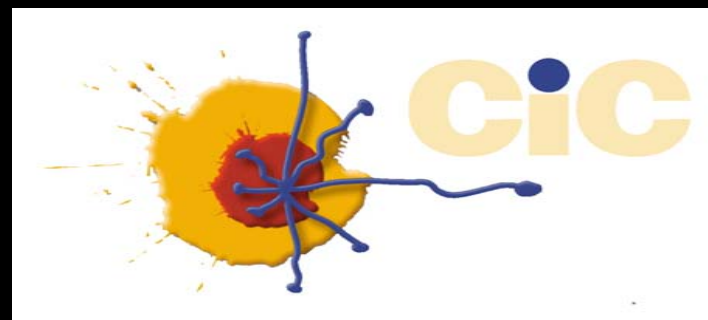


Review Of New Agents Discussed at ASH 2007

J. F. San Miguel

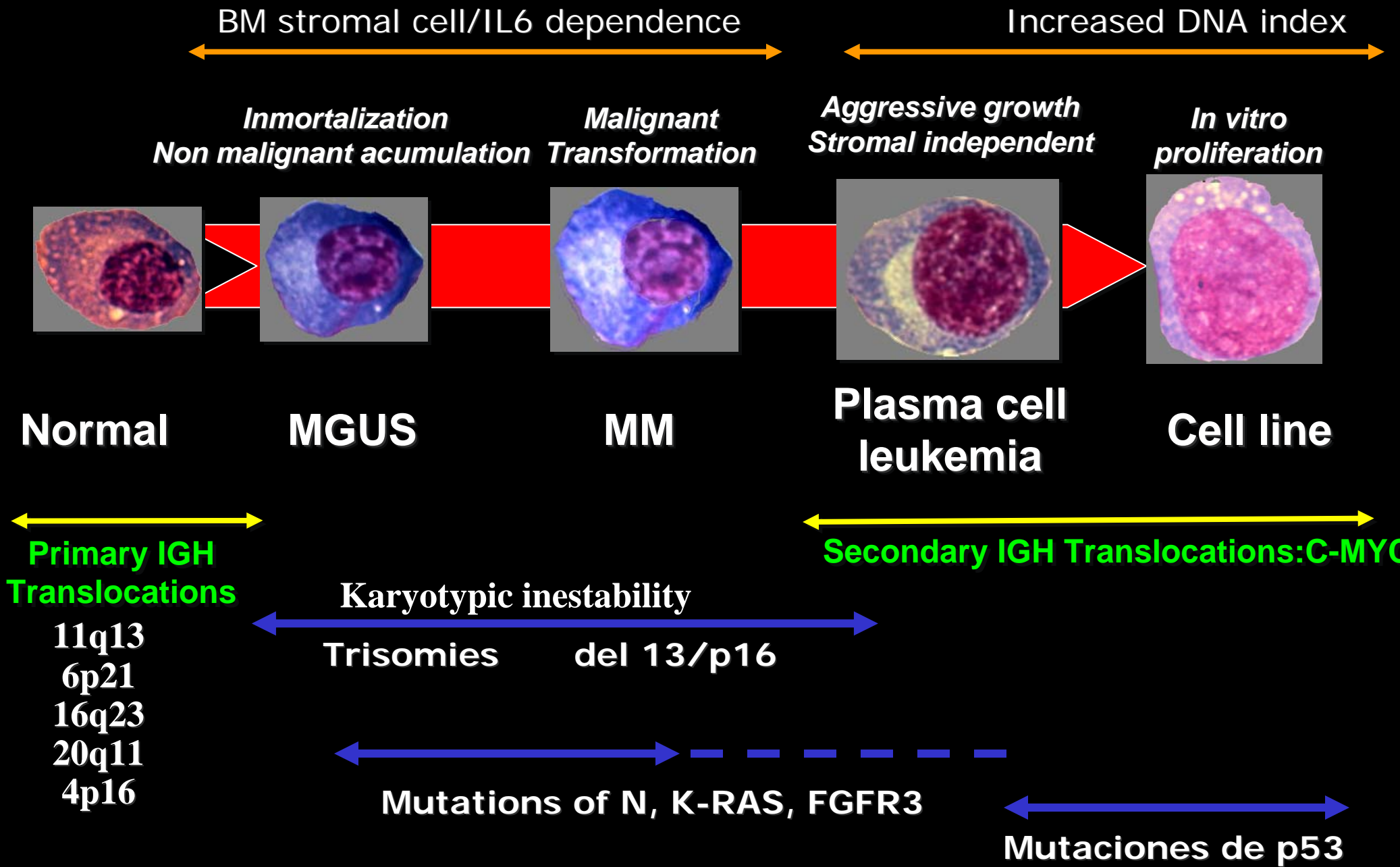


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