

# IMiDs in MM

Jean-Luc Harousseau



Inter groupe Francophone du Myélome



# THALIDOMIDE

# THALIDOMIDE IN MM

## THE REVIVAL OF AN OLD DRUG

- Initially used as a sedative agent
- Withdrawn in 1962 due to teratogenic effects
- Occasionally used as an immunomodulator in a variety of rare diseases

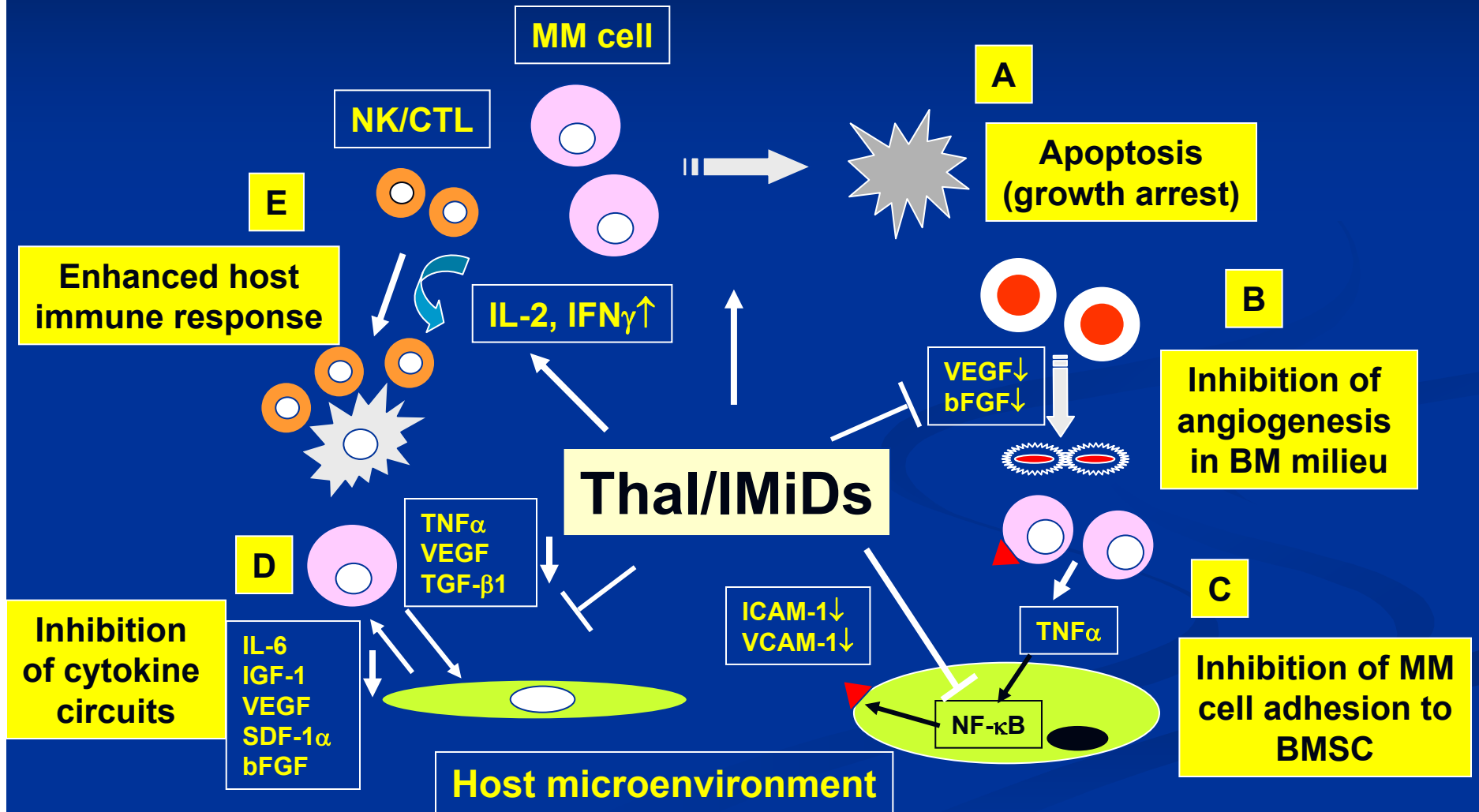
**1999**      **Antitumor activity of Thalidomide  
in refractory Multiple Myeloma**  
*Singhal et al NEJM*

