FDA Review

NDA 22-374

Omapro™ (omacetaxine mepesuccinate)

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NDA 22-374

- Proposed indication

  Omapro is indicated for the treatment of adults with chronic myeloid leukemia who have had failure on prior therapy with imatinib and have the Bcr-Abl T315I mutation.

- Efficacy basis for the application

  Response rate in each disease phase from one single-arm trial (CML-202) in 66 patients with T315I mutation

Outline of Presentation

- Background Information
- Key regulatory history milestones
- Pivotal trial CML-202
- Major Issues
- FDA review results
  - Efficacy
  - Safety
- Questions to ODAC

Main Concerns with this NDA

- Small and incomplete efficacy trial
- Uncertainty in response determination and duration
- Uncertain clinical meaningfulness of response rates
- Assays for detection of T315I mutation
  - Multiple assay methods
  - Patient enrollment without mutation confirmation
- Safety concerns with overfilled vial size
  - Potential for overdose
  - Environmental concerns

Omacetaxine (homoharringtonine)

- Omacetaxine is a New Molecular Entity (NME) and first in class of cephalotaxines
- Under clinical development in the U.S. since 1981
- Cardiac toxicity with intravenous administration

Mechanism of Action

- Reversible inhibitor of protein elongation
- Transient inhibition of peptide synthesis, selectively impacting short-lived proteins
- Does not directly inhibit Bcr-Abl protein or T315I mutation

CML Treatment

Imatinib

- AA 2001: 2nd-line after IFN failure
  - Chronic phase : 49% MCyR[1]; duration NA
  - Accelerated phase: 21% MCyR + 63% HR[2]; duration NA
  - Blast phase: 13.5% MCyR + 26% HR; duration NA
- AA 2002: newly-diagnosed CP-CML
  - Chronic phase : 97.2% PFS at 12 months
    75.8% MCyR , median follow-up 14 mo
- RA 2003: newly-diagnosed CP-CML
  - Chronic phase 87.3% PFS at 30 mo
    85.2% MCyR

[1]MCyR: CCyR+PCyR
[2]HR: CHR + NEL + RCP

Imatinib Failure

- **Dasatinib**
  - AA 2006: 2nd-line after imatinib resistance/intolerance
    - CP (n=167): 63% MCyR + 92% CHR; median duration 5.6 months
    - AP (n=158): 39% MCyR + 66% MaHR; median duration 5.5 months
    - BP (n= 75): 28% MCyR + 28% MaHR; median duration 3.5 months
  - RA 2009: duration of follow-up 24 months from previous studies
- **Nilotinib**
  - AA 2007: 2nd-line after imatinib resistance/intolerance
    - CP (n=232): 40% unconfirmed MCyR; minimum follow-up 6 months
    - AP (n=105): 26% MaHR; minimum follow-up 4 months

[1]MCyR: CCyR+PCyR
[2]MaHR: CHR + NEL

Single-arm Trials

- Reliance on historical data for efficacy comparisons
- Questionable homogeneity of patient population
- Difficulty in evaluating safety due to lack of comparator
- Difficulty in assessing risk benefit ratio

Key Regulatory Milestones

- 04/2001: IND activated
- 2006: Orphan drug designation and fast track designation granted
- 12/2006: Meeting with the Applicant to discuss registration trial CGX-635-CML-202
  - 2.5% lower bound of 95% CI for RR too low to estimate sample size
  - Primary endpoints:
    - CP: MCyR
    - AP/BP: MaHR (CHR + NEL) + MCyR

