Hello my name is Barry Goldspiel and I willbe talking about FDA approval considerations

I have no disclosures

The objectives of my lecture are to reviewkey concepts from Dr Kluetzs presentation and then introduce a new clinical trial endpointmetastasisfree survival using some of the concepts from Dr Kluetzs presentation

The oncology endpoints for clinical trialsare a good example of how the FDA uses other than overall survival as an endpoint

Dr Kluetz reviewed response rate progressionfreesurvival symptomrelated events and overall survival as possible endpoints

The ultimate endpoint is overall survivaland the other endpoints are surrogates for overall survival and surrogate markers dependon whether or not they predict for overall survival in terms of whether a drug can beapproved

The strongest of endpoints for oncology trialsis overall survival

Any endpoint other than overall survival eithermeasures how a patient feels functions or survives which are referred to as directmeasures or a surrogate endpoint which predicts clinical benefit and ultimate results in overallsurvival if its a good surrogate marker

Often surrogate markers are radiographicor other imaging findings particularly used in cancer clinical trials and it dependson the accuracy timing and magnitude of changes as to whether a surrogate endpointis a good predictor of overall survival

I refer you to several FDA guidances thathad been published on clinical trial design over the last two years

The FDA has really made a concerted effortto change the way they look at oncology clinical trials and hasten the approval of oncologydrugs where approval is warranted

If we look at clinical trial endpoints andthe types of study designs the randomized study design is the best for any trial

In some cases you may not need to do a randomizedtrial if youre using a surrogate endpoint under the accelerated approval pathway ifthe endpoint in an accelerated approval pathway drug has to be confirmed in a later trialthat is often randomized

A few years ago investigators dealing withprostate cancer found that metastasisfree survival may be a good surrogate endpointfor critical trials

And why did they think that they needed adifferent endpoint?

For nonmetastatic prostate cancer theresa very long survival period

That would mean clinical trials would haveto go for a long time

Five six seven eight years or more to reachthe endpoint

That would make the availability of potentialmedications delayed

Theres also many drugs that have been approvedfor various stages of prostate cancer mostly latestage prostate cancer that have beenmoved up to earlystage prostate cancer thus making the availability of drugs more so forearlystage prostate cancer and therefore doing a comparison of new drugs to the olddrugs makes the trials more complicated

Metastasisfree survival is defined as thetime from randomization to confirmed evidence of distant metastases on imaging or deathfrom any cause

Several investigators have shown that progressionto detectable metastatic disease is a clinically relevant event that often results in painillness andor intervention in prostate cancer

There have been several studies that havelooked at the correlation between metastasisfree survival and overall survival

This is an example of one of the studies thatlooked at trials with over 000 participants

At the patient level there was a 009 correlation

And if you look at the KaplanMeier curveshown in this diagram theres almost complete overlap between metastasisfree survival inthe yellow line and overall survival in the blue line

Now is metastasisfree survival perfect forpredicting overall survival?

No

And when the FDA decided to use or investigatethis in clinical trials one of the important factors besides overall survival is whetheror not metastasisfree survival showed a substantial difference between nonintervention or placebo

There have been three trials in nonmetastaticcastrateresistant prostate cancer using androgen receptor blockers with metastasisfree survivalas the primary endpoint

Remember this is a surrogate endpoint

However for all of these trials anotherconcept that Dr Kluetz reviewed is these drugs were not approved under acceleratedapproval

They were given full approval which meansthat no further trials need to be completed

The first drug that was approved was Apalutamidein the PROSPER trial and I will define these acronyms in the next slide

That trial used several secondary and exploratoryendpoints to confirm whether metastasisfree survival is a good surrogate endpoint

Enzalutamide in the SPARTAN trial also usedmetastasisfree survival as the primary endpoint and several secondary endpoints

And the latest which is not yet approvedbut most likely will be soon Darolutamide in the ARAMIS trial

In these cases to predict metastasisfreesurvival radiography was performed every weeks

And as I mentioned because radiology is oftenused and is the important measure of metastasisfree survival the assessment of the radiographicevents was done both locally and also independently

Patients on these trials also received gonadotropinreleasinghormone analog with the androgen receptor blocker

The trial acronyms in this has an importantpoint that for any drug to be approved you have to have a catchy acronym often createdfrom some of the words of either the type

of mechanism of action of drug or the trial

So Apalutamide which is the SPARTAN trialSelective Prostate Androgen Receptor Targeting with ARN09 which was the number of thedrug when it was first in clinical trials

Enzalutamide was the PROSPER trial and Darolutamidewas the ARAMIS trial Androgen Receptor Agent for Metastasisfree Survival

Sometimes I think they think more about theacronym than the trial design

Heres the results of the three trials

Shown on the gold or brown bars are the isthe placebo arm and the blue bar are the drug treatment arm

All of these trials were done as a : randomizationwhich they often do when you expect the intervention to have significant benefit

And if you look at the difference betweenmetastasisfree survival each of these trials was about to months difference in favorof the medication

And the FDA believe that or monthsalmost two years was a significant difference between the drug and the placebo to approvethem

If we look at the adverse effects seen inthe trials which is important because whenever you approve a drug its a risk benefit determinationthat the adverse effects are many that you can predict for when you take androgens awayfrom male patients

And each of the drugs has their own uniqueset of adverse effects

In particular Enzalutamide has several cardiovascularеffects and this was interesting because the patients were excluded from this trialif they had any predetermined cardiovascular abnormalities

Darolutamide the main adverse effect wasfatigue

So if you look at the indications theseare pretty broad indications

Apalutamide treatment of patients with nonmetastaticcastrateresistant prostate cancer

Enzalutamide treatment of patients with castrateresistantprostate cancer

So that has several indications beyond thenonmetastatic setting

And Darolutamide its approval is pendingby priority review

To review what priority review means fromDr Kluetzs presentation this is a designation by the FDA for a medication where it is predictedto have significant benefit either in terms of efficacy or improved safety

The difference is six months versus a 0monthreview time

So in conclusion metastasisfree survivalhas been established as a new endpoint in trials for nonmetastatic castrateresistantprostate cancer which means from a trial design standpoint that you need an activecontrol arm in the trial

Placebo is probably not ethically acceptableat this point

And whether metastasisfree survival for othermalignancies is uncertain

Remember surrogate endpoints have to be evaluatedin context of the disease and in some cases the stage to make sure it is an appropriatesurrogate endpoint that would ultimately predict survival

Thank you for listening to this lecture forthe Principles of Clinical Pharmacology course