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Thyroid Dysfunction in Patients Receiving Immune Checkpoint Inhibitors

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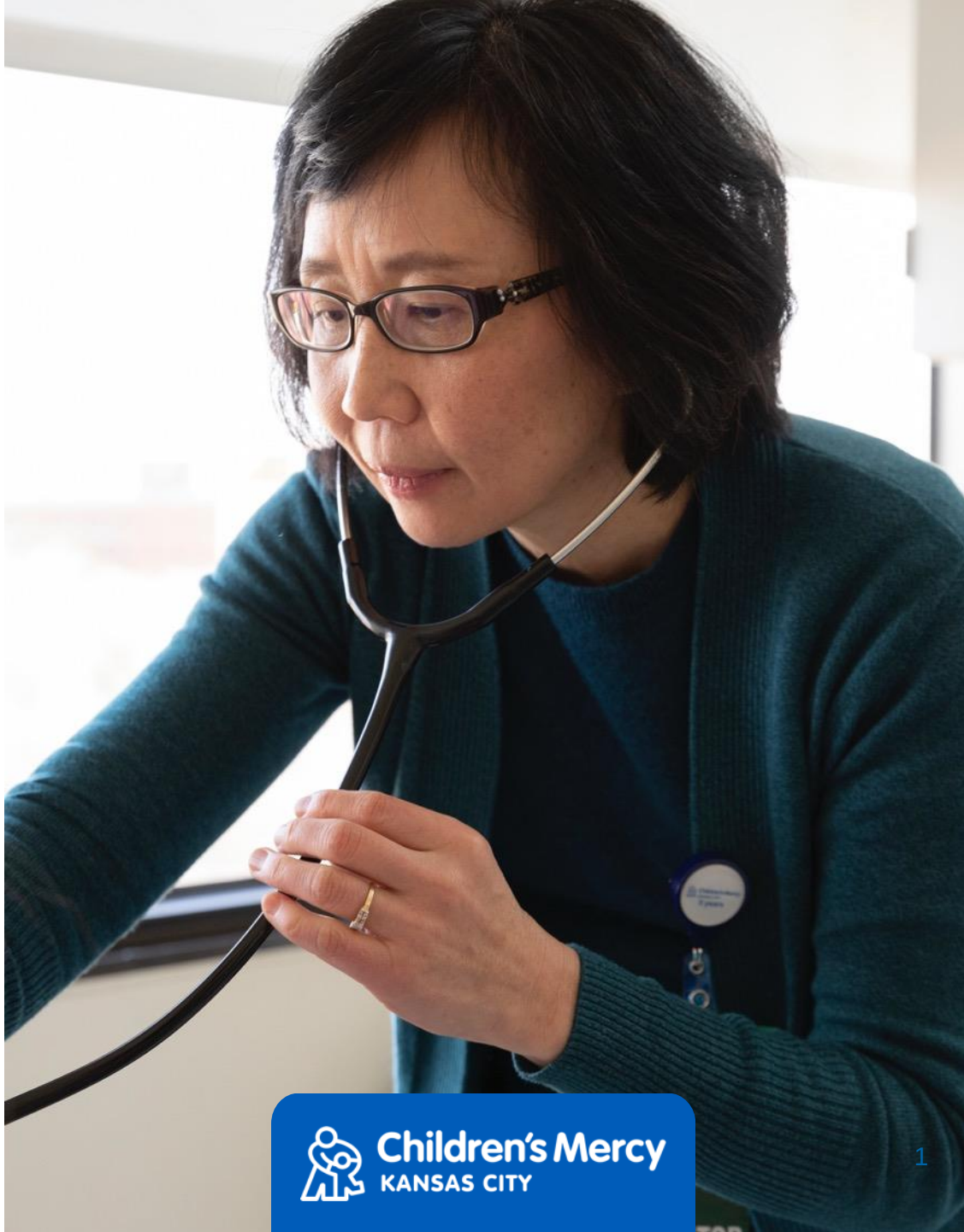
CMH Research Days



Outline

- Background
  - Immune Checkpoint Inhibitors (ICI)
- Methods
- Results
- Conclusions
- Acknowledgements

