Poll Everywhere Audience Response

PollEv.com/USHP

For best CE participation experience

Download the Poll Everywhere app and join USHP

Text USHP to 22333

USHP

1

Speaker Introduction

Julia grew up in the San Francisco Bay Area, then migrated to Southern California for undergraduate studies at Harvey Mudd College. After two years working in vaccine research, she returned to school for her PharmD at the University of California, San Francisco. She then moved to Salt Lake City for her PGY1 at University of Utah Health, and continues as a PGY2 resident in hematology/oncology at the Huntsman Cancer Institute. Her interests include learning about novel therapies (of which there is no shortage in the hematology/oncology world) and pharmacy education.

USHP

2

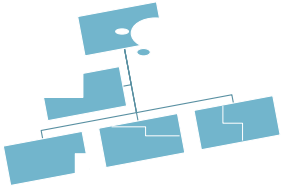
USHP

UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Julia S. Lee, PharmD
November 18, 2021

3

Common Pitfalls in Oncology Clinical Trials



Julia S. Lee, PharmD
PGY2 Hematology/Oncology Pharmacy Resident
Huntsman Cancer Institute at University of Utah Health
Julia.Lee@utah.edu

4

Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Julia S. Lee, PharmD**
    - No relevant conflicts of interest exist
  - **CE Mentor, Dylan Barth, PharmD, BCPS**
    - No relevant conflicts of interest exist
- Off-Label Uses of Medications
  - Bevacizumab

USHP

5

Learning Objectives

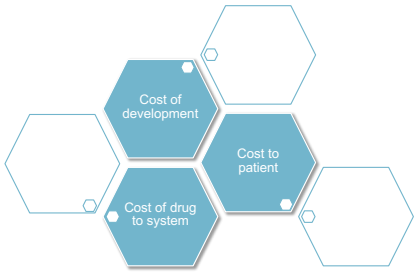
P	Interpret measurements of oncology drugs' cost and clinical benefit
P/T	Describe endpoints required by the FDA after accelerated approval has been granted for an oncology drug
T	Use NCCN guidelines to predict whether a chemotherapy regimen will be covered by payers
P/T	Define internal and external validity, *and evaluate the effect of study design parameters on a clinical trial's validity*
P/T	Identify ways pharmacy staff can advocate for evidence-based cancer care

Abbreviations: FDA = Food and Drug Administration; NCCN = National Comprehensive Cancer Network

USHP

6

How do we measure a cancer treatment's cost and benefit?



USHP

Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA.* 2020;323(9):844-853.

7

How do we measure a cancer treatment's cost and benefit?

Intended for provider-patient discussions
Focused on efficacy, toxicity, and cost

Quality adjusted life years
- 1 QALY = 1 year of life in perfect health

Net health benefit scores
- ASCO Value Framework
- ESMO Magnitude of Clinical Benefit Scale (MCBS)

Used for EMA approval and guideline formulation

Not correlated with one another!

Abbreviations: ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; EMA = European Medicines Agency

USHP

Cherny NI, Sullivan R, Dafni U, et al. *Ann Oncol.* 2015;26(8):1547-1573.
Delos Santos S, Witzke N, Arciero VS, Rahmadian AP, Everest L, Chan KK. *JCO.* 2020;38(15):7011.

8

ASCO Value Framework

Clinical benefit	Toxicity	Bonus points	Net health benefit	Cost
/80	/20	/30	/130	Drug acquisition cost: Patient payment:

Delos Santos S, Witzke N, Arciero VS, Rahmadian AP, Everest L, Chan KK. *JCO*. 2020;38(15):7011.

9

Assessing cost-benefit measurements

Which of the following statements about measurements of cost and benefit in cancer treatment is **true**?

a) The higher cost per QALY, the more effective the drug
b) The ASCO Value Framework and ESMO-MCBS have a high level of agreement for a given treatment regimen
c) The ASCO Value Framework requires the assessed regimen to have data against a comparator

10

Process → Outcomes

11

Outcomes in cancer trials

Overall survival
- Percent alive within a prespecified time period
- Median time period over a longer duration of follow-up

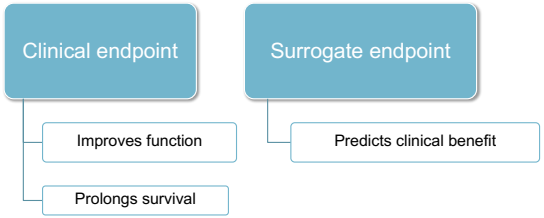
Disease-free survival
- Time from randomization until recurrence or death from any cause

