Carfilzomib for PTCL

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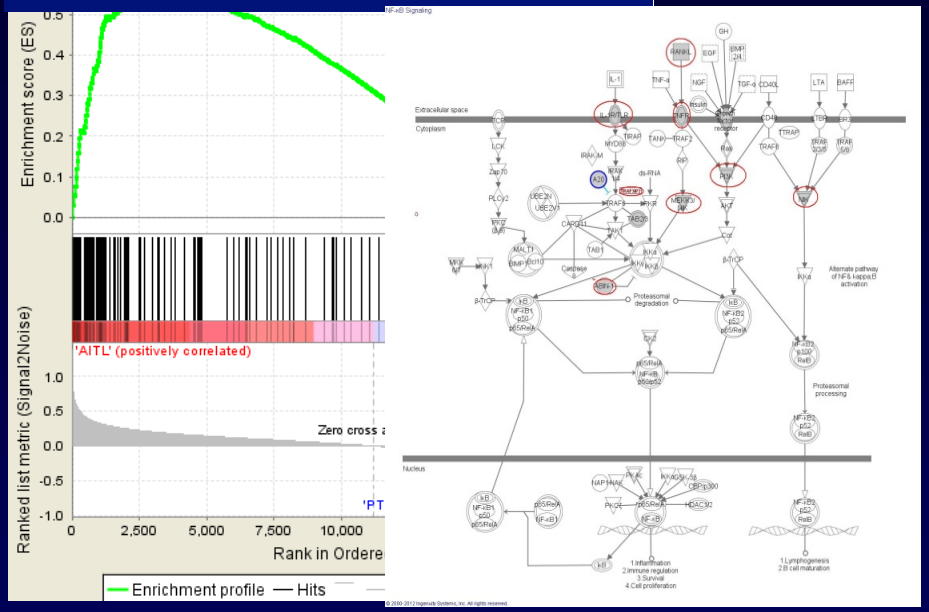
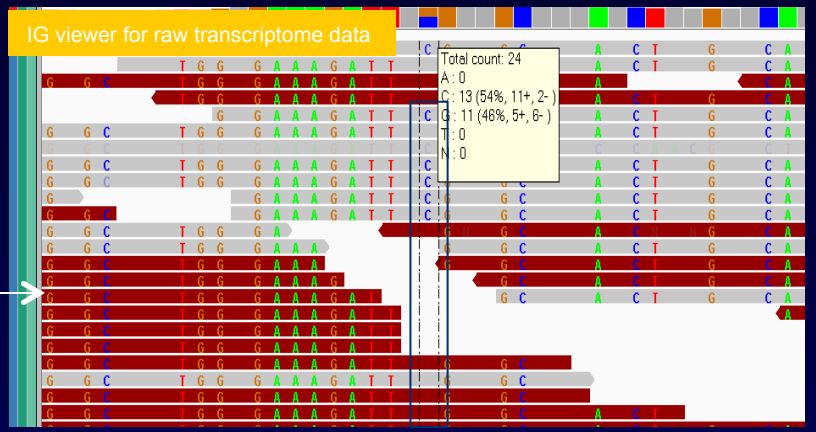
A spectrum of mutations observed in AITL target NF-κB pathway

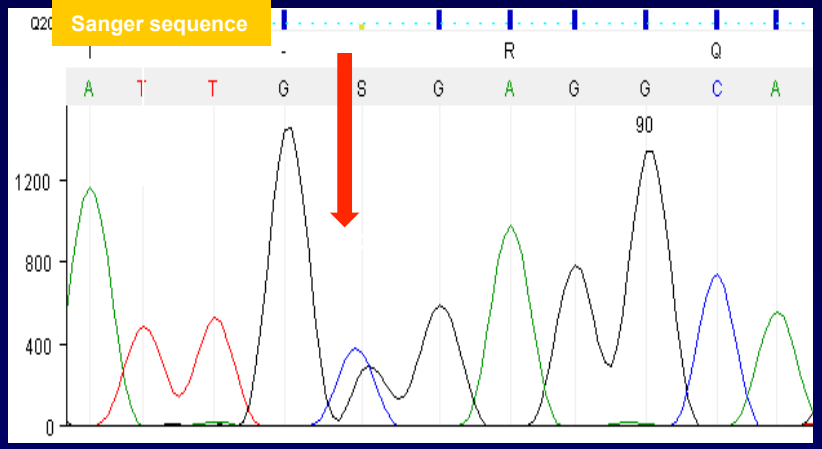
GEP: Enrichment of NF-κB Pathway in AITL

