Initial results from a phase 1 trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with NSCLC refractory or resistant to prior anti–PD-1/PD-L1 agents

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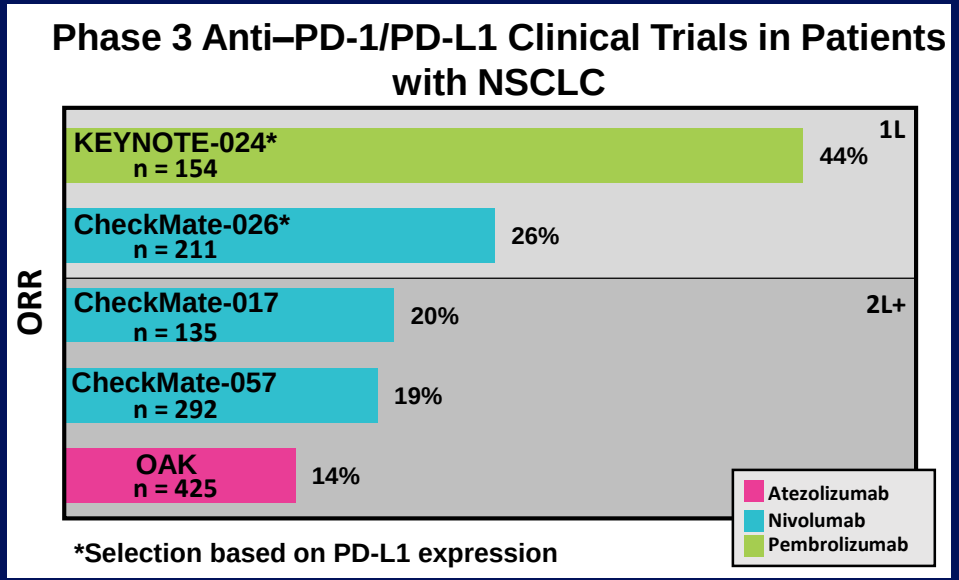
Disclosures

- **I have no competing financial interest to declare**

Anti–PD-1/PD-L1 Therapy in NSCLC

- Anti–PD-1/PD-L1 monotherapies have demonstrated promising efficacy and safety as first- and later-line treatment in patients with advanced NSCLC, with ORRs ranging from 14% to 44% depending on prior treatment and PD-L1 selection[1-5]
  - Frequently, disease progression occurs despite initial response to treatment
- Currently, there are only limited data reporting on the efficacy and safety of agents in patients with NSCLC who are primary refractory or who developed acquired resistance to anti–PD-1/PD-L1 therapies[6-10]
- Notably, TGF-β plays an important role in tumor immune escape,[11] and inhibition of the TGF-β pathway may aid in overcoming treatment failure to anti–PD-1/PD-L1 agents

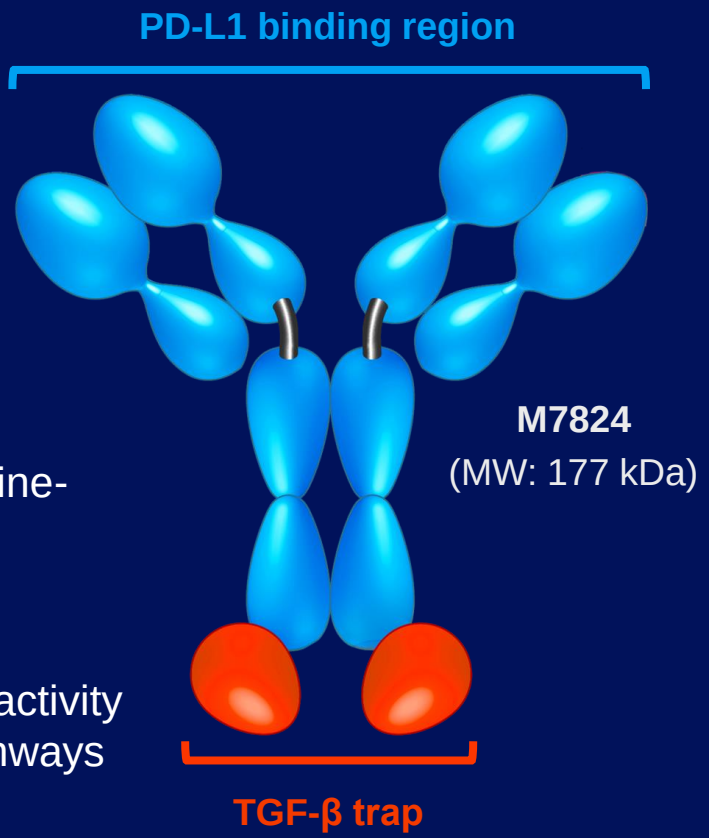


NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; TGF-β, transforming growth factor-β.

1. Reck et al. *NEJM*, 2016; 2. Brahmer et al. *NEJM*, 2015. 3. Borghaei et al. *NEJM*, 2015. 4. Fehrenbacher et al. *Lancet*, 2016. 5. Rittmeyer et al. *Lancet*, 2017. 6. Bhattacharya S, et al. ASCO, 2017. 7. Fong L, et al. ASCO, 2017. 8. Grigg C, et al. ASCO, 2017. 9. Leger PD, et al. ASCO, 2017. 10. Schvartsman G, et al. ASCO, 2017. 11. Colak et al. Trends Cancer, 2017.