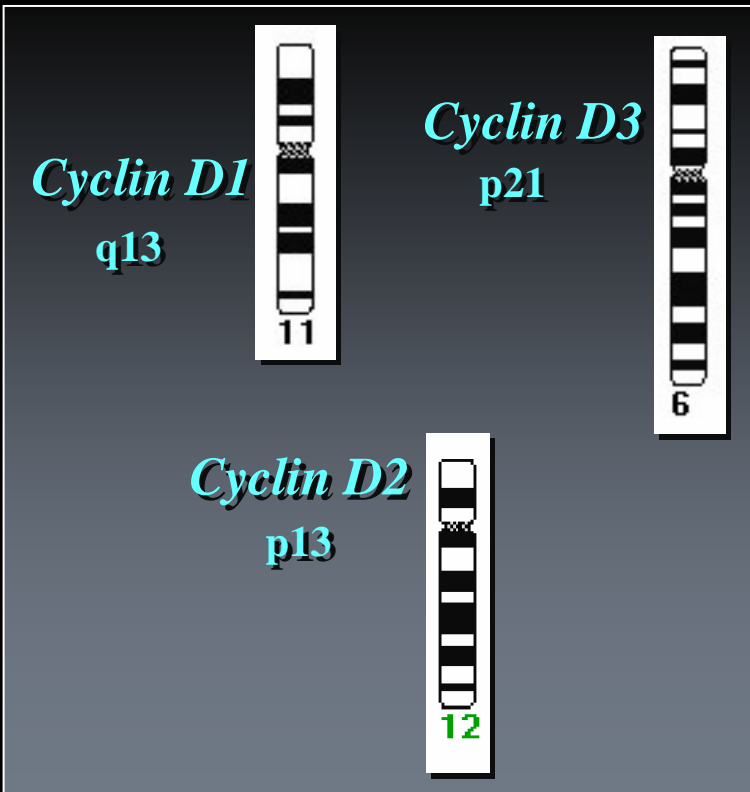


Adapted from Hallek, Blood 1998

PRIMARY TRANSLOCATIONS

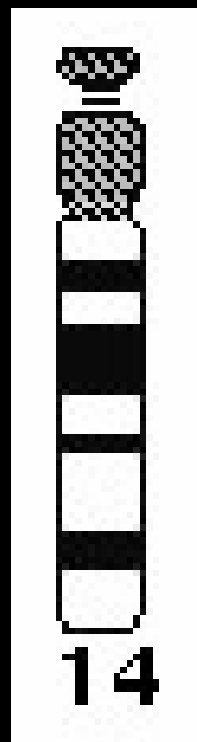
;THERAPEUTIC TARGETS?

