

# #406P Adrenal insufficiency induced by immune checkpoint inhibitors: Clinical characteristics of 145 cases.

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## Background

- Adrenal insufficiency (AI) is one of the immune-related adverse events (irAEs) associated with Immune checkpoint inhibitor (ICI). [1]
- The incidence of AI induced by ICI has been reported to be 0.3-1.7%. [2]
- Delayed diagnosis of AI could lead to serious outcomes such as adrenal crisis.
- Few studies have described the detailed clinical features of this rare, but potentially life-threatening irAE.

## Objectives

The aims of this study were to summarize the clinical characteristics and treatment course of ICI associated AI and to identify symptoms and laboratory findings for its early detection and diagnosis.

## Results

### ■ Patient characteristics

|                              | n=145 | %       |
|------------------------------|-------|---------|
| <b>Age</b><br>[median,range] | 68    | [30-85] |
| <b>Gender</b>                |       |         |
| Male                         | 104   | 71.7    |
| Female                       | 41    | 28.3    |
| <b>ECOG PS</b>               |       |         |
| 0                            | 68    | 46.9    |
| 1                            | 72    | 49.7    |
| 2-3                          | 5     | 3.4     |

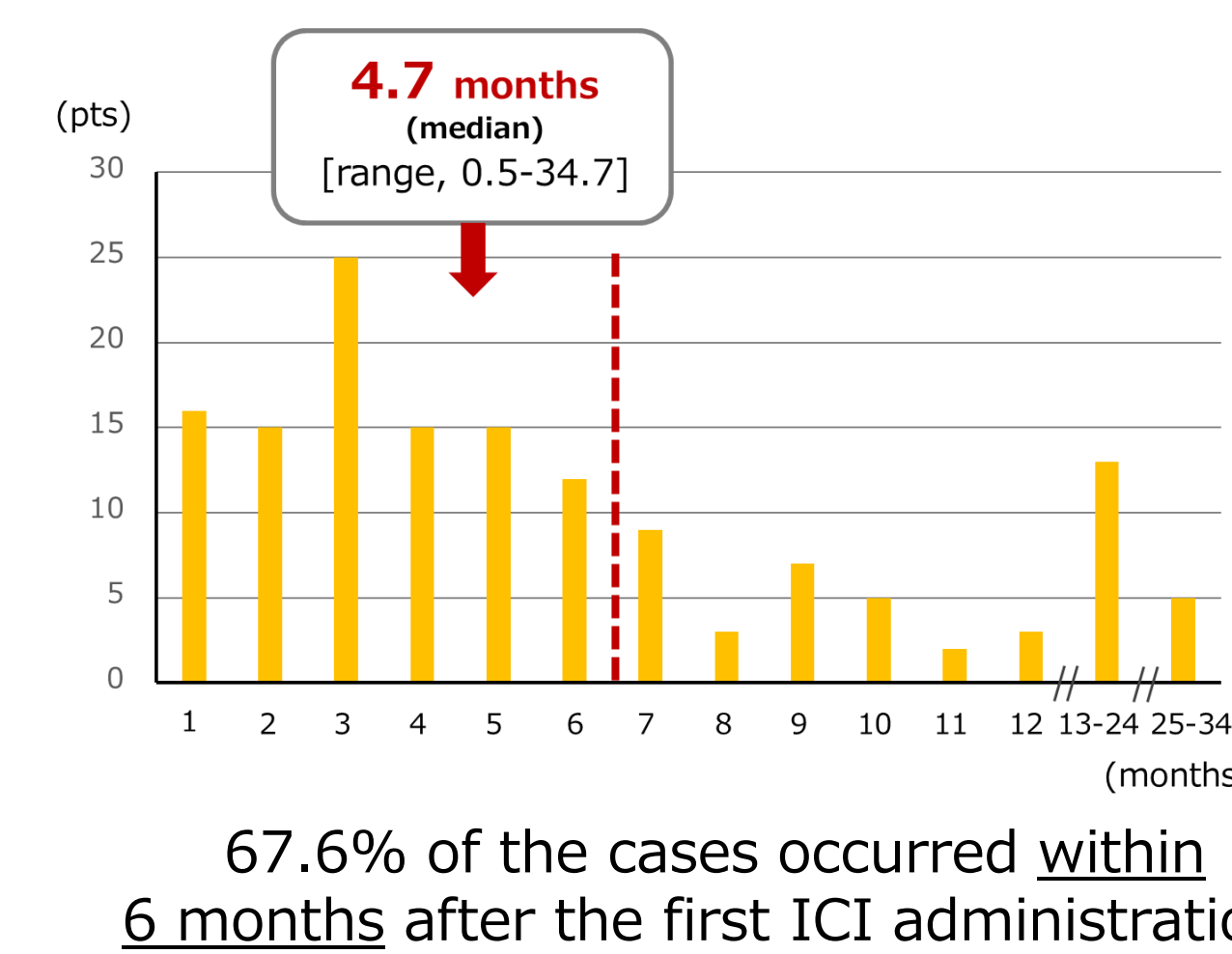
|                        | n=145 | %    |
|------------------------|-------|------|
| <b>Treatment lines</b> |       |      |
| 1 <sup>st</sup>        | 66    | 45.5 |
| 2 <sup>nd</sup>        | 45    | 31.0 |
| 3 <sup>rd</sup>        | 19    | 13.1 |
| ≥ 4 <sup>th</sup>      | 15    | 10.3 |
| <b>Tumor types</b>     |       |      |
| Lung                   | 54    | 37.2 |
| Melanoma               | 35    | 24.1 |
| Renal cell             | 16    | 11.0 |
| Head and neck          | 14    | 9.7  |
| Gastrointestinal       | 11    | 7.6  |
| Others*                | 15    | 10.3 |

