</sup> ≤ 0.01%	26	22
CMR (Undetectable BCR-ABL)*	2	2

\*With a sample sensitivity of ≥ 4.5 logs .

Hughes et al. ASH 2011 (Abstract #606)

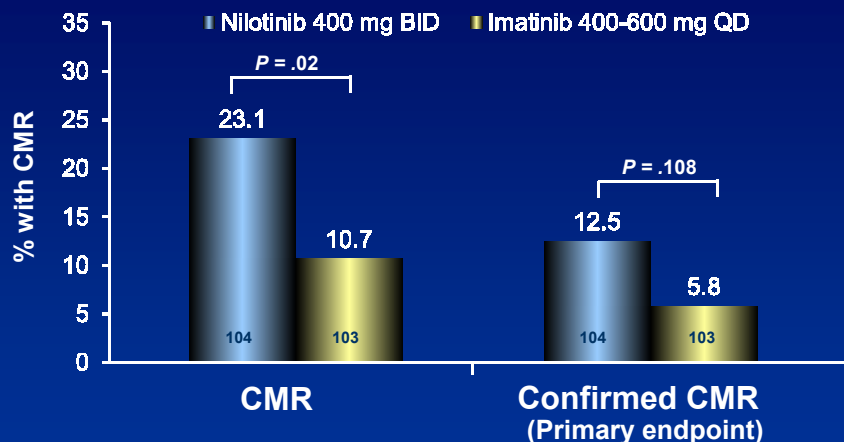
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12 month follow-up

# ENESTcmr: CMR (Undetectable BCR-ABL\*) by 12 Months (ITT)#



BCR-ABL, cKIT



Of patients on study at 12 months, 14.9% on nilotinib vs 6.1% on imatinib achieved confirmed CMR (P = .04)

\*With ≥ 4.5-log assay sensitivity.

#Intention-to-treat analyses included all patients randomized to the study, whether or not they received study drug (n = 3 pts on nilotinib did not) or had CMR at baseline (n = 2 on nilotinib; n = 2 on imatinib).

Hughes et al. ASH 2011 (Abstract #606)

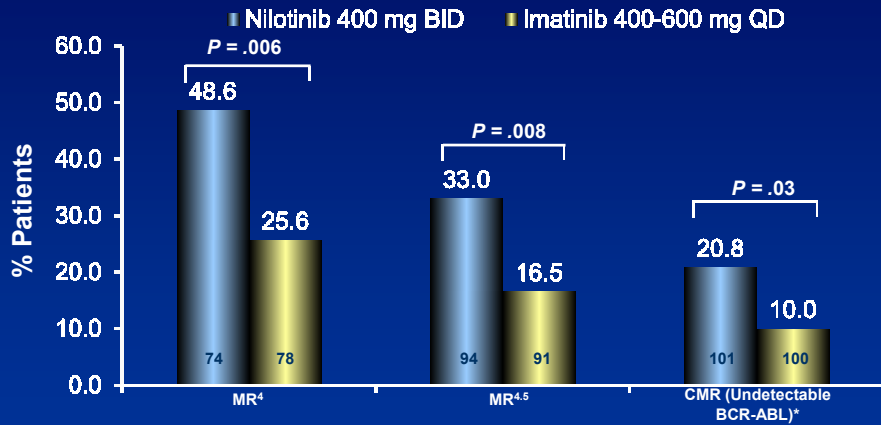
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12 month follow-up

## ENESTcmr: Molecular Response Rates by 12 Months (in patients without indicated response at baseline)



BCR-ABL,  
cKIT



\*With  $\geq 4.5$ -log assay sensitivity.

