Nivolumab in mismatch-repair deficient (MMR-d) non-colorectal cancers: NCI-MATCH Trial (Molecular Analysis for Therapy Choice) Arm Z1D preliminary results

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Rationale

- DNA repair defects due to mismatch repair deficiency (MMR-d) are most commonly caused caused by silencing of mismatch repair proteins MLH1 or MSH2 and less commonly MSH6 or PMS2 through mutation or promoter methylation

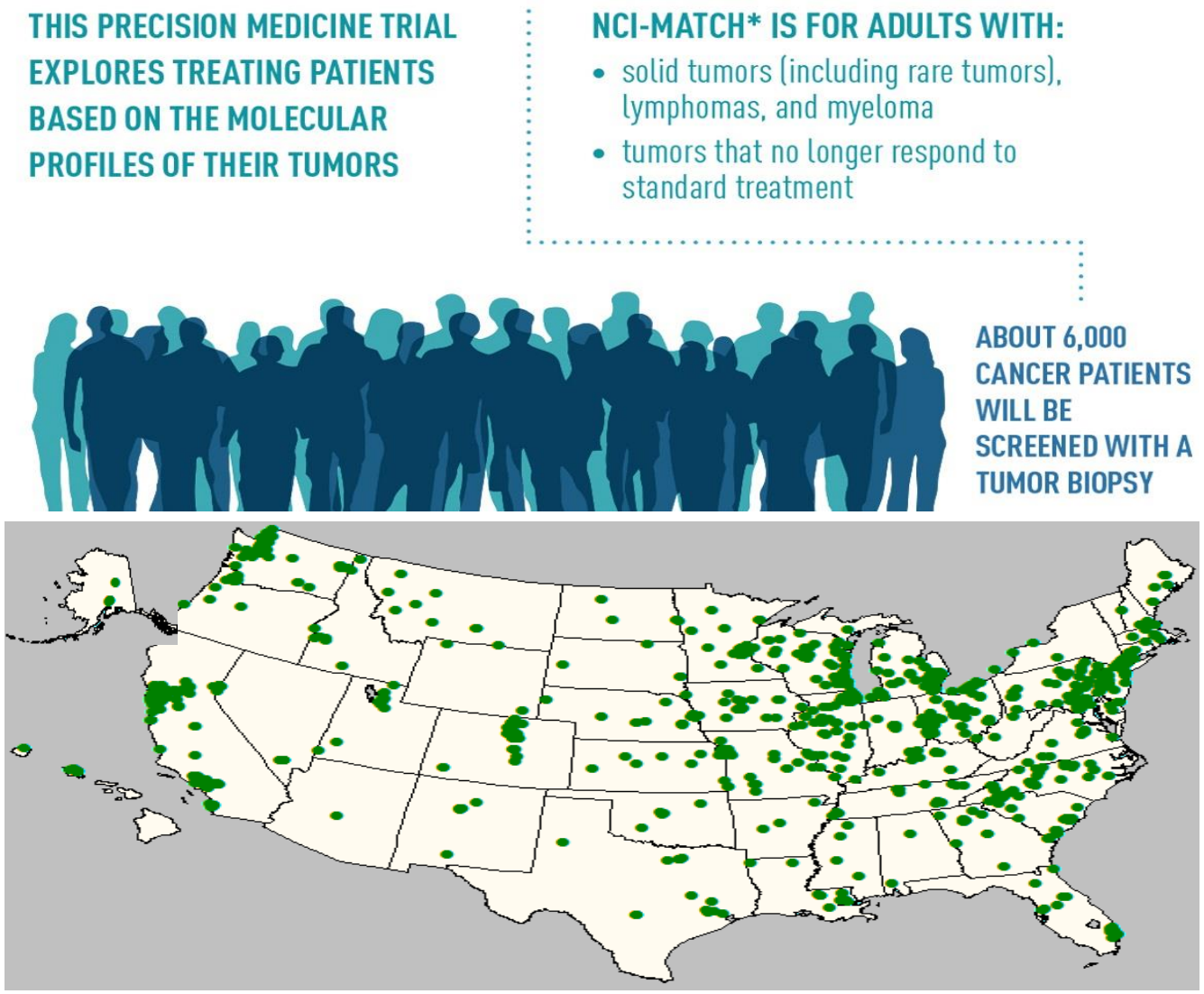
- MMR-d tumors are hypermutated, with 100s to 1000s of mutations per tumor