\*Esophageal cancer, Urothelial cancer, Hodgkin's lymphoma, Pleural cancer, Unknown primary carcinoma, Merkel cell tumor and Endometrial cancer.

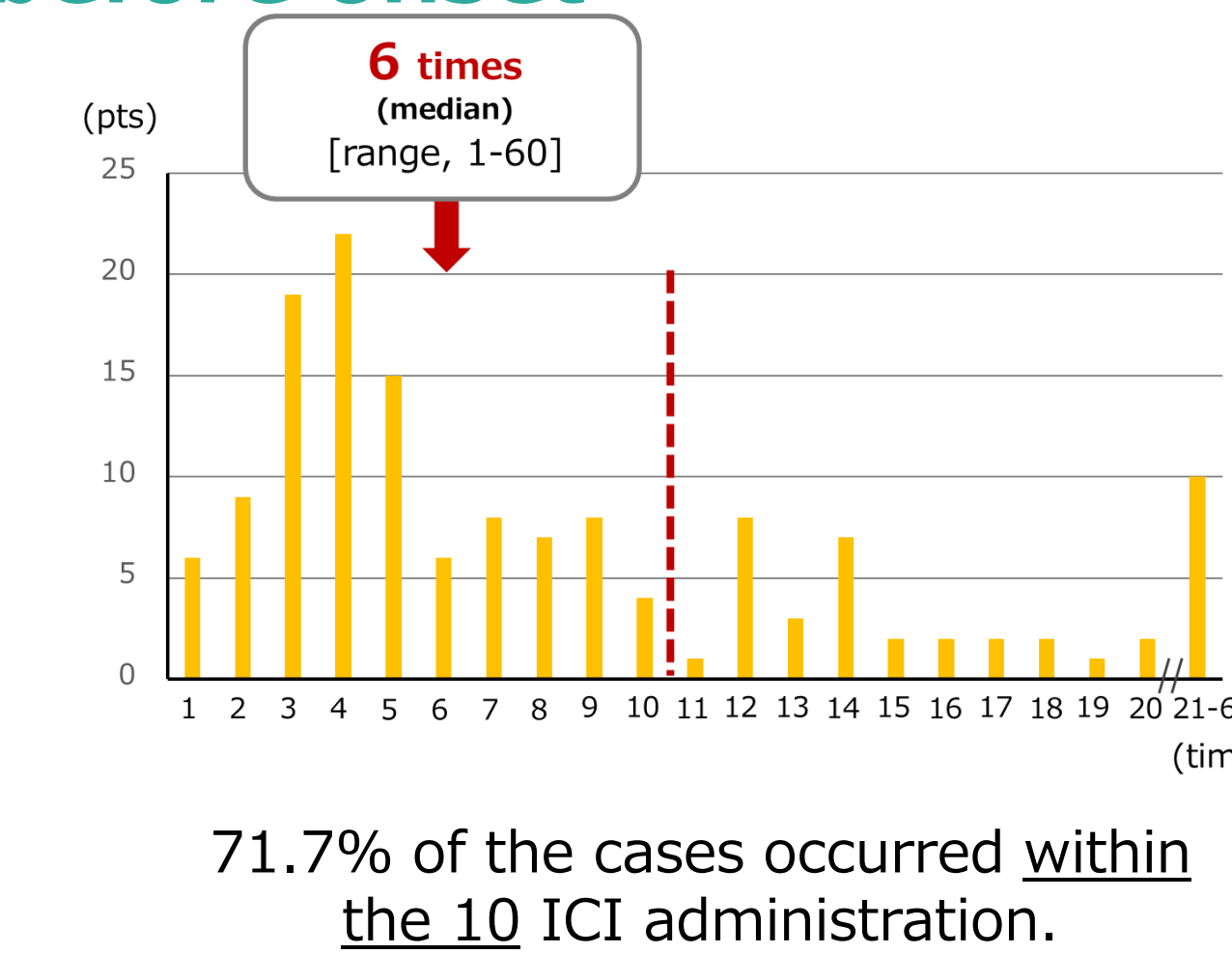
### ■ Treatment regimen

|  | n=145 | %    |
|--|-------|------|
| <b>Monotherapy</b> : anti-PD-1 or anti-PD-L1 | 102   | 70.3 |
| Nivolumab                                    | 67    | 46.2 |
| Pembrolizumab                                | 33    | 22.8 |
| Atezolizumab                                 | 1     | 0.7  |
| Durvalumab                                   | 0     | 0    |
| Avelumab                                     | 1     | 0.7  |
| <b>Monotherapy</b> : anti-CTLA-4(Ipilimumab) | 3     | 2.1  |
| <b>Combination therapy</b>                   | 40    | 27.6 |
| Nivolumab+Ipilimumab                         | 26    | 17.9 |
| Pembrolizumab+cytotoxic                      | 10    | 6.9  |
| Atezolizumab+cytotoxic                       | 4     | 2.8  |

