კლინიკა მედულა

დავით თაბაგარის

კლინიკური კვლევების ცენტრი

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

Main principles of management of Oncology patients

10 Years with Medulla

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კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

Medulla

- Medulla is Medical Institution which provides Hospital and Ambulatory services
- Certificated Medical Clinic (Has been awarded ISO 9001-2008)
- Participant in creating of future of Georgian Medicine – Residency Program in Oncology
- Leader by the experience, quantity and quality of conducted Clinical Trials


CERTIFICATE
OF REGISTRATION

This is to certify that

I.S.E. RESEARCH LTD.

1734 Broadway Street, Port Coquitlam, British Columbia V3C 2M8 Canada

operates a

Quality Management System

which complies with the requirements of

ISO 9001:2008

for the following scope of registration

International Partners

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ASCO
American Society of Clinical Oncology
Making a world of difference in cancer care

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

NCCN
National Comprehensive Cancer Network®

esso
The European Society of Surgical Oncology

CLERMONT-FERRAND
www.cice.fr
CiCE
International Center for Endoscopic Surgery

Departments

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

Department	Number of Doctors
Oncology	15
Internal Medicine(Rheumatology/Cardiology/General Practice/gastroenterology)	10
Endocrinology	4
Neurology	3
Surgery	11
Gynecology	10
Urology	4
Anesthesiology/Intensive Care Unit	10
Radiology	8
Stem Cell Bank	3
Laboratory(Clinical Laboratory/Cytology/Morphology)	10