- Higher mutational loads are associated with increased tumor-associated neoantigens, increased tumor-infiltrating lymphocytes, and immune checkpoint expression

- Anti-PD1 therapy with nivolumab +/- anti-CTLA-4 inhibitor ipilumumab has shown activity in MMR-d colorectal cancer, and pembrolizumab is now approved in pretreated MMR-d cancers

Overman et al. Lancet Oncology 2017
Le et al. NEJM 2015
Le et al. Science 2017

What is NCI-MATCH?



- Master protocol with multiple phase II treatment arms
  - Eligibility defined by molecular characteristics
- Single agents or combinations with recommended phase II dosage(s) known
  - FDA-approved for another indication or investigational
- US-based sites across NCTN and NCORP (1089 sites)

Participation Rates by Site Type:
NCORP ~ 90%
NCI Cancer Centers ~ 80%

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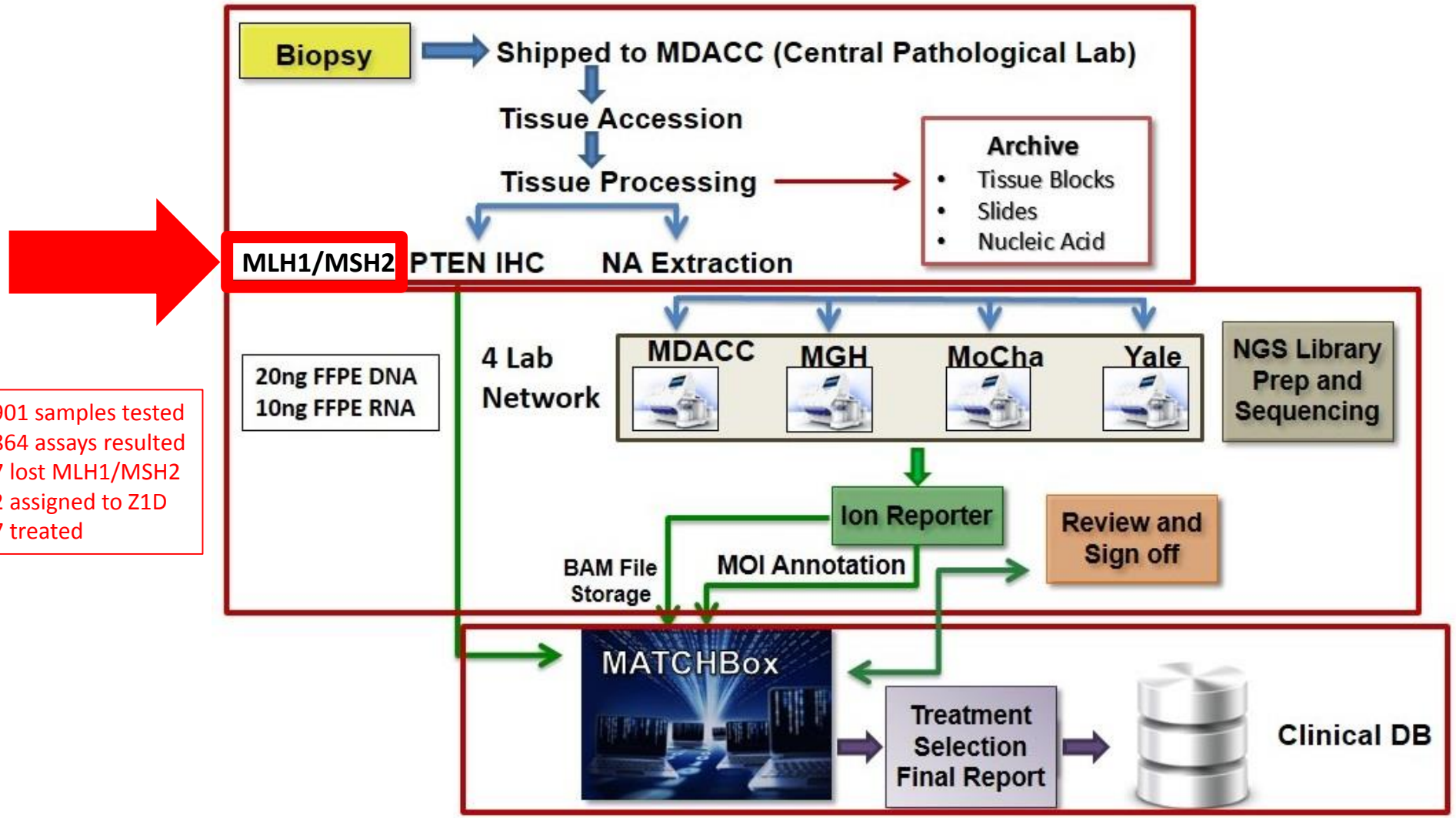
NCI-MATCH Assay Workflow

