Piecing Together the Oncology Pharmacy Puzzle

Objectives

- List examples and characteristics of oncology drug reversals and revisions
- Describe the evolution of antineoplastic drug use over the lifespan of a drug
- Create a process for critiquing new oncology drug approvals or uses

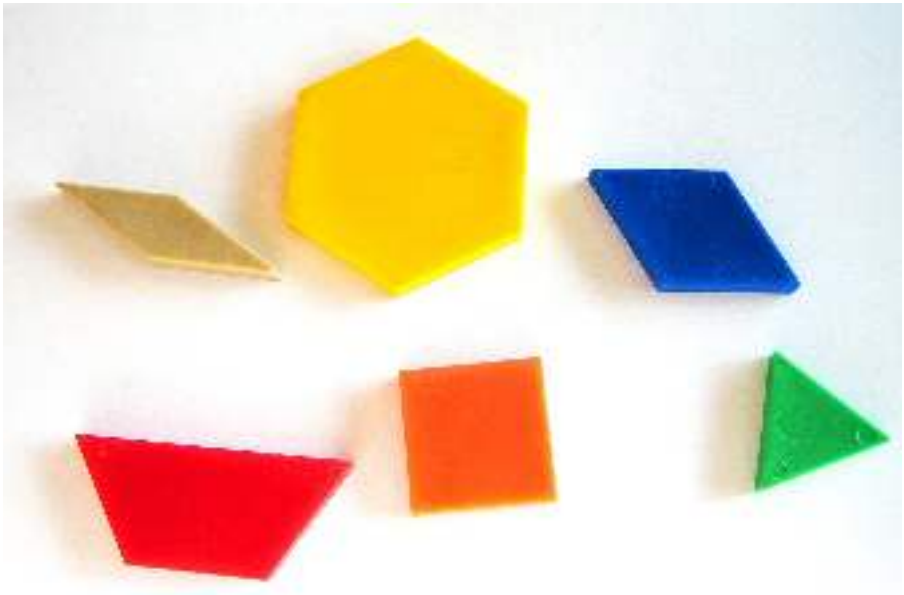
Keynote Who?

Prologue


W Wayne St
E Wayne St
Fairground St
Fairground St
N Clark St
N Harrison St
N Main St
White County Fairgrounds
W Logan St
E Logan St
N Boone St
N Main St
Pine St
W 1st St
E 1st St
St. Clement Lutheran Church
Reynolds Clerk/Treasurer
Marathon Gas Station
Morris Country Kitchen
E Rusell Ln
United States Postal Service
Reynolds
E 2nd St
E 2nd St
W 2nd St
Pizza King
Red Rose Liquor
S Boone St
S Main St
S Church St
W 3rd St
E 3rd St
E 3rd St
Pavich Motorsports
S German St
S German St
W Hillside Dr
E Hillside Dr
W 4th St
E 4th St
E 4th St
Railroad St
S Main St
Reynolds Baseball Fields
St. Joseph Catholic Cemetery
Saint Joseph Catholic Church
S Main St

Google

Puzzling Memories



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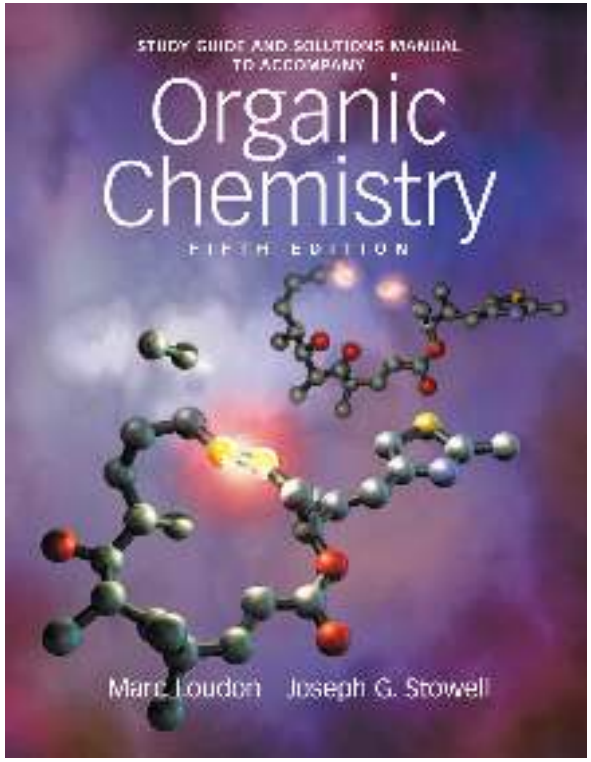
Pharmacy School

Wetherill 200 Lecture Hall, Purdue University



MUSC

PGY1

This Photo by Unknown Author is licensed under CC BY

PGY2

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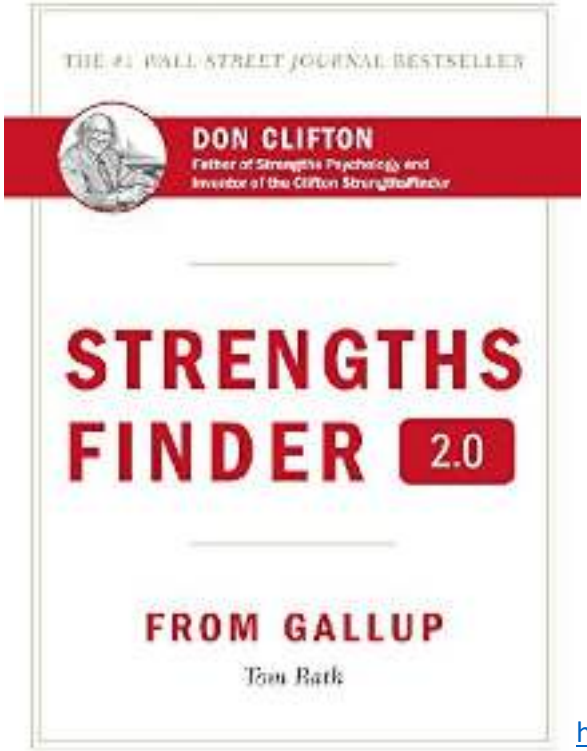
New Practitioner & Educator

- Clinical Practice
  - Prior training mostly malignant Heme
  - New practice mostly medical oncology
- Teaching
  - Pedagogical Novice

"I'll just figure it out."

"Context focuses on understanding the *past* in order to make sense of the present and to chart a course forward."



https://www.gallup.com/cliftonstrengths/en/249824/context-theme-productively-aim-your-cliftonstrengths-talent.aspx

Janke KK, et al. StrengthsFinder Signature Themes of Talent in Doctor of Pharmacy Students in Five Midwestern Pharmacy Schools. Am J Pharm Ed 2015;79(4):Article 49.

Chapter 1

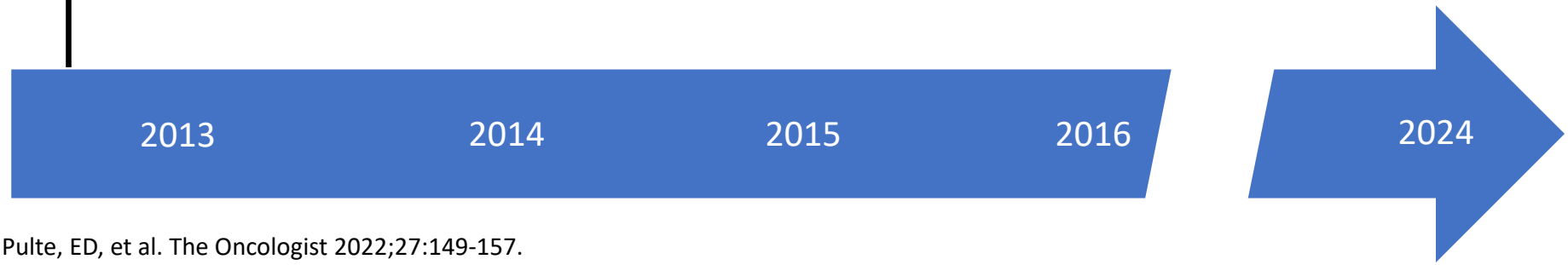
Doses Matter

Ponatinib's Story

Dec. 2012

Accelerated approval (CP-CML)

- Resistance/intolerance to 2+ TKIs
- First TKI approved with T315I activity
- 45 mg PO



Pulte, ED, et al. The Oncologist 2022;27:149-157.
FDA Drug Safety Communication, Dec. 20, 2013.

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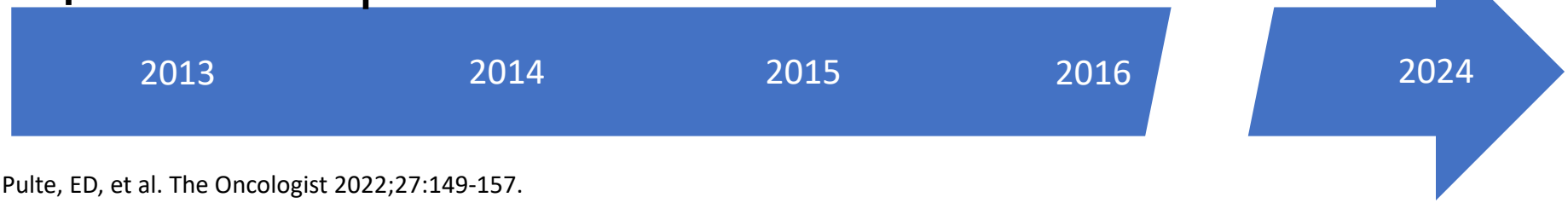
Oct. 2013

Voluntary withdrawal

- Higher rates of arterial thrombotic events in post-marketing data



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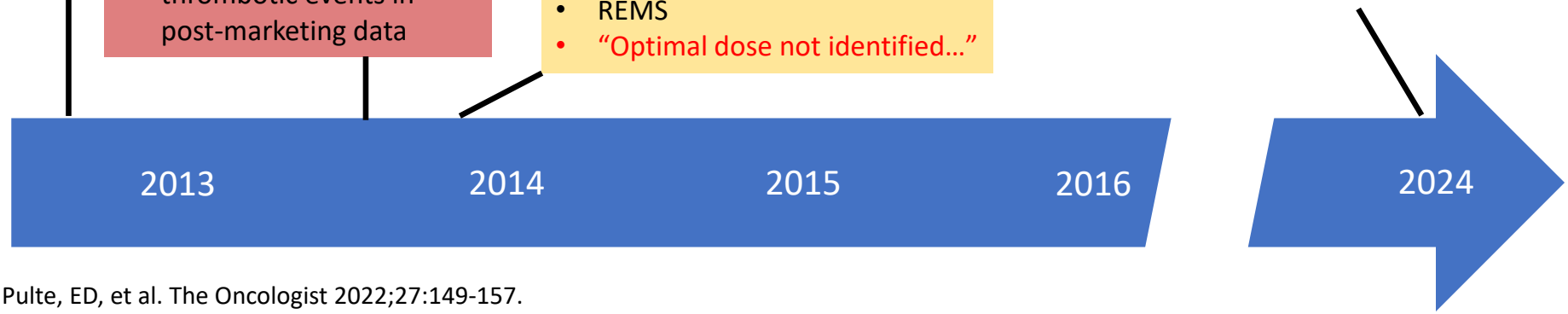
Voluntary withdrawal
- Higher rates of arterial thrombotic events in post-marketing data

Dec. 2013
Revised Approval
- CML (any phase); Ph^+ ALL
  - T315I mutation
  - No other TKI option
- Warnings/Precautions updates
- REMS
- "Optimal dose not identified…"



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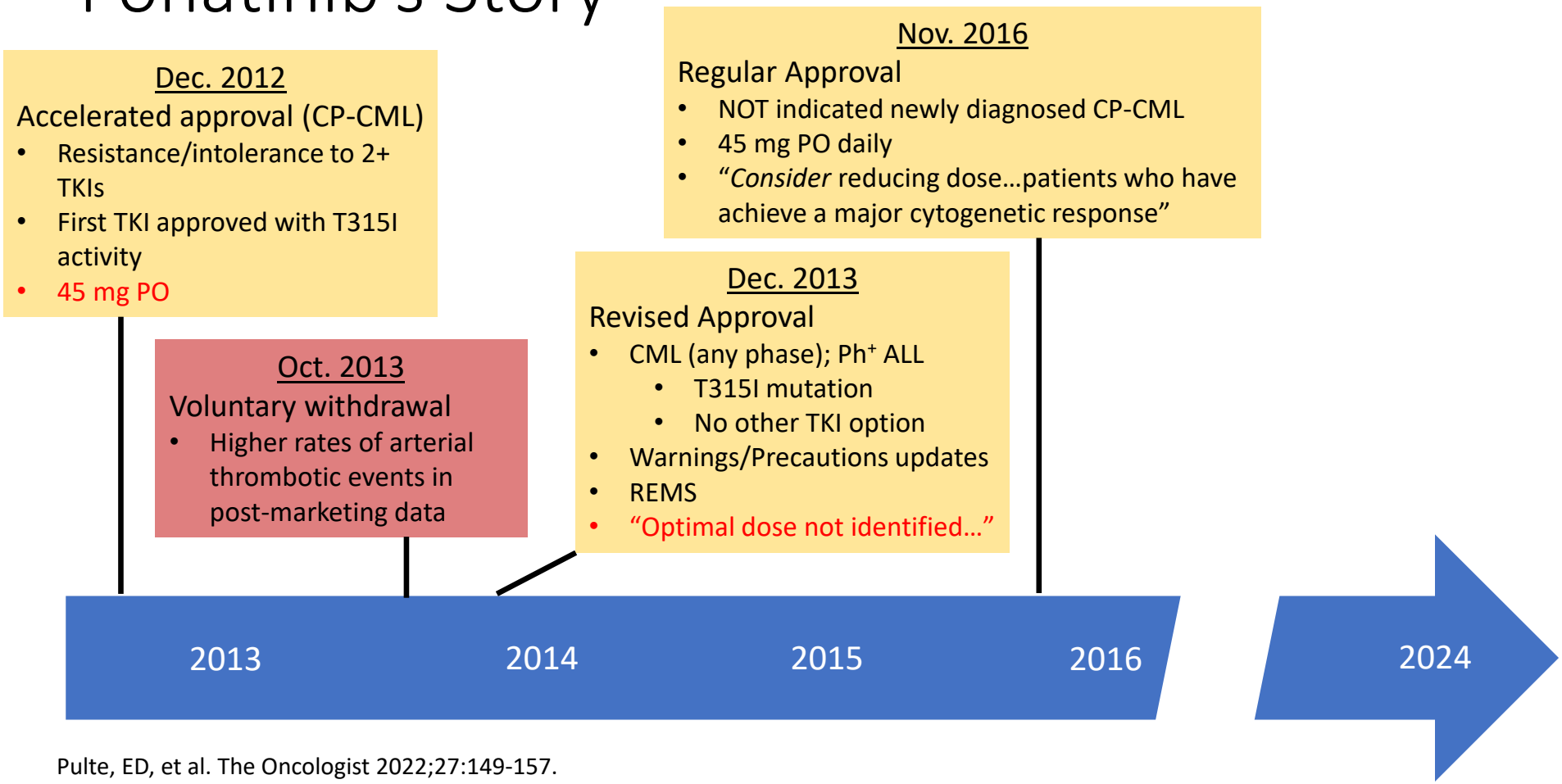

