Leiden University Medical Center

B.G. Sibinga Mulder, L.S.F. Boogerd, C.E.S. Hoogstins, D.P. Schaap, M. Kusters, H.J.M. Handgraaf, A. Farina Sarasqueta, K.C.M.J. Peeters, F.A. Holman, I.H.J.T. de Hingh, S.W. Nienhuijs, G.A.P. Nieuwenhuijzen, J.S.D. Mieog, C.J.H. van de Velde, H.J.T. Rutten, J. Burggraaf, B. Framery, M. Gutowski, A. Pelegrin, F. Cailler, A.L. Vahrmeijer

Tumor-targeted detection of primary and recurrent colorectal cancer using a carcinoembryonic antigen-targeting near-infrared fluorescent agent (SGM-101): impact on surgical decision making

BACKGROUND

Tumor-targeted fluorescence imaging has the potential to revolutionize current practice of oncologic surgery by selectively highlighting tumor cells, enabling radical tumor resections. Carcinoembryonic antigen (CEA) is overexpressed in the majority of colorectal cancers (CRC) and a promising tumor-target for cancer imaging.

The aim of this phase I/II study was to:

- Determine pharmacokinetics (PK), safety, and tolerability of SGM-101, a fluorescent anti-CEA monoclonal antibody.
- Investigate the feasibility to detect (colo)rectal cancer (CRC) with intraoperative fluorescence imaging (FI).

METHODS

Patients suffering from primary or recurring CRC, with increasing serum CEA since diagnosis, scheduled for open or laparoscopic tumor resection, were included in this phase I/II multicenter trial.

Two or four days prior to surgery, 5.0, 7.5 or 10 mg SGM-101 was administered intravenously to primary CRC patients to optimize the dose and time of FI.

Accuracy of the technique was investigated in an exploratory cohort of patients with recurring CRC using the optimal dose.

Characteristics	Primary cohort *N* (%)	Recurring cohort *N* (%)
Patients	9	17
Gender		
male	5 (56%)	10 (59%)
female	4 (44%)	7 (41%)
Age, median (range)	69 (63 - 80)	62 (46 - 75)
Preoperative serum CEA	4.0 (3.0 - 9.1)	4.3 (0.9 - 303)
Neoadjuvant therapy		
Yes	6 (67%)	14 (82%)
No	3 (33%)	3 (18%)
Method of surgery		
open	4 (44%)	16 (94%)
laparoscopic	4 (44%)	0 (0%)
transanal inspection	1 (11%)	1 (6%)
Additional intraoperative therapy		
IORT	n/a	10 (59%)
HIPEC	n/a	4 (24%)
Positive surgical margin	0 (100%)	6 (50%)

