Access to Promising Anticancer Agents: Available U.S. Avenues and Regulatory Challenges

Acknowledgement to Tatiana Prowell who provided much of this presentation

Best Access for is Approval!
Guiding Principles

- Patients want access to investigational agents
  - Expanded access
  - Seamless designs
- Our goals
  - Provide greater access to investigational agents
  - Improve outcomes for every patient
  - Learn from every patient
  - Expedite approval for effective drugs
- More inclusive clinical trials can accomplish these goals
  - Modernize eligibility criteria
    - Provide greater access
    - Study same population who will receive the drug in post-marketing setting if approved
  - Encourage rational use of biomarkers for patient selection but keep an open mind
  - Use creative approaches to study drugs in patients with rare tumors

Why Modernize Eligibility Criteria?

- Many potential participants excluded from trials:
  - CNS involvement
  - Performance status
  - Organ dysfunction
  - HIV positivity
  - Age
  - Prior malignancy
  - Comorbidities
- Exclusions may result in
  - Slow accrual
  - Non-representative trials

J. Beaver & R. Pazdur. NEJM 2017

Why Are Patients (Really) Being Excluded?

- Potential to confound interpretation of treatment effect (e.g. recent other malignancy)
- Potential for drug-drug interaction (e.g. anti-seizure or antiretroviral medications)
- Concerns for patient safety and risk to development (e.g. risk of brain herniation with tumor flare or lowering of seizure threshold in patients with brain metastases)
- Outdated concerns (e.g. limited life expectancy in patients with treated HIV or brain metastases)
- Convention, aka the cut and paste phenomenon (e.g. exclusion of men from breast cancer trials)

Case Study

Alectinib

Alectinib Phase 3 Trial

- Randomized P3 trial: Alectinib vs. crizotinib
  - 40% of the study population had brain metastases at baseline
- Alectinib demonstrated overall improvement in PFS
- CNS efficacy for alectinib
  - ORR 81% in pts with measurable CNS disease
  - Median duration of intracranial response 17 months
- If alectinib trials had excluded patients with brain metastases:
  - Pool of eligible patients decreased by nearly half
    - Slower accrual
    - Patients with high unmet need denied access to effective new treatment
  - Clinically meaningful info for patients, clinicians, & pharmaceutical company on CNS efficacy would have been lost.

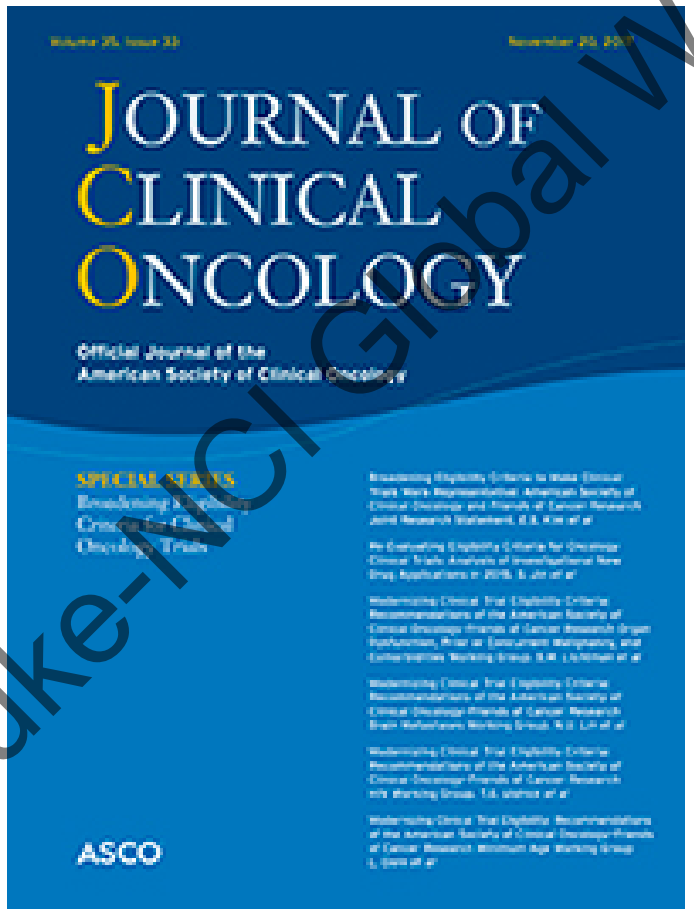
S. Peters et al., NEJM 2017
N. Lin et al., JCO 2017

Lessons Learned

- Consider inclusion of patients with brain metastases in trials
  - Addresses unmet medical need
  - Improve patient access to novel investigational agents
  - Provides opportunity to learn from all patients
  - May help avoid need for post-marketing studies
  - May be a key differentiating factor among multiple agents in class
- Patients with brain metastases WILL be treated in the post-marketing setting. They deserve, and clinicians need, enough data to weigh the risks/benefits of a treatment *in patients like themselves*.

