Role of Compendia in Determining what Drugs are Reimbursed

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October 2012

A day in the life…

- Monday, Nov 16, 2009
  - Half day multi-disciplinary melanoma clinic
  - 14 patients including 4 new patients
  - Off-label drugs a part of 8/14 discussions
- DD - 66 yo wife & caregiver of elderly mother
  - Originally with a R leg melanoma and groin adenopathy, now with liver metastases
    - Originally delayed interferon due to need to care for her mother (and ?age)
    - Too old for IL2, BRAF negative, considered CTLA-4 antibody and other clinical trial
  - Temozolomide vs dacarbazine

A day in the life…

- DD - 66 yo wife & caregiver of elderly mother
  - I prescribed temozolomide
  - *Shame on me?*

Off-label prescribing in oncology

- Definition
  - Prescription of pharmaceuticals for an unapproved indication or in an unapproved age group, unapproved dose or unapproved form of administration

- Off-label prescribing is common and expensive
  - 1991: GAO reported that up to 33% of all anticancer drug prescriptions were written for off-label indications
  - 2005: NCCN estimated that 50% to 75% of all uses of cancer therapy were off-label

Off Label Prescribing in Oncology

- Forces behind off-label prescribing
  - Clinical urgency
  - Biological plausibility
  - Aggregating evidence
  - Regulatory decisions often lag behind evidence
  - Reinforced by payment system
- Forces hindering evidence development
  - Ability to rely on Phase II data
  - Narrow scope of RCTs with too many clinical clinical questions
  - Lack of post-regulatory incentives
  - Uncoordinated data collection and cost

Is the problem the doctor?

Oncology Clinical Trials Compared to Other Specialties

	Oncology	Non-Oncology
Masking	(n=8346)	(n=31,525)
Open	88%	47%
Blinded (single & double)	12%	53%
Allocation	(n=7995)	(n=31,245)
Randomized	36%	77%
Non-randomized	64%	33%
Study Arm	(n=8438)	(n=30,805)
Single-Arm	62%	24%
Multi-arm	38%	76%

Hirsh, BR; Califf, RM; Cheng, SK; Tasneem, A; Horton, J; Chiswell, K; Schulman, KA; Dilts, DM; Abernethy, AP. "The State of the Oncology Clinical Trial Portfolio: Insights from a Systematic Analysis of ClinicalTrials.gov." [under review]

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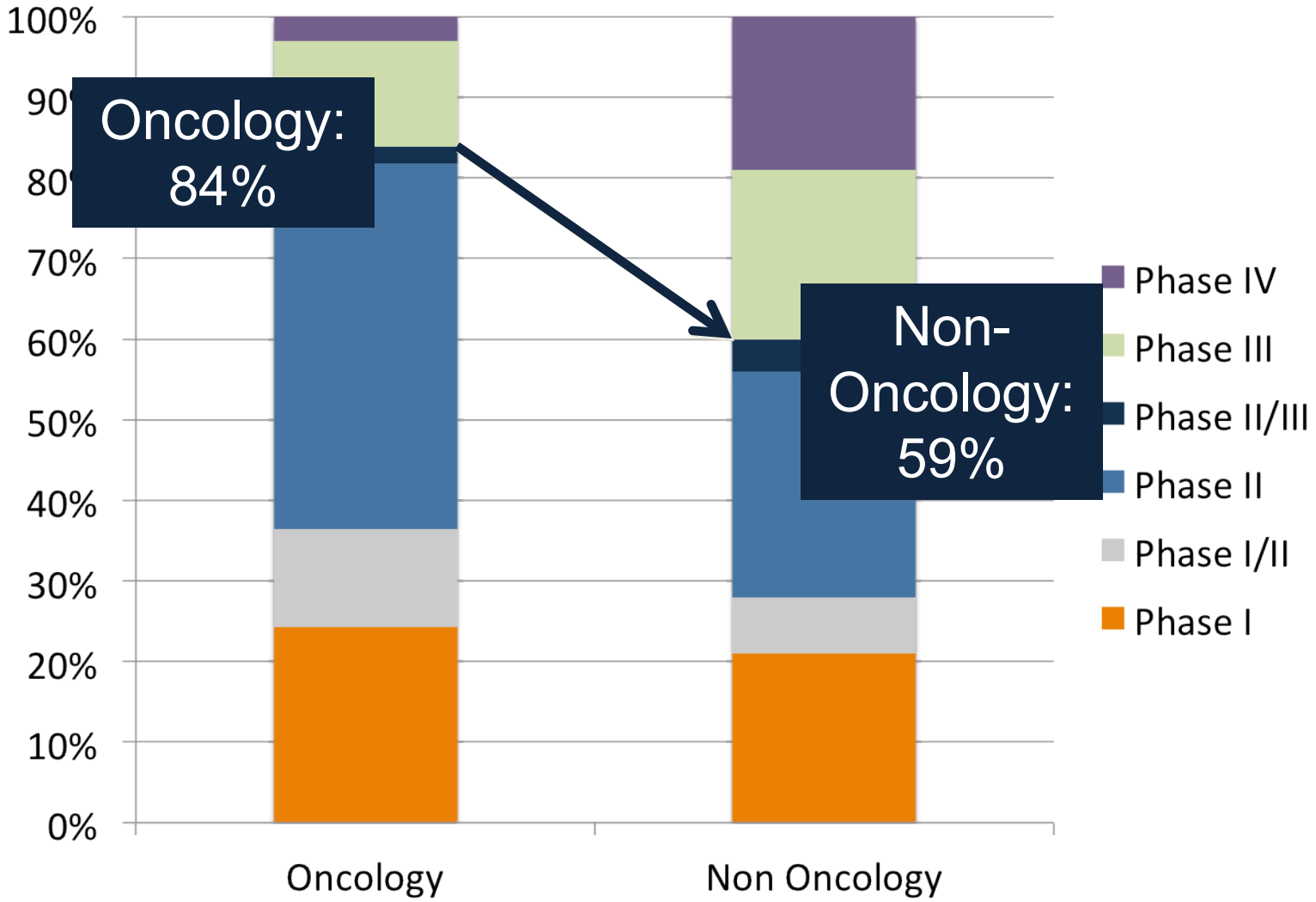
Oncology trials more often early phase



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Analysis of the Renal Cell Carcinoma Trial Portfolio

Agents included in study (N=108)	Total Trials		Randomized		Blinded		Phase III or IV	
	n	%	n	%	n	%	n	%
NCCN-recommended only	55	51%	19	33%	3	7%	8	16%
Other FDA-approved	17	16%	1	6%	0	0%	0	0%
Novel (non-FDA approved)	36	33%	11	37%	4	13%	4	12%

Hirsch et al. Presented at the 2012 ASCO conference

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Off label: 67%

Novel: 33%

Hirsch et al. To be presented at the 2012 Annual American Society of Clinical Oncology Meeting.