Medical Staff

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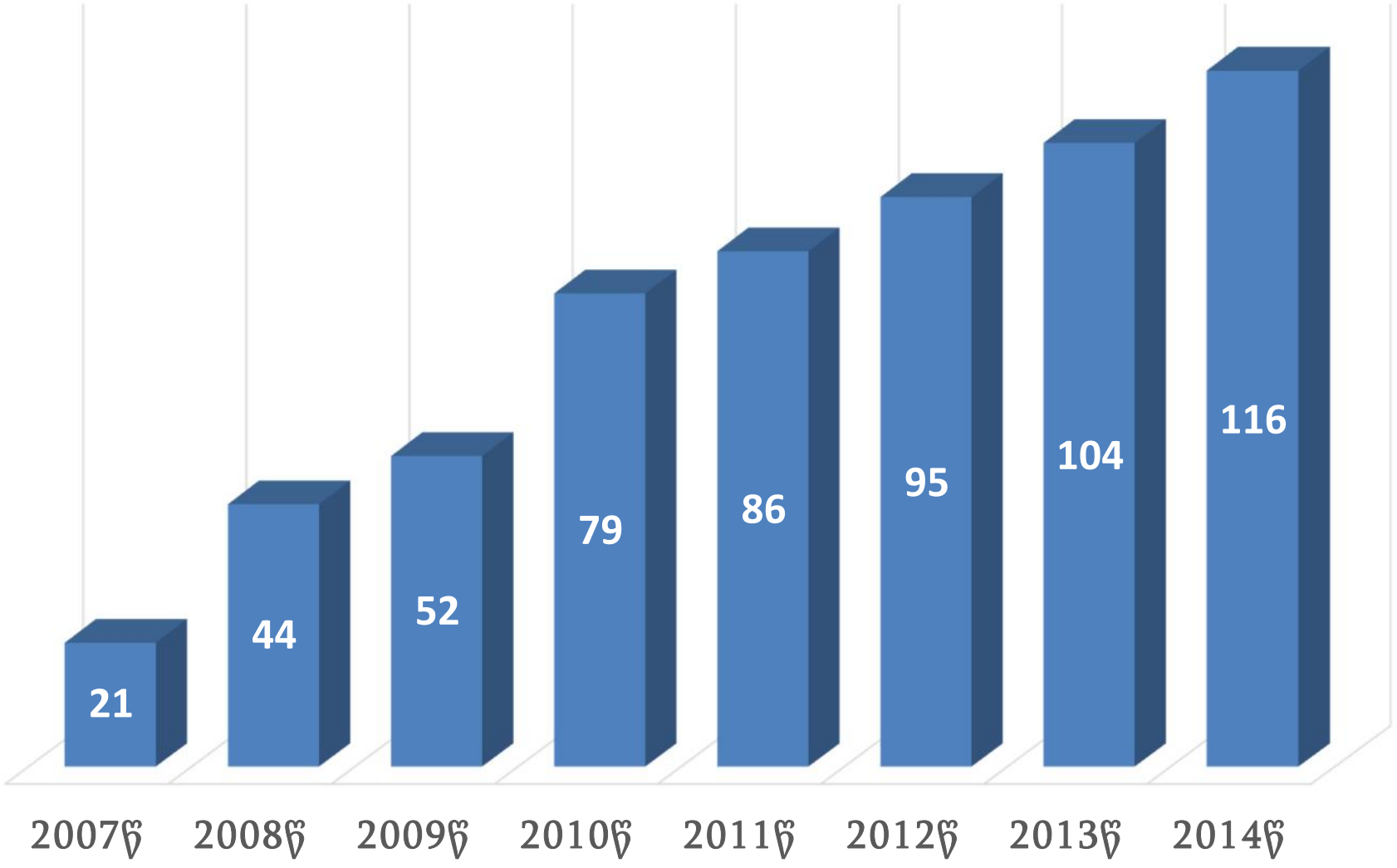
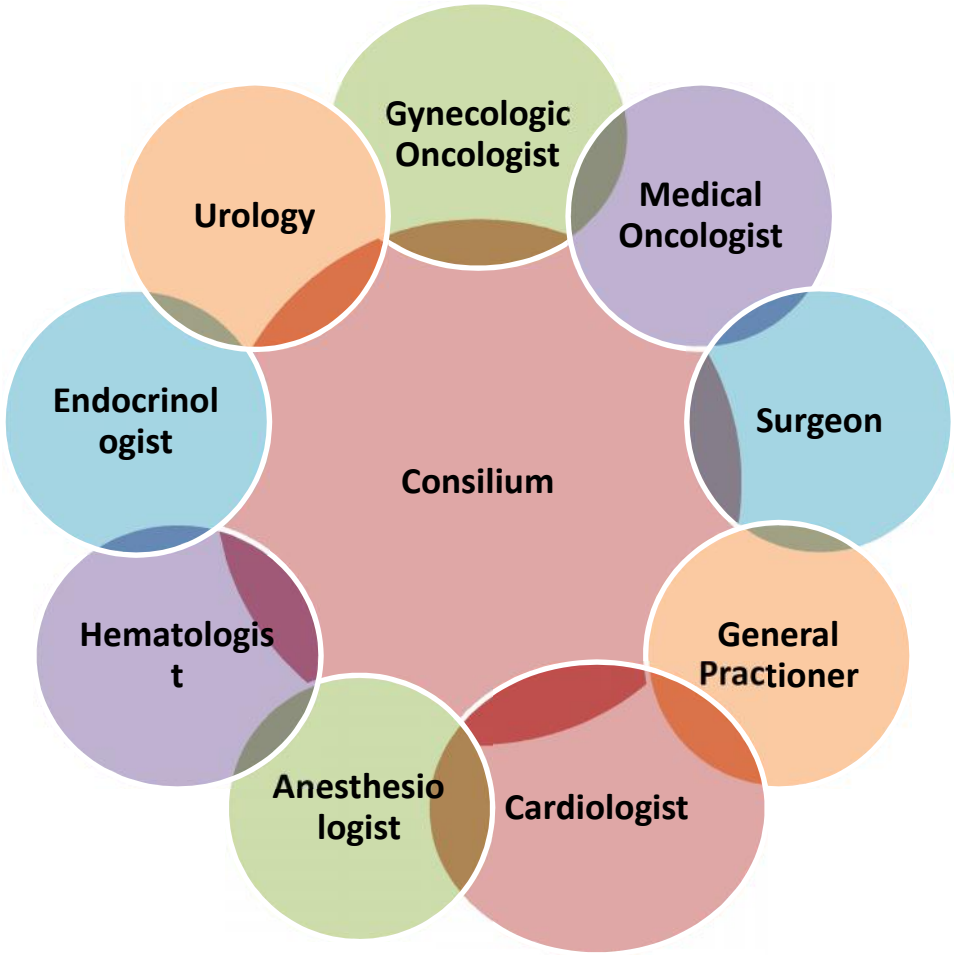
კლინიკური კვლევების ცენტრი