M7824 is an Innovative First-in-Class Bifunctional Fusion Protein

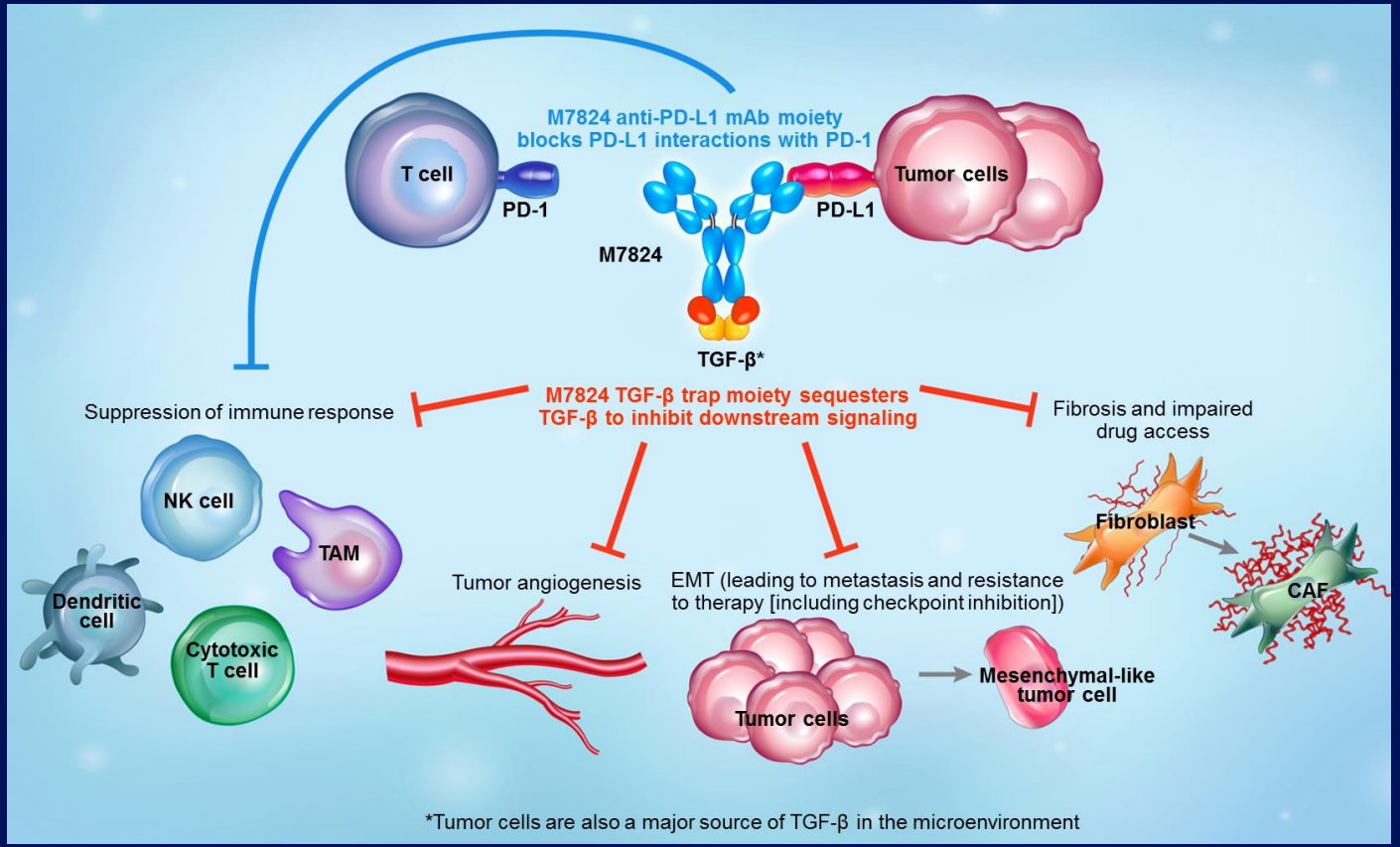
- PD-L1 antibody component
  - Fully human IgG1 mAb against human PD-L1
- TGF-β–neutralizing trap component
  - Extracellular domain of human TGF-βRII
  - Binds TGF-β1, -β2, and -β3
  - Fused to CH_3-C terminus of the IgG via a flexible glycine-serine linker
- Dual targeting of the PD-L1 and TGF-β pathways
  - Preclinical testing demonstrated enhanced antitumor activity relative to each individual agent by targeting both pathways with M7824



Ig, immunoglobulin; mAb, monoclonal antibody; MW, molecular weight; TGF-βRII, transforming growth factor β receptor type II.

