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A Phase 1 Study of Tasquinimod in Patients with Relapsed or Refractory Multiple Myeloma

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Imids
thalidomide
lenalidomide
Pomalidomide
iberdomide

PIs
bortezomib
carfilzomib
ixazomib

MoAbs
daratumumab
isatuximab
elotuzumab

Cytotoxics
melphalan
cyclophosphamide
doxorubicin
bendamustine

Steroids
Dexamethasone
Prednisone

HDACi
panobinostat

XPO1i
selinexor

BCMA-directed
Belantamab
CAR T cells
BiTEs

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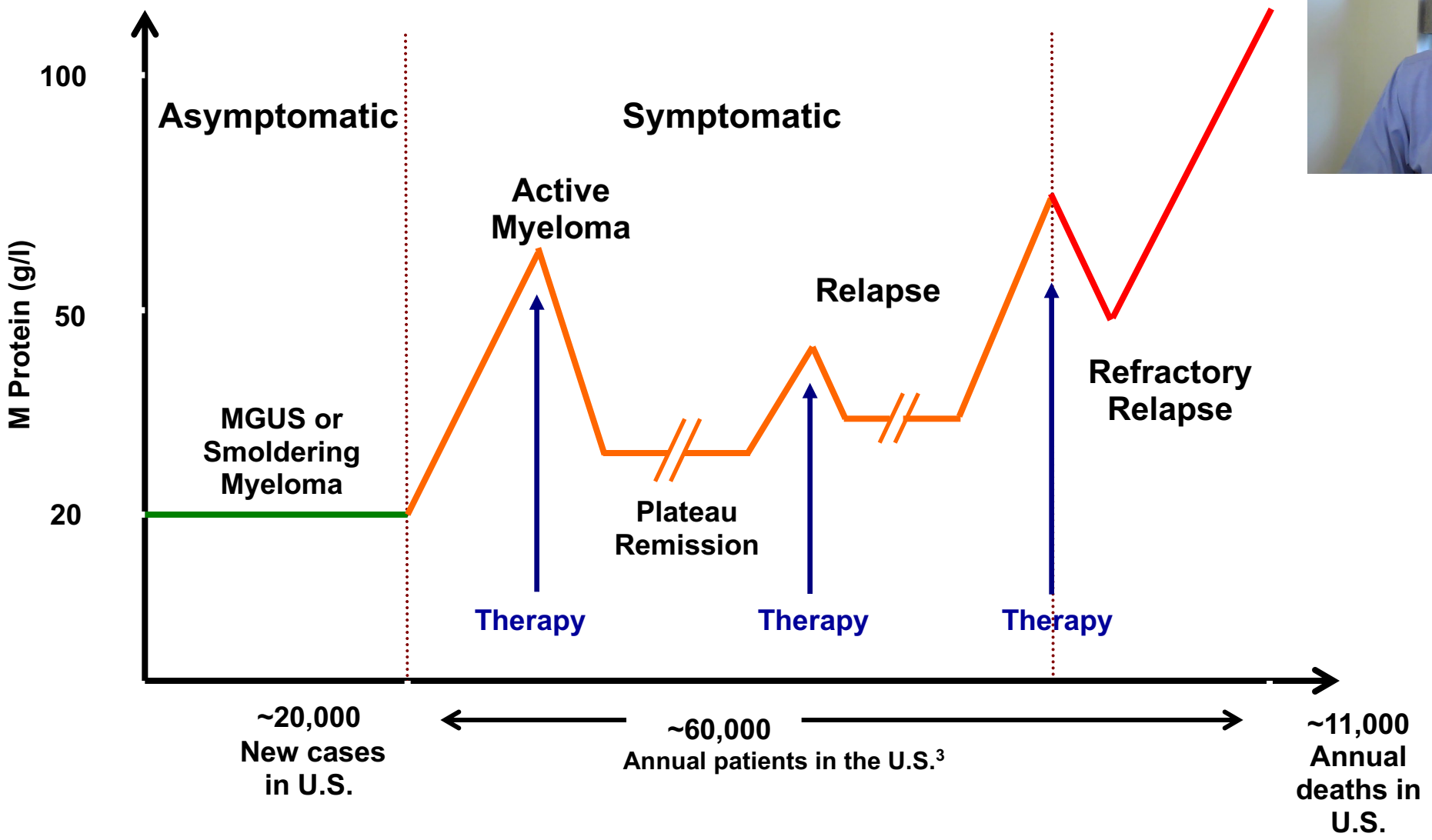
Myeloma – Treatment and Progression



1. Adapted from International Myeloma Foundation; 2001. Reprinted with permission.
2. American Cancer Society. *Cancer Facts & Figures*; 2003. 3. Millennium Pharmaceuticals, Inc., 2003.