Key Regulatory Milestones

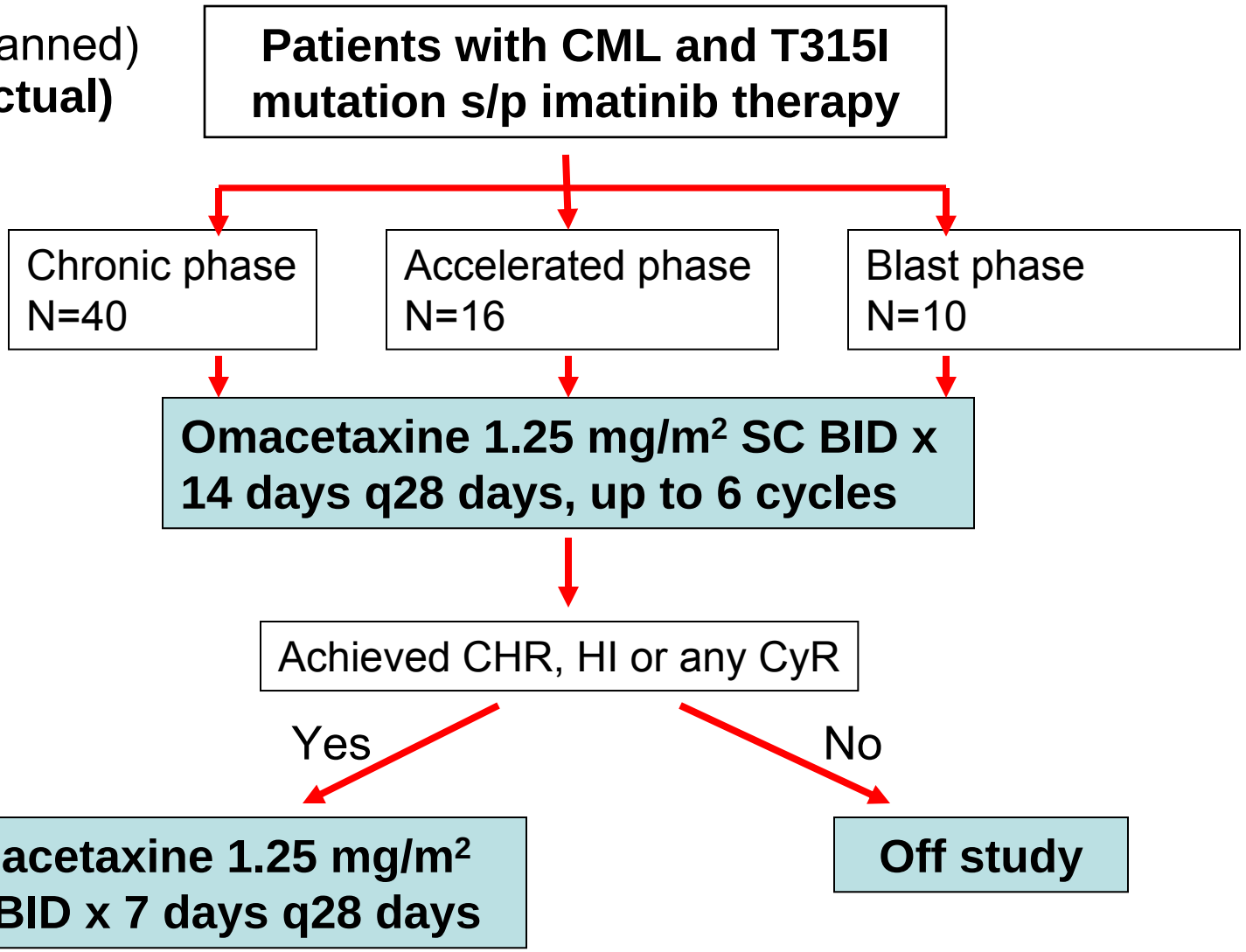
- 03/2008: EOP2 meeting
  - CP cohort of 24 patients too small for an efficacy claim
  - CHR is secondary, supportive endpoint in CP
- No SPA agreement
- 03/2009: Pre-NDA meeting
  - Applicant must demonstrate safety and efficacy separately for each disease phase

CGX-635-CML-202

A Phase II Open-Label Study of the Subcutaneous Administration of Omacetaxine (CGX-635) in the Treatment of Patients with Chronic Myeloid Leukemia (CML) with the T315I Bcr-Abl Gene Mutation.

Study 202 Design

N = 100 (Planned)
66 (Actual)



Study 202: Key Inclusion Criteria

- Ph+ CML in chronic, accelerated or blast phase with loss of hematologic or cytogenetic response on current or most recent therapy
- Presence of the T315I Bcr-Abl gene mutation
- Prior imatinib therapy failure
- Hydroxyurea permitted immediately prior to and during the first two cycles for patients with rapidly proliferating disease

Required Assay Performance Characteristics

- Specimen selection and storage
- Sensitivity and Specificity
- Reproducibility (especially near cut-off)
- Proportion of patient near cut-off
- Clinical significance of rare versus prevalent T315I load for drug effect