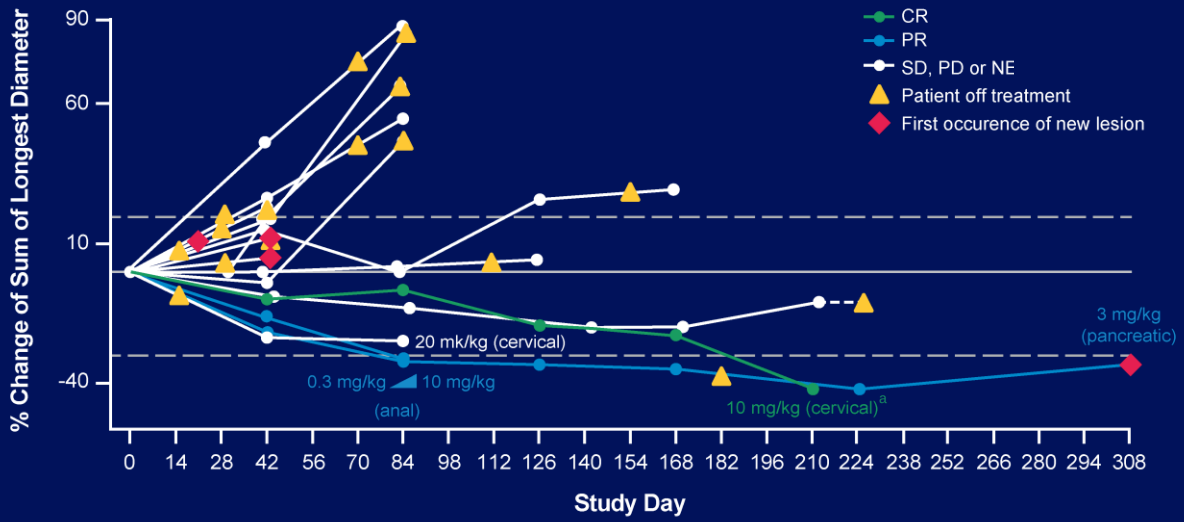
Lan et al., manuscript submitted

Mechanism of Action of M7824



CAF, cancer-associated fibroblast; EMT, epithelial-mesenchymal transition; NK cell, natural killer cell; TAM, tumor-associated macrophage.

Phase 1 Dose-Escalation Trial (NCT02517398)



- Ongoing confirmed CR (cervical)
- Durable confirmed PR (pancreatic)
- Durable confirmed PR (anal)
- Near-PR (cervical)

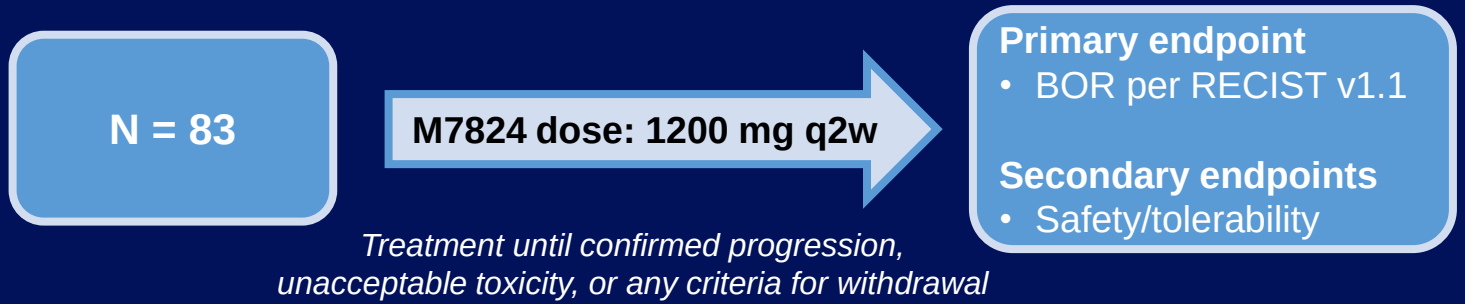
- Evidence of clinical activity observed across dose levels
- Manageable safety in patients with heavily pretreated advanced solid tumors
- M7824 saturated peripheral PD-L1 and sequestered all circulating TGF-β1, -β2, and -β3

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

[a] The % change of sum of longest diameter was not −100% because the patient had only lymph node lesions.

Gulley et al., ASCO, 2017

Study Design



- Expansion cohort of an ongoing, phase 1, open-label trial of M7824 (NCT02517398)
  - Heavily pretreated patients with advanced NSCLC who were primary refractory or who developed acquired resistance to prior treatment with anti–PD-1/PD-L1 therapy

→ Primary refractory: progression following treatment initiation (investigator-assessed BOR to prior anti–PD-1/PD-L1 agent was PD)

→ Acquired resistance: initial disease control with subsequent progressive disease (investigator-assessed BOR to prior anti–PD-1/PD-L1 agent was SD or better)

- Database cutoff date: 7 September 2017

BOR, best overall response; q2w, every 2 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

Baseline Patient and Disease Characteristics

Characteristics, n (%)	N = 83
Sex	
Male	56 (67.5)
Age	
<65 years	46 (55.4)
≥65 years	37 (44.6)
ECOG performance status	
0	27 (32.5)
1	55 (66.3)
2	1 (1.2)
Tumor PD-L1 expression[a]	
≥ 1%	54 (65.1)
< 1%	21 (25.3)
Unknown	8 (9.6)
EGFR mutation status[b]	
Mutated	4 (7.3)

