2022 ASCO® ANNUAL MEETING

Cabozantinib Plus Atezolizumab or Cabozantinib Alone in Patients With Advanced Non-Small Cell Lung Cancer Previously Treated With an Immune Checkpoint Inhibitor: COSMIC-021 Study Cohorts 7 and 20

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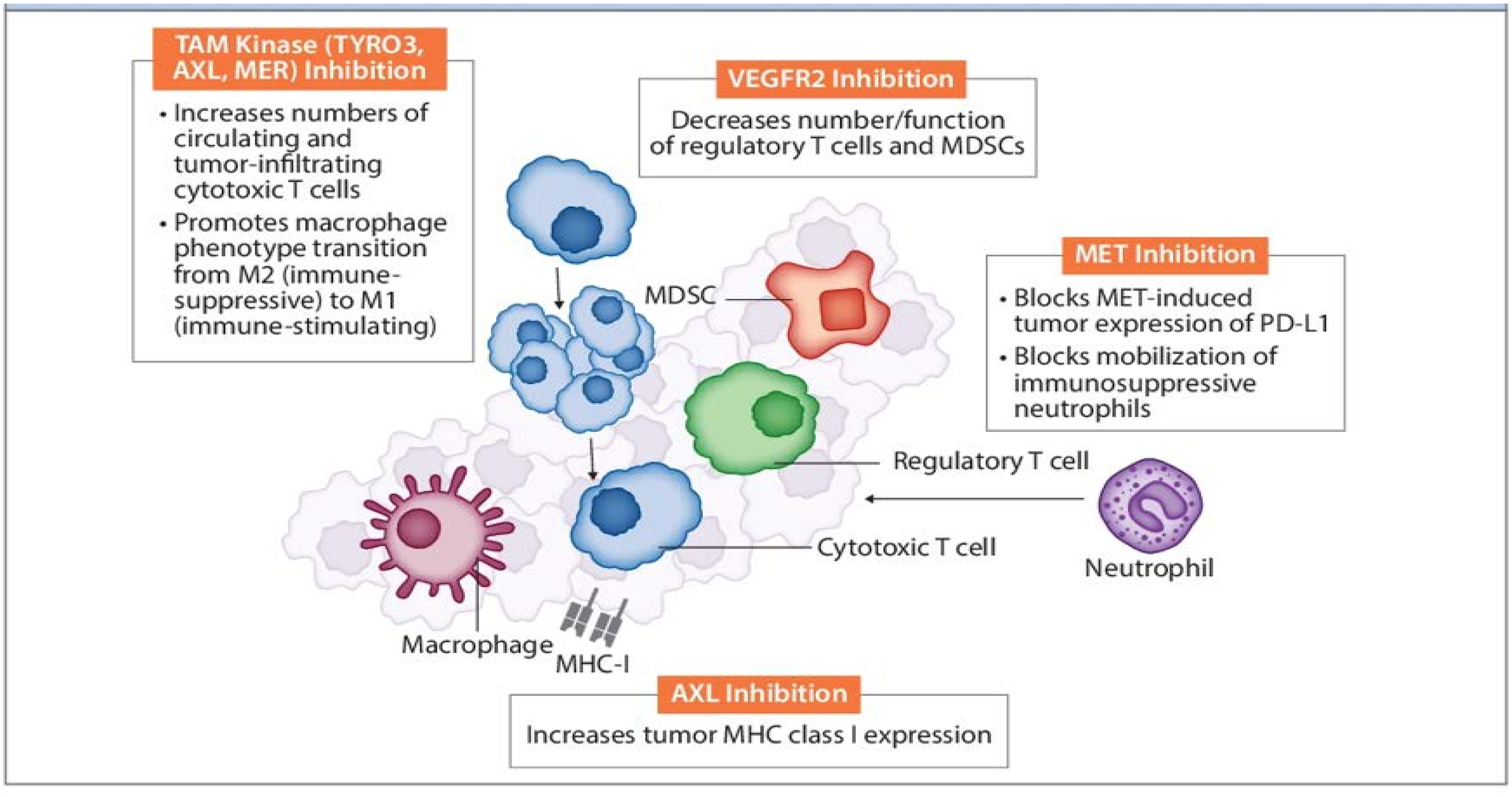
Resistance to Immune Checkpoint Inhibitors