Is the problem the evidence and/or the sponsors of cancer research?

Off Label Oncology

- Clinicians need a method to make sense of rapidly evolving evidence
- Compendia for comparative effectiveness research (CER)
- Reimbursement – reinforces the approach

Ann Intern Med. 2009;150:336-343.

REVIEW | Annals of Internal Medicine

Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications

Amy P. Abernethy, MD; Gowri Raman, MD; Ethan M. Balk, MD, MPH; Julia M. Hammond, PharmD; Lori A. Orlando, MD, MHS; Jane L. Wheeler, MSPH; Joseph Lau, MD; and Douglas C. McCrory, MD, MHS

The Compendia System

- Section 1861 (t)(2)(B)(ii)(I) of the Social Security Act lists three drug compendia that may be used in determining the "medically accepted indication" of drugs and biologics used off-label in an anti-cancer chemotherapeutic regimen:
  - American Hospital Formulary Service – Drug Information (AHFS-DI)
  - American Medical Association Drug Evaluations (AMA-DE)
  - United States Pharmacopeia – Drug Information (USP-DI)

- AMA-DE - no longer in publication
- USP-DI – DrugPoints subsumed contents 2007

Purpose of Compendia

	AHFS-DI	CP	DRUG-DEX	F&C	NCCN	USP-DI
Purpose	Evidence-based	Usable, concise	Unbiased info to prescribe, order, disp, admin	Timely, accurate, unbiased, comparative info	Support decision-making for appropriate use (in Ca)	Safe & effective use *once prescribed*

Key feature: Purpose = guide use “once a drug prescribed” and not to provide comparative information to guide choice

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Subjective processes for validity assessment, choice of citations, and policy on equivocal evidence

Inclusion of 14 Indications

Table 3. **Presence of the 14 Agent and Cancer Combinations in Each Compendium**

Agent and Cancer Combination	*American Hospital Formulary Service Drug Information*	*Clinical Pharmacology*	DRUGDEX	*Drug Facts and Comparisons*	*National Comprehensive Cancer Network Drugs and Biologics Compendium*	Compendia That Included This Indication, *n*
Bevacizumab for breast cancer	No	No (Yes)*	Yes	No	Yes	2 (3)*
Bevacizumab for lung cancer	No	Yes	Yes	Yes	Yes	4
Oxaliplatin for breast cancer	No	Yes	Yes	No	No	2
Oxaliplatin for lung cancer	No	No	Yes	No	No	1
Irinotecan for breast cancer	No	No	Yes	No	No	1
Docetaxel for esophageal cancer	No	No	Yes	Yes	Yes	3
Docetaxel for gastric cancer	No	Yes	Yes	Yes	Yes	4
Docetaxel for ovarian cancer	No	Yes	Yes	Yes	Yes	4
Gemcitabine for biliary tract cancer	No	No	Yes	Yes	Yes	3
Gemcitabine for bladder cancer	Yes	Yes	Yes	Yes	Yes	5
Gemcitabine for ovary cancer	Yes	Yes	Yes	Yes	Yes	5
Rituximab for chronic lymphocytic leukemia	No	Yes	Yes	No	Yes	3
Erlotinib for head and neck cancer	No	Yes	Yes	Yes	No	3
Erlotinib for pancreatic cancer	No	Yes	Yes	No	No†	2
Indications discussed in each compendium, *n*	2	9 (10)*	14	8	9	–

* Indicates a ch
† A trial is disc

Off-label drug-disease indications reviewed were chosen after conversation with CMS based upon reimbursement activity, older/newer drugs, common/rarer tumors

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Docetaxel for esophageal cancer	No	No	Yes	Yes	Yes	3
Docetaxel for gastric cancer	No	Yes	Yes	Yes	Yes	4
Docetaxel for ovarian cancer	No	Yes	Yes	Yes	Yes	4
Gemcitabine for biliary tract cancer	No	No	Yes	Yes	Yes	3
Gemcitabine for bladder cancer	Yes	Yes	Yes	Yes	Yes	5
Gemcitabine for ovary cancer	Yes	Yes	Yes	Yes	Yes	5
Rituximab for chronic lymphocytic leukemia	No	Yes	Yes	No	Yes	3
Erlotinib for head and neck cancer	No	Yes	Yes	Yes	No	3
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* Indicates a change between the 2006 and 2008 reviews.
† A trial is discussed.

2 AHFS-DI

9 Clin Pharm

14 DRUG DEX

8 F&C

9 NCCN

1-5 Overall Ind Incl

Gemcitabine for Bladder Cancer

- Present detailed review because oldest and most established combination with greatest amount of accumulating evidence
- Published Phase I-III studies
  - 43 in 2006 (including 1 Phase III)
  - 68 in 2008 (22 Phase II, 3 Phase I/II, 4 case reports)
    - + 2 updates of the Phase III study
    - + 3 conference abstracts

Appendix Table 2. Comparison of Compendia Content for Gemcitabine for Bladder Cancer