Background

- Immune checkpoint inhibitors (ICIs)
  - Monoclonal antibodies that target various immune checkpoints
  - Increasing in cancer treatment
  - Targets
    - Programmed cell death protein 1 (PD-1):
      - Nivolumab, Pembrolizumab
    - Programmed death ligand 1 (PD-L1):
      - Atezolizumab, Durvalumab
    - Cytotoxic T-lymphocytes associated protein 4 (CTLA-4):
      - Ipilimumab, Tremelimumab

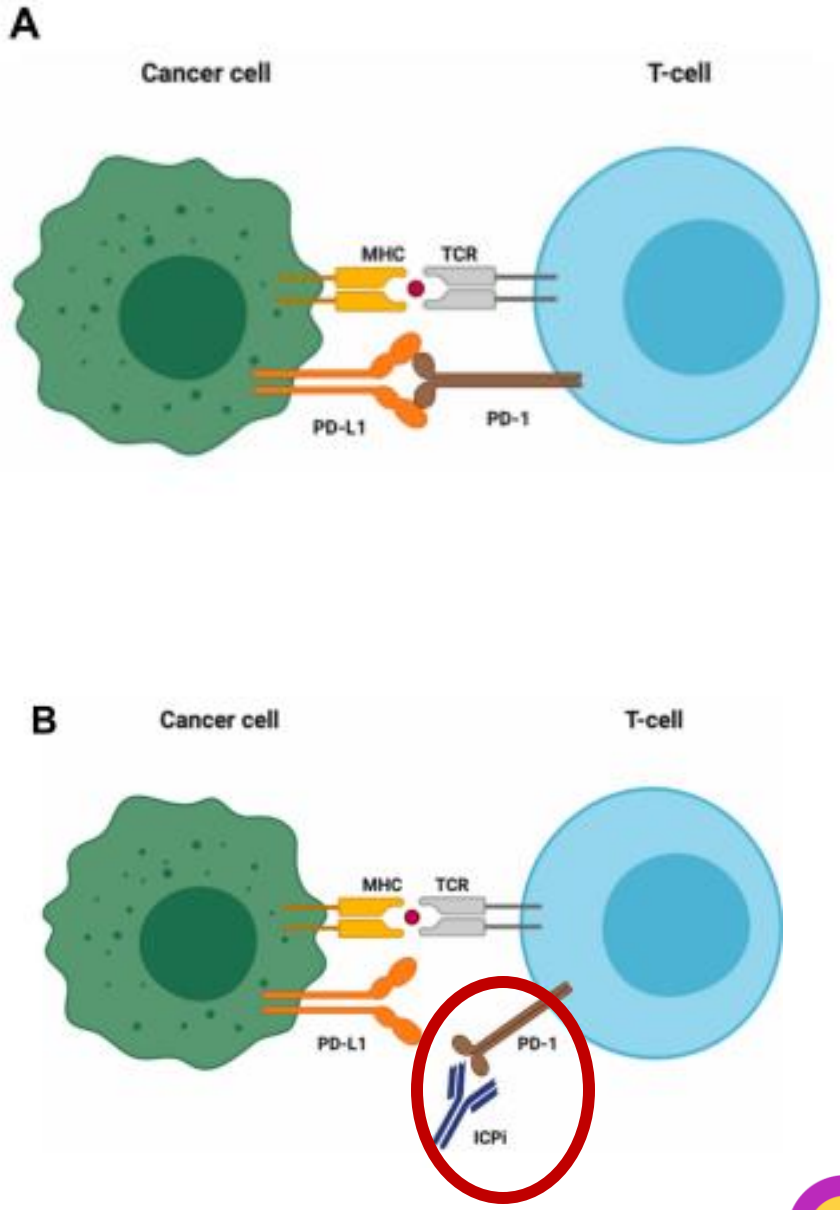


Figure From: El Sabbagh, et al. Thyroid dysfunctions due to Immune Checkpoint Inhibitors: A Review. *International Journal of General Medicine*. 2020: 13: 1003-1009.