Characteristics, n (%)	N = 83
Primary tumor type	
Squamous cell carcinoma	28 (33.7)
Adenocarcinoma	50 (60.2)
Other	5 (6.0)
Number of prior anticancer drug therapies[c]	
1	0 (0.0)
2	21 (25.3)
3	26 (31.3)
≥ 4	36 (43.4)
Best response to prior anti–PD-1/PD-L1 therapy	
Primary refractory (PD only)	36 (43.4)
Acquired resistance (SD or better)	44 (53.0)
Missing	3 (3.6)

- Heavily pretreated patient population
  - 74.7% of patients received ≥ 3 prior therapies

[a]PD-L1 positivity was defined by a threshold level of ≥1% positive tumor cells of any intensity detected by immunohistochemistry (IHC) using a proprietary assay (Dako PD-L1 IHC 73-10 pharmDx; Dako, Carpinteria, CA, USA); [b]Percent was calculated based on the number of non-squamous histology subjects (n=55)
[c]Prior therapy in any setting (adjuvant, advanced, and metastatic disease).

Efficacy According to RECIST v1.1 (Investigator Assessed)

	Total N = 83	Primary Refractory[a] n = 36	Acquired Resistance[a] n = 44
DCR, n (%)	**20 (24.1)**	7 (19.4)	13 (29.5)
DCR at 6 months	**9 (10.8)**	3 (8.3)	6 (13.6)
BOR, n (%)			
CR	**0**	0	0
PR	**2 (2.4)**	2 (5.6)	0
SD	**18 (21.7)**	5 (13.9)	13 (29.5)
PD	**47 (56.6)**	23 (63.9)	22 (50.0)
Not evaluable[b]	**16 (19.3)**	6 (16.7)	9 (20.5)

- Initial clinical activity was observed both in patients who were refractory or developed acquired resistance to prior anti–PD-1/PD-L1 therapy

[a] Primary refractory or acquired resistance status unknown for 3 patients; [b] 8/16% of the patients not evaluable were due to death without post-baseline scan.

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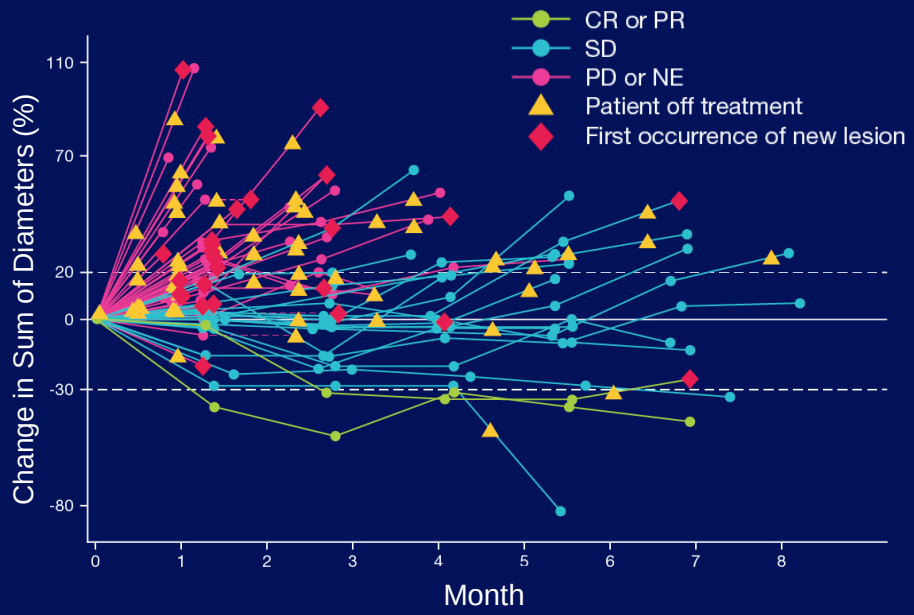
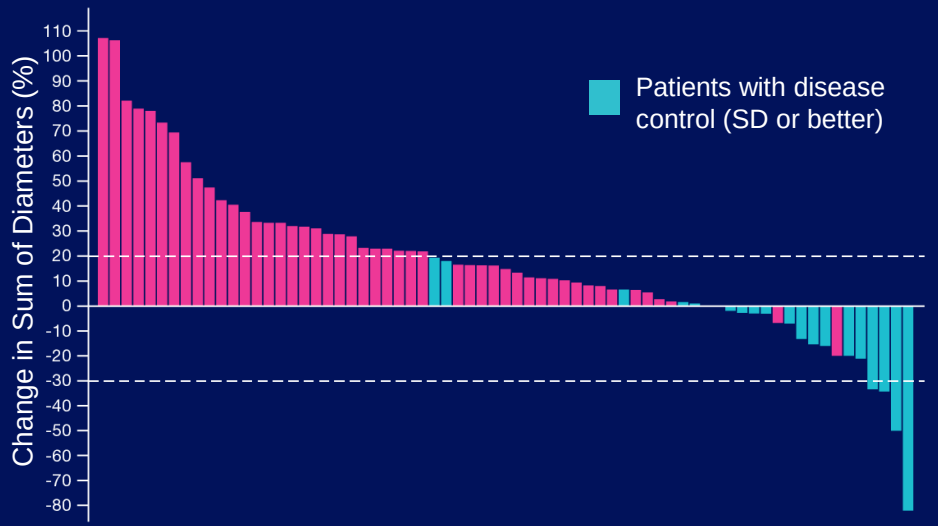
Not evaluable[b]	**16 (19.3)**	6 (16.7)	9 (20.5)
PR post data cutoff	**4 (4.8)**	3 (8.3)	1 (2.3)

- Initial clinical activity was observed both in patients who were refractory or developed acquired resistance to prior anti–PD-1/PD-L1 therapy
- ORR **4.8%** (3 confirmed and 1 unconfirmed PR) with most recent data cutoff

[a] Primary refractory or acquired resistance status unknown for 3 patients; [b] 8/16% of the patients not evaluable were due to death without post-baseline scan.

