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PHC and Tumor Agnostic Development

Requirement for innovation and collaboration

Todd Riehl, PharmD, BCOP

Global Development Lead: Tumor Agnostic

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- Cancer is HUMAN problem
- Better treatments for patients are desired
  - More effective…cost-effective
- Precision medicine and PHC hold promise of better individual treatments for each patient
- Making PHC a feasible reality through mechanisms like Tumor Agnostic approaches requires collaborative/innovative HUMAN solutions

Moving deeper into PHC and Precision Medicine

Following science to move PHC closer to the individual (n=1)

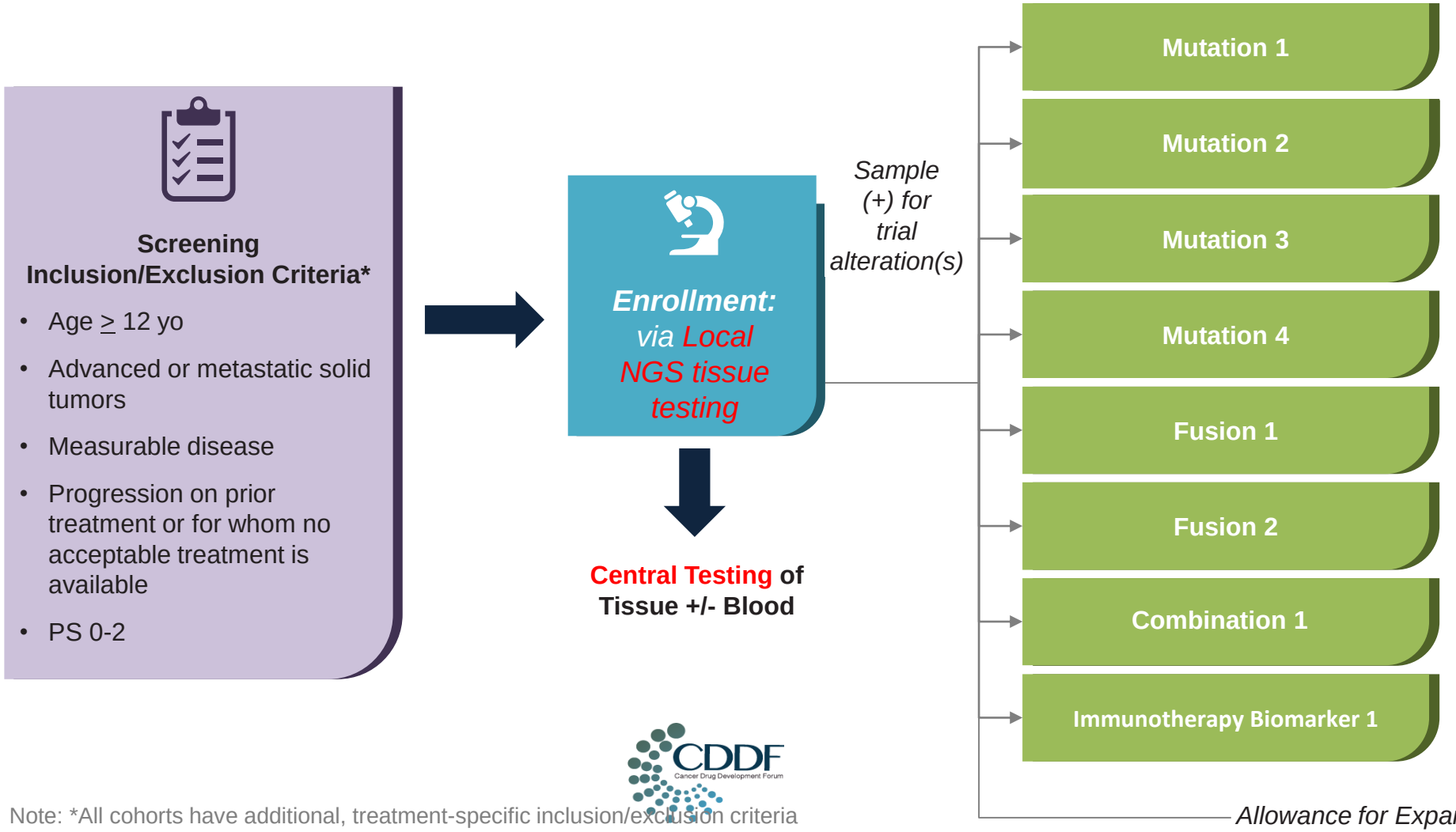
- Genome project has led to identification of somatic alterations
  - Greater understanding of the heterogeneity of diseases/tumors
  - Allows for targeting of the molecular cause of “subpopulations”
- Improving technology allows for better patient selection
  - Selection matched to therapeutic targeting of the molecular cause
  - Leads to more homogeneous, but smaller population sizes
  - Comprehensive genomic profiling (CGP) can also help discern resistance patterns
- PHC drug development
  - Development of more specific medicines and more personalized for each patient
  - Challenges the trial design and statistical standards that can be applied to larger populations

Genomically Driven Trials:

BASKET Trials:

Umbrella Trials:

Tumor Agnostic Umbrella of Baskets Trials



Note: *All cohorts have additional, treatment-specific inclusion/exclusion criteria

From where have we come?