# THALIDOMIDE IN MM

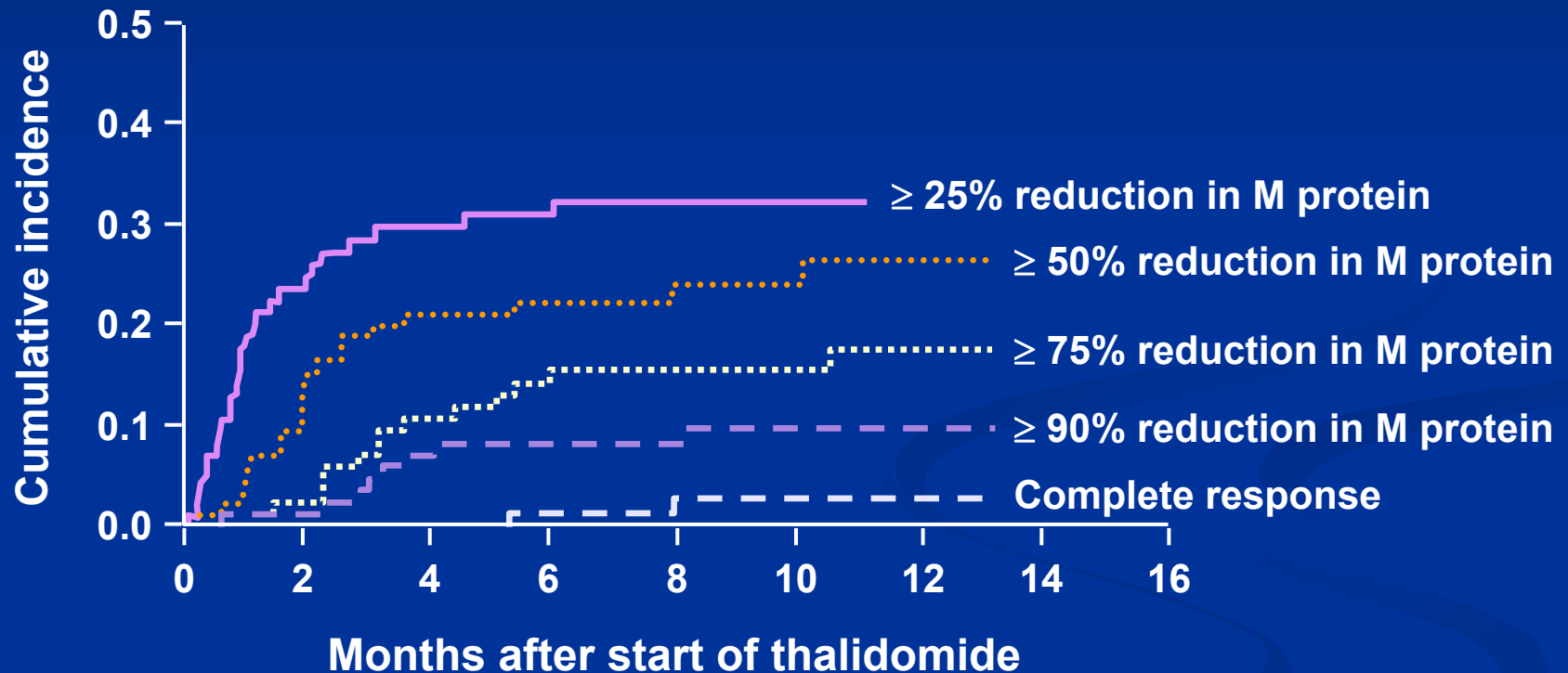
## RATIONALE

- Increased microvessel density in MM is related to disease progression (*Vacca 1994, Rajkumar 2000*)
  - Thal inhibits angiogenesis (*D'Amato 1994*)
- Immunomodulatory effects (including inhibition of TNF  $\alpha$  production) of Thal have provided rationale for its use in a variety of diseases (leprosy, Behcet, C-GVHD)