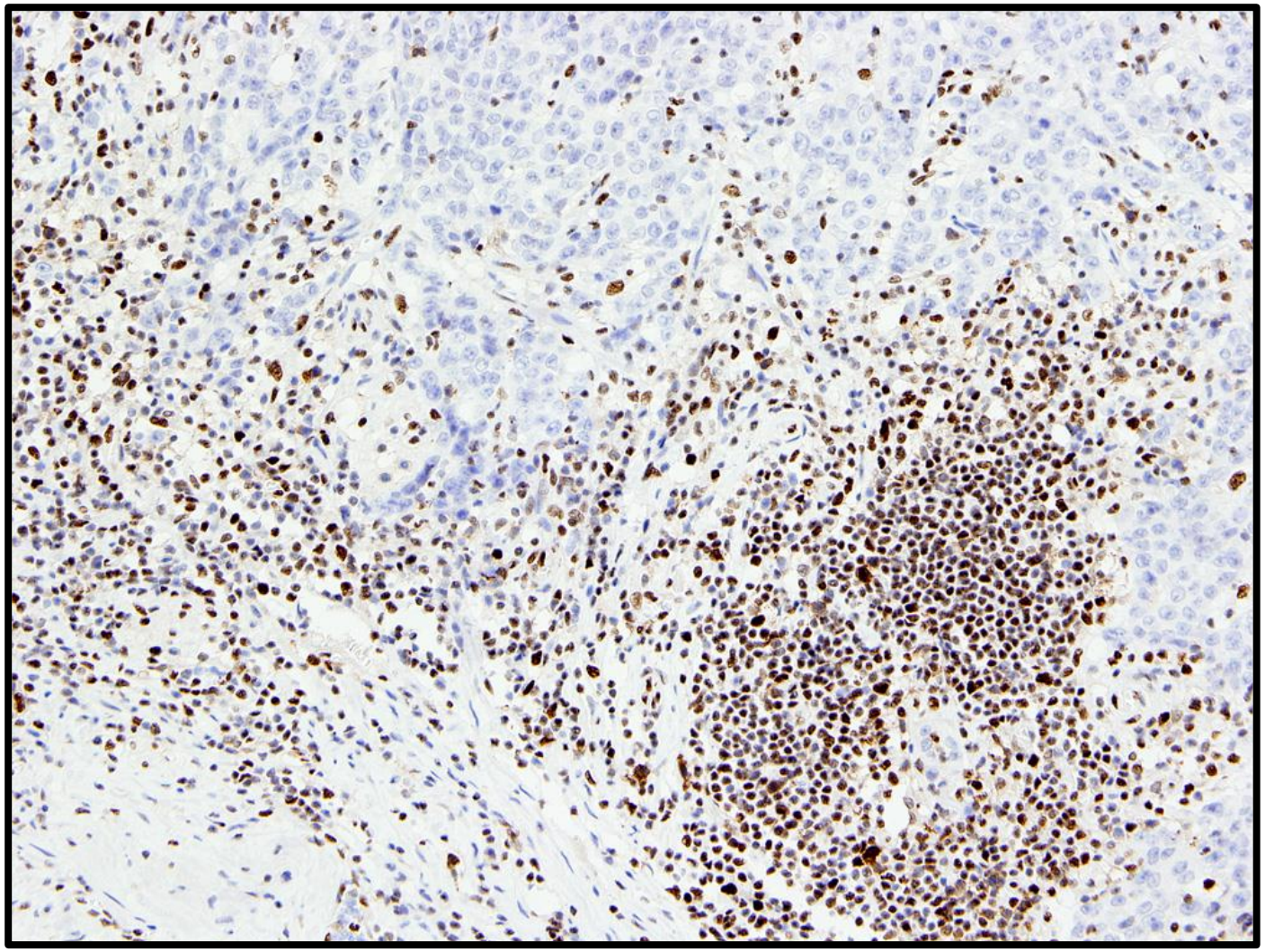


- 4901 samples tested
- 4864 assays resulted
- 77 lost MLH1/MSH2
- 62 assigned to Z1D
- 47 treated

MLH1, MSH2 IHC assay (abbreviated IDE)

- IHC was performed on 4 µm deparaffinized & rehydrated FFPE tissue sections.
  - Primary MLH1 antibody (Cell Marque™, clone G168-728) & primary MSH2 antibody
- **Interpretation:**
  1. **Complete Loss of expression (required for dMMR eligibility):** complete loss of nuclear expression by tumor cells & retention of staining in non-neoplastic cells (internal control).
  2. **Intact nuclear expression**: Nuclear expression of any intensity within tumor cells**.**
  3. **Cannot be determined:** Insufficient specimen, technically inadequate IHC assay, or cytoplasmic staining without definite nuclear staining.

Complete loss of nuclear expression by tumor cells and retention of staining in non-neoplastic cells (internal control).



NCI-MATCH Trial Milestones

- Opened on August 12, 2015, with **10** treatment arms
- Paused enrollment of *new* patients on November 11, 2015, for planned interim analysis
- Increased 3000-patient goal to 6000 in fall 2016 -- completed in June 2017
- **How will reaching the 6000 goal change the study?**
- Biggest change – the trial lab network will no longer collect and test biopsy materials for the purpose of assigning patients to treatments
- Will now use CLIA-certified external labs