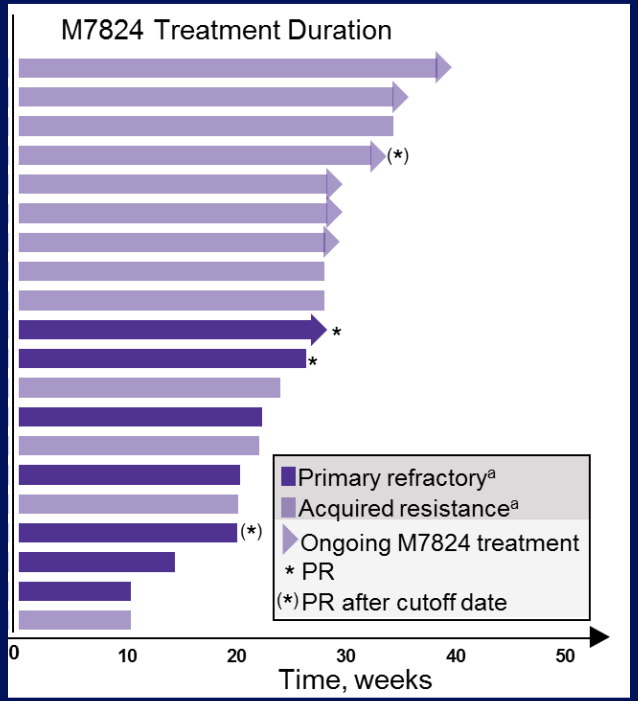
Efficacy According to RECIST v1.1 (Investigator Assessed)





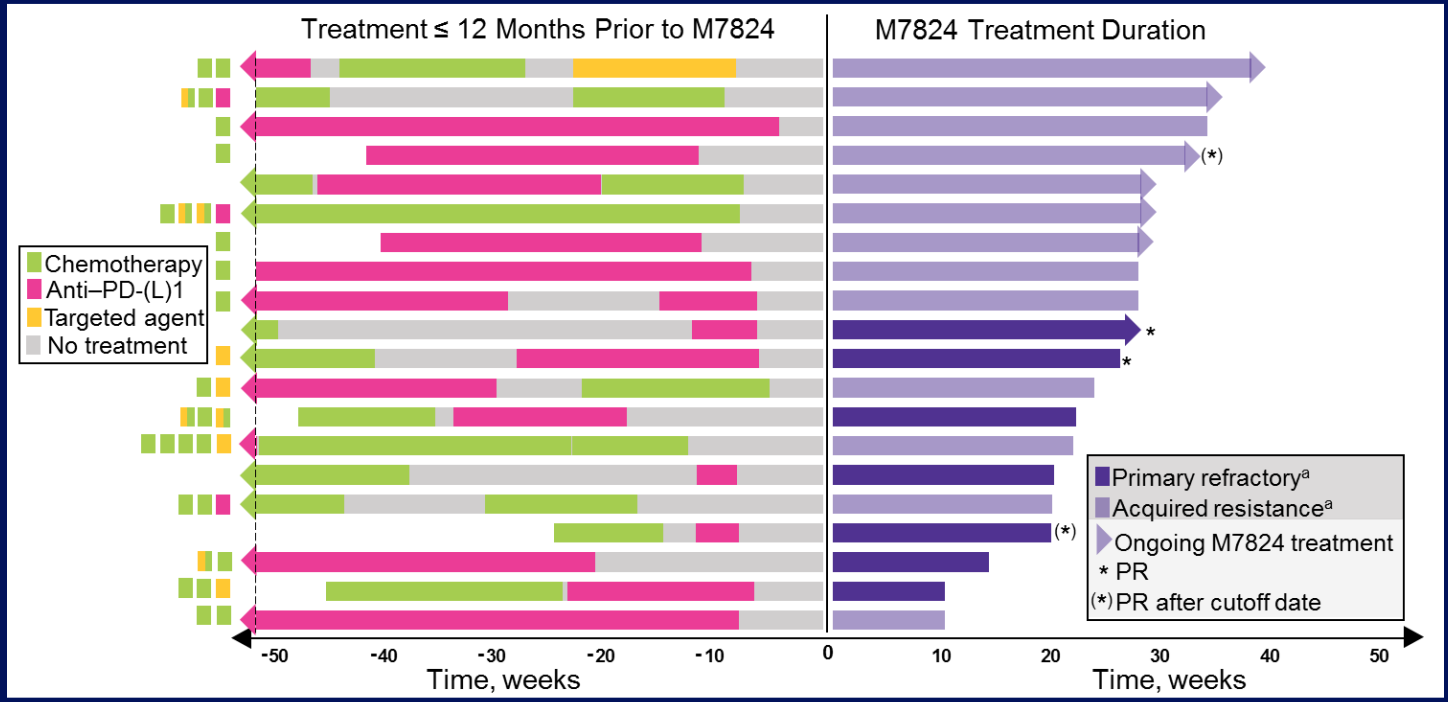
- Evidence of clinical activity and disease control in heavily pretreated population
- Median duration of treatment with M7824 was 8.0 weeks (range 2.0 – 40.1)
  - Median follow-up was 27.3 weeks (range 0.3 – 50.1)
  - 8 patients (9.6%) remain on active treatment