20%



Inhibitors of cyclin dependent kinases*2

*2 CDK inh (Flavopiridol); PD-0332991

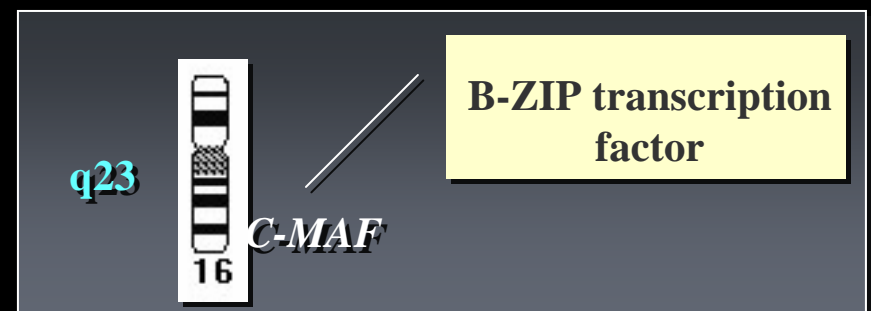
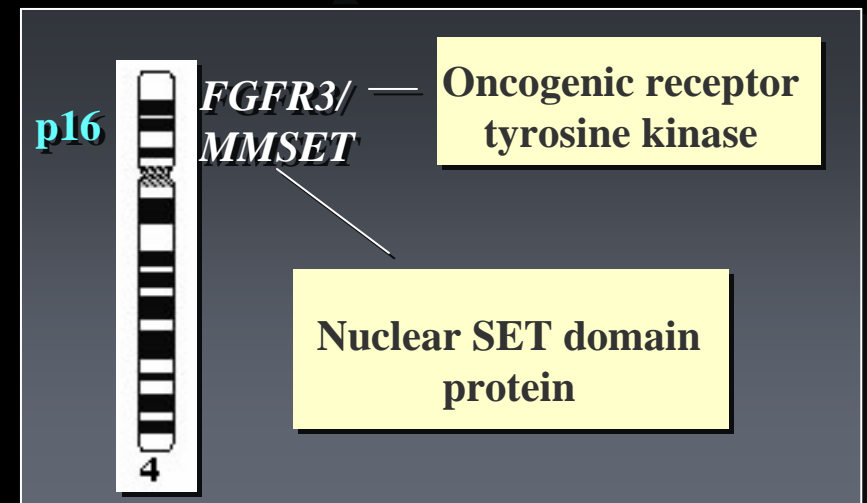


IGH
q32

Inhibitors of tyrosine kinases*1

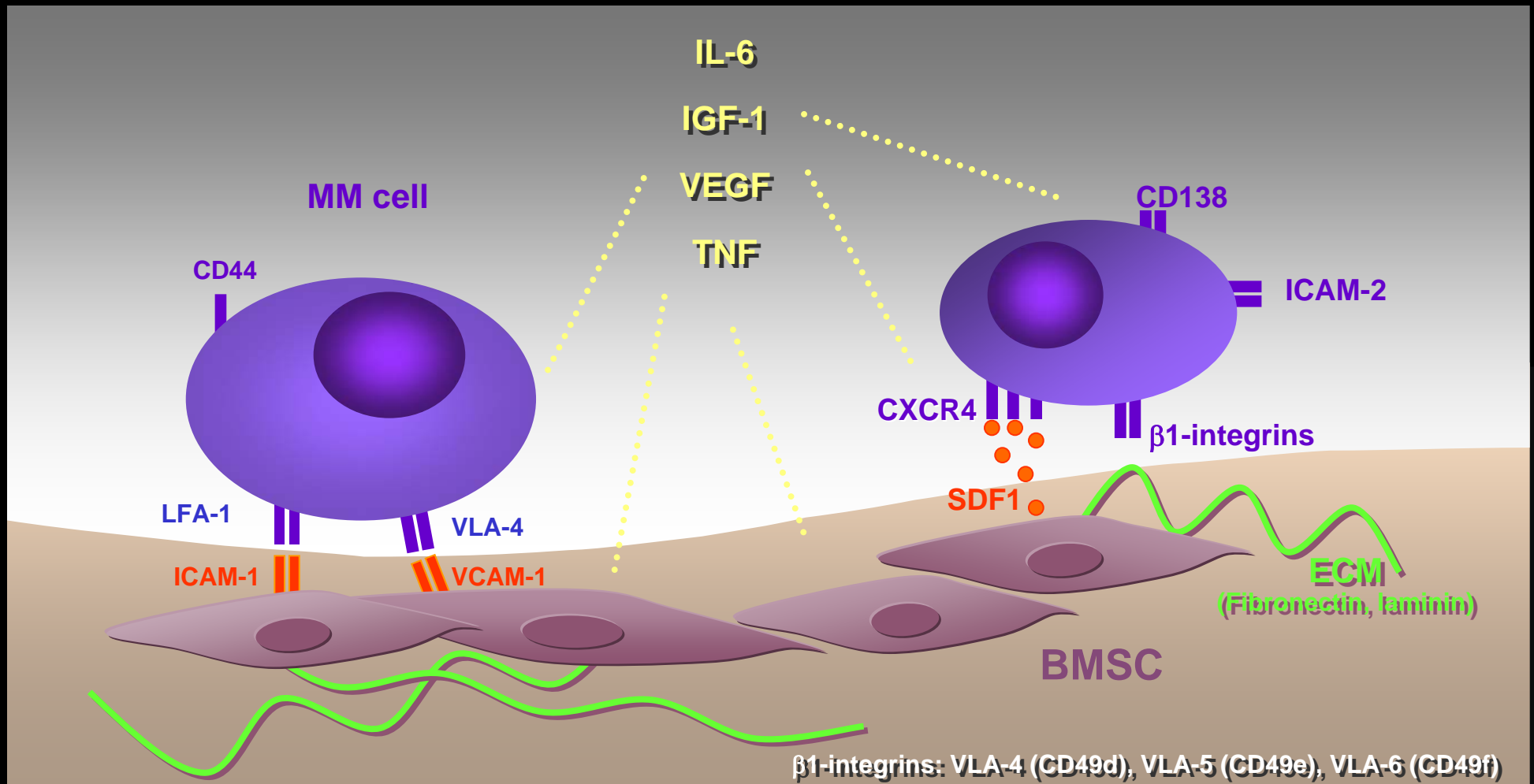
*1 CHIR-258/ TKI 258 (non-specific TK inh.)
and PRO-001 (anti-FGFR3 Ab)