T315I Mutation Testing

- Two central laboratories with different methodologies
  - University of Texas MDACC, Houston, TX
    qRT-PCR and rapid pyrosequencing
  - Medizinische Universitätsklinik, Mannheim, Germany
    Denaturing high-performance liquid chromatography
- No bridging study for these two assays
- 23 (35%) of patients enrolled did not have central laboratory confirmation of mutation at enrollment

Study 202: Endpoints

- Primary endpoints
  - Chronic phase:
    - Complete hematologic response
    - Major cytogenetic response
  - Accelerated/Blast phases:
    - Complete hematologic response
    - No evidence of leukemia (NEL)
    - Return to chronic phase (RCP)
    - Major cytogenetic response

Cytogenetic Response Criteria

- Cytogenetic response
  - Complete cytogenetic response: 0% Ph+ cells
  - Partial cytogenetic response: 1-35% Ph+ cells
- **Response to be confirmed by repeat cytogenetics of the bone marrow aspirate**

Complete Hematologic Response Criteria

Chronic phase

- WBC < 10 × 10^9/liter
- Platelets < 450 × 10^9/liter
- Myelocytes + metamyelocytes < 5% in blood
- No blasts or promyelocytes in blood
- < 20% basophils in blood
- No extramedullary disease

Complete Hematologic Response Criteria

- Accelerated phase/Blast phase
  - Absolute neutrophil count ≥ 1.5×10^9/liter
  - Platelets ≥ 100×10^9/liter
  - No blood blasts
  - Bone marrow blasts < 5%
  - No extramedullary disease
- Basophils <20% in PB not included in criteria

Complete Hematologic Response Criteria

"For the CML-CP patients, only the peripheral hematologic results were necessary for assessment of response; for CML-AP and CML-BP patients, both the peripheral blood and bone marrow assessments were necessary in order to be meaningful."

Primary Endpoint Evaluations

- Clinical evaluation
- Bone marrow aspirate/biopsy
- Complete blood count

Response Adjudication

- An independent DMC adjudicated all responses included for the primary analysis
- The DMC assessed hematologic response based on all available hematology data (rather than at end of a study cycle)

CML-202 Results

Study 202-Previous TKI Therapy

Cohort	Chronic N=40	Accelerated N=16	Blast N=10	Total N=66
1 TKI (%) (imatinib only)	12 (30)	1 (6.3)	1 (10)	14 (21.2)
2 TKIs* (%)	20 (50)	8 (50)	6 (60)	34 (51.5)
3 TKIs (%)	6 (15)	6 (37.5)	3 (30)	15 (22.7)
>3 TKIs (%)	2 (5)	1 (6.3)	0	3 (4.5)

*May include dasatinib, nilotinib, bosutinib, other investigational TKIs

Study 202: Bcr-Abl T315I Mutation Confirmed by Central Reference Lab at Enrollment

	Chronic N=40	Accelerated N=16	Blast N=10	Total N=66
Yes (%)	28 (70)	8 (50)	7 (70)	43 (62.5)
No (%)	7 (17.5)	3 (18.8)	1 (10)	11 (16.7)
Not done (%)	5 (12.5)	5 (31.3)	2 (20)	12 (18.2)

Patients without T315I Mutation Confirmation

Cohort	Negative	Poor quality sample	Not collected	Lost/broken
Chronic phase	5	4	3	0
Accelerated phase	4	1	3	0
Blast phase	1	0	1	1
Total (n=23)	**10**	**5**	**7**	**1**

Main Concerns with the Assays

- Multiple assay methods
  - No “bridging” study to establish the threshold for positivity
  - Unknown false positive/negative rates
- Undefined population in study CML 202
- Patients with false positive results not receiving effective therapies for imatinib-resistant or intolerant disease

CML-202 Efficacy Results

Main Concerns with the Efficacy

- Small sample size
- Uncertainty in response determination and duration
- Uncertain clinical meaningfulness of response rates
- T315I mutation status

Study 202: Response in Chronic Phase

Chronic N=40	Response per Applicant	Response per FDA
CCyR	6* (15%)	4 (10%)
PCyR	4* (10%)	2 (5%)
MCyR	10 (25%)	6 (15%)
Median duration (months)	6.0	7.7
Min, Max	2.1, 14.1	2.1, 14.1