- Defects in antigen presentation machinery
- Aberrant Immunity of T-Cells
    - Insufficient T cell Infiltration & exhausted T cells
- Defects in IFN-γ signalling
    - JAK STAT pathway mutations
- Immunosuppressive Tumour Microenvironment
    - Adenosine- mediated by CD 73
- **Angiogenesis modulating factors & immunosuppression**
- Upregulation of other T cell checkpoints (TIM3, LAG3, VISTA)

Schoenfeld & Hellmann. Cancer Cell 2020;37:443-455
Boyero et al. Cancers (Basel) 2020;12:3729
Yuan Y et al. Cancers 2021, *13*(4), 663

Cabozantinib Targets Pathways Associated with Tumor Immune Suppression



COSMIC-021 Study Design for NSCLC Cohorts

Key Eligibility Criteria

- Stage IV non-squamous NSCLC with radiographic progression on or after one prior ICI for metastatic disease
- ≤2 prior lines of systemic anticancer therapy*
- Patients with known *EGFR*, *ALK*, *ROS1*, or *BRAF* V600E tumor mutations excluded

Cohort 7†
Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV
(N=80)

Cohort 20‡
Cabozantinib 60 mg QD PO
(N=30)

Tumor assessment per RECIST v1.1 by investigator every 6 weeks for the first year and every 12 weeks thereafter

Primary endpoint:	ORR per RECIST v1.1 by investigator
Secondary endpoint:	Safety (AEs, SAEs, AESIs)
Exploratory endpoints:	DOR, PFS per RECIST v1.1 by investigator, OS

*Prior treatment with platinum-based chemotherapy was not required. †Patients were initially enrolled to cohort 7 (n=35). Following an initial assessment of clinical activity, subsequent patients were randomized between cohorts 7 and 20. ‡Patients in cohort 20 may receive combination therapy after radiographic disease progression per RECIST v1.1 by the investigator.
SAEs, serious adverse events; AESIs, adverse events of special interest

Baseline Demographics and Clinical Characteristics

	Cabozantinib + Atezolizumab (N=81)	Cabozantinib (N=31)
Median age, y (range)	67 (38–93)	70 (48–92)
Female / Male, %	43 / 57	42 / 58
ECOG performance status, %		
0 / 1	35 / 64	29 / 71
Smoking history, %		
Current / former / never	17 / 68 / 15	10 / 74 / 16
Adenocarcinoma / large cell carcinoma / other histology, %	94 / 2 / 1	100 / 0 / 0
PD-L1 status available / PD-L1 positive*†, %	74 / 68	90 / 71
Tumor sites, %		
Lung / liver / bone	84 / 21 / 30	87 / 23 / 29
Lymph node / brain / adrenal	54 / 14 / 16	61 / 6 / 23
Prior lines of systemic anti-cancer therapy‡, %		
0 / 1 / ≥2	0 / 43 / 57	3§ / 45 / 52
Prior platinum-based chemotherapy‖, %	83	84
Most recent therapy, %		
ICI alone / ICI + chemo / ICI + other / chemo / other	52 / 23 / 5 / 16 / 4	55 / 23 / 6 / 16 / 0

As of November 30, 2021, median follow-up (range) was 24.7 mo (10.7–42.8) for cohort 7 and 21.5 mo (17.3–27.6) for cohort 20

*PD-L1 status from local testing (not required for enrollment). †The PD-L1 positive percentage is based on the number of patients with known tumor PD-L1 status. ‡For locally advanced or metastatic disease. §Received ICI at adjuvant setting. ‖At neoadjuvant, adjuvant, or locally advanced/metastatic setting.

