Phase 3b UPFRONT Study: Interim Results from a Community Practice-Based Prospective Randomized Trial Evaluating Three Bortezomib-Based Regimens in Elderly, Newly Diagnosed Multiple Myeloma Patients

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Disclosures for Ruben Niesvizky

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Background

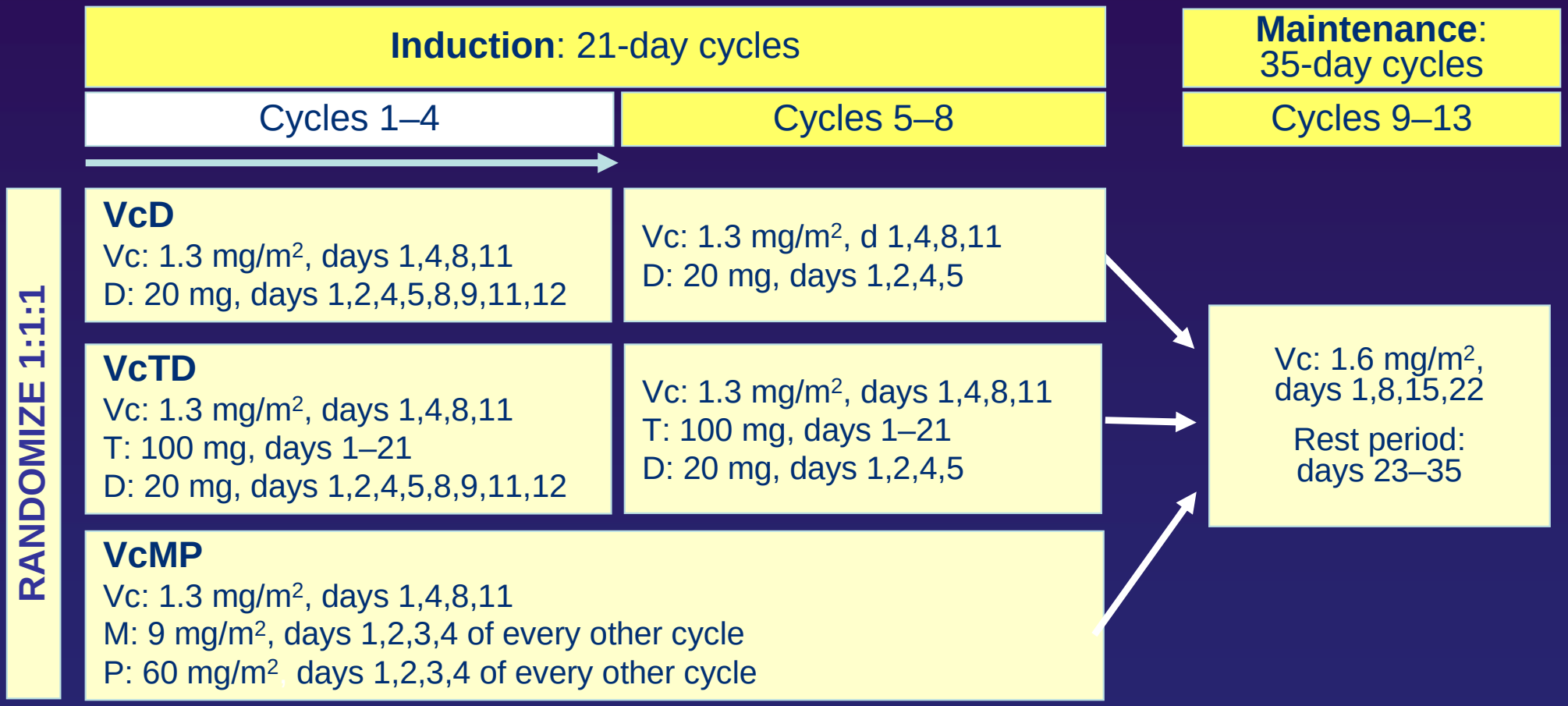
- Elderly patients with multiple myeloma (MM) have limited treatment options
  - Ineligible for HDT-SCT due to factors such as age and co-morbidities
- Several bortezomib-based regimens have shown activity in newly diagnosed MM in phase 2 and 3 clinical trials:
  - Bortezomib and dexamethasone (VcD)[1]
  - Bortezomib, thalidomide, and dexamethasone (VcTD)[2]
  - Bortezomib, melphalan, prednisone (VcMP)[3,4]
- VcMP: investigated specifically in elderly patients ineligible for HDT-SCT
- VcD and VcTD: assessed in younger patients as induction therapy prior to SCT
- The randomized, open-label, multicenter, phase 3b UPFRONT study aims to assess VcD, VcTD, and VcMP in newly diagnosed MM patients ineligible for HDT-SCT in the community-practice setting