RESULTS

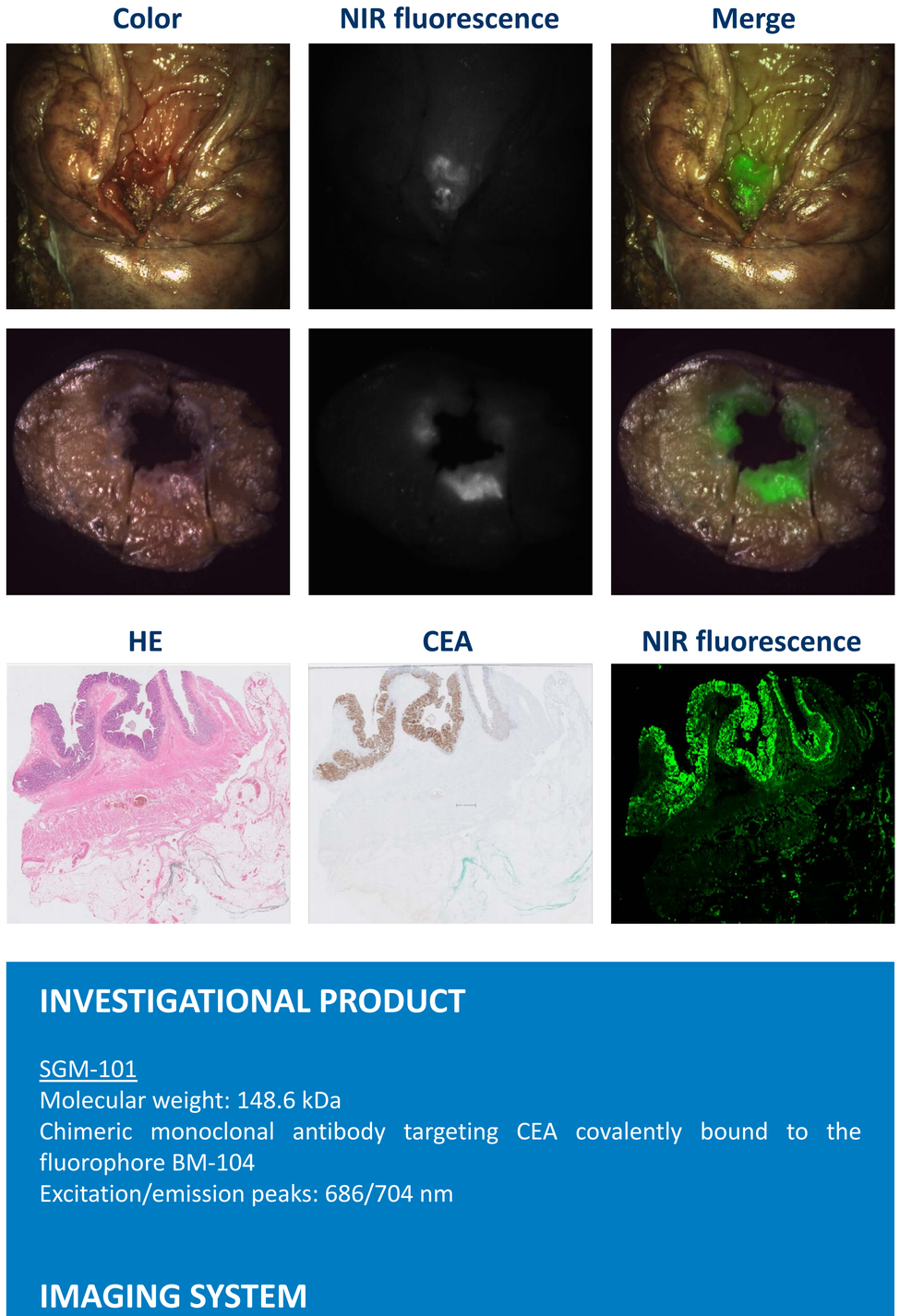
Nine patients with primary and 17 with recurring CRC were included. SGM-101 did not cause any treatment-related adverse events. A dose of 10 mg, administered 4 days prior to surgery, showed the highest tumor-to-background ratio. FI allowed detection of 19 additional malignant lesions, which changed the treatment strategy in five patients (29%).

	Sensitivity	Specificity	Accuracy
Primary cohort	93%	67%	85%
Recurring cohort	98%	62%	84%

