bevacizumab maintenance in primary ovarian cancer

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Patient H-P-L

- 74 y old otherwise healthy, non Ashkenazi

- Presented on 11.2013 with urinary incontinence
- VUS – semi solid mass posterior to the uterus , no clear border between uterus and mass
- CT – same findings, interpretation – benign leiomyoma

- Tumor markers – performed prior to operation but **result receive post op** : ca125 – 2609, others within normal limits

- Referred for abdominal hysterectomy

At surgery (29.12.2013)

- 10 cm left ovarian mass – heterogenic – adherent to pelvic wall and to distal sigmoid . Small right ovarian mass.
- Seeding on pelvic peritoneum , omental cake, small solid diaphragmatic masses
- Tumor invading the pouch of Douglas with severe adhesions – cannot be excised

- Debulking : uterus, adnexas, omentum, peritoneum, diaphragm, nodes
- Upon separation from sigmoid – suspected perforation of colon : revised and sealed

- >> sub optimal debulking (sub total hysterectomy and Douglas disease)

Had we known…

- Patient suitable for NACT : disseminated upper abdominal and peritoneal disease, adhesions

  >> low probability of optimal debulking

- Could we evaluate better pre-surgery???

Had we known….

- Risk prediction models for optimal primary debulking:

  Radiographic evaluation:

  - Bowel mesentery involvement
  - Diffuse peritoneal thickening / implants
  - Diaphragmatic disease
  - Large volume ascites
  - Liver involvement
  - Suprarenal aortic lymph nodes

  Clinical Clinical – PS 0-1 vs 2

Models to predict incomplete surgery in advanced ovarian cancer have limited predictive ability and their reproducibility is questionable

Rutten et al , Gyn Oncol Jan 2016

Had we known…

If starting with NACT >> IDS

- **Should we add bevacizumab to NACT?**

study	Pts no	End point	Time from bev to surg	Best results	Complications Gr 3/4
Chereau	5 St IV	Safety outcome	54 days	100% optimal	1 (20%) gr 3 lymphocyst
Salani w. Taxol dose escalation	9 5 st IIIc 4 st IV	Toxicity	63 days	100% optimal	3 gr 3 neutropenia 2 gr 3 VTE 1 gr 4 rectal leak
Petrillo Case control	25 (50)	Toxicity Outcome PFS	27 days	80% (control 72%) No difference.. PFS 18 m vs 10 m (s)	1 gr 5 perforation

Chereau , Int J Gynecol Cancer sept 2013
Salani . Int J Gynecol Cancer May 2014
Petrillo, Ann Surg Oncol Dec 2015

H-P-L – post surgery

- 2 days post op – bowel obstruction >> resolved
- Surgical wound infection >> resolved
- Ca125 post surgery – 854
- Pathology – high grade serous ca of ovary in ovaries, uterus, nodes, omentum and pelvic masses
- **Diagnosis: stage IIIc high grade serous ovarian cancer**

H-P-L – post surgery treatment

- 1 month later – started systemic therapy:

  carboplatin AUC5 , weekly paclitaxel 80 mg/$m^{2,}$, Bevacizumab 7.5 mg/kg

- treatment tolerance – moderate to poor (nausea – maximally treated, severe fatigue, severe dyspepsia, progressive neuropathy, myelotoxicity)

- 6 courses full treatment (dose reductions)
- 2 more courses of carboplatin , ongoing bevacizumab for 1 year

- Ca125 – at 4th cycle – 16. At end of chemotherapy - 13

H-P-L follow up and treatment

- CT at chemotherapy end – new lesion in the LLL lung 1.2 cm.
  ca125 stable : suspected infection??
- Received antibiotics >> repeated CT scan after 2 months
- Lung lesion resolved, new lesion in the 4th segment of the liver
  ca125 stable (11.8)
- PET CT : no absorption in lung or liver (focal fatty infiltration)