M7824 Treatment Durations and Prior Therapies for Patients with SD or Better



[a]BOR to prior anti–PD-1/PD-L1 treatment assessed by investigator.

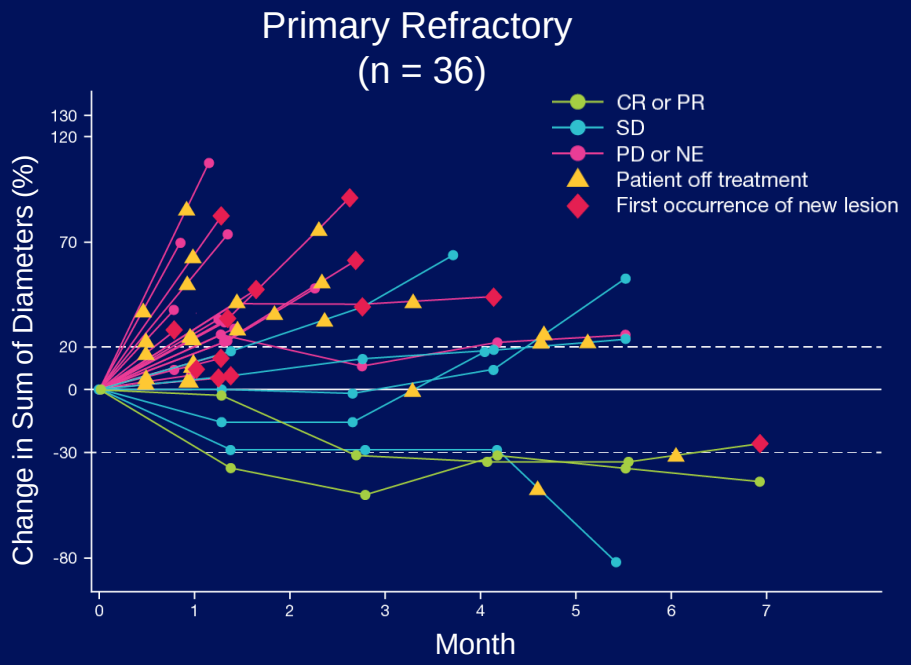
M7824 Treatment Durations and Prior Therapies for Patients with SD or Better

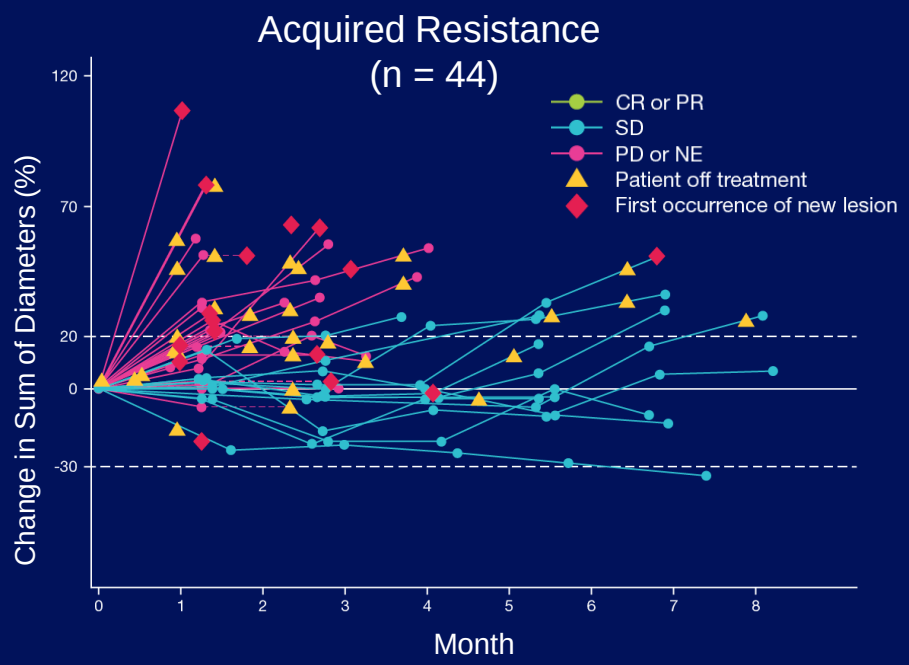


- Clinical activity noted across a range of prior treatments and treatment responses
  - 4 patients with PR received prior anti–PD-1/PD-L1 treatment, had disease progression, and then began M7824 treatment

[a]BOR to prior anti–PD-1/PD-L1 treatment assessed by investigator.