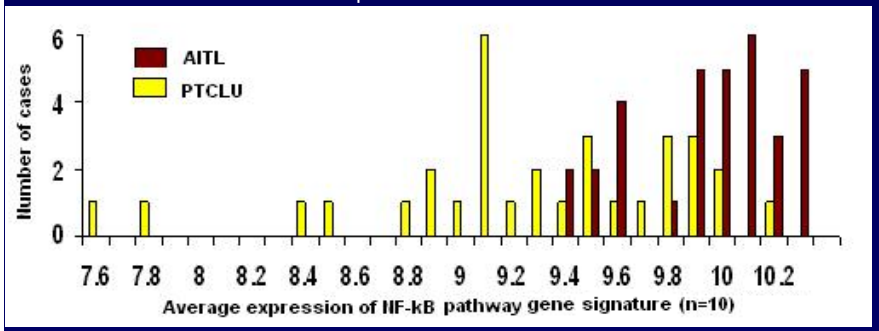


IG viewer for raw transcriptome data



Sanger sequence





RNA-seq validation of mutation affecting NF-κB pathway
TRAF3IP2 mutation /chr6q21:111912532 G>C

Biologic Prognostic Markers in PTCL

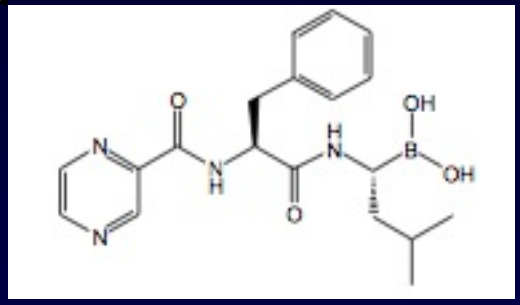
Prognostic Marker	Outcome
EBV +	Unfavorable
Ki-67% $\geq$ 80	Unfavorable
Cytotoxic granule expression	Unfavorable
T-helper receptor profile – CCR3 or CCR5	Favorable
% transformed cells > 70%	Unfavorable
Proliferative signature	Unfavorable
NFkB signature	**Favorable**

Proteasome—Present and Future Therapies

- Bortezomib: 1st proteasome inhibitor
- 2nd generation proteasome inhibitors moving from bench to bedside
  - Carfilzomib
  - Ixazomib
  - Marizomib
- Can block ubiquitin proteasome cascade upstream of the proteasome
  - Deubiquitylating enzyme inhibitors

Anderson KC. *J Clin Oncol*. 2012;30:445-452.

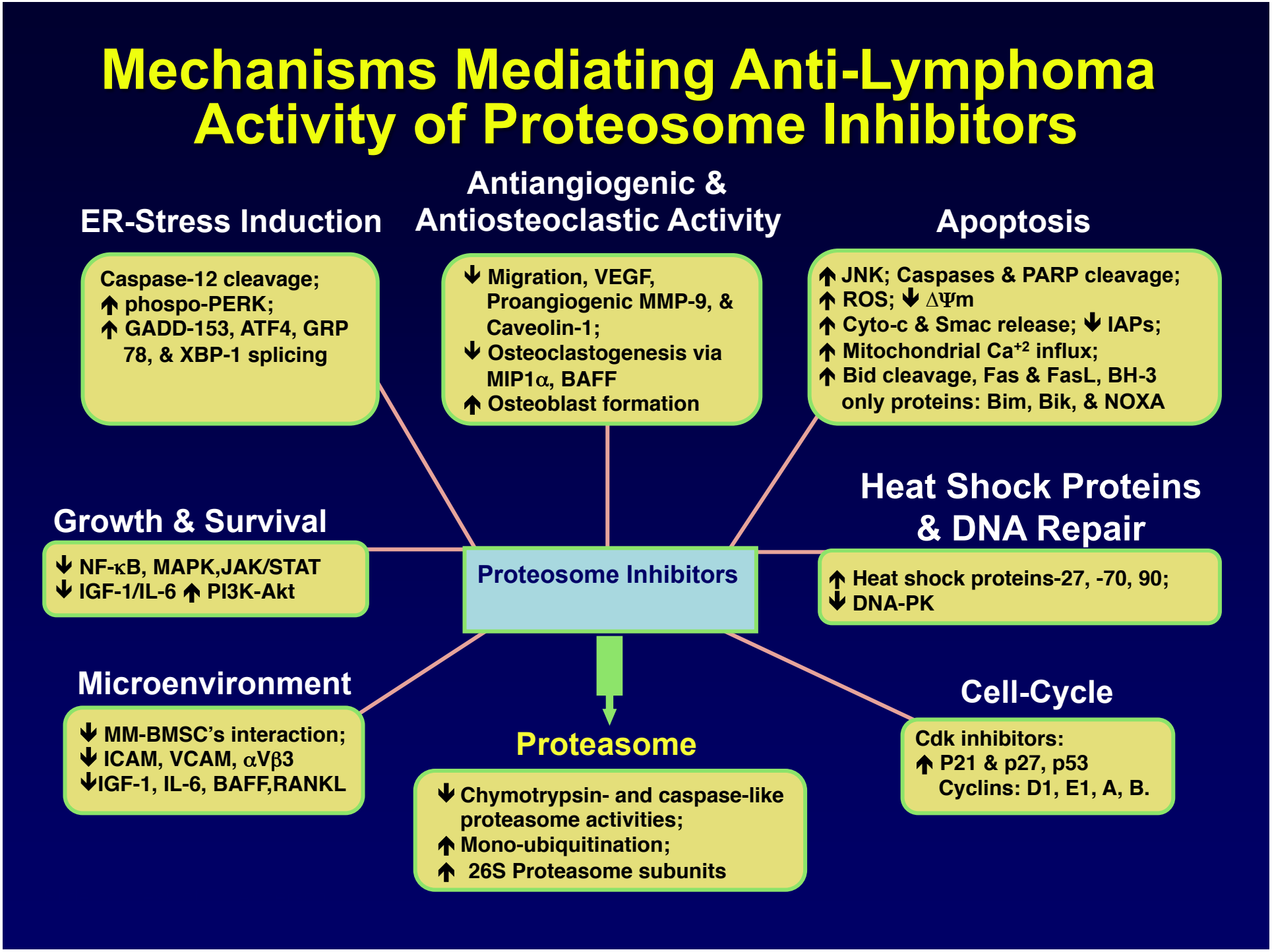
Bortezomib—The First Approved Proteasome Inhibitor