H-P-L follow up and treatment

- Continues bevacizumab 7.5 mg/kg q3w
- Approaches 1 year of bev :

  repeated PET CT – no evidence of disease

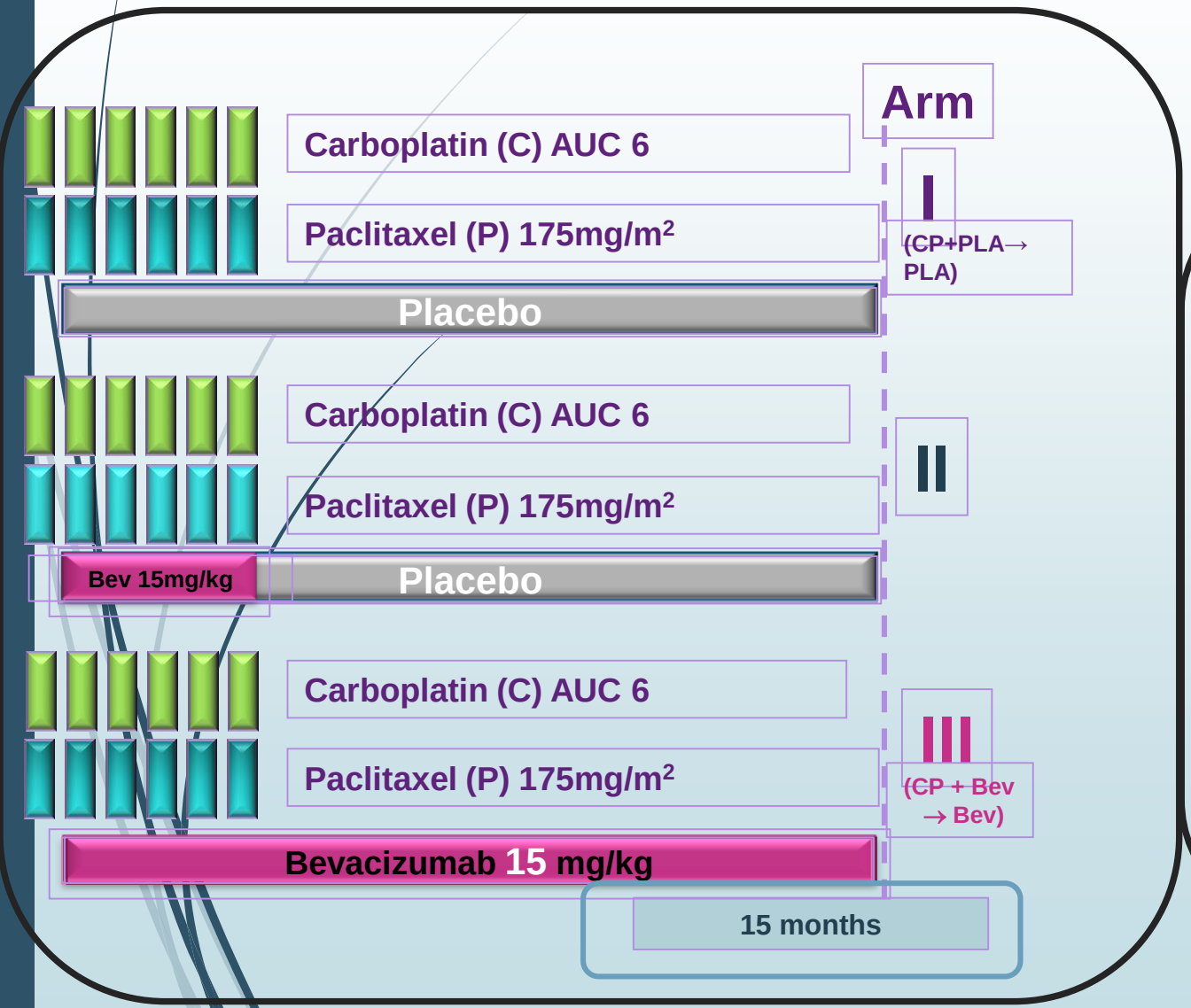
  ca125 – 7

Discussion at patient wish : to continue or not to continue bevacizumab?