N. Lin et al., JCO 2017

Special Issue of JCO Dedicated to Modernizing Eligibility Criteria



Biomarkers:
More Than Prediction of Response

- Biomarkers have potential value across the full spectrum of cancer drug development and clinical care.
  - Facilitate diagnosis
  - Inform prognosis
  - Patient selection (in trials or in practice)
  - Predict response to therapy
  - Inform trial designs
- Incorporate them whenever possible.
- We cannot learn if patients' tumors are not assessed

Important Points

- Not every drug will have an identifiable, testable biomarker.
- Not every biomarker will be essential to safe and effective use of the drug.
- Some drugs will have more than one biomarker.
- The best biomarker may not be the first one you find.
- Inclusion of some “marker-negative” patients early in development may be beneficial.

Case Study

Crizotinib

Crizotinib

- Crizotinib approved in U.S. in 2011 for ALK+ NSCLC
  - Two single-arm studies with ORR ~50-60%
  - Median response duration of ~11 months
- Subsequent randomized trial of crizotinib vs. standard of care in 2nd line ALK+ NSCLC
  - Median PFS increased from 3 to 7.7 months (HR 0.49)
- Response in pt with refractory NSCLC that was ALK- but ROS1-rearranged → single-arm trial to assess activity of crizotinib in ROS1-rearranged NSCLC

A. Shaw et al, NEJM 2014

Why Study "Marker-Negative" Patients?

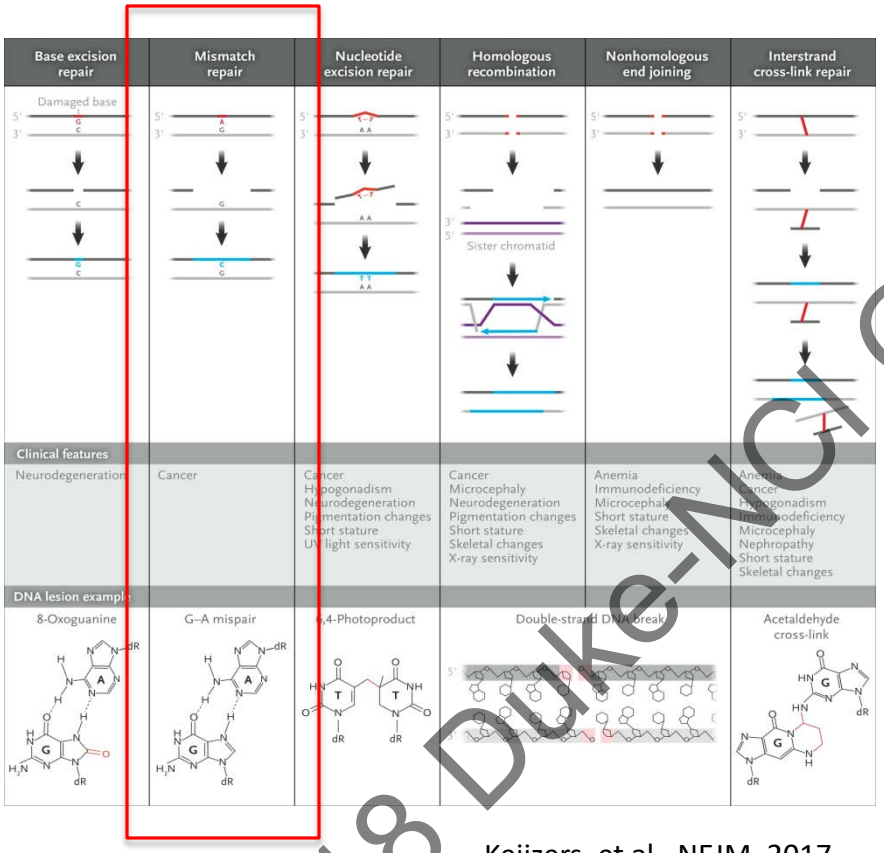
- Characterize interaction of the drug/test
- Help to define the cut-off threshold for "marker-positive"
- Even when we (believe that we) understand the science, we still get proven wrong (often).
  - May incorrectly assume biomarker is required for response→ deny effective therapy to marker-negative patients
    - Even if less effective in marker-negative, may still be meaningful treatment effect in diseases with unmet need
    - Ideally answer this question early in development so don't find ourselves having to backtrack
  - May select the wrong biomarker→ abandon development of a potentially active drug if no efficacy observed
  - May be more than one biomarker predictive of response

Biomarker Case Study

Pembrolizumab dMMR/MSI-H tissue-agnostic approval

Mismatch repair deficiency (dMMR):