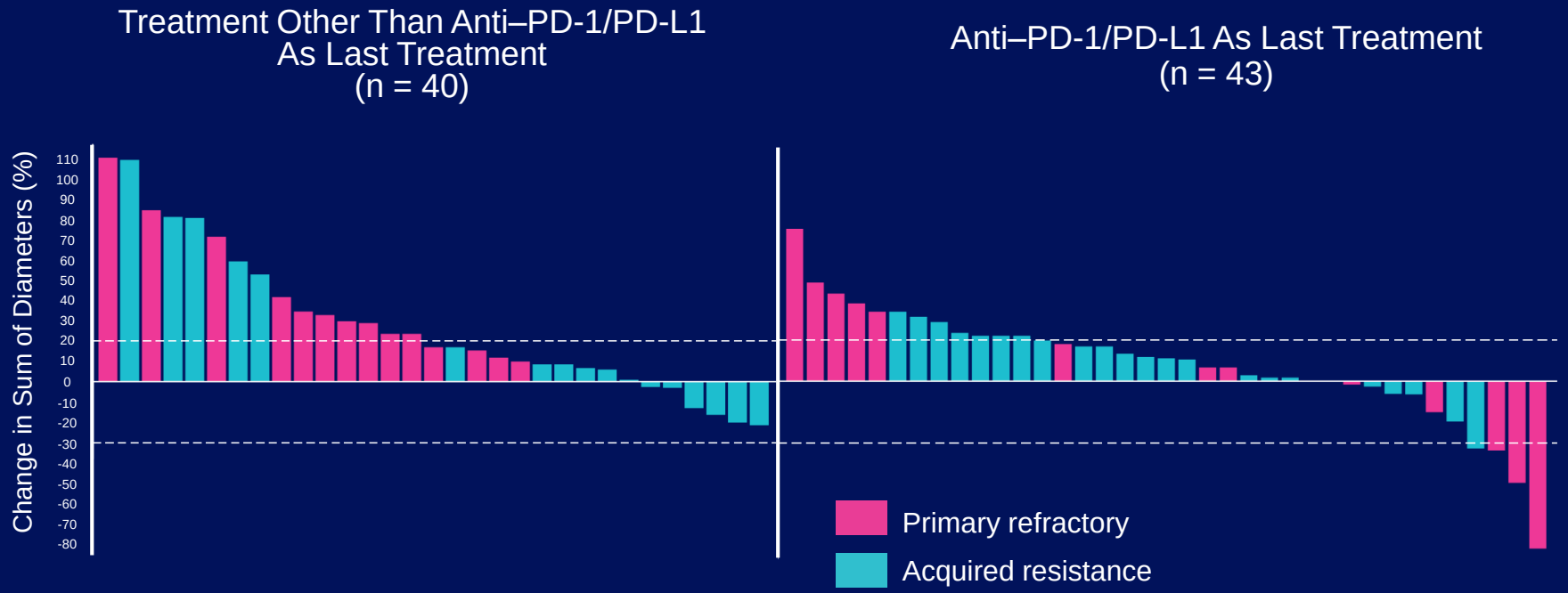
Efficacy According to RECIST v1.1 (Investigator Assessed) by BOR to Prior Anti–PD-1/PD-L1 Treatment





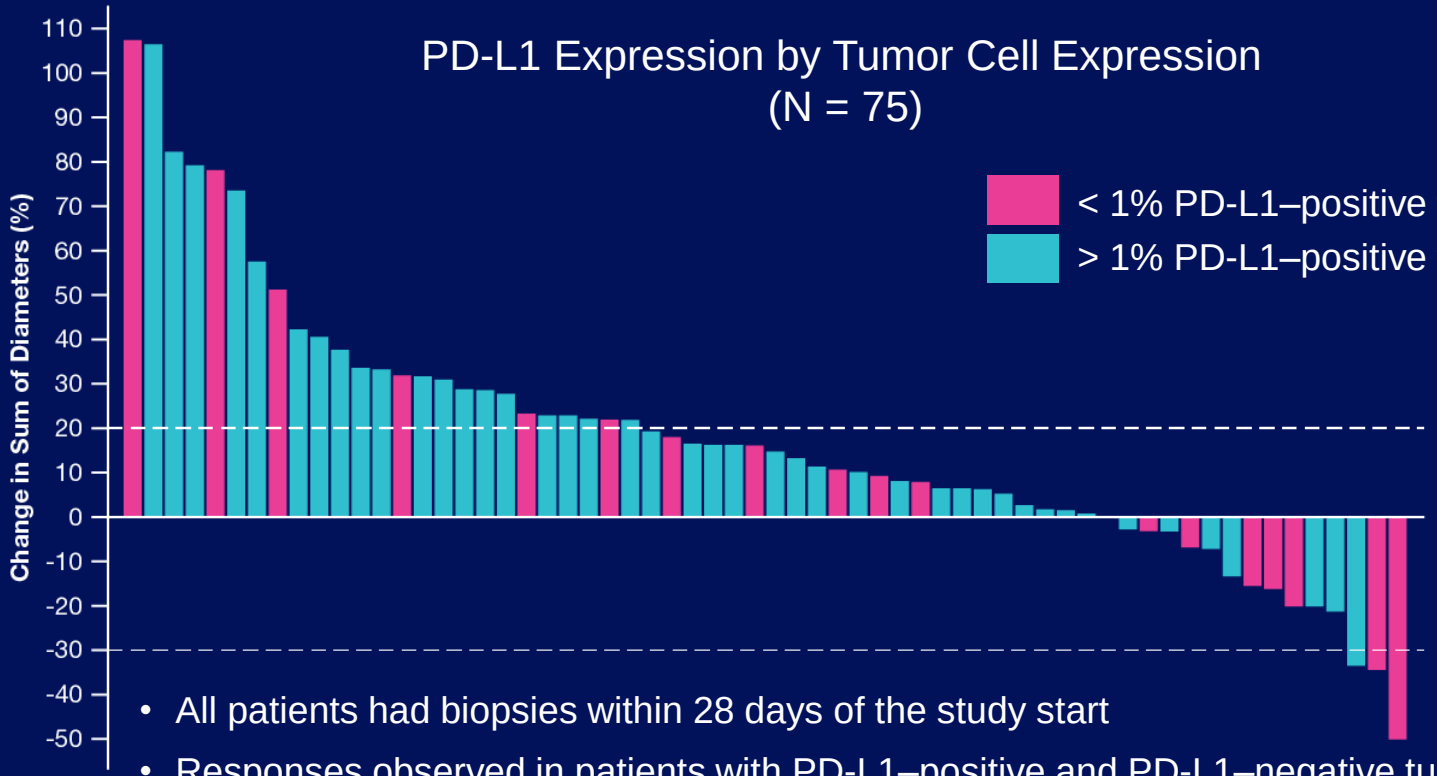
- Evidence of clinical activity observed both in patients who were primary refractory and who developed acquired resistance to prior anti–PD-1/PD-L1 treatment