Hughes et al. ASH 2011 (Abstract #606)

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12 month follow-up

## ENESTcmr: BCR-ABL Ratio (%) Over Time



BCR-ABL,  
cKIT

Sample timepoint	Median BCR-ABL ratio (%)	
	Nilotinib 400 mg BID n = 104	Imatinib 400-600 mg QD n = 103
Baseline	.0234	.0311
3	.0152	.0258
6	.0094	.0298
9	.0070	.0205
12	.0065	.0220

Hughes et al. ASH 2011 (Abstract #606)

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12 month follow-up

## ENESTcmr: Drug-Related Adverse Events



BCR-ABL,  
cKIT

Drug-related adverse events (AEs), %	Nilotinib 400 mg BID n = 104	Imatinib 400-600 mg QD n = 103
Any AE	88	53
Grade 3/4 AEs	29	2
AEs leading to discontinuation	9	0
Serious AEs	4	0

- Patients experienced AEs early on nilotinib after switch from long-term imatinib therapy. These changes were expected and consistent with the safety profile of nilotinib observed in other studies

Hughes et al. ASH 2011 (Abstract #606)

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## ENESTcmr: Drug-Related Adverse Events Nilotinib safety profile was consistent with prior studies



BCR-ABL,  
cKIT

AEs (≥ 10%), %	Nilotinib 400 mg BID n = 101			
	Grade 1	Grade 2	Grade 3	Grade 4
Headache	17	14	2	0
Pruritis	17	5	1	0
Rash	16	6	1	0
Nausea	10	5	0	0
Fatigue	11	2	1	0
Myalgia	7	4	1	0
<b>Laboratory abnormalities (≥ 5%), %</b>				
Increased liver enzymes	9	4	5	0
Increased lipase	3	3	7	1
Increase bilirubin	5	7	1	0
Hypophosphatemia	1	4	2	0
Increased amylase	4	2	0	0

Hughes et al. ASH 2011 (Abstract #606)

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12 month follow-up

# ENESTcmr: Summary & Conclusions



BCR-ABL,  
cKIT

## Summary

- By 12 months, 12.5% vs 5.8% of patients achieved confirmed CMR on nilotinib vs imatinib ( $P = .108$ )
- Twice as many patients achieved MR<sup>4</sup>, MR<sup>4.5</sup> and CMR on nilotinib
- Patients remaining on imatinib had minimal evidence of improvement in molecular response
- Patients switched to nilotinib had a median 0.5-log reduction in BCR-ABL
- Nilotinib safety profile was consistent with prior studies

## Conclusions

- For patients with ongoing BCR-ABL positivity on imatinib, switching to nilotinib leads to faster, deeper molecular responses
- Deeper molecular responses on nilotinib may increase patient eligibility for future TKI discontinuation studies
- Ultimate success of this strategy will be assessed in the discontinuation study under evaluation

Hughes et al. ASH 2011 (Abstract #606)

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# Ruxolitinib: Phase III Trial COMFORT-I Study Design

INC424

JAK1/JAK2

## ASH 2011 update:

- To evaluate the efficacy of ruxolitinib across patient subgroups in COMFORT-I
  - Primary analysis cutoff: November 2, 2010
- To update overall survival in the COMFORT-I study
  - Analysis cutoff: March 1, 2011

### Key Inclusion Criteria

- PMF or PPV-MF, or PET-MF
- Intermediate-2 or High Risk by IWG-MRT
- Palpable spleen  $\geq 5$  cm
- Platelet count  $\geq 100 \times 10^9/L$
- JAK2 V617F positive or negative

1:1

R  
A  
N  
D  
O  
M  
I  
Z  
E

Ruxolitinib  
15 or 20 mg BID

Placebo

- Cross over to ruxolitinib possible prior to Week 24
- Study unblinded when half of patients remaining in study completed the Week 36 visit and all completed the Week 24 evaluation or discontinued treatment

