Coverage Analysis for Oncology Trials:

Understanding the Nuances and Keys to Success

Introductions

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Today's Agenda

1. Start Reading the Agenda to the Audience
2. Do My Best to Prove to You Why This is Important
3. Best Practices
4. Complex Study Designs and Unique Trial Types
5. Quick Break to Stare Into the Void
6. Conclusion and Audience Questions

What Makes Oncology Special?

Differences in oncology vs. non-oncology studies

Oncology

- Resources:
  - NCCN (National Comprehensive Cancer Network)
  - Medicare approved journals for anticancer drugs
- Complex disease staging
- Complex studies
  - Disease indications, treatment options, lots of arms, oh my
- More, but I don't want to scare anyone else off

Non-Oncology

- Resources:
  - Whatever you can find
    - Well, not **whatever** you can find. It needs to be peer reviewed
    - Less stringent requirements on journals used for drug analysis
- More straight-forward disease staging (most of the time)
- Typically simpler study designs

Best Practices

Do your best to remember the WHY behind a coverage analysis

For the study start-up process:

- The CA is the first building block in study start-up
- CA → internal budget → budget negotiations
- A thorough CA is critical for ensuring all costs of the trial are accounted for

For the site:

- Document the payer (sponsor or Medicare/insurance) for each protocol required item to prevent double billing
- Helps prevent compliance errors if followed correctly
- Important to have on hand in case of audits

For the patient:

- Patients shouldn't receive bills for items not necessary for treatment (especially if they might be denied by insurance)

Best Practices

NCDs and LCDs

- Medicare's item-specific coverage policies
- NCDs/LCDs often list indications (will be covered by Medicare) and limitations (will NOT be covered by Medicare)
- Must be incorporated into a CA because sites must comply with Medicare regulations within the clinical trial

NCD (National Coverage Determination)

- Applies to all states
- May need to consult the Covered Code List to confirm if an ICD-10 is covered
- NCD 310.1: Routine Costs in Clinical Trials – can be used for qualifying clinical trials to bill items that are conventional care, the administration of the study drug, and items used to prevent/monitor side effects

LCD (Local Coverage Determination)

- Applies to certain states
- Different regions/states may have different rules for the same item
- Important to consider if you are creating a CA for a network of sites

Best Practices

Before beginning your coverage analysis

- Gather all necessary/relevant documents

Must have	Nice to have ☺
1. Protocol	1. Sponsor budget 2. Informed consent 3. CTA 4. Investigator's brochure

- Know your patient indications – these can be very specific or very general
- Know any site-specific preferences

Complex Study Designs and Unique Trial Types

How to approach a study with a complicated design

- Start with the study schema! *What is this study all about? How many cohorts? What are the treatments in this study?*
- Look at the Schedule of Events. *How many different arms are there*?
- Look at the sponsor budget/CTA. *How many different grids? How many visit totals?*
- Check the sponsor budget/CTA for language such as “if not SOC” or “if not routine care”
- Examine the invoiceable section of the sponsor budget/CTA. *Does it specify the circumstances where an item can be invoiced?*
- Review site-specific preferences

Complex Study Designs and Unique Trial Types

Common study designs

Open-label

- Patients and staff will know which treatment is being given (or even lack of treatment)
- Depending on institutional preference, items may have differing designations between arms
- Make sure that you know when randomization occurs!

Blinded

- Single-blind: Only the patient is blinded
- Double-blind: Patients and treating staff are blinded
- Triple-blind: Patients are blinded, staff are blinded, data analysts are blinded, everyone is blinded!
- Quadruple: My personal record for largest cheeseburger eaten in one sitting