# Targeting the Myeloma Cell in Its BM Microenvironment



# Single-agent thalidomide salvage therapy in MM



# SYSTEMATIC REVIEW OF PHASE II TRIALS OF THALIDOMIDE MONOTHERAPY IN RELAPSED MM

## Glasmacher A BJH 2005

- 42 communications (24 full papers)
- 1629 patients

CR or VGPR (> 90%)	1.6	} 43.2%
PR (>50%)	27.8	
MR	13.8	

### -Survival data

- 1 y EFS 35 % med EFS 3 to 16m
- 1 y SV 60 % med SV 14 m

# THALIDOMIDE ALONE

## TOXICITY IS RELATED TO THE DAILY DOSE

Incidence of grade  $\geq 1$  adverse effects (*Singhal 1999*)

	200 mg N = 83	400 mg N = 72	600 mg N = 57	800 mg N = 46
Constipation	35	44	44	59
Weakness/Fatigue	29	31	39	48
Somnolence	34	43	40	43
Tingling/Numbness	12	14	19	28
Dizziness	17	25	23	28
Rash	16	18	21	26
Mood changes	16	24	23	22
Incoordination	16	17	14	22
Tremor	10	13	19	22

# THALIDOMIDE ALONE TOXICITY

- **Grade > 3 toxicity is rare (10-20%)**
- ***Barlogie (Blood 2001)***
  - 28/169 pts (16.5%) stopped treatment because of toxicity**
- **No myelosuppressive effects**
- **Long-term toxicity**
  - peripheral neuropathy
  - chronic fatigue
- **DVT is very rare in patients treated with Thal alone (2%)**

# THALIDOMIDE + DEXAMETHASONE

- **Objective: increase efficacy and decrease the doses of Thalidomide**
- **Response rate is apparently increased (40 to 70 %) in relapsed patients but no randomized study**
- **TD > Conventional chemotherapy (historical comparison Palumbo Hematol J 2004)**
- **With 100-200mg/d Thal is better tolerated but new toxicities (related to Dex specially infections and DVT ++)**
- **Currently tested as frontline therapy**

# THALIDOMIDE + CHEMOTHERAPY

- **Thalidomide: no hematological toxicity**
- **Synergy in preclinical studies**
- **Effective in relapsed /refractory patients (TCD,DT-PACE): 50 to 80 % rate**
- **but high incidence of DVT (up to 30 % with anthracyclines )**
- **Currently tested as frontline therapy**

# TERATOGENICITY

- **Avoid drug exposure in women with child-bearing potential**
  - **Special programs organized at the national level (ie STEPS program)**
  - **Although the median age at diagnosis is 65-70 years**
- **Prophylactic measures for men as well (barrier contraception if partner of child-bearing age)**

# PERIPHERAL NEUROPATHY

- **Clinical symptoms : mostly sensitive neuropathy**
  - Numbness, paresthesia
  - Pain in the hands or arms, feet or legs
- **Electrophysiologic studies**
  - Mostly axonal damage
- **Incidence depends on dose and duration +++**
  - 28% overall (*Glasmacher 2005*)
  - Up to 75% in patients with prolonged treatments (*Tosi 2004*)
  - Role of previous Tx and previous neuropathy
- **Prognosis**
  - Grade > II 6% overall (27.5% in patients treated > 1yr)
  - Can be irreversible if Tx not promptly withdrawn