*2 CCyRs and 2 PCyRs unconfirmed

Efficacy Issues – Chronic Phase

- 2/6 CCyRs unconfirmed by repeat BM
- 2/4 PCyRs were unconfirmed
  - 1 unconfirmed by repeat BM
  - 1 patient had 100% Ph+ cells on next BM evaluation

Study 202: Response in Accelerated Phase

Accelerated N=16	Response per Applicant	Response per FDA
CCyR	1 (6.3%)	1 (6.3%)
PCyR	0	0
CHR	5 (31.3%)	5 (31.3%)
NEL	0	0
RCP	1 (6.3%)	NA
Median duration of hematologic response (months)	6.6	5.1
Min, Max	0.9, 14.8	0.9, 14.8

Efficacy Issues – Accelerated Phase

- Adjudicated complete hematologic responses without confirmed BM evaluations
- Adjudicated complete hematologic responses while basophils >20%

Study 202: Response in Blast Phase

Blast N=10	Response per Applicant	Response per FDA
CCyR	0	0
PCyR	0	0
CHR	2 (20%)	0
NEL	0	0
RCP	1 (10%)	NA
Median duration of hematologic response (months)	2.2	NA
Min, Max	1.2, 4.4	NA

Efficacy Issues – Blast Phase

- Complete hematologic responses not confirmed with BM evaluations
- Extramedullary disease was not recorded as resolved at the time of the adjudicated response

Responders without T315I Mutation Confirmation

Phase	Response	Central lab result
Chronic	confirmed CCyR	No sample sent
Chronic	confirmed CCyR	Poor quality sample
Accelerated	confirmed CCyR	Negative
Accelerated	confirmed CHR	Poor quality sample
Accelerated	confirmed CHR	No sample sent

Efficacy Summary

- Omacetaxine
  - CP (n=40): 15% MCyR
  - AP (n=16): 6.3% MCyR and 31.3% CHR
  - BP (n=10): 0

- Dasatinib
  - CP (n=167): 63% MCyR + 92% CHR
  - AP (n=158): 39% MCyR + 66% MaHR
  - BP (n= 75): 28% MCyR + 28% MaHR
- Nilotinib
  - CP (n=232): 40% unconfirmed MCyR
  - AP (n=105): 26% MaHR

Safety Results

Study Group 2

	CML-202 (n=66)	CML-203 (n=65)	Total (n=131)
Chronic Phase	40	30	70 (53%)
Accelerated Phase	16	20	36 (27%)
Blast Phase	10	15	25 (19%)

Drug Exposure

	CML-202 and CML-203 Studies (Study Group 2)			
	CP-CML (n=70)	AP-CML (n=36)	BP-CML (n=25)	Combined (n=131)
Duration of exposure (months)				
Mean (SD)	9.4 (7.6)	4.9 (5.9)	2.6 (3.1)	6.9 (7.0)
Median	8.0	2.7	1.7	4.5
Min-Max	0.3-34.6	0.5-21.4	0.1-14.0	0.1-34.6
Total number of cycles				
Mean (SD)	8 (6.7)	5 (5.4)	3 (2.4)	6 (6.2)
Median	6	3	2	4
Min-Max	1-31	1-29	1-12	1-31

Most Common Gr 3-4 TEAEs

AE	CML Disease Phase		
	Chronic (n=70)	Accelerated (n=36)	Blast (n=25)
Thrombocytopenia	66%	47%	36%
Neutropenia	50%	14%	24%
Anaemia	44%	28%	16%
Febrile neutropenia	9%	14%	20%
Leukopenia	20%	6%	0
Lymphopenia	20%	0	0
Bone marrow failure	14%	0	0
Fatigue	4%	11%	8%
Diarrhoea	1%	11%	8%
Pancytopenia	4%	8%	4%

Cardiovascular TEAEs

	# of events	# of patients (n=131)
Cardiac Events	**44**	**26 (20%)**
Rhythm abnormality	37	21 (16%)
Other cardiac event	7	5 (4%)
Vascular Events	**39**	**27 (21%)**
Hypotension	8	7 (5%)
Other vascular event	31	20 (15%)