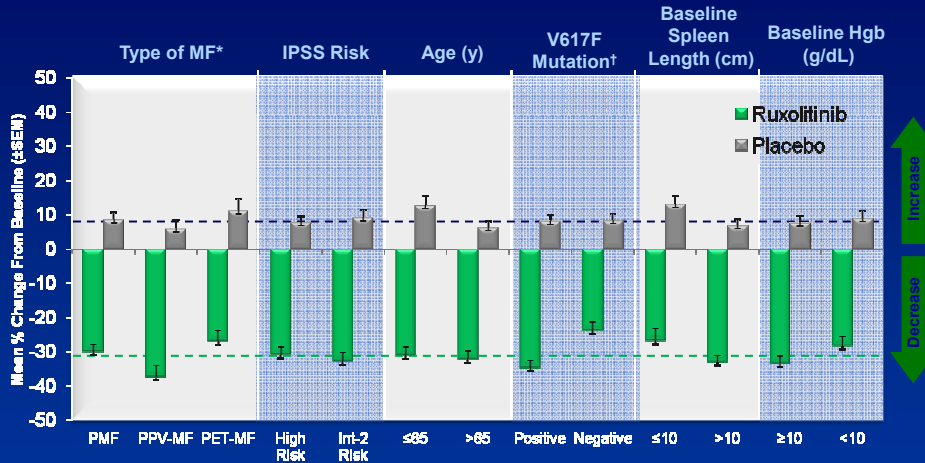
Verstovsek et al. ASH 2011 (Abstract #278)

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# COMFORT-I Spleen Volume: Percent Change From Baseline to Week 24

INC424

JAK1/JAK2



SEM, standard error of mean.

\*P-value for interaction of MF subtype by treatment=0.52; †P-value for interaction of mutation status by treatment=0.07.

Note: Dashed lines represent the mean percent change from baseline for overall treatment group.

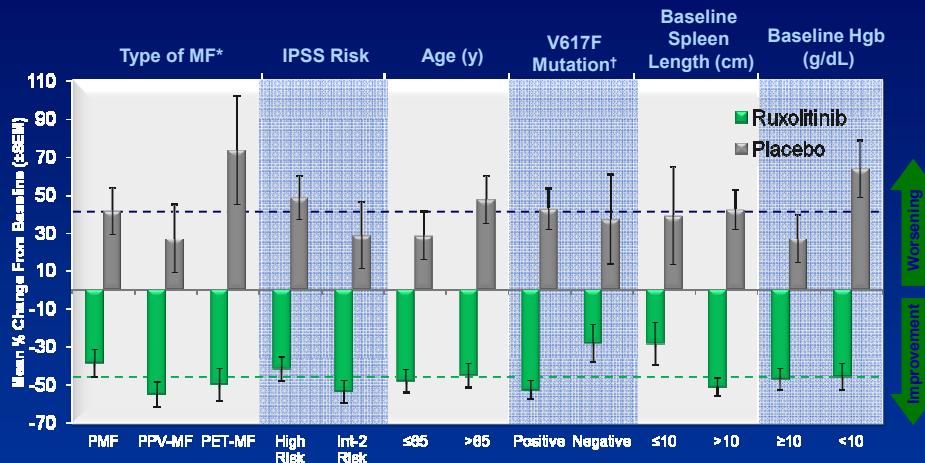
Verstovsek et al. ASH 2011 (Abstract #278)

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# COMFORT-I TSS: Percent Change From Baseline to Week 24

INC424

JAK1/JAK2



SEM, standard error of mean; TSS, total symptom score.

\*P-value for interaction of MF subtype by treatment=0.46; †P-value for interaction of mutation status by treatment 0.11.

Note: Dashed lines represent the mean percent change from baseline for overall treatment group.