Efficacy Summary

	Cabozantinib + Atezolizumab (N=81)				Cabozantinib (N=31)*
	All patients (N=81)	PD-L1 <1% (n=19)	PD-L1 ≥1% (n=41)	PD-L1 unknown (n=21)	
ORR, n (%)	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Best overall response, n (%)					
Complete response	**0**	0	0	0	**0**
Partial response	**15 (19)**	2 (11)	8 (20)	5 (24)	**2 (6)**
Stable disease	**50 (62)**	12 (63)	25 (61)	13 (62)	**18 (58)**
Progressive disease	**13 (16)**	3 (16)	8 (20)	2 (10)	**6 (19)**
Missing / not evaluable	**3 (4)**	2 (11)	0	1 (5)	**5 (16)**
Disease control rate, n (%)	**65 (80)**	14 (74)	33 (80)	18 (86)	**20 (65)**
PFS, mo (95% CI)	**4.5 (3.5–5.6)**	4.0 (2.6–5.6)	4.7 (2.7–5.6)	5.4 (2.9–10.9)	**3.4 (1.4–5.6)**
Median DOR, mo (95% CI)	**5.8 (4.2–6.9)**	3.4 (2.6–NE)	6.5 (3.5–NE)	6.2 (4.2–NE)	**10.6 (6.3–NE)†**
OS, mo (95% CI)	**13.8 (7.2–15.7)**	6.8 (5.1–15.4)	10.4 (5.9–17.1)	17.4 (9.4–NE)	**9.4 (4.5–11.7)**

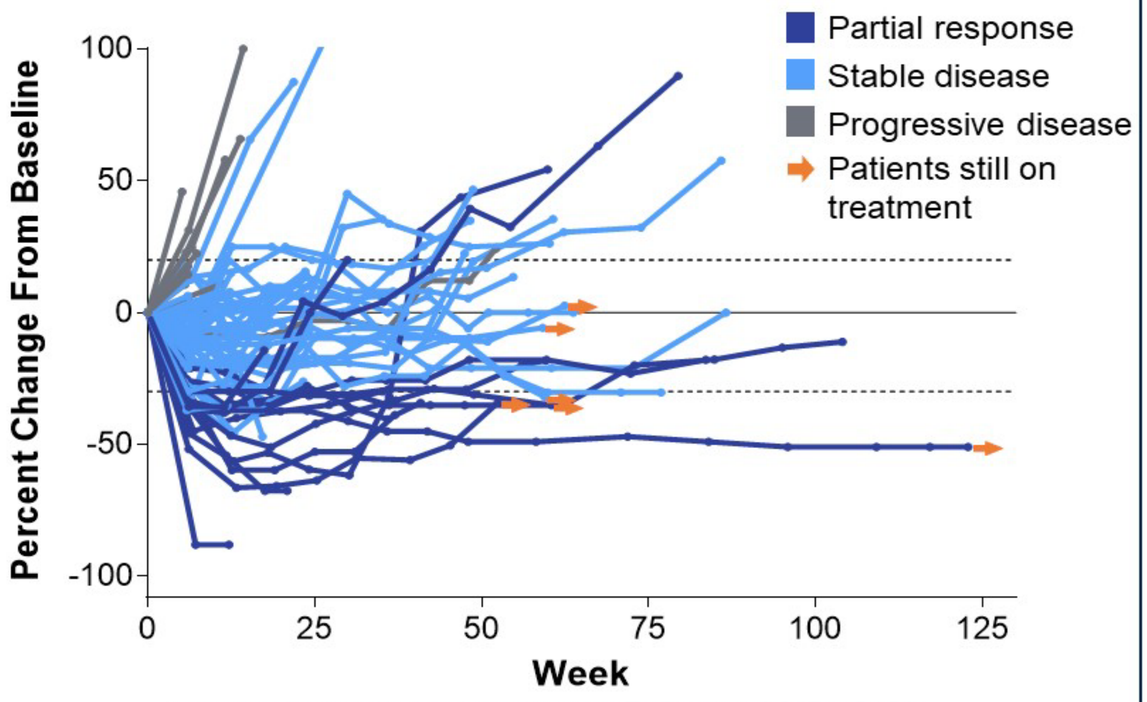
*Eight patients in the cabozantinib alone cohort were crossed over to receive cabozantinib plus atezolizumab after experiencing disease progression; the efficacy data of these patients are not reported in this presentation except for OS. †The DOR of the 2 responders was 6.3 and 14.8 months.