15%



5%

HOST-TUMOR INTERACTIONS: direct contact & soluble molecules



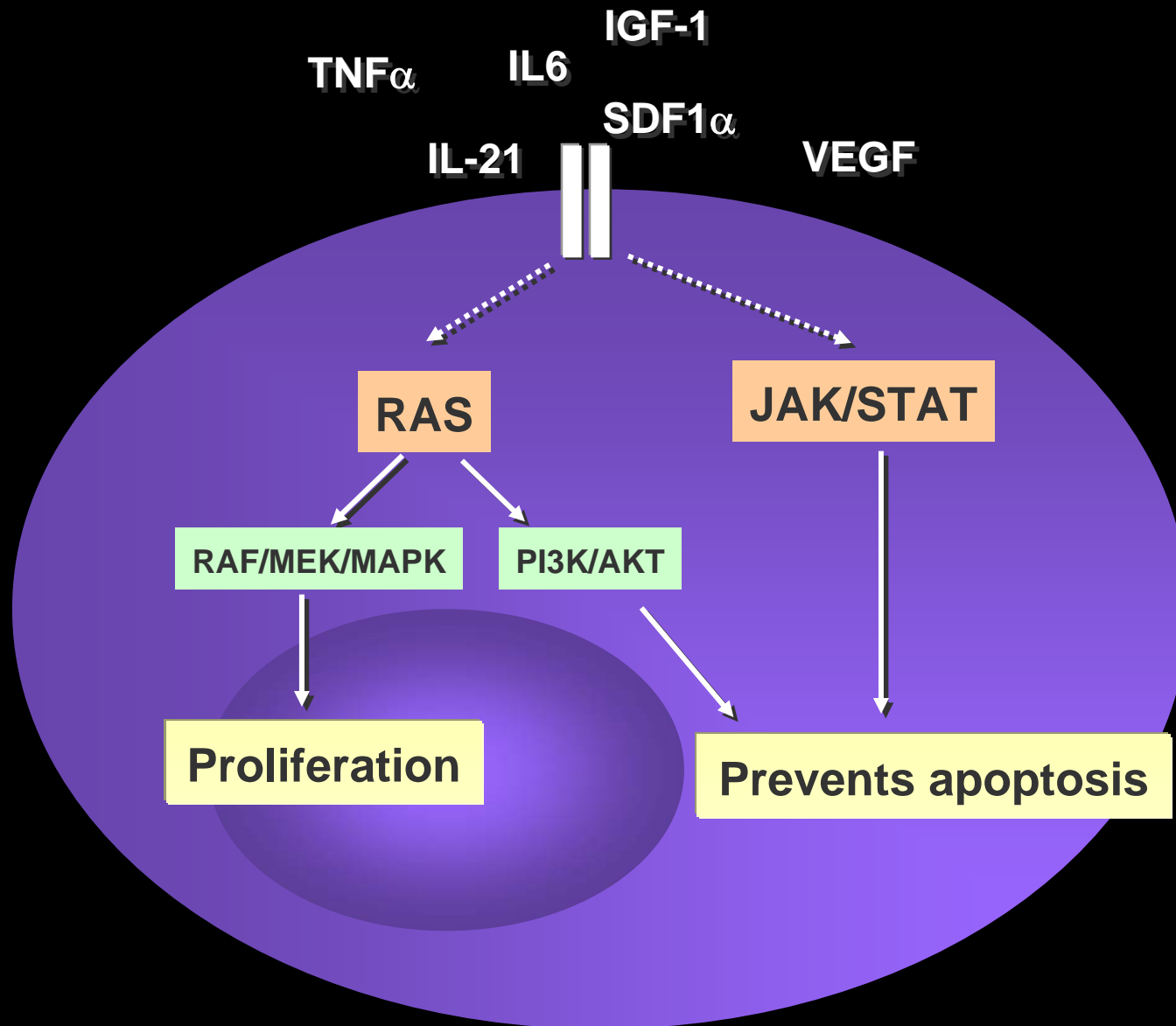
Cell adhesion induces drug resistance:

1) cell cycle arrest (\uparrow p27); 2) apoptosis inhibition (\uparrow FLIP-1 –FAS inhibitor-); 3) protection from drug-induced DNA damage

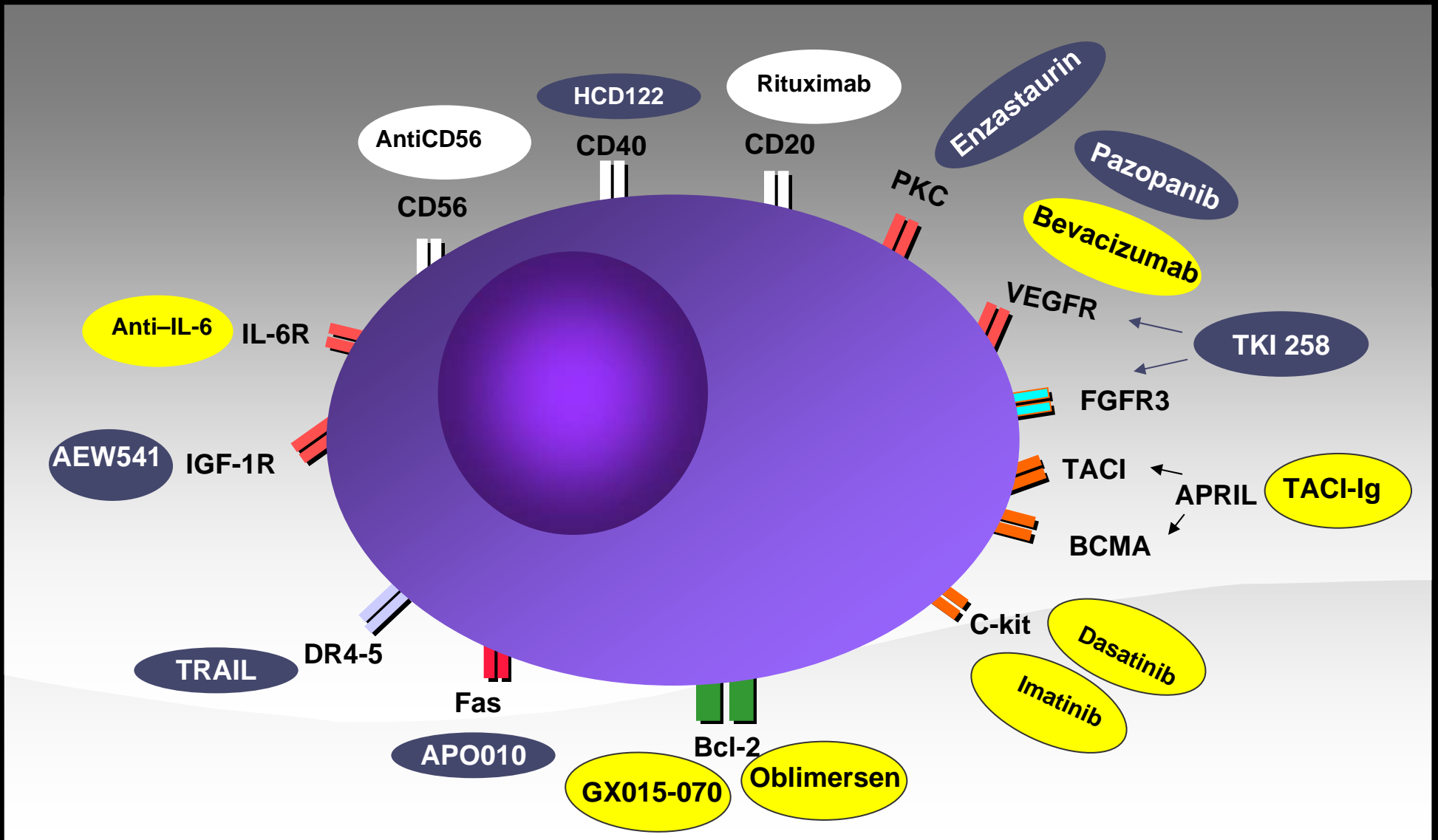
PC adhesion to Fn induces overexpression of 53 genes (11 regulated by NFkB)