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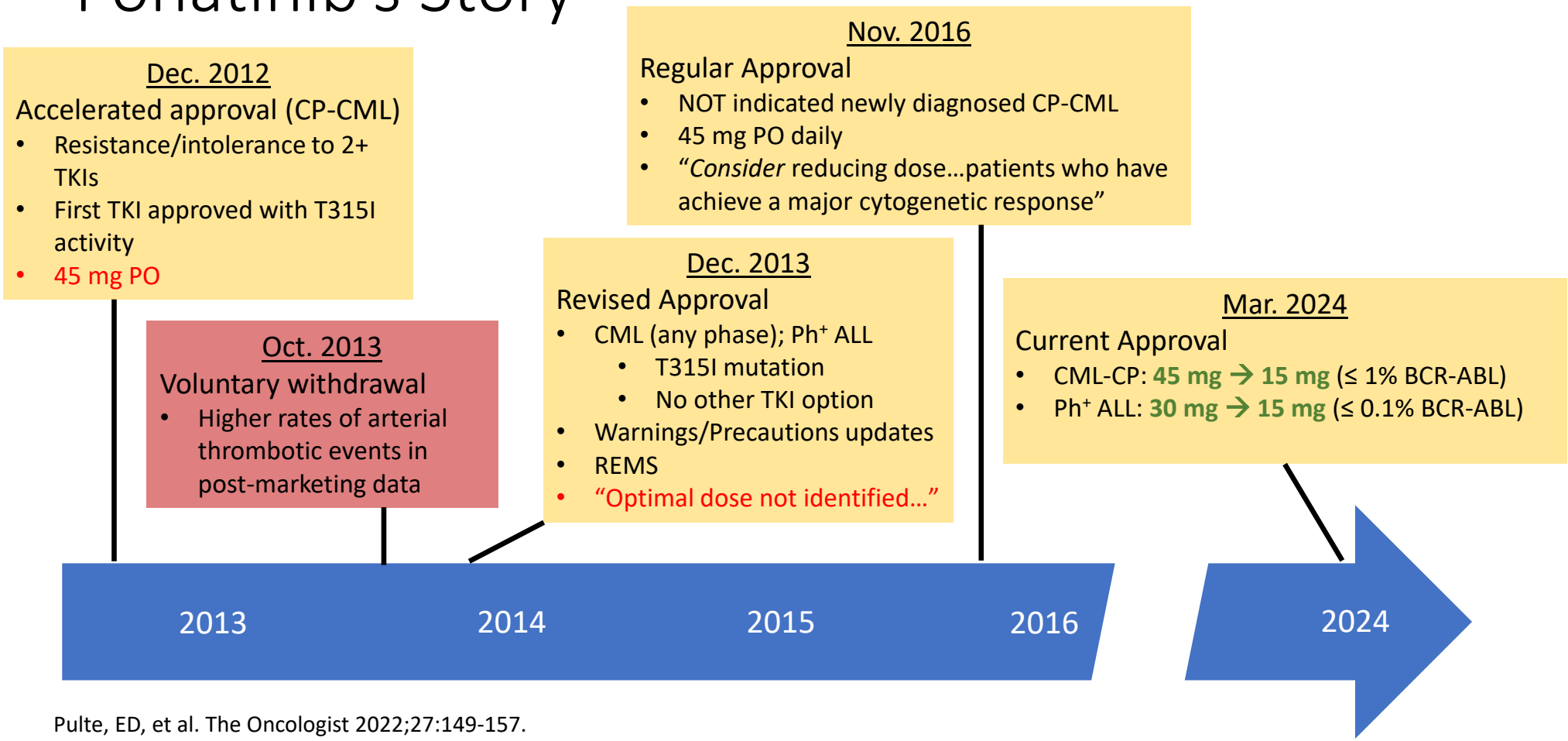

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Ponatinib Phase I Data

<u>Phase 1 Primary Objective</u>: Determine MTD (or recommend daily PO dose) based on DLTs detected in **Cycle 1**

Dose	Number of Patient	DLTs
2 mg	3	0
4 mg	6	0
8 mg	7	0
15 mg	8	0
30 mg	7	0
45 mg	31	1 (rash)
60 mg	6	4 (pancreatitis) 1 (fatigue) 1(↑ LFTs)

Cortes JE, et al. N Engl J Med 2012;367:2075-88.

MTD, maximum tolerated dose; DLT, dose-limiting toxicity
pCRKL, a surrogate marker for BCR-ABL inhibition

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Theoretical/Alternative Phase 1 Primary Objective: Minimum effective dose where majority of patients have significant BCR-ABL inhibition

Dose	Number of Patients	50% pCRKL Reduction
2 mg	2	%
4 mg	1	0%
8 mg	6	67%
15 mg	3	67%
30 mg	4	100%
45 mg	10	90%
60 mg	17	100%

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Ponatinib Phase I Data

Recommended Phase II Dose: 8 mg?

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Dasatinib Phase I (?) Study

Prior imatinib

CP-CML	MCyR
15 mg QD	0
30 mg QD	0
50 mg QD	2/3
75 mg QD	0/3
105 mg QD	1/3
140 mg QD	1/3
180 mg QD	2/3
25 mg BID	0
35 mg BID	1/7
50 mg BID	1/3
75 mg BID	4/6

CP-CMP, chronic phase CML; MCyR, major cytogenetic response

Talpaz M, et al. N Engl J Med 2006;354:2531-41.

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15 mg QD	0
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50 mg QD	2/3
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105 mg QD	1/3
140 mg QD	1/3
180 mg QD	2/3
25 mg BID	0
35 mg BID	1/7
50 mg BID	1/3
75 mg BID	4/6

While we shouldn't be evaluating efficacy based on Phase I data….

But, no clear or obvious trend of higher dose → better outcomes

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75 mg BID	4/6

Recommended Phase II Dose?

- Toxicity
  - Grade 3/4 neutropenia: 45%
    - *"We cannot tell whether the myelosuppression was solely the result of the action of dasatinib…. or a of a more general hematopoietic toxic effect. Myelosuppression typically resolved in patients who had cytogenetic remission and has not been a complication of dasatinib treatment in patient with solid tumors."*
  - Pleural effusion (15 patients)
  - Grade 3/4 transaminitis (7 patients)
  - Grade 1/2 hypocalcemia (60%)

CP-CMP, chronic phase CML; MCyR, major cytogenetic response

Talpaz M, et al. N Engl J Med 2006;354:2531-41.

”Intermittent target inhibition with 100 mg daily…”

CP-CML	100 mg QD	50 mg BID	140 mg QD	70 mg BID
Imatinib duration > 3 years	46%	36%	41%	42%
Prior therapy Interferon-alpha Chemotherapy	 52% 23%	 52% 31%	 56% 25%	 49% 26%
Efficacy				
MCyR	59%	54%	56%	55%
CCyR	41%	42%	44%	45%
Toxicity				
Pleural effusion	7%	11%	15%	16%

“Treatment with 100 mg once daily provides the most favorable overall benefit-risk profile, with improved tolerability and consistent efficacy to the recommended 70 mg twice daily dose...

On the basis of these findings, the ***100 mg once daily regimen should be used*** for patients with CP-CML…”

Shah N, et al. J Clin Oncol 2008;26:3204-3212

Dasatinib: Daily vs. BID

- *"An **extensive** phase II program confirmed the efficacy and safety of dasatinib 70 mg twice daily in all phases of CML…"*
- Prior dose finding studies found
  - 140 mg daily looks more effective
  - 70 mg BID looks more toxic (pleural effusions)

AP-CML	140 mg QD (n = 158)	70 mg BID (n = 159)
Imatinib status		
Resistant	74%	73%
Intolerant	26%	27%
Efficacy		
MCyR	39%	42%
CCyR	32%	33%
Toxicity		
Pleural effusion	**20%**	**39%**

AP-CMP, accelerated phase CML

Kantarjian H, et al. Blood 2009;113:6322-9.

Dasatinib Label Today

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL® safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use

Initial U.S. Approval: 2006

---------- **RECENT MAJOR CHANGES** ----------

Warnings and Precautions (5.11) 2/2023

----------**INDICATIONS AND USAGE** ----------

SPRYCEL is a kinase inhibitor indicated for the treatment of

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)
- pediatric patients 1 year of age and older with Ph+ CML in chronic phase. (1, 14)
- pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. (1, 14)

----------**DOSAGE AND ADMINISTRATION** ----------

- Chronic phase CML in adults: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily. (2)

Sprycel (package insert). Bristol-Myers Squibb. Princeton, NJ. Updated 2/2023.

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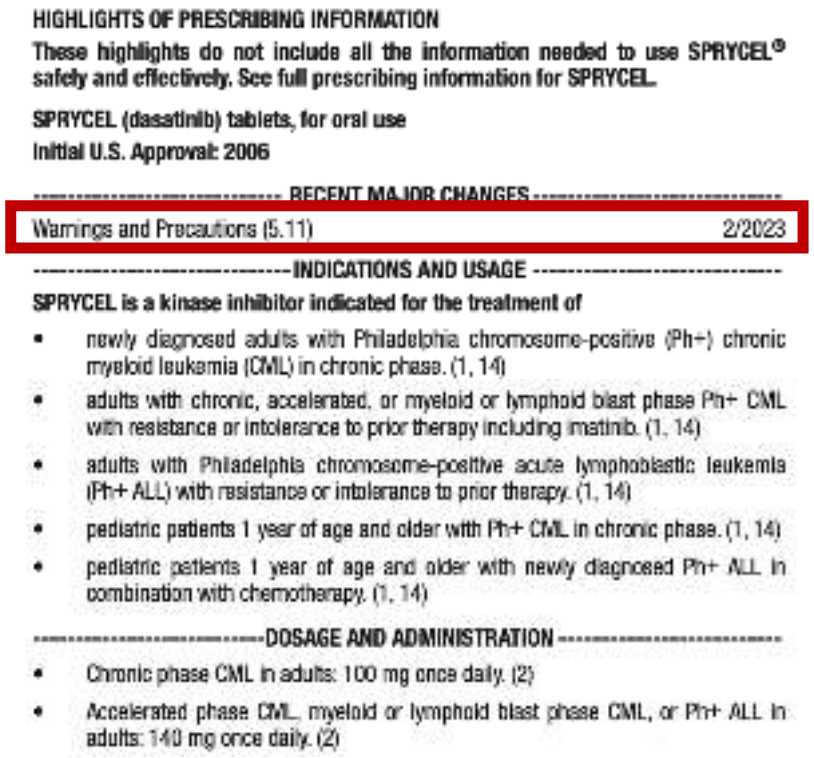

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- Warnings and Precautions
  - Myelosuppression
  - Fluid retention
  - Cardiovascular Toxicity
  - Pulmonary Artery Hypertension
  - QT Prolongation
  - Severe Dermatologic Reactions
  - Tumor Lysis Syndrome
  - Embryo-Fetal Toxicity
  - Effects on Growth & Development in Pediatric Patients
  - Hepatotoxicity

Sprycel (package insert). Bristol-Myers Squibb. Princeton, NJ. Updated 2/2023.

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- Warnings and Precautions

5.11 Hepatotoxicity

SPRYCEL may cause hepatotoxicity as measured by elevations in bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase *[see Adverse Reactions (6.1)]*. Monitor transaminases at baseline and monthly or as clinically indicated during treatment. Reduce dose, withhold, or permanently discontinue SPRYCEL based on severity *[see Dosage and Administration (2.5)]*. When SPRYCEL is administered in combination with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Monitor hepatic function when SPRYCEL is used in combination with chemotherapy.

- Hepatotoxicity

Sprycel (package insert). 2023. Bristol-Myers Squibb. Princeton, NJ. Updated.

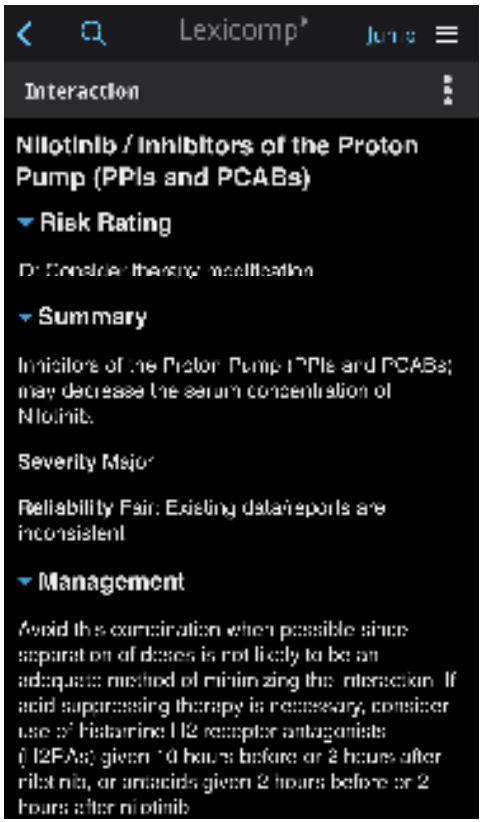
Dasatinib Dosing, cont.

Reference	Design	Results
Gener-Ricos, et al *"Based on the findings from the phase I trial and the anecdotal evidence that lower dose dasatinib…."*	Single-arm (n = 83), 50 mg daily. 5-year f/u	MMR: 95% MMR^{+}: 82% 5-year OS: 96%
E Jabbour, et al	50 mg (n = 83) vs. 100 mg (n = 150). Propensity score analysis. Median f/u = 5 years	<u>3-year MMR</u> • D50: 92% • D100: 84% <u>MR 4.5</u> • D50 77% • D100 62% <u>4-year OS</u> • D50 97% • D100 96%

Gener-Ricos, et al. Clin Lymphoma Myeloma Leuk 2023;23:742-748.
Jabbour E, et al. Am J Hematol 2022;97:1413-1418

Nilotinib PPI Drug-Drug Interaction: One Puzzle Piece

- Drug Interactions: PPIs
  - ”[Nilotinib] displays pH-dependent aqueous solubility. Coadministration of multiple doses of esomeprazole (a PPI) decreased the nilotinib AUC by 34%.”
  - ”Avoid concomitant use of PPIs with [nilotinib]”



Tasigna (package insert). 2024. Novartis Pharmaceuticals, Corp. East Hanover, NJ.
LexiComp Intertactions. Accessed April 30, 2024. Wolters Kluwer Health, Inc.

