



## Development at Roche

### *Participating in and driving the paradigm shift*

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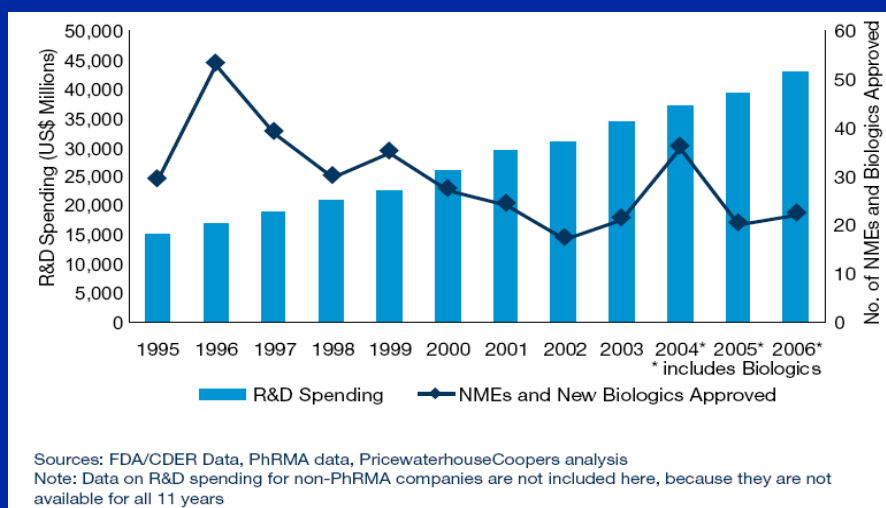
## Our new R&D model: Paradigms changes

### Franchises and assets

### Summary

## Decreasing R&D productivity

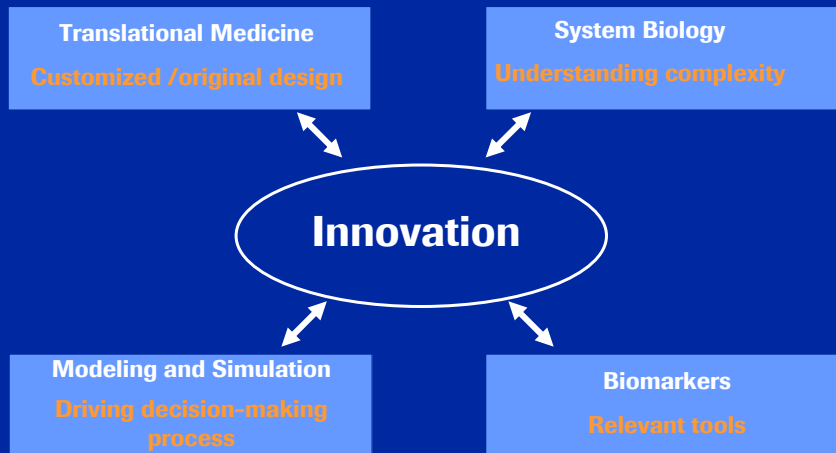
*Need for new approaches to reverse the trend*



Source: Price Waterhouse Coopers; Pharma 2020

## New R&D model

*Innovation truly at its core*



## Creating New Differentiated Medicines

*Achieved in a sustained fashion*

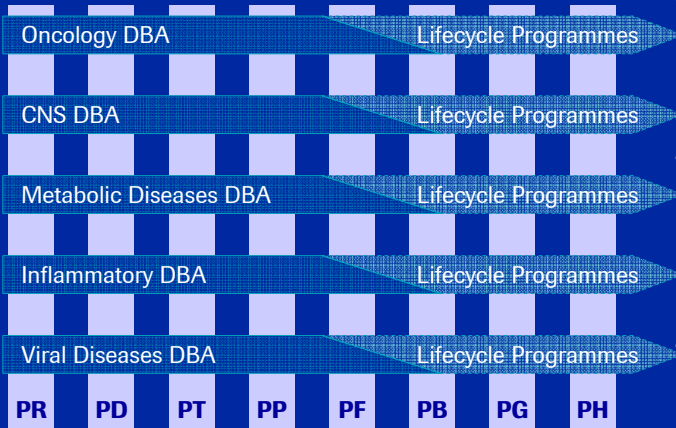


- Informed decisions based on **deep knowledge of target and disease biology**:
  - Biomarkers
  - Importance of focus
- Encourage teams to take on non-chartered territories and **take risks**:
  - Innovation does not come from well established pathways
- Create interface between R&D that allows **collaborative, multi-disciplinary work**
- Leverage the **new methodologies**