Content	*American Hospital Formulary Service Drug Information*	*Clinical Pharmacology*	DRUGDEX	*Drug Facts and Comparisons*	*National Comprehensive Cancer Network Drugs and Biologics Compendium*
Recommendation for off-label indication					
Off-label indication explicitly stated	Yes	Yes	Yes	Yes	No
Subcategory of indication (accepted or acceptance not established)	Not described	Not described	Efficacy: adult, evidence favors efficacy Recommendation: adult, class IIb Strength of evidence: adult, category B	Not described	Category 1 for gemcitabine + cisplatin ("considered the standard first-line choice for most patients"); "investigational" for gemcitabine + paclitaxel, gemcitabine + docetaxel, and cisplatin + gemcitabine + docetaxel
Stage of cancer for the treatment to be used	"Advanced or metastatic cancer"	"Locally advanced or metastatic bladder cancer"	"Transitional cell carcinoma of bladder"	"Metastatic bladder cancer"	"Neoadjuvant, adjuvant, and metastatic" bladder cancer for gemcitabine + cisplatin; differs for other combinations
Treatment order (first line or other)	Other	Not described	Not described	Not described	First line for gemcitabine + cisplatin; other for gemcitabine + paclitaxel and for other combinations
Method of delivery	Intravenous	Intravenous	Intravenous	Intravenous	Intravenous
Uses of agent (monotherapy or combination therapy)	Monotherapy and combination	Combination	Monotherapy and combination	Not reported	Combination
Comparator (placebo, standard treatment, other agents)	Standard treatment	Standard treatment	Standard treatment and other agents	Not discussed	Yes (not described)
Outcomes mentioned for the off-label use (survival, tumor response, adverse effects)	Overall median survival, median time to progressive disease, complete response rate, partial response rate, and symptomatic improvement	Survival time, time to disease progression, time to treatment failure, and response ratio compared with standard treatment	Overall survival, time to disease progression, time to treatment failure, and response ratio compared with standard treatment	Not described	Survival response for gemcitabine + cisplatin; relapse, locally advanced disease, limited metastatic recurrence for patients who may be candidates for consolidation surgery as an indication for other combinations
Toxicity of the agent					
Overall	Yes	Yes	Yes	Yes	No
Cancer-specific	Yes, by organ	Yes	Yes	No	No
Severity	Yes	Yes	Yes	Yes	No
By organ	Yes	Yes	Yes	Yes	No
Frequency	No	Yes	No	No	No
Dose indicated for the off-label use	Yes	Yes	Yes	Yes	Yes for gemcitabine + cisplatin; no for other combinations

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Evidence cited by compendia and systematic review across 2 time points					
2006 analysis					
Reported date of last compendium update	8 December 2005	9 November 2005	2006	2005	2006
Evidence citations in compendia monograph, *n*	8	1	3*	0	2
Reports identified in systematic review cited by compendia, *n*†	1 phase III, 2 phase II, 1 phase I/II, and 3 conference abstracts	1 phase III	1 phase III, 1 phase I/II, and 1 conference abstract	0	1 phase III and 1 phase II
2008 update					
Reported date of last compendium update	28 June 2008	6 June 2008	2008	2008	7 January 2008
Evidence citations in compendia monograph, *n*	9	1	11	0	3
Reports identified in systematic review cited by compendia, *n*‡	1 phase III, 2 phase II, and 1 phase I/II	1 phase III	1 phase III (2 separate reports), 6 phase II, and 2 phase I/II	0	1 phase III and 2 phase II

* Information generated in the 2006 review and fully updated for 2008 review in June 2008.
† Our 2006 systematic review identified 1 phase III, 28 phase II, and 14 phase I to II studies and 15 conference abstracts.
‡ Our 2008 systematic review update identified 1 phase III, 50 phase II, and 17 phase I to II studies and 3 conference abstracts.

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Currently we rely on the compendia for continuous systematic review, but…

Is the compendia's task feasible?

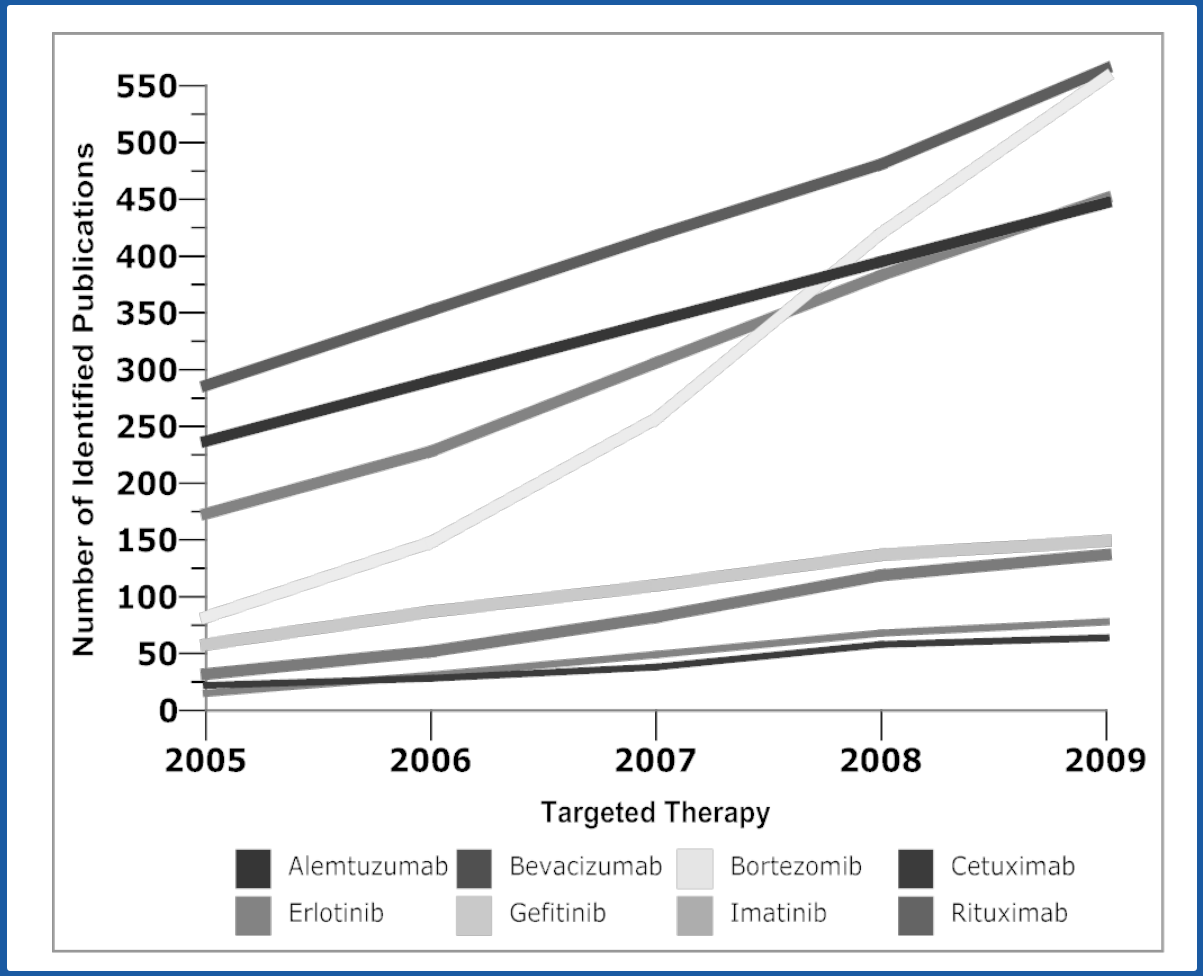
EPC Systematic Review vs the Compendia

- Medications were included if they met the following inclusion criteria:
  - Targeted agent
  - FDA-approved
  - Marketed in January 2007 or before
  - Having compendia-listed indications other than the FDA-approved indication, in one of the following four compendia as of December 2006: AHFS-DI (2006 version), NCCN (online version), USP-DI (2006 version), and Clinical Pharmacology (online version)