Best Change From Baseline in Target Lesions

Cabozantinib + Atezolizumab	Cabozantinib

Change in Sum of Target Lesions Over Time

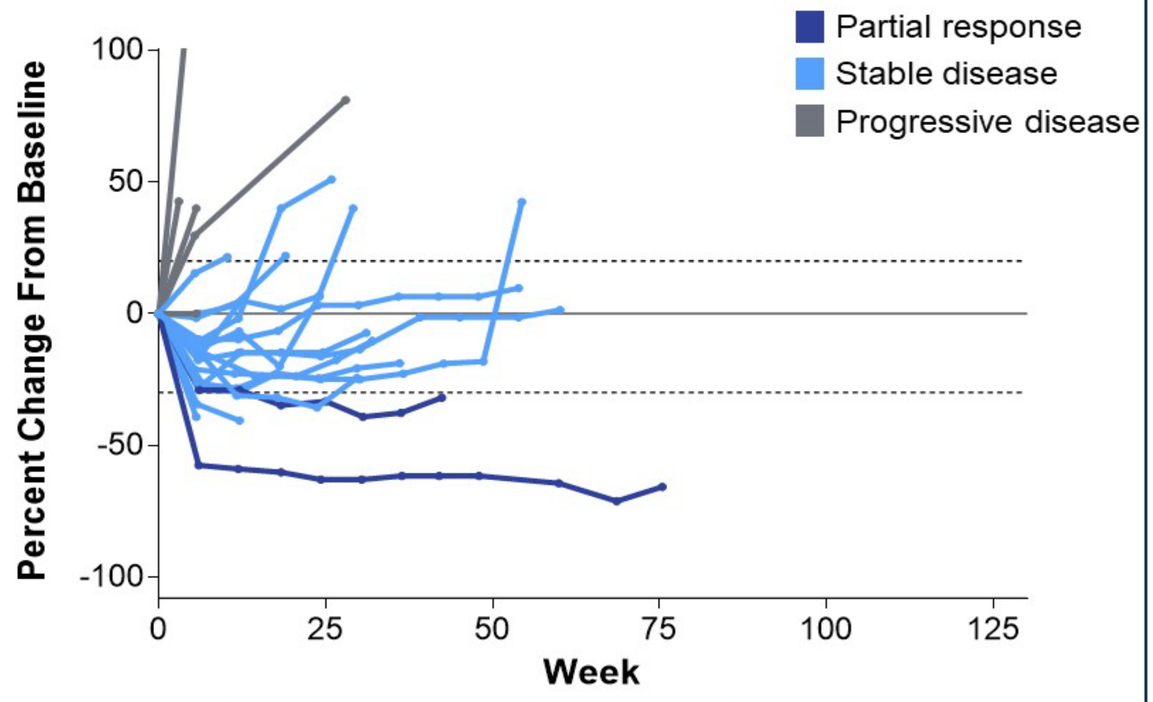
Cabozantinib + Atezolizumab



Median DOR, mo (95% CI): 5.8 mo (4.2–6.9)