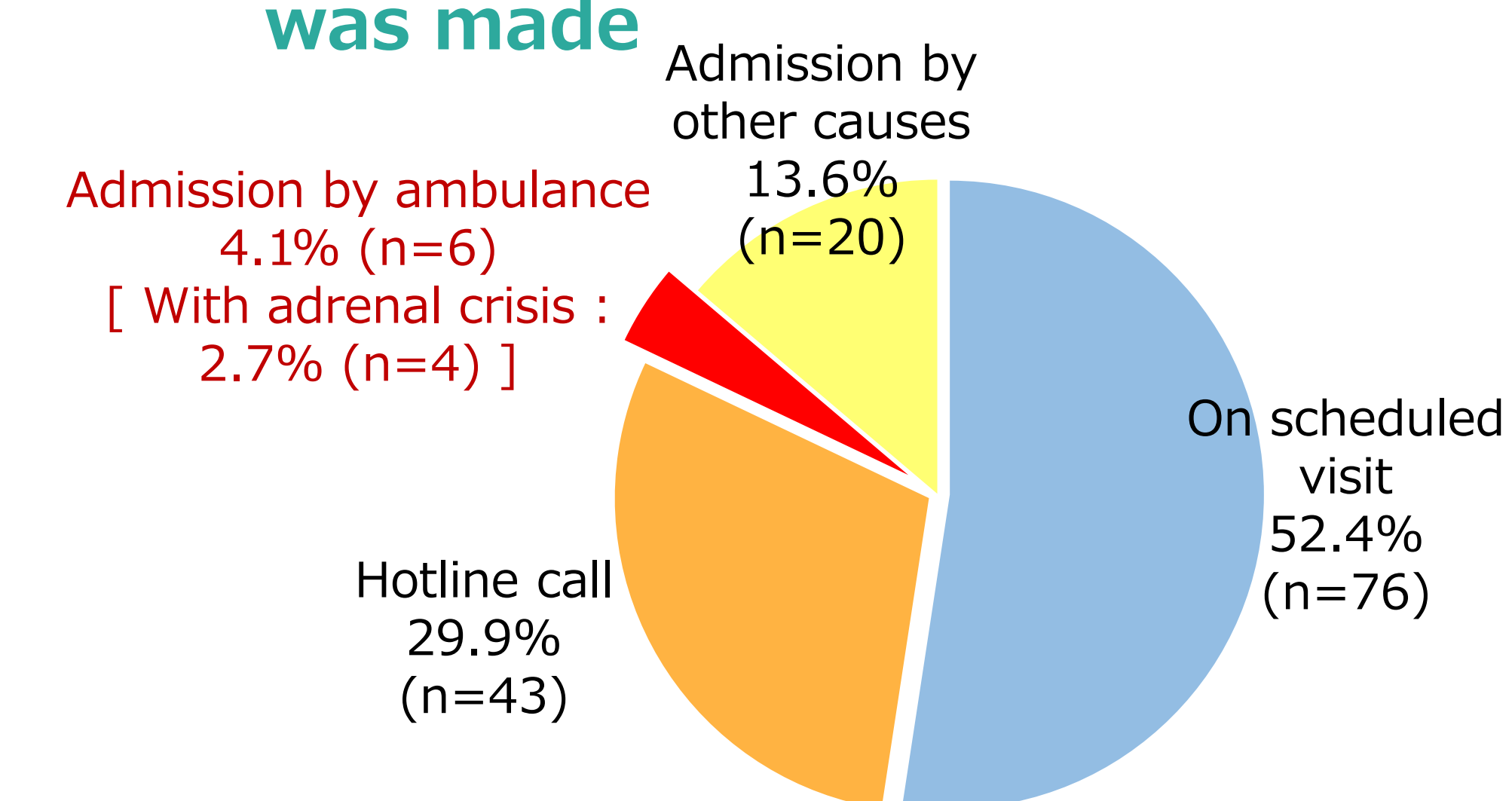
### ■ Time to clinical diagnosis



### ■ Number of ICI administrations before onset



### ■ Occasion when the diagnosis was made



### ■ Endocrinological findings

#### Diagnosis

- Primary : 2 pts (1%)\*
- Secondary : 136 pts (99%)\* (pituitary)

\*138 patients in which both cortisol and ACTH levels were available

#### L/D at diagnosis

|                         | [n=145]      |
|-------------------------|--------------|
| <b>Cortisol (µg/dL)</b> |              |
| Median                  | 1.40         |
| [range]                 | [0.05-30.90] |
| <b>ACTH (pg/mL)</b>     |              |
| Median                  | 3.70         |
| [range]                 | [0.5-177.0]  |

### ■ Treatment

#### Types and Dosages of Glucocorticoids

| Initial dosage           | (n)       | (%)         |
|--------------------------|-----------|-------------|
| <b>HC (≤20mg/day)</b>    | <b>63</b> | <b>43.4</b> |
| <b>HC (&gt;20mg/day)</b> | <b>41</b> | <b>28.3</b> |
| PSL                      | 30        | 20.7        |
| mPSL                     | 4         | 2.8         |
| DEX                      | 4         | 2.8         |