Complex Study Designs and Unique Trial Types

Common study designs

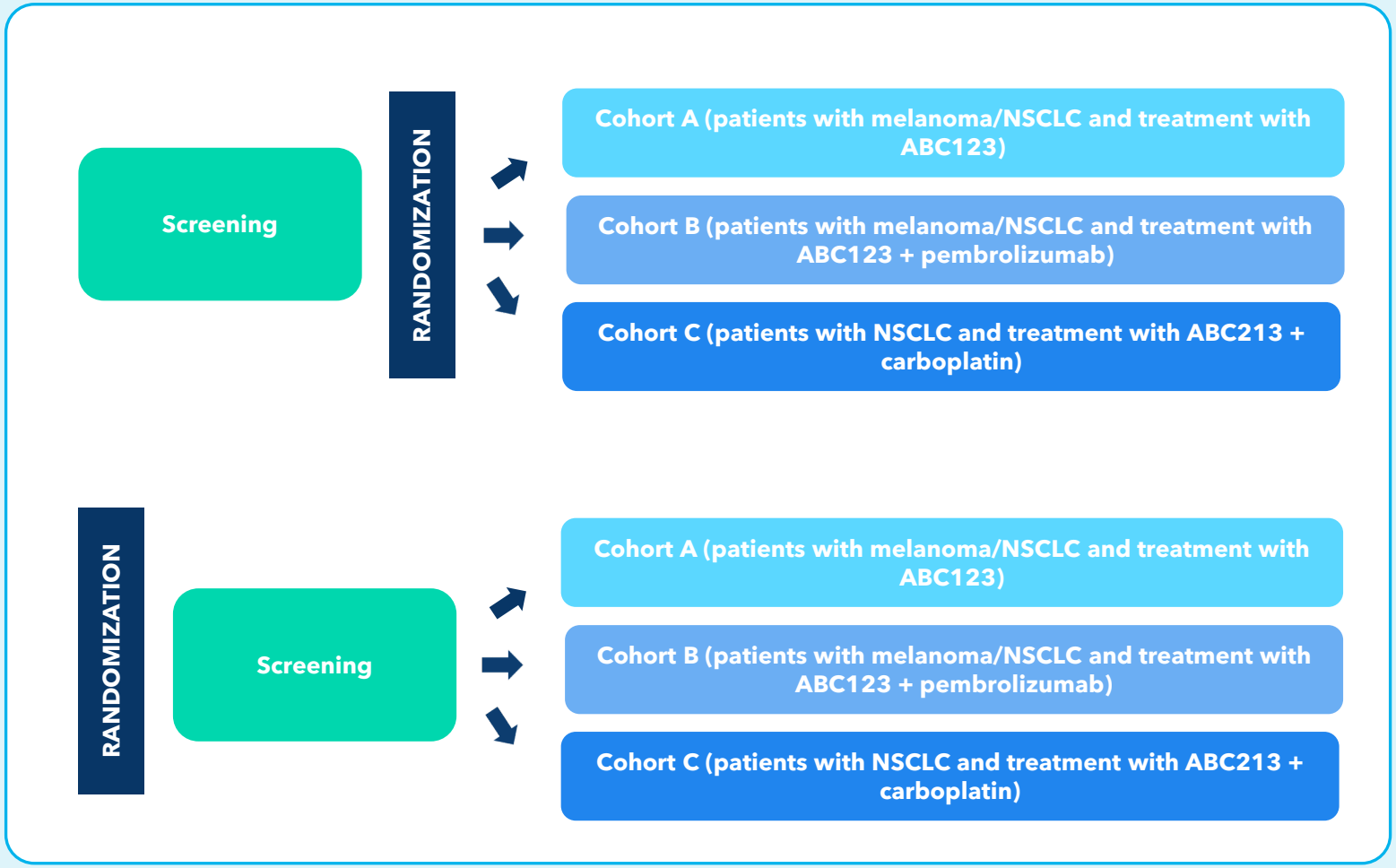
Randomized

- Patients are assigned to a treatment
- Can be open-label or blinded
- Randomization can occur anytime prior to treatment (e.g., at enrollment, at screening, or on C1D1)

Complex Study Designs and Unique Trial Types

Considerations with randomized studies

- Randomization commonly occurs prior to screening or after screening
- What are the implications for our coverage analysis if randomization occurs before screening vs. after screening?



Complex Study Designs and Unique Trial Types

How many grids should I build?