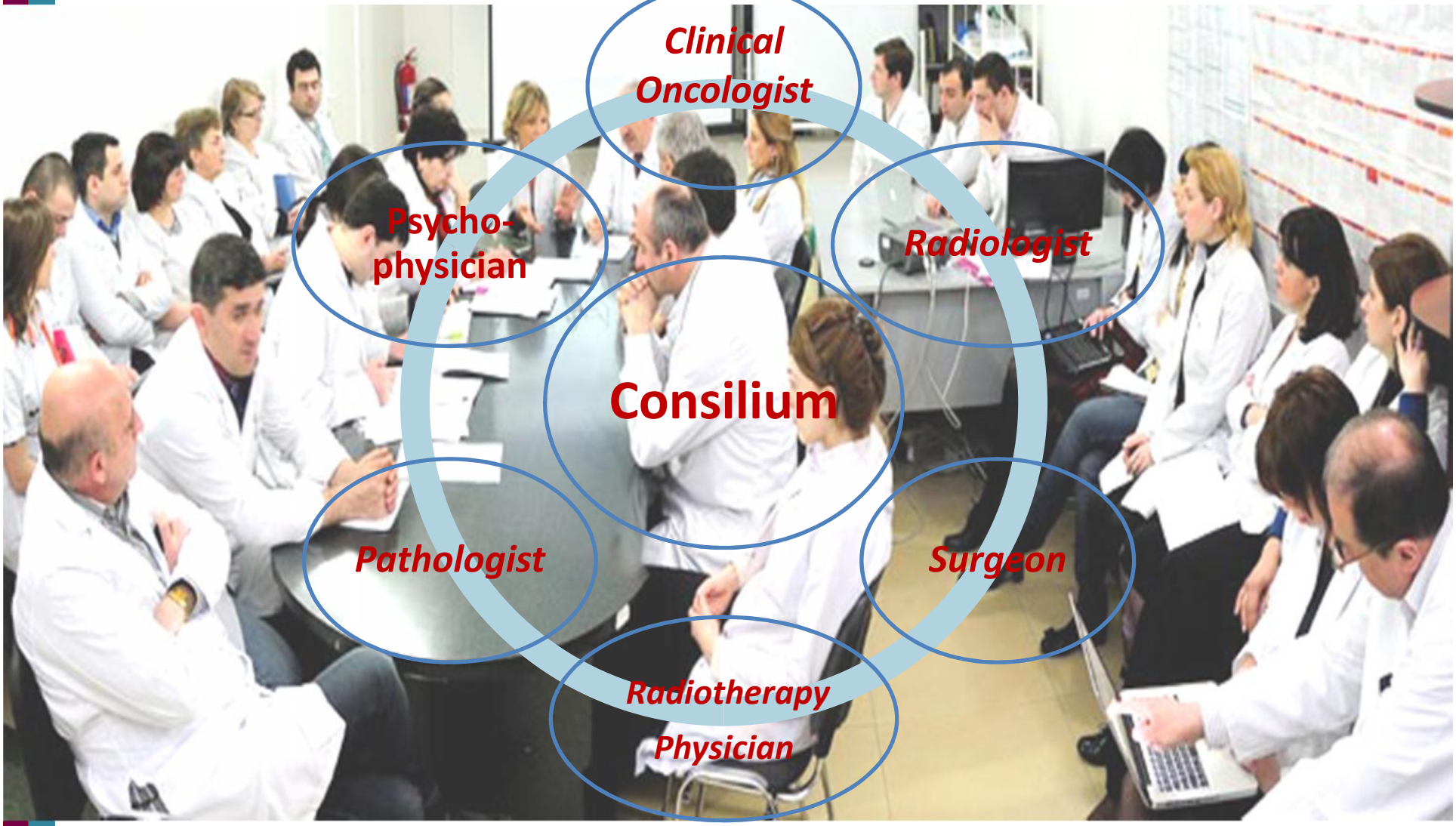


Multidisciplinary approach



Management of the cancer patient

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი



ESMO EXAM

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

- From 1989 ESMO is conducting examinations in Medical Oncology. The aim of this examination is to evaluate special skills and knowledge of Medical Oncologists - necessary to treat cancer patients
- Four our young Medical Oncologists passed ESMO exam in Amsterdam in 2013

ESMO EXAM

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