## New R&D Model

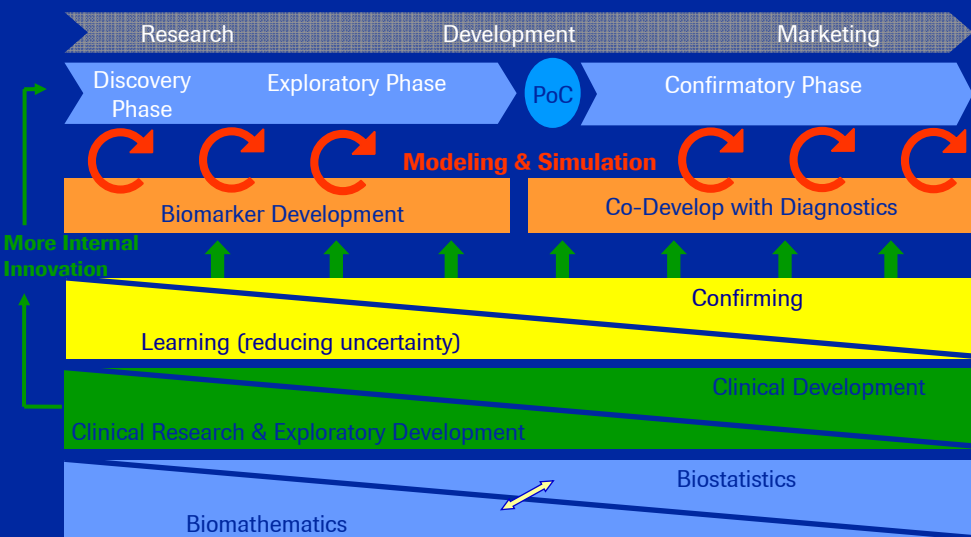
*Cross - functional, translational, differentiated*



- Integrate exploratory development expertise in cross-functional projects
- Deliver translational medicine approaches to select high-quality compounds for full development
- Apply and implement better-profiled and differentiated molecules in late-stage development