Nilotinib PPI Drug Interaction: Additional Puzzle Pieces

Nilotinib 34% AUC decrease with PPI based on single dose nilotinib study…

Design	Nilotinib Dose	PPI or famotidine (n = 94)	No PPI or H2RA (n = 373)	p-value
Retrospective analysis of ENESTnd trial	400 mg BID	1-year MMR: 44.4%	1-year MMR: 40.4%%	0.13 0.14*
	300 mg BID	1-year MMR: 55.1%	1-year MMR: 41.7%%	

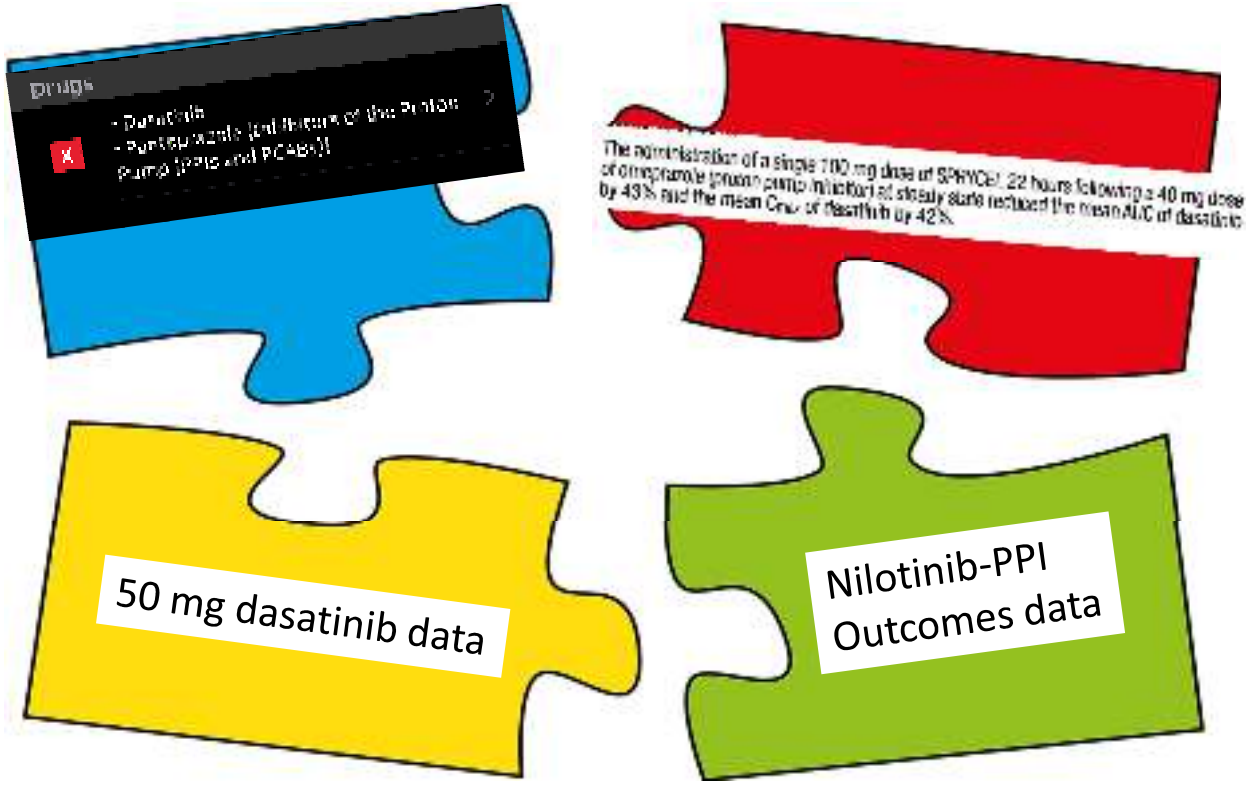
Design	Nilotinib Dose	PPI or famotidine (n = 77)	No PPI or H2RA (n =170)	p-value
Retrospective analysis of CAMN107A2101 trial	400 BID	1-year MCyR: 62.3%%	1-year MCyR: 57.6%	0.40 0.82*

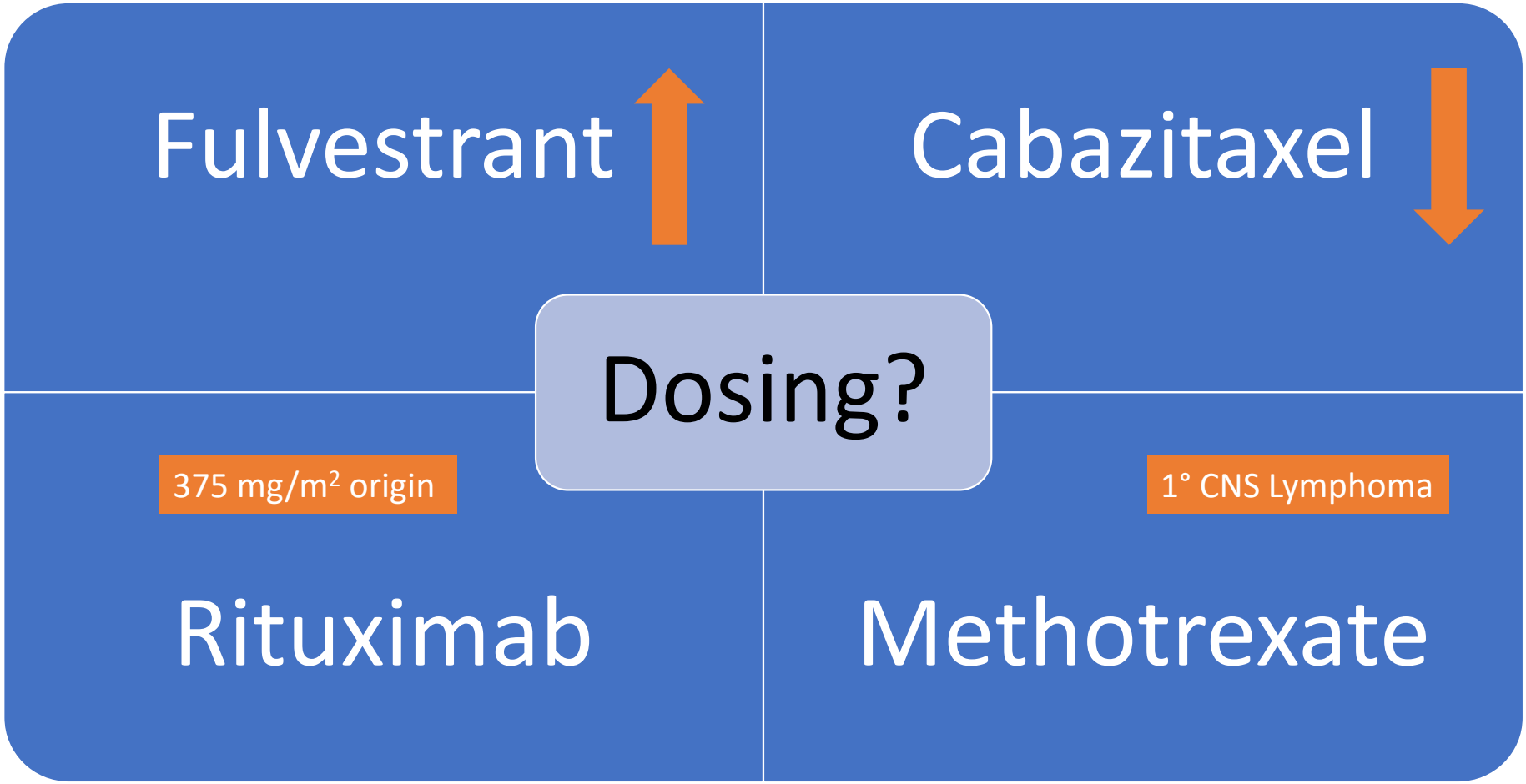
*(sensitivity analysis for > 50% PPI possession time)

Yin OQ, et al. J Clin Pharmacol 2010;50:960-967.
Yin OQ, et al. Cancer Chemother Pharmacol 2012;70:345-350.

Putting the pieces together….

- A 30-year-old male with newly diagnosed chronic phase CML
  - **Initial Rx**:
    - dasatinib 100 mg
  - **PMH**:
    - GERD
  - **Meds**:
    - pantoprazole




Fulvestrant
Cabazitaxel
Dosing?
375 mg/m2 origin
1° CNS Lymphoma
Rituximab
Methotrexate

Drug Use Evolution Mirrors Biologic Insights

Chapter 2

Cetuximab Story

2004
- FDA approval for EGFR-expressing metastatic colorectal cancer

2009
- Approval narrowed to KRAS-wild type colon cancer

Today
- Use recommendation limited to KRAS, NRAS, BRAF wild type and left sided colon cancer

NCCN Clinical Practice Guidelines in Oncology for Colorectal Cancer. Version 2.2024

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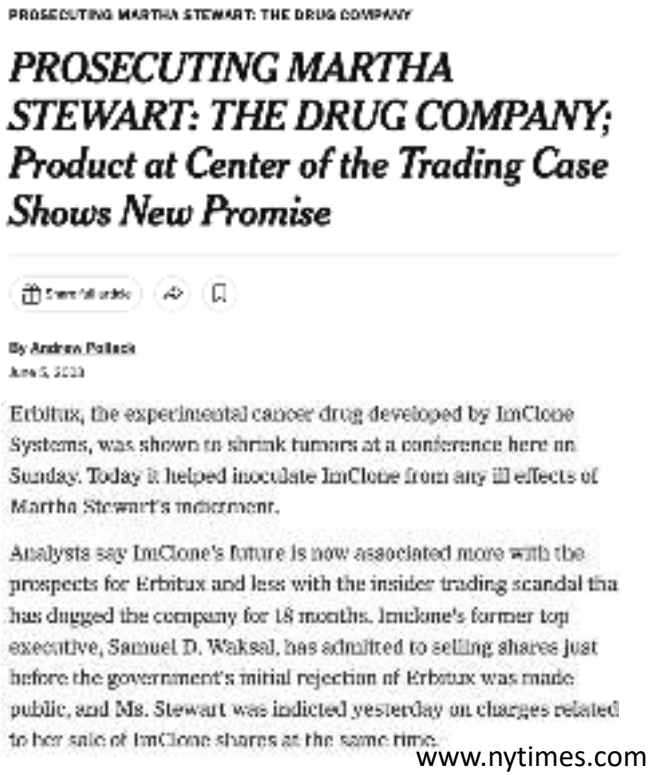


PROSECUTING MARTHA STEWART: THE DRUG COMPANY

PROSECUTING MARTHA STEWART: THE DRUG COMPANY; Product at Center of the Trading Case Shows New Promise

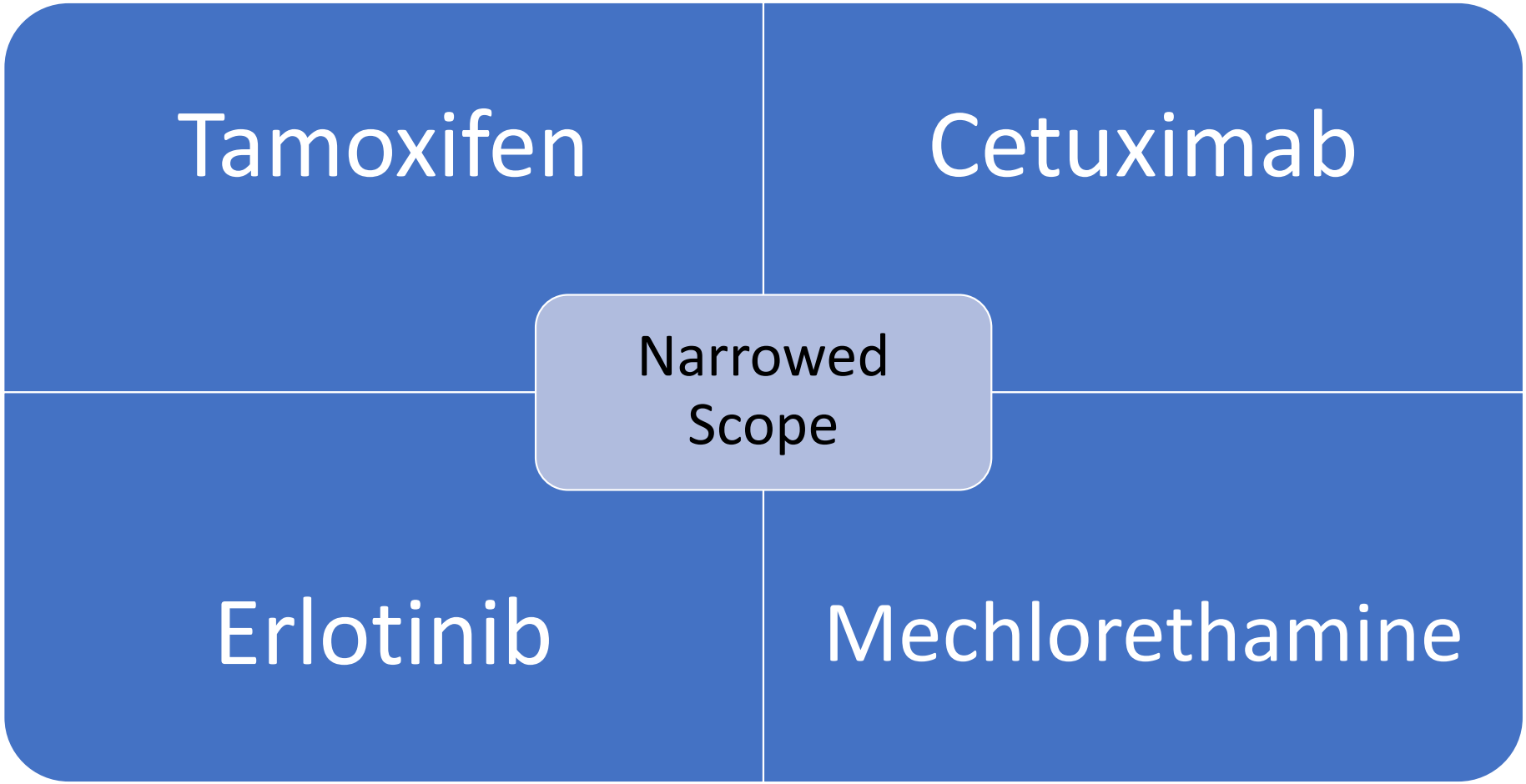
By Andrew Pollack

Erbitux, the experimental cancer drug developed by ImClone Systems, was shown to shrink tumors at a conference here on Sunday. Today it helped inoculate ImClone from any ill effects of Martha Stewart's indictment.

Analysts say ImClone's future is now associated more with the prospects for Erbitux and less with the insider trading scandal that has dogged the company for 18 months. Imclone's former top executive, Samuel D. Waksal, has admitted to selling shares just before the government's initial rejection of Erbitux was made public, and Ms. Stewart was indicted yesterday on charges related to her sale of ImClone shares at the same time.

www.nytimes.com

NCCN Clinical Practice Guidelines in Oncology for Colorectal Cancer. Version 2.2024


Tamoxifen
Cetuximab
Narrowed Scope
Erlotinib
Mechlorethamine

EGFR Inhibiting TKIs in NSCLC: One Step Forward for All

	Erlotinib (n = 488)	Placebo (n = 243)
Age, median	62	59
Asian race/ethnicity	13%	12%
Histology		
Adenocarcinoma	50%	49%
Squamous cell	30%	32%
Prior chemotherapy		
1 regimen	51%	50%
2^{+} regimens	49%	50%
Smoking status		
Current smoker	73%	77%
Never smoker	31%	17%
EGFR Expression Unknown	57%	53%

Shepherd FA, et al. N Engl J Med 2005;353:123-132.

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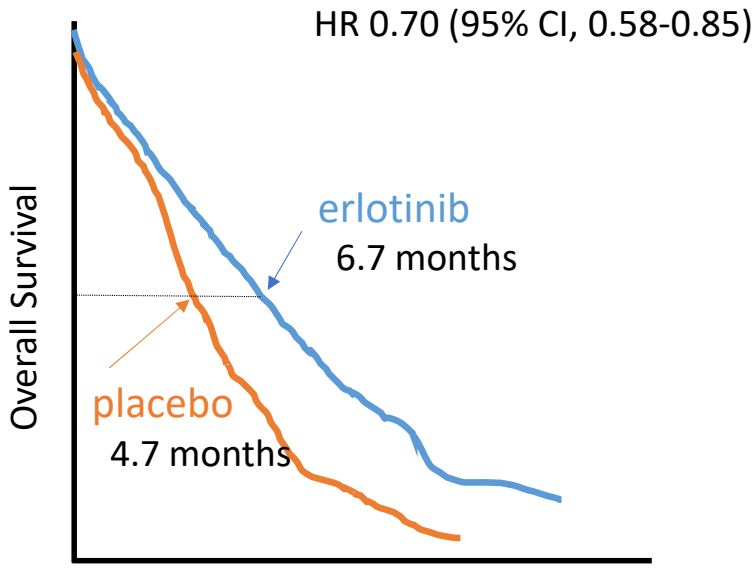
Never smoker	31%	17%
EGFR Expression Unknown	57%	53%



Pivotal trial that established erlotinib as SOC in third line metastatic NSLCL

Image adapted from Shepherd FA, et al. N Engl J Med 2005;353:123-132.