Treatment with NCCN and ESMO Guidelines

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

- Georgian version was developed by our team of young Medical Oncologists

NCCN

National Comprehensive Cancer Network®

ESMO

ESMO

Consillium-Medulla Clinic

of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350: 1081–1092 [erratum, N Engl J Med 2004; 351: 2641].

et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006; 354: 809–820.

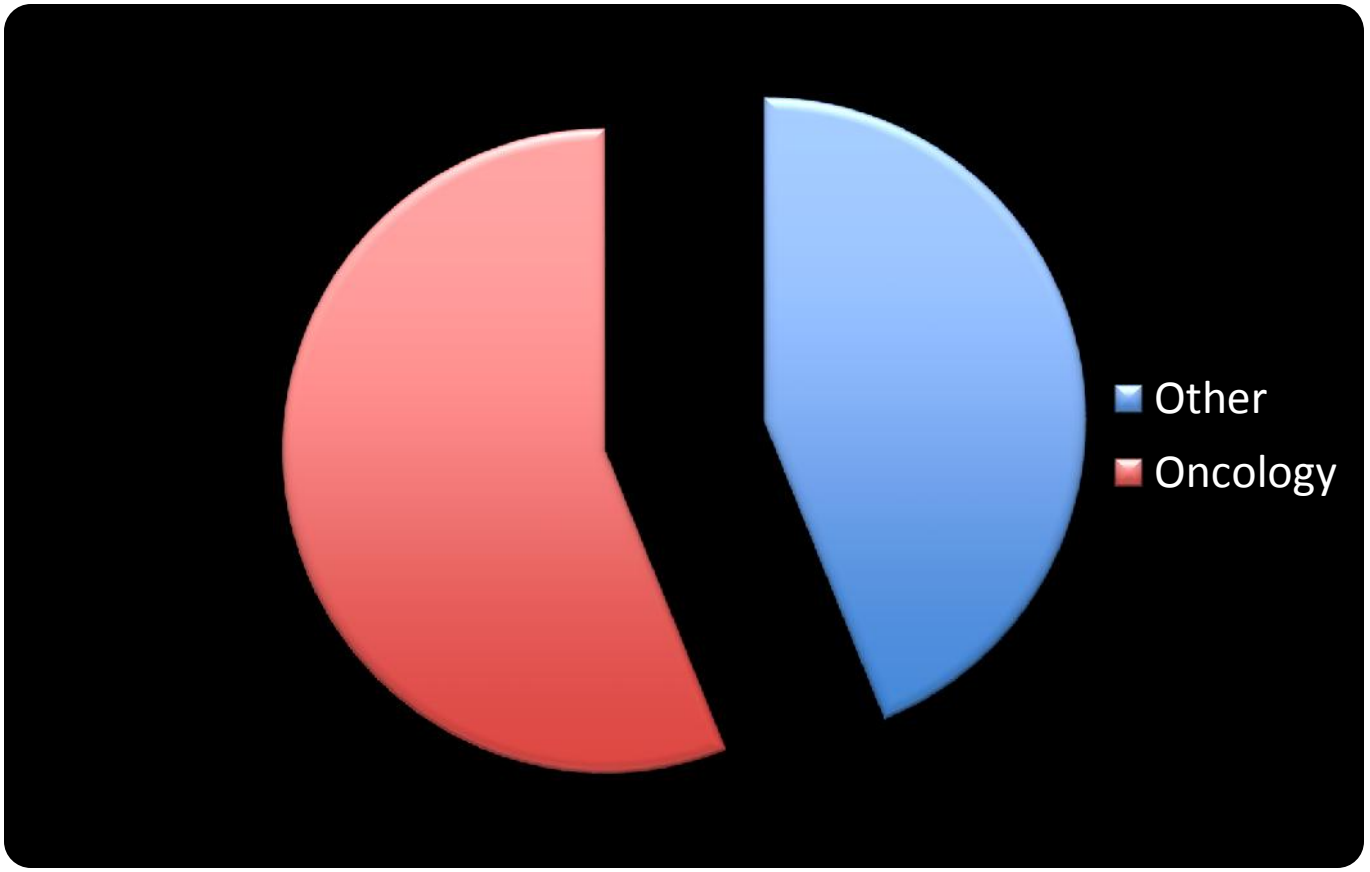
ლია, უნდა იქნეს მიღებული ჰისტოპა-თოლოგიური ან ციტოპათოლოგიური დადასტურება.