Abernethy AP, Coeytaux RR, et al. *Technology Assessment: Report on the evidence regarding off-Label indications for targeted therapies used in cancer treatment.* Rockville, MD: United States Agency for Healthcare Research and Quality; May 2010.

Targeted therapy	Off-label indication(s)
Alemtuzumab (Campath®)	Cutaneous T-cell lymphoma
	Non-Hodgkin lymphoma
	T-cell prolymphocytic leukemia
Bevacizumab (Avastin®)	Breast cancer*
	Epithelial ovarian cancer
	Pancreatic adenocarcinoma
	Renal cancer*
Bortezomib (Velcade®)	Non-Hodgkin lymphoma
Cetuximab (Erbitux®)	Pancreatic adenocarcinoma
Erlotinib (Tarceva®)	Head and neck cancer
Gefitinib (Iressa®)	Head and neck cancer
Imatinib (Gleevec®)	Acute lymphoblastic leukemia*
	Chronic eosinophilic leukemia*
	Dermatofibrosarcoma protuberans*
	Myelodysplastic syndrome*
	Systemic mastocytosis*
Rituximab (Rituxan®)	Chronic lymphocytic leukemia
	Nodular lymphocyte-predominant Hodgkin disease
	Waldenstrom's macroglobulinemia*

Increasing Number of Reports Supporting Off-Label Indications

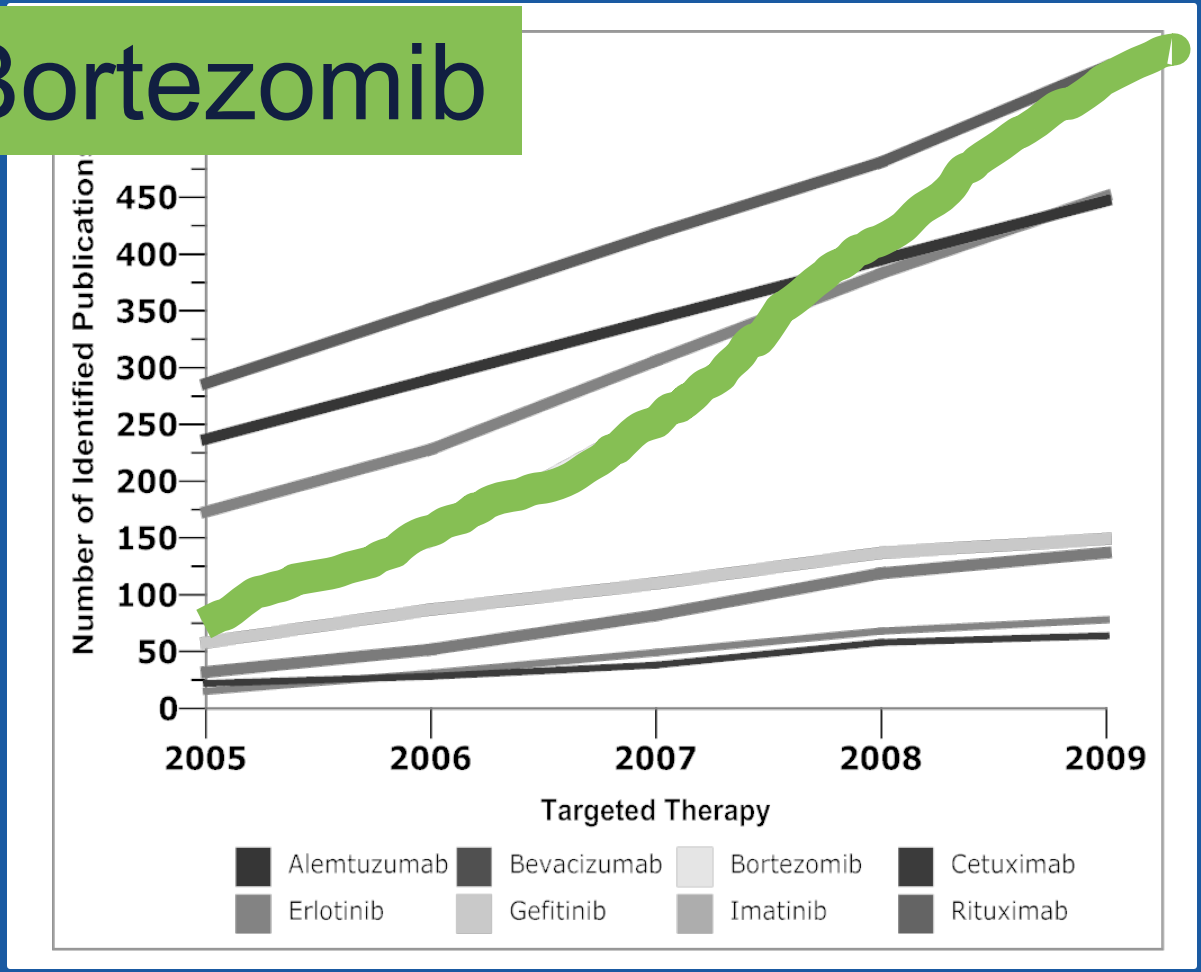


DukeMedicine

Duke Cancer Care Research Program

Increasing Number of Reports Supporting Off-Label Indications

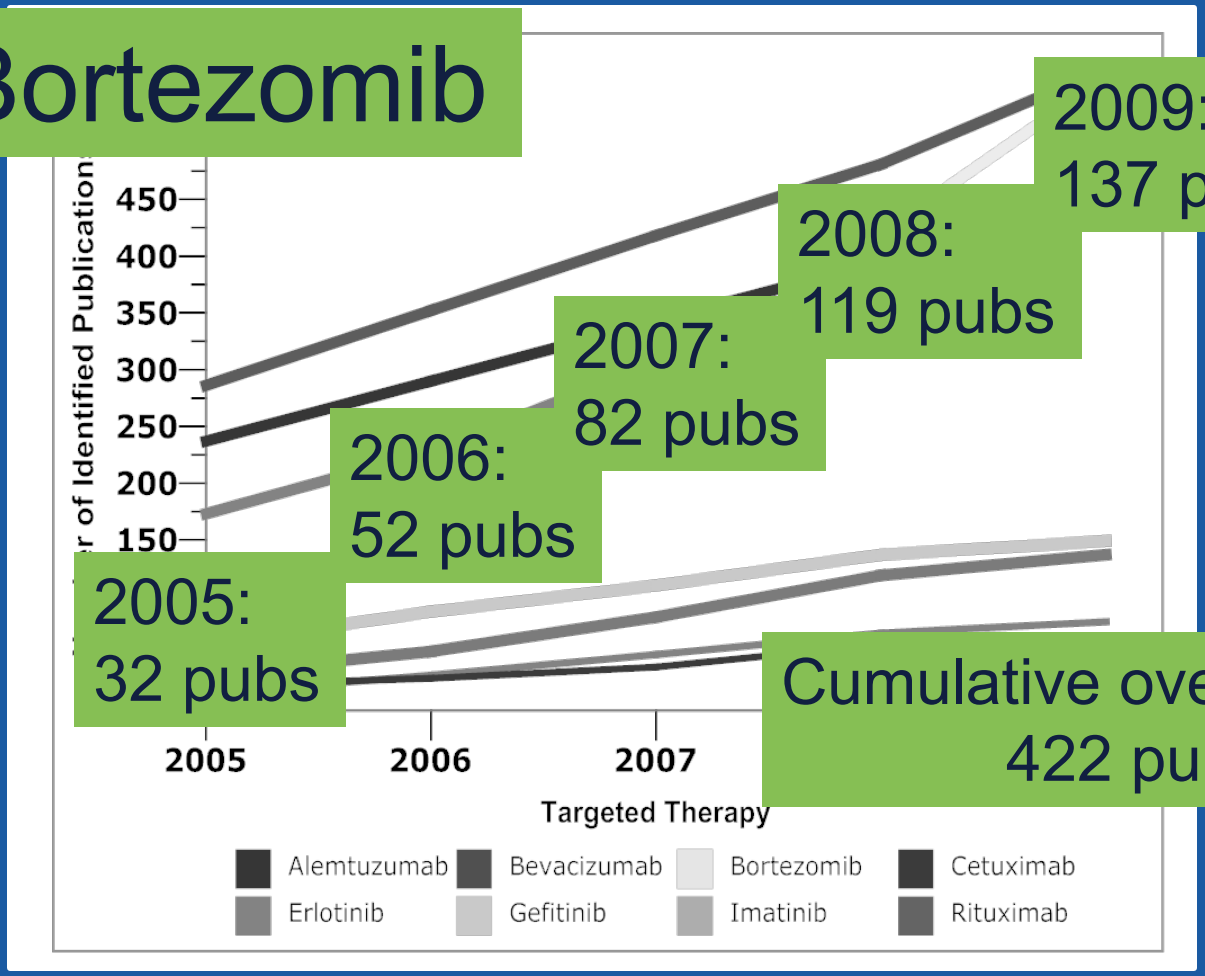
Bortezomib



DukeMedicine

Duke Cancer Care Research Program

Increasing Number of Reports Supporting Off-Label Indications



DukeMedicine

Duke Cancer Care Research Program