## Development does never stop

*Continuous with integration of biomarkers across development*



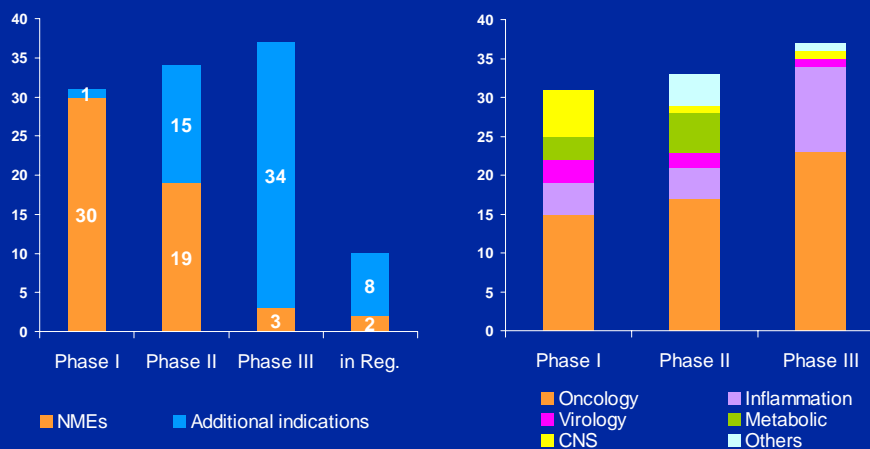
## Our new R&D model: Paradigms changes

### Franchises and assets

### Summary

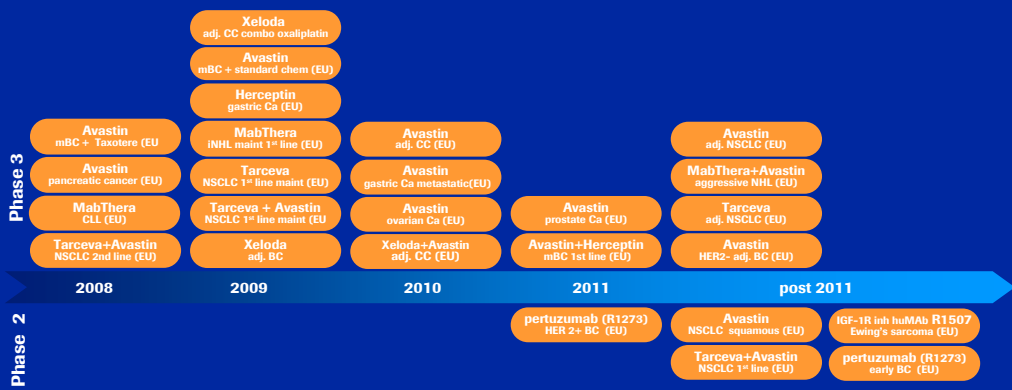
## Pipeline: 54 NMEs and 58 additional indications

*Staying strong in oncology and diversifying into new areas*





# Projected Oncology Submissions (Roche-Managed) Over the coming years



Status as of December 31, 2007 Unless stated otherwise, submissions will occur in US and EU

# Avastin still early in its journey Realising full potential across tumour types



Tumour	Early/adjuvant (Potential for cure)	Advanced/metastatic (Extending life)	
		1 <sup>st</sup> -line of treatment	2 <sup>nd</sup> -line of treatment
Colon/rectal	Phase III (AVANT, NSABP C-08, E5202, E5204)	<b>Launched</b> [EU, US, JP; broad label in 1st and subsequent lines]	
Lung (NSCLC)	Phase III (E1505)	<b>Launched</b> [EU majority of chemos, US carboplatin/paclitaxel]	Phase III (BETA Lung w/Tarceva)
Breast (HER2-)	Phase III (BEATRICE, E5103)	<b>Launched</b> [EU paclitaxel] Phase III (AVADO, RIBBON-1)	Phase III (RIBBON-2, incl. w/Xeloda)
Breast (HER2+)	Phase III (BETH w/Herceptin)	Phase III (AVEREL w/Herceptin)	-
Kidney (RCC)	-	<b>Launched</b> [EU; with interferon]	

**Avastin also trialed in gastric, ovarian, prostate, aNHL, and brain (GBM)**

(Trial names) [Approval status]. More trials are ongoing than listed above.

## Attacking the HER2 pathway from multiple angles



*Pertuzumab moving forward, Trastuzumab-DM1 in-licensed*

	Herceptin	Pertuzumab	Trastuzumab-DM1
<b>Mechanism</b>	Specifically targeting HER2  Inhibits HER2-mediated signalling	First in class HER dimerization inhibitor  Inhibits multiple HER-mediated pathways	Binds to HER2 and delivers intracellularly a potent cytotoxic agent in a targeted manner
<b>Phase of development</b>	Approved for adjuvant and mBC (HER2+)	Phase III CLEOPATRA FPI Q1 2008	Phase II FPI Q3 2007
<b>Efficacy data</b>	Survival benefit In adjuvant and metastatic HER2+ BC	18% response rate 39% clinical benefit rate	Promising phase I data at ASCO 2007
<b>Newsflow</b>	Unprecedented benefit – standard of care	Phase II final results in 2008	Partnered with Genentech

## Examples of new market opportunities



### Trastuzumab-DM1- *Very promising early data (Phase 1 data)*

(24 pts evaluated, - 6 objective responses, 4 responses on-going at the last data cut-off; the longest has persisted over 8 months- No unexpected cardiotoxicity so far

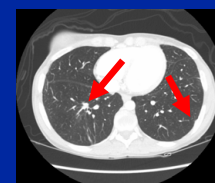
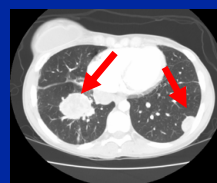
**Moved into Phase II**

### 3rd generation Anti-CD20s *Acquisition of Glycart paying off*

Increased CD20 binding and apoptosis  
Increased ADCC; Reduced CDC

**Moving into Phase II soon**

### IGF1-R Inhibitor – *Impressive early results Eligibility as multi-tumor compound?*



Restaging Week 6

**Unique Features-** Selective to IGF pathway which is a key factor in tumor growth

**Drivers for Value** – IGF pathway linked to many tumor types

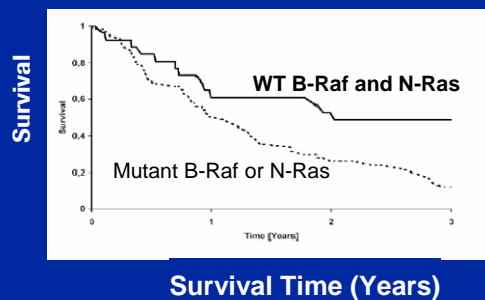
**Moved into Phase II**

ADCC= (antibody dependent cell-mediated cytotoxicity); CDC= (complement dependent cytotoxicity)