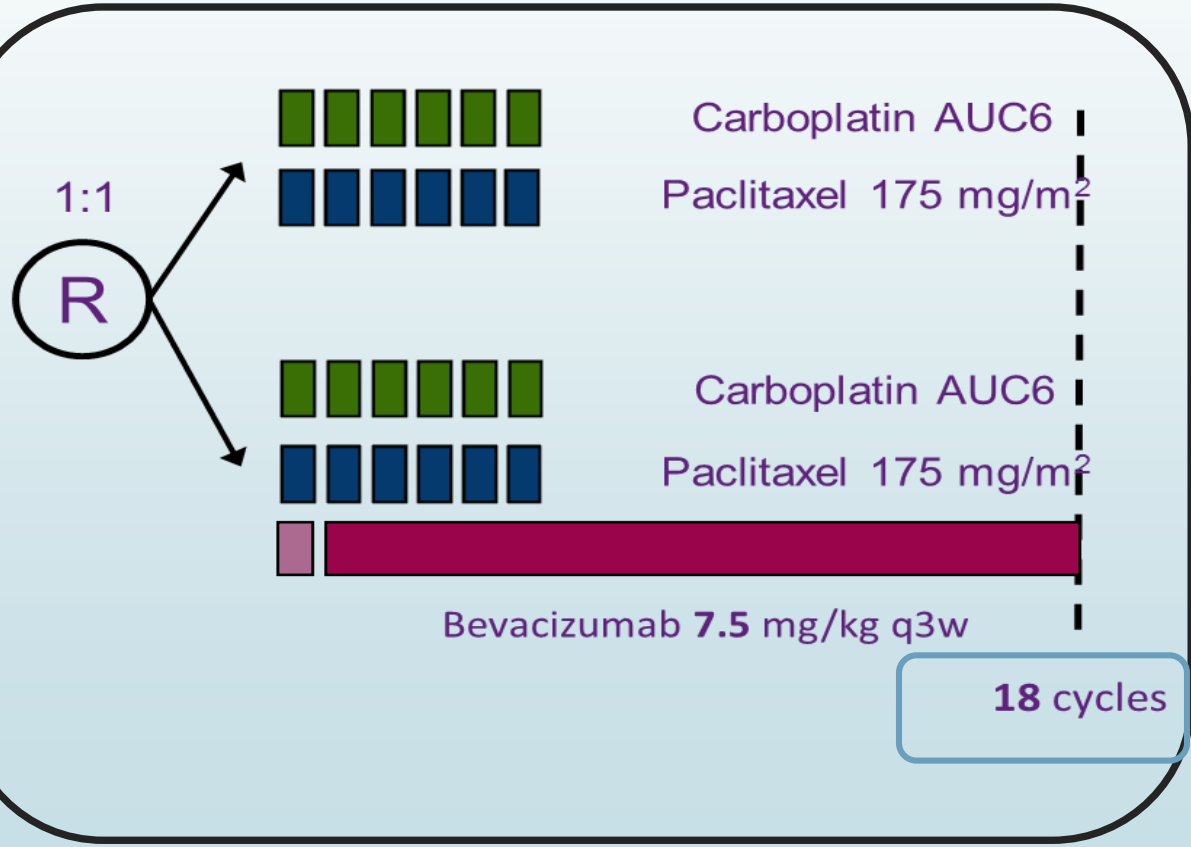
(patient has private insurance)

Study design

GOG 218



ICON7



Bevacizumab in 1st line ovarian cancer – studies GOG218 and ICON7

- Patient treatment with bevacizumab:

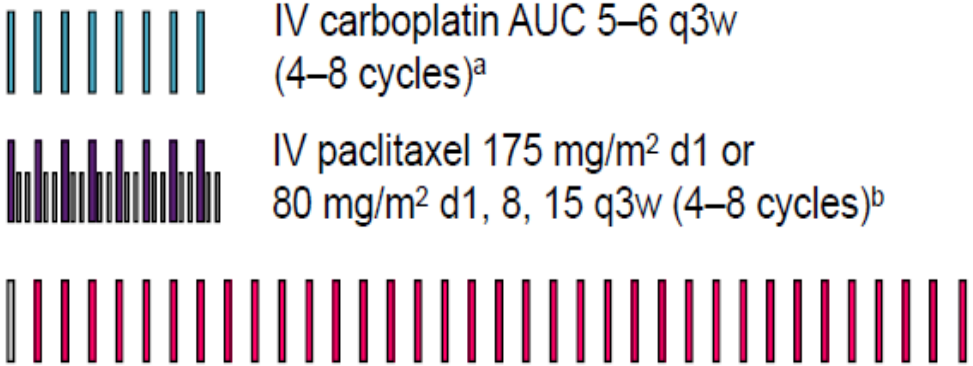
- Based on OS benefit from ICON7
- Bevacizumab dose – 7.5 mg/kg – based on ICON7