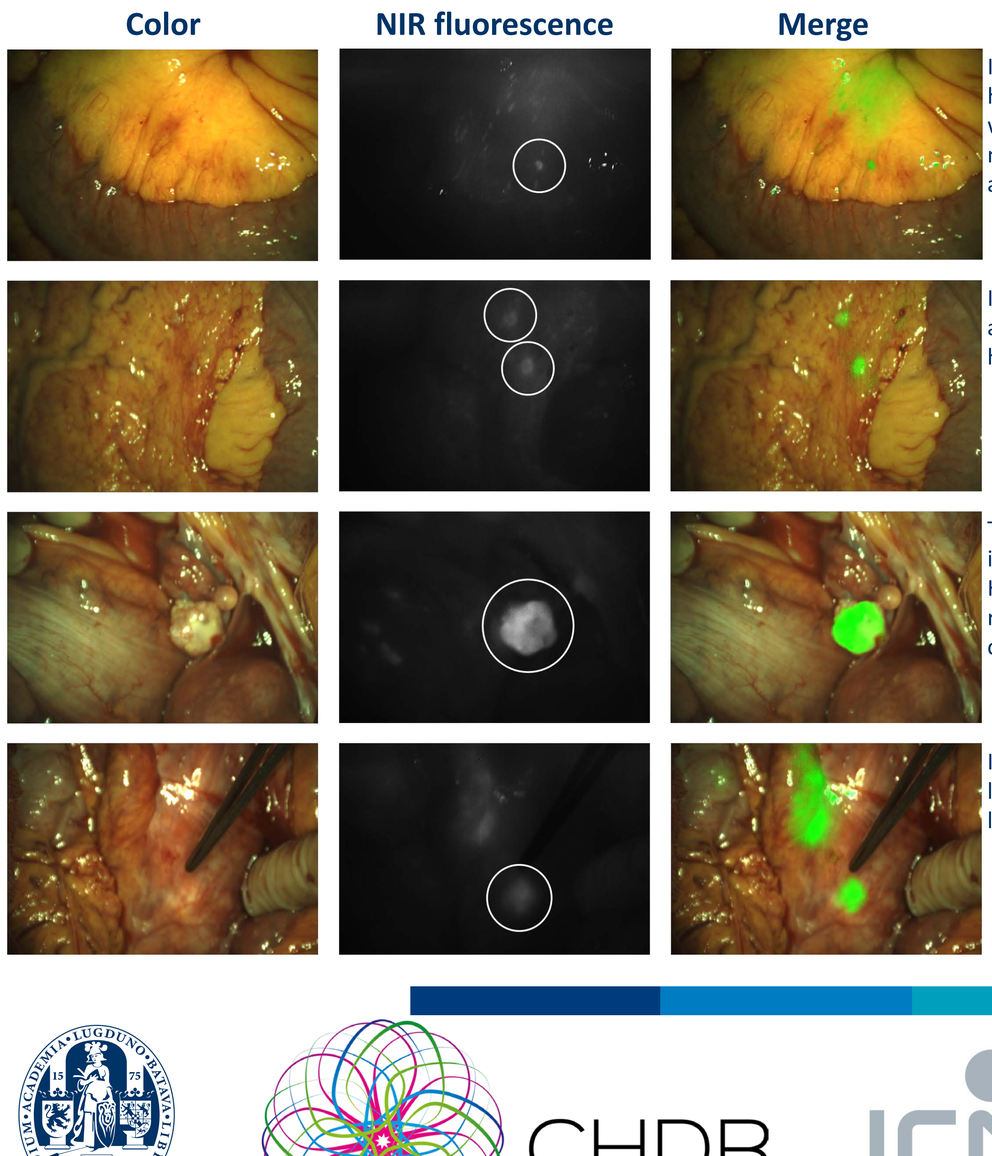
CONCLUSION

This study demonstrates the first clinical experience of CEA-targeted detection of CRC and shows that SGM-101 is safe.
Detection of more lesions and hence adaptation of treatment strategy in 29% of the patients suggests that the approach can change CRC practice significantly.

Ex vivo fluorescence imaging of a primary rectal cancer



Intraoperative fluorescence detection of additional metastases



Identification of a fluorescent hotspot in the bowel mesentery, which was confirmed to contain malignant cells by frozen section analysis.

Identification of two small, additional fluorescent tumor hotspots in the omentum.

The right ovary shows an intense fluorescence signal. Histopathological analysis revealed involvement of tumor cells.

Identification of retro-peritoneal lymph nodes, underneath a layer of overlying tissue.

INVESTIGATIONAL PRODUCT

SGM-101
Molecular weight: 148.6 kDa
Chimeric monoclonal antibody targeting CEA covalently bound to the fluorophore BM-104
Excitation/emission peaks: 686/704 nm

IMAGING SYSTEM

Artemis and Spectrum fluorescence imaging system
Quest Medical Imaging, Middenmeer, The Netherlands
Wavelenght-isolated light sources:
- "white" light source
- NIR light source Cy5.5 filter setting (range 680±30 nm)

Display: color video, fluorescence images and pseudo-colored merged image
Average gain setting: 25
Exposure time: 60-120ms
Laparoscopic setting: average gain 25, exposure 100-200ms