1. Harousseau et al. J Clin Oncol 2008;26; Abstract 8505.
2. Cavo et al. Blood 2008;112:Abstract 158.
3. Mateos et al. Haematologica 2008;93:560-5.
4. San Miguel et al. NEJM 2008; 359:906–17.

UPFRONT objectives

- Primary endpoint:
  - Progression-free survival
- Other endpoints:
  - Response rate (IMWG criteria)
  - Safety and tolerability
    - Grade ≥3 adverse events (AEs)
    - All serious AEs (SAEs)
    - Peripheral neuropathy (PN)
  - Patient-reported quality of life (QoL)
- The study is ongoing

UPFRONT: Treatment schema



- VcD and VcTD: reduced dexamethasone dosing in cycles 5–8 versus 1–4
  - Here we report results of a pre-planned interim analysis (after 4 cycles or ~12 weeks)

Study Design

- Key inclusion criteria:
  - Previously untreated MM patients ineligible for HDT-SCT
  - Karnofsky Performance Status ≥50%
  - Measurable disease
    - M-protein in serum IgG or IgM >1 g/dL; IgA or IgD >0.5 g/dL
    - Urine light chain >200 mg/24hr urine collection
- Key exclusion criteria:
  - Grade ≥2 peripheral neuropathy
- **VcTD arm**: prophylactic aspirin, full-dose warfarin, or low-molecular weight heparin was required unless medically contraindicated[1]
- Prophylaxis for herpes zoster recommended
- Patients were not eligible for transplant due to age, presence of important co-morbid conditions, or subject preference

1. Palumbo et al. Leukemia 2008;22:414–22.

Protocol-specified interim analysis

- To be conducted after 70 patients/arm (210 total), had 4 cycles (12 weeks) of therapy (or discontinued prior to completion of 4 cycles)
  - Enrolled at ~200 sites from June 2007–October 2008
- Independent Data Monitoring Committee (IDMC) to assess which arm should be discontinued, based on:
  - Efficacy (≥10% difference in ≥VGPR between arms)
  - Safety

Baseline patient demographics and disease characteristics

	VcD (N=70)	VcTD (N=70)	VcMP (N=70)
Median age, years (range)	74 (51–91)	72.5 (38–88)	71.5 (42–86)
Age ≥75 years, n (%)	34 (49)	28 (40)	22 (31)
Male, %	61	41	56
Race, %			
Caucasian	79	77	67
Black	11	14	21
Other	10	8	11
IgG / IgA / Light chain, %	59 / 29 / 12	53 / 33 / 14	57 / 26 / 16
KPS 50–60 / 70–80 / 90–100, %	9 / 44 / 47	13 / 30 / 57	12 / 48 / 40
ISS Stage I / II / III, %	17 / 55 / 28	42 / 35 / 23	27 / 43 / 30
Serum creatinine >1.5 x ULN, n (%)	13 (19)	6 (9)	8 (11)

Efficacy: Investigator-assessed confirmed response

- Response-evaluable population: received at least one dose of study drug and ≥1 post-baseline M-protein measurement