Adverse Effects

- Immune-related adverse events (IrAEs)
  - Endocrine system
    - Thyroid dysfunction
    - Hypophysitis
    - Adrenal Insufficiency
    - Type 1 diabetes
- Literature from adult studies

ICIs and Thyroid Dysfunction

- Mechanism: unknown
  - Autoimmune reaction in thyroid gland
  - Alter thyroid related gene expression
- Highest incidence in PD-1 inhibitors and combo therapy
- Pathology
  - Hypothyroidism (too little)
  - Hyperthyroidism (too much)
  - Thyroiditis

ICI	ICI Target	Summary Incidence [% (95% CI)]		
		Hypothyroidism	Hyperthyroidism	Thyroiditis
Ipilimumab	CTLA-4	3.8 (2.6-5.5)	1.4 (0.8-2.4)	2.1 (1.1-4.1)
Tremelimumab	CTLA-4	Up to 5.2%	Up to 5.2%	Up to 5.2%
Nivolumab	PD-1	8.0 (6.4-9.8)	2.8 (2.1-3.8)	1.6 (0.2-10.2)
Pembrolizumab	PD-1	8.5 (7.5-9.7)	3.7 (2.8-4.7)	2.3 (1.2-4.6)
Atezolizumab	PD-L1	6.0 (4.2-8.4)	unknown	Unknown
Durvalumab	PD-L1	4.7 (2.5-8.8)	unknown	Unknown
Ipilimumab + Nivolumab	CTLA-4 + PD-1	16.4 (11.7-22.5)	9.4 (7.1-12.3)	3.8 (1.4-9.4)
Ipilimumab + Pembrolizumab	CTLA-4 + PD-1	15.1 (10.6-21.8)	10.4 (6.6-16.1)	4.6 (2.2-9.3)
Durvalumab + Tremelimumab	PD-L1 + CTLA-4	10.2 (5.6-17.9)	unknown	unknown

Adapted from Filette, et al. A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Event Associated with Immune Checkpoint Inhibitors. Horm Meta Res 2019; 51: 145-156.

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Thyroid Dysfunction in Children Exposed to ICIs

OTHER THERAPEUTIC MODALITIES — **ANTIBODY-BASED IMMUNE THERAPIES (CONT)**

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
163	Other antibody-based immune therapies, including antibody drug conjugates (e.g., blinatumomab, brentuximab vedotin, inotuzumab, gemtuzumab ozogamicin, dinutuximab, naxitamab, pembrolizumab, ipilimumab, nivolumab, atezolizumab)	Insufficient information currently available regarding late effects		SYSTEM = No Known Late Effects SCORE = N/A

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Objective

Investigate the prevalence of thyroid dysfunction in patients who received ICIs at one pediatric institution (Children's Mercy Hospital)

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Methods

- Retrospective, descriptive study
  - Received one or more of the following ICIs
    - PD-1 Inhibitors: Nivolumab, Pembrolizumab
    - PD-L1 Inhibitors: Atezolizumab, Durvalumab
    - CTLA-4 Inhibitors: Ipilimumab, Tremelimumab
  - Excluded:
    - Diagnosed at OSH and records were unavailable
    - Patient death within 35 days of receiving initial ICI
- Thyroid function tests recorded
  - Considered abnormal if outside reference range for age