- Request for Bevacizumab for further 3 months (15 m)- Based on GOG 218

4 Study design

- **Epithelial ovarian, fallopian tube or primary peritoneal cancer:**
  - Stage IIB–IV
  - Grade 3 stage I/IIA
  - Clear-cell carcinoma (any stage)
  - Carcinosarcoma
- **Maximally debulked (prior neoadjuvant chemotherapy allowed)**
- **ECOG PS 0–2**

Dec 2010–May 2012: 1021 patients enrolled



Patients without progression at cycle 36 could continue therapy after discussion with the Steering Committee

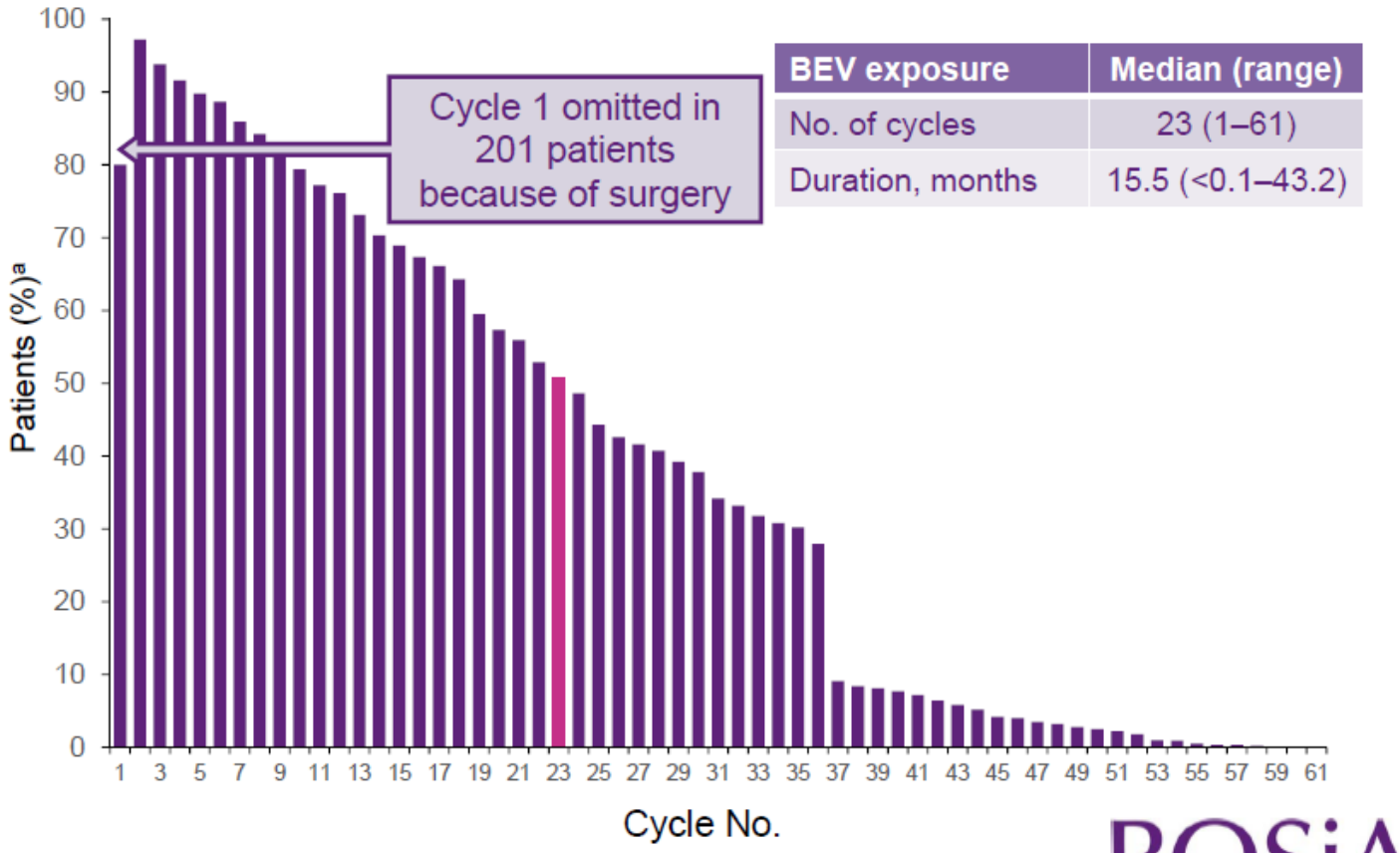
- Primary endpoint: Safety (AEs by NCI-CTCAE version 4.03)
- Secondary endpoints: PFS, ORR, duration of response, overall survival
- Exploratory objectives: Optional translational research