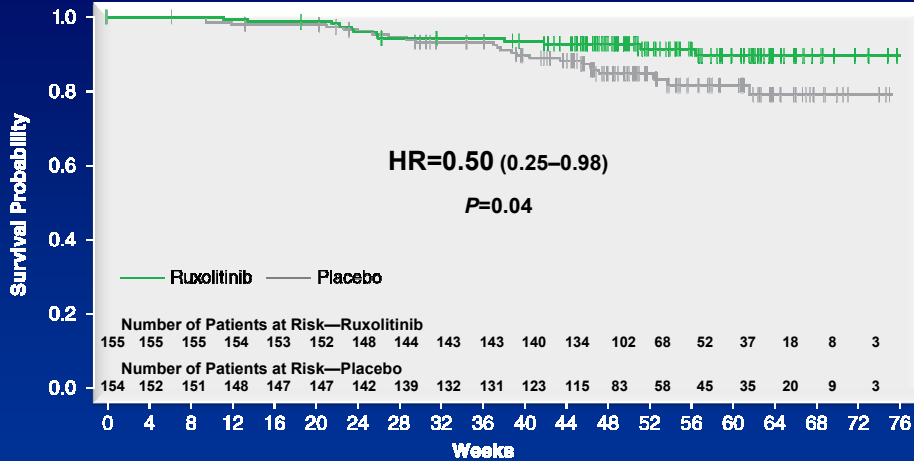
Verstovsek et al. ASH 2011 (Abstract #278)

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# COMFORT-I Overall Survival Update: ITT

INC424

JAK1/JAK2



- Overall survival analysis conducted at the time of a preplanned safety update with data cutoff 4 months after primary analysis cutoff date
- After a median follow up of 51 weeks, 13 (8.4%) deaths in ruxolitinib group and 24 (15.7%) deaths in placebo group

Verstovsek et al. ASH 2011 (Abstract #278)

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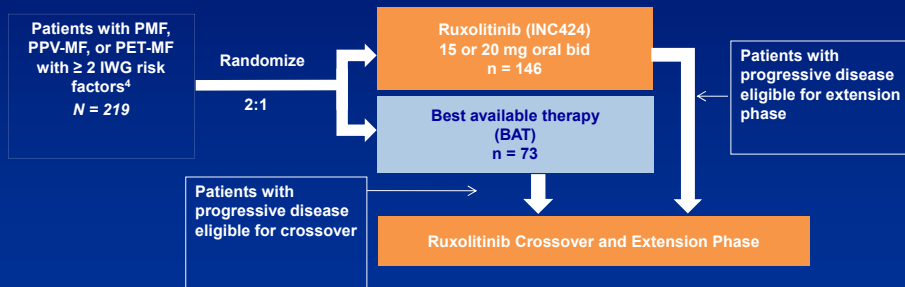
# Ruxolitinib: Phase III Trial COMFORT-II

INC424

JAK1/JAK2

## ASH 2011 update:

- To evaluate the reduction of spleen volume (primary endpoint) from baseline at week 48 across patient subgroups in COMFORT-II



- Patients were stratified based on baseline IWG risk category<sup>4</sup>

Harrison et al. ASH 2011 (Abstract #279)

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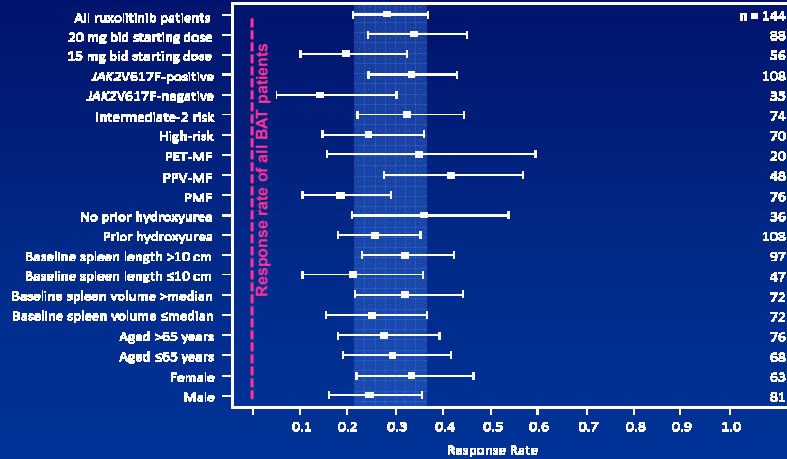
1. Verstovsek S, et al. Oral presentation at ASCO Annual Meeting; June 3-7, 2011. Abstract 6500.
2. Harrison C, et al. Oral presentation at 16th Congress of EHA; June 9-12, 2011. Abstract 1020.
3. Verstovsek S, et al. Oral presentation at ASH Annual Meeting; Dec 10-14, 2011. Abstract 278.
4. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