San Miguel J. *Hematol J.* 2003;4(suppl 3):201-207.

SIGNALING CASCADES IN MM CELLS: targets for novel therapies



Drugs Targeting Cell Receptors



Results with Experimental Agents (1)

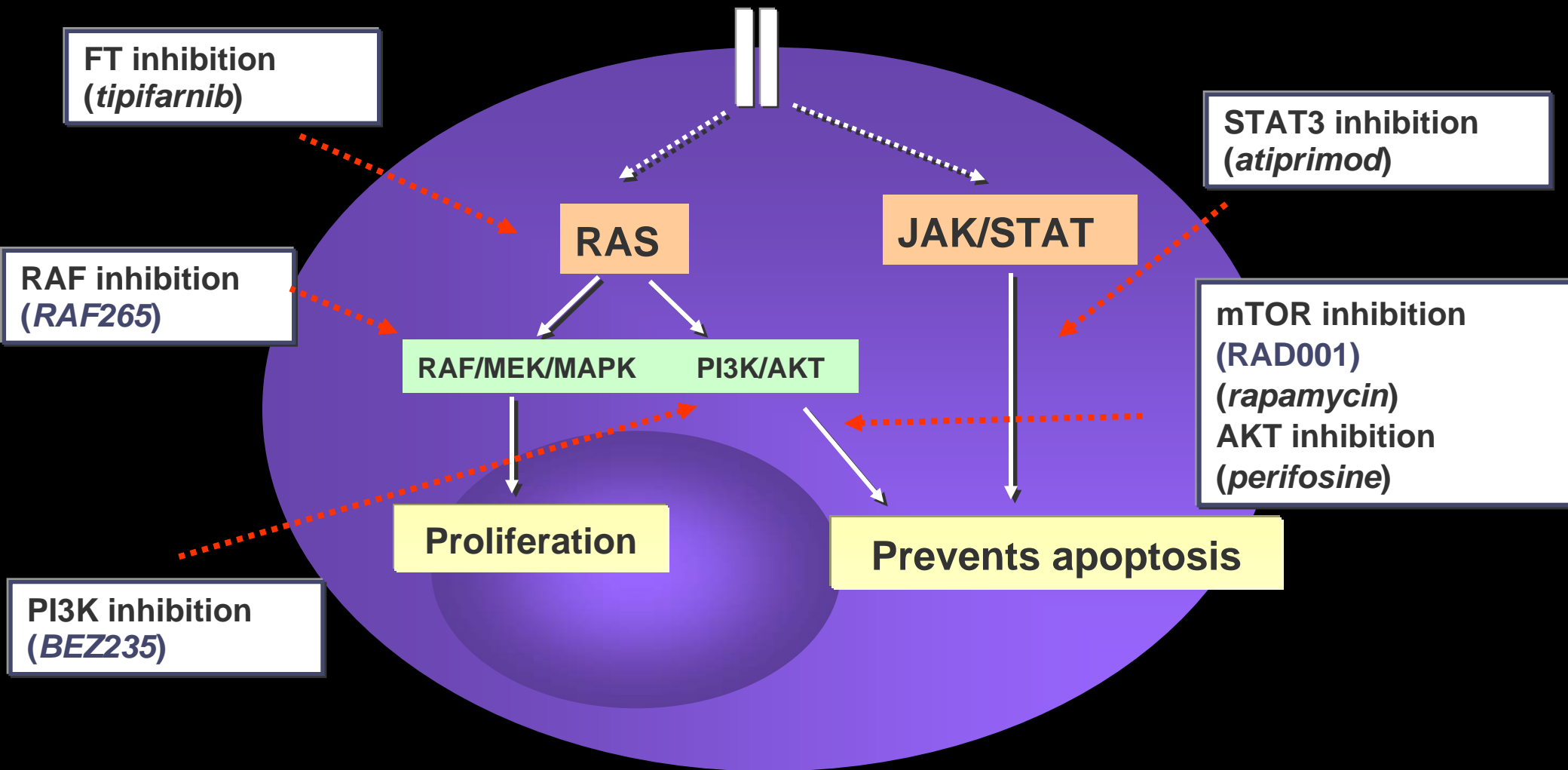
- **Anti CD40** (*Advani ASH 2006*) – Phase I (96 pts)
 - 7 MM pts..... SD
- **Hu N901-DM1 (Anti-CD56)** (*Chanan-Khan, ASH 2007. abstr 1174*)
 - 12 pts..... 1 mR
- **HuLuc 63 (Anti-CS1)** (*Bensingher ASH 2007. abstr 1180*)*
 - 7 pts..... No clinical responses
- **CNTO 328 (Anti-IL6)** (*Manges ASH 2007.abstr 1182*) + **Bz**
 - 6 pts..... 3 confirmed PR / 3 unconfirmed PR

