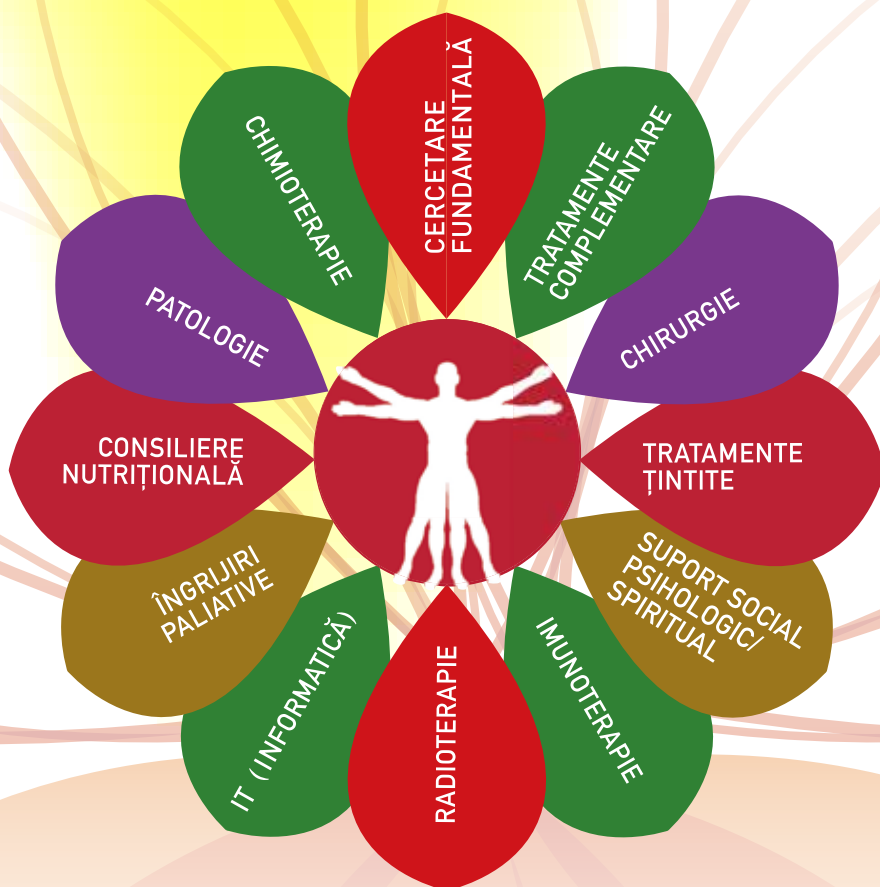




# A 2-a ediție a Simpozionului Translațional de Oncologie Personalizată pentru combaterea cancerului



## STOP CANCER

13-15 Aprilie 2018

Hotel Crowne Plaza, București, România

un eveniment de excepție • reunește nume internaționale

15 profesori româno-americani • comunicări științifice medicale

<http://www.stop-cancer-romania.ro>

[contact@stop-cancer.org](mailto:contact@stop-cancer.org)

În numele Comitetului de Organizare ne revine o deosebită plăcere de a vă ura bun venit la al doilea **Simpozion Translațional de Oncologie Personalizată pentru Combaterea Cancerului** care are loc în perioada 13-15 Aprilie 2018, în București, România, la Hotelul Crowne Plaza, Str. Poligrafiei nr. 1.

**Simpozionul Translațional de Oncologie Personalizată (STOP Cancer-România)** se desfășoară sub egida "Asociației Române de Chirurgie" și "Societății Transdisciplinare de Oncologie Personalizată pentru Combaterea Cancerului".

La această a doua ediție participă chirurghi-oncologi, radioterapeuți, oncologi medicali, hematologi, anatomopatologi, bioinformaticieni și cercetători în domeniul științelor fundamentale atât din țară, din Statele Unite ale Americii și din Europa.

Intenția noastră este pe de o parte de a facilita dialogul între specialiștii oncologi din România și diaspora, iar pe de altă parte de a crea o platformă de oncologie translațională pentru schimbul de informații și idei între cercetătorii din diferite domenii ale științelor fundamentale și clinicienii oncologi în scopul dezvoltării de proiecte comune.

Sperăm ca această platformă de colaborare să îmbunătățească atât modalitățile de diagnostic ale cancerului cât și prognosticul și calitatea vieții pentru pacienții cu cancer din România.

Prezența lectorilor de peste hotare precum și a dumneavoastră ne onorează și garantează succesul Simpozionului.

Limba oficială a Simpozionului este limba română.

**Prezentările de la simpozion vor fi postate pe situl:**

<http://www.stop-cancer-romania.ro>

**Simpozionul va fi creditat cu credite EMC!**

Bine ați venit!