Poor Quality Evidence

- Compendia are attempting continuous systematic review of poor quality evidence
- Large number of phase II trials for off-label indications
- Phase II or case series?
- Rapid publication cycle, with short time from submission to appearance in print
  - June effect
- Minimal reporting standards, including funding and COI

The Compendia System

- Section 1861 (t)(2)(B)(ii)(I) of the Social Security Act lists three drug compendia that may be used in determining the "medically accepted indication" of drugs and biologics used off-label in an anti-cancer chemotherapeutic regimen:
  - American Hospital Formulary Service – Drug Information (AHFS-DI)
  - American Medical Association Drug Evaluations (AMA-DE)
  - United States Pharmacopeia – Drug Information (USP-DI)

- AMA-DE - no longer in publication
- USP-DI – DrugPoints subsumed contents 2007
- 2008 – added NCCN, Clin Pharm, and DRUGDEX

Observations

- Evidence accumulating fast and compendia system is not designed for the task that we are asking of it
  - Is this the evidence we need?
  - Are the compendia the CER reference that we need?
  - Should Compendia-driven CER be linked to reimbursement?
- Perverse angle:
  - The chaos (and system developed to deal with it) promotes indiscriminate prescribing and reimbursement

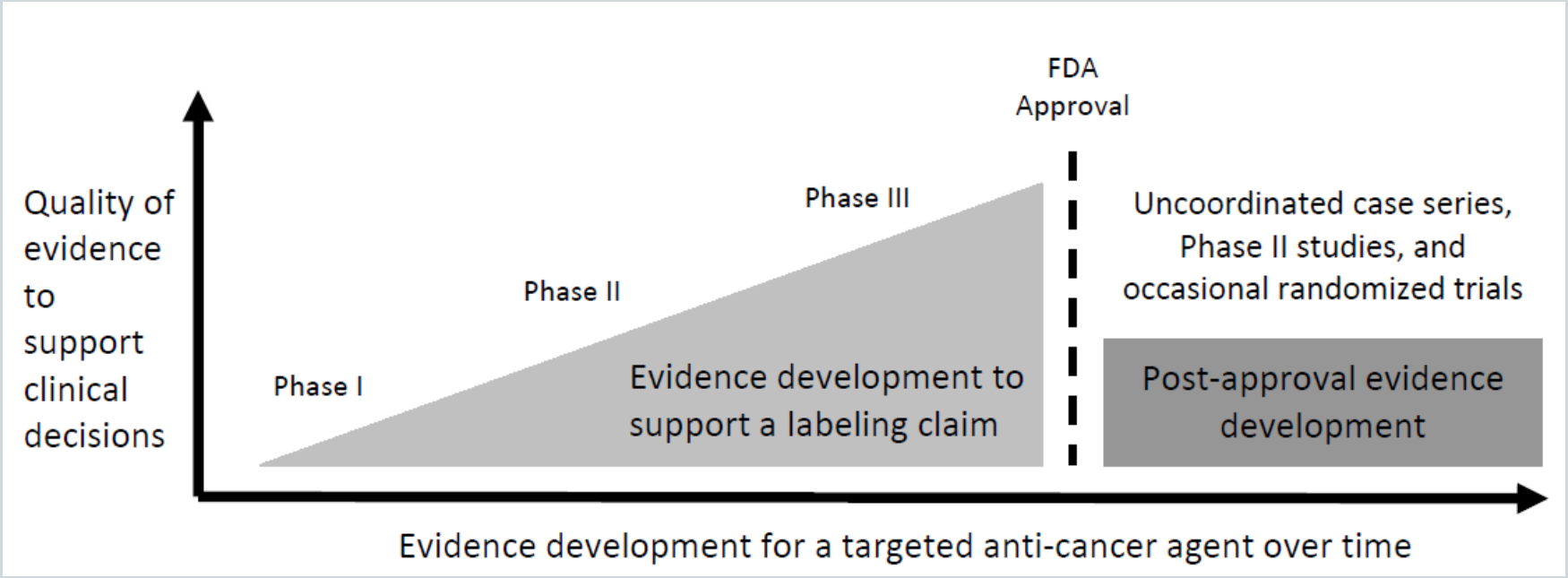
Is the problem the compendia system and its influence on reimbursement?