- History of randomized clinical trial
  - Origin dates to 1948 British Medical Research Council evaluation of streptomycin for TB
  - Kefauver-Harris Amendment to US FDCA in 1962, led to US (and other global HAs) to require RCTs for registration
  - Statistical approach adapted from work around games of chance
  - P-value statistical significance level offered by Fisher for consideration (not intended to become a permanent standard)[1]

- Premise of randomized clinical trial:
  - Little was known about condition (Lung cancer)

  and/or
  - Condition is common and affects many people (hypertension)
  - Little was known about the treatment (chemo kills rapidly proliferating cells)

- Concern:
  - If an effect of treatment Is observed, it quite possibly could be due to chance
  - Application of this to a large population could negatively impact many patients (and health care budgets)

- Solution:
  - Agreement that randomized clinical trials are necessary
  - Agreement on the threshold for success (HR < 0.7-0.8, p < 0.05, etc.)

> No scientific worker has a fixed level of significance at which from year to year, and in all circumstances, he rejects hypotheses; he rather gives his mind to each particular case in the light of his evidence and his ideas.[1]
>
> - Ronald A. Fisher

1. Fisher RA. Statistical methods and scientific inference. Edinburgh: Oliver & Boyd, 1956.

Where are we now?

Should we consider that the circumstances have changed?

- Understand much more about diseases under study
  - Histopathologic differences (Adenocarcinoma, Squamous carcinoma, etc.)
  - Molecular driver(s) of disease (point mutation, rearrangement/fusion)
  - Overexpression of surface targets on cells can be effective targets (HER2, CD20, CTLA4, PD1/PDL1)

- Understand the MOA and potential of drugs under study
  - Designed to block the effects of mutation or modulate signaling via binding of cell surface markers
  - Preclinical and early clinical PK/PD evidence of this effect

- Randomized clinical trials not always feasible
  - Molecular testing better characterizes diagnosis
  - Molecularly-driven subsets are legitimately unique populations
  - Prevalence is low for many molecularly-driven populations (rare populations)

Tumor Agnostic Prevalence Rarity

Alteration	Prevalence Across All Solid Tumors*
ROS1 fusions	<0.1%
NTRK1/2/3 fusions	<0.20%
ALK fusions	<0.2%
RET fusions	<0.5%
BRAF V600 mutations	<0.5%
PIK3CA multiple mutations	<1%
AKT1/2/3 mutations	<1%
HER2 mutations	1-2%
KRAS G12C mutations	3-4%
EGFR mutation (short variants)	4-5%
TMB-high	5-10%

*Based on single database with >200,000 solid tumors profiled

How can we be sure that PHC drugs work in rare and TA populations?

- Rarity precludes traditional statistical significance approach
  - Can we agree that a new paradigm exists and not compromise PHC?
  - Can we agree that the conditions of patient selection and specificity of drugs gives us greater certainty in positive data?
  - Can we find a path to a “total data package” that can replace the RCT in small PHC populations and support confidence in efficacy?