  - Foundation Medicine -- MDACC/MSKCC
  - Caris Life Sciences -- Other labs being assessed

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STUDY DESIGN

MMR-deficient, non colorectal cancer subjects
N=35*

Nivolumab 3 mg/kg IV q2weeks x 4 cycles**
After cycle 4, nivolumab 480 mg IV q4weeks

Baseline imaging and then reassessment every 2 cycles

Treatment until progression***

* 12 additional patients enrolled in expansion – not reported here
**Cycle = 28 days
***Treatment past progression allowed if patients were clinically stable, per provider discretion, in the first 24 weeks of therapy if no more than 4 new lesions and less that 40% change in sum of index lesions

Key eligibility criteria

- Master protocol eligibility
  - Inclusion
    - Solid tumor, lymphoma or myeloma progressed on at least one therapy
    - Biopsiable disease or tissue available within last 6 months with no molecularly targeted therapies after specimen taken
    - Age ≥18 years old
    - ECOG 0-1
    - Good end-organ function
- Z1D arm-specific eligibility
  - Inclusion
    - MMR-deficient as defined by complete loss of tumor staining for MLH1 or MSH2 by immunohistochemistry
  - Exclusion
    - History of autoimmune disease
    - History of interstitial lung disease
    - Prior therapy with anti-PD1/PD-L1 antibodies or other immune checkpoint inhibitors
    - Colorectal cancer