Off Label Prescribing in Oncology

- Forces behind off-label prescribing
  - Clinical urgency
  - Biological plausibility
  - Aggregating evidence
  - Regulatory decisi… …hind evidence
  - Reinforced h… …tem
- Forces h… …idence development
  - A… …h Phase II data
  - …cope of RCTs with too many clinical clinical …tions
  - Lack of post-regulatory incentives
  - Uncoordinated data collection and cost

Wild Wild West!

Evidence Development for Off-label Oncology Indications



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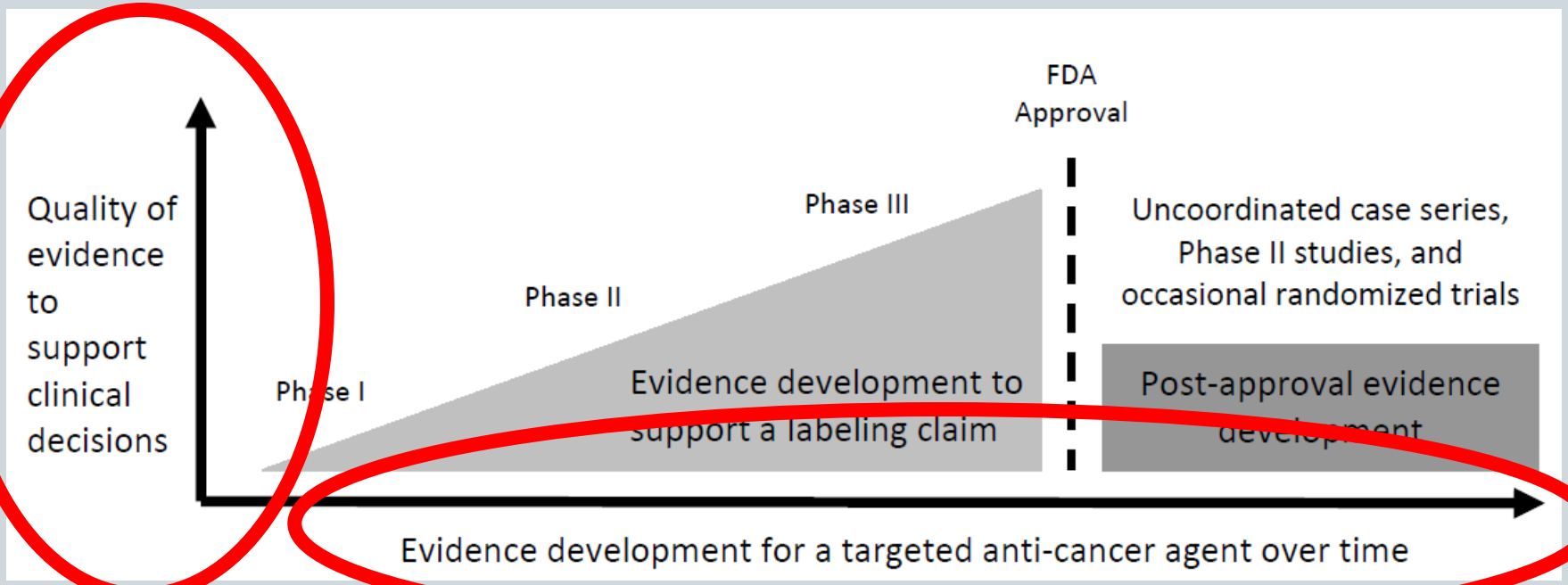