ადიუვანტური მკურნალობის ჩატარება ქიმიო-, ჰორმონ- და/ან რადიოთერაპიით [II, B]. სიმსივნე უნდა ამოიკვეთოს

Clinical Trials

კლინიკა მედულა
დავით თაბაგარის
კლინიკური კვლევების ცენტრი

We have participated in 47 international, multicenter Phase I, II, III, Device and Bioequivalence clinical trials and enrolled up to 1000 patients in accordance with ICH-GCP guidelines.



Phase II study of bavituximab plus docetaxel in locally advanced or metastatic breast cancer (interim results)

D. Tabagari, G. Nemsadze, M. Janjalia, M. Jincharadze, J. Shan

Chemotherapy and Immunotherapy Clinic Medulla, Tbilisi, Georgia; JSC National Cancer Centre, Tbilisi, Georgia; Ltd. Tbilisi Oncological Dispensary, Tbilisi, Georgia; Ltd. Oncological Centre of Adjarian Autonomous Republic, Batumi, Georgia; Peregrine Pharm Inc, Tustin, CA.

Introduction

Bavituximab is a novel chimeric IgG$_1$ monoclonal antibody that is being investigated as a new solid tumor therapy. Specifically, bavituximab selectively targets the membrane phospholipid phosphatidylserine (PS) complexed with the plasma protein β2-glycoprotein I that is exposed on the external surface of vascular endothelial cells in tumors.

Preclinical models show macrophage maturation and a switch from M2 (pro-6) to M1 (pro-inflammatory) immune response as measured by cytokine profile produces host effector cell-mediated destruction of tumor vasculature and enhancement of anti-tumor immunity. Preclinical data suggest synergistic anti-tumor activity using PS-targeting antibodies in combination with chemotherapy or radiation in several tumor types (e.g., glioma, breast, pancreatic, prostate, etc.).

Objectives

- Determine the overall response rate (CR+PR) to a combination of bavituximab plus docetaxel in patients with locally advanced or metastatic breast cancer
- Determine time to progression, duration of response, overall survival and safety (type, frequency, severity and relationship of adverse events to study drugs)

Methods

Study Design

- Phase II, open-label, single-arm study utilizing a Simon 2-stage design
- Fifteen patients were initially enrolled and exceeded the pre-specified response rate and the trial was expanded to a total of 46 patients.
- The study was conducted in 2 phases, a Treatment Phase and a Follow-up Phase.
  - During the treatment phase, qualified patients received study treatment according to the table below.
  - After completion/discontinuation of chemotherapy, patients who had not progressed entered the Follow-up Phase and continued bavituximab weekly until progression or toxicity.
- Clinical and laboratory assessments were performed every 2 weeks, and tumor response performed every 2 cycles during the treatment phase, then every 2 months until disease progression.
- Survival data are collected every 3 months until 80% of patients have discontinued treatment.

