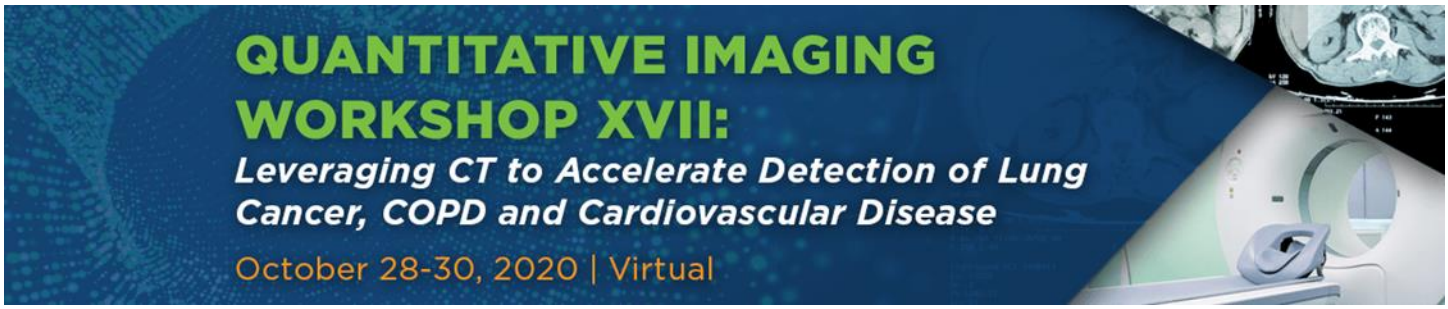

SUMMARY

Breakout 2: Approach to Advancing Combined Modality Therapy for Early Stage Screen-Detected Disease—Adjuvant/Neoadjuvant Therapy

Q1: We have some success in early stage trials for Stage IB or Stage 2…

- Early Stage IA trials with chemotherapy suggested adverse outcome so no trial yet to study stage IA disease.
- With the increase frequency of detection of Stage IA disease with lung cancer screening reconsideration of adjuvant therapy for "aggressive Stage I disease" needs to be considered.
- Careful consideration of the risk/benefit analysis with Stage IA must be considered in determining benefit of stage IA adjuvant therapy
- Moving forward with fuller implementation of LC screening frequency of Stage IA will continue to rise
- With current surgical approaches for screen-detected small tumors, there is still a consistent 10% recurrence rate and mortality rate
- Pattern of recurrence is important: some cancers will recur locally, others local/ regionally and some with distant site of disease; therefore type of adjuvant therapy should be evaluated

Risk of recurrence: Radiologic characteristics

  - subsets of adeno with higher likelihood of recurrence
  - subsets of patients with more aggressive tumor

- Histologic and Radiologic features -> select for adjuvant therapy
- ADAURA trial: only patients with certain activating EGFR mutations
- Will not treat all stage I, will look at histologic/radiologic/molecular features to look for elevations
- Previous presentation: PCR markers from Jablons et al in CA cohort and cross validated in cohort from china: identified a panel of RNA? markers that define aggressive stage I
- Currently, no standardized approach to diagnostic approach to evaluate resected primary stage I cancers important to allow an efficient and economical approach to identify all targetable types of genotypes/phenotypes to allow most approach adjuvant therapy
- Challenge to having international collaborations due to lack of standardized molecular pathological evaluation of resected primary tumor

  ➔ Collaboration for molecular pathologic evaluation of resected stage I tumor could support refinement of molecular classification of early lung cancer to facilitate personalized therapy

  ➔ Need pre-competitive collaboration with relevant diagnostic companies to harmonize and make technologies available to all sites to minimize cost toxicity

Q2: What is the threshold safety profile for a drug to be considered for adjuvant administration to a Stage IA cohort?