Progression-free survival
- Time from randomization to disease progression or death

Response rate
- % of patients who achieve response (varies by disease state)

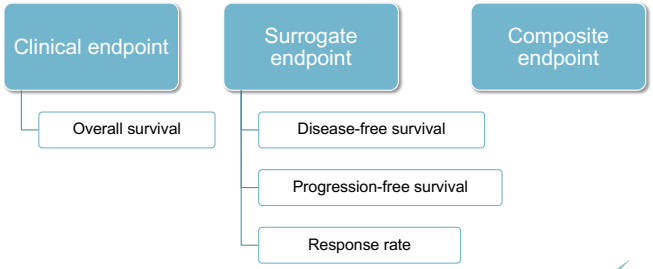
12

Outcomes in cancer trials



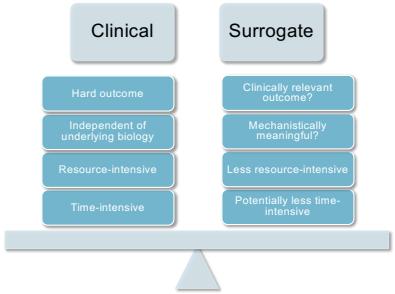
13

Outcomes in cancer trials



14

Cancer trials and endpoint selection



18

What does the FDA require?

	Regular approval	Accelerated approval
Trial evidence	Improved **survival**, quality of life, or established surrogate	Benefit based on outcome **reasonably likely to predict clinical benefit**
Postmarketing requirements	Safety	**Verification of clinical benefit** Safety

21 CFR 314.510 – Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
Accelerated Approval Program. *FDA*. Accessed October 9, 2021. https://www.fda.gov/drugs/information-healthcare-professionals-drugs/accelerated-approval-program

21

Give the FDA what it wants

The ECHELON-1 study was an open-label, multicenter, randomized phase 3 trial of brentuximab vedotin assessing a surrogate outcome.

Population	Adults with untreated stage III-IV Hodgkin's lymphoma
Intervention	Brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD)
Comparator	Bleomycin, doxorubicin, vinblastine, dacarbazine (ABVD)
Outcome	Modified progression-free survival (mPFS), defined as time to progression, death, or noncomplete response and use of subsequent therapy

Assuming mPFS is deemed an established surrogate outcome by the FDA, which approval pathway(s) would be reasonable?

22

Give the FDA what it wants

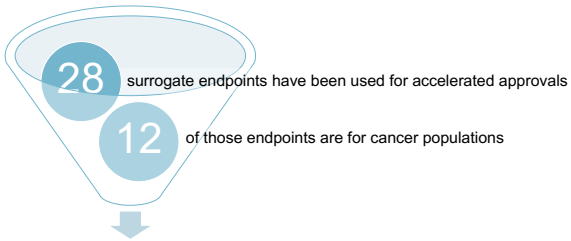
The ECHELON-1 study was an open-label, multicenter, randomized phase 3 trial of brentuximab vedotin assessing a surrogate outcome.

Assuming mPFS is deemed an established surrogate outcome by the FDA, which approval pathway(s) would be reasonable?

a) Regular approval, based on improved survival
b) Regular approval, based on improved mPFS
c) Accelerated approval, based on improved survival
d) Accelerated approval, based on improved mPFS

23

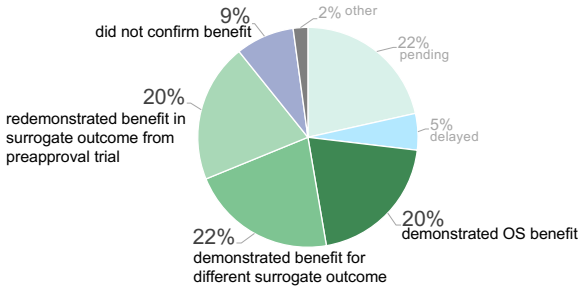
Has accelerated approval been fruitful for cancer therapy?



24

Has accelerated approval been fruitful for cancer therapy?