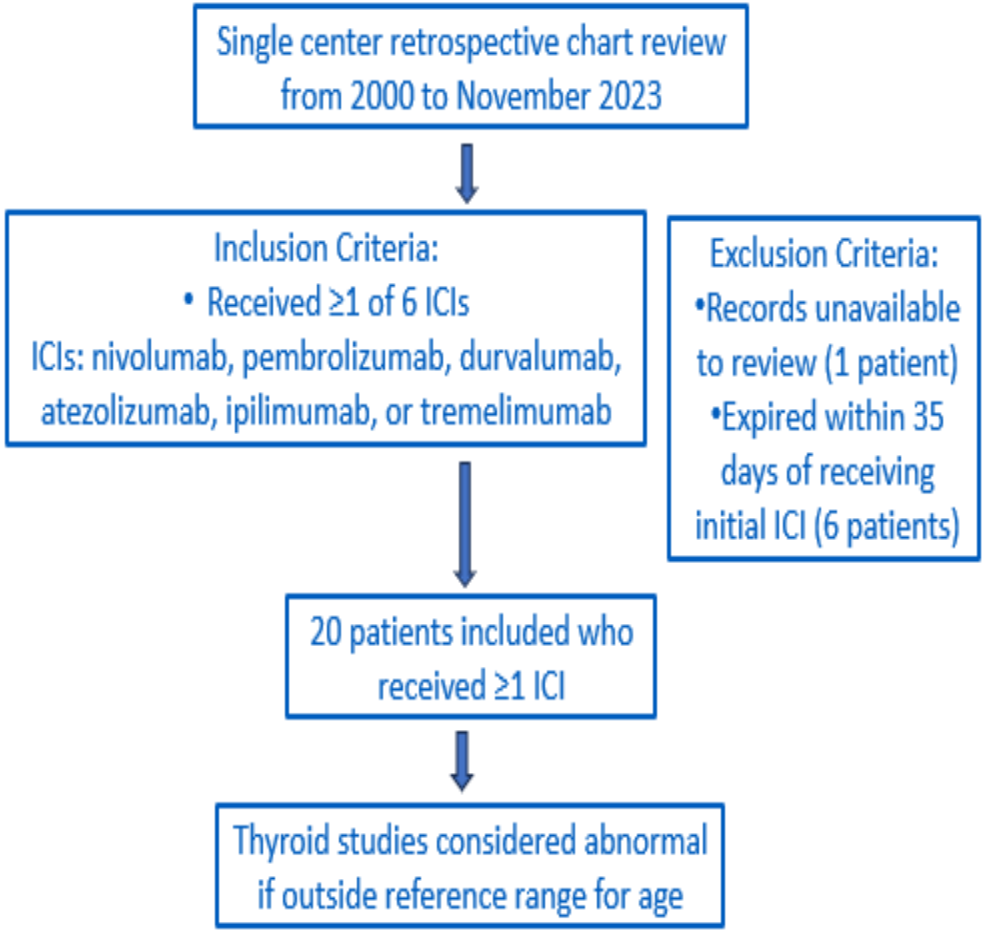

Figure 1: Breakdown of patients included in study.

Results: Characteristics

Patient Characteristics		
Sex	Male (n)	9
	Female (n)	11
Age at Diagnosis	Median (yr)	14.4
	Mean (yr)	12.5
Deceased	n	6
Relapse or Progression	N (%)	11 (55%)
Cancer Type	Blood (Leukemia/Lymphoma)	12 (60%)
	Solid	6 (30%)
	Melanoma	2 (10%)
Age at initial ICI	Median (yr)	14.9
	Mean (yr)	14.5

Table 1: Patient characteristics (n=20)

Immune Checkpoint Inhibitor Therapy	n (%)
Nivolumab	14 (70%)
Pembrolizumab	7 (35%)
Ipilimumab	1 (5%)
Atezolizumab	2 (10%)
Tremelimumab	2 (10%)
Durvalumab	2 (10%)
Received multiple ICIs	3 (15%)

Table 2: Immune checkpoint inhibitor therapy received

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Results: Thyroid Monitoring

- TFTs
  - Before or at time of initial ICI: 15 patients
  - After initial ICI: 16 patients
  - Before and after initial ICI: 12 patients
- Levothyroxine treatment
  - Before initial ICI: 3 patients
  - After initial ICI: 6 patients

- TFTs
  - TSH – thyroid stimulating hormone
  - FT4 – free thyroxine (T4)

Results: Thyroid Dysfunction

- Thyroid dysfunction seen in 6 patients after initial ICI
  - Hypothyroidism – 5 (25%)
    - Levothyroxine required in 4 patients
    - One case of central hypothyroidism
    - Three new diagnoses of hypothyroidism
  - Hyperthyroidism – 1 (5%)
    - Resolved with discontinuation of levothyroxine
      - Previous diagnosis of hypothyroidism
    - After initial ICI, initially hyperthyroid which proceeded to hypothyroidism requiring increased levothyroxine dose

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Table 3: Thyroid monitoring and levothyroxine treatment before and after ICI therapy