N (%)	VcD (N=60)	VcTD (N=60)	VcMP (N=62)
CR / near-CR	8 (13)	11 (18)	9 (15)
≥VGPR	9 (15)	14 (23)	15 (24)
PR (minus VGPR)	27 (45)	28 (47)	17 (27)
ORR (≥PR)	36 (60)	42 (70)	32 (52)
Stable disease	9 (15)	9 (15)	17 (27)
Progressive disease	1 (2)	0	4 (6)

- All three regimens demonstrated substantial activity

Non-hematologic AEs

- Safety profiles were similar to those reported in previous phase 3 trials
- Lowest incidence of grade ≥3 AEs in the VcD arm (58% vs 71% for both VcTD and VcMP)

Grade ≥3 AEs, n (%)	VcD (N=69)	VcTD (N=66)	VcMP (N=69)
Fatigue	2 (3)	8 (12)	4 (6)
Pneumonia	7 (10)	3 (5)	1 (1)
Deep vein thrombosis	3 (4)	2 (3)	1 (1)
Pulmonary embolism	1 (1)	3 (5)	0
Peripheral neuropathy	4 (6)	8 (12)	9 (13)

Data to be confirmed

Hematologic AEs

n (%)	VcD (N=69)	VcTD (N=66)	VcMP (N=69)
Neutropenia			
Grade 3	0	0	13 (19)
Grade 4	0	0	2 (3)
Thrombocytopenia			
Grade 3	0	3 (5)	4 (6)
Grade 4	3 (4)	0	3 (4)

Incidence of peripheral neuropathy

- Grade ≥3 PN incidence was similar to rates at the end of previous phase 3 trials[1]
- PN was more common in the VcTD arm
- Some patients discontinued due to grade 1, 2 PN

	VcD (N=69)	VcTD (N=66)	VcMP (N=69)
Any grade PN, n %	20 (29)	32 (48)	21 (30)
Grade ≥3 PN, n %	4 (6)	8 (12)	9 (13)
Any grade PN resulting in discontinuation, n %	4 (6)	3 (5)	6 (9)
Grade ≥3 PN resulting in discontinuation, n %	1 (1)	1 (2)	6 (9)

