Safety and efficacy of Wnt inhibition with a DKK1 inhibitor, DKN-01, in combination with atezolizumab in patients with advanced oesophagogastric adenocarcinoma (OGA): Phase IIa results of the WAKING trial

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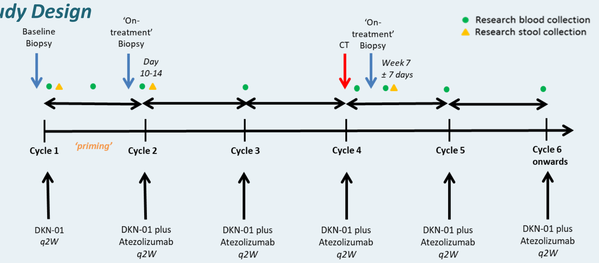
BACKGROUND

- Dickkopf-1 (DKK1) modulates Wnt/β-catenin signalling and promotes an immunosuppressive tumour microenvironment (TME) by activating MDSCs and downregulating NK cell activity [1,2,3]
- DKK1 is frequently overexpressed in OGA and associated with poor prognosis [1,4]
- DKN-01 is a DKK1 neutralising antibody
- Preclinical studies show that DKN-01 can favourably reprogram the TME by:
  - Increasing infiltration of NK cells[5]
  - Reducing function of MDSCs[5]
  - Upregulating PD-L1 expression[5]
- Clinical studies have shown promising response rates with DKN-01 combined with anti-PD-1 therapy ± chemotherapy in patients with microsatellite stable OGA [6,7]
- Patients with DKK1-high tumours appear to benefit most from these combinations [6,7]
- We report the safety and anti-tumour activity of DKN-01 and atezolizumab, anti-PD-L1 antibody, as the second or third-line therapy in patients with advanced OGA enrolled onto the dose escalation phase of the WAKING study

METHODS

Study Design



- WAKING is an open-label, single-arm phase IIa/b non-randomised trial
- Phase IIa is the dose-finding phase that followed a "3+3" design
- **Primary objective:** to recommend a safe and tolerable dose of DKN-01 combined with atezolizumab for use in the main efficacy phase of the study
- **Tumoural DKK1 mRNA expression:** assessed by RNAscope on tissue samples (Advanced Cell Diagnostics at Flagship biosciences) and assigned a tumour percentage score (TPS). TPS ≥ 20% was considered DKK1-high
- **Tumoural MDSC level:** assessed by flow cytometric analysis on peripheral blood

Key eligibility criteria

- Aged ≥18 years
- PD-L1 unselected
- PS 0-1
- ≤ 2 prior lines
- Histologically/cytologically confirmed advanced OGA
- Immunotherapy naïve
- MMRp/MSS

Dosing cohorts

Drug	Dose level 0	Dose level +1	Dose level -1
DKN-01	300mg	600mg	150mg
Atezolizumab	840mg	840mg	840mg

RESULTS

Treatment

- 12 patients were treated in phase IIa
- One patient was still on treatment at data cut-off date (16th August 2022)
- 7 patients discontinued due to radiological progression
- 4 patients discontinued due to clinical progression
- Median time on treatment was 1.9 months
- Longest time on treatment was 6.7 months

Safety

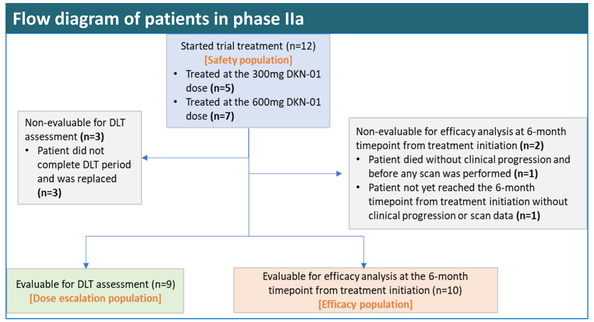
- No DLT was observed and no formal MTD was reached
- 23 TRAEs were reported during phase IIa; 17 related to DKN-01, 14 related to atezolizumab
- 1 patient experienced a grade 3 TRAE (urticaria)
- No treatment-related deaths occurred
- No dose reductions were required
- 7 patients experienced AEs which led to treatment being delayed/discontinued

Patient characteristics (n=12)

Gender, n (%)	
Female	5 (42)
Male	7 (58)
Age, year	
Median (IQR)	61 (54 – 69)
Min - Max	36 - 72
Ethnicity, n (%)	
Caucasian	9 (75)
Mixed race	1 (8)
Asian	1 (8)
Other	1 (8)
HER2 status, n (%)	
Positive	1 (8)
Negative	11 (92)
Baseline DKK1 (TPS) expression, n (%)	
Low (<20%)	6 (50)
High (≥20%)	4 (33)
N/A	2 (17)
ECOG, n (%)	
0	5 (42)
1	7 (58)
Number of prior lines for advanced disease, n (%)	
1	9 (75)
2	3 (25)
Sites of metastases at trial entry, n (%)	
Liver	4 (33)
Lung	3 (25)
Lymph nodes	6 (50)
Peritoneum	4 (33)
Other	9 (75)
Any history of prior radiotherapy, n (%)	
Yes	1 (8)
No	11 (92)
Time from initial diagnosis to trial entry, month	
Median (IQR)	13 (7.4 – 31.6)
Min - Max	3.2 – 61.8
Duration of last line of prior anti-cancer therapy, month	
Median (IQR)	2.1 (2.0 – 4.5)
Min - Max	1.0 – 9.0