## Tailoring Early Clinical Trials: Example Prospective Patient Selection and Co-development of Pharmacodiagnosics



- About 15% of all human cancers have B-Raf mutations. V600E BRAF is causally involved in tumor growth and maintenance and is associated with worse prognosis.
- The efficacy of a BRAF inhibitor is assessed in Phase I in V600E-bearing tumors, including melanoma and CRC patients.
- Development of a pharmacodiagnostic assay for BRAF V600E mutation for Phase I, essential to allow prospective selection of patients for the trial.



Cancer Res 2006; 66: (2). January 15, 2006  
Houben et al. Journal of Carcinogenesis, 2004

## The future: Combination of targeted therapies

*Roche in lead*



	NSCLC			Breast Cancer				Pancreatic
<b>Study</b>	ATLAS (Phase III)	BETALung (Phase III)	Phase II	AVEREL (Phase III)	Pegram (Phase II)	Phase III	Phase II	AVITA (Phase III)
<b>Patient population</b>	1 <sup>st</sup> line maintenance non-squam.	2nd line	2nd line	1st line	1st line	Adjuvant	2nd line	1st line
<b>Treatment regimen</b>	CT + Avastin - > Avastin ± Tarceva	Tarceva ± Avastin	Avastin + Tarceva vs. Avastin + CT vs. CT	Herceptin + Taxotere ± Avastin	Herceptin + Avastin	Herceptin + Avastin tbd	Herceptin + Omnitarg	Gemcitabine/ Tarceva ± Avastin
<b>Status</b>	Started Q4'05	Started Q2'05	Presented ASCO'06 SABC '06	Started Q3 '06	Presented SABC '06	Planned	Ongoing	Started H1'06

### Potential patient benefits

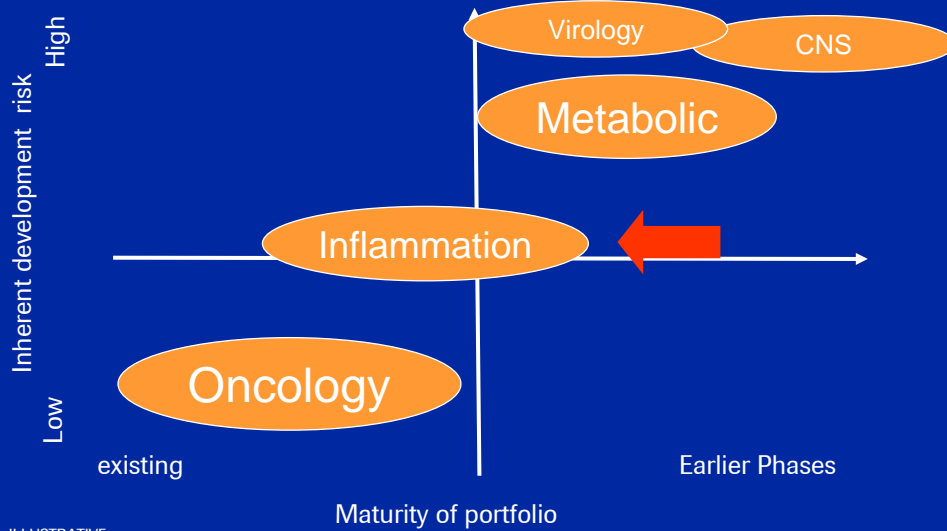
- higher efficacy
- individualized treatment
- better tolerability