*Gp at high levels in PC, CD8+ and NK cells

Results with Experimental Agents (2)

- **AVE 1642 (anti IGF-1R M.Ab)** (*Moreau ASH 2007, Abstr 1166*)
- 14 pts..... 1 mR
- **CP-751 (anti IGF-1R M.Ab)** (*Lacy ASH 2007, Abstr 1171*) + **Dex or RAPA**
if SD or PD.
- 47 pts..... 4% CR + 8% PR
- **Bevacizumab (VEGF-R Inhib)** (*Raschko, ASH 2007. abstr 1173*) + **LEN- Dex**
- 17pts..... 70% PR
- **AB 1010 (FGFR3 TK inhib)** (*Arnulf ASH 2007, Abstr 413*) + **Dex** if PD (all)
- 11 MM pts (t4 ; 14)..... 1 nCR, 1 PR, 1mR

Signaling Cascades in MM Cells: Targets for Novel Therapies



Src-family kinase inhibitors (AP23464); P38 MAP inhibitor (SCIO-469).

Results with Experimental Agents (3)

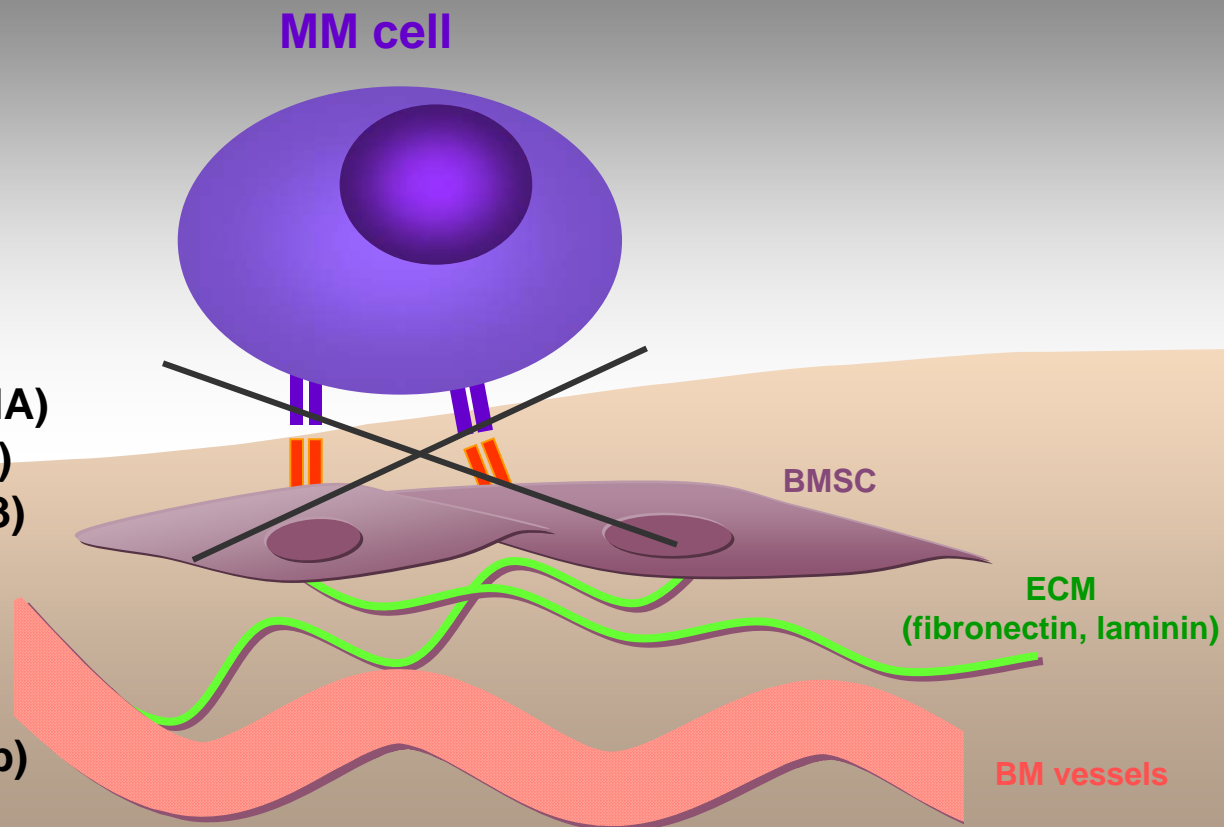
- **Dasatinib** (*Vildes ASH 2007. abstr 1182*)
13 pts..... 4 SD
- **FT inhibitor** (*Alsina, Blood 2004*)
43 pts..... 10% mR + 54% SD
- **SCIO-469 (P38 MAPK inhibitor)** (*Siiegel ASH 2006*) + **BZ if PD or SD**
62 pts..... 35% PR + 12% mR
- **Perifosine (AKT phosph. inhib)** (*Richardson ASH 2007 Abstr 1164, 1169 & 79*)
 - (+Dx) 48 pts 13% PR + 25% mR + 47% SD
 - (+Bz ± Dex) 15 pts.... 33% (2 PR + 3 mR)
 - (+Len-Dx) 9 pts..... 66% (1nCR + 4PR + 1 mR)