NCI-MATCH Arm Z1D Statistical Considerations

- Primary endpoint
  - Overall response rate
- Secondary endpoints
  - Progression free survival (PFS) at 6 months 15% (median PFS 2.2 m) vs 35% (median PFS 4 m)
  - Toxicity
- One-stage design
- Allowing for 10% ineligibility rate, 35 patients would be accrued to obtain 31 evaluable patients for each arm
  - If the observed objective response rate is ≥ 5/31 (16%), it will then be concluded that the agent is promising and worthy of further testing.
- 91.8% power to conclude an agent is promising if its true OR rate is 25%
- Type 1 error rate (one-sided) is 1.8%

Baseline Characteristics

Patient characteristic	(N = 34*)
Median age, y	60
Range	44-85
Sex	
Male	32%
Female	68%
ECOG PS	
0	32%
1	68%
Race	
White	76%
Black	12%
Asian	9%
Not reported	3%
Hispanic	3%

Patient characteristic	(N = 34)
Prior therapies	
1	24%
2	21%
3	12%
>3	42%
Weight loss in past 6 months	
<5%	53%
5-10%	29%
>10%	18%
IHC results	
MLH1 Neg, MSH2 Pos	24 (71%)
MLH1 Pos, MSH2 Neg	10 (29%)

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* 1 patient without data at data cut-off (not included in analyses)

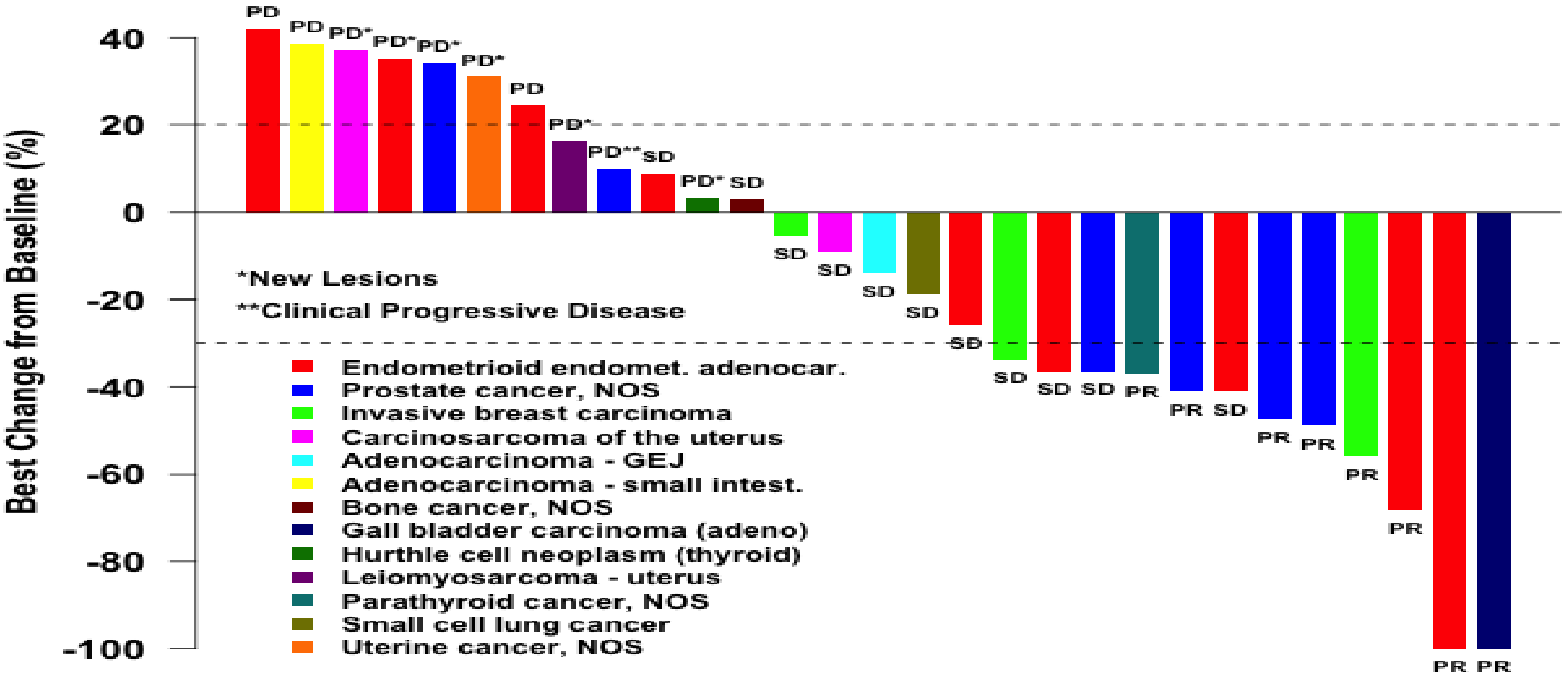
Histologic type	(N = 34)
Adenocarcinoma - GEJ	1
Adenocarcinoma - small intestine	1
Cholangiocarcinoma	1
Gall bladder carcinoma	1
Endometrioid endometrial adenocarcinoma	11
Uterine cancer, not specified	1
Carcinosarcoma of the uterus	3
Leiomyosarcoma - uterus	1
Hurthle cell neoplasm	1
Parathyroid cancer	1
Prostate cancer	6
Invasive breast carcinoma	3
Salivary gland cancer	1
Small cell lung cancer	1