Results: Thyroid Dysfunction

- New diagnosis of hypothyroidism following ICI in 3 patients

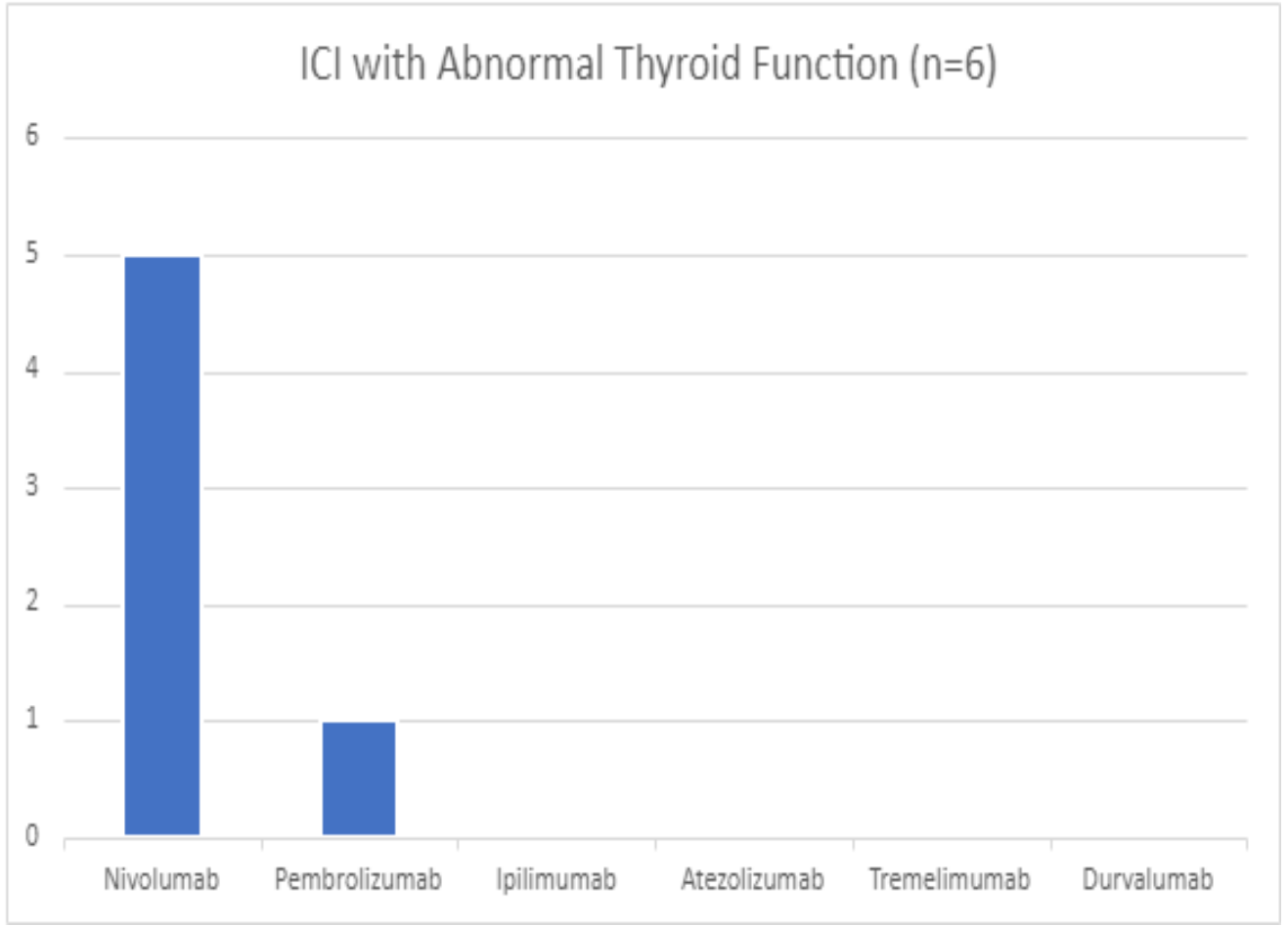
Time to Thyroid Dysfunction		
n = 3	Average	Median
Abnormal TFT	3.5 months	2.4 months
Levothyroxine Treatment	4.2 months	2.8 months

Table 4: time to thyroid dysfunction in patients with new diagnosis of hypothyroidism following initial ICI therapy

Results: Thyroid Dysfunction with Previous History of Hypothyroidism

- 3 patients on levothyroxine for hypothyroidism prior to initial ICI
  - Primary hypothyroidism secondary to tyrosine kinase inhibitor (TKI)
  - Primary hypothyroidism secondary to radiation
  - Unknown
- 67% with thyroid dysfunction following initial ICI (67%)
  - Average time to dysfunction: 0.85 months