# COMFORT-II Efficacy by Subgroup

Proportion of Patients in Each Subgroup With  $\geq 35\%$  Reduction in Spleen Volume From Baseline at Week 48

INC424

JAK1/JAK2



- Response rates were observed for ruxolitinib-treated patients in all subgroups and were higher than patients receiving BAT

Harrison et al. ASH 2011 (Abstract #279)

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# Ruxolitinib : Program Status Update

INC424

JAK1/JAK2

Myelofibrosis

- Approved in US
- Filed in EU
- Expanded Access Program ongoing

Polycythemia Vera

- Global Phase III trial ongoing
- Filing expected in 2014

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# THALASSA study rationale in non-transfusion dependent thalassemias (NTDT)



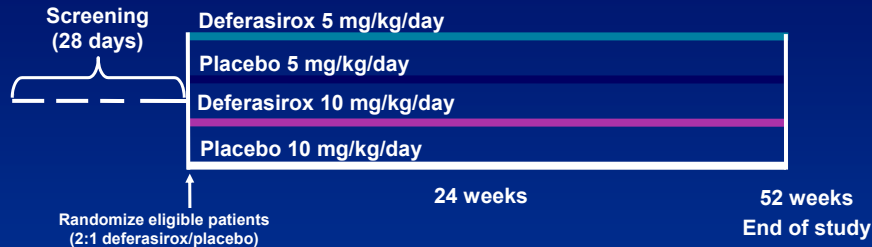
- $\beta$ -thalassemia intermedia ( $\beta$ -TI), HbE  $\beta$ -thalassemia and HbH  $\alpha$ -thalassemia patients require only occasional/no transfusions
  - Patients can develop clinically relevant iron overload<sup>1</sup> mainly as a result of increased intestinal iron absorption driven by ineffective erythropoiesis<sup>2,3</sup>
- Iron overload in NTDT increases with age and is associated with serious age-related complications<sup>4</sup>
  - Iron loads in NTDT patients in their 30s and 40s are comparable with transfusion-dependent thalassemia patients<sup>2</sup>
  - Elevated LIC is a marker of increased morbidity in  $\beta$ -TI<sup>5</sup>
  - Serum ferritin underestimates iron burden and LIC<sup>6</sup>
- Iron chelation – only option for decreasing iron burden
  - Phlebotomy contraindicated due to anemia
  - Neither deferoxamine nor deferiprone has been evaluated in prospective, well-controlled studies<sup>7-11</sup>
  - Two small, uncontrolled studies have reported on efficacy and safety of deferasirox in patients with NTDT<sup>12,13</sup>

<sup>1</sup>Taher A et al. 2008; <sup>2</sup>Pippard MJ et al. 1979; <sup>3</sup>Pootrakul P et al. 1988; <sup>4</sup>Taher AT et al. 2010; <sup>5</sup>Musallam KM et al. 2011; <sup>6</sup>Origa R et al. 2007; <sup>7</sup>Cossu P et al. 1981;137; <sup>8</sup>Chan JC et al. 2006; <sup>9</sup>Olivieri NF et al. 1992; <sup>10</sup>Pootrakul P et al. 2003;122; <sup>11</sup>Rombos Y et al. 2000;85; <sup>12</sup>Ladis V et al. 2010; <sup>13</sup>Voskandou E et al. 2010.