Comitetul de organizare:

Prof. Dr. Carmen Ardeleanu

Prof. Dr. Florin Bacanu

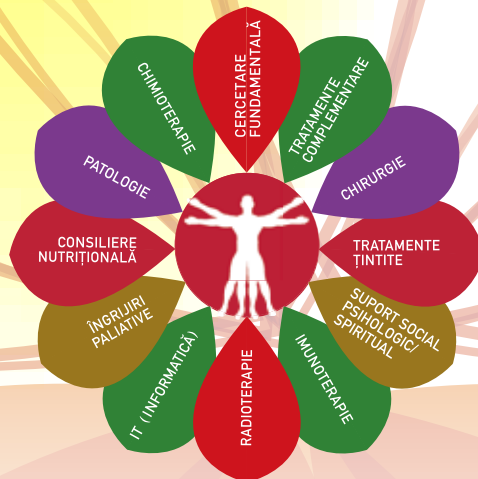
Prof. Dr. Silviu Constantinoiu

Conf. Dr. Adina Croitoru

Conf. Dr. Serban Negru

Șef lucrări Dr. Allna Musetescu

Prof. Asistent Dr. Doru Paul



## STOP CANCER

**STOP CANCER ROMÂNIA**  
**13-15 Aprilie 2018, Bucuresti**  
**VINERI 13 Aprilie 2018**

**Ziua 1, 13 Aprilie 2018**

**8.00-9.00 Înregistrare conferință**

**9.00-9:15 Mesajul administratiei prezidentiale: DIANA PĂUN (Consilierul de Stat, Departamentul Sanatate Publica, Administratia Prezidentiala)**

**9.15-10:45 IMUNOTERAPIA**

**Moderatori: PROF. DR. VIRGIL PAUNESCU, PROF. ASISTENT DR. DORU PAUL**

9:15-9:45 PROF. ASISTENT DR. DORU PAUL (Northwell Health-Hofstra University, New York, SUA) – “Orchestra imună în cancer: o introducere”

9:45-10:05 CONF. DR. ȘERBAN NEGRU (Centrul de oncologie OncoHelp, UMF “Victor Babeș” Timișoara) – “Bazele imunologiei și imunoterapiei în oncologie”

10:05-10:25 CONF. DR. ADINA CROITORU (Institutul Clinic Fundeni-Universitatea Titu Maiorescu, Bucuresti) – “Imunoterapia in tratamentul cancerelor digestive- Cenusareasa sau...Regina?”

10:25-10:45 DR. LAURENTIU BUJOR (Centrul Oncologic Sanador, Bucuresti) – “Efectele imunogenice ale radioterapiei si implicatiile lor clinice”

**10:45-11:00 PAUZĂ DE CAFEA**



**11:00-12:40 CANCERE DIGESTIVE**

**Moderatori: CONF. DR. CROITORU ADINA, PROF. DR. CATALINA POIANA**

11:00-11:20 PROF. DR. CATALINA POIANA (Institutul National de Endocrinologie C.I.Parhon, UMF “Carol Davila”, Bucuresti) – “Actualitati in tratamentul tumorilor neuroendocrine gastro-entero-pancreatice”

11:20-11:40 DR. RALUCA MITITELU (Spitalul Militar Central, UMF “Carol Davila”, Bucuresti) - “Tratamentul tumorilor neuroendocrine cu LUTHETIUM 177”

11:40-12:00 CONF. DR. DIANA PĂUN (Institutul National de Endocrinologie C.I.Parhon, UMF “Carol Davila”, București) – “Actualitati in genetica feocromocitomului”

12:00-12:20 CONF. DR. GABRIEL BECHEANU (Institutul Clinic Fundeni, UMF “Carol Davila”, Bucuresti) - “Cancer de colon metastatic cu MSI”

12:20-12:40 PROF. DR. SILVIU CONSTANTINOIU, DR. DRAGOS PREDESCU, DR. ION FLORIN ACHIM (Spitalul Clinic Sfanta Maria-UMF "Carol Davila", Bucuresti) – "Progrese recente în esofagectomia minim invazivă"

#### 12:40-13:50 MELANOMUL MALIGN SI SARCOAME

**Moderatori: PROF. ASOCIAT DR. ROXANA DRONCA , PROF. DR. LUCIAN MIRON**

12:40-13:00 DR. DAN JINGA (Clinica Neolife, Bucuresti) – "Terapia moleculara si imunoterapia: imbunatatirea prognosticului in melanomul malign"

13:00-13:30 PROF. ASOCIAT DR. ROXANA DRONCA (Mayo Clinic, SUA) – "Terapia cu virus oncolitic in melanomul malign"

13:30-13:50 PROF. DR. LUCIAN MIRON (Institutul Regional de Oncologie, UMF "Gr T Popa", Iasi) – "Sarcoame maligne avansate-tratamente sistemice în stadiile avansate: standard si tratamente viitoare"