**Roche setting the standard of care in combined targeted therapies**

## Key drivers for long term development in place



*Develop the short term drivers while not 'leaving' the others*

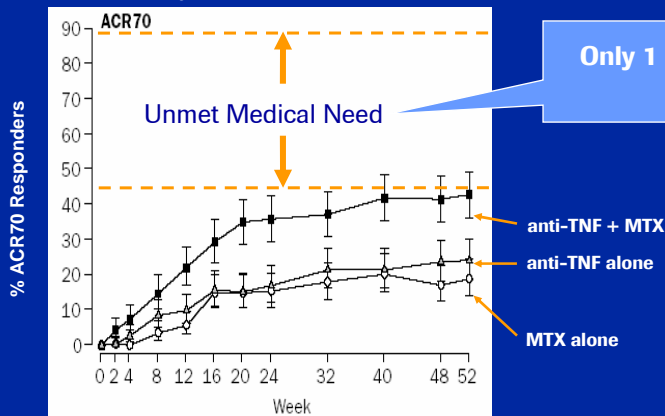


ILLUSTRATIVE

## Rheumatoid Arthritis: Not all patients respond to current therapy



Gold standard therapy  
anti-TNF + MTX



Only 1 of 3 patients receives significant benefit

Unmet Medical Need

ACR 70 = 70% Improvement in:

- Disease activity - patient
- Disease activity - physician
- Patient assessment of Pain
- Physical disability
- Acute phase reactants - CRP, ESR

## Actemra



*Potential to become a significant new RA treatment*

### First-in-class agent

- Humanized monoclonal antibody blocking the activity of IL-6 via inhibition of the IL-6 receptor
- Conclusions from phase III Jap trials
  - Impressive efficacy in DMARD inadequate responders
  - Effective as monotherapy
  - Well tolerated

Approved in Japan in April 2008

### Large international phase III program

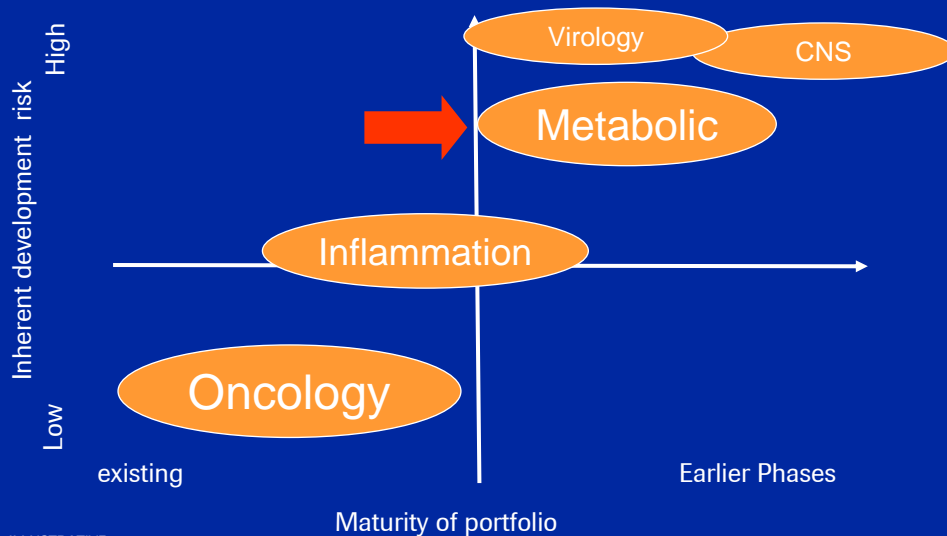
- 5 registration trials (>4'000 patients)
- Mono and combo therapy
- Patient populations studied:
  - MTX inadequate responders
  - DMARD inadequate responders
  - Anti-TNF $\alpha$  inadequate responders
  - MTX naïve patients
- **First 4 trials all met primary endpoint**

Global filing Nov 2007

## Key drivers for long term development in place



*Develop the short term drivers while not 'leaving' the others*



## Metabolic Portfolio

### *Promising Late-Stage Assets*



- CETPi first phase III entry
- Compounds approaching phase III
  - GLP-1
  - DPP-IV
  - Aloglitazar
- Update on Diabetes portfolio at ADA, June 2008

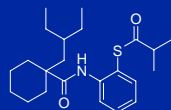
## CETP Inhibitors

### *R1658 is a unique CETPi*

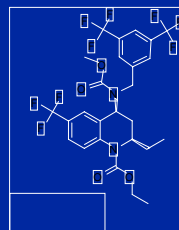


- In contrast to the majority of other CETPi, R1658 has a different chemical backbone to Torcetrapib
- In patients treated with R1658, HDL is of normal composition
- In pre-clinical models and in clinical trials up to phase II, data showed that R1658 at therapeutic doses had a similar safety profile to placebo, including effects on blood pressure and RAAS activation

