1388P: Efficacy of 2nd line immunotherapy in advanced upper gastrointestinal tract malignancies; a pooled analysis of randomized clinical trials

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The use of immune checkpoint inhibitors in upper track gastrointestinal malignancies is a major and rapidly evolving field of research. As a result, in the last 5 years a lot of data have emerged from randomized clinical trials in the 2nd line treatment and beyond 2nd line and even more are expected in the future.

***Methods*:**
We performed a systematic literature search and a pooled analysis of published articles and conference abstracts.

Trials included:
- **Randomized clinical trials (RCTs) in the 2nd line or beyond.**
- **Patients with advanced or metastatic upper gastrointestinal malignancies**
- **Evaluating use of Immunotherapy plus chemotherapy compared to chemotherapy.**

Endpoints:
- **Overall Survival (OS)**
- **Progression Free Survival (PFS)**
- **Objective Response rate (ORR)**
- **Subgroup analysis:** Squamous cell carcinomas (SCC), Adenocarcinomas (ADC), PDL1-score

Setting: IO + Chemo vs Chemo Study *(Investigational Agent)*	Overall Survival *HR (95%CI)*		Progression Free Survival *HR (95%CI)*		Objective Response Rate *OR (95%CI)*	
ATTRACTION 3[1] *Nivolumab*	0.77 (0.62-0.96)		1.08 (0.87 – 1.34)		0.87 (0.51 – 1.49)	
ESCORT[2] *Carmelizumab*	0.71 (0.57-0.87)		0.69 (0.56 – 0.86)		3.72 (1.98 – 6.99)	
KEYNOTE-061[3] *Pembrolizumab*	0.94 (0.79 -1.12)		1.49 (1.25 - 1.57)		0.77 (0.48 – 1.24)	
KEYNOTE-063[4] *Pembrolizumab*	n.a.		n.a.		0.62 (0.20 - 1.90)	
KEYNOTE-181[5] *Pembrolizumab*	0.89 (0.75-1.05)		1.11 (0.94 - 1.31)		2.09 (1.21 – 3.64)	
Pooled Analysis *(IO+Chemo vs Chemo)*	**Pooled OS** *(Studies included)*	***p.***	**Pooled PFS** *(Studies included)*	***p.***	**Pooled ORR** *(Studies included)*	***p.***
Any PDL1 status	**0.84 (0.76 - 0.93)** *(ATTRACTION 3, ESCORT, KEYNOTE-061, KEYNOTE-181)*	***0.0004***	1.06 (0.79 - 1.42) *(ATTRACTION 3, ESCORT, KEYNOTE-061, KEYNOTE-181)*	*0.70*	1.31 (0.69 - 2.49) *(ATTRACTION 3, ESCORT, KEYNOTE-061, KEYNOTE-063, KEYNOTE-181)*	*0.41*
Only SCC	**0.75 (0.67 - 0.85)** *(ATTRACTION 3, ESCORT, KEYNOTE-181)*	***<.0001***	0.88 (0.69 - 1.14) *(ATTRACTION 3, ESCORT, KEYNOTE-181)*	*0.34*	1.98 (0.81-4.84) *(ATTRACTION 3, ESCORT, KEYNOTE-181)*	*0.13*
Only ADC	0.99 (0.85 -1.15) *(KEYNOTE-061, KEYNOTE-181)*	*0.89*	n.a.		0.75 (0.48 - 1.15) *(KEYNOTE-061, KEYNOTE-063)*	*0.19*
PDL1 >1%	**0.73 (0.63 - 0.84)** *(ATTRACTION 3, ESCORT, KEYNOTE-061)*	***< .0001***	0.88 (0.43 - 1.79) *(ESCORT, KEYNOTE-061)*	*0.72*	1.08 (0.66 - 1.77) *(KEYNOTE-061, KEYNOTE-063)*	*0.76*
PDL1 > 10%	**0.68 (0.56 - 0.82)** *(ATTRACTION 3, ESCORT, KEYNOTE-061, KEYNOTE-181)*	***< .0001***	**0.71 (0.56 - 0.89)** *(ESCORT, KEYNOTE-061, KEYNOTE-181)*	***0.003***	**3.82 (1.91 - 7.66)** *(KEYNOTE-061, KEYNOTE-181)*	***0.0002***
PDL1 > 10%, SCC	**0.65 (0.51 - 0.83)** *(ATTRACTION 3, ESCORT, KEYNOTE-181)*	***0.0004***	n.a.	n.a.	n.a.	n.a.
PDL1 > 10%, ADC	0.76 (0.54 – 1.07) *(KEYNOTE-061, KEYNOTE-181)*	*0.11*	n.a.	n.a.	**3.83 (1.42-10.32)** *(KEYNOTE-061, KEYNOTE-181)*	***0.008***
PDL1 <1%	0.93 (0.79 – 1.10) *(ATTRACTION 3, ESCORT, KEYNOTE-061)*	*0.41*	1.27 (0.50 - 3.25) *(ESCORT, KEYNOTE-061)*	*0.62*	n.a.	n.a.
PDL1 <10%	0.83 (0.68 – 1.02) *(ATTRACTION 3, ESCORT, KEYNOTE-181)*	*0.08*	n.a.	n.a.	n.a.	n.a.