Study of confirmatory trials of 93 cancer drug indications granted accelerated approval 1992-2017



25

Accelerated approval: bevacizumab

Progressive glioblastoma		Metastatic breast cancer
	Basis of accelerated approval	
	Follow-up study endpoint	
	Follow-up study endpoint met?	
	FDA ruling	

26

Accelerated approval: bevacizumab

Progressive glioblastoma		Metastatic breast cancer
Phase 2 objective response	Basis of accelerated approval	
OS	Follow-up study endpoint	
NO	Follow-up study endpoint met?	
Approve	FDA ruling	

27

Accelerated approval: bevacizumab in metastatic breast cancer

Miller *et al.*, NEJM 2007

Adults
Confirmed metastatic breast cancer without prior cytotoxic therapy for metastases
ECOG 0-1
n = 722

Paclitaxel
Bevacizumab
n = 347

Paclitaxel
n = 326

Progression-free survival
+Bevacizumab 11.8 months
-Bevacizumab 5.9 months
HR 0.6 (0.51-0.7)

Overall survival
+Bevacizumab 26.7 months
-Bevacizumab 25.2 months
HR 0.88 (NS)

Miller K, Wang M, Gralow J, et al. *N Engl J Med*. 2007;357(26):2666-2676.

28

Accelerated approval: bevacizumab

Progressive glioblastoma		Metastatic breast cancer
Phase 2 objective response	Basis of accelerated approval	Phase 3 PFS benefit
OS	Follow-up study endpoint	PFS
NO	Follow-up study endpoint met?	
Approve	FDA ruling	

29

Accelerated approval: bevacizumab in metastatic breast cancer

Miles *et al.*, JCO 2010

Adults
Locally recurrent or metastatic breast cancer without prior cytotoxic therapy for metastases
ECOG 0-1
n = 736

Docetaxel
Bevacizumab 7.5 mg/kg
n = 248

Docetaxel
Bevacizumab 15 mg/kg
n = 247

Docetaxel
Placebo
n = 241

Progression-free survival
+Bevacizumab 7.5 mg/kg 9.0 months
+Bevacizumab 15 mg/kg 10.1 months
-Bevacizumab 8.2 months

Overall survival
+Bevacizumab 7.5 mg/kg 30.8 months
+Bevacizumab 15 mg/kg 30.2 months
-Bevacizumab 31.9 monhts

USHP

Miles DW, Chan A, Dirix LY, et al. JCO. 2010;28(20):3239-3247.

30

30

Accelerated approval: bevacizumab in metastatic breast cancer

Robert *et al.*, JCO 2011

Adults
Locally recurrent or metastatic breast cancer without prior cytotoxic therapy for metastases
ECOG 0-1
n = 622

Taxane or anthracycline
Bevacizumab
n = 415

Taxane or anthracycline
n = 207

Progression-free survival
+Bevacizumab 9.2 months
-Bevacizumab 8.0 months

Overall survival
HR 1.03 (0.77, 1.38)

USHP

Robert NJ, Diéras V, Glaspy J, et al. *J Clin Oncol*. 2011;29(10):1252-1260.

31

31

Accelerated approval: bevacizumab

Progressive glioblastoma		Metastatic breast cancer
Phase 2 objective response	Basis of accelerated approval	Phase 3 PFS benefit
OS	Follow-up study endpoint	PFS
NO	Follow-up study endpoint met?	YES
Approve	FDA ruling	Deny

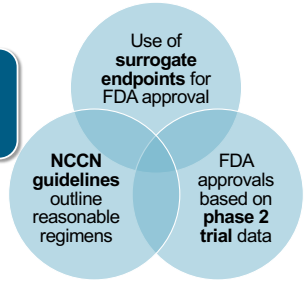
USHP

32

32

What makes cancer drugs different?

CMS, other payers generally cover category 1 or 2A NCCN recommended regimens



USHP

33

33

FDA approvals and NCCN guidelines

You are reviewing a treatment plan for a patient with metastatic breast cancer and notice it is for bevacizumab and paclitaxel.

Even though bevacizumab's FDA approval for metastatic breast cancer was revoked, bevacizumab/paclitaxel regimen remains "Useful in Certain Circumstances" in the NCCN breast cancer guidelines as a category 2A recommendation.