Arrhythmias

AE	Outcome	SAE	Grade	Action required	CML Phase
Arrhythmia	Fatal	Y	5	Hospitalization	BP
Arrhythmia	Resolved	Y	4	Hospitalization	BP
Extrasystoles	Resolved	Y	2	Medication Required	CP
Tachycardia	Not resolved	N	3	Medication Required	BP
Sinus tachycardia	Resolved	N	2	Medication Required	BP
Atrial fibrillation	Resolved	N	2	Medication Required	BP

Hypotension

#	AE	Outcome	SAE	Grade	Action required	CML Phase
1	Hypotension	Resolved	N	1	None	BP
1	Hypotension	Not Resolved	N	3	Non-Drug therapy	BP
2	Orthostatic hypotension	Not Resolved	N	1	Non-Drug therapy	CP
3	Orthostatic hypotension	Resolved	N	1	None	BP
4	Hypotension	Resolved	N	2	None	CP
5	Hypotension	Resolved	Y	2	Hospitalization	BP
6	Hypotension	Resolved	N	2	Non-Drug therapy	BP
7	Hypotension	Not Resolved	N	2	None	CP

Hyperglycemia

- 64 (49%) patients had rising blood glucose
  - Normal at baseline
    - 2 had a grade 3 event
    - 5 had grade 4 event
- 16 TEAEs
  - 11 (8%) patients
    - 7 CP, 3 AP, 1 BP
    - 3 grade 2
    - 3 grade 3
  - 6 required “medication”

Hyperbilirubinemia

- 47 (36%) patients with rising bilirubin
  - Maximum CTCAE toxicity
    - 15 Grade 2
    - 7 Grade 3
    - 4 Grade 4
  - Improved/resolved in most patients
- 11 (8%) patients with reported TEAE
  - 1 subject with AP-CML developed liver failure
  - Patients was receiving posaconazole

Safety Issue: Overfilled Vial Size

- Applicant has developed product in 5-mg vials for single-dose use by patient at home
- Average dose in CML-202 was 2.4 mg
- Overdose potential
- Environmental impact of unused drug disposal

Main Concerns with this NDA

- Small, single-arm, incomplete efficacy trial
- Uncertainty in response determination and duration
- Uncertain clinical meaningfulness of response rates
- Safety concerns-overfilled vial

Main Concerns with this NDA: Assay Method Deficiencies

- 21 CFR 314.126: "The method of selection of subjects provides adequate assurance that they have the disease or condition being studied."
  - 35% of patients enrolled without mutation confirmation
  - 10/66 patients identified with T315I mutation at outside labs with negative results at central lab
  - 5/11 responders without T315I mutation confirmation at central laboratory
- Multiple assay methods for detection of T315I mutation
  - Lack of bridging studies between tests: reliability, reproducibility and concordance of results unknown
- Unreliable assays may falsely identify patients who would otherwise receive more effective and less toxic therapies

Companion Diagnostic Issues

NDA 22-374

Omapro™(omacetaxine mepesuccinate)

ODAC March 22, 2010

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BCR-ABL/T315I Testing

- BCR-ABL testing used to monitor CML
- For monitoring, how to standardize assays?
- Effect from tumor burden, mutation prominence?
- No test designed to guide OMAPRO™ therapy.

Companion Diagnostics

- Therapeutic decisions driven by single test results -- personalized medicine
- Enable specific therapeutic products to achieve their expected safety and efficacy
- FDA approved test needed for therapy-directing in vitro diagnostic claims
- Intent to optimize risk/benefit trade-offs

Performance of the Drug Depends on Performance of the Test

OMAPRO™ (omacetaxine mepesuccinate) is indicated for the treatment of adults with chronic myeloid leukemia who have failed prior therapy with imatinib, and have the Bcr-Abl T315I mutation.

- Given CML progression on imatinib, a T315I mutation can rule OMAPRO™ usage in or out.
- Clinical trade-offs:
  - Expecting resistance to other second line drugs, omit their use.
  - Accept the higher toxicity and the lesser therapeutic effect expected with OMAPRO™ compared to dasatinib or nilotinib.

Clinical Risks

- False positive T315I test: OMAPRO™ in lieu of other therapies expected to be effective after progression on imatinib
- False negative T315I test: Failure to treat with OMAPRO™
- Risks from ill-chosen positive/negative cut-off

Who are the T315I-Positive Patients?