**R1658**

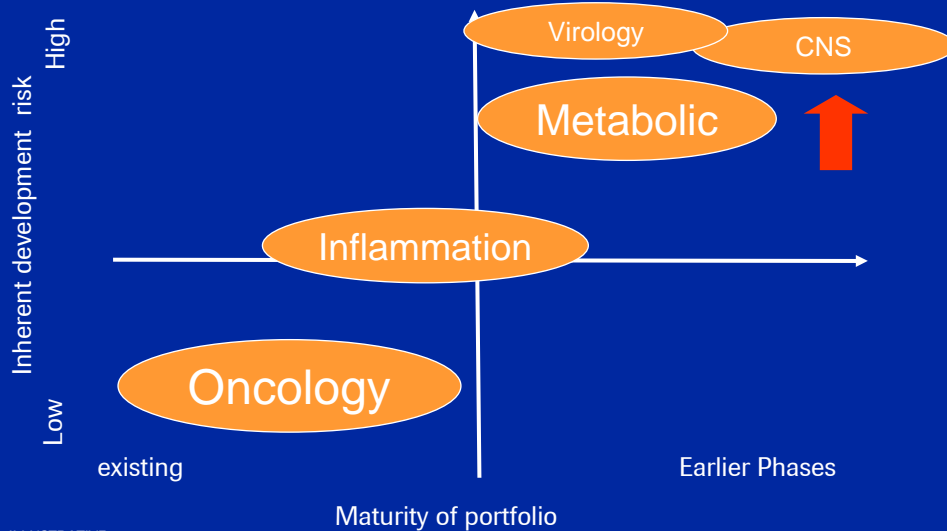


**Torcetrapib**



## Key drivers for long term development in place

*Develop the short term drivers while not 'leaving' the others*



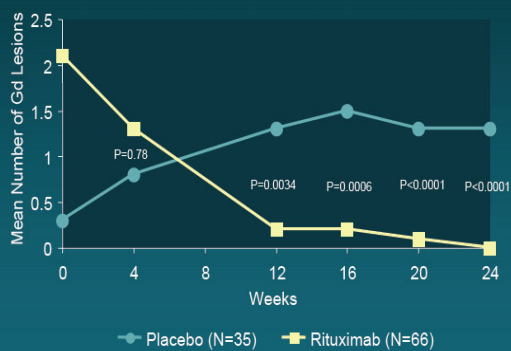
ILLUSTRATIVE

## New market opportunities: Anti-CD 20 Strategies in MS



*Very promising signals from Phase II*

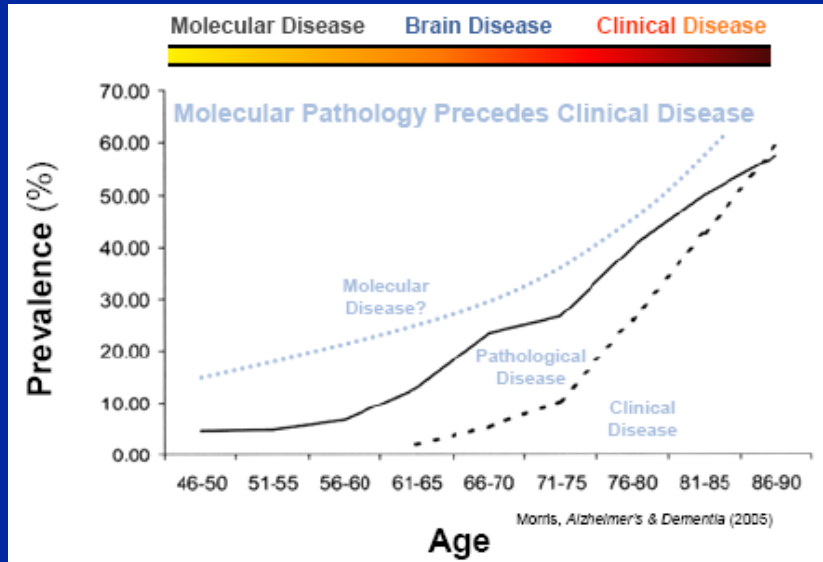
**Mean Gd-Enhancing Lesion Count (ITT Population)**



Missing values imputed by average of available data

- Total cumulative mean number of gadolinium lesions was reduced by 91 % (p<0.0001)
- Patients with relapses over 24 weeks in the treated arm was 14.5 % compared to 34.3 % in the placebo (58 percent relative reduction, p = 0.0238)
- Ocrelizumab Phase II placebo-controlled program ongoing in RRMS