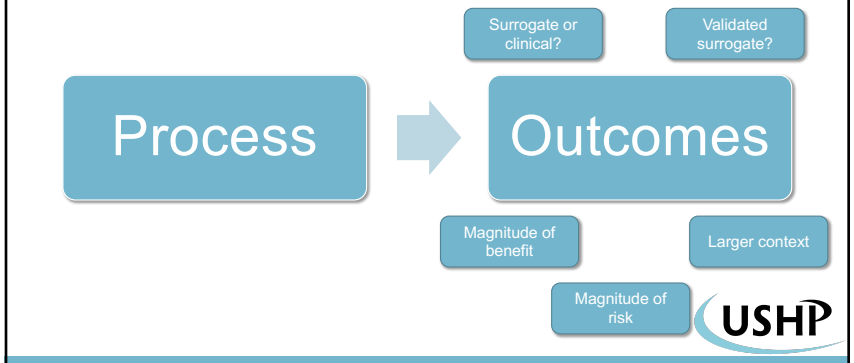
Assuming this patient fits within the criteria under which a bevacizumab/paclitaxel regimen would be useful, what is the likelihood that insurance would cover this treatment regimen?

a) High
b) Low

USHP

34

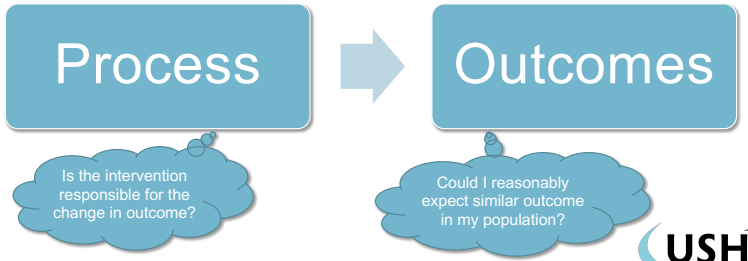
34



35

35

Validity



USHP

36

36

Internal vs. external validity

You are looking at a newly approved cancer drug, alphabetsuplimab-asdf.

The drug's phase 2 trial reported change in tumor size as a secondary endpoint. Digging through the Supplementary Material, you find that subjects' tumor size was measured using different methods between baseline and follow-up visits. This variation would be a threat to….

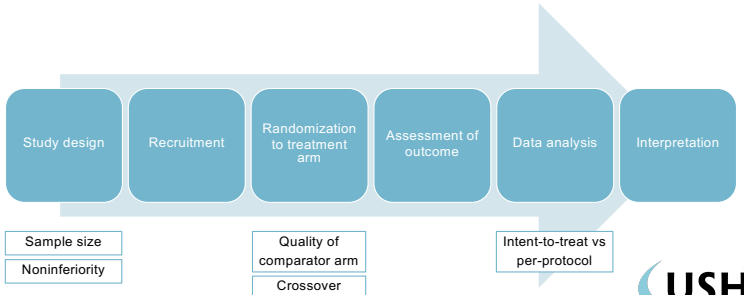
a) Internal validity
b) External validity

USHP

37

37

Clinical trial process

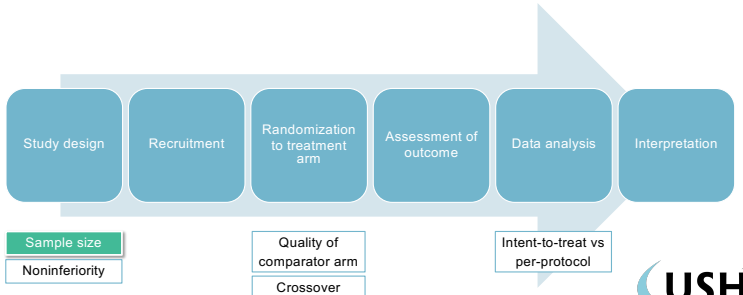


USHP

38

38

Clinical trial process

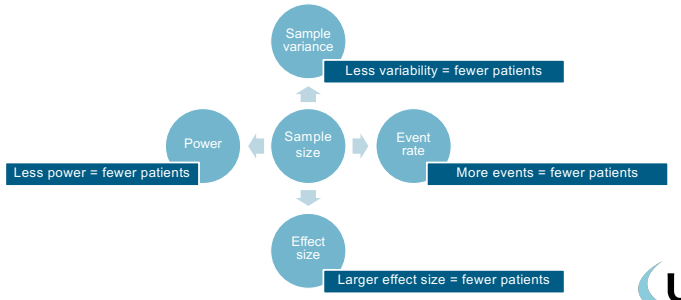


USHP

39

39

Sample size



USHP

40

40

Neratinib in HER2-positive metastatic breast cancer

Saura *et al.* JCO 2020

Adults with HER2-positive metastatic breast cancer
Prior treatment with at least 2 previous therapies for metastatic breast cancer
n = 621