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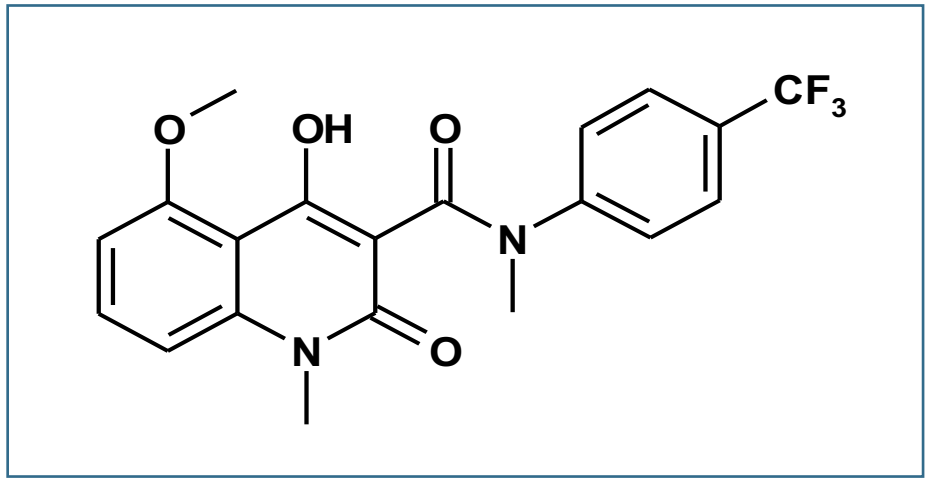
Tasquinimod

- Oral once-daily dosing
- Novel mechanism of action
- Prior evidence of safety and anti-cancer activity in human trials
  - Safety data from more than 650 person-years of exposure
  - Statistically significant PFS benefit in patients with prostate cancer

Sternberg et al. J Clin Oncol 2016;34:2636-2643



Preclinical Data and Mechanism of Action

- Tasquinimod inhibits S100A9, thereby:
  - Decreasing localized immune suppression in the bone marrow microenvironment
  - Decreasing production of pro-inflammatory cytokines
  - Decreasing production of pro-angiogenic factors

- Reduces tumor growth and improves survival of myeloma-bearing mice

- Synergistic or additive effects in combination with standard myeloma agents
  - Bortezomib (proteasome inhibitor)
  - Lenalidomide (immunomodulatory drug)

TASQ – tasquinimod; i.v. – intravenous; s.c. - subcutaneous

Lin et al. 25th Annual Meeting of European Hematology Association (EHA) June 11-21 2020: EP896

Dose Rationale for Phase 1 Trial in Myeloma

- Well tolerated In healthy volunteers
  - At repeat doses up to 1.0 mg but not at 2.0 mg
  - Intermediate doses not studied
- MTD initially determined to be 0.5 mg daily in patients with solid tumors
  - Based on toxicities that are not necessarily dose limiting (tachycardia and elevated amylase)
- Long-term dosing at 1.0 mg daily was feasible in patients with prostate cancer
  - Studies have used a dose up-titration run-in (0.25 mg x2 weeks, 0.5 mg x2 weeks)
- Subsequent studies:
  - Have not evaluated starting at a full dose of 1.0 mg daily
  - Have not evaluated doses between 1.0 and 2.0 mg

Objectives

1. Establish the Maximum Tolerated Dose (MTD) and optimal schedule of single-agent tasquinimod in patients with relapsed or refractory Multiple Myeloma (rrMM)
   - Explore faster up-titration schedules
   - Explore doses between 1.0 and 2.0 mg daily
2. Investigate the MTD of tasquinimod in combination with ixazomib, lenalidomide, and dexamethasone (IRd)
3. Assess preliminarily the efficacy of tasquinimod alone and in combination with IRd

Clinical Phase 1 Study

Population:
MM relapsed or refractory after ≥1 line of anti-MM therapy and refractory or intolerant to lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 mAb

Population:
MM relapsed or refractory after ≥1 line of anti-MM therapy and refractory to most recent PI/IMiD-combination

Part A1
Tasquinimod dose-escalation (TASQ)

Part A2
Cohort expansion at tasquinimod-MTD (TASQ)

Part B1
Tasquinimod dose-escalation (TASQ + IRd)

Part B2
Cohort expansion at MTD of tasquinimod in combo (TASQ + IRd)

Primary objective:
Tolerability and optimal schedule for TASQ

Secondary objectives:
Safety and preliminary assessment of clinical response

IRd = Ixazomib + Revlimid® (lenalidomide) + dexamethasone
PI / IMiD = Proteasome Inhibitor / Immunomodulator
TASQ = Tasquinimod