Dosing Schedule		
Test Product	Dose	Time
Bavituximab	3 mg/kg	Weekly until disease progression
Docetaxel	35 mg/m^2	Days 1, 8, and 15 of every 28-Day cycle (For up to 6 cycles)

Criteria for Evaluation

- SAFETY: Physical exams, vital signs, complete blood counts (CBCs), coagulation assays (PTT, PT/INR), hypercoagulability marker (d-dimer), serum chemistries, human anti-chimeric antibody (HACA), adverse events and concomitant medications.
- EFFICACY: Overall response and disease progression was evaluated by RECIST criteria and assessed according to the schedule above.

Results

Patient Demographics

A total of 46 Caucasian female patients were enrolled in this study and received an average of 28.1 doses (range 2-77) of the study drug.

Patient Characteristics		Patients N=46
Age	Median in years (Range)	49.4 (32.4-73.7)
Baseline ECOG	0	8 (17.4%)
	1	32 (69.6%)
	2	6 (13.0%)
HER2 Status	0	2 (4.3%)
	+1	10 (21.7%)
	+2	1 (2.2%)
	+3	6 (13.0%)
	Unknown	27 (5.8%)
	Total	46 (100%)

Safety

Table 1 Adverse Events Occurring in >30% of all AE-Reporting Patients

Adverse Event	Subjects (N=46)	Percent
Any AE	44	96.0%
Alopecia	34	73.9%
Diarrhoea	29	63.0%
Epistaxis	28	60.9%
Lacrimination Increased	25	54.3%
Fatigue	20	43.5%
Onycholysis	19	41.3%
Face Oedema	18	39.1%
Arthralgia	17	37.0%
Infusion-related Reaction	16	34.8%
Nasal Dryness	14	30.4%

- To date, AEs (any grade or causality) have been reported in 96% (44 out of 46) of subjects, most events were mild to moderate. Alopecia (73.9%), diarrhoea (63.0%), epistaxis (60.9%), lacrimination increase (54.3%), fatigue (43.5%), and onycholysis (41.3%) were the most common adverse events.
- Grade 3/4 AEs were experienced by 15 out of 46 (32.6%) of subjects. The most common Grade 3/4 AEs were leaukopenia (8.7%) and neutropenia (8.7%).
- Seven out of 46 subjects (15.2%) reported SAEs, of which 5 experienced bavituximab-related SAEs. Three of these 5 subjects developed pulmonary embolism (one had preceding event of deep vein thrombosis), all of which were resolved with sequelae. In addition, one subject experienced fatigue (resolved with sequelae) and another experienced Grade 3 (non-cardiac) chest pain.
- Deaths due to AEs occurred in 2 of 46 subjects (4.3%). One death was due to liver failure and the other was due to exacerbation of chronic obstructive pulmonary disease (COPD); neither of which were bavituximab-related.

Efficacy

In the intent-to-treat analysis, the best overall response rate is 61% (28/46). Figure 1 illustrates the greatest reduction in the Sum of the Longest Diameters (SLD) of the target lesions for each subject. Almost all subjects in this study had some reduction in the SLD of their target lesions. Figure 2 is a Kaplan Meier plot of Time to progression. The median time to progression is estimated to be 7.4 months. For those achieving objective response, the duration of response was 6.0 months. Median overall survival has not been reached.