Results: Thyroid Dysfunction and ICI



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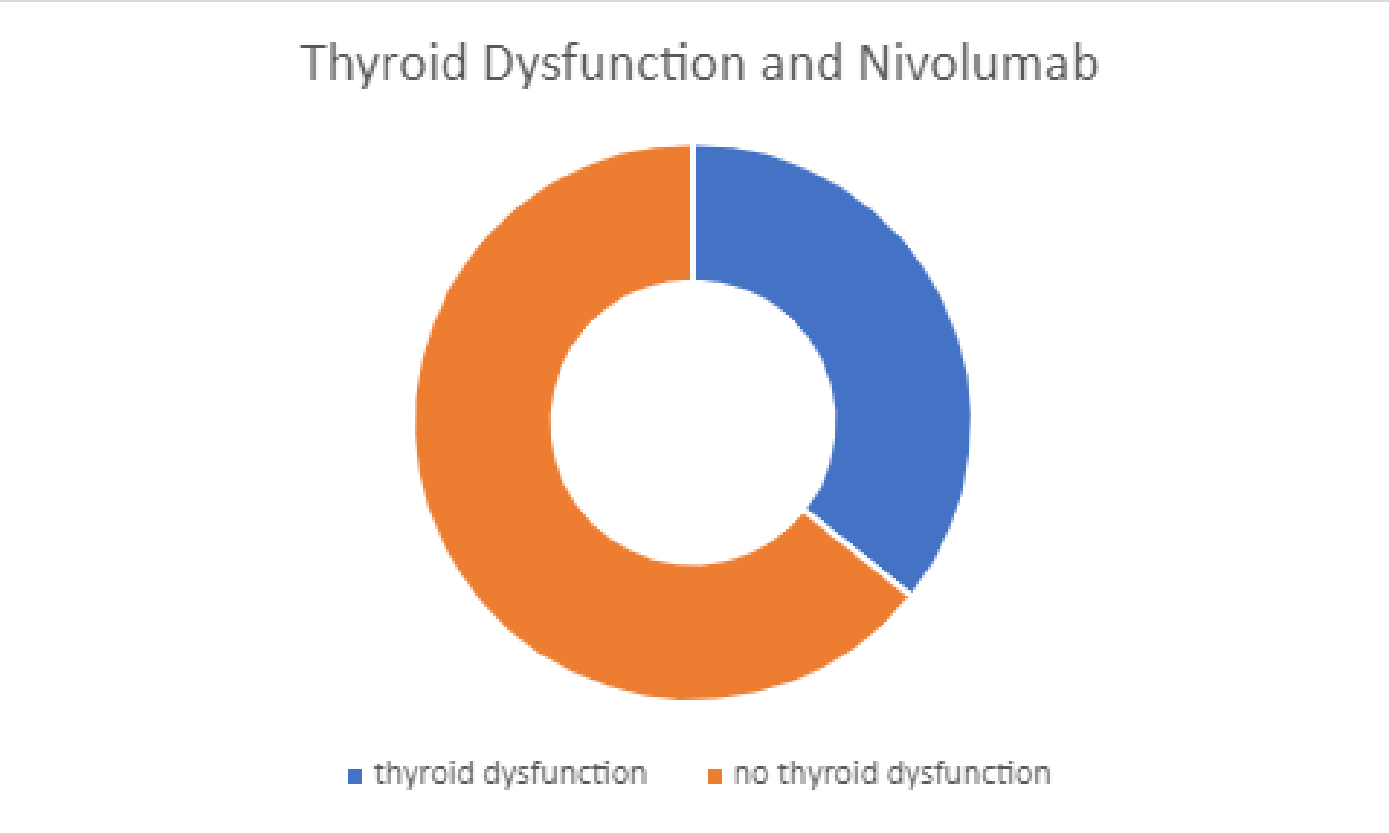
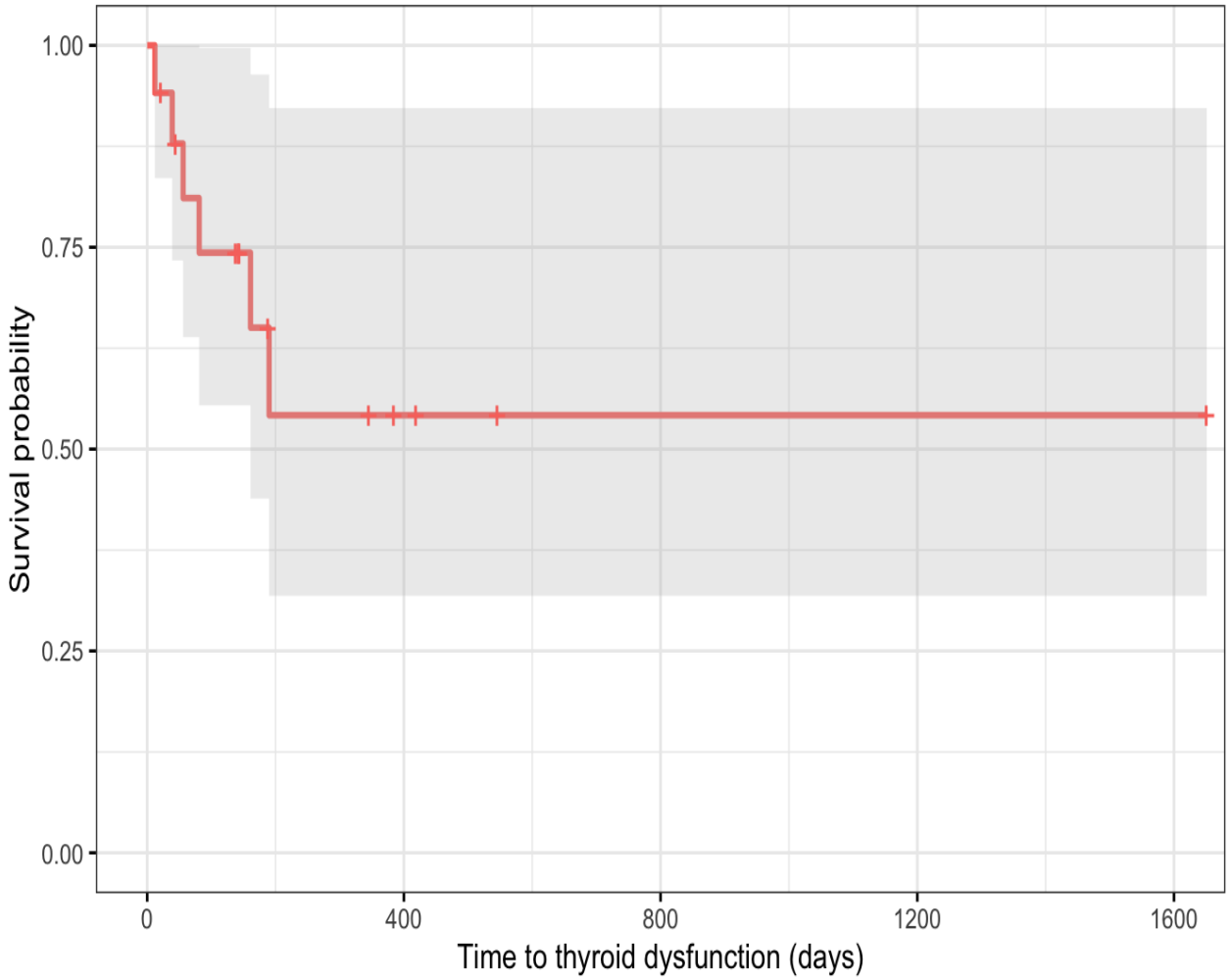
Results: Thyroid Dysfunction and Nivolumab