78 out of 81 patients had at least one post-baseline tumor assessment

Cabozantinib



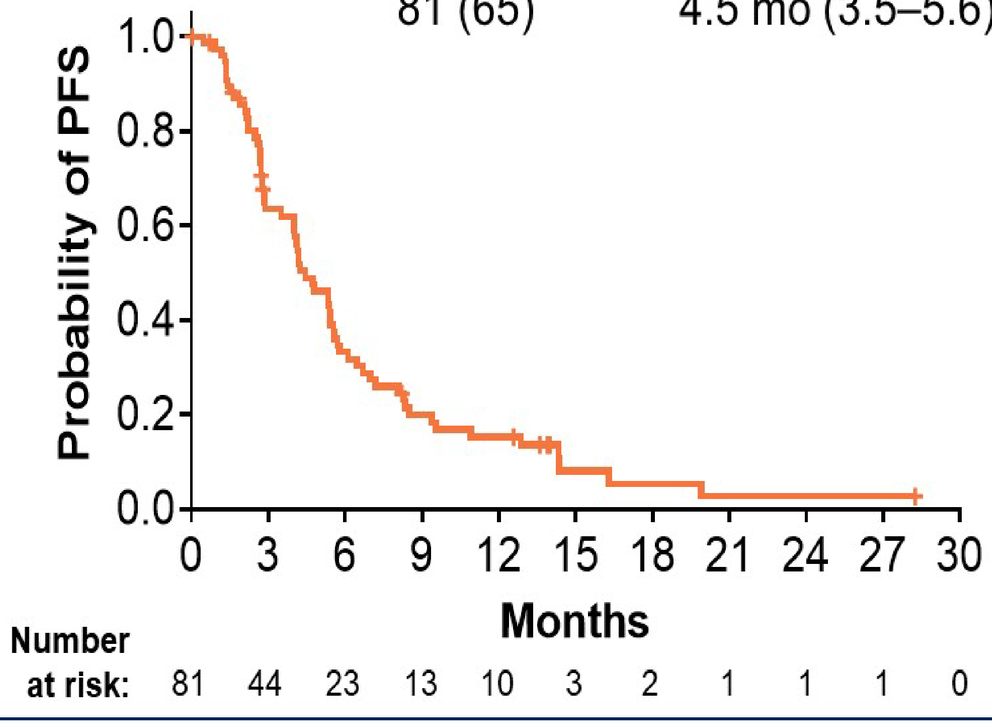
Median DOR, mo (95% CI): 10.6 mo (6.3–NE)

26 out of 31 patients had at least one post-baseline tumor assessment

Progression-Free Survival

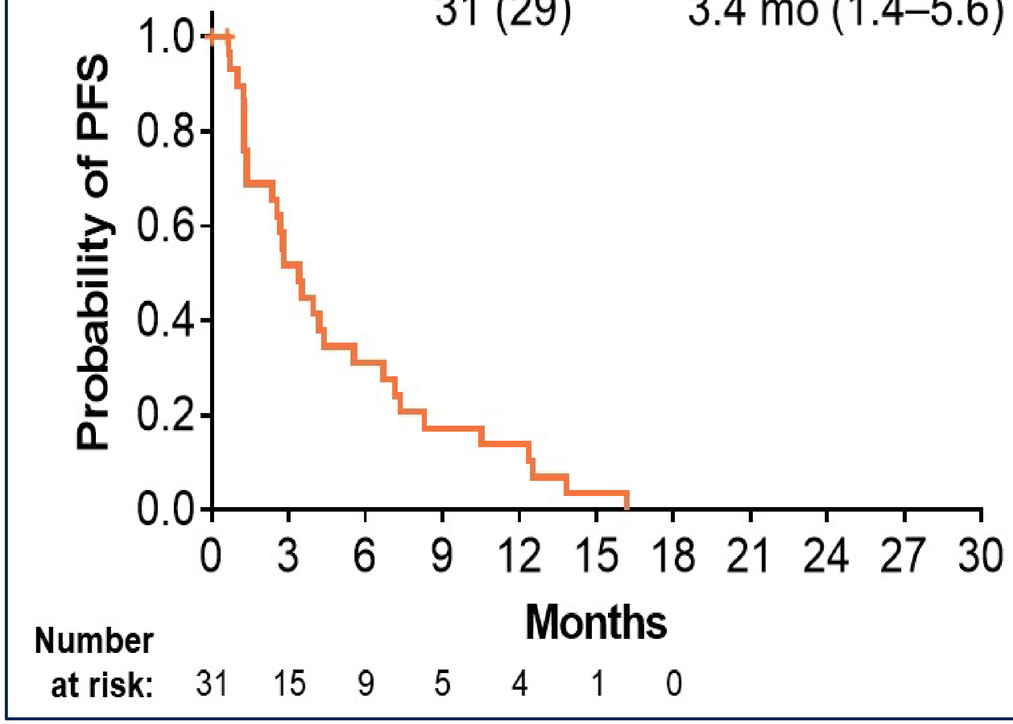
Cabozantinib + Atezolizumab

N (events)	Median (95% CI), mo
81 (65)	4.5 mo (3.5–5.6)