IPASS: Two Steps Forward for Fewer

	Gefitinib (n = 609)	Chemo* (n = 608)
Age, median	57	57
Female	80%	79%
East Asian race/ethnicity	99.7%	99.2%
Histology Adenocarcinoma	95%	97%
Stage IIIB IV	27% 70%	27% 68%
Smoking status Never smoker	94%	94%

*Carboplatin/paclitaxel

Previously Untreated Advanced NSCLC

EGFR TKIs seemed to work better in patients with certain characteristics

- Adenocarcinoma histology
- East Asian
- Female
- Never Smoker

IPASS, Iressa® (gefitinib) Pan-Asia Study

Mok TS, et al. N Engl J Med 2009;361:947-957

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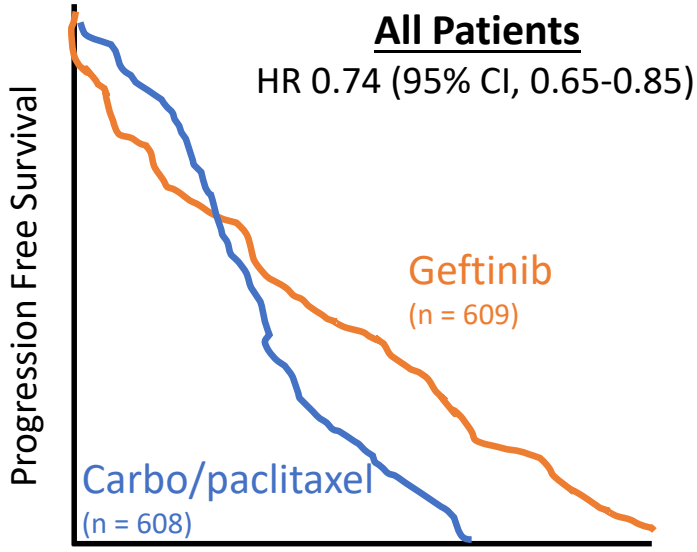

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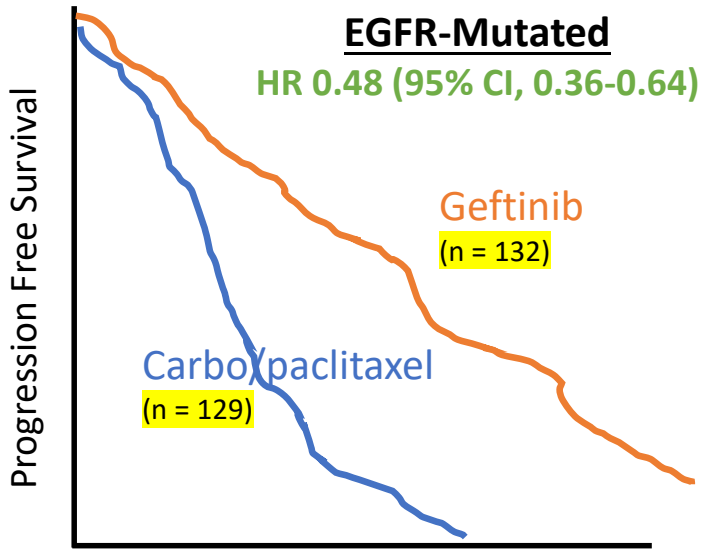

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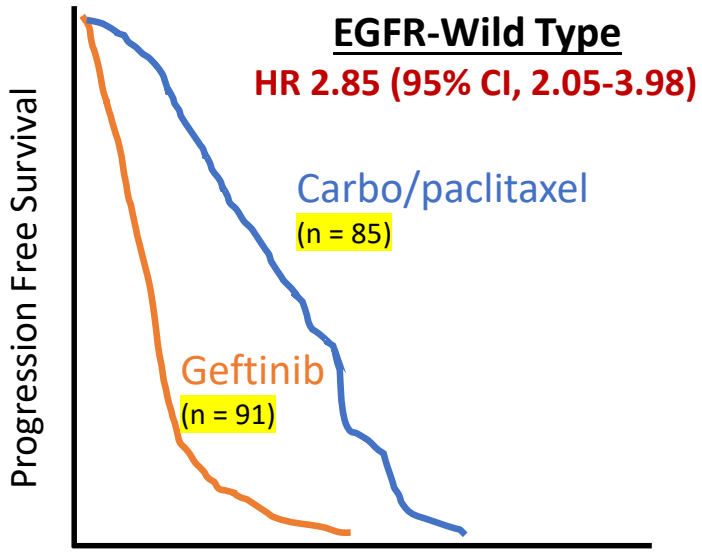

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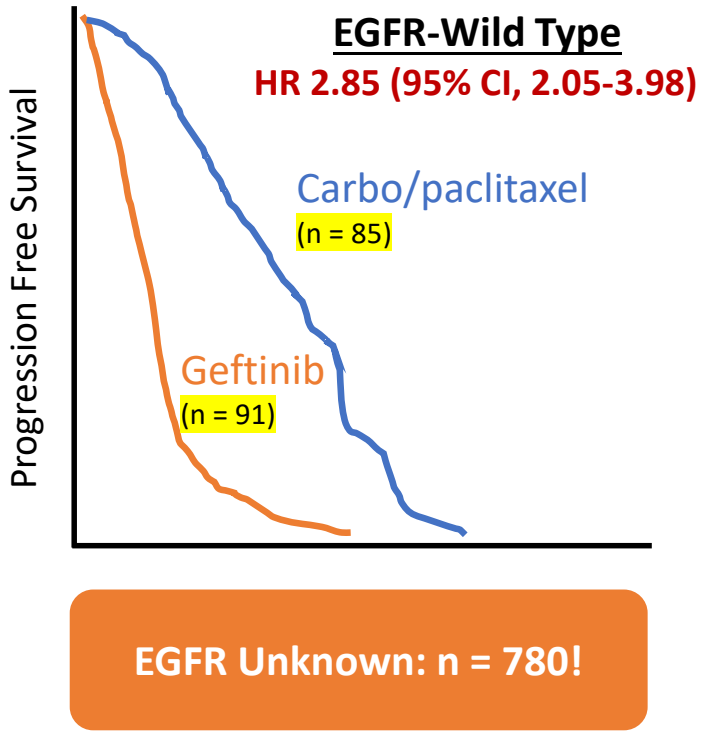
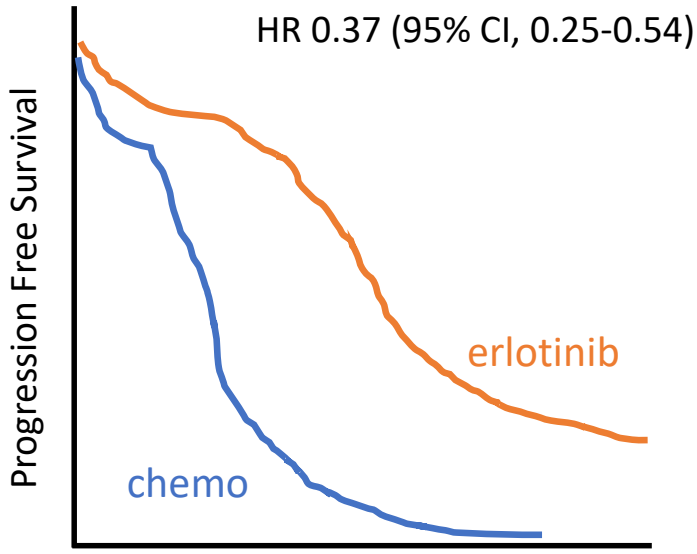


IPASS, Iressa® (gefitinib) Pan-Asia Study

Image adapted from Mok TS, et al. N Engl J Med 2009;361:947-957

EURTAC: Three Steps Forward for Even Fewer

	Erlotinib (n = 86)	Chemo (n = 87)
Age, median	63	64
Female	67%	78%
Histology		
Adenocarcinoma	95%	90%
Stage		
IV	91%	94%
Smoking status		
Never smoker	66%	72%
Former smoker	26%	14%
EGFR mutation		
Exon 19 deletion	66%	67%
L858R (exon 21 mutation)	34%	33%



EURTAC, European Tarceva® (erlotinib) vs. Chemotherapy

Image adapted from Rosell R, et al. Lancet Oncol 2012;13:239-46.

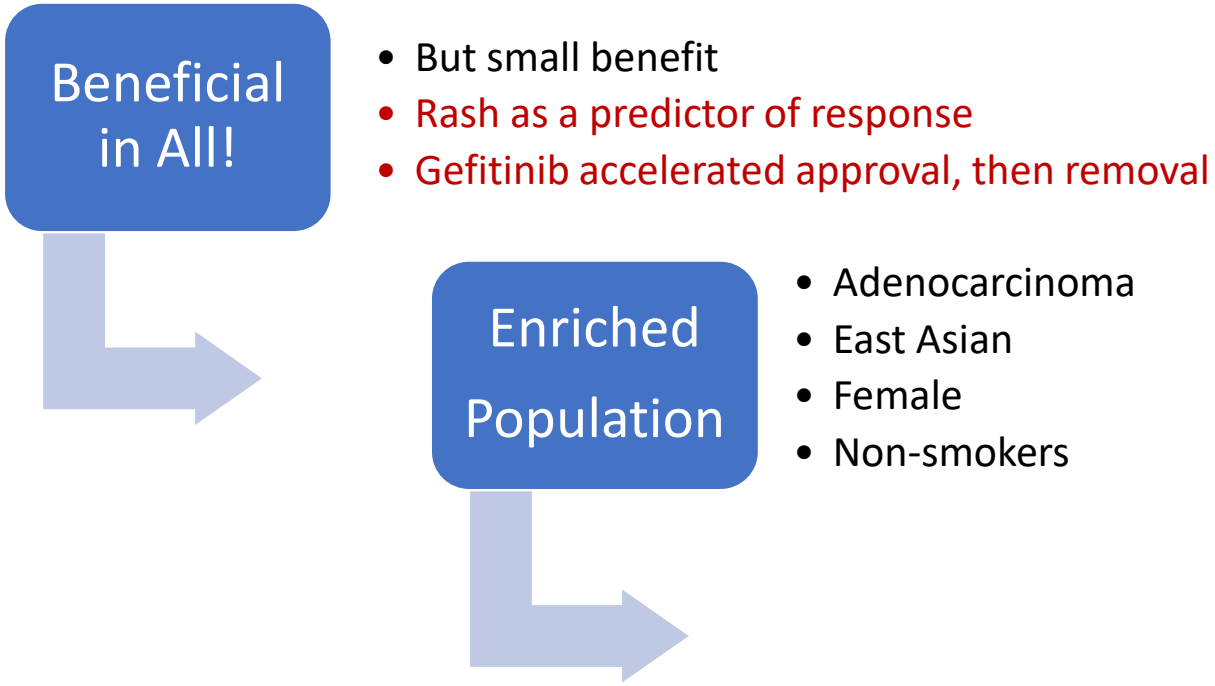
EGFR TKIs in NSCLC Recap

Beneficial in All!

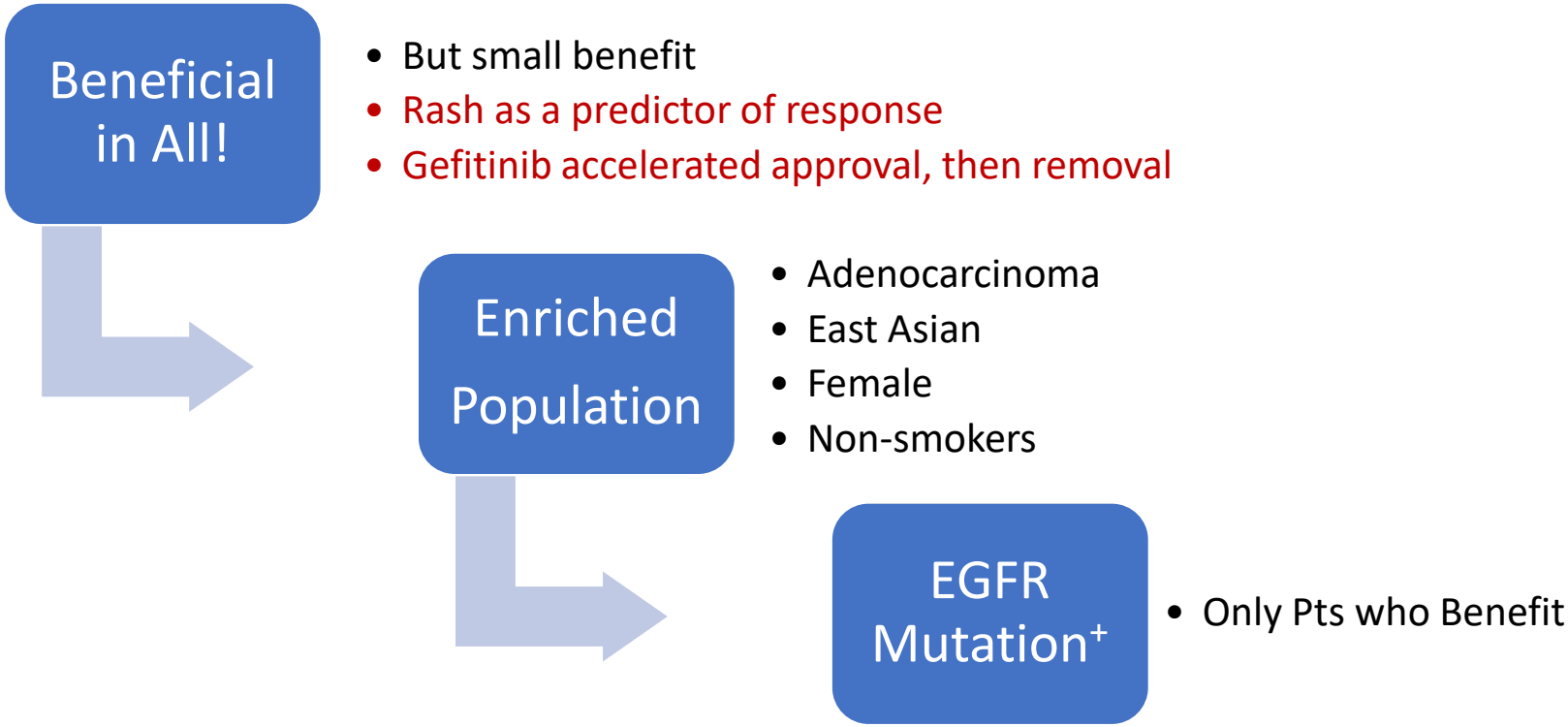
Discarded Puzzle Pieces

- But small benefit
- Rash as a predictor of response
- Gefitinib accelerated approval, then removal

EGFR TKIs in NSCLC Recap



EGFR TKIs in NSCLC Recap



Expanded Uses & Indications

Chapter 3

The Imatinib Era (of Expanded Indications)