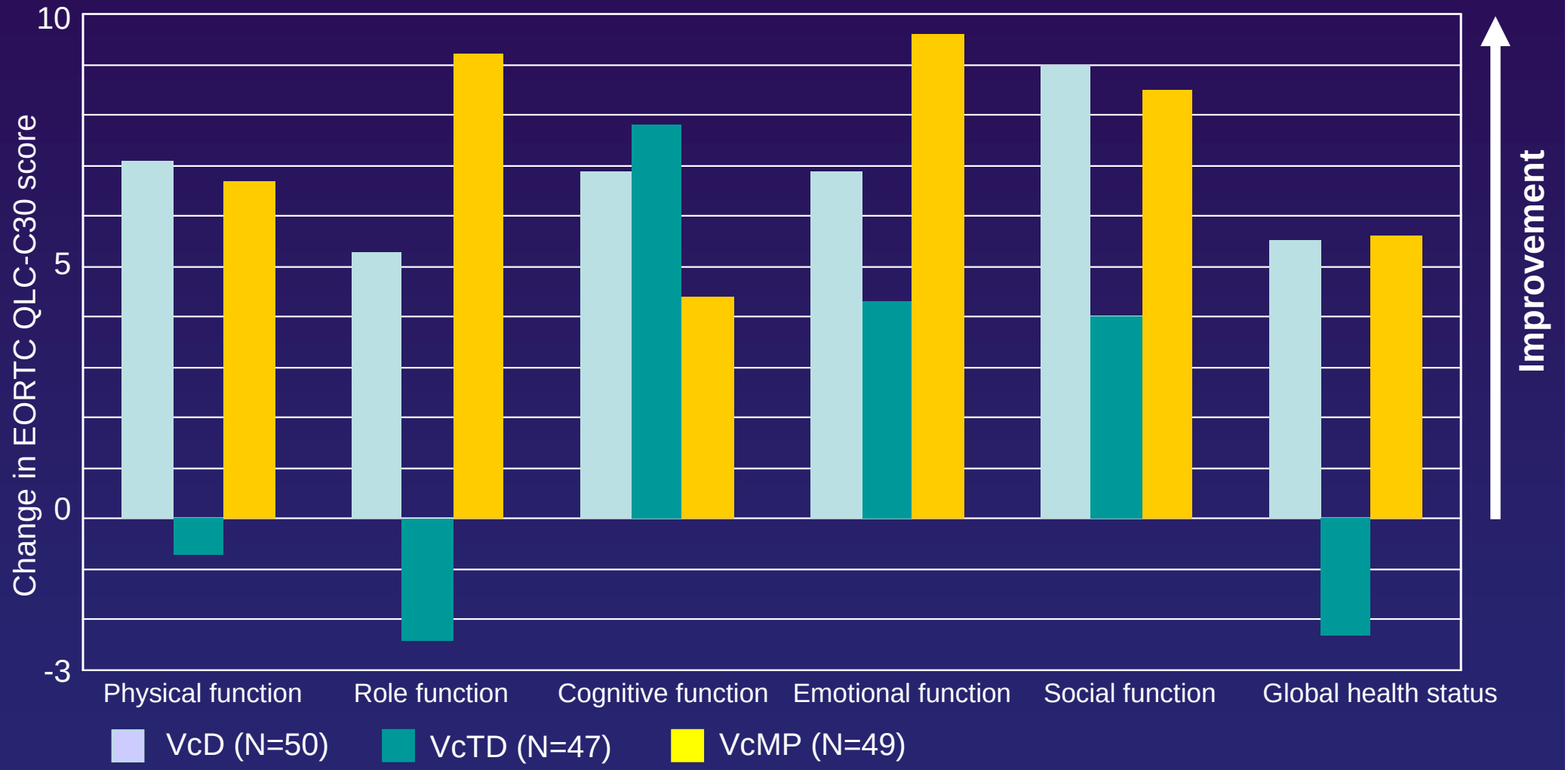
1. Harousseau et al. J Clin Oncol 2008;26; Abstract 8505.

Serious AEs

	VcD (N=69)	VcTD (N=66)	VcMP (N=69)
SAEs, n (%)	27 (39)	33 (50)	25 (36)
Pneumonia	8 (12)	3 (5)	2 (3)
Nausea / vomiting	1 (1)	4 (6)	2 (3)
Deep vein thrombosis	3 (4)	2 (3)	1 (1)
Pulmonary embolism	1 (1)	2 (3)	0
Peripheral neuropathy	1 (1)	3 (5)	1 (1)

- 11 patients died; 6, 3, and 2, in the VcD, VcTD, and VcMP arms, respectively
- The rate of cycle 1–4 treatment discontinuations was similar in all three arms
  - 18 (26%), 20 (30%), and 21 (30%) patients in the VcD, VcTD, and VcMP arms, respectively

Patient quality of life: Improvement in functional score



- QoL function scores generally improved in all arms

  VcTD: Physical function, role function and global health status worsened

Summary

- This 12-week interim analysis of a large, randomized, community-based study in patients in the US showed:
  - VcD, VcTD, and VcMP regimens were active with predictable toxicities
    - Good response rates and similar rates of AEs reported for all arms
    - Patient-reported QoL generally improved in all arms
- At the pre-planned interim analysis, the IDMC concluded that the VcD, VcTD, and VcMP regimens had similar risk/benefit profiles after 4 cycles
  - IDMC recommended that the study continue to enroll patients in all three arms