Cabozantinib

N (events)	Median (95% CI), mo
31 (29)	3.4 mo (1.4–5.6)



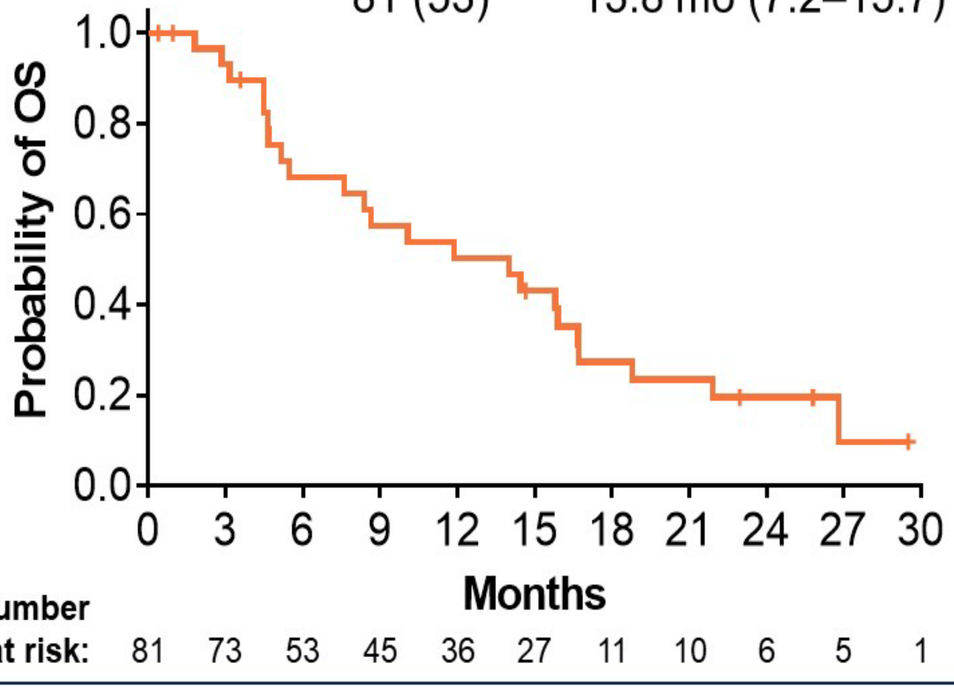
Median PFS (95% CI):	4.0 mo (2.6–5.6) for PD-L1 negative
	4.7 mo (2.7–5.6) for PD-L1 positive
	5.4 mo (2.9–10.9) for PD-L1 unknown

Per investigator by RECIST v1.1.