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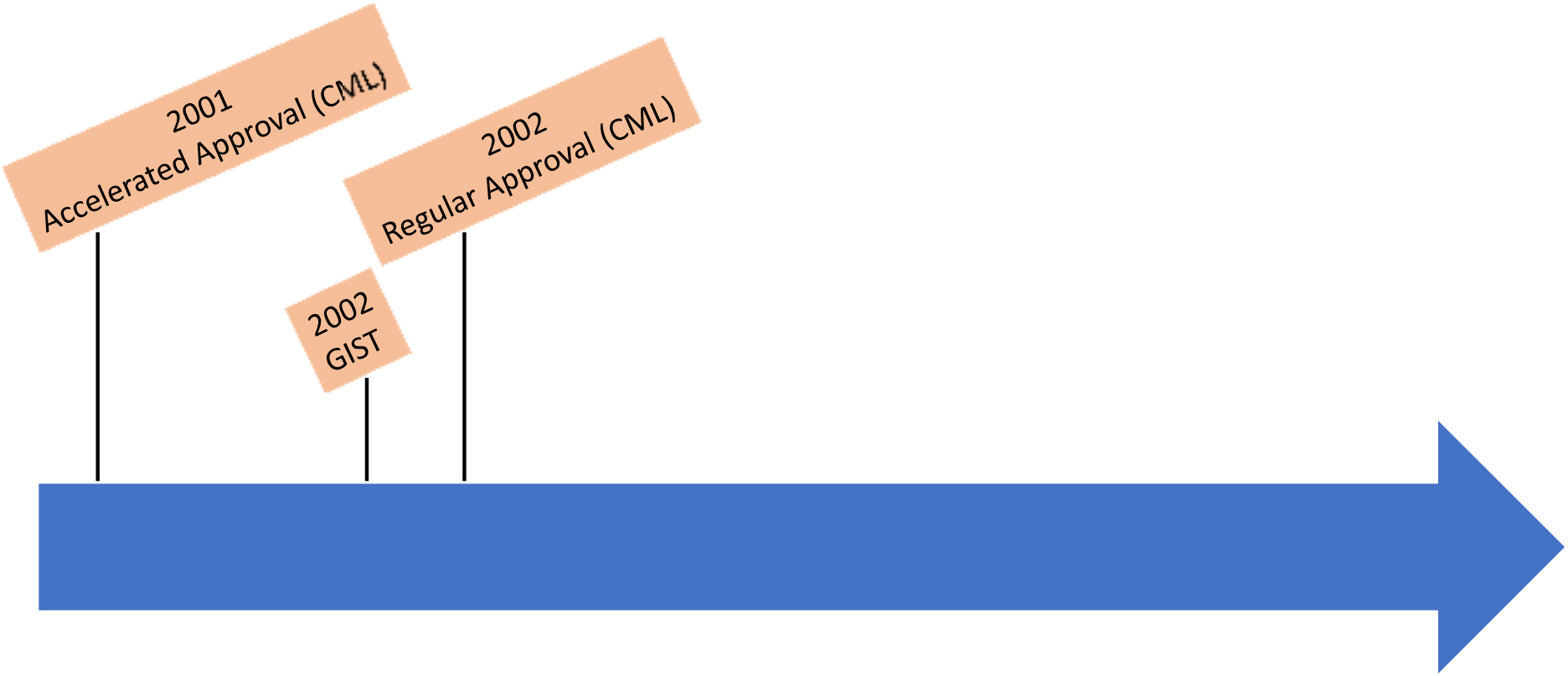
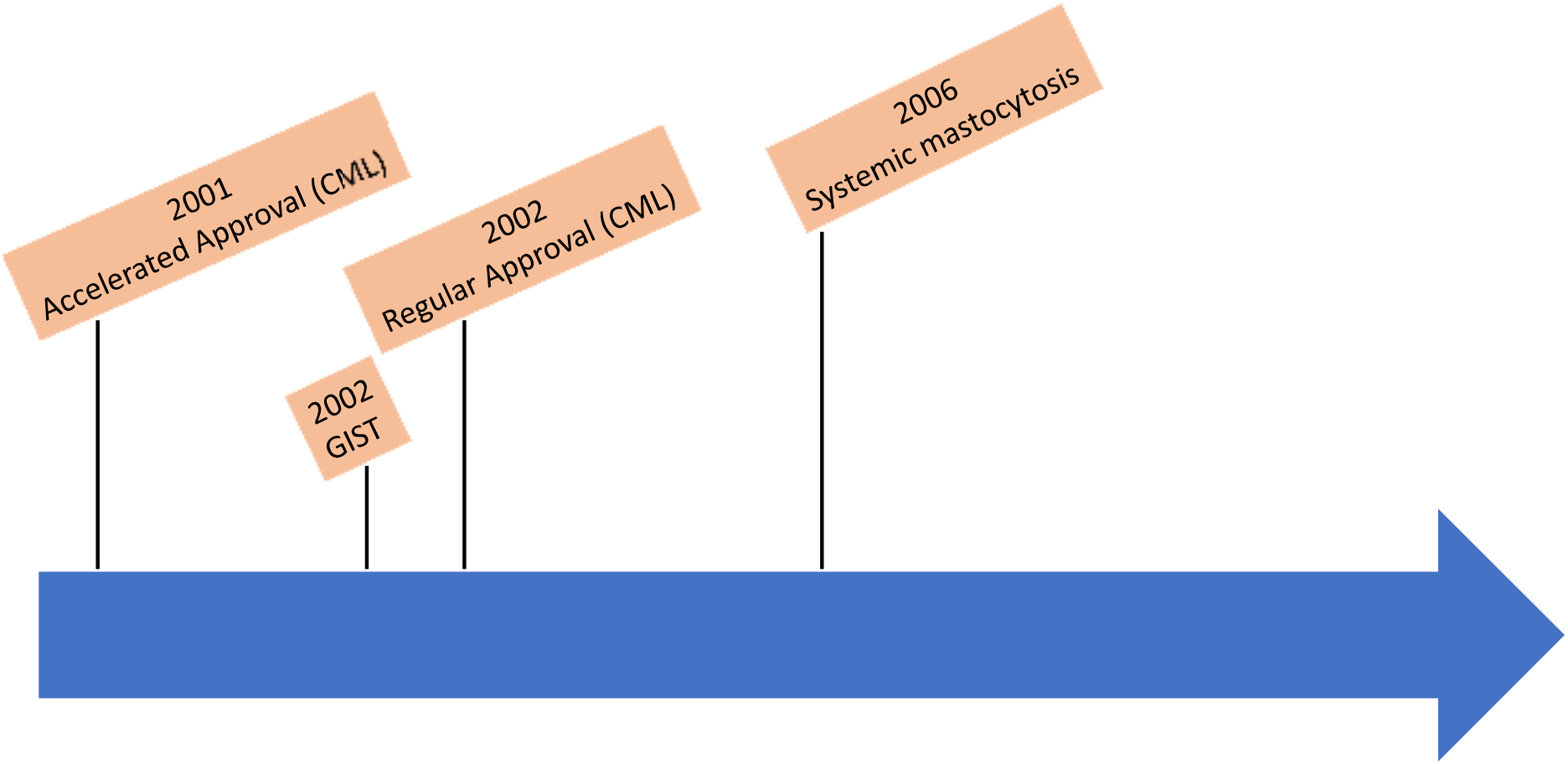


The Imatinib Era (of Expanded Indications)



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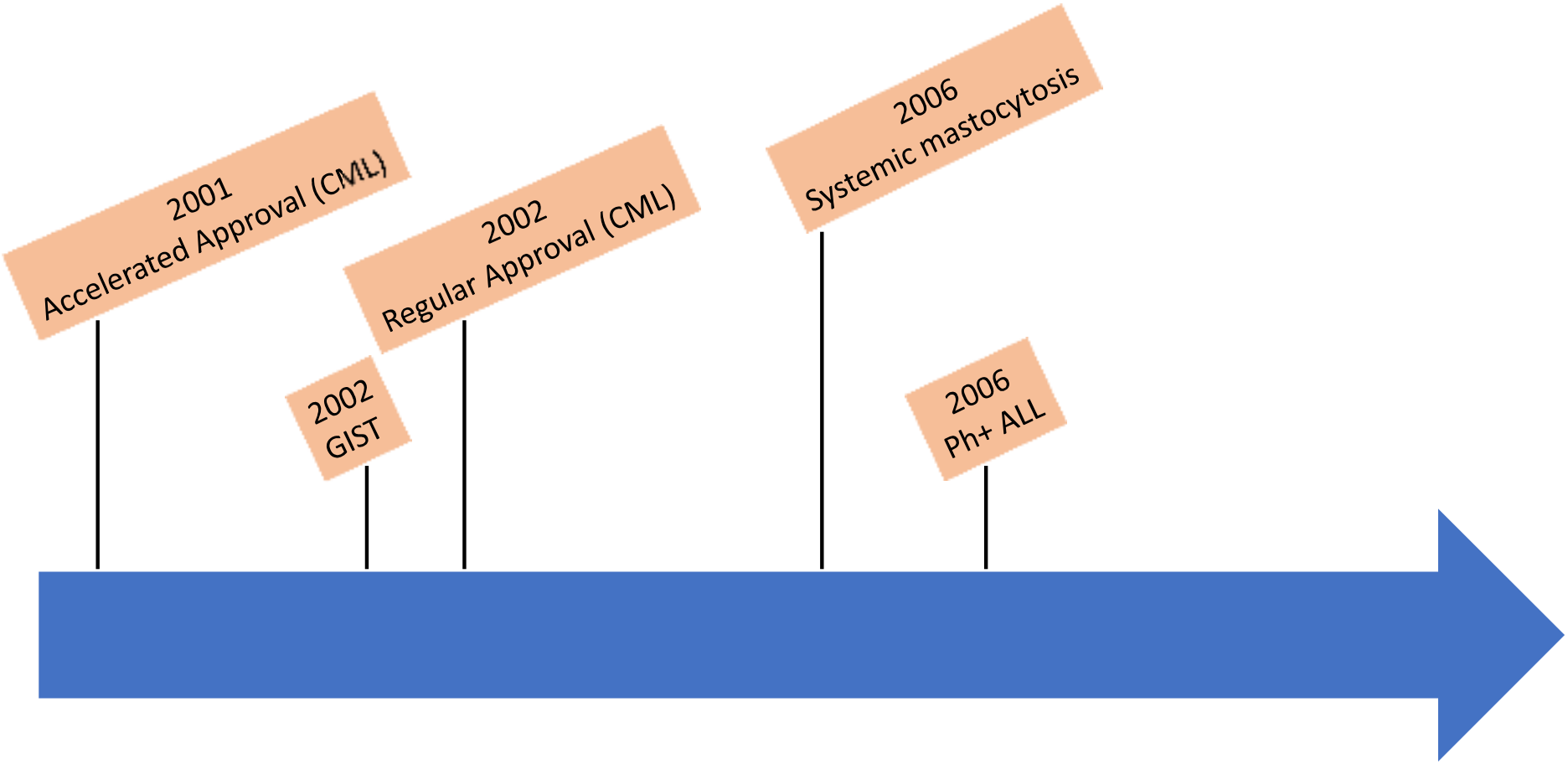

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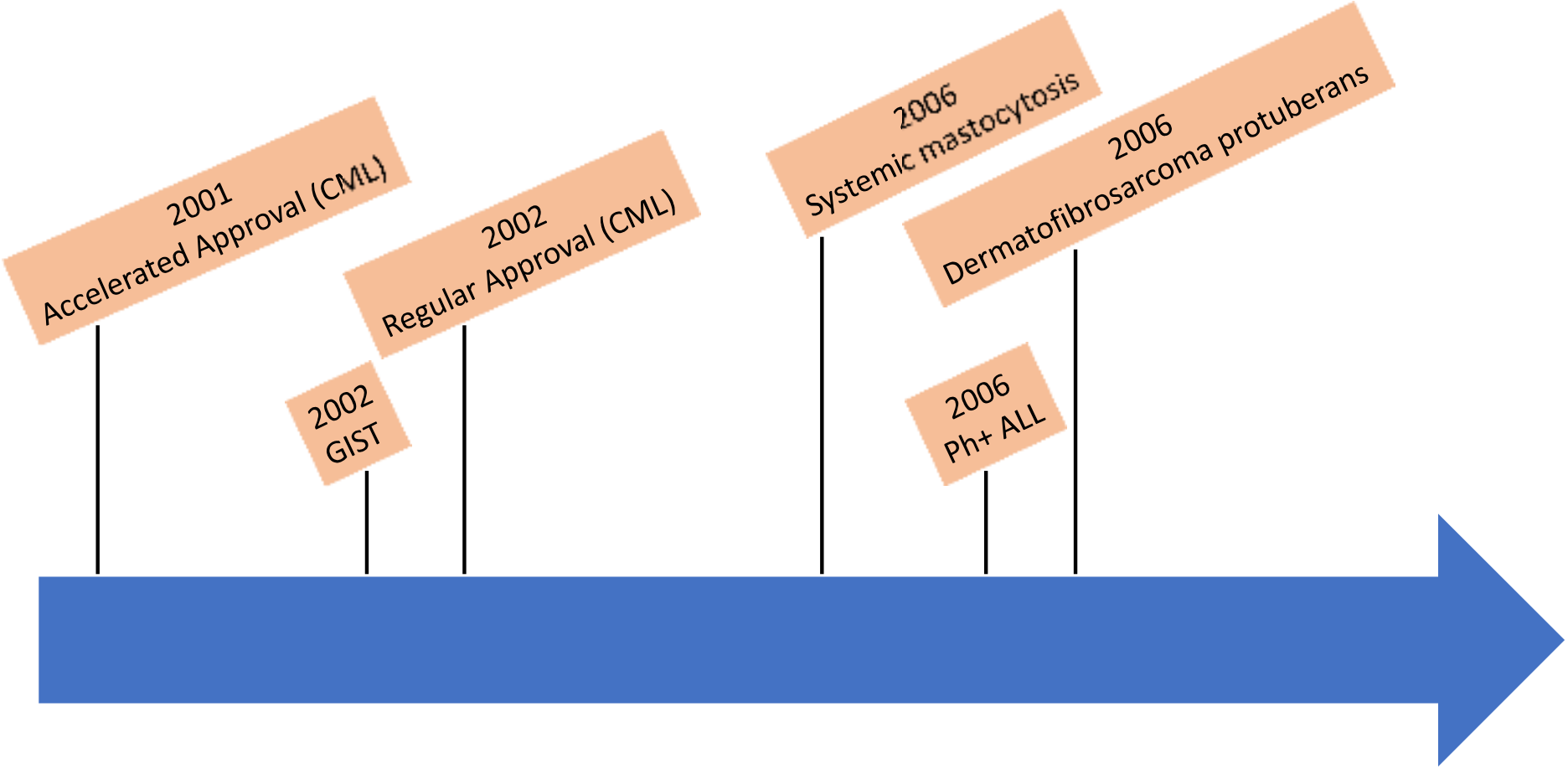