[a]Cisplatin permitted in patients with hypersensitivity to carboplatin
[b]A change from one paclitaxel regimen to the alternative during the study was not permitted
ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = overall response rate

ROSiA

Rosia study

7 Bevacizumab exposure by cycle



BEV exposure	Median (range)
No. of cycles	23 (1–61)
Duration, months	15.5 (<0.1–43.2)

[a]Denominator at each cycle is 1021

ROSiA

Exposure :

53% of pts above 15 m

Median PFS – 26 m

H-P-L follow up

- Request for bevacizumab authorized by insurance for 3 more months
- Ongoing bevacizumab (since 5.2.2014)
- Tolerance – good (gr 2 fatigue for 3 days post bev)
- PET CT 12.2015 – no evidence of active disease
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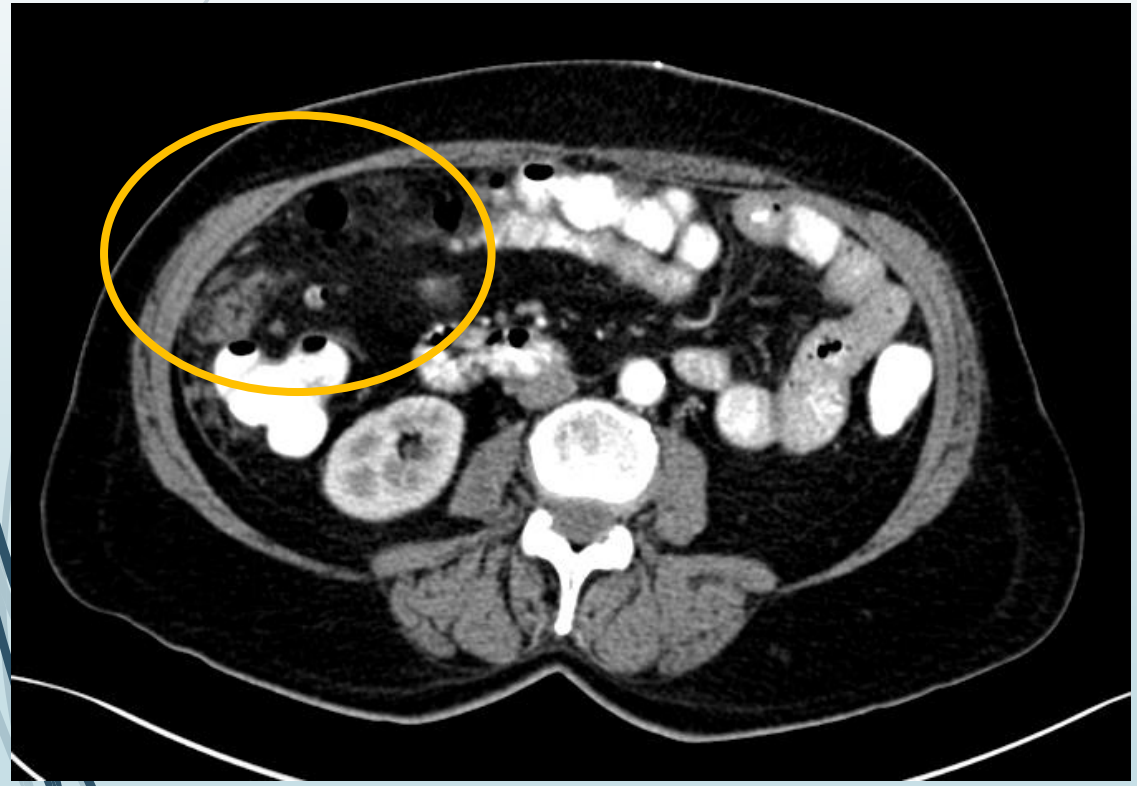
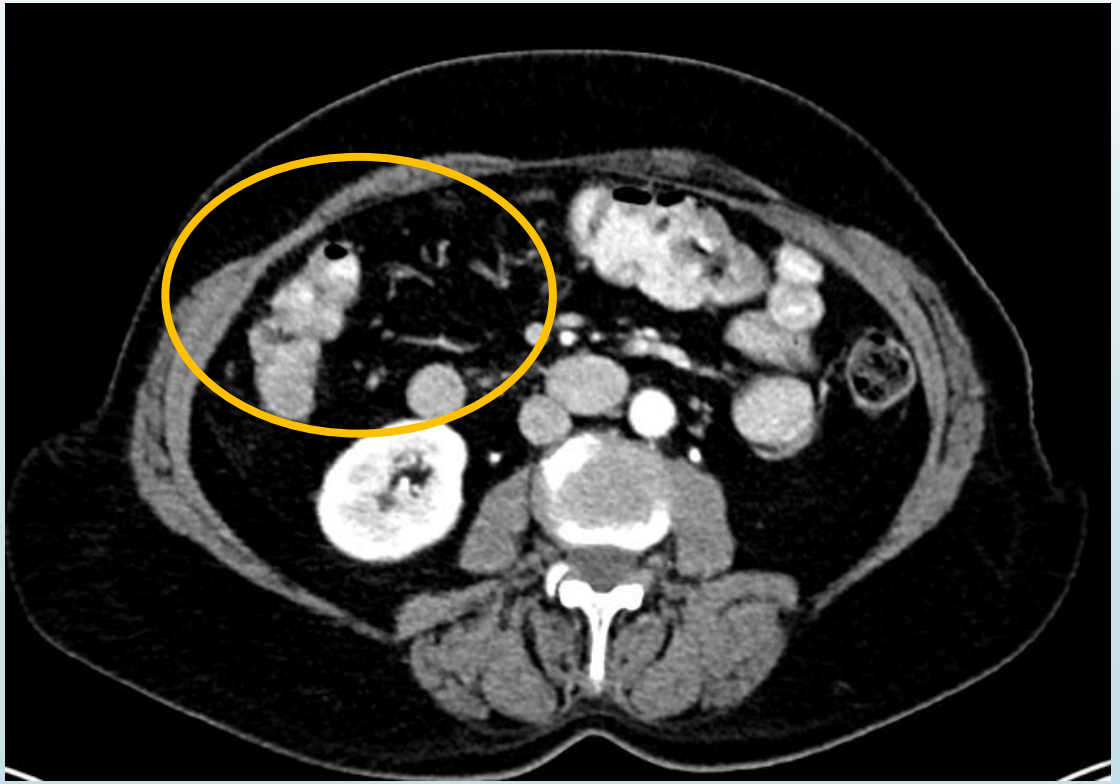
Imaging

