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Analysis of Immune-Related Adverse Events and Time-to-Treatment Discontinuation of Atezolizumab and Bevacizumab in Patients with HCC : A Multicenter Cohort Study

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Aims of study

- Outcomes
  - Overall survival (OS), Progression free survival (PFS)
  - **Time to treatment discontinuation (TTD)**

- Cause of treatment discontinuation
  - progression or adverse events (AEs)
  - **Immune related adverse events (irAEs);** Grade ≥3 (CTCAE)

Materials and Methods

- Retrospective multi-center study
- Consecutive HCC patients received A+B
- At six centers affiliated with the Catholic University of Korea, from September 2020 to December 2022

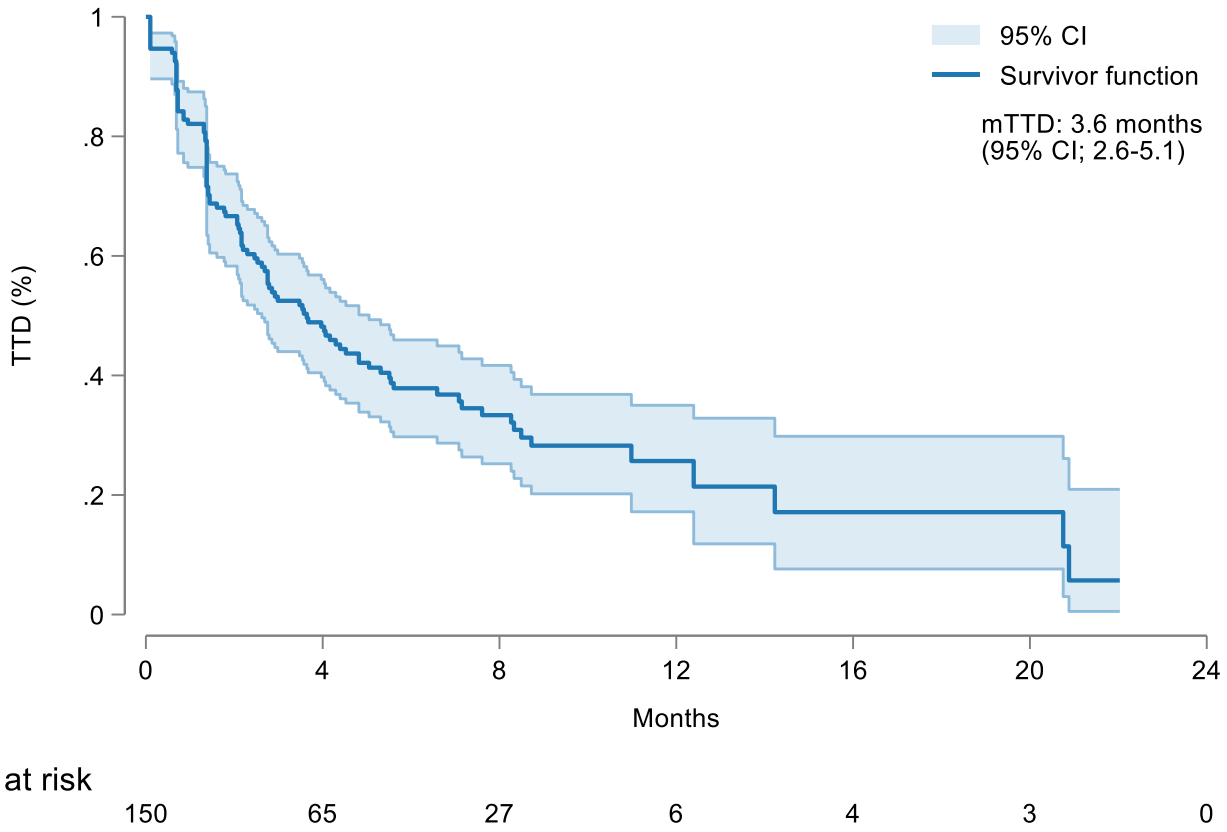
- Total (n=150)
- Mean F/U; 7.2 months ± 5.1