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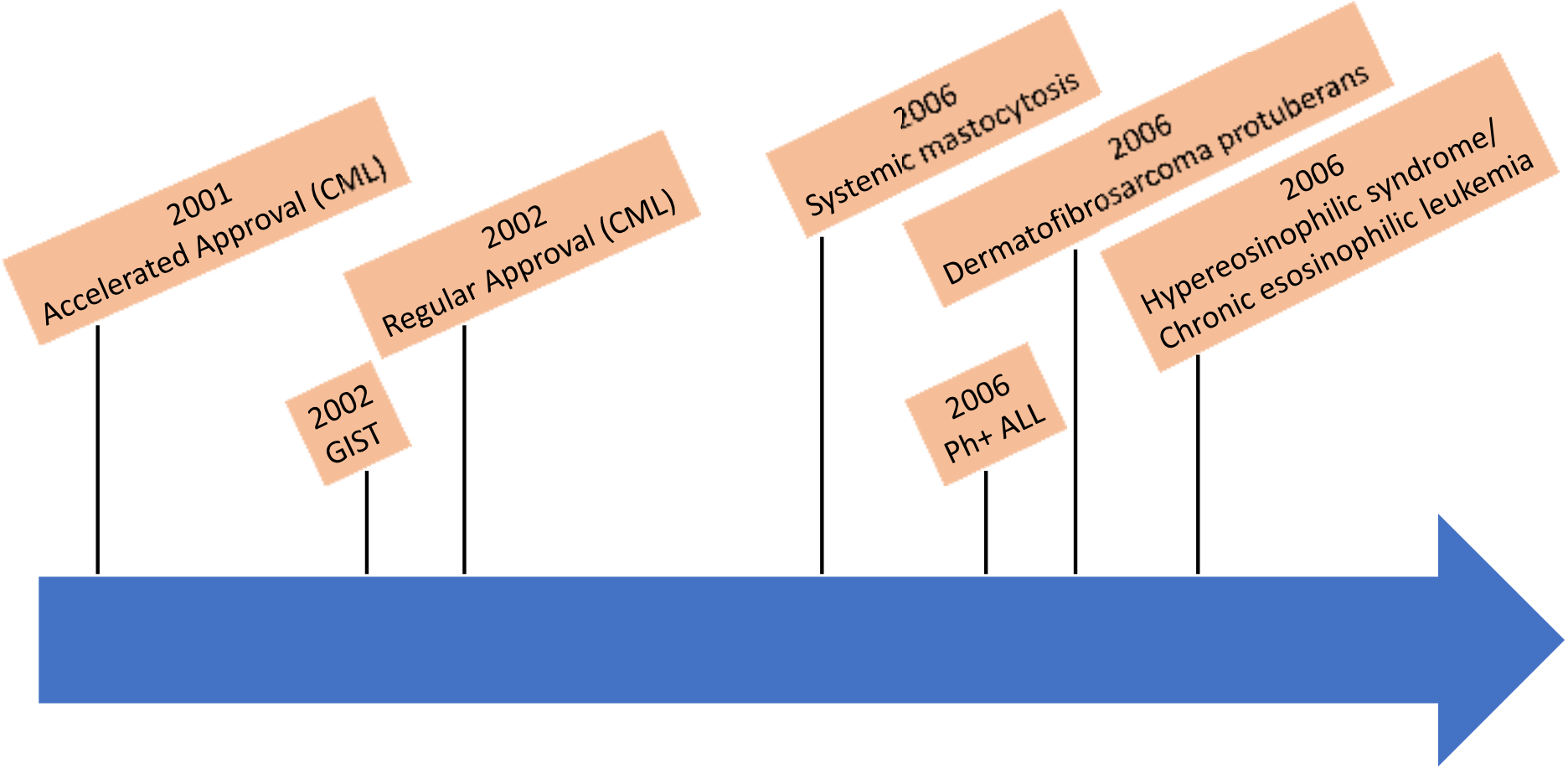

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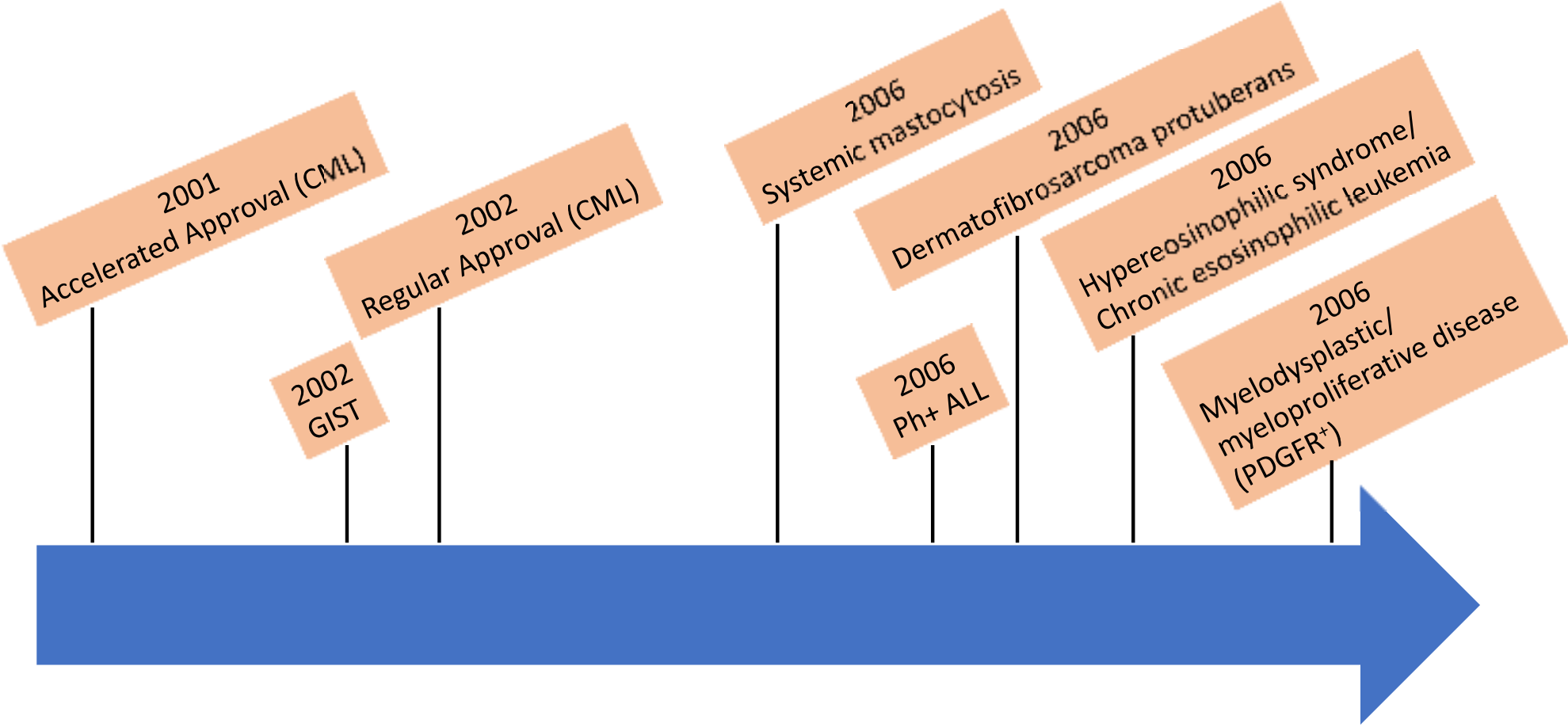


Pembrolizumab FDA-Approved Uses

2014

- Metastatic Melanoma
  - Prior ipilimumab
  - Prior BRAF inhibitor (if BRAF V600 mutation positive)

2024

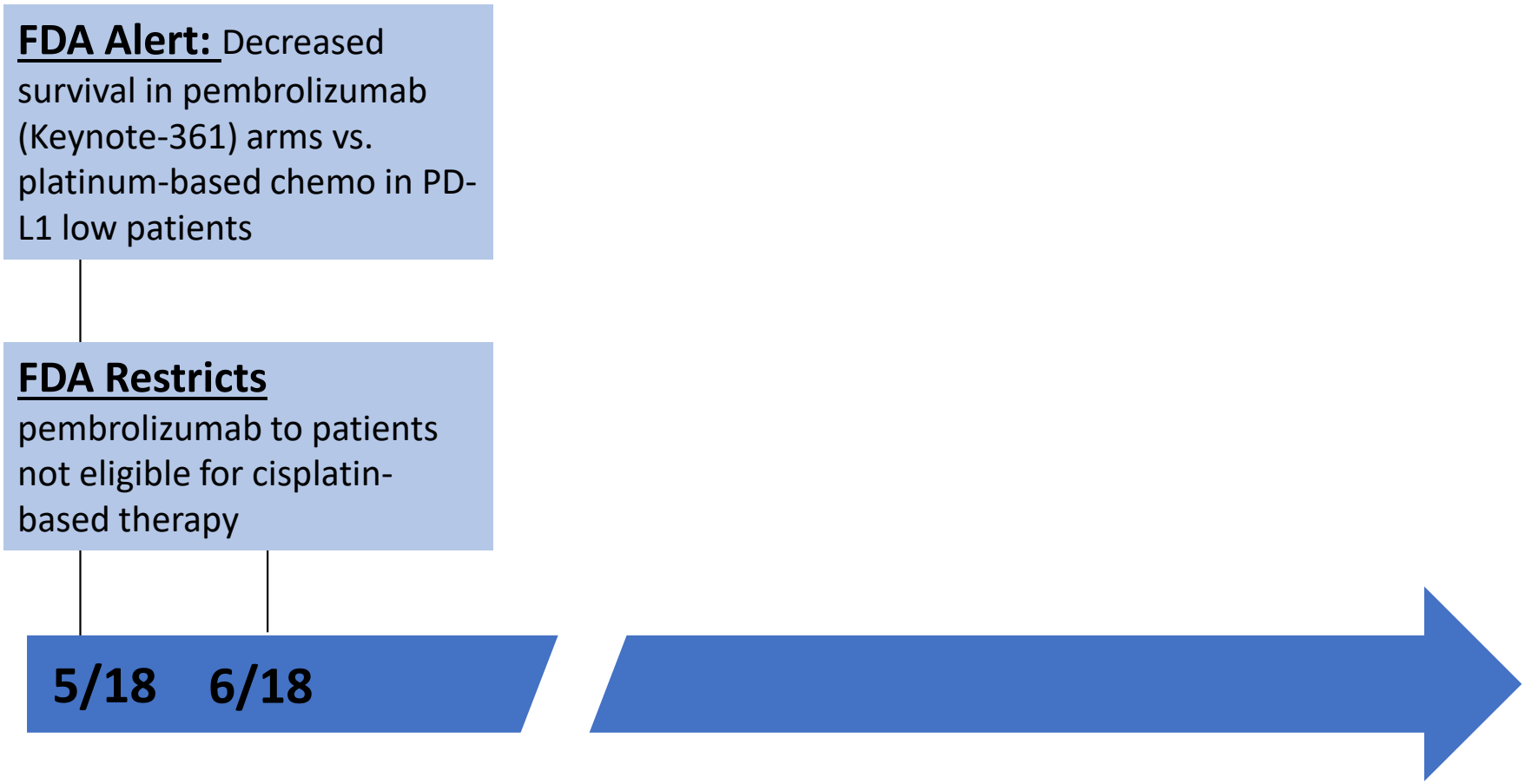
- Melanoma
- NSCLC
- Head/Squamous Cell Cancer
- Hodgkin Lymphoma
- Primary Mediastinal B-Cell Lymphoma
- Urothelial Cancer
- MSI-h/MMRd Cancer
- MSI-h/MMRd Colorectal Cancer
- Gastric Cancer
- Esophageal Cancer
- Cervical Cancer
- Hepatocellular Cancer
- Biliary Tract Cancer
- Merkel Cell Carcinoma
- Renal Cell Carcinoma
- Endometrial Cancer
- TMB-h Cancer
- Cutaneous Squamous Cell Carcinoma
- TNBC

Pembrolizumab Evolution in Bladder Cancer

FDA Alert: Decreased survival in pembrolizumab (Keynote-361) arms vs. platinum-based chemo in PD-L1 low patients

5/18

Pembrolizumab Evolution in Bladder Cancer



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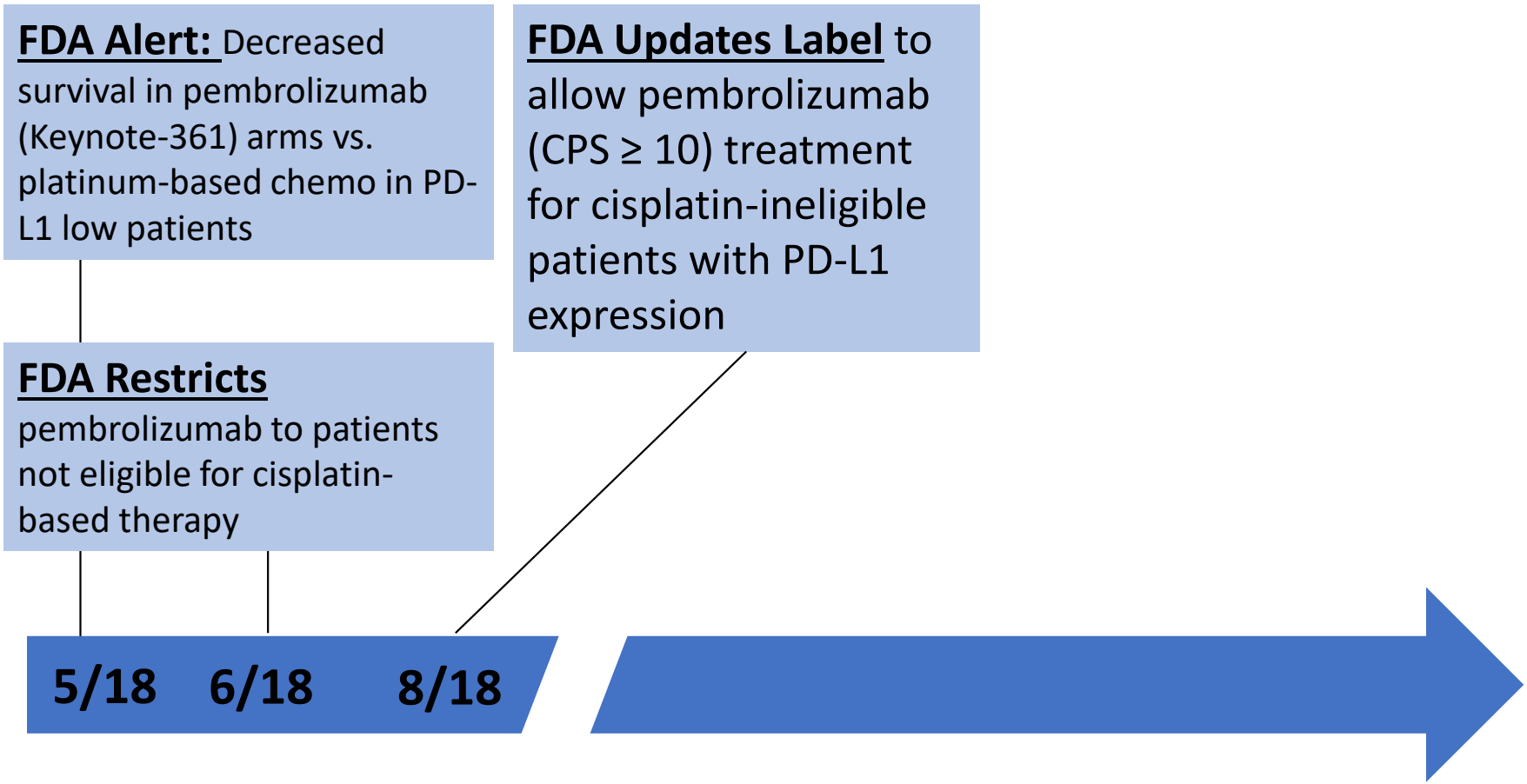