Neratinib
Capecitabine
n = 307

Lapatinib
Capecitabine
n = 314

Overall survival
N+C 21 months
L+C 18.7 months
HR 0.88 (0.72-1.07)

Progression-free survival
N+C 5.6 months
L+C 5.5 months
HR 0.76 (0.63-0.93)

USHP

Saura C, Oliveira M, Feng Y-H, et al. *J Clin Oncol.* 2020;38(27):3138-3149

41

41

Neratinib in HER2-positive metastatic breast cancer

The NALA trial estimated 419 PFS events and 378 OS events were required to obtain 85% power to detect an HR of 0.70 for PFS and 0.725 for OS. Approximately 600 patients were to be enrolled.

The study enrolled 621 patients, reported 433 PFS events, and reported 410 OS events.

Which of the following statements about the study is most accurate?

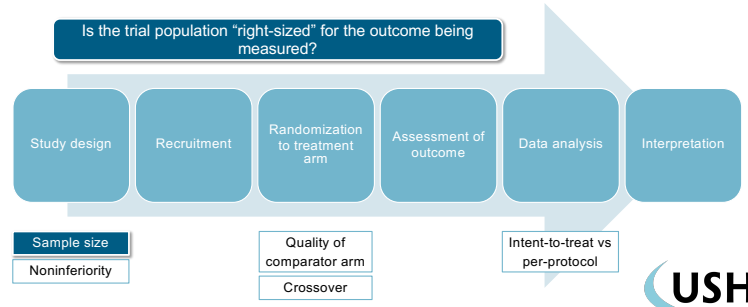
a) The trial was underpowered due to a lower than anticipated event rate
b) The trial was underpowered due to a lower than projected sample size
c) The trial's PFS results are clinically significant
d) The trial's OS results are statistically significant
e) None of the above

USHP

42

42

Clinical trial process

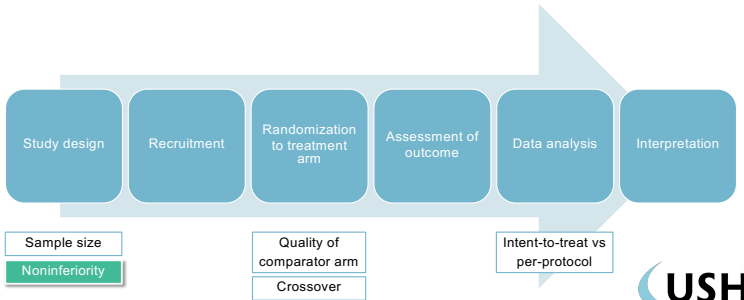


USHP

43

43

Clinical trial process



USHP

44

44

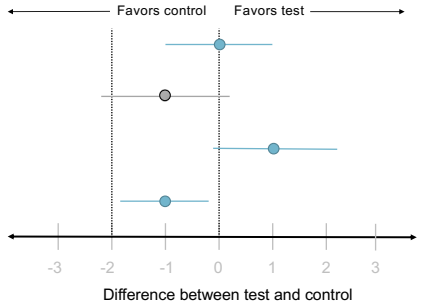
Noninferiority study design

USHP

45

45

Noninferiority study design



How to set the magnitude?

Navigating ethical concerns

47

Noninferiority study design

- 2019 systematic review of cancer drug trials using noninferiority design
  - 31% of identified trials (23/74) used OS as a primary/coprimary endpoint
  - Justifications: oral vs injectable, intermittent vs continuous
  - 39% of noninferiority trials were not justified

48

Noninferiority study design

You are now reviewing a Phase 3 noninferiority study of alphabetsuplimab-asdf. It is compared against mumblijumblimab-hjkl, an approved drug with an identical mechanism of action.

What would be an acceptable rationale for using a noninferiority design for this trial?