Efficacy analysis

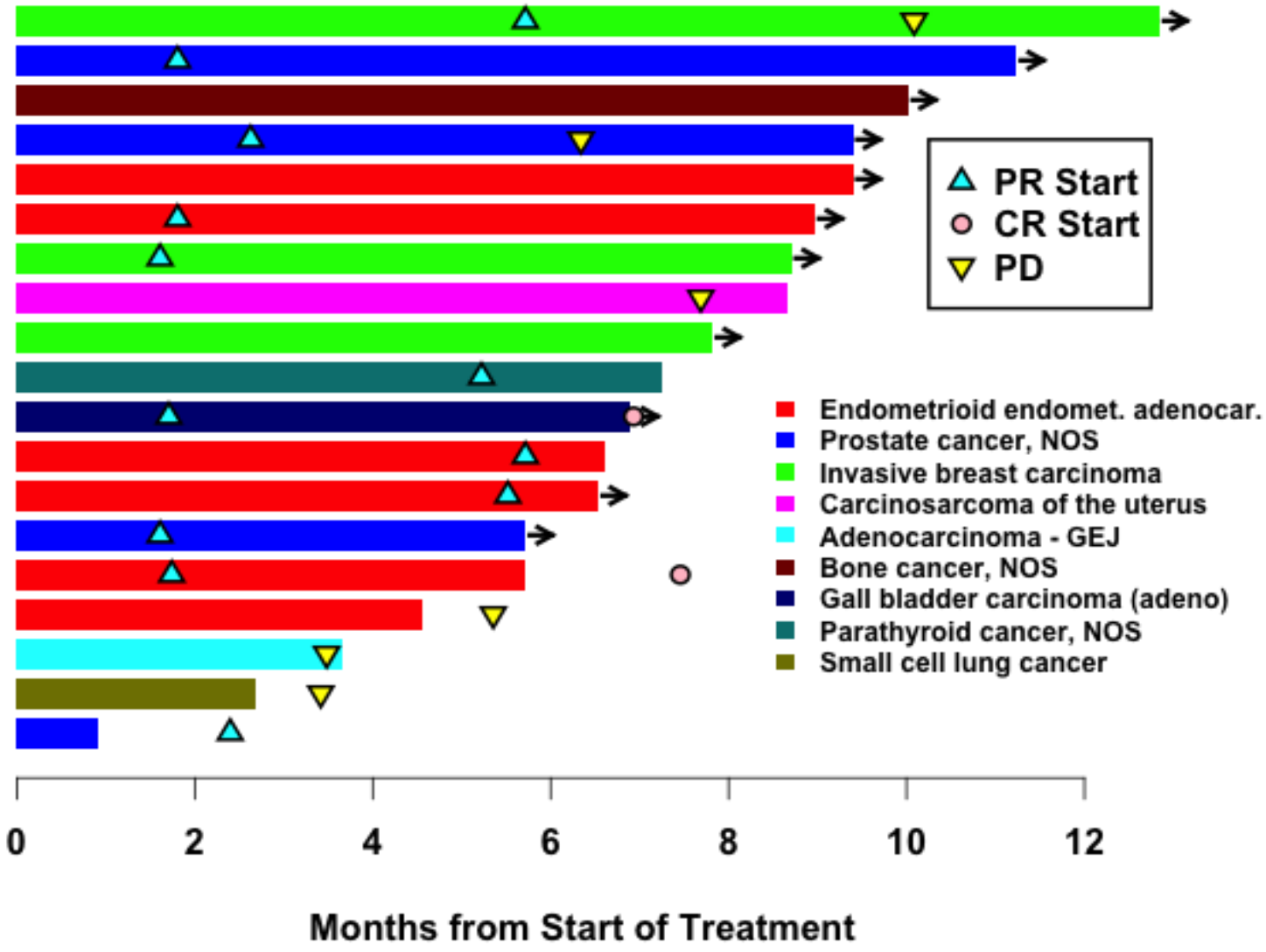
Confirmed Response per RECIST v1.1	N=34
ORR (95% CI)	8 (24%) (11%, 41%)
CR*	0 (0%)
PR**	8 (24%)
SD (at 2 cycles and beyond)	11 (32%)
DCR (CR+PR+SD)	19 (56%)
PD	10 (29%)
NE	5 (15%)

NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*2 unconfirmed CRs – one treatment stopped due to AE, another ongoing treatment
** 3 unconfirmed PRs – one on treatment, one off for subsequent progression, two off for AE

Depth of response



Efficacy: Duration of Treatment and Response – PR and SD Patients



- Median cycles 3.5 (range 1-13+ cycles)
- Median time to first response was 2.1 months (includes unconfirmed PR's)
- 6-Month PFS was 49% (95% CI: 32-67%)
- Median duration of response has not been reached (3.7-7.4+ months; 7/8 still under treatment at time of data-cutoff)
- 11 patients remain on therapy at time of data cutoff

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Safety Summary

Grade of AE (33 patients*)	Treatment-related reported AEs (%)
Grade 1-2 AEs	17 (51%)
Grade 3 AEs	13 (39%)
Grade 4 AEs	2 (6%)
Grade 5 AEs	0 (0%)
AEs leading to withdrawal from study treatment	7 (21%)

Treatment-related AEs (> 15% incidence)	All Grade	Grade 3
Fatigue	15	1
Anemia	10	7
Hypothyroid	6	0
Anorexia	6	0
Rash - maculopapular	5	1
Nausea	5	1

* 2 patients with no AE information recorded at data cut-off

Future Work

- Clinical data still maturing for patients who remain on study and 12 additional patients on the expansion cohort
- Baseline tumor samples from biopsies performed at screening are available for correlative work
  - Up to 44 samples with sufficient tumor cellularity for correlative studies
    - PD-L1 and CD8+ T-cell IHC, as well as exploratory multiplex IF and IHC planned
- Research Blood was drawn at baseline, prior to cycle 3 and at the end of treatment
  - Analysis of circulating T-cell populations and cytokine analyses planned

Conclusions

- We report the results for the first sub-study of NCI-MATCH
- Nivolumab is active in patients with mismatch repair-deficient, non-colorectal cancer patients as defined as MLH1 or MSH2 loss by IHC, with durable responses in a sizable minority of patients
- Tolerability of nivolumab matched that reported in previous studies of the agent
- Further clinical follow-up on this primary cohort, as well as an expansion cohort of MMR-deficient, non-colorectal cancer patients, is pending
- Future work includes interrogating tumor tissue/blood to identify and refine biomarkers of response and resistance to this immunotherapy strategy

Acknowledgements

- Our patients and their families and loved ones

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- National Clinical Trials Network (NCTN)
- National Community Oncology Research Program (NCORP)

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