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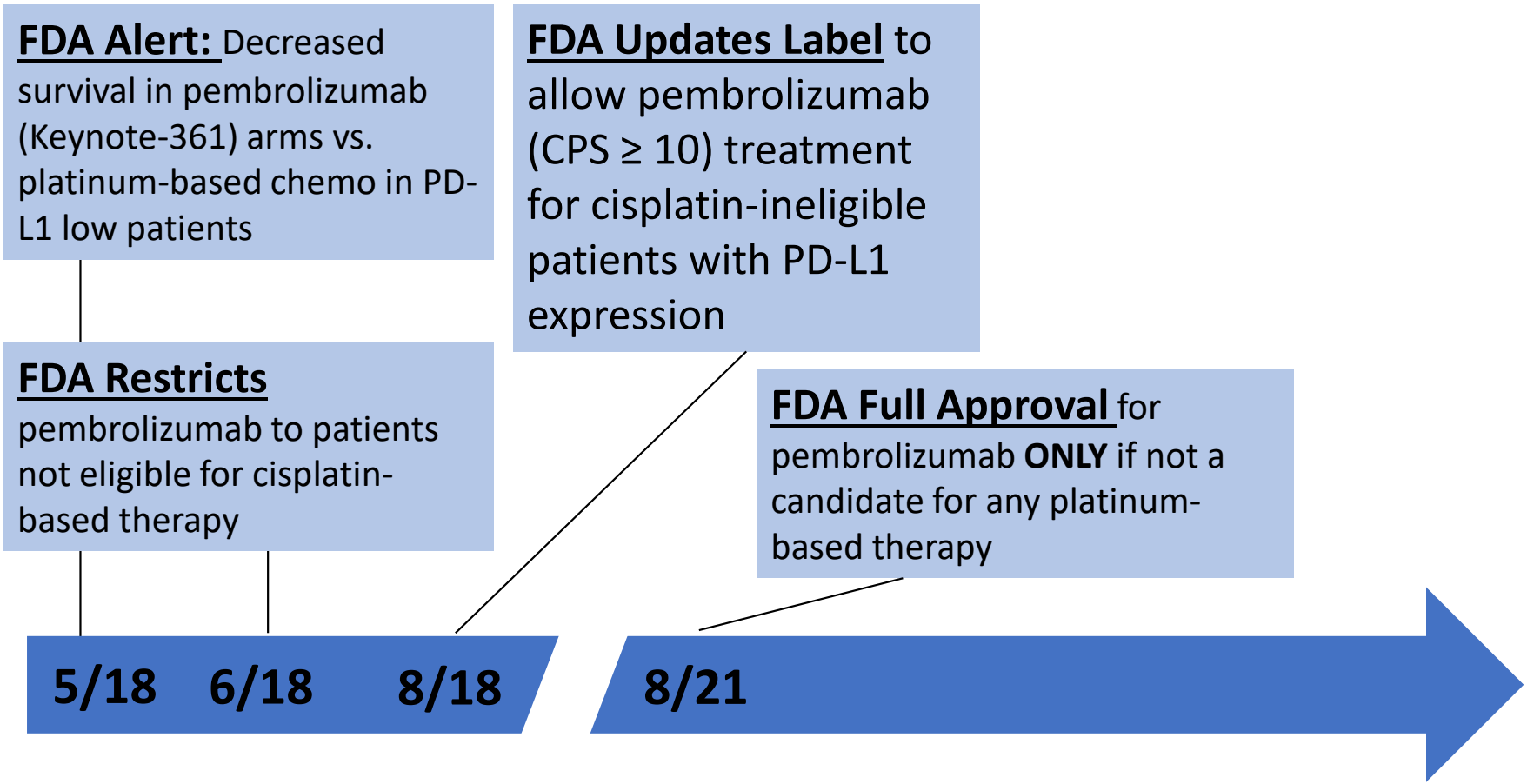

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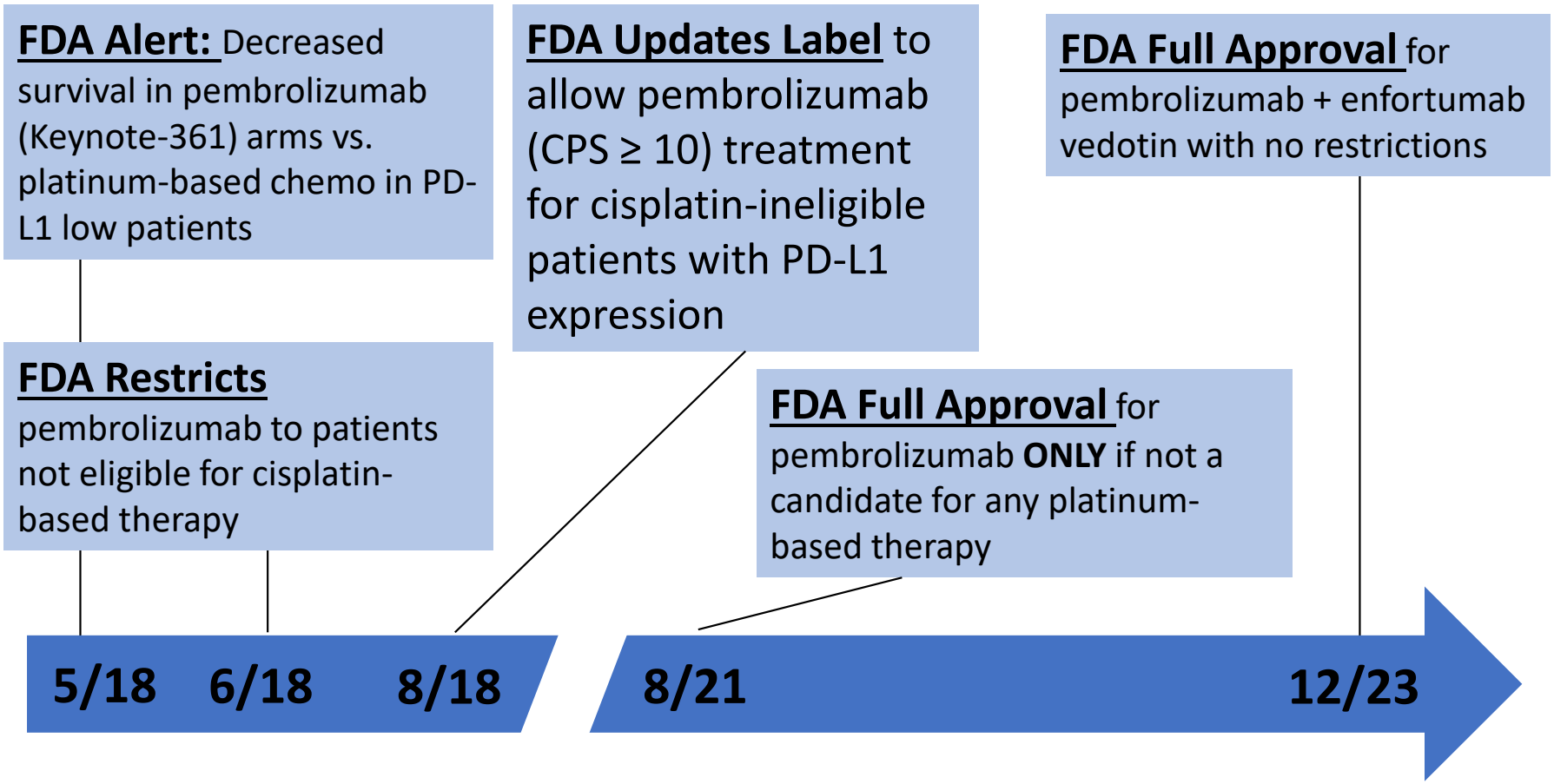

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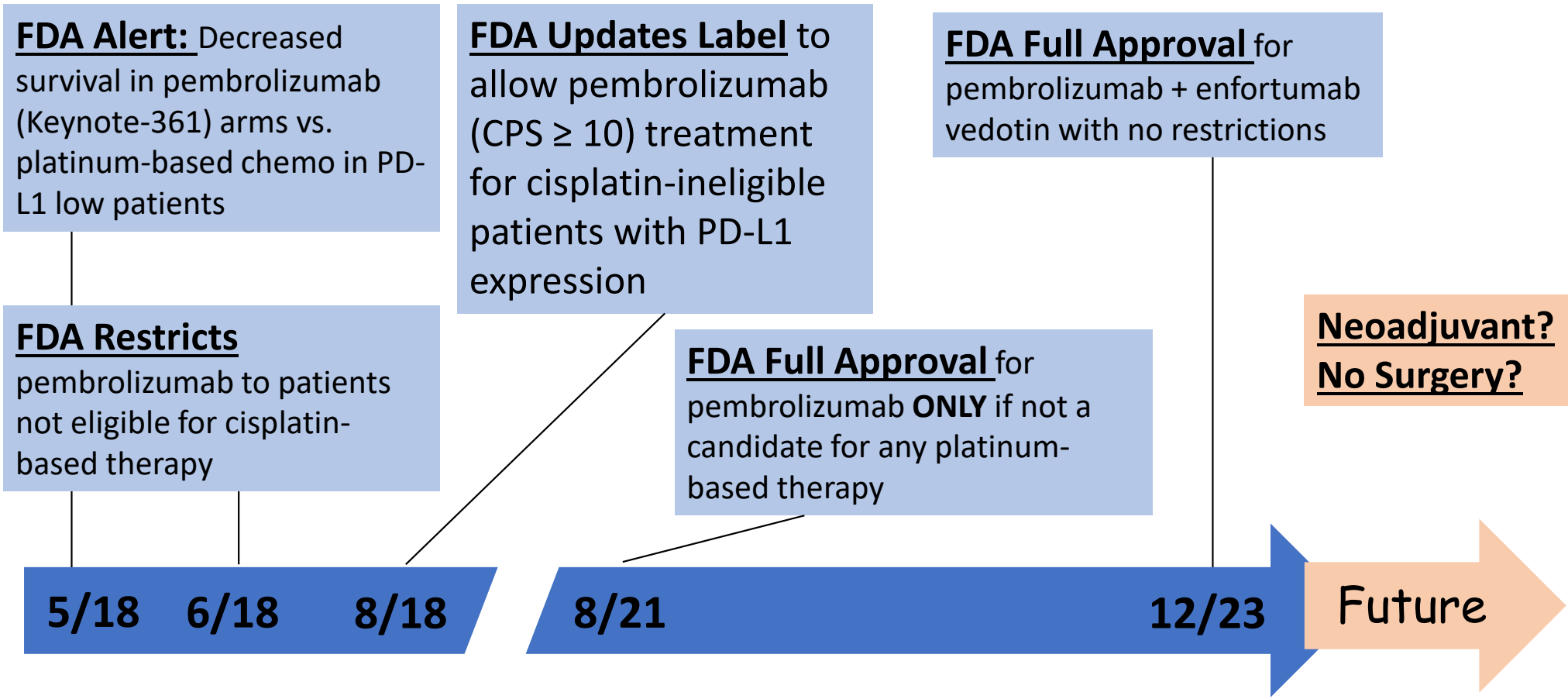

How confident are we in PD-L1 as a biomarker for ICIs?

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Not All Pieces Are Equal

Chapter 4

Olaparib Phase I Study

- BRCA Mutated Ovarian Cancer
  - 200 mg BID or higher
  - ORR = 63.6% (n = 11)
- BRCA Wild Type (solid tumors)
  - ORR = 0% (n = 38)

Fong PC, et al. N Engl J Med 2009;361:123-34.

Olaparib Phase I Study

- BRCA Mutated Ovarian Cancer
  - 200 mg BID or higher
  - ORR = 63.6% (n = 11)

- Hype!

- BRCA Wild Type (solid tumors)
  - ORR = 0% (n = 38)

- Strong evidence PARPi benefit limited to BRCA-mutated

Fong PC, et al. N Engl J Med 2009;361:123-34.

CLL Puzzle Pieces

Drug A: Phase I/II Data

- Overall response rate = 72%
  - PR = 72%
  - CR = 0%

Drug B: Phase I/II Data

- Overall response rate = 71%
  - PR = 67%
  - CR = 4%

Byrd JC, et al. N Engl Med 2013;369(1):32-42
Brown JR, et al. Blood 2014;123(22):3390-3397

CLL Puzzle Pieces

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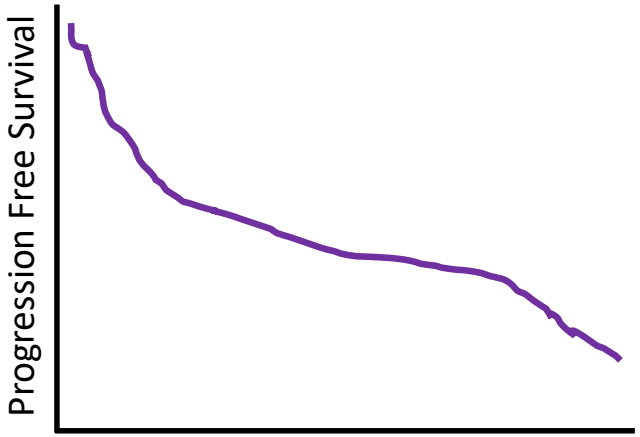

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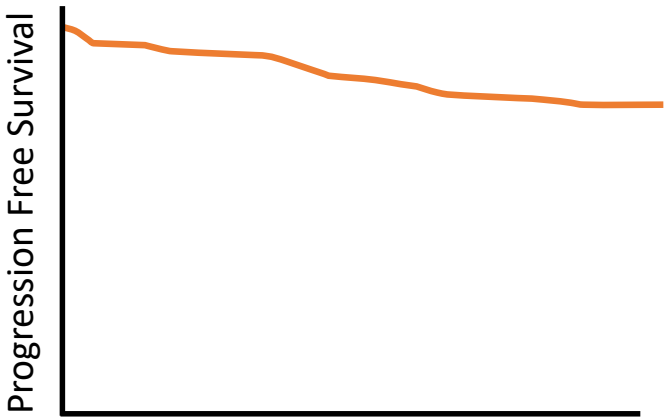

Byrd JC, et al. N Engl Med 2013;369(1):32-42
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CLL Puzzle Pieces

Idelalisib

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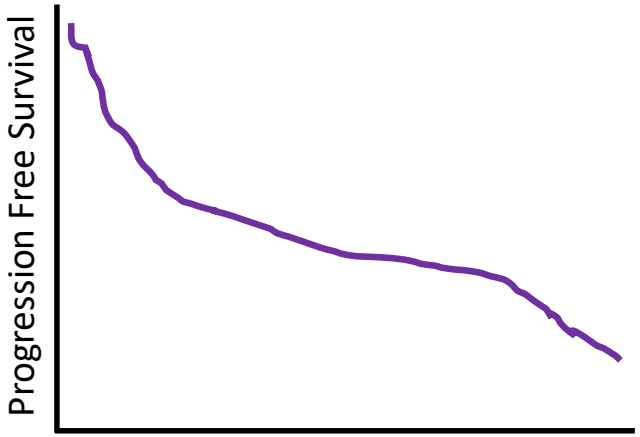

Ibrutinib

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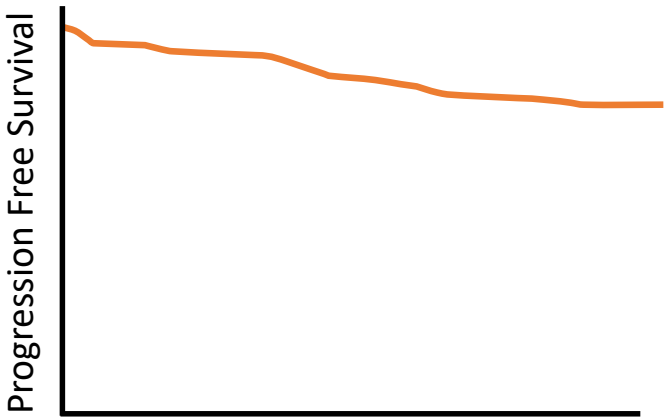
  - CR = 4%



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Olaratumab's Story: Phase II Hype

- Phase II Soft Tissue Sarcoma

  - Median PFS
    - DO: 6.6 months
    - D: 4.1 months
    - HR 0.672, 95% CI, 0.442-1.021
  - Median OS
    - DO: 26.5 months
    - D: 14.7 months
    - **HR 0.463**, 95% CI, 0.301-0.710