Efficacy According to RECIST v1.1 (Investigator Assessed) by Last Prior Treatment



- Disease control was achieved in both patients who had anti–PD-1/PD-L1 as last treatment and patients who had last treatment other than anti–PD-1/PD-L1
- 4 patients who had PR had anti–PD-1/PD-L1 as last treatment

Efficacy According to RECIST v1.1 (Investigator Assessed) by Biomarker



- All patients had biopsies within 28 days of the study start
- Responses observed in patients with PD-L1–positive and PD-L1–negative tumors
- Further biomarker analysis is ongoing[a]

[a]Circulating TGF-β1 was not predictive of response (data not shown).

Treatment-Related AEs

Most Common TRAEs[a]

N = 83	Any Grade	Grade ≥ 3
Any TRAE, n (%)	**60 (72.3)**	**19 (22.9)**
Asthenia	23 (27.7)	3 (3.6)
Pruritus	18 (21.7)	2 (2.4)
Decreased appetite	14 (16.9)	1 (1.2)
Epistaxis	8 (9.6)	0 (0.0)
Fatigue	7 (8.4)	2 (2.4)
Arthralgia	6 (7.2)	1 (1.2)
Diarrhea	6 (7.2)	0 (0.0)
Rash maculopapular	6 (7.2)	1 (1.2)
Anemia	5 (6.0)	1 (1.2)
Dry skin	5 (6.0)	0 (0.0)

[a]Any grade in ≥ 5% of patients based on the worst grade per patient

- 19 patients (22.9%) experienced grade ≥ 3 TRAEs
  - 2 patients discontinued the treatment due to a TRAE (acute kidney injury and adrenal insufficiency)
- Cutaneous lesions occurred in 5 patients (6.0%) and were well managed by surgical excision
  - Squamous cell carcinoma of skin (n = 2 [2.4%]) and/or keratoacanthoma (n = 4 [4.8%])
- One patient died from pneumonia that was assessed by the investigator as treatment related
- The safety profile was comparable between patients who were primary refractory and who developed acquired resistance to prior anti–PD-1/PD-L1 treatment

AE, adverse event; TRAE, treatment-related AE.

Conclusions

- Treatment with M7824 results in initial clinical activity in patients with heavily pretreated NSCLC who were primary refractory or who developed acquired resistance to prior treatment with anti–PD-1/PD-L1 therapy
  - 74.7% of patients had received ≥ 3 prior therapies
    - Currently there are 4 patients with PR (ORR of 4.8%) and DCR of 24.1%
  - All 4 patients with PR had progression on anti–PD-1/PD-L1 as most recent therapy prior to receiving M7824
- Clinical activity was observed in patients who were primary refractory or who developed acquired resistance regardless of prior treatment type (chemotherapy, targeted treatment, or anti–PD-1/PD-L1)
  - Responses were observed in patients with both PD-L1–positive and PD-L1–negative tumors
  - Circulating levels of TGF-β1 were not predictive of response in this ongoing study
- M7824 has a manageable safety profile in this patient population
- Based on initial activity in patients with NSCLC who were primary refractory or who developed acquired resistance to prior treatment with anti–PD-1/PD-L1 therapy and promising emerging data in 2L NSCLC patients naïve to anti–PD-1/PD-L1 agents from an ongoing expansion cohort, further studies in NSCLC are warranted

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