- A covalent, reversible inhibitor of proteasome chymotryptic activity[1,2]
- Induces apoptosis in solid tumors and hematologic cancers, including multiple myeloma[3]
- Alters the bone marrow microenvironment to reduce tumor cell growth[3]
- Efficacy in both previously untreated and relapsed multiple myeloma and relapsed MCL.

Bortezomib Prescribing Information. 2. Adams J, et al. *Cancer Res*. 1999;59:2615-2622. 3. Adams J. *Cancer Cell*. 2004;5:417-421

Mechanisms Mediating Anti-Lymphoma Activity of Proteosome Inhibitors

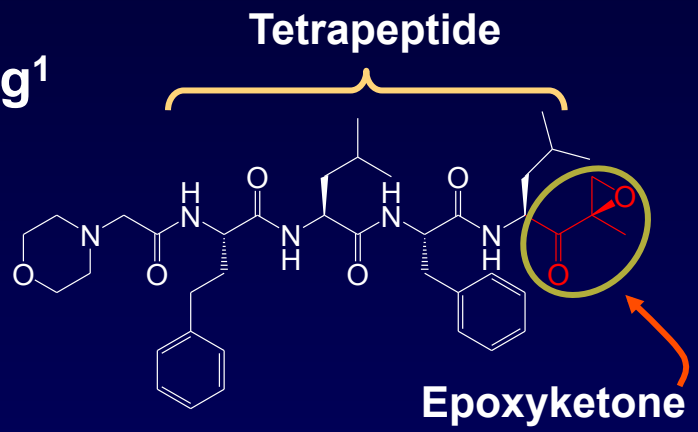


Bortezomib PTCL

- Handful of small studies using bortezomib for PTCL (Zinzani, et al; JCO 20: 4293-7, 2007)
- Combination trials with bortezomib (HDAC inhibitors, gemcitabine, etc)
- Some data using bortezomib in transplant regimens for PTCL

Carfilzomib—A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding[1]
- Improved antitumor activity with consecutive day dosing[1]
- No neurotoxicity in animals[2]
- Mechanisms of action[1]
  - Induction of apoptosis
  - Cell cycle arrest
  - Activation of stress response pathways (hsp27, hsp70)



. Demo SD, et al. *Cancer Res*. 2007; 67:6383-6391. 2. Kirk CJ, et al, *Blood.* 2008;112:abstract 2765. 3. Siegel DS, et al. *Blood* 2012:120:2817-2825.

Carfilzomib Phase I/II Trial for PTCL

- 3 sites - UNMC, MDACC, Emory Sites
- 13 patients enrolled so far
- Dose levels
  - Dose level 0 = 20 mg/m2 day 1, 2 then 27 mg/m2 day subsequently
  - Dose level + 1 = 20 mg/m2 day 1,2 then 36 mg/m2 subsequently

Phase I/II Carfilzomib for PTCL – Histologies

- Angioimmunoblastic (n = 6)
- Cutaneous gamma-delta lymphoma (n =1)
- T-cell NOS (n = 1)
- ALCL, ALK negative (n = 1)
- PTCL, NOS (n = 1)
- Not available, just enrolled (n = 3)