- Thyroid dysfunction in 36% of patients who received Nivolumab
  - Appears higher than reported in adults



Results: Kaplan-Meier Estimate



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Conclusions

- Thyroid dysfunction can be seen in patients receiving ICI therapy
  - Supports monitoring thyroid function tests before, during, and after therapy
    - TSH (thyroid stimulating hormone) and FT4 (free thyroxine)
  - If previous history of thyroid dysfunction, thyroid dysfunction appears to occur earlier (0.85 months vs 3.5 months)
    - However, n is very small (2 vs 3)
    - Thyroid needs may be higher → increased levothyroxine dose
  - Highest risk in those who receive Nivolumab (PD-1 inhibitor)
    - Consistent with adult studies

Limitations

- Small study
  - n = 20
  - Data not separated by specific ICI
- Descriptive study
  - No comparison group

Future Directions

- Additional endocrinopathies
  - Adrenal Insufficiency
  - Diabetes Mellitus
  - Hypophysitis
- Increase study size
  - Multiple centers

Acknowledgements

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  - Jennifer Boyd, DO
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  - Christopher Klockau, RPh, BCOP
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References

- Filette, et al. A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Event Associated with Immune Checkpoint Inhibitors. *Horm Meta Res* 2019; 51: 145-156.
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Thank You!

Questions?