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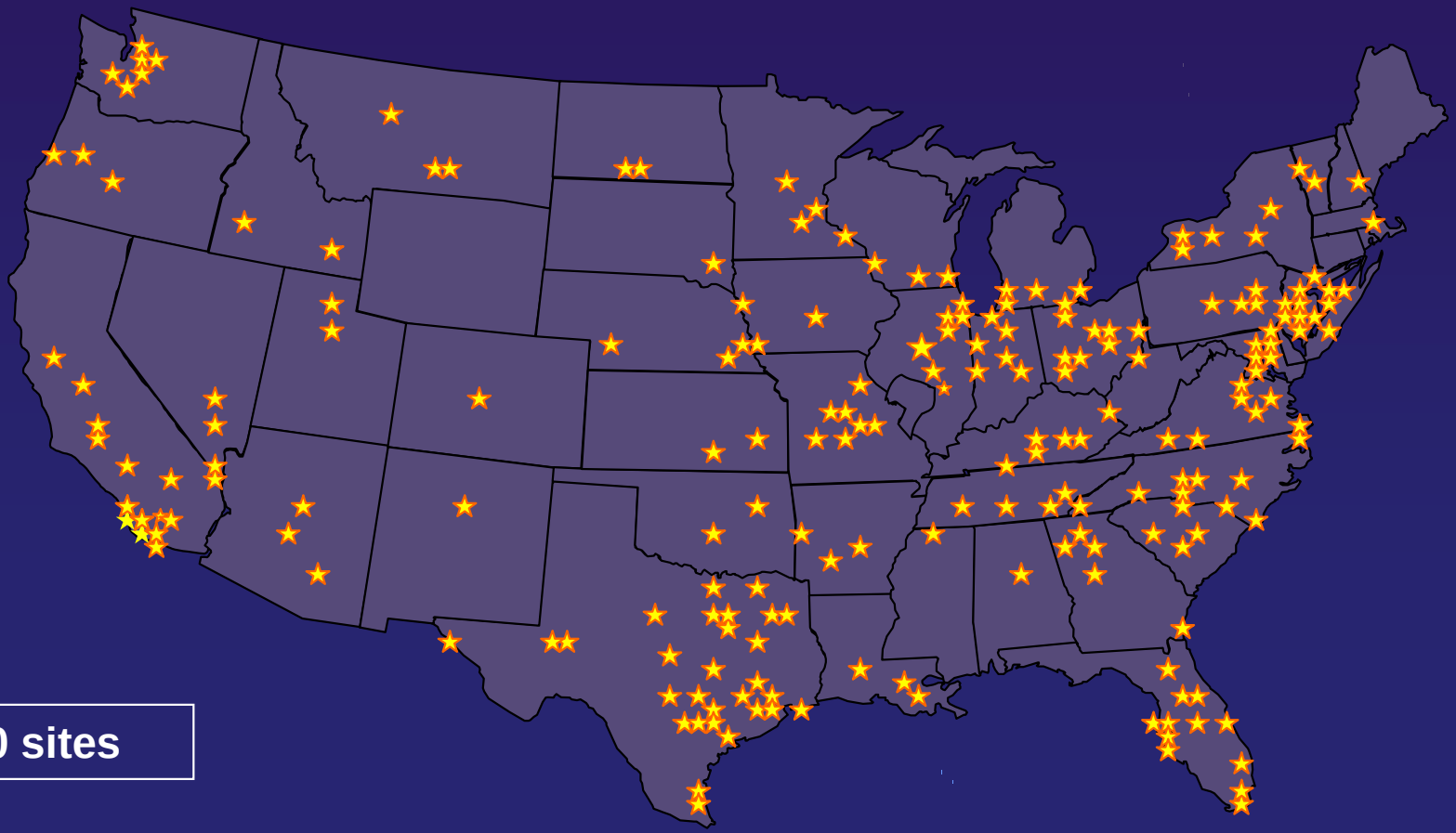

~200 sites