Tap WD, et al. Lancet 2016:388:488-497
Tap WD, et al. JAMA 2020:323:1266-1276

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Doxorubicin + olaratumab **1:1** Doxorubicin + placebo

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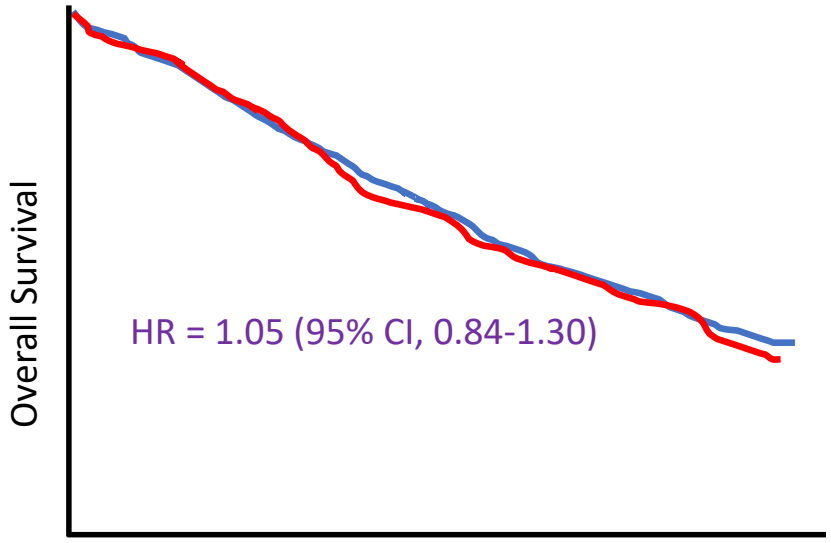

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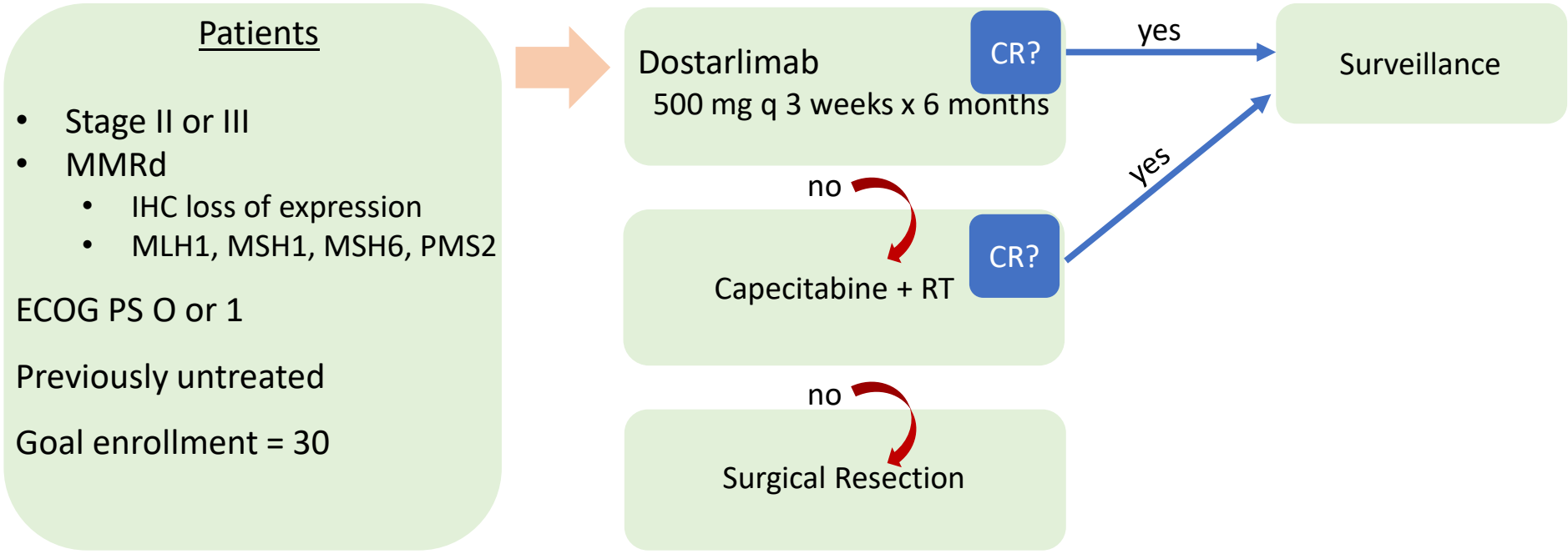
Dostarlimab in dMMR Rectal Cancer: More Phase II Hype

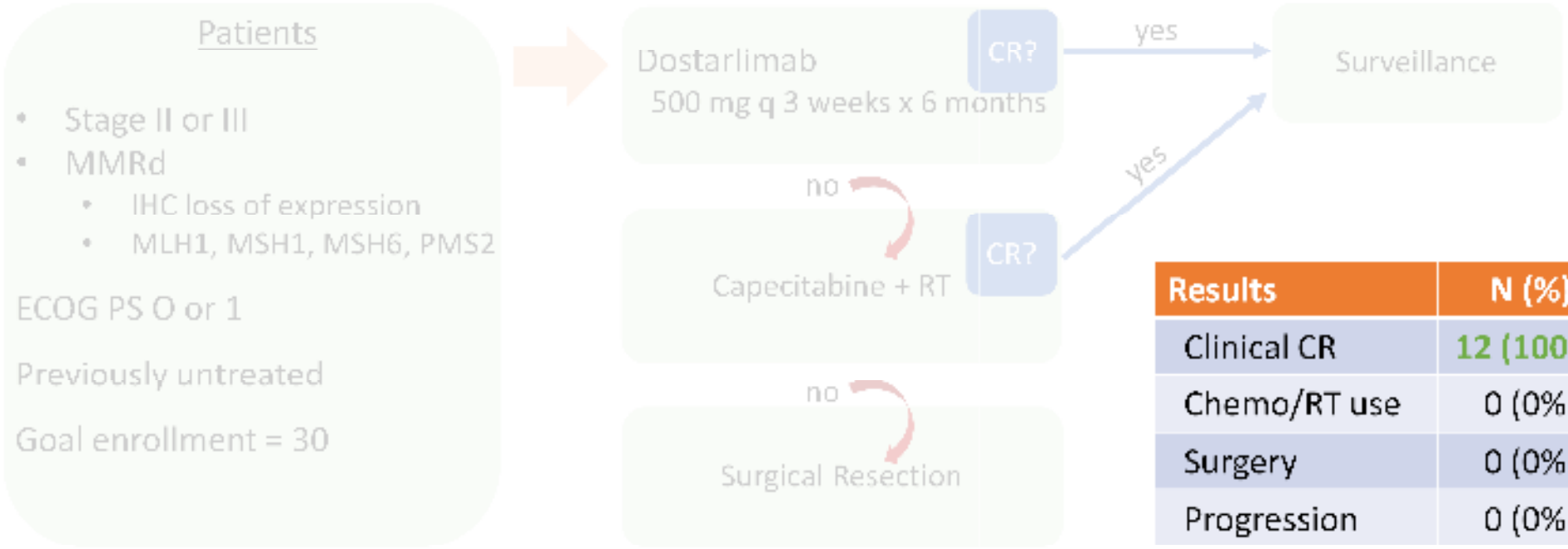


5-10% of rectal cancers may be dMMR

CR, complete response: no residual disease on digital & endoscopic exam & MRI

Cerek A, et al. N Engl J Med 2022;386:2263-2376

Dostarlimab in dMMR Rectal Cancer: More Phase II Hype



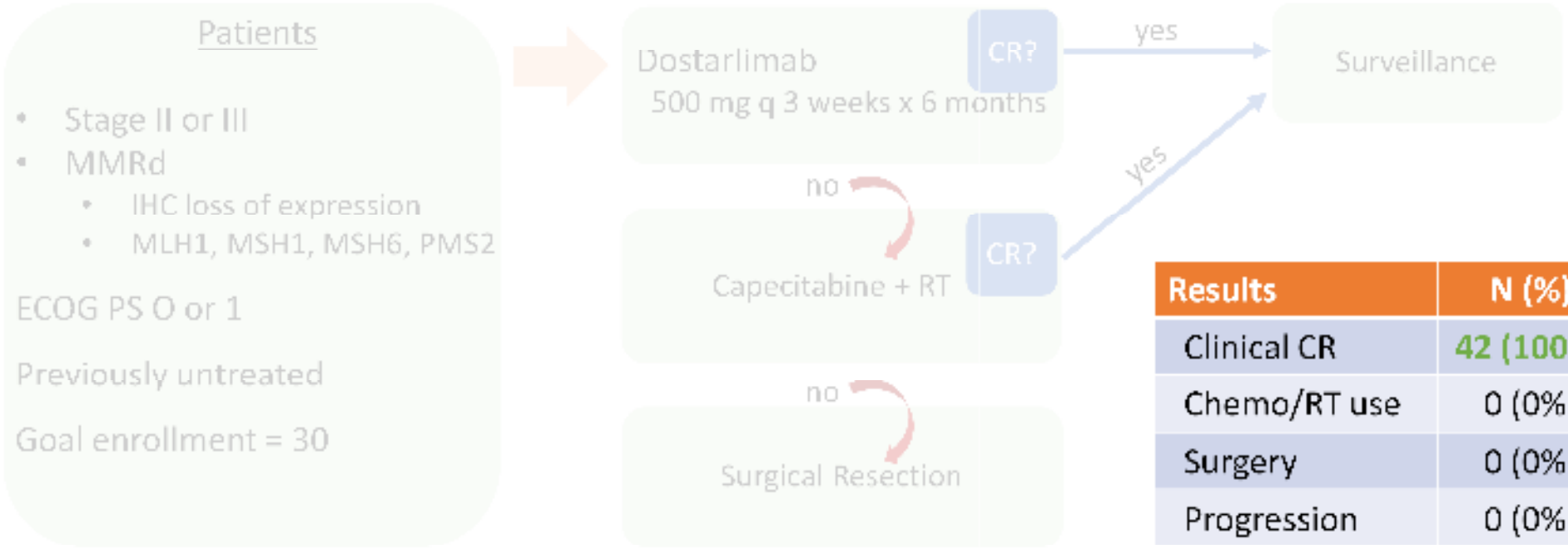
Results	N (%)
Clinical CR	12 (100%)
Chemo/RT use	0 (0%)
Surgery	0 (0%)
Progression	0 (0%)

5-10% of rectal cancers may be dMMR

CR, complete response: no residual disease on digital & endoscopic exam & MRI

Cercek A, et al. N Engl J Med 2022;386:2263-2376

Dostarlimab in dMMR Rectal Cancer: More Phase II Hype



Results	N (%)
Clinical CR	42 (100%)
Chemo/RT use	0 (0%)
Surgery	0 (0%)
Progression	0 (0%)

5-10% of rectal cancers may be dMMR

CR, complete response: no residual disease on digital & endoscopic exam & MRI

Cercek A, et al. J Clin Oncol 42, 2024 (suppl 17; LBA3512)

Don’t Force the Pieces to Fit…

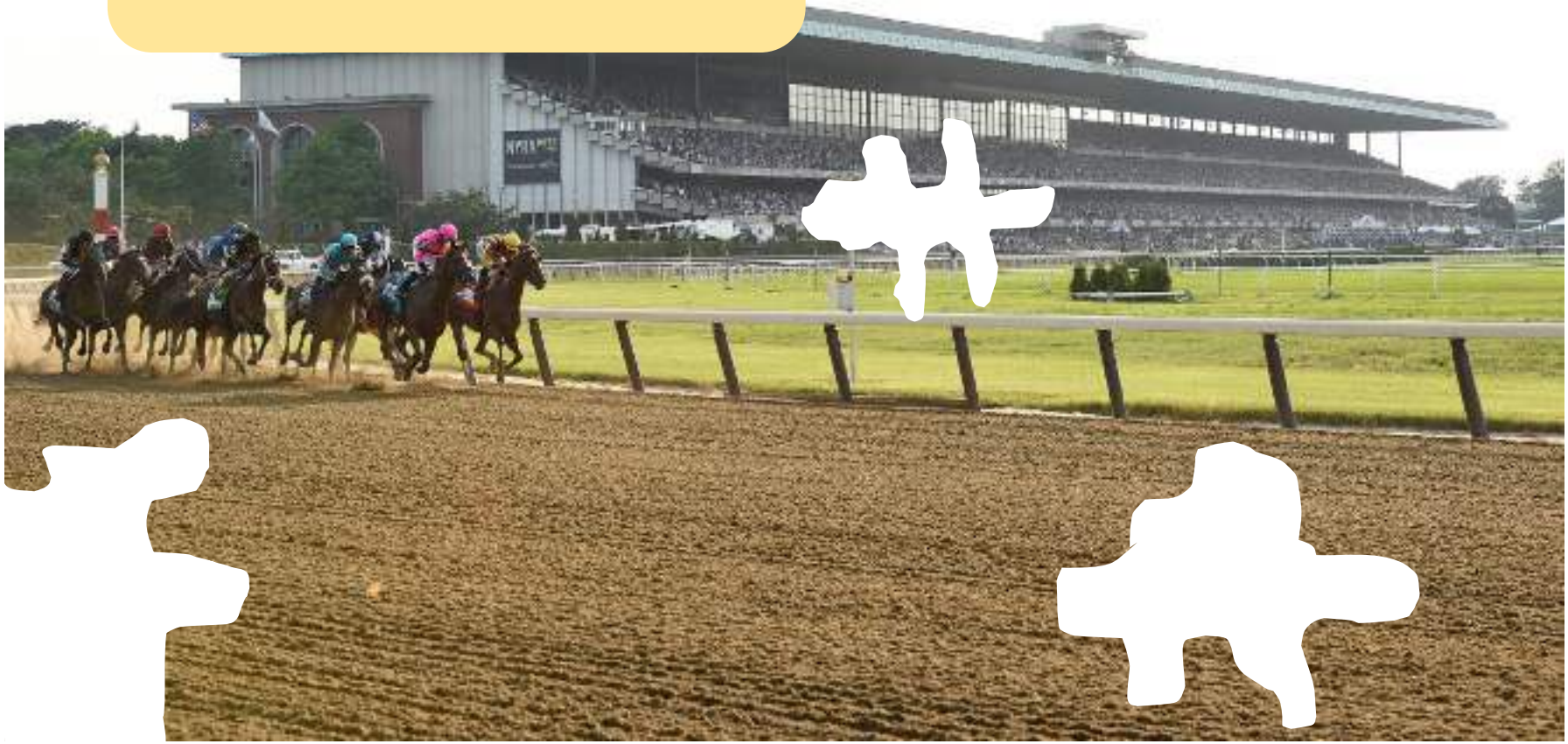
- Common Pitfalls when evaluating new evidence
  - Overvaluing surrogate endpoints
  - Overvaluing phase II data (or similar small *n* studies)
  - Acceptances of control arm as “standard of care”

How to keep track of all the new puzzle pieces?

- Email Table of Contents (eTOC)
  - Title > Abstract > Skim > Deep Dive
- Podcasts
- Professional Meetings
- Social Media

- **Active** Reading of Clinical Trial Publications
  - Control arm appropriateness/history, baseline demographic composition
  - Reference mining, introduction critiques, awareness of author “damage control” or spin

Who wins?



Questions?

Epi	Pen	Dauno	Ret
Ice	Ida	Chop	Axl
Carb	Met	Matrix	Mono
Vegfr	Doxo	Ceph	Epoch

Questions?

Beta-lactam class prefixes

_____ rubicin

Lymphoma regimens

Cabozantinib targets