| BBP                      | 2         | 1.4         |
| none                     | 1         | 0.7         |

| Maintenance              | (n)       | (%)         |
|--------------------------|-----------|-------------|
| <b>HC (≤20mg/day)</b>    | <b>98</b> | <b>67.6</b> |
| <b>HC (&gt;20mg/day)</b> | <b>15</b> | <b>10.3</b> |
| PSL                      | 25        | 17.2        |
| mPSL                     | 0         | 0           |
| DEX                      | 3         | 2.1         |
| BBP                      | 2         | 1.4         |
| none                     | 2         | 1.4         |

HC: hydrocortisone, PSL: prednisolone, mPSL: methylprednisolone, DEX: dexamethasone, BBP: betamethasone

### ■ Onset of Adrenal insufficiency

#### Symptoms at diagnosis

|                      | n=145 | %    |
|----------------------|-------|------|
| Anorexia             | 84    | 57.8 |
| Fatigue              | 78    | 53.7 |
| Nausea and vomiting  | 43    | 33.3 |
| Fever (≥38.0°C)      | 22    | 15.0 |
| Diarrhea             | 15    | 10.2 |
| Muscle weakness      | 7     | 4.8  |
| Arthritis or Myalgia | 5     | 3.4  |
| Adrenal crisis       | 8     | 5.4  |
| No symptoms          | 15    | 10.9 |