Efficacy outcomes

2nd Line, Upper GI Malignancies

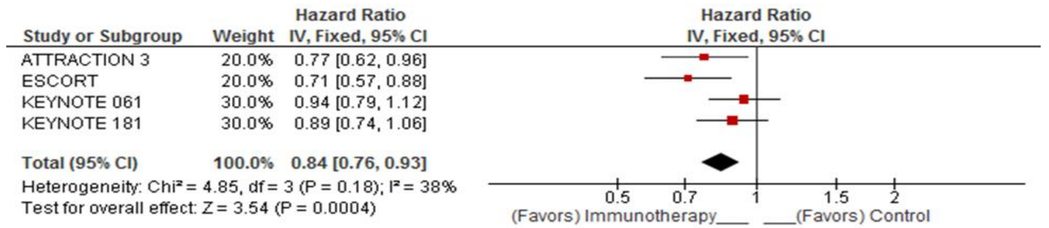
Immunotherapy plus Chemotherapy

vs

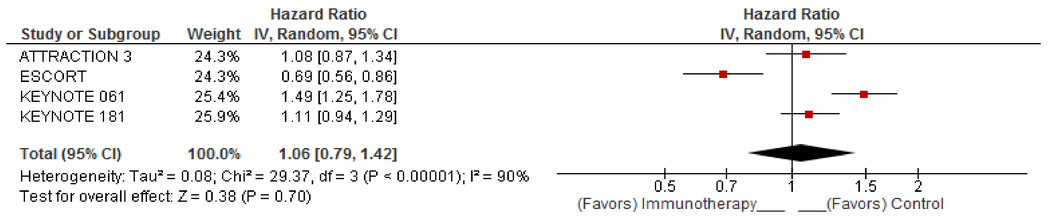
Chemotherapy

Abbreviations
***IO**: immunotherapy, **SCC**: squamous cells carcinomas, **ADC**: adenocarcinomas, **HR**: Hazard Ratio, **OS**: Overall survival, **PFS**: progression free survival, **ORR**: objective response rate, **OR**: odds ratio, **CI**: confidence intervals, n.a.: not applicable*

Pooled Hazard Ratio for Overall Survival



Pooled Hazard Ratio for Progression Free Survival



Results:

- 5 RCTs, Attraction 3, Escort, Keynote 061, Keynote 063, Keynote 181 [1-5] evaluated the addition of immunotherapy to chemotherapy vs. standard chemotherapy in patients with advanced or metastatic upper gastrointestinal malignancies who have progressed after initial therapy.
- A total of **2190** patients were randomized
  → **1096** received combination chemotherapy with immunotherapy
  → **1094** received standardized chemotherapy
- In the overall population, the addition of immune checkpoint inhibitors after progression demonstrated an **improved overall survival** with a significant 16% lower risk of death compared to chemotherapy alone.
  → Pooled **OS** *Hazard Ratio* ***(HR) 0.84, 95% CI 0.76-0.93, p = 0.0004***
- **No survival benefit** was confirmed in patients with **ADC** histology
  → Pooled OS *HR 0.99, 95% CI 0.85 - 1.15, p = 0.89*
- **Progression free survival** (PFS) was **not** increased in the overall population by the addition of immunotherapy to chemotherapy
  → Pooled *PFS HR 1.06 , 95% CI 0.79 - 1.42, p = 0.70*
- The addition of immunotherapy to chemotherapy appears to **increase** the **objective responses** compared to chemotherapy alone only in the **PDL1 > 10%** population
  → Pooled **ORR** *Odds Ratio* ***(OR) 3.82, 95%CI 1.91 - 7.66, p = 0.0002***

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