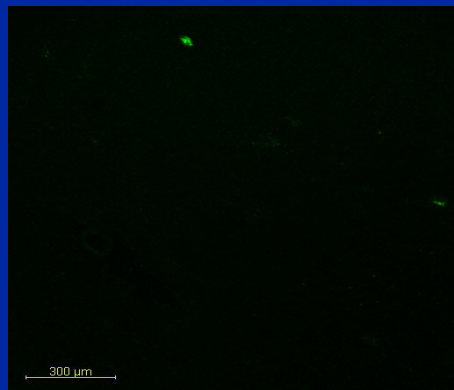
## Future Role of Biomarkers – Prodromal AD



## Efficacy of RO4909832 (mAb-31) *In Vitro* Removal of plaques from human AD brain



- Postmortem sections of human AD brain incubated with mAb-31 and human monocytes
- Increased concentrations cause increased clearance of amyloid plaques



Control

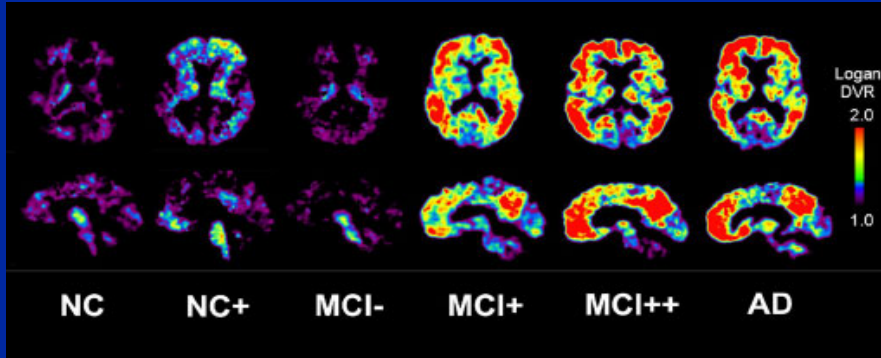
Dose 1

Dose 2

Dose 3

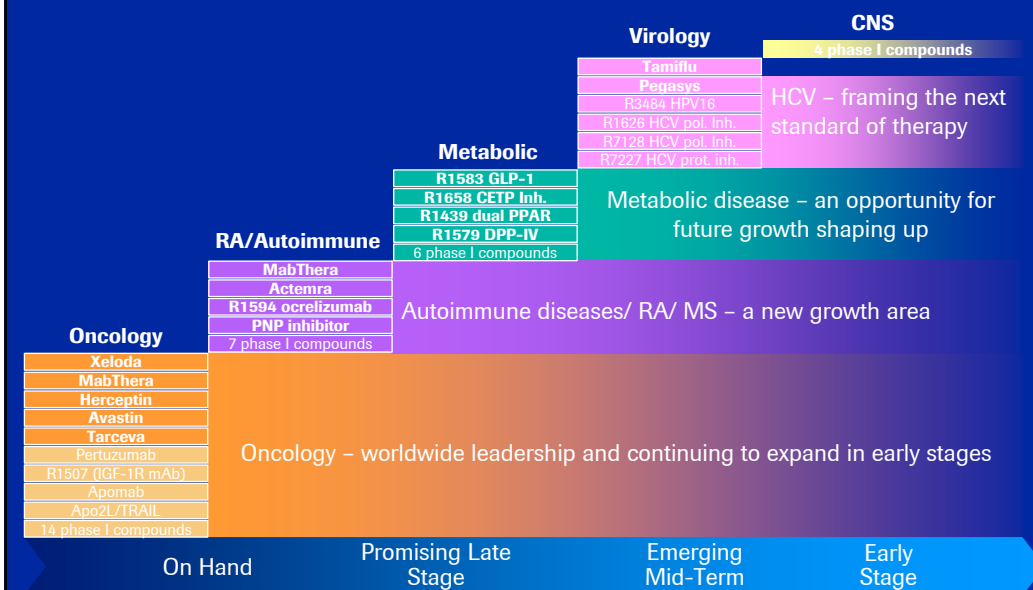
Dose 4

# 11C-PIB to measure amyloid load



Mathis et al.  
Nucl Med Biol 2007; 34(7); 809-22

# Roche key therapeutic areas Current and future pillars of growth





*We Innovate Healthcare*