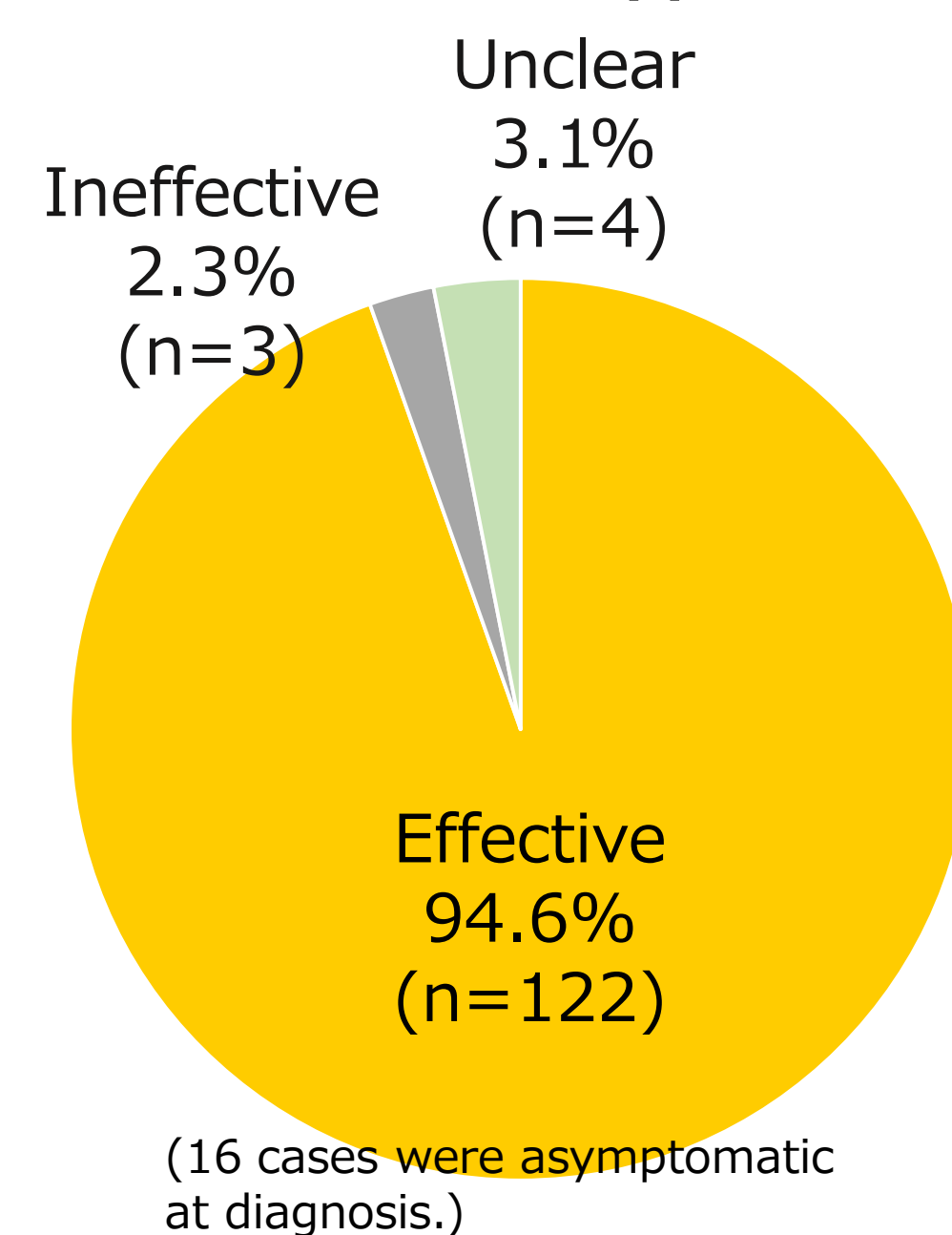
(overlapping)

#### Laboratory and Imaging findings at diagnosis

|                                 | n=145 | %    |
|---------------------------------|-------|------|
| <b>Laboratory findings</b>      |       |      |
| Hyponatremia(Na ≤135mEq/L)      | 59    | 40.7 |
| Eosinophilia(≥500/µL or ≥8%)    | 56    | 38.6 |
| Hypotension(SBP ≤100mmHg)       | 42    | 29.0 |
| Hypoglycemia(BS ≤70mg/dL)       | 6     | 4.1  |
| No abnormal laboratory findings | 17    | 11.7 |
| <b>MRI findings</b>             |       |      |
| Enlarged pituitary gland on MRI | 11*   | -    |
| Normal                          | 41    | -    |
| Not done                        | 93    | -    |

\* Patients treated with anti-PD-1 + anti-CTLA-4: 8, anti-PD-1: 3 (overlapping)

