



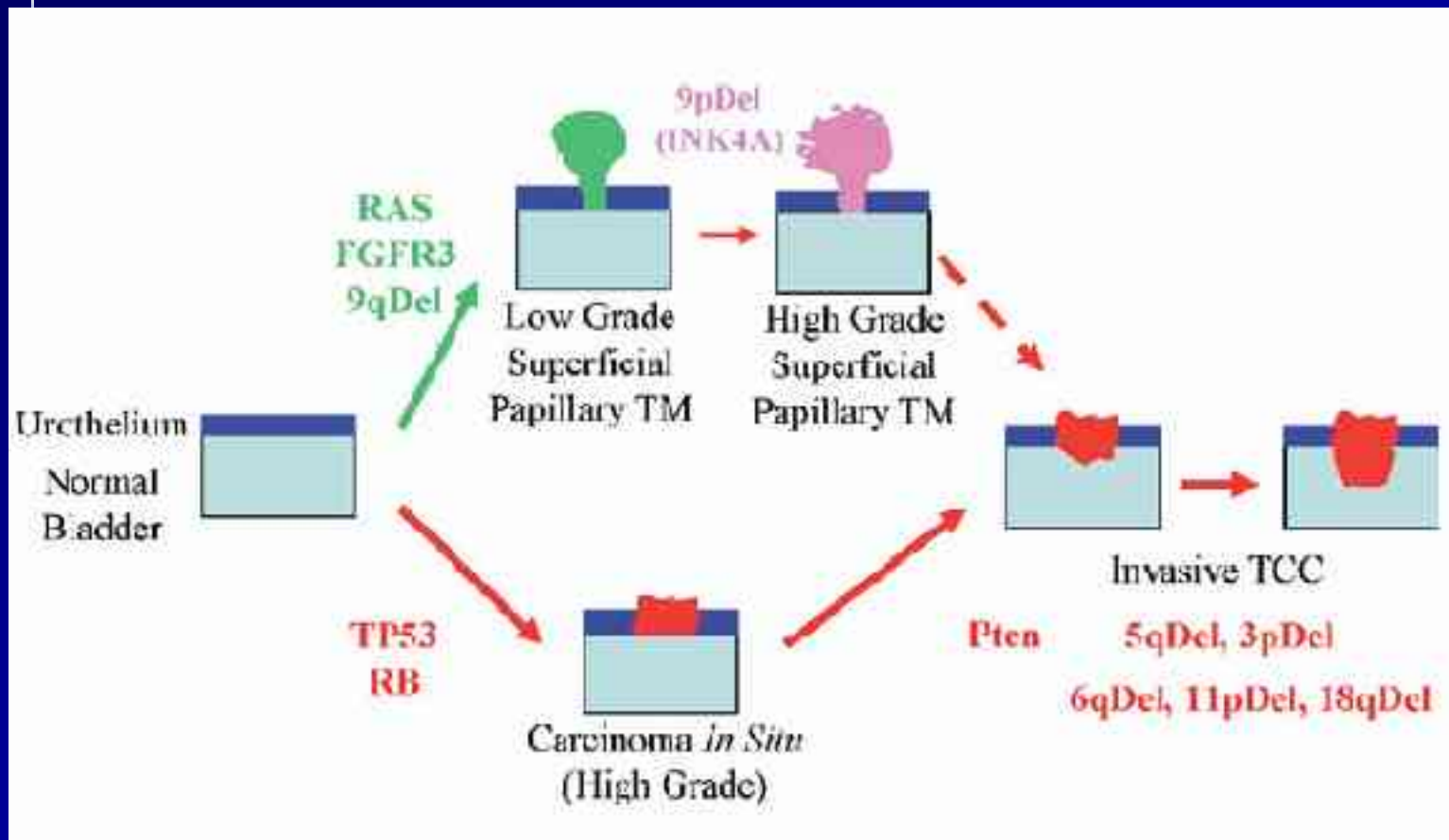
Intravesical Treatment with LBH589: Novel therapy of Superficial Bladder Cancer

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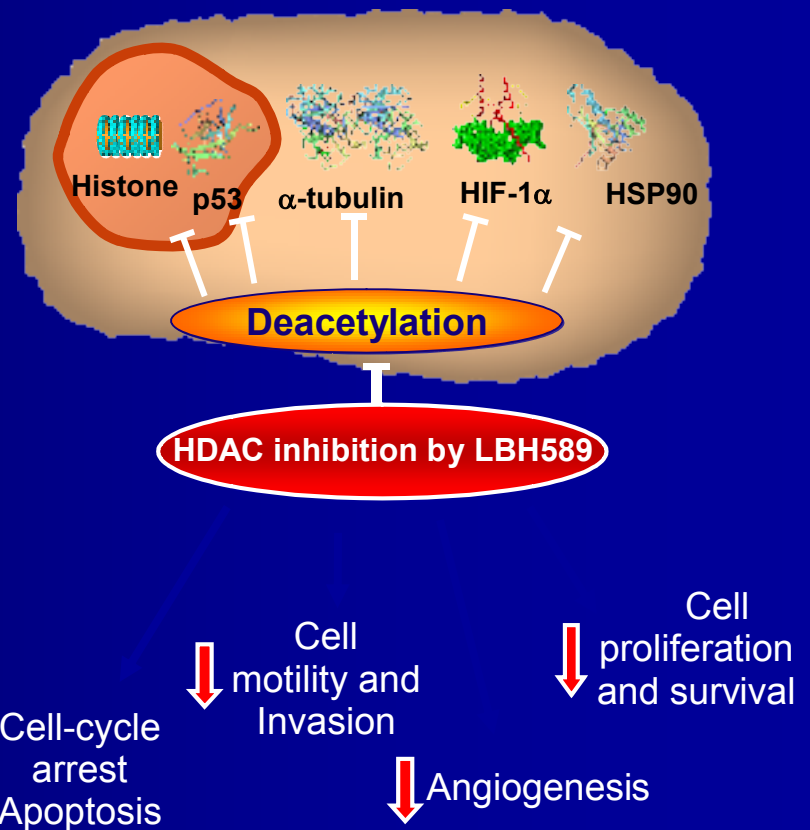
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Molecular Pathways in Bladder Cancer



LBH589 (panobinostat) - Multi-targeted Deacetylase Inhibitor (DACi)

- Pan-HDAC inhibitor with nM IC50
- Interferes with multiple hallmarks of cancer by targeting several cancer-relevant mechanisms
- In preclinical studies, demonstrates very potent anti-tumor activity as a single agent and in combination with current therapies
- Showed objective clinical responses in hematological and solid malignancies.



Panobinostat Demonstrates Strong Preclinical Potency in Solid Tumors and Hematologic Malignancies

- **Panobinostat induces reactive oxygen species, upregulates pro-death and downregulates anti-apoptosis proteins**
- **Cell lines of most hematological malignancies and subsets of solid tumor types, exhibit very high sensitivity to Panobinostat-induced cell death**
- **As a single agent, Panobinostat induces regression or stasis of a wide variety of tumor xenografts in mice at tolerable doses**
 - **HCT116 (colon), A549 (lung), MDA-MB-435 (breast), PC3-M2AC6 (prostate), CWR22Rv1 (prostate), and HH (CTCL) tumor models**
- **Panobinostat inhibits HSP90 chaperone function through its acetylation and causes degradation of HSP90 client proteins,**
 - **ER, HER2/ *neu* in breast cancer , androgen receptor (AR) in prostate cancer cells**
 - **Other proteins involved in cancer cell growth and survival pathways, e.g., CDK4, cyclin D1, mutant b53, Aurora kinases, EZH2, AKT and mutant B-RAF**

The Usual Stats: Bladder Cancer

- 63,210 new cases 2005
- 4th most common cancer in men, 8th in women
- 67,160 new cases and 13,750 anticipated deaths 2007
- Median age at diagnosis 65*

Three types of bladder cancer - Three Goals of Therapy

- Non-invasive tumors*
 - Reduce recurrences
 - Prevent progression
- Invasive disease
 - Cystectomy or not?
 - Additional therapies to improve cure?
- Metastatic disease
 - Prolong life

"Superficial tumors"

- Ta – papillary lesion with no BM invasion (60%)
- T1 – Through the basement membrane but no invasion (30%)
- Tis – carcinoma in situ (10%)
- Up to 80% will recur
- 15-50% of recurrences will be invasive

Grade - Determines risk of relapse

- G1 (well diff) to G4 (undifferentiated) - old.
- Low grade vs. High grade – new.
- Low grades recur, usually don't invade. High grades invade.

TX of Superficial Tumors

- TURBT- a complete cystoscopic resection of visible tumor, and selected biopsies of the bladder mucosa and prostatic urethra.
- A repeat TURBT is generally advocated to decrease the likelihood of a staging error in patients whose tumors involve the lamina propria, even if the initial resection was complete.

Tx of Low Risk Disease

- Managed by TURBT alone. Follow-up surveillance cystoscopy and screening urinary cytology at three to six month intervals for three to five years is recommended.
- A single post-TURBT dose of intravesical epirubicin may significantly decrease the recurrence rate (by one-half), and improve recurrence-free survival, but its impact on overall survival and the risk of invasive disease is unclear. J Urol 2002;168:981.

Tx of high risk disease

- High risk superficial bladder tumors have a higher rate of both recurrence and progression to more invasive disease. Intravesical therapy is generally recommended after complete resection. As with low risk disease, aggressive surveillance following treatment is recommended, with periodic cystoscopy and urinary cytology.

Intravesical Therapy

■ BCG q week x 6

- RCT: intravesical BCG was associated with a significantly higher 10-year progression-free survival (61 versus 37 percent), and disease-specific survival rate (75 versus 55 percent). JCO 1995 Jun;13:1404.
- Toxicities associated with the use of BCG consisted of frequency (71%), cystitis (67 %), fever (25 %), and hematuria (23 %). Cochrane Database Syst Rev 2000.
- Re-evaluate week 6, may repeat x 1

Management of recurrent or persistent disease

- Superficial papillary tumor (Ta) —managed with repeat TURBT.
- Carcinoma in situ (Cis) —cannot be controlled with TURBT alone. If intravesical therapy fails, cystectomy is the only alternative (controversial).
- T1 disease — Patients who relapse with recurrent T1 tumors within six months to one year after TURBT and one or two courses of BCG are currently best treated with cystectomy (controversial) .

Proposal

- A phase I study of the use of LBH 589 in the treatment of refractory superficial TCC of the bladder: Molecular and clinical assessments of efficacy.

Rationale

- TSA demonstrated a 70% reduction in tumor volume in two bladder xenograft models Int J Cancer 2005;113,841.
- HDACi combined with TRAIL restored apoptosis in TRAIL resistant cell lines Cancer Res 2006;66,499.
- Belinostat induced cell cycle arrest, reduced bladder cancer cell growth, and decreased bladder weights in a cell line/xenograft model Journal Trans Med 2007;5,49.
- SAHA inhibited growth in 2 of 6 patients with Met TCC in phase I human trials Clin Can Res 2003;9,3578.

Objectives

- Primary objectives
 - MTD/DLT of intra-vesicle LBH 589
 - Safety
 - Efficacy
 - Pharmacokinetics
- Secondary Objectives
 - Histone acetylation
 - Chromosomal aberrations, gene expression changes, H-ras expression, her-2-neu expression, TP 53 expression, cytology

Design - Phase I

- DX of recurrent superficial bladder cancer, sample/biopsy collection
 - tumor histone acetylation, tumor H-ras expression, tumor Her-2-nue expression, tumor TP53 status, Urovysion fish for chromosome 9 abnormalities, urine cytology
- Weekly x 6 installations of LBH589 from dx to TURBT, Fibonacci dose-escalation to MTD (3 x 3 design), PKs, weekly safety monitoring

Design - Phase I

- Five Cohorts

- Dose Level

Dose

- D0

3mg/m²

- D1

6 mg/m²

- D2

9 mg/m²

- D3

12mg/m²

- D4

20 mg/m²

Molecular alterations targeted in BC

- 35% with H-Ras mutations and downstream activation of Raf/Mek/Erk pathway
- 42% with her-2-neu over-expression
- TP 53 mutations in 50%
(Since it acetylates and inhibits hsp90, LBH589 treatment depletes the levels of Raf, Her-2, AKT and mutant p53, all hsp90 client proteins)
- Abnormalities of Chr 3, 7, 17, 9p21

Correlative Biomarkers Analysis

PK Studies

- Plasma samples
 - Pre-Rx, 1 hour Rx, and 6, 24, 48 hours post-Rx for LBH589 levels
- Urine samples
 - Pre-Rx, 1 hour Rx, and 6, 24, 48 hours post-Rx for LBH589 levels

PD Biomarker Studies

- Exfoliated and curettaged cancer cells (Pre-Rx, 1 hour post 1st Rx and post 1 hour last Rx):
 - Urovision cytogenetics
 - Urine cytology
 - H-Ras expression and mutation
 - TP-53 expression and mutation
 - Her-2-neu expression
 - Histone H3 & H4 acetylation, P21 levels, Hsp70 and 90 levels and acetylation, alpha-tubulin acetylation, c-RAF, AKT, CDK4, and MYC levels

Design- Phase I

- Tx completed, TURBT, sample collection
 - tumor histone acetylation, tumor H-ras expression, tumor Her-2-nue expression, tumor TP53 status, Urovysion fish for chromosome 9 abnormalities, urine cytology
- CR-> Stop, Surveillance cystoscopy q 3 months with sample collection (of prior positives) until relapse
- No CR ->Cystectomy or systemic chemotherapy and radiation per treating physician