Overall Survival

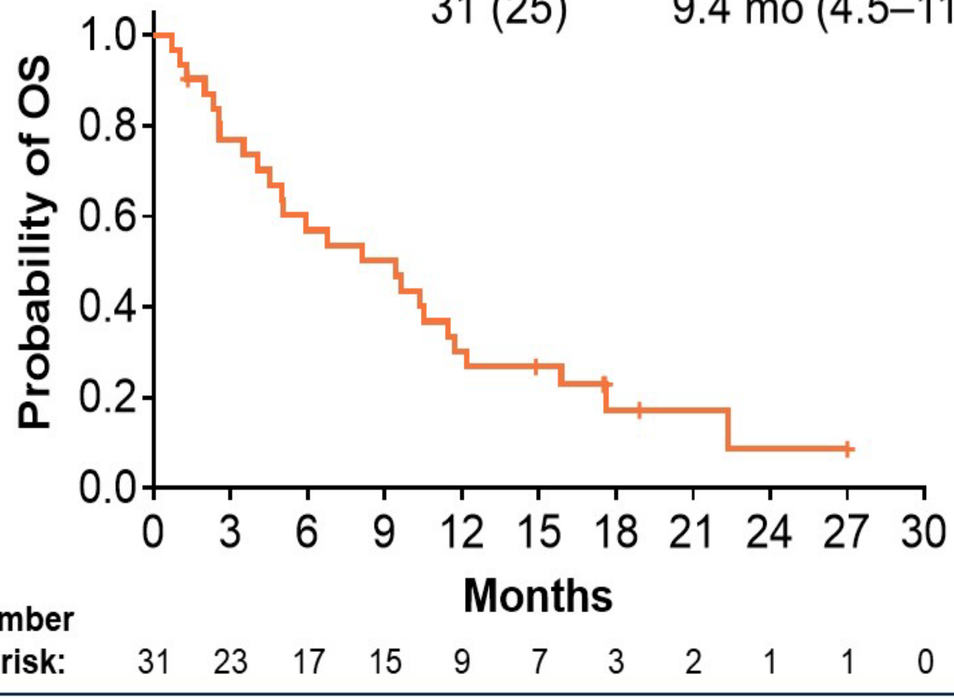
Cabozantinib + Atezolizumab

N (events)	Median (95% CI), mo
81 (53)	13.8 mo (7.2–15.7)



Cabozantinib

N (events)	Median (95% CI), mo
31 (25)	9.4 mo (4.5–11.7)



Median OS (95% CI):

- 6.8 mo (5.1–15.4) for PD-L1 negative
- 10.4 mo (5.9–17.1) for PD-L1 positive
- 17.4 mo (9.4–NE) for PD-L1 unknown

Safety Summary

	Cabozantinib + Atezolizumab (N=81)	Cabozantinib* (N=31)
Patients on study treatment at data cut-off, n (%)	6 (7)	2 (6)
Duration of exposure, median (range), months		
Cabozantinib + Atezolizumab†	5.2 (0.3–28.8)	4.8 (0.7–19.4)
Cabozantinib	5.2 (0.3–28.8)	4.8 (0.7–19.4)
Atezolizumab	4.6 (0–28.0)	1.6 (0–11.8)
AEs leading to cabozantinib dose reductions, n (%)	32 (40)	18 (58)
AEs leading to cabozantinib dose hold, n (%)	60 (74)	25 (81)
AEs leading to atezolizumab dose delay, n (%)	41 (51)	2 (6)
Discontinuation due to TRAEs, n (%)		
Cabozantinib	11 (14)	3 (10)
Atezolizumab	8 (10)	1 (3)
Either	13 (16)	3 (10)
Both	5 (6)	1 (3)

*Includes the 8 patients who crossed over to receive cabozantinib + atezolizumab therapy after experiencing disease progression. In patients who were treated with cabozantinib only (n=23), the duration of exposure was 3.5 months (range, 0.7–16.4) and rates of AEs leading to cabozantinib dose reductions and holds, and discontinuation due to TRAEs were similar to all patients.

†The duration between the day of the first dose of any study treatment and the day of discontinuation of the last component of study treatment.

Treatment-Emergent Adverse Events*

	Cabozantinib + Atezolizumab (N=81)		Cabozantinib (N=31)†	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE, n (%)	81 (100)	43 (53)	31 (100)	22 (71)
Diarrhea	36 (44)	1 (1)	16 (52)	3 (10)
Decreased appetite	30 (37)	1 (1)	11 (35)	1 (3)
Fatigue	29 (36)	4 (5)	11 (35)	2 (6)
Nausea	28 (35)	2 (2)	15 (48)	2 (6)
Asthenia	24 (30)	5 (6)	12 (39)	3 (10)
Constipation	21 (26)	0	5 (16)	0
Pyrexia	20 (25)	0	2 (6)	0
AST increased	19 (23)	2 (2)	9 (29)	0
Hypertension	19 (23)	5 (6)	10 (32)	7 (23)
Vomiting	19 (23)	0	9 (29)	1 (3)
ALT increased	17 (21)	3 (4)	10 (32)	1 (3)
PPE	17 (21)	3 (4)	6 (19)	0
Hypomagnesemia	16 (20)	1 (1)	5 (16)	0
Weight decreased	16 (20)	3 (4)	4 (13)	2 (6)
Pneumonitis	3 (4)‡	0	0	0
Gastric ulcer hemorrhage	0	0	1 (3)§	0

*Occurring in ≥20% of patients or TRAEs with grade 5 events by investigator assessment. †Includes TEAEs of all patients including the eight patients who crossed over to receive cabozantinib + atezolizumab after experiencing disease progression. The rates of adverse events in patients treated with cabozantinib only (n=23) were similar to all patients.
‡One grade 5 event of pneumonitis occurred. §One grade 5 event of gastric ulcer hemorrhage occurred.