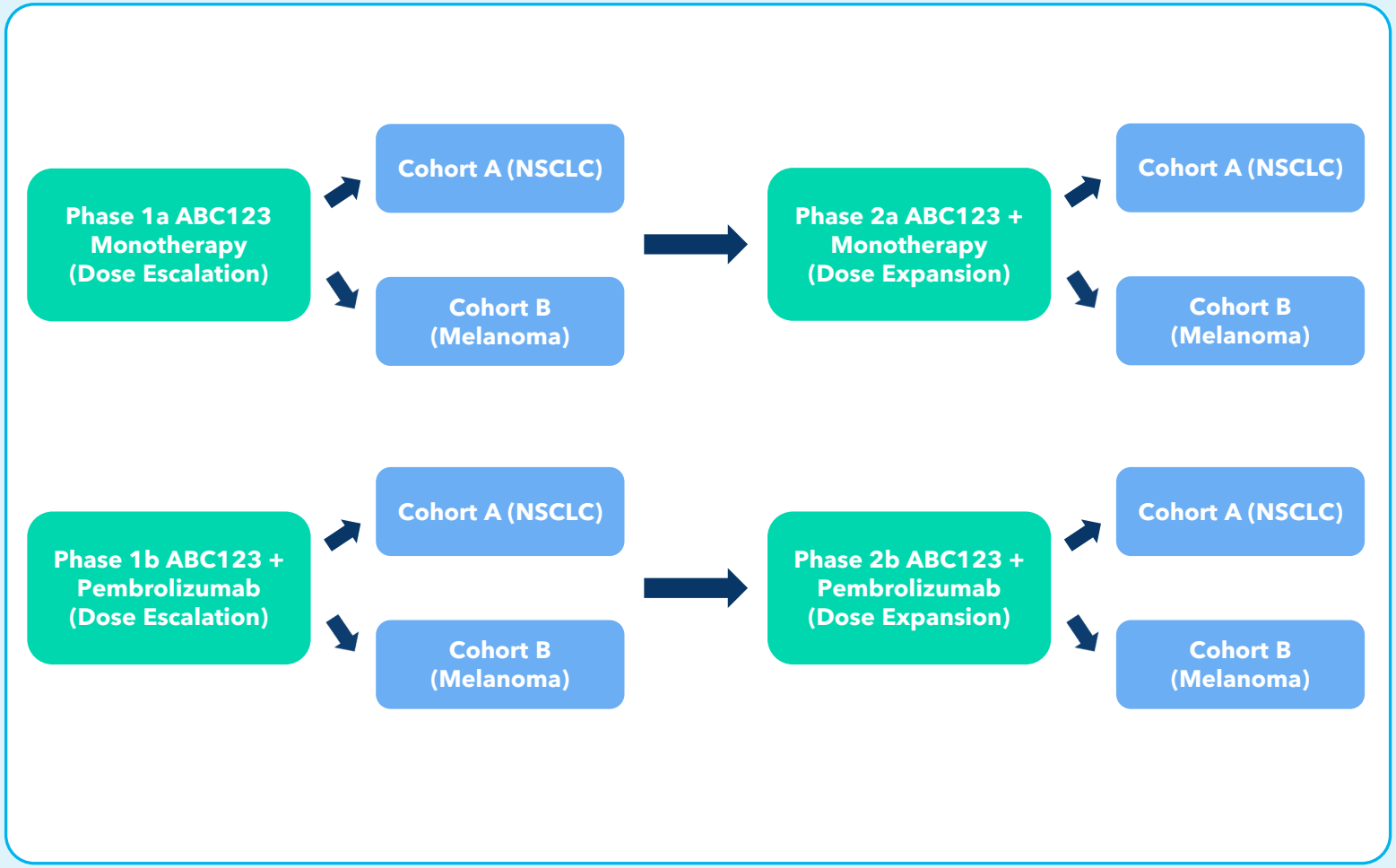
Example study!

Schedule of Events has **2** grids: Phase 1 and Phase 2

Sponsor budget has **4** grids: Phase 1a, Phase 1b, Phase 2a, and Phase 2b

Study design shows **8** different cohorts

Should you build 2 arms, 4 arms, or 8 arms?



Complex Study Designs and Unique Trial Types

How many grids should I build?

If you build **2** grids to match the Schedule of Events (*Phase 1, Phase 2*):

- An item needs to be supported by BOTH the NSCLC and melanoma guidelines to bill
- We can't use pembrolizumab side effects/immunotherapy guidelines since not all patients will be receiving the medication
- Any cohort-specific items will need to be invoiced if research related – may be more work for study staff once the trial is up and running
- Advantages to this approach: The fewer the grids, the faster the CA build

Complex Study Designs and Unique Trial Types

How many grids should I build?

If you build **4** grids to match the sponsor budget (*Phase 1a, Phase 1b, Phase 2a, Phase 2b*):

- An item needs to be supported by BOTH the NSCLC and melanoma guidelines to bill
- We CAN use pembrolizumab side effects/immunotherapy guidelines since all patients in Phase 1b and Phase 2b will be receiving the medication
- Any cohort-specific items will need to be invoiced if research related – may be more work for study staff once the trial is up and running
- Advantages to this approach: Easiest to compare to the sponsor budget when building the CA and internal budget

Complex Study Designs and Unique Trial Types

How many grids should I build?

If you build **8** grids to match the study design diagram (*Phase 1a Cohort A, Phase 1a Cohort B, Phase 1b Cohort A, Phase 1b Cohort B, Phase 2a Cohort A, Phase 2a Cohort B, Phase 2b Cohort A, Phase 2b Cohort B*)

- An item only needs to be supported by one guideline to bill
- We CAN use pembrolizumab side effects/immunotherapy guidelines since all patients in Phase 1b and Phase 2b will be receiving the medication
- Any cohort-specific items do not need to be invoiced since they will only be included in applicable grids
- Advantages to this approach: More items can be billed

Complex Study Designs and Unique Trial Types

Considerations when combining multiples arms into 1 grid

- **Do patients in all arms have the same indication?**
  - -Yes: Great! Treat as normal
  - -No: Each guideline needs to have recommendations to bill an item
- **Will all patients be getting the same study drug/s?**
  - -Yes: Great! Treat as normal
  - -No: Each treatment option needs to have relevant side effects to bill an item
- **Are items/procedures performed for patients in all arms?**
  - -Yes: Great! Treat as normal
  - -No: Analyze based on patients receiving the item/procedure. Invoice if research-related

TL;DR: if an item/procedure isn't billable for ALL patients receiving it, it's billable for NO patients.