- Rarely see impressive threshold like the current ADAURA EGFR inhibitors with major reduction in overall hazard ration.
- Consider two scenarios when a marker only identify small fraction (2%?) subset of the population but highly effective compared to a marker with a higher frequency of positivity but with only 10-15% effectiveness on a higher fraction of the resected stage I cancers? What is the threshold for activity we want to see? How good does the drug has to be to justify adjuvant application?
- By corollary, what is the acceptable threshold for toxicity? How safe does the ideal early adjuvant therapy agent have to be?
- Immunotherapy and targeted treatments: tolerability is much better; not concern about delaying surgery
- New systematic treatments are better tolerated.
- Considerations: With targeted treatments, are we curing patients? Or are we essentially delaying the action? Can we see overall survival benefit (need for mature follow-up data)?
- Endpoints for immunotherapy with neoadjuvant studies: effect on surgical tissue as surrogate; may not have data to show survival benefit
- In patients with high chance of cure in stage IA settings, potential consequences of drug administration are very important (consider EGFR therapy with moderate side effects vs immunotherapy with rare but disturbing /life interfering vs. death)
- Immunotherapy: side effects- mostly manageable mild toxicity; rare to have severe toxicity; Difficult to discuss risk and benefit of neoadjuvant immunotherapy with patients
- Surgeon consideration on neoadjuvant use of immunotherapy: more onerous because of possible impact on dissection for stage IA

Q3: Adjuvant vs. neoadjuvant?

- Surgeons' concern about delays in surgery? Complexity in operation?
    - Why different surgeons react differently on immunotherapy?
- Importance of Stakeholder buy-in
- Can see important improvement in immunotherapy, should be studying on trial basis-still equipoise: for more advanced patients use chemo only? Or chemo+rad? based on individual's experience and comfort level
- For LCs that are usually resectable with no nodal disease, challenge to use therapies in neoadjuvant fashion and not adjuvant->hard to get buy in from patients

->>Focus on adjuvant therapy

- Neoadjuvant window trials (only as experimental Phase II POC) not for routine adjuvant
- Fundamental challenge: finding group with high likelihood of recurrence
    - If we can identify that group, then it becomes an easier sell to patients

❖ Who's the wolf in sheep's clothing? Small stage I with 90%+ cure rate. However, even though some stage I meet the criteria for stage I based on traditional prognostic factors, they actually have higher risk of recurrence and should be of higher stage.

Q4: Can basket trials accelerate the speed of evaluating agents for benefit in adjuvant and/or neoadjuvant trials? What have been the critical lessons learned from previous basket trials?

- Basket trials could be important mechanisms
- For stage IA– setting up basket trials based on molecular subtypes and mutation profiles, giving different therapies based on patient profiles (oncotype? Mutational targets? Immune cell profiling? use to tailor treatment)
- Given 10% of stage IA, not a vast population; some of these molecular targets/immune celltyping, if we don't have large catchment, never be able to get them done
    - Create a mechanism (basket trials) to match through drug candidates would enhance efficiency and reduce cost
- Use of some kind of blended basket type approach otherwise too costly monetarily and financially
    - Can we make these kinds of trials happen sooner? Having mechanisms such as basket trials so we have a catchment area to constantly offer these therapies to patients

Q5: Historically, accruing highly curable stage I participants to experimental drug trials has been challenging. What approach would you suggest to ensure robust participations in the proposed early stage disease trials.

- It is usually at low risk (95% of time you are cure), but 5% if you have these features, you are at higher risk of recurrence
    - Need to develop compelling basis for patient participation – help PT to understand potential benefit
    - Adjuvant trial in patients with higher risk

Q6: What message to send to patient, worthwhile?

- Even with small lung cancers, some PT just want to get it out,
    - If we can accurately risk stratify PT with high risk of recurrence, then that would help convince these patients enroll into these trials (improve PT understanding)
- Risk stratify: stage I doesn't mean it is going to be cured. They may metastasize or have a recurrence. Even Stage IA can have a heterogeneous outcome. Work to refine staging system to include independent markers of bad outcomes

- TNM is the best way to characterize the disease and plan treatment but is not always indicative of a favorable clinical course
- Integration of immune-profiling may allow for a more predictive prognostic marker of outcome accuracy. Similarly may integrate other risk factors to improve prediction of recurrence.
- Personalized staging: Increasing knowledge about a particular individual. Will keep evolving

Final Comments:

➔ Neoadjuvant window trials are different class of investigation-proof of concept (drug development) and not routine management which is what we are discussing in the first stage of development of early therapy for Stage IA disease (outside context of this discussion)