# THALASSA (Randomized Double blinded placebo controlled Trial): Study Design



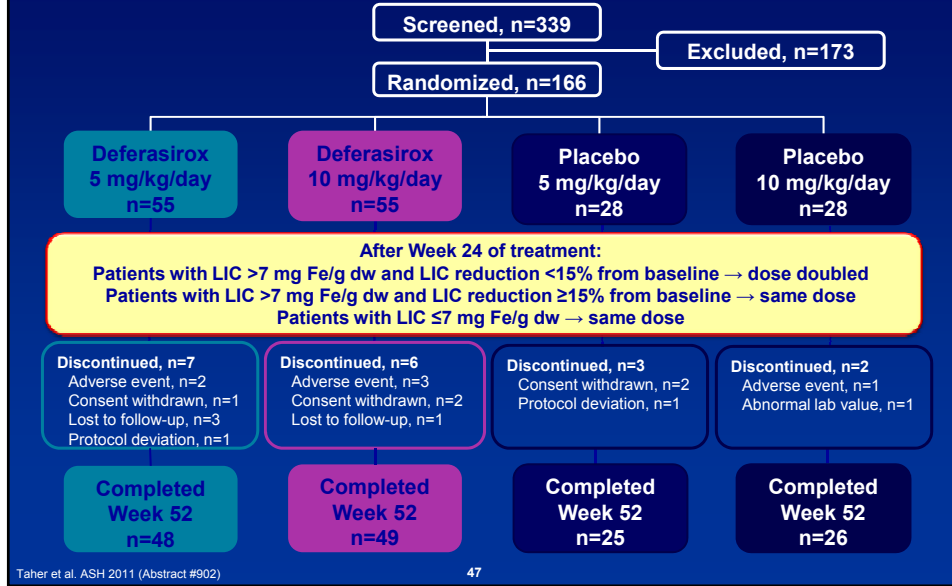
Primary Objectives: Compare efficacy of 5 & 10 mg/kg/day deferasirox to placebo in patients with NTDT based on change in LIC from baseline after 1 year of treatment



LIC by MRI		x		x
SF	-----	Evaluated monthly	-----	x
Safety	-----	Throughout	-----	x

After 6 months of treatment, patients whose LIC showed insufficient efficacy had their treatment dose doubled