Figure 1
Waterfall Plot of the Greatest Percent Reduction In SLD from Baseline

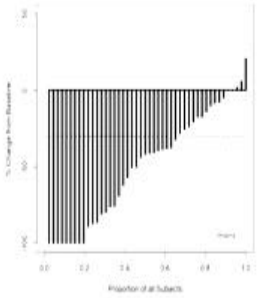


Figure 2
Kaplan Meier Plot of Time to Progression

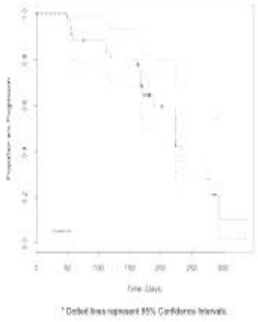
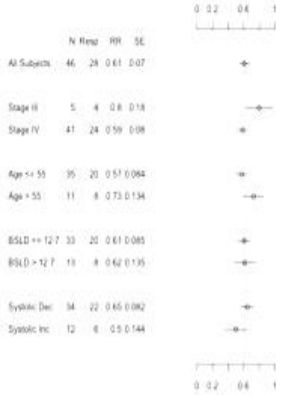


Table 2: Summary of Criteria for Evaluation for Efficacy

Best Overall Tumor Response Rate (CR + PR) (95% C.I.)	Median Duration of Response in Months (95% C.I.)	Median Progression Free Survival in Months (95% C.I.)
60.9% (45.4%, 74.9%)	6.0 (5.6, 7.4)	7.4 (6.0, 9.0)

Figure 3 presents a forest plot of response rates for several subgroups. The plot displays the response rate along with an interval representing + 1 standard error. Because of the small sample size for the study, the response rates in all subgroups are consistent with the response rate for the study population as a whole. Note that the subgroup involving systolic blood pressure categorized subjects according to whether there was any increase or decrease in systolic blood pressure in the first 30 days following initiation of treatment.

Figure 3
Forest plot of Response Rates for Sub-Groups



Conclusions

- Bavituximab, a unique PS-targeting monoclonal antibody which induces immune enhancement and immune cell-mediated destruction of tumor vasculature, produced a promising 61% best overall response rate in this single arm study of 46 patients with locally advanced or metastatic breast cancer.
- Median time to progression was an encouraging 7.4 months.
- No differences were seen in response rate by age, stage at study entry, histology or baseline tumor total.
- The safety profile of bavituximab when combined with docetaxel was acceptable.
- Rates of epistaxis, onycholysis and infusion reactions were higher than expected, but non-limiting.
- Although 3 patients (6.7%) experienced pulmonary embolism on study which were attributed to study drug, the overall incidence of venous thromboembolism events is in line with expected spontaneous VTE rates in advanced breast cancer patients.
- Randomized trials of chemotherapy and bavituximab in patients with advanced breast cancer are warranted.

References

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- Huang X, Bennett M, Thorpe P. *Cancer Res* 2005; 65 (10): 4408-4416.
- Liang Y, Besch-Williford C, et al. *Breast Cancer Res Treat* (2010) Published Online 27 March 2010.

Abstract : Presented at the 2010 ASCO Annual Meeting, Chicago, IL, USA, June 4-8 2010.

Clinical Trials

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კლინიკური კვლევების ცენტრი

Department		Bioequivalence	Phase I	Phase II	Phase III
Oncology	26	4	4	5	11
Rheumatology	11	-	2	7	2
Surgery	2	-	-	-	2
Urology	3	-	2	-	1
Neurology	2	-	-	2	-
Endocrinology	2	-	-	2	-
Pulmonology	1	-	-	-	1
Sum 47		**4**	**8**	**16**	**17**

Clinical Trials

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Medulla – Chemotherapy and Immunotherapy clinic was inspected by FDA audit in 2010. No critical and major findings were found.

Residency Program

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Our goal

- Use of the American model of medical residency
- Development of the best training program for our residents and students
- To generate future leaders in Georgian Medical Oncology

Residency program In Medical Oncology

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დავით თაბაგარის
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Main Mission

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დავით თაბაგარის
კლინიკური კვლევების ცენტრი

- **ASCO and ESMO developed global curriculum to adapt the teaching program for Medical Oncologists**
- **Based on existed recommendations Patient's Management and Treatment Guidelines were developed in Georgia version**

Main principles of study

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კლინიკური კვლევების ცენტრი

- Seminars / Presentations
- Discussion of theory
- Patient case discussion
- Clinical Trials evaluation

Multidisciplinary evaluation

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Main principles of teaching process

Thank you for attention

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