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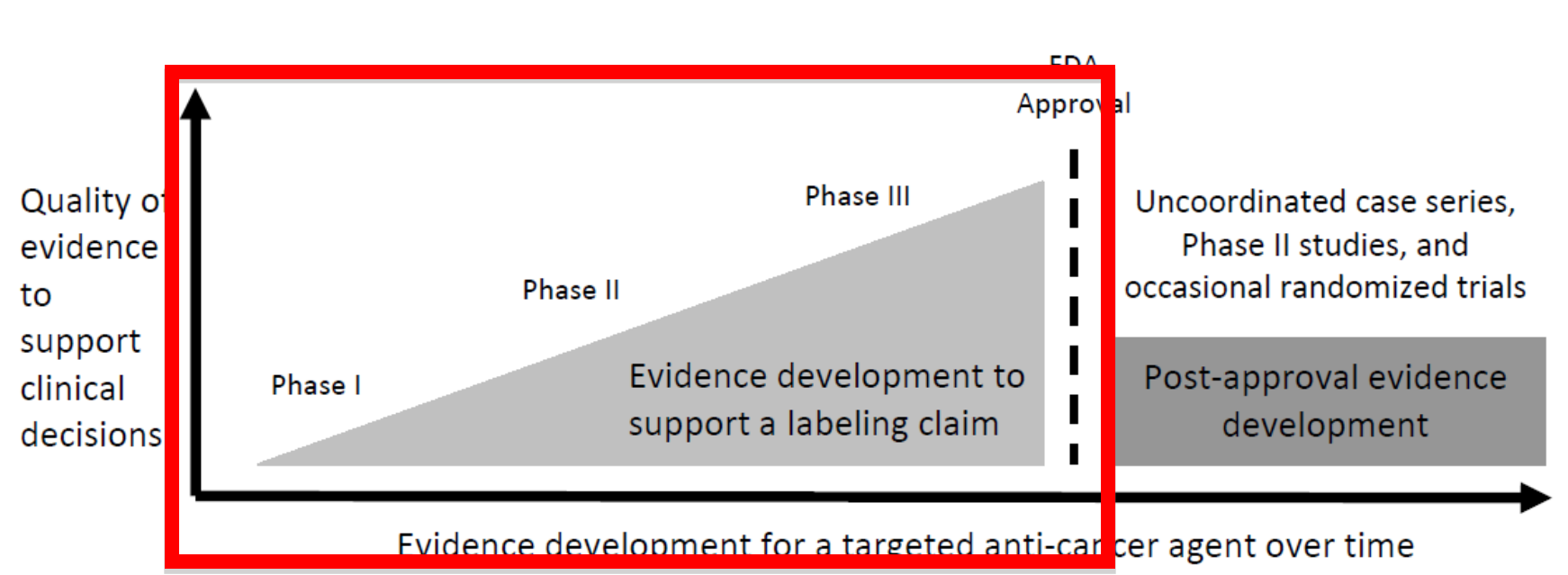

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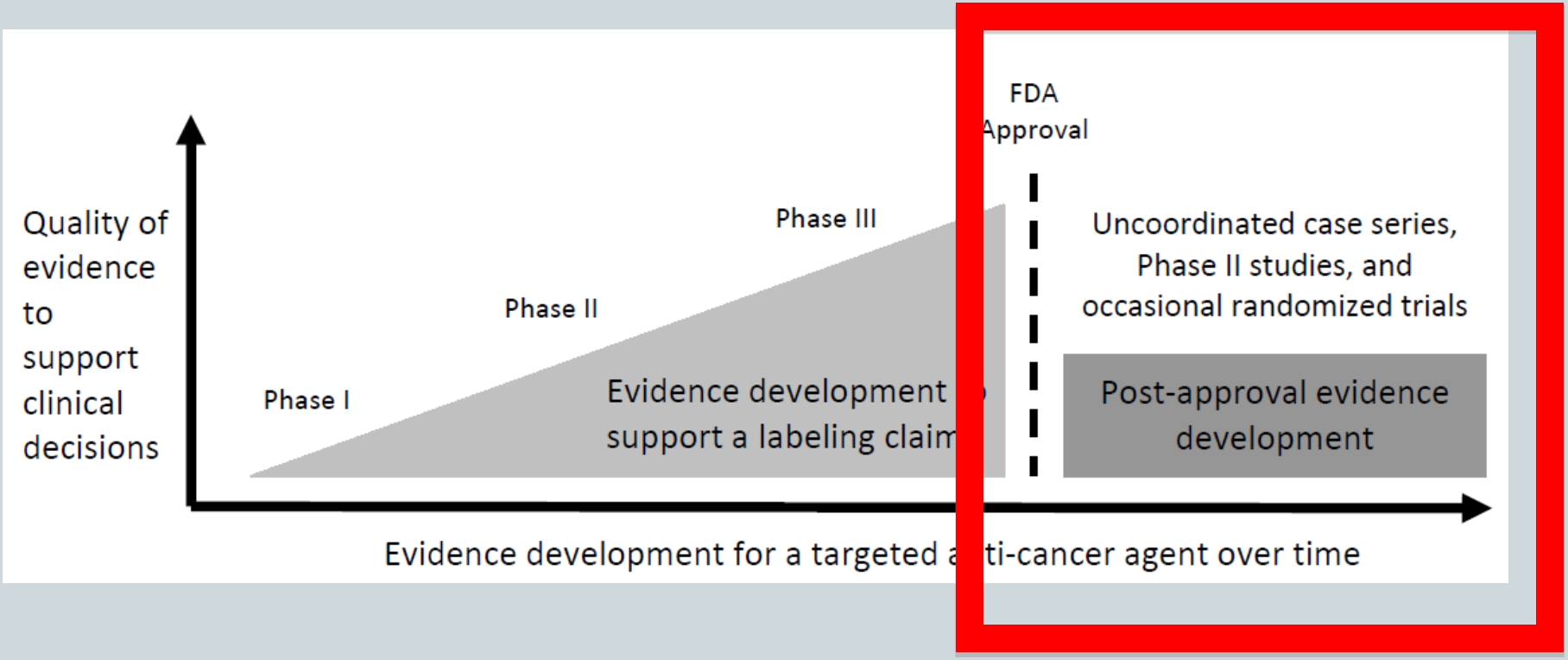

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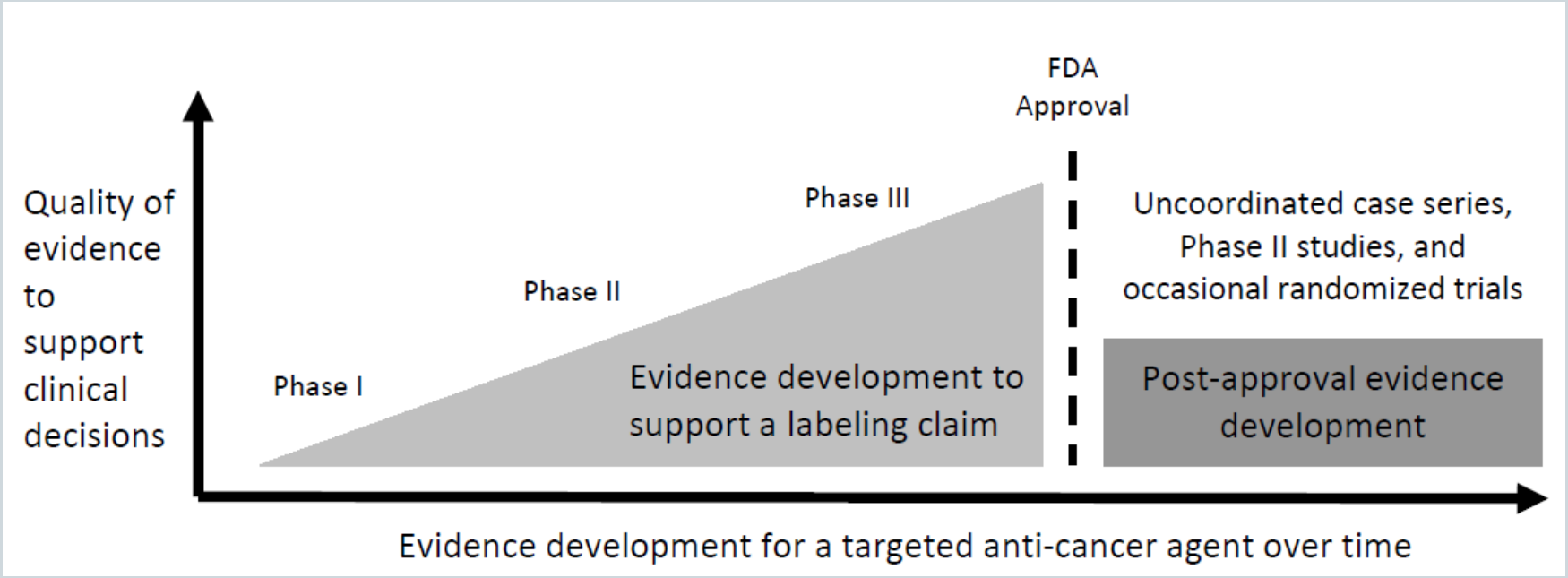