## THALASSA patient disposition

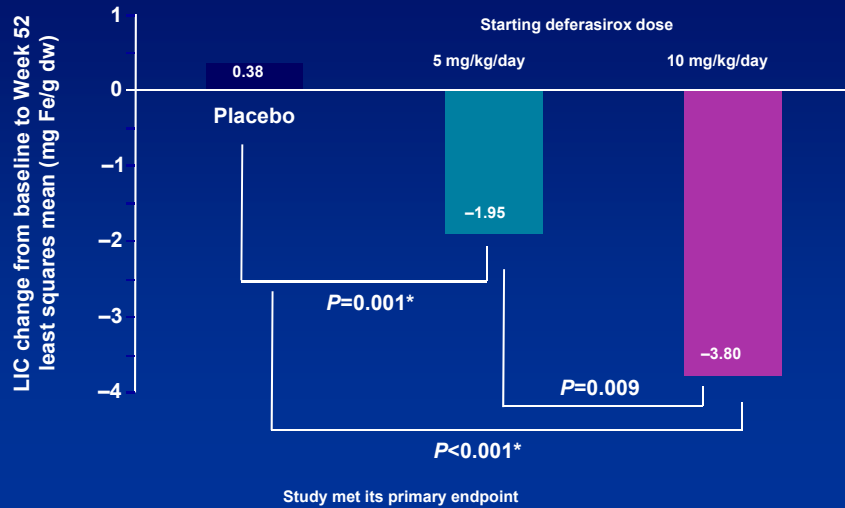


## Baseline patient characteristics

	Deferasirox 5 mg/kg/day n=55	Deferasirox 10 mg/kg/day n=55	Placebo (5 and 10 mg/kg/day) n=56
Disease, n (%)			
β-thalassemia intermedia	32 (58.2)	30 (54.5)	33 (58.9)
α-thalassemia	5 (9.1)	9 (16.4)	8 (14.3)
HbE/β-thalassemia	18 (32.7)	16 (29.1)	15 (26.8)
Median age, years (min, max)	33 (10, 60)	31 (12, 69)	32 (10, 59)
Pediatric patients <18 years, n (%)	6 (10.9)	7 (12.7)	8 (14.3)
Male:female, n	29:26	29:26	31:25
Prior transfusions, n (%)	49 (89.1)	50 (90.9)	46 (82.1)
Previous chelation, n (%)			
Deferoxamine (DFO)	8 (14.5)	16 (29.1)	20 (35.7)
Deferiprone (DFP)	7 (12.7)	15 (27.3)	17 (30.4)
Deferiprone (DFP)	-	1 (1.8)	3 (5.4)
DFO + DFP	1 (1.8)	-	-
Mean LIC ± SD, mg Fe/g dw	13.1 ± 7.3	14.6 ± 7.9	15.9 ± 10.9
Median SF, ng/mL (min, max)	988 (370, 5609)	1015 (342, 4224)	994 (304, 6419)

Taher et al. ASH 2011 (Abstract #902) 48

## Deferasirox significantly reduces LIC compared with placebo



Taher et al. ASH 2011 (Abstract #902)

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## Most common ( $\geq 10\%$ in any group) investigator-assessed AEs regardless of study drug relationship



Adverse events, n (%)	Deferasirox 5 mg/kg/day n=55	Deferasirox 10 mg/kg/day n=55	Placebo 5 mg/kg/day n=28	Placebo 10 mg/kg/day n=28	Total n=166
Any AE	42 (76.4)	43 (78.2)	20 (71.4)	25 (89.3)	130 (78.3)
Upper respiratory tract infection	7 (12.7)	8 (14.5)	5 (17.9)	6 (21.4)	26 (15.7)
Headache	2 (3.6)	9 (16.4)	4 (14.3)	4 (14.3)	19 (11.4)
Nausea	4 (7.3)	5 (9.1)	1 (3.6)	6 (21.4)	16 (9.6)
Diarrhea	3 (5.5)	5 (9.1)	2 (7.1)	4 (14.3)	14 (8.4)
Nasopharyngitis	5 (9.1)	4 (7.3)	2 (7.1)	3 (10.7)	14 (8.4)
Oropharyngeal pain	4 (7.3)	6 (10.9)	–	2 (7.1)	12 (7.2)
Rash	2 (3.6)	6 (10.9)	1 (3.6)	2 (7.1)	11 (6.6)
Abdominal pain	2 (3.6)	4 (7.3)	1 (3.6)	3 (10.7)	10 (6.0)

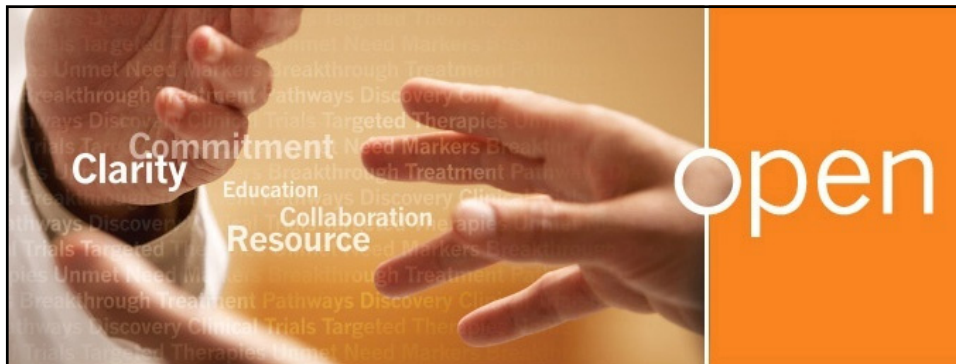
Overall AE incidence comparable between deferasirox and placebo