#### 13:50-14:40 PAUZĂ DE PRÂNZ



#### 14:40-16:00 CANCERE MAMARE SI GINECOLOGICE

**Moderatori: DR. MIRCEA DEDIU, DR. DAN JINGA**

14:40-15:00 CONF. DR. DANA STANCULEANU (Institutul Oncologic Bucuresti, UMF "Carol Davila", Bucuresti) – "Oportunitati terapeutice in cancerul ovarian"

15:00-15:20 DR. MARIA COMANESCU (Onco Team Diagnostic, UMF "Carol Davila", Bucuresti) – "Heterogenitatea profilului molecular in diferite tipuri de cancer mamar"

15:20-15:40 DR. DANA GRECEA (Institutul Oncologic Cluj) – "Cancerul de san Her2 + unde suntem azi?"

15:40-16:00 DR. GABRIEL RICU (Clinica Amethyst, Bucuresti) – "Toxicitatea cardiaca dupa iradierea sanului dupa interventie chirurgicala conservatoare"

#### 16:00-17:10 SIMPOZIOANE DE FIRMA

16:00-16:20 SIMPOZION "ROCHE PHARMA"

DR. IULIA GRAMATICU (Institutul Clinic Fundeni, Bucuresti)- "Bevacizumab in cancerul ovarian"

16:20-16:50 SIMPOZION "BRISTOL-MYERS SQUIBB"

CONF. DR. DANA STANCULEANU (Institutul Oncologic Bucuresti, UMF "Carol Davila", Bucuresti)- "Opdivo- Noua paradigma de tratament in cancerul bronhopulmonar nonmicrocelular, cancerul renal si melanom"

16:50-17:10 SIMPOZION "ASTRA-ZENECA"

CONF. DR. DANA STANCULEANU (Institutul Oncologic Bucuresti, UMF "Carol Davila", Bucuresti)- "Cancerul bronhopulmonar nonmicrocelular : modern, corect, complet - de la diagnostic la terapia tinta"

#### 17:10-17:25 PAUZĂ DE CAFEA



#### 17:25-19:25 CANCERE HEMATOLOGICE

**Moderatori: CONF. DR. ALINA TANASE, PROF. ASISTENT DR. CRISTINA GHIUZELI**

17:25-17:45 DR. CAMELIA DOBREA, DR. BOTAS AL., DR. PORCESCU F., DR. POPOV V., DR. VLADAREANU AM., DR. LUPU A., PROF. DR. DANIEL CORIU (Onco Team Diagnostic, UMF "Carol Davila", Bucuresti) – "Limfomul cu celula T al adultului in sudul Romaniei, o abordare clinico-patologica"

- 17:45-18:15 PROF. ASISTENT DR. CRISTINA GHIUZELI (Northwell Health-Hofstra University, New York, SUA) – “Tratamentul contemporan al leucemiei mieloide acute”
- 18:15-18:35 CONF. DR. MIHNEA ZDRENGHEA (UMF “Iuliu Hatieganu”, Cluj-Napoca) – “Axa PD-1-PD-L1 in limfoamele agresive: promisiuni si certitudini”
- 18:35-18:55 CONF. DR. ALINA TĂNASE (Institutul Clinic Fundeni-Universitatea de Medicina, “Titu Maiorescu”, Bucuresti) – “Allotransplantul de celule stem hematopoietice cu donator haploidentific asociat cu administrarea de doza mare de Ciclofosfamida posttransplant in limfoamele maligne”
- 18:55-19:25 PROF. ASISTENT DR. GABRIELA GHEORGHE (Children’s Hospital Minnesota, SUA) – “Limfoproliferarile posttransplant: Relevanta clinica a noii clasificari OMS/WHO”

**19:30-19:50 ASPECTE PSIHIATRICE IN ONCOLOGIE**  
**Moderator: DR. FLORIN BACANU**

- 19:30-19:50 PROF. DR. ROBERT BOTA (University of California, Irvine) – “Efectul cancerului si tratamentului anticancer asupra creierului: interfata dintre tratamentul cancerului si psihiatrie”

**20:00-21:00- CINA** 

**Ziua 2, 14 Aprilie 2018**

**9:00-11:00 CERCETARE FUNDAMENTALĂ ȘI NOI DIRECȚII DE TRATAMENT**  
**Moderatori: PROF. DR. ADRIAN SALIC, PROF. DR. IRINEL POPESCU**

- 9:00-09:30 KEY NOTE SPEAKER PROF. DR. GEORGE CĂLIN (MD Anderson, Houston, SUA) – “Despre genomul ultraconservat si RNAuri non-codificante si semnificatia pentru pacientii cu cancer”
- 9:30-10:00 PROF. DR. ADRIAN SALIC (Harvard Medical School, Harvard University) – “Tintirea caii de semnalizare”Hedgehog” in cancer”
- 10:00-10:30 PROF