Tumor Agnostic Challenges:
Randomization and Control Arms

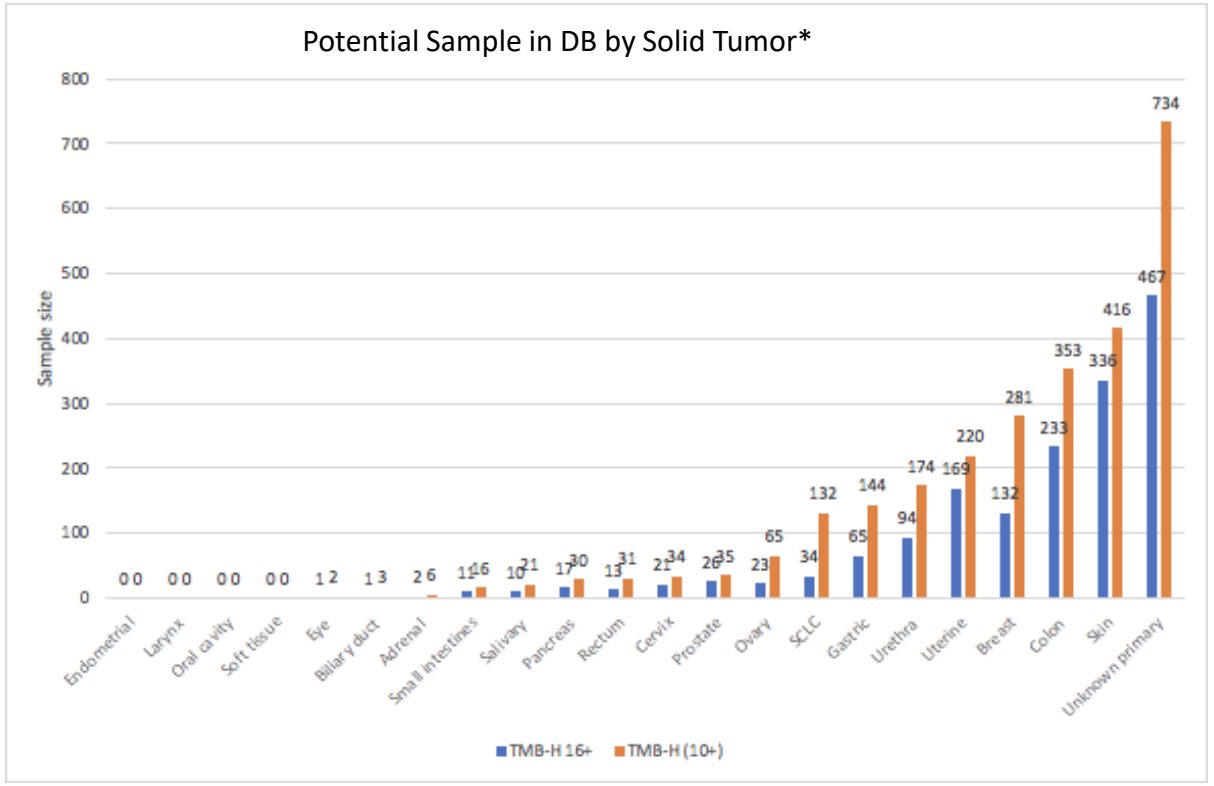
- Size of populations makes randomization difficult
  - Difficult to match and stratify across broad heterogeneity
- Choice of control arm also difficult
  - Differing SOC across tumor types and lines of therapy

Tumor Agnostic Proposals:

RWE and Natural History

- Consider developing the story differently (total data package)
  - Preclinical model evidence across tumor types and cell lines
  - Utilize large databases and RWD/registries to develop “natural history” of the mutation-selected population
    - Need to know how alteration-selected populations perform with SOC(s)
    - Helpful to know if the mutation confers prognostic implications
  - Consider whether such a RWD cohort could be used as a control arm
    - Is the RWE data contemporaneous?
    - Factors for matching and stratification could still be challenging

Feasibility of RWD Control



Cannot match on (N=0):

- Endometrial
- Larynx
- Oral cavity
- Soft tissue

Match on tumor type only for (N<15):

- Eye
- Biliary duct
- Adrenal
- Small intestines
- Salivary

Match potentially on tumor type and one additional characteristic (N>15):

- Rectum
- Cervix
- Prostate
- Ovary
- SCLC
- Gastric
- Urethra
- Uterine
- Breast
- Colon
- Skin
- Unknown primary
- NSCLC (not shown on graph)

*Based on DB containing 37,000+ Solid Tumor patients

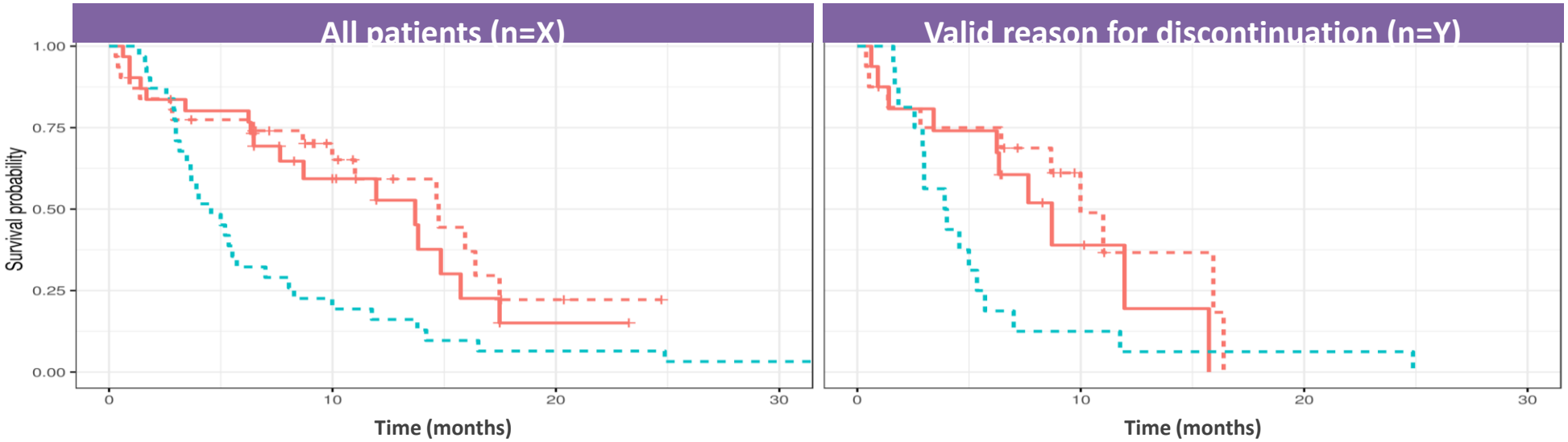
Tumor Agnostic Proposals:
Clinical Trial Statistical considerations