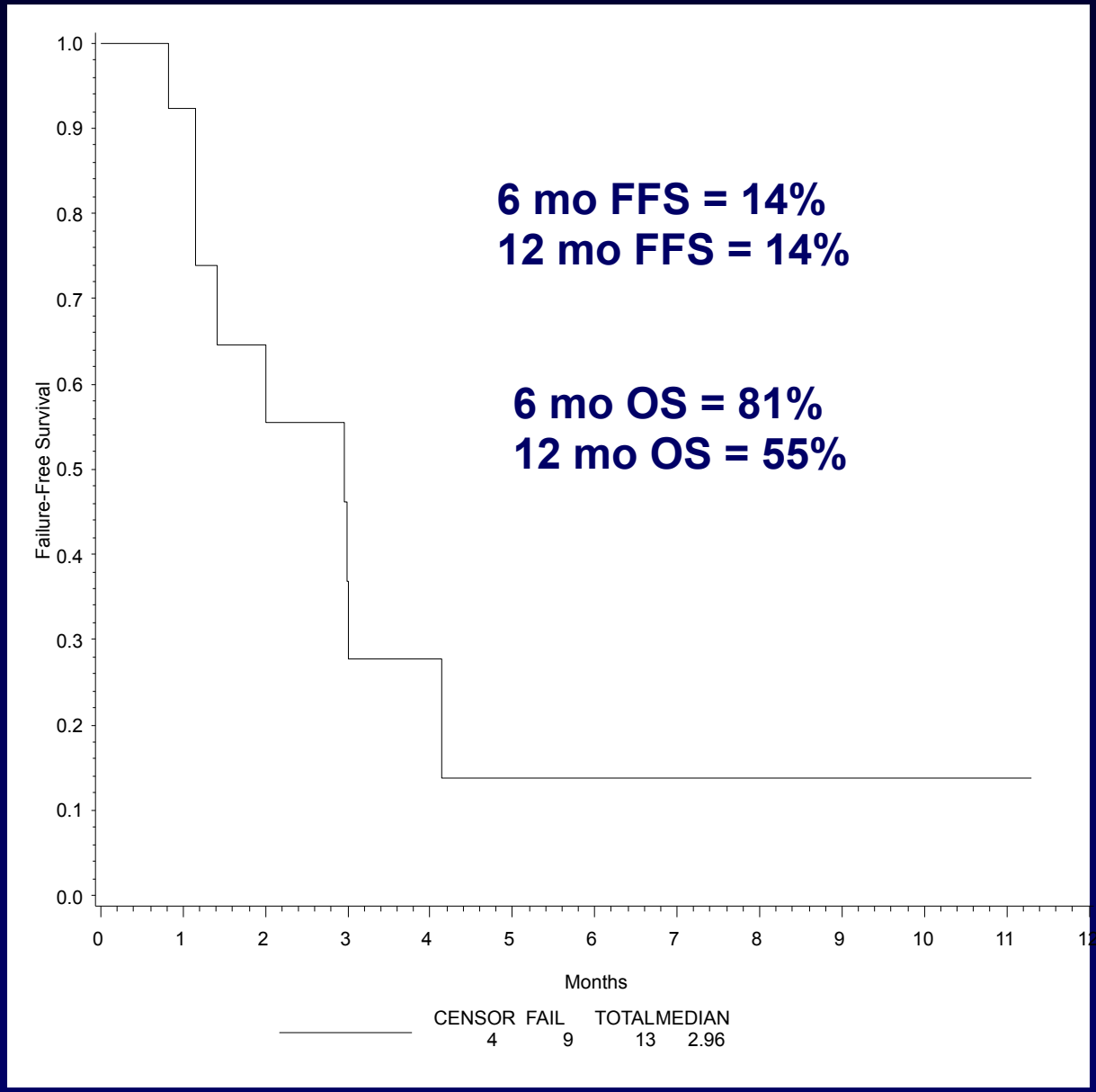
Toxicity - Moderate

- Grade 3 or 4 – Hematologic 11 episodes (anemia, thrombocytopenia)
- Grade 3 or 4 infection – 3 episodes (pneumonia, sepsis)
- Grade 3 or 4 pleural effusion/cardiac – 7 episodes

responses

- CR 1 (ALCL, ALK neg , 7+ months)
- PR 1 (Angioimmunoblastic, 6 months)
- SD 1
- PD 7
- Net yet evaluated 3

Phase I/II Trial – Carfilzomib in PTCL Failure-free Survival



Carfilzomib for PTCL

- Some early activity – 1 PR, 1 CR
- Potential for more activity with combinations – HDAC inhibitors, Imids, other cytotoxics or pathway agents
- Toxicity – moderate in end stage patients
- Plans – finish the Phase I/II and go on to combinations.