- For accrual to the CML-202 trial:
  - "The patient will have the T315I BCR-ABL gene mutation."
- Assay: Various locally developed laboratory tests.
  - "Positive" result with any detectable T315I level (not standardized).
  - Retested to confirm positives at one of two central labs (each with its own test).
  - Mainly peripheral blood. (At least three were marrow samples.)

T315I Central Lab Tests Used

- MD Anderson, USA
  - Direct sequencing for mutations
  - Stated “sensitivity”: 1:10 cells
- Universitatsklinikum Mannheim, Germany
  - Denaturing high-performance liquid chromatography for mutation detection
  - Stated “detection limit”: 1:1000 cells

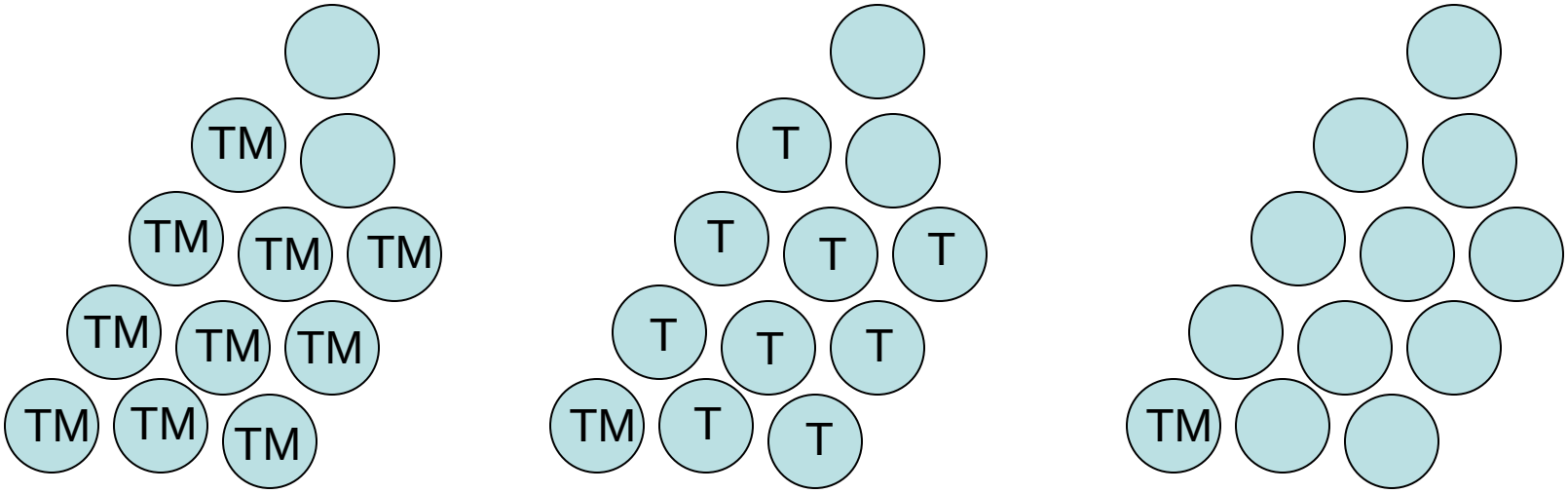
T315I Testing in Local Labs

- No specific information submitted
- Some methods with detection limit near 1:10 or 1:5 cells (like MD Anderson?)
- ARMS-based method (1:100 cells)
- Some methods more “sensitive” (1:1000 cells)
- Other performance characteristics?