# DEEP VEIN THROMBOSIS

- **Clinical manifestations**

  - At the site of CVL or at distant sites**
  - Including pulmonary embolism**

- **Date of onset : median time 42 D**

- **More frequent in pts with high tumor burden**

- **Incidence (FDA report + clinical studies)**

**Thal alone**

**< 5%**

**Thal + Dex**

**10 – 15%**

**Thal + Chemo**

**up to 30%**

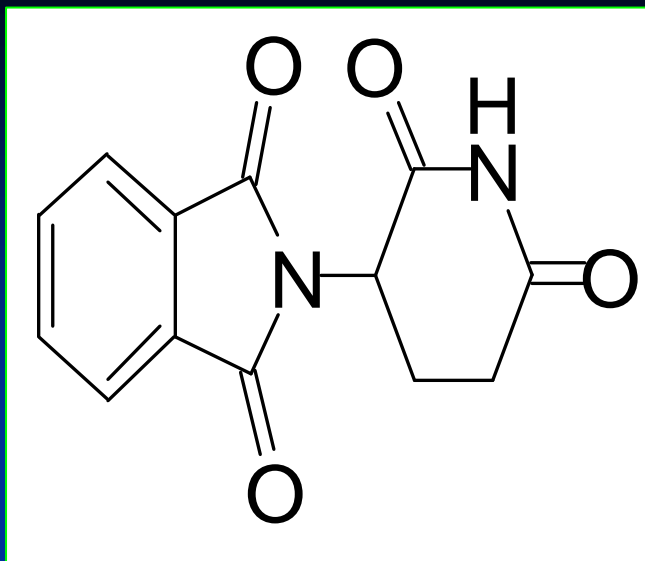
# Thalidomide in newly diagnosed patients

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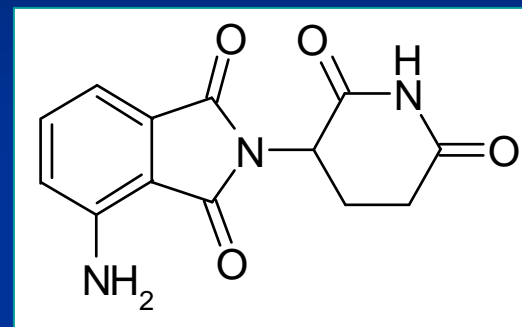
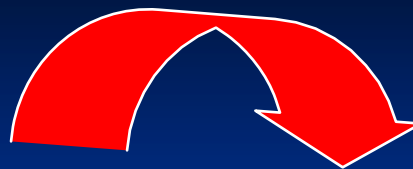
- Younger patients
  - Induction treatment prior to ASCT
    - \* Thal/D
    - \* DT PACE
    - \* VTD
  - Maintenance Treatment after ASCT
- Older patients
  - \* MPT
  - \* Thal/Dex

Approved by FDA but not by EMEA

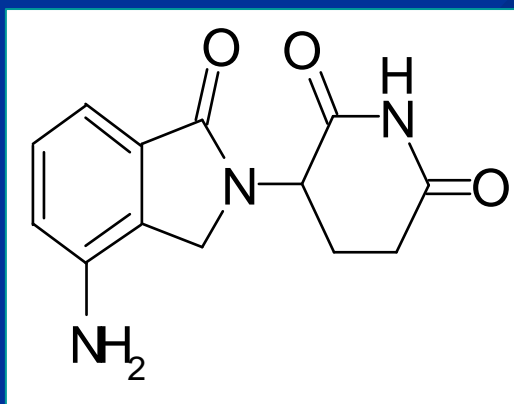
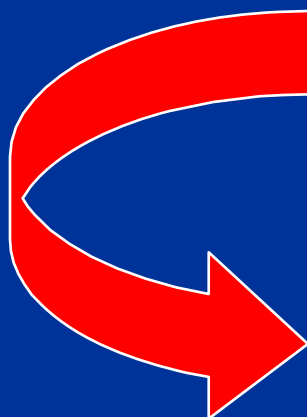
# LENALIDOMIDE



**Thalidomide**



**Actimid™ (CC-4047)**



**Revlimid™ (Lenalidomide)  
(CC-5013)**

# Lenalidomide vs Thalidomide

- Both are given orally
- Identical modes of action
- Different in vitro activity. Compared to Thal, Len
  - has more potent antiinflammatory properties
  - is a more potent T-cell stimulator
  - is >10 fold more antiangiogenic
- Not teratogenic in animal models
- Has a different toxicity profile +++