Usually results in microsatellite instability



Keijzers, et al., NEJM, 2017

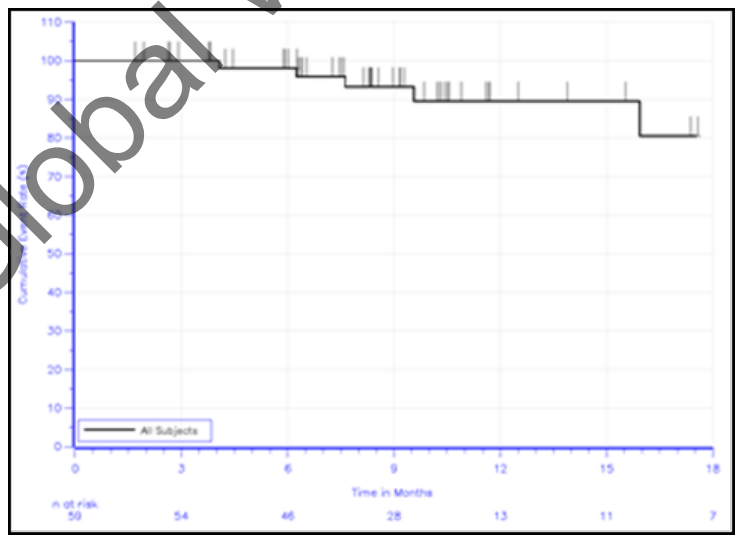
- Causes of dMMR:
  - Mutation in DNA repair proteins
    - e.g., Lynch syndrome
  - Inactivation of DNA repair proteins
  - ↑ mutation burden / tumor antigens

Pembrolizumab dMMR / MSI-H approval considerations

- Strong scientific / biological rationale
- Compelling clinical data
- Extensive prior experience
- For MSI-H/dMMR, approved for patients without available therapies
- Facilitated access to drug for patients with rare tumor types

Background: data supporting pembrolizumab MSI-H/dMMR approval

	N	ORR N (%)	95% CI
CRC	**90**	**32 (36%)**	**(26, 46)**
Non-CRC	**59**	**27 (46%)**	**(33, 59)**
Endometrial	14	5 (36%)	(13, 65)
Biliary	11	3 (27%)	(6, 61)
Gastric/GEJ	9	5 (56%)	(21, 86)
Pancreatic	6	5 (83%)	(36, 100)
Small Int.	8	3 (38%)	(9, 76)
Breast	2	PR, PR	
Prostate	2	PR, SD	
Bladder	1	NE	
Esophageal	1	PR	
Sarcoma	1	PD	
Thyroid	1	NE	
Retroperitoneal	1	PR	
SCLC	1	CR	
RCC	1	PD	



KM-DOR in 59 responding patients

At time of approval, responses observed in *at least* 14 MSI-H/dMMR tumor types; many ongoing

Source: Keytruda labeling, BLA submission, FDA review documents

Biomarkers can also facilitate novel designs

- Test multiple drugs at one time
  - One cancer
    - I-SPY
    - GBM-AGILE
    - LUNG-MAP
    - BATTLE
  - Multiple cancers
    - NCI-MATCH
- Registries or RWD
  - e.g., ASCO TAPUR

Expanded Access

Can expanded access data support labeling expansion or approvals?

- Yes!
  - Glucarpidase (for toxic MTX concentrations in patients with renal impairment)
    - Primary basis for approval
  - Uridine triacetate (for 5FU overdose or severe toxicity)
    - Primary basis for approval
  - Eculizumab (atypical HUS)
    - Supported pediatric expansion of labeling Dinutuximab
  - Dinutuximab (high-risk neuroblastoma)
    - Provided safety data to support approval
  - Lutetium lu 177 dotatate (NE tumors)
    - Provided data to support broader indication

Overview of SPIs in oncology

- FDA analysis of 1332 SPIs/eINDs from 2012 – 2014
  - Two placed on hold (one subsequently allowed to proceed)
  - Four withdrawn prior to FDA decision
  - Median review time for SPIs (2 days)
  - Median review time for eINDs (< 24 hours)
  - ~157 Unique drugs
  - Estimated 2/3 from major university hospital

Lemery et al., ASCO (poster presentation), 2016

What is the evidence regarding risks of EA?

- EA studied over *10* year period (1/2005 to 1/2014)
- Over 10,000 EA IND requests
  - Only 2 (of 1033) commercial programs with referenced INDs were placed on hold/partial hold due a serious adverse event in an EA IND.
    - One hold removed months later
    - Other was a partial hold limited to a specific population

Source: Jarow et al., TIRS, 2016.

Data regarding non-approval decisions in oncology

- Review of all CR (or not-approvable) letters for NDA (NME) marketing applications reviewed from 3/2005 to 3/2015.
- Fifteen letters
  - Most Due to lack of efficacy (67%)
  - Others due to trial design flaws (33%)
  - None due to EA

Source: Khozin et al., Nature Reviews Drug Discovery, 2015

Conclusions

- More inclusive approach to cancer drug development is needed
  - Modernize eligibility criteria
  - Rational use of biomarkers for patient selection
  - Use creative approaches to study drugs in rare tumors
- Our obligations to current & future cancer patients:
  - Ensure appropriate access to investigational agents, preferably in the context of clinical trials
  - Characterize efficacy and safety to ensure:
    - Patients can make an informed choice whether to take a drug based upon in data in *patients like themselves*
    - Clinicians can counsel patients as to drug benefits/risks
    - Data collected can support regulatory and payer decisions to maximize global patient access to effective therapies

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Thank you for your attention!