Adverse Events of Special Interest*†

	Cabozantinib + Atezolizumab‡ (N=81)		Cabozantinib§ (N=31)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any adverse events of special interest (AESI), n (%)	59 (73)	21 (26)	23 (74)	4 (13)
Rash	34 (42)	7 (9)	12 (39)	2 (6)
Hepatitis (lab abnormalities)	28 (35)	5 (6)	14 (45)	1 (3)
Pancreatitis	14 (17)	5 (6)	2 (6)	0
Hypothyroidism	13 (16)	0	8 (26)	0
Colitis	3 (4)	1 (1)	2 (6)	1 (3)
Hyperthyroidism	3 (4)	0	0	0
Pneumonitis	3 (4)	0	0	0
Hepatitis (diagnosis)	2 (2)	1 (1)	2 (6)	0
Infusion-related reactions	2 (2)	1 (1)	0	0

*AESI are potential immune-related AEs for atezolizumab provided by the sponsor and summarized as grouped MedDRA terms irrespective of causality.
†Occurring in ≥2 patients. ‡One grade 5 event of pneumonitis and one grade 4 event of myocarditis occurred. §Includes AESIs of all patients including the 8 patients who crossed over to receive combination therapy after experiencing disease progression. The rates of adverse events in patients treated with cabozantinib only (n=23) were similar to all patients.

Authors' Conclusions

- In patients with advanced non-squamous NSCLC previously treated with ICIs:
  - Cabozantinib plus atezolizumab demonstrated encouraging clinical activity
  - Cabozantinib alone demonstrated modest clinical activity
- Responses were observed with cabozantinib plus atezolizumab irrespective of known PD-L1 expression
- Toxicities with both cabozantinib plus atezolizumab, and cabozantinib alone, were consistent with those previously reported

Questions that arise……..

1) Can we really conclude that benefit is seen irrespective of PD-L1 expression??

- PD-L1 status unknown- 26% in the Atezo + Cabozantinib cohort 7
- Better outcomes (ORR,PFS,OS) in unknown vs PD-L1 <1%
- Possibility→ this group may have been enriched with patients with higher PD-L1 expression

2) Atezo + Cabozantinib→ will this benefit be replicated in larger population?

3) Number of patients with RET or MET driver mutations in these cohorts?

4) Single agent Cabozantinib in an unselected population- Real Benefit??

5) Crossover allowed in 8 patients in cohort 20, detailed data not available yet.

- The combination of Atezolizumab + Cabozantinib promising signal→needs confirmation in larger studies
- Need to wait for full results from the
  - Phase 2 EA5191: Cabo + Nivo versus standard chemotherapy
  - Phase 3 CONTACT-01: Cabo+ Atezo versus Docetaxel

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Innovation for patient care

PRESS RELEASE

Ipsen provides update on Phase III CONTACT-01 trial evaluating cabozantinib in combination with atezolizumab in patients with metastatic non-small cell lung cancer previously treated with immunotherapy and chemotherapy

- The trial did not meet its primary endpoint of overall survival (OS)
- The safety profile of the combination of cabozantinib and atezolizumab was consistent with the known safety profiles for each single agent
- The clinical trial results will be presented at a future medical meeting

PARIS, FRANCE, 8 December 2022 – Ipsen (Euronext: IPN; ADR: IPSEY) announced today that the CONTACT-01 study did not meet its primary endpoint of overall survival (OS) at the final analysis. CONTACT-01 is a phase III clinical trial evaluating Cabometyx® (cabozantinib) in combination with atezolizumab (Tecentriq®) versus docetaxel in patients with unmutated metastatic non-small cell lung cancer (NSCLC) who experienced disease progression on or after treatment with an immune checkpoint inhibitor and platinum-containing chemotherapy.

THANK YOU!