# LENALIDOMIDE (REVLIMID) : DEVELOPMENT IN MYELOMA

- 2000 Preclinical : targets MM (caspase 8 mediated apoptosis) and microenvironment *in vitro* and *in vivo*
- 2001 Phase I trial (2001):n=25 pts
- 2003 Phase II open-label trial (2003): n= 222 pts  
27 % >PR
- 2004 Phase II randomized trial (2004):n= 102 pts  
2 regimens with addition of Dex
- 2004 Phase III trials (2004): Len/Dex vs Dex/placebo in relapsed MM  
2 studies (MM-009 n= 341 pts MM-010 n= 351 pts)
- 2006 FDA approval
- 2007 EMEA approval pending

# PHASE I STUDY OF LENALIDOMIDE IN RELAPSED / REFRACTORY MM

- 5, 10, 20, 50 mg/d
- 25 pts
- No DLT within 28 d
  - . DLT of G 3/4 myelosuppression > 28d
  - . MTD 25 mg/d
- No significant somnolence, constipation or neuropathy at any dose
- Response
  - . MR or better ( $\geq 25\%$  paraprotein  $\downarrow$ ) 71%
  - . SD 8%

# PHASE III TRIALS

Lenalidomide 25 mg, d 1–21  
Placebo, d 22–28  
Dex 40 mg, d 1–4, 9–12, 17–20

> × 4 COURSES →

Same except  
Dex, d 1–4

Continue until PD

Placebo, d 1–28  
Dex 40 mg, d 1–4, 9–12, 17–20

TTP

OS

RR

Safety

1<sup>st</sup> SRE

↓ PS

# MM- 009/010 Grade 3/4 Hematologic Toxicity

	MM-009		MM-010	
	LD N = 170	D N =171	LD N = 176	D N =175
Neutropenia, %	30.0	3.5	17.6	1.1
Febrile Neutropenia	2.9	0	1.1	0
Thrombocytopenia	10.6	6.4	9.7	5.7
Anemia	10.6	3.5	4.5	4.0

# MM- 009/010 Grade 3/4 Other Adverse Events

	MM-009		MM-010	
	L/D N = 170	D N =171	L/D N = 176	D N =175
DVT/PE, %	15.3	3.5	8.5	4.5
Atrial Fibrillation	4.7	0	0.6	1.7
CHF	2.4	0	0.6	0
Constipation	1.8	0	1.7	0.6
Diarrhea	2.4	0	2.4	1.2
Fatigue	5.9	4.7	6.8	3.4
Neuropathy	2.9	1.2	1.1	0.6

# Increased risk of thromboembolic complications with concomitant EPO

- Subgroup analysis of MM-009/010

Incidence of DVT/PE with concomitant EPO

Patients with  $\geq 1$  thrombotic episode

	EPO	No EPO	P
Lenalidomide + dex	23%	5%	0.022
Dex	9%	1%	0.036

# Lenalidomide and renal failure

- Thal can be given in patients with renal dysfunction (hyperkalemia in patients with end-stage renal failure)
- Lenalidomide
  - Median AUC increases in relation with creatinine clearance decrease
  - Len/Dex is equally effective in pts with creatinine clearance  $\geq$  or  $<$  50 ml/min
  - Grade  $\frac{3}{4}$  thrombocytopenia is significantly more frequent in pts with  $<$  50 ml/m

# LENALIDOMIDE: CURRENT DEVELOPMENT IN MYELOMA

- **Studies in Relapsed/Refractory patients**
  - Combinations with chemotherapy (RAD,DVd-R)
  - Combinations with novel agents Bortezomib (Rev/Vel)
  
- **Studies in newly diagnosed patients**
  - MPR in older patients
  - Len/Dex upfront (with or without ASCT)
  - Len as maintenance after ASCT (IFM 2005-02)