Results

- Median OS
  13.6 months (95% CI; 8.0 – 20.6)
- Median PFS
  5.7 months (95% CI; 4.0 – 12.5)
- Median TTD
  3.6 months (95% CI; 2.6 – 5.1)

Factor	Total (n=150)
Age, mean (SD)	63.3 (11.3)
Male sex	128 (85.3%)
Etiology	
viral	104 (69.3%)
non-viral	46 (30.7%)
BMI, mean (SD)	23.2 (3.5)
Child-Pugh class (A)	134 (89.3%)
ALBI grade	
1	61 (40.7%)
2	89 (59.3%)
Tumor size (largest)	6.8 (2.7-11.0)
Tumor number (multiple)	109 (72.7%)
PVTT (yes)	78 (52.0%)
Extrahepatic spread (yes)	91 (60.7%)
mUICC stage	
3	16 (10.7%)
4	43 (28.7%)
5	91 (60.7%)
AFP, median (IQR)	184.0 (8.5-4587.6)
PIVKA, median (IQR)	1255.0 (158.7-16418.0)

Time to treatment discontinuation (TTD)



Status	n (%)
Total	150
Ongoing therapy	40 (26.7%)
Discontinuation	110 (73.3%)
Progression	59 (39.3%)
AEs, liver dysfunction	38 (25.3%)
F/U loss, etc.	9 (6.0%)
Complete remission	4 (2.7%)

Immune related adverse events (irAEs)