Drugs Targeting Host-Tumor Interactions

- Bortezomib*
- Thalidomide
- Lenalidomide

- HDAC inh (LBH589, SAHA)
- Hsp90 inh (17AGG, KOS)
- Telomerase inh (GRN163)
- Aplidin

- Statins
- Anti-VEGF (bevacizumab)



* Oral Proteasome inhibitors: Carfilzomib (PR-171) & NPI 0052

Results with Experimental Agents (4)

➤ **Tanespymicin (HSP90 inhib)** (*Richardson ASH 2007, Abstr 1165*) + **Bz**

63 pts..... 5% CR + 9% nCR + 22% PR

➤ **HDAC inh alone**

- **SAHA alone** (*Richrdson ASH 2007, Abstr 1179*): 10 pts: 1mR

- **ITF2357** (*Galli ASH 2007, Abstr1175*): 15 pt: 1PR

➤ **HDAC inh + Bz**

- **Depsipeptide+Dex** (*Prince ASH 2007, Abst 11679*) 7 pts..... 1CR+ 3PR+ 1mR

- **SAHA** (*Badros ASH 2007, abstr. 1168*) 16 pts..... 50% PR

- **SAHA** (*Weber ASH 2007, abst 11729*) 17 pts..... 35% (4PR+ 2mR)

Results with Experimental Agents (5)

➤ **Carfilzomib (Proteas. Inhib)^a Phase I**

- **6 MM pts** (5d/14d)..... **1PR, 2mR** (*Orlowsky ASH 2007 Abstr 409*)

- **13 MM pts** (2d/wx3w)..... **4 PR, 1mR(durables)** (*Alsina ASH 2007. Abstr 411*)

➤ **Aplidin** (*Ocio ASH 2007, abstr 1514*)

41 pts..... **7% PR + 14% mR + 31% SD**

^a Inhibitor of the Chymotrypsin-like activity, but not other catalytic sites. No painful PN

Conclusions on Experimental Agents in Relapse/ Refractory MM

- Target therapies have **little efficacy as single agents**
- Combination therapies should be based on “**in vitro**” and **animal studies**
- Treatment with experimental agents should be reserved for patients refractory to IMID´s & Proteasome inhibitors
- **Attractive drugs** for combinations : *HsP90 inhibitors, HDAC inhibitors, pAKT inhibitors, oral proteasome inhibitors and novel IMID´s*