ECOG, Eastern Cooperative Oncology Group

Flow diagram of patients in phase IIa



TRAEs related to DKN-01 experienced by ≥ 2 patients or any grade ≥ 3 (n=12)

Adverse event	All grades, n (%)	Grade ≥ 3, n (%)
Fatigue	4 (33)	0 (0)
Anaemia	2 (17)	0 (0)
Pain	2 (17)	0 (0)
Vomiting	2 (17)	0 (0)

n(%), number (proportion) of patients experiencing each TRAE

TRAEs related to atezolizumab experienced by ≥ 2 patients or any grade ≥ 3 (n=12)

Adverse event	All grades, n (%)	Grade ≥ 3, n (%)
Fatigue	2 (17)	0 (0)
Hypothyroidism	2 (17)	0 (0)
Pain	2 (17)	0 (0)
Urticaria	1 (8)	1 (8)

n(%), number (proportion) of patients experiencing each TRAE

Immune-related AEs (n=12)

Adverse event	All grades, n (%)	Grade ≥ 3, n (%)
Hyperthyroidism	1 (8)	0 (0)
Hypothyroidism	2 (17)	0 (0)
Infusion related reaction	1 (8)	0 (0)
Pneumonitis	1 (8)	0 (0)

n(%), number (proportion) of patients experiencing each irAE

Efficacy

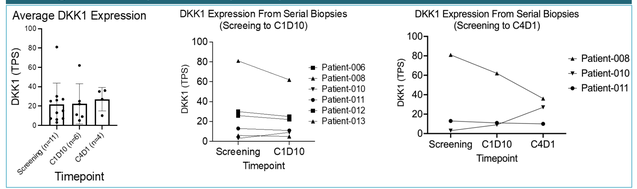
- 10 patients were evaluable for response at the time of data cut-off
- 1 patient with baseline DKK1 expression of 81% TPS had a PR during treatment (best ORR 10%); duration of this response was 2.7 months
- Disease control rate during treatment was 50%; median duration of disease control was 1.9 months (IQR 1.6, 2.7)]
- 3 patients with the longest time on treatment received 600mg DKN-01
- Elevated baseline DKK1 expression (TPS ≥ 20%) may be associated with clinical response (of the 4 DKK1-high patients: Best ORR 25% (1 PR, 1 SD, 1 PD 1 NE))
- DKN-01 and atezolizumab do not appear to effect DKK1 expression or peripheral MDSC levels over time

Best response on treatment by baseline DKK1 expression (RECIST 1.1), n(%) (n=12)

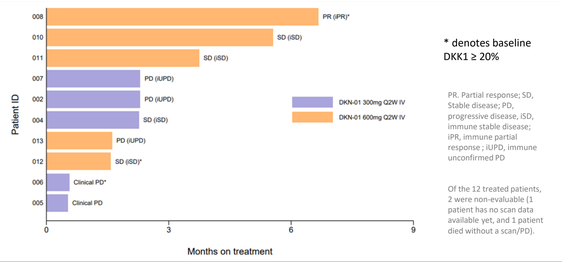
	Partial response	Stable disease	Progressive disease*	Non-evaluable
DKK1-high (N=4)	1 (25)	1 (25)	1 (25)	1 (25)
DKK1-low (N=6)	0	3 (50)	3 (50)	0
DKK1-unknown (N=2)	0	0	1 (50)	1 (50)

*Includes radiological or clinical disease progression; percentages calculated across rows.

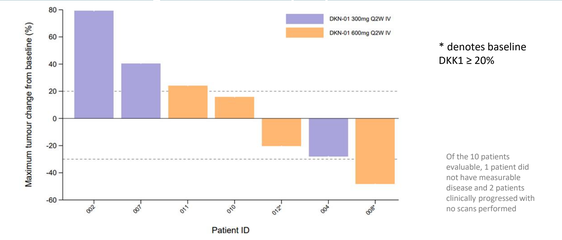
Average DKK1 expression by timepoint



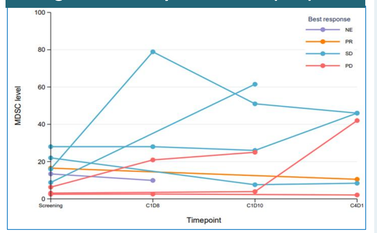
Duration of treatment and best response by RECIST v1.1 (iRECIST) (n=10)



Maximum tumour change from baseline (n=7)



MDSC level by timepoint and best response during treatment by RECIST v1.1 (n=9)



CONCLUSIONS

- DKN-01 up to 600mg in combination with atezolizumab 840mg was considered safe
- DKN-01 600mg was determined as the recommended phase 2 dose
- Phase IIB is now recruiting
- At time of data cut off (16th August 2022), 18 patients were enrolled in the study across both Phase IIA and IIB
- Translational analyses and assessment of PD-L1 status are ongoing

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Disclosures: F Turkes has no conflicts of interest to declare
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