49

Clinical trial process

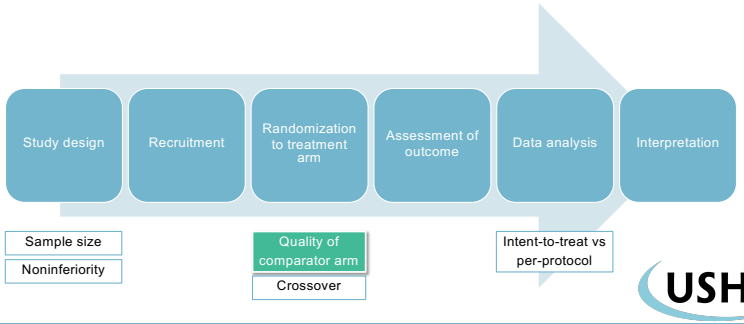
Does the treatment offer a non-efficacy related benefit?
Is the noninferiority margin reasonable?

Study design | Recruitment | Randomization to treatment arm | Assessment of outcome | Data analysis | Interpretation

Sample size
Noninferiority
Quality of comparator arm
Crossover
Intent-to-treat vs per-protocol

50

Clinical trial process



51

51

Comparator arm

97 RCTs used as evidence for approval of 95 cancer drugs 2013-2018

Suboptimal control arm based on analysis of guidelines 1 year prior to patient accrual

- Restrictions placed on control choice **excluding a recommended agent**
- Control arm specified but **not recommended agent**
- Control agent **inferior to available alternative**

16/95 (17%) approvals were based on RCT with suboptimal control arm

15/16 gained regular FDA approval

Abbreviations: RCT = randomized controlled trial

Hilal T, Sonbol MB, Prasad V. *JAMA Oncol*. 2019;5(6):887-892.

52

52

Glasdegib in acute myeloid leukemia

Cortes *et al*., Leukemia 2019

Adults ≥ 55 years old
Newly diagnosed, untreated AML or high-risk MDS
Unsuitable for intensive chemotherapy
ECOG 0-1
n = 132

Glasdegib
Low-dose cytarabine (LDAC)
n = 88

LDAC
n = 44

Overall survival
+Glasdegib 8.8 months
-Glasdegib 4.9 months

FDA regular approval 2018

…but LDAC is **not** commonly used for these patients!

Cortes JE, Heidel FH, Hellmann A, et al. *Leukemia*. 2019;33(2):379-389.

53

53

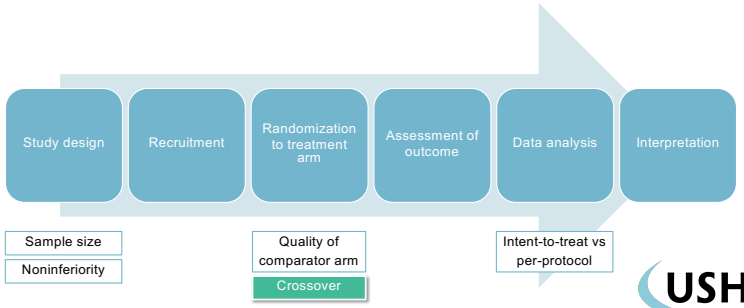
Clinical trial process

If the trial did not exist, what treatment would be recommended?

54

54

Clinical trial process

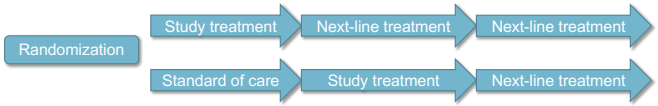


55

55

Crossover

- Allowing patients on an assigned treatment arm to switch treatment



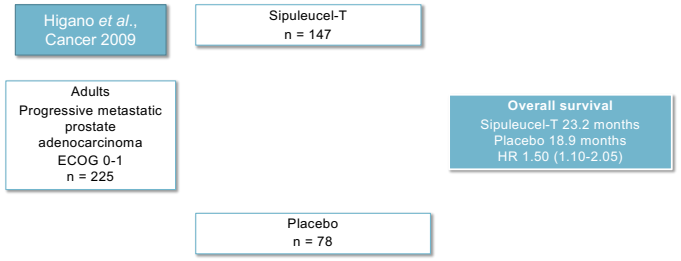
- Undesirable when assessing baseline efficacy
- Desirable when efficacy established in subsequent line of therapy and trying to move into earlier line

Haslam A, Prasad V. *Ann Oncol.* 2018;29(5):1079-1081.