Complex Study Designs and Unique Trial Types

Patient indications

- Cancer type
- Staging
- Previous Therapies
  - -Treatment naïve?
  - -How many previous lines of treatment?
  - -What were the previous treatments?
  - -Surgery?
  - -Progression? Relapse?
- Rinse and repeat

Complex Study Designs and Unique Trial Types

Treatment options

Common

- Monotherapy (typically the IMP)
- Combination therapy (typically the IMP + FDA approved drug/s)
- Device (typically a type of study that makes me question everything that I know)

Less Common

- Coformulation
- Immunotherapy
- Cell therapy
- Radiation therapy
- Observation

Complex Study Designs and Unique Trial Types

Solid tumor and first in human studies

Solid Tumor

- Inclusion criteria can be general (e.g., “any type of solid tumor”) or specific (e.g., “NSCLC, SCLC, melanoma, breast cancer, colon cancer, or rectal cancer”)
- Are patients eligible for procedures and/or drugs based on inclusion criteria?

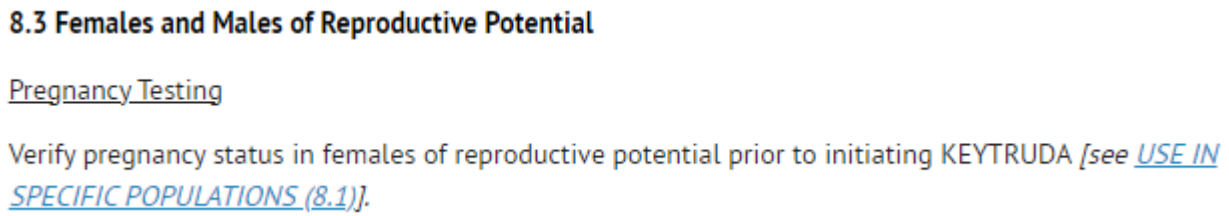
First in Human

- Are there any side effects?
- How many patients have received the drug to date? What’s your threshold?
- Do you have any site-specific preferences about using:
  - Animal side effects
  - Mechanism of action
  - Side effects of drug class/similar medications
- Is this study monotherapy or combination therapy?

Complex Study Designs and Unique Trial Types

Immunotherapy

- NCCN guidelines outline the principles of routine monitoring for FDA approved **immune-checkpoint inhibitors** (e.g., pembrolizumab, nivolumab, durvalumab, etc.)
  - -Recommendations for pre-therapy assessment, monitoring frequency, and evaluation for abnormal findings/symptoms
  - -Primarily useful for analyzing physical exams and local labs → be careful of frequency!
  - -Refer to specific cancer guidelines for imaging
- What if DailyMed/drug label provides specific recommendations not referenced in the NCCN guidelines?



8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating KEYTRUDA *[see USE IN SPECIFIC POPULATIONS (8.1)]*.

- If your study includes a non-immunotherapy drug, you can bill outside of the immunotherapy guidelines

Complex Study Designs and Unique Trial Types

Cell therapy: CAR-T, CAR-NK, TIL, TCR, ABCDEFG?

CAR-T

- NCD 110.24
- Has specific recommendations in the NCCN Guidelines
- This may seem like an "ordinary" treatment, but the CA approach is not ordinary
- May require leukapheresis and lymphodepletion
- Commonly used lymphodepletion drugs are not FDA approved for this purpose

The Rest of Them

- No national guidelines/ guideline support
- No approved products (yet)
- Still shares a few similarities with CAR-T
- How do I analyze?
- Underlying condition
- Study product side effects (probably not)

Complex Study Designs and Unique Trial Types

Stem cell transplant studies can be complicated? Who would've thought?

- NCD 110.23 includes a very detailed list of supported indications
- Vary between allogeneic and autologous
- Is the stem cell transplant the investigational item, or are patients already planning on undergoing transplant?
- If patients are already planning on undergoing the transplant:

  - Assume transplant is billable independent of the study and that all billing criteria of NCD 110.23 will be met

- If stem cell transplant is the investigational item:

  - If in NCD: transplant and associated items are all billable to insurance

  - If not in NCD: Nothing associated directly with the transplant is billable to insurance

- Additional indications may be covered under Coverage with Evidence Development

Study Drug Administration Routes

Wait, you're putting that needle where?!

- Intrathecal
- Blood brain barrier/other brain administration routes
- Intralesional
- Chemoradiation
- Continuous Infusions and Infusion Pumps
- Injections: Self-administered or administered by study staff?
- Radiation Therapy

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