8 days post operation



12.2015 2 years post operation



Tumor markers

Full Name	Units	29/12/2013 15:08 סרום 840157		05/02/2014 09:29 סרום 871664		19/02/2014 09:28 סרום 884915		19/03/2014 09:29 סרום 909377	30/04/2014 09:48 סרום 943876	22/05/2014 10:27 סרום 962218	09/07/2014 09:20 סרום 201506	30/07/2014 09:29 סרום 219003	20/08/2014 10:26 סרום 236509	10/09/2014 12:24 סרום 253303
CA 125 - new	U/ml	1950.4	H	511.6	H*	153.1	H*	16.6	13.1	13.4	12.4	12.2	11.8	10.7
CA 19-9 (new)	U/ml													3.1
CA 15-3 - new	U/ml	68.8	H	45.9	H	37.3	H					17.3		17.8
CEA - new	ng/ml													1.2

Full Name	Units	29/04/2015 13:06 סרום 851297	20/05/2015 10:30 סרום 869676	10/06/2015 12:24 סרום 887854	01/07/2015 11:04 סרום 905848	22/07/2015 10:22 סרום 934502	12/08/2015 13:00 סרום 925114	09/09/2015 13:39 סרום 978513	21/10/2015 12:49 סרום 212509	01/12/2015 16:50 סרום 248787	21/12/2015 13:18 סרום 266866
CA 125 - new	U/ml	11.4	11	14.5	13.4	13	13.5	12.7	15	11.8	11
CA 15-3 - new	U/ml	16.4	16.4	16	15.9	17.6	14.9		16.1		16.5
CEA - new	ng/ml				0.8					0.8	