NCT 04405167

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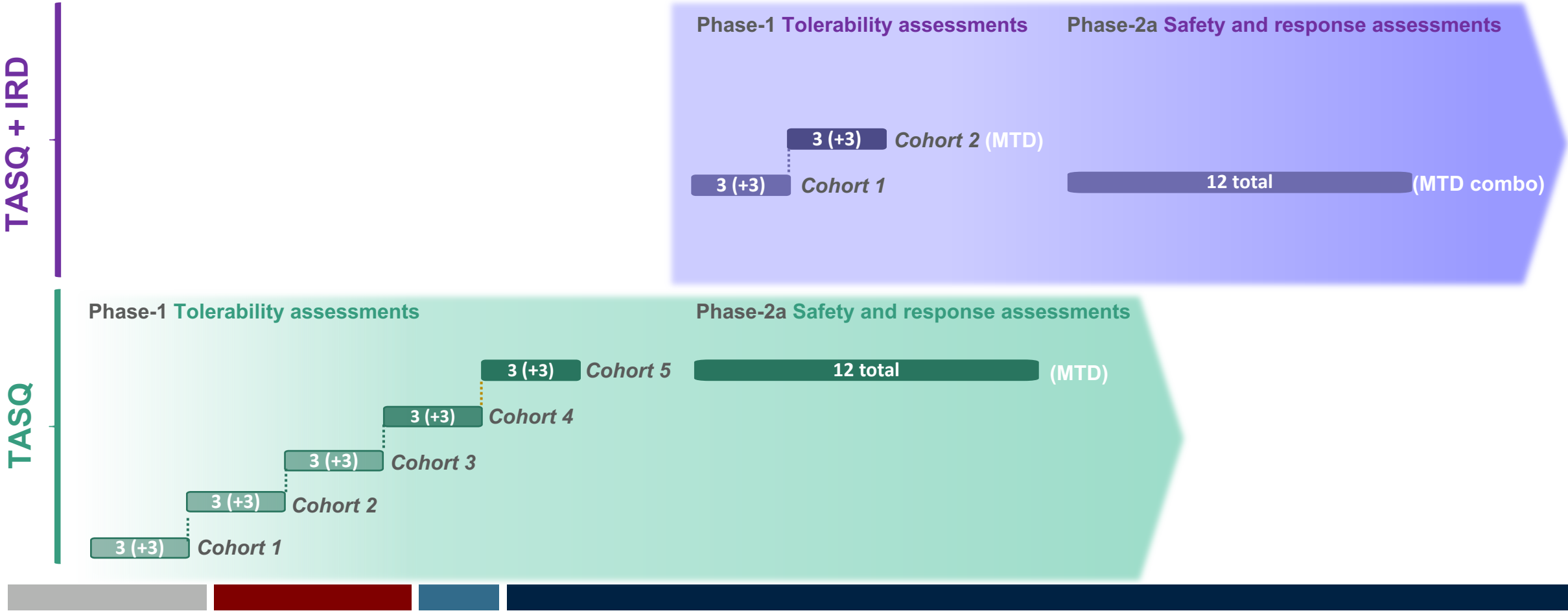
Study Design

Open-label, two-part, dose-escalation with subsequent exploratory cohort expansion



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Dose Escalation: Single Agent

Dose-level	Daily dose of tasquinimod (TASQ)
5	1.5 mg
4	1.25 mg
3	1 mg
2	0.5 mg x 1 week, then 1 mg
1	0.25 mg x 1 week, 0.5 mg x 1 week, then 1 mg

Dose Escalation: Drug Combination

Dose-level	Daily dose of tasquinimod
2	MTD
1	One dose-level below MTD*

* - OR - same as dose-level 1 for tasquinimod as single agent, if lower

In 4-week cycles:

- Ixazomib: 4 mg on days 1, 8, and 15
- Lenalidomide: 25 mg on days 1 through 21
- Dexamethasone: 40 mg on days 1, 8, 15, and 22

NCT 04405167

Assessments

- Tolerability (Maximum Tolerated Dose, MTD):
  - Dose-limiting toxicities based on treatment-emergent grade 3/4 Adverse Events (AEs) using the National Cancer Institute (NCI) Common Toxicity Criteria for AEs (CTCAE, version 5)
- Preliminary anti-myeloma activity:
  - Overall Response Rate (ORR, partial response or better) based on IMWG response criteria
  - Time-to-event endpoints (Time to progression, Progression-Free Survival, Overall Survival)
- Biomarkers in bone marrow and plasma for exploratory mechanistic studies:
  - S100A9 levels in peripheral blood and bone marrow plasma
  - S100A9 expression in peripheral blood and bone marrow cells
  - Frequencies of myeloid derived suppressor cells, dendritic cells, monocytes, and T cells and expression of S100A9 receptors TLR4, RAGE, and CD147
  - Immune suppressive ability of bone marrow myeloid derived suppressor cells
  - Levels of pro-inflammatory and angiogenic factors in plasma samples
  - Number of megakaryocytes and blood vessel density in bone marrow core biopsies.

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