Taher et al. ASH 2011 (Abstract #902)

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## Conclusions

- High baseline iron burden and increasing LIC and SF in placebo highlight the need for iron chelation therapy
- Compared with placebo, deferasirox at starting doses 5 and 10 mg/kg/day with dose escalations up to 20 mg/kg/day in patients with high levels of iron overload significantly reduced LIC and SF
  - Deferasirox 10 mg/kg/day was superior to 5 mg/kg/day in reducing LIC
  - Lower dose range than required in transfusion-dependent thalassemia patients (20–40 mg/kg/day)
- Overall frequency of AEs with deferasirox in both dose groups was comparable with placebo
- Based on benefit/risk profile of deferasirox in NTD patients, chelation therapy should be considered when LIC >5 mg Fe/g dw



### Conclusion

Hervé Hoppenot  
President, Oncology

December 13, 2011

## 2011: a good year for Novartis Oncology, with an exciting year ahead in 2012

- Strong data in H2 – pivotal studies meeting primary endpoint:
  - *Afinitor*® – BOLERO-2 in ER+/HER2- Advanced Breast Cancer
  - *Afinitor*® – EXIST-2 in TSC AML<sup>1</sup>
  - *Exjade*® – THALASSA Trial in NTD<sup>2</sup>
- Major approvals in 2011:
  - *Afinitor*® – pNET<sup>3</sup>
  - *Afinitor*® – TSC-SEGA<sup>4</sup>
- Major approvals expected in 2012:
  - *Afinitor*® – ER+HER2-Advanced Breast Cancer
  - *Afinitor*® – TSC-AML
  - INC424 – MF<sup>5</sup> (EU)
  - *Exjade*® – NTD<sup>2</sup>
  - SOM230 – Cushing's Disease
  - *Glivec*® – 3 yr adjuvant GIST<sup>6</sup>

1. Tuberous sclerosis complex angiomyolipoma 2. Non transfusion-dependent Thalassemia 3. Neuroendocrine tumors of pancreatic origin 4. Tuberous sclerosis Complex, subependymal giant cell astrocytoma 5. Myelofibrosis 6. Gastrointestinal Stromal Tumors

53 | Novartis Oncology Year-end Investor Call 2011 | December 13 2011 | Business Use Only



## Appendix

54 | Novartis Oncology Year-end Investor Call 2011 | December 13 2011 | Business Use Only

## Planned filings 2011 to ≥ 2015

2011	2012	2013	2014	≥ 2015	
INC424 Myelofibrosis	Afinitor® Gastric cancer	LBH589 Multiple Myeloma	BEZ235 Solid Tumors	HCD122 Hemat. tumors	Afinitor® Lymphoma
Afinitor® TSC AML <sup>1</sup>	SOM230 Acromegaly	PKC412 ASM <sup>3</sup>	BKM120 Solid tumors	AUY922 Solid tumors	
Exjade® NTDT <sup>2</sup>		TKI258 Renal cell carcinoma	LDE225 Basal Cell Carcinoma		
Afinitor® ER+ Breast cancer		Afinitor® HER2+ Breast cancer	INC424 Polycythemia vera		
		Afinitor® HCC <sup>4</sup>	PKC412 AML <sup>5</sup>		
		SOM230 Carcinoid	Tasigna® cKIT Melanoma		

1. Tuberosus sclerosis complex angiomyolipoma®  
 2. Non-Transfusion-Dependent Thalassemia  
 3. Aggressive systemic mastocytosis  
 4. Hepatocellular carcinoma  
 5. Acute myeloid leukemia

Legend:  
New molecule  
New Indication