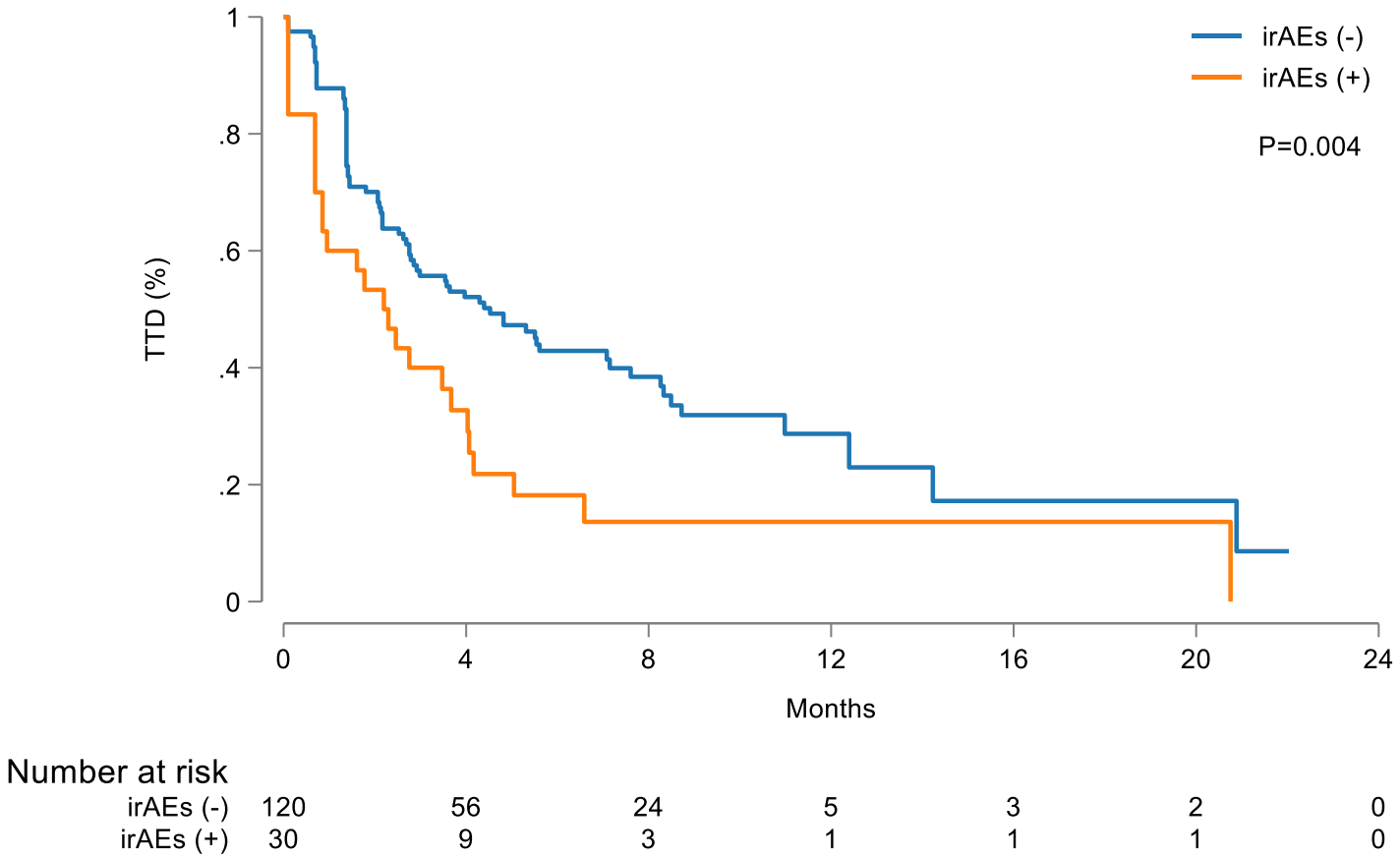
- **CTCAE grade;** Grade ≥3

	Grade 1	Grade 2	**Grade 3**	**Grade 4**
Alanine aminotransferase increased	>3.0 xULN	>3.0-5.0 xULN	**>5.0-20.0 xULN**	**>20.0 xULN**
Colitis	Asymptomatic	Abdominal pain	**Severe pain, peritoneal signs**	**Life-threatening**
Fatigue	relieved by rest	not relieved by rest	**limiting self care**	-
Pneumonitis	Asymptomatic	Symptomatic	**Severe symptoms; oxygen indicated**	**Life-threatening**
Biliary tract infection	-	Oral intervention indicated	**invasive intervention indicated**	**Life-threatening**
Eczema	Asymptomatic or mild symptoms	Moderate; topical or oral intervention indicated	**Severe; IV intervention indicated**	-
Hyper-/Hypo-thyroidism	Asymptomatic	Symptomatic; thyroid replacement indicated	**hospitalization indicated**	**Life-threatening**

irAEs	N (%)
Total	**30 (20.0%)**
hepatitis	14 (9.3%)
colitis	5 (3.3%)
fatigue, severe	3 (2.0%)
pneumonitis	3 (2.0%)
cholangitis	2 (1.3%)
skin rash	2 (1.3%)
anaphylactic shock	1 (0.7%)
myositis	1 (0.7%)
asthma	1 (0.7%)

Time to treatment discontinuation (TTD)