Discovery – translational and clinical scientists; FDA

Clinical decision-making – clinicians, patients, payers

Effectiveness Development Guideline

- CMTP
- Akin to FDA guidelines
- Addresses to the needs of clinical decision-makers
- Stakeholder-based process
- Recommendations for pragmatic clinical trials

JOURNAL OF CLINICAL ONCOLOGY

January 17, 2012

Recommendations for Clinical Trials of Off-Label Drugs Used to Treat Advanced-Stage Cancer

C. Daniel Mullins, Russ Montgomery, Amy P. Abernethy, Arif Hussain, Steven D. Pearson, and Sean Tunis

Off-label Oncology EGD Recs – Important Features

- Consider real-world comparators
- Real world populations
- Define outcomes carefully
  - Survival
  - Carefully define and validate disease-free survival (DFS) and/or progression-free survival (PFS) as surrogates for survival
  - Select a parsimonious set of patient-centric outcomes that are most “clinically meaningful”
- Incorporate biomarkers
- Prepare for biological sciences

Table 1. Trial Design Recommendations for Off-Label Advanced-Stage Cancer Drugs

Category	Recommendation
Trial design and data analysis	1. Design study protocol to test drug in intended therapeutic application
	2. Prespecify subpopulations of interest to avoid misinterpretation of spurious findings
	3. Incorporate biomarkers within trial with expectation that use within trial will drive clinical practice and coverage decisions
	4. Use blinded reviewer to assess PFS to reduce bias
	5. Capture key covariates that may represent confounders or effect modifiers of relationship between treatment and outcomes, particularly in patient subgroups not explored in registration trials
Patient and site recruitment	6. Develop recruitment strategy that addresses patient and physician reluctance to participate in trial of currently available drugs
	7. Recruit patients from variety of clinical practice settings
	8. Provide appropriate incentives, including reimbursement, for clinicians to recruit patients from variety of sites
Comparators	9. Select comparators from among commonly used FDA-approved drugs for targeted new indication that decision makers deem to have greatest clinical net benefit
	10. Clearly define comparators, including other components of treatment
	11. Use clinically relevant dosing regimen for comparator drug, allowing for evidence-based comparisons
Outcomes	12. Whenever feasible, use actual survival rather than surrogate for survival as primary outcome
	13. Provide evidence of validity of DFS or PFS as surrogate for survival within targeted indication whenever primary outcome is DFS or PFS
	14. Select parsimonious set of patient-centric outcomes that are most clinically meaningful

Abbreviations: DFS, disease-free survival; FDA, US Food and Drug Administration; PFS, progression-free survival.

Learning Health Care

Data that are routinely collected in patient care feed into an ever-growing databank, or set of coordinated databases.

Accommodate spectrum from personalized medicine to CER, healthcare redesign, and quality

IOM 2007
NCPF, 2009

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Rapid-Learning System for Cancer Care

Amy P. Abernethy, Lynn M. Etheredge, Patricia A. Ganz, Paul Wallace, Robert R. German, Chalapathy Neti, Peter B. Bach, and Sharon B. Murphy

A B S T R A C T

Compelling public interest is propelling national efforts to advance the evidence base for cancer treatment and control measures and to transform the way in which evidence is aggregated and applied. Substantial investments in health information technology, comparative effectiveness

France's New Framework for Regulating Off-Label Drug Use

Joseph Emmerich, M.D., Ph.D., Nathalie Dumarcet, M.D., and Annie Lorence, Pharm.D.

Off-label use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence. Studies in the United States have shown that off-label use may account for approximately 20% of prescriptions, or 150 million presc
In addition to its
on the health ca
appropriate off-l

A major challenge for regulatory agencies is balancing the need for rapid access to drugs for new indications against the limited information on their benefit–risk ratio for

The intention of the French law and the TRU decree is to open a relatively long observation window in order to assess the benefits and risks of a marketed drug for an unlicensed indication and to collect scientific information to ensure its safe use. A TRU

proposed.[4] A recently passed French law aimed at strengthening the safety of medicines and health care products (Law number 2011-2012, December 29, 2011) and a related decree regarding "Temporary Recommendations for Use" (TRUs; Decree number 2012-743, May 9, 2012) fill part

Third, the prognosis associated with a given disease must be considered: it makes more sense to issue a TRU for a severe disease than for a mild or trivial one. Indeed, regulators as well as caregivers and patients are more willing to accept greater uncertainty regarding the benefit–risk assessment for a life-threatening disease with no alternative treatment. For this reason, TRUs will probably be used most often in oncology and hematology, followed by infectious diseases.

Key Messages

- Off label prescribing in oncology is a real part of care and substantial contributor to cost
- Reinforced by the Compendia-based reimbursement mechanism
- Rapidly evolving evidence/information without mechanism to make sense of it all
- Need a strategy to define appropriate off-label use
  - Conduct thoughtful pragmatic trials with comparators whenever possible
  - Collect the data about what is happening in real practice – and learn from it

Contact

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