NMIBC BCG Refractory Public Workshop: Summary of FDA Workshop

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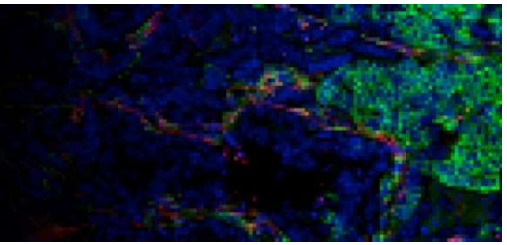
Disclosures



- Clinical trials
  - Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), UroGen, Viventia
- Advisory Board/Consultant
  - Anchiano Therapeutics, Ferring, Genentech, QED Therapeutics, UroGen, Vaxiion
- Honoraria
  - Dava Oncology, MSD Korea, Nucleix

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Cystectomy is the Standard of Care for Patients Who are Medically Fit

AUA/ASCO/ASTRO 2016

In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

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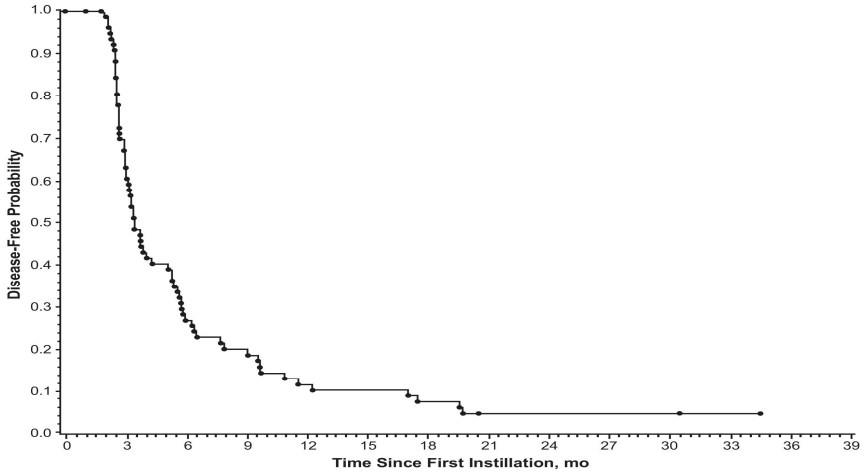
Valrubicin

Dinney et al Urol Onc 31:1635,2013

1998 - FDA approved treatment for patients with BCG refractory CIS for whom immediate cystectomy would be associated with unacceptable morbidity or mortality

- 80 patients with CIS
  - 39% had at least 2 prior courses of BCG
- Received 6 or 9 weeks of Valrubicin
- 35% NED at 3 months
  (positive cytology allowed)
- CR at 6 months 18%
- 4% disease-free at 2 years



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FDA/AUA 2013

FDA Public Workshop
Clinical Trial Design Issues – Development of New Therapies for Non-Muscle Invasive Bladder Cancer
May 6, 2013

Manchester Grand Hyatt - San Diego, CA
Douglas Pavilion C & D

Co-sponsored by the U.S. Food and Drug Administration (FDA) & the American Urological Association (AUA)

Co-Chairs: Jonathan Jarow, MD and Seth P. Lerner, MD, FACS

- Is it appropriate to conduct trial with mixed population of CIS and papillary Ta,T1?
  - What is trial design with single endpoint using time to event analysis?
- What is appropriate comparator for a RCT?
- Is natural hx of CIS well defined to determine magnitude of treatment effect and durability in a single arm trial?
- Is it feasible to conduct a RCT that employs no treatment or placebo as the control arm in any risk strata of patients with NMIBC?
- For peri-op therapy, what primary endpoint and what magnitude of benefit is clinically meaningful?

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FDA/AUA/SUO Guidance

Special Report

Urology 83:262, 2014

Clinical Trial Design for the Development of New Therapies for Nonmuscle-invasive Bladder Cancer: Report of a Food and Drug Administration and American Urological Association Public Workshop

Jonathan P. Jarow, Seth P. Lerner, Paul G. Kluetz, Ke Liu, Rajeshwari Sridhara, Dean Bajorin, Sam Chang, Colin P. N. Dinney, Susan Groshen, Ronald A. Morton, Michael O'Donnell, Diane Zipursky Quale, Mark Schoenberg, John Seigne, and Bhadrasain Vikram

Bladder Cancer 1 (2015) 29–30
DOI 10.3233/BLC-159002
IOS Press

Short Communication

3/30/2015

Clarification of Bladder Cancer Disease States Following Treatment of Patients with Intravesical BCG

10/26/2015

IOS Press BLADDER CANCER www.iospress.com

BI Cancer. 2015; 1(2): 133–136.
Published online 2015 Oct 26. doi: 10.3233/BLC-150016

PMCID: PMC4832566
NIHMSID: NIHMS776513

Development of Systemic and Topical Drugs to Treat Non-muscle Invasive Bladder Cancer

Jonathan Jarow,[a] V. Ellen Maher,[b,*] Shenghui Tang,[c] Amna Ibrahim,[b] Geoffrey Kim,[b] Rajeshwari Sridhara,[c] and Richard Pazdur[b]

SUO-CTC sponsored joint meeting with CDER and CBER at FDA 4/18/2016

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Workshop Recommendations

- Defined BCG-refractory disease as patients who received 2 induction courses of BCG, induction plus maintenance (usually within 6 months), or were intolerant of BCG
- No agreement on SOC for the treatment of these patients to use as a control arm but did agree that additional BCG is not appropriate
- A placebo arm was inappropriate for ethical and practical reasons and endorsed single-arm trial design

Urology 83:862, 2014

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Workshop Recommendations

- In patients with CIS, an initial 6 mo. complete RR of 40%-50% and a durable RR of at least 30% for 18-24 months with the lower bound of the 95% confidence interval excluding 20% could be clinically meaningful.
- Broad consensus by the panel that a placebo control could be used in low-risk patients
- For patients undergoing radical cystectomy, an intravesical agent could be compared with a placebo or active control using pathologic response as the primary endpoint

Urology 83:862, 2014

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Workshop Recommendations

- There was broad consensus that a placebo control could be used in an add-on trial design, for example, BCG plus X vs BCG plus placebo.
- Endpoints:
  - Recurrence of high grade disease or progression in stage
  - Upper tract second primary in patients treated with a systemic agent
  - Patients who recur with a low grade tumor can stay on study treatment

Urology 83:862, 2014

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"BCG Unresponsive" High Risk NMIBC

- Recurrent/persistent high grade urothelial carcinoma after completion of at least induction and one cycle maintenance BCG ("5+2") for high grade Ta/T1 or CIS
  - Never achieved CR or recurred within 6 months of last BCG dose
- T1HG at first evaluation after induction BCG – at least 5 of 6 induction doses
- These patients are "extremely unlikely" to respond to further BCG

Bladder Cancer 1:29, 2015

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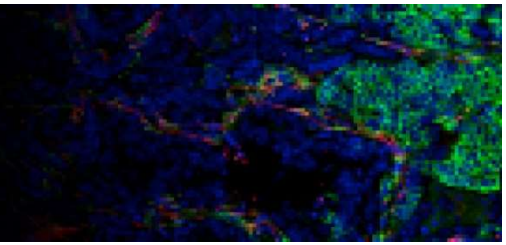
Final FDA Guidance February 2018



BCG-Unresponsive Nonmuscle Invasive Bladder

Jonathan Jarow (FDA): "If you adopt the right attitude it can be amazing to see how long things can take in our bureaucracy even when folks are pushing hard to get something out" 1/22/2018 – day of government shutdown
Final guidance Februrary, 2018

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2018
Clinical/Medical

"BCG Unresponsive" High Risk NMIBC

Revised

- Recurrent CIS +/- Ta or T1 within 12 months of completion of adequate BCG - ("5+2")
- Recurrent/persistent high grade Ta or T1 within 6 months of completion of adequate BCG – no change
- T1HG at first evaluation after induction BCG – at least 5 of 6 induction doses – no change
- "Flexibility" in use of 6 and 12 month time periods

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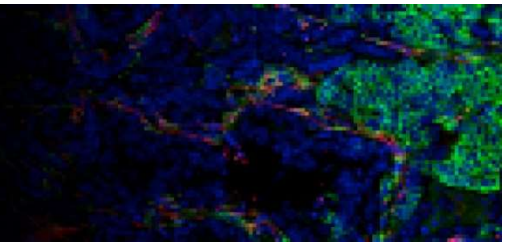
Clinical Trial Design FDA Guidance



- Randomizing patients with BCG-unresponsive disease to a minimally effective drug as a concurrent control raises ethical concerns.
- Because effective drugs are not available and the alternative treatment is cystectomy, single-arm trials of patients with BCG unresponsive CIS disease with or without papillary disease are appropriate.
- Primary endpoint should be complete response and durability in patients with CIS

Final FDA Guidance Feb, 2018

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Alternatives to Cystectomy When BCG Fails the Patient

- BCG/IFN – patients treated w/induction only
- BCG unresponsive
  - Valrubicin – only FDA approved drug
  - Gemcitabine
  - Optimized MMC
  - MMC + Heat or Microwave
  - Gem/MMC
  - Gem/Docetaxel
- *Clinical trial*

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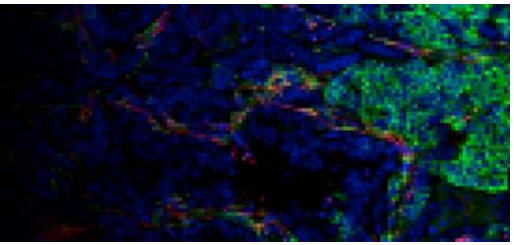
Clinical Trials



- Ad-IFN gene therapy (FKD– SUO-CTC)
- Atezolizumab (SWOG S1605 - Roche/GNE)
- BCG + ALT-803 (Altor BioScience)
- BC-819 (Archiano Therapeutics)
- BGJ 398 FGFR targeted therapy – Ta but no CIS (MSKCC)
- CG0070 (Cold Genesys)
- Cabazitaxel, gemcitabine, and cisplatin Phase I (Columbia)
- ChemoXRT for T1 (RTOG 0926)
- Gemcitabine/Pembro (ECOG 11/8/2019)
- Nab-Rapamycin-ABI-009 Phase I/II (AADi)
- Nivolumab or Nivolumab Plus BMS-986205 (BMS)
- Pembrolizumab (Merck) – reporting at ESMO and SUO
- sEphB4-HAS (USC)
- Viccinium (Eleven Biotherapeutics)

Clinicaltrials.gov 8/5/2019