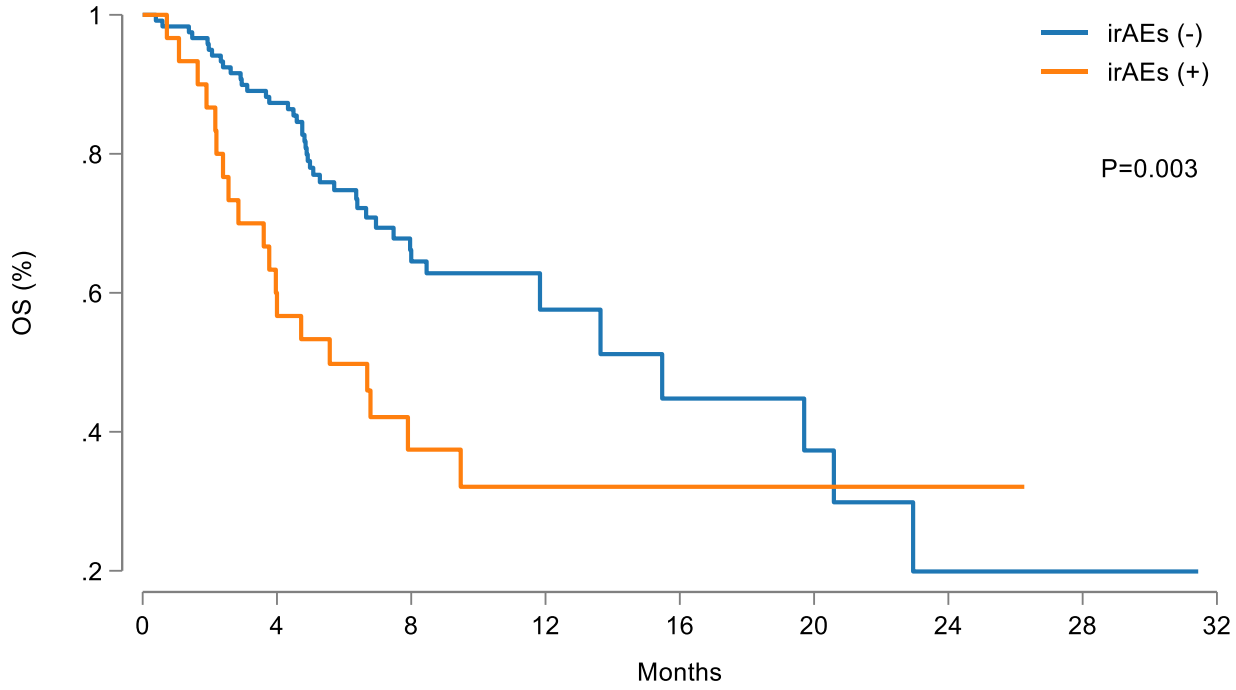
Univariate analysis	
Variables	***p* value**
Age (≥65)	0.413
Sex (male)	**0.019**
Etiology (viral)	0.242
NLR (≥3)	**0.041**
Child-Pugh class (B)	**0.033**
ALBI grade (≥2)	**0.005**
AFP (≥400)	0.190
Tumor size (≥7cm)	0.757
PVTT (yes)	0.636
EHS (yes)	0.339
irAEs (yes)	**0.004**



Time to treatment discontinuation (TTD)

Multivariate analysis		
Variables	*p* value	HR (95% CI)
Sex (female)	0.042	1.687 (1.018 – 2.795)
ALBI grade (≥2)	0.028	1.639 (1.054 – 2.550)
irAEs (yes)	0.017	1.765 (1.108 – 2.813)
NLR (≥3)	0.225	1.293 (0.854 – 1.959)
Child–Pugh class (B)	0.447	1.284 (0.674 – 2.448)

Overall survival (OS)



Number at risk

irAEs (-)	120	98	40	10	7	5	2	2	0
irAEs (+)	30	18	7	1	1	1	1	0	0

	P value		P value
Age (〉65)	0.278	NLR (≥3)	0.089
Sex (male)	0.428	AFP (≥ 400)	0.077
Etiology (viral)	0.545	**Tumor size (≥7cm)**	**0.006**
Child-Pugh class (B)	**〈0.001**	**PVTT (yes)**	**0.027**
ALBI grade (≥2)	**〈0.001**	EHS (yes)	0.107
		irAEs (yes)	**0.003**

	P-value	HR	95% CI
Child-Pugh class (B)	**0.005**	2.685	1.358 - 5.308
ALBI grade (≥2)	**0.001**	2.926	1.511 - 5.667
irAEs (yes)	**0.002**	**2.423**	**1.371 - 4.280**
PVTT (yes)	**0.013**	2.029	1.159 - 3.552
Tumor size (≥ 7cm)	0.151	1.475	0.868 - 2.508

Conclusions

- A+B demonstrated considerable efficacy
  - mOS 13.6 mo (8.0–20.6), mPFS 5.7 mo (4.0–12.5)
- TTD can serve as a crucial outcome
  - treatment duration; progression + treatment discontinuation
  - insight for sequential therapy after 1st line treatment
- Clinical implication of irAEs
  - independent prognostic factor
  - **monitoring, managing irAEs is essential**