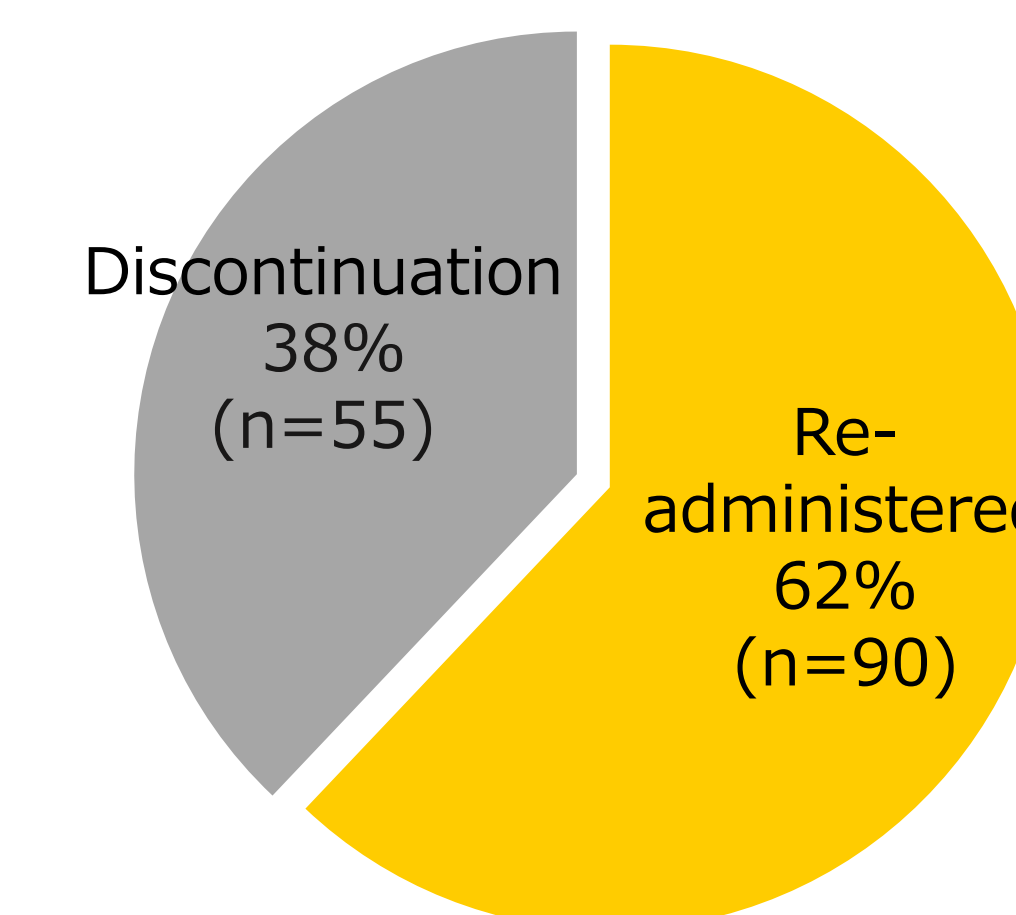
#### Effect of corticosteroid supplementation



### ■ Re-administration of ICI after the onset of AI

#### Reason for discontinuation

|                          | (n) |
|--------------------------|-----|
| PD or cPD                | 29  |
| Follow-up to maintain PR | 13  |
| Other adverse events     | 8   |
| Onset of AI              | 5   |



## Summary

- In this study, almost all of the AI cases were secondary to ACTH deficiency.
- In about 70% of the cases, AI occurred within the 6 months and 10th cycles after the initiation of ICIs.
- Patients showed similar symptoms and findings to those of general AI, but those were not always present in each case. Also, in certain proportion of patients, the diagnosis was made before the onset of overt symptoms by regular measurement of ACTH and cortisol levels.

## Conclusion

- We should measure ACTH and cortisol levels regularly at least during the first 6 months for early detection of AI, so that asymptomatic AI in patients treated with ICI is not overlooked.
- To notify the patients to contact the healthcare professionals immediately when typical symptoms appear is essential.

## Reference

- [1]Michael A, et al. NEJM, 2018.
- [2]Wang PF, et al. Front Pharmacol, 2017.Higashiyama, et al. ASCO-SITC, 2017.
- [3]Arima H, et al. Endocr J, 2019.
- [4]Yanase T, et al. Endocrine Journal, 2016.
- [5]Ariyasu R, et al. Anticancer Res, 2017.

## Conflicts of interest

All authors declare that they have no conflicts of interest to declare related to the content of this presentation.

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