- Single Arm cohorts with ORR as primary endpoint (no control arm)
  - Sample size set to ensure lower bound of 95% CI excludes relative SOC:
    a) Late line salvage only
       1. Compare to Phase 1 Study/BSC (10% ORR, based on Therapeutic Area Expert feedback)
          - » Limited Data establishing Target alteration as predictive/prognostic driver across tumors
          - » Lack of or inconsistent data establishing confidence in drug utility across tumors
       2. Likely limit scope of intended label

    b) All lines of Tx (including earlier lines in tumors where approved/effective SOC)
       1. Comparison: chemotherapy/immunotherapy (30% ORR; basis HA/TAE feedback)

Tumor Agnostic Proposals:

Intrapatient Comparison to Last Prior Therapy



Treatment	EP	Median (CI), mos
Most Recent Prior Therapy	TTNT	5 (4, 8)
Trial Treatment	TTNT	15 (10, NA)
Trial Treatment	PFS*	14 (8, NA)

Treatment	EP	Median (CI), mos
Most Recent Prior Therapy	TTNT	4 (3, 7)
Trial Treatment	TTNT	10 (6, NA)
Trial Treatment	PFS*	9 (6, NA)

Agnostic Challenges:

Variance of Effect in Different tumors

- Tumor agnostic enrollment to facilitate development
  - True tumor agnostic effect may not always be demonstrated
  - Limited/lack of effect may be observed in tumor type(s)
- How does a lack of effect in tumor(s) affect the approach?
  - Should not deter development/registration where efficacy observed
  - Data and labeling should be reflective of tumors with demonstrated efficacy (possibly more limited than “tumor agnostic”)

Agnostic Proposals:
Futility and Labeling

Consider prospective two-tiered futility analyses in statistical planning

a) Tumor Agnostic futility: consider data look with 50% target patient enrollment to establish tumor agnostic efficacy

b) Tumor Type futility: Simon 2-stage-like approach per cohort per tumor type for further enrollment (expansion vs. halting for lack of effect)

Consider variant labeling approaches

a) Tumor Agnostic label, if no clear evidence of lack of effect in any tumor type

b) Labeling exclusionary of tumor types with lack of effect demonstrated

- ”all solid tumors, except tumor type X”
- Statistical analysis and data could be focused on the population scope of the label

Are there other data that can support benefit-risk analysis?

- Given rarity of populations and difficulty of prospective enrollment:
  - Can registries or other RWD populations treated with the drug supplement the experience from clinical trials for registration?
  - …or for datasets to support conversion to full/regular approval?
  - What concerns exist about these types of data and how can the data be improved to overcome them?

What is needed next?

Collaboration & Agreement on new solution(s)

- Need agreement within stakeholders (Health Authorities, HTA bodies, industry, and academia)
  - Current EU Regulatory and HTA body guidances call for randomized controlled data
  - Rare populations do not allow for randomized clinical trials
  - Key is well validated diagnostics for patient selection and appropriately targeted drugs
  - Starting premises of molecularly-driven populations warrant confidence in single arm trial data

- Collaboration and agreement on approach to providing appropriate supportive data
  - How many patients can be reasonably prospectively enrolled at various prevalence levels?
  - Need to better characterize natural history of disease and prognostic implication of alteration/biomarker
    - Real world/registry data for mutation/biomarker-selected populations with SOC treatment(s)
  - Consider use of intrapatient comparison to last prior therapy as alternate control mechanism
  - Criteria for use of real world/registry data to supplement trial data
  - Trade-offs: longer follow-up may more feasible than enrolling large numbers of patients

- Pragmatic new solutions in this new paradigm, rather than adherence to current standards
  - Facilitate, not prevent TA & PHC development …and more effective treatment for patients