56

56

Sipuleucel-T in advanced prostate cancer

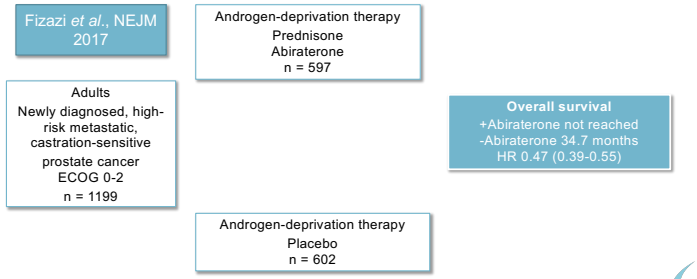


Higano CS, Schellhammer PF, Small EJ, et al. *Cancer.* 2009;115(16):3670-3679.

57

57

Abiraterone in metastatic prostate cancer



Fizazi K, Tran N, Fein L, et al. *N Engl J Med.* 2017;377(4):352-360.

58

58

Crossover

Alphabetsuplimab-asdf has been approved in the relapsed/refractory setting and its manufacturer is now looking at studying its utility first-line.

Which statement(s) about designing a study for first-line use of this drug is/are most accurate?

a) It should be compared against commonly accepted regimen(s) used in the first-line setting
b) Crossover should not be permitted as we are uncertain of this drug's first-line utility
c) If a noninferiority design is used, the manufacturer must estimate the effect in the comparator arm and set an appropriate noninferiority margin

USHP

59

59

Clinical trial process

For established therapy: were patients able to access it upon progression?
For new therapy: did patients receive it when they could have used other effective therapy?

Study design | Recruitment | Randomization to treatment arm | Assessment of outcome | Data analysis | Interpretation

Sample size
Noninferiority

Quality of comparator arm
Crossover

Intent-to-treat vs per-protocol

USHP

60

60

Clinical trial process

Study design | Recruitment | Randomization to treatment arm | Assessment of outcome | Data analysis | Interpretation

Sample size
Noninferiority

Quality of comparator arm
Crossover

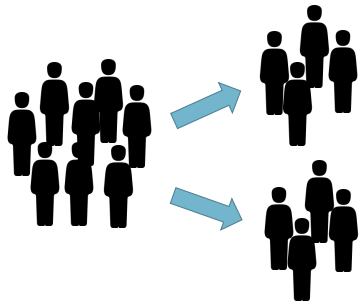
Intent-to-treat vs per-protocol

USHP

61

61

Intent-to-treat and per protocol analysis



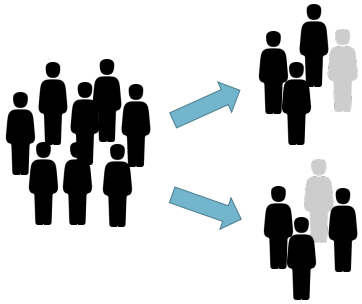
Intent-to-treat
All patients randomized to a treatment arm are analyzed within that arm

USHP

62

62

Intent-to-treat and per protocol analysis



Per protocol
Includes only patients who adhered to protocol

USHP

63

63

Clinical trial process

What happened to people who did not make it to per protocol analysis?

Study design | Recruitment | Randomization to treatment arm | Assessment of outcome | Data analysis | Interpretation

Sample size
Noninferiority

Quality of comparator arm
Crossover

Intent-to-treat vs per-protocol

USHP

64

64

Putting it all together

Process → Outcomes

Stakeholders

USHP

65

65

Pharmacist and Technician Roles

- FDA approval processes
- Context for new drugs' role in therapy
- Real world data
  - EHR
  - Claims databases
  - Devices and applications
- Diversity in clinical trials

USHP

66

66

Pharmacist and Technician Roles

What are some ways pharmacy staff can be involved in enhancing evidence-based cancer care?

67

Take-home points

- Regulatory bodies, professional organizations, and individual providers interpret and use cancer trial outcome data for different purposes
- Cancer trial outcomes take multiple forms
- Trial design parameters should be scrutinized for their effect on internal and external validity of the trial outcomes
- Pharmacy staff play a key role in promoting evidence-based cancer care

68

Learning Objectives

P	Interpret measurements of oncology drugs' cost and clinical benefit
P/T	Describe endpoints required by the FDA after accelerated approval has been granted for an oncology drug
T	Use NCCN guidelines to predict whether a chemotherapy regimen will be covered by payers
P/T	Define internal and external validity, *and evaluate the effect of study design parameters on a clinical trial's validity*
P/T	Identify ways pharmacy staff can advocate for evidence-based cancer care

Abbreviations: FDA = Food and Drug Administration; NCCN = National Comprehensive Cancer Network

69