T315I/ OMAPRO™ Questions

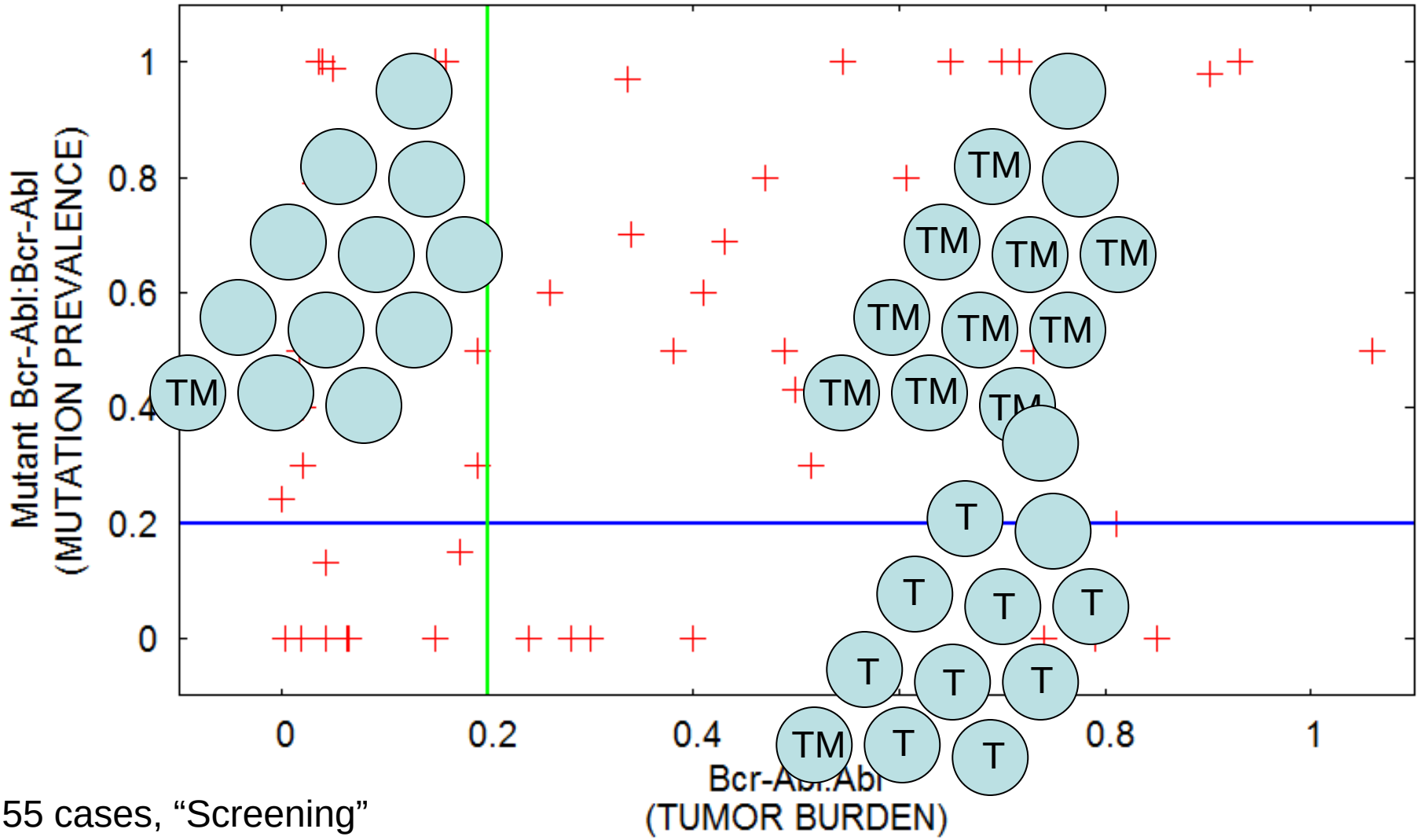
- Is OMAPRO™ efficacy affected by tumor burden and/or mutation prevalence?
- Will assays in post-approval use identify a patient population similar to the one studied in the clinical trial?

Tumor Burden, Mutation Prevalence



- Variable tumor cell burden
- Variable mutation prevalence within tumor
- Variable detection limits across assays

Mutation Prevalence and Tumor Burden



55 cases, “Screening”

Accruing Per "Detectable" T315I

- Different cut-offs, different patients
- Impact on the trial results? On efficacy in the post-approval market?
- Clinical effect as better technology drives down T315I detection limits?
- Setting a higher "cut-off" (e.g., "20%") for positive vs negative makes both analytical (e.g., site-to-site) and clinical conclusions from the current dataset problematic.

Summary

- The Indication proposed for OMAPRO™ depends on a companion diagnostic test for T315I mutation.
- Significant clinical impact is likely from any false results (especially false positives).
- Reliable test performance (matching the clinical trial) is needed to assure patients similar to those in the trial are identified post-approval.
- A variety of non-standardized, non-reviewed assays was used to accrue patients for the trial. Reliable test performance is not assured by the trial.
- The appropriate “positive” cut-point is unknown.
- Reliable selection of patients for post-approval treatment with OMAPRO™ is not yet assured.