Devices Referencing Drugs
November 16, 2017

QUESTION 7

What challenges exist at the investigational application stage, and how can those challenges be addressed?

PRODUCT EXPERIENCE

- Devices referencing drugs as a group will encompass products for which there may be a range of experience concerning the safety and effectiveness of the devices and drugs separately

- In some instances the device will have been cleared or approved previously for use without the drug

- Drugs for use in DRD submissions will be previously approved, and have safety and effectiveness data, although not for the indication in question

- In instances where both medical products have a demonstrated history of being safe and effective, that knowledge should be taken into account in the review of IDE and PMA submissions

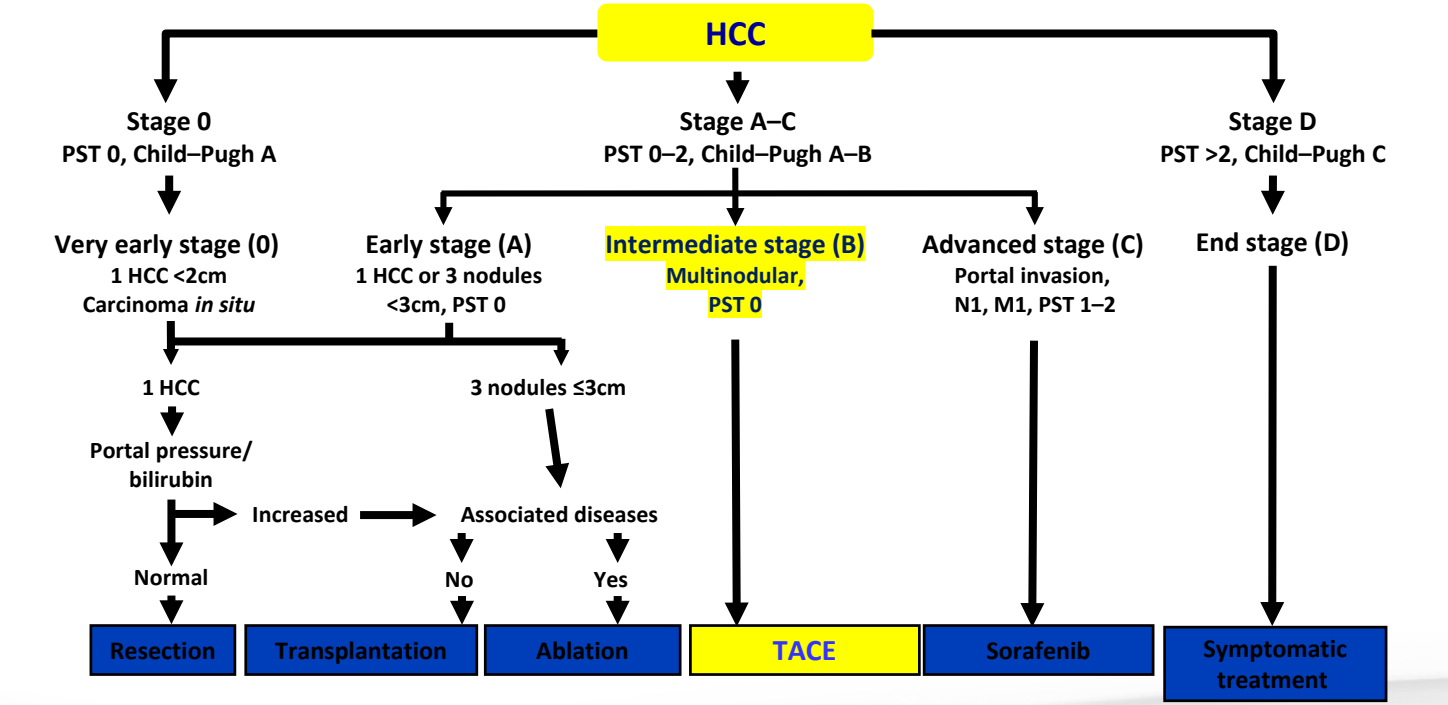
GOALS

- Well designed phase III, prospective studies are critical, but should be realistic in scope
- The IDE process and subsequent PMA should not be prohibitively burdensome
- The DRD's response to an unmet medical need should be taken into account

CASE IN POINT: Chemoembolization for Hepatocellular Carcinoma

- Worldwide Hepatocellular carcinoma is the 2nd most frequent cause of cancer related death
  - US cancer update by ACS, CDC, NCI and NAACCR for 2016 found a decline in death rates for cancers overall 2003-2012, BUT death rates increased significantly for HCC 2008-2012
- Transarterial chemoembolization (TACE) has been the most common treatment for intermediate stage HCC for >30 years
- TACE is identified as a standard of care treatment by ACS, ASCO, NCCN, ASLD, and SIR, among others
- But no embolic has ever been FDA approved for the indication of chemoembolization of HCC

Treatment Algorithm and Staging System for HCC



adapted from Llovet JM, et al. J Natl Cancer Inst 2008;100:698-711

UNMET MEDICAL NEED

- PubMed search Nov 3, 2017 using terms *chemoembolization* + *hepatocellular carcinoma* resulted in 244,000 publications found

- Difficult to compare outcomes in studies due to variability in embolic agents, chemotherapy types/combinations/doses, treatment intervals, and endpoints

- With no embolic FDA approved for TACE, US patients with HCC receiving this standard of care treatment, by definition, are all being treated off-label

EXAMPLE OF IDE PROCESS FOR A DRD

- BioSphere Medical/Merit Medical sought to address this unmet need with an IDE submission to conduct a phase III study of embolic microspheres capable of loading doxorubicin ionically to provide targeted, sustained drug delivery in TACE for HCC

- Embolic had been cleared for treatment of hypervascular tumors (without drug) 3 years previously

- Same embolic was CE marked for delivery of doxorubicin for chemoembolization of HCC 2 years previously

- Doxorubicin had decades of safety and effectiveness data

IDE REVIEW PROCESS

- Pre-IDE package sent to FDA June 2009; telephone feedback August 2009
- IDE submission sent October 2009
- November 2009--August 2010 the review process included:
  - 3 IDE amendments in response to 3 deficiency letters
  - 5 conference calls
  - Face to face meeting
  - Multitude of emails and calls
- Appeal submitted August 2010
- Conditional approval granted November 2010

IMPROVEMENTS TO IDE PROCESS FOR DRDs NEEDED

- IDE review for devices referencing drugs should take into account:
  - Extent of existing safety and efficacy data for products
  - Degree and impact of unmet medical need
  - Requirement of reasonable data to demonstrate DRD safety and effectiveness
- Prospective, well-designed, phase III studies are imperative, but must also be feasible to accomplish
- PMA review should consider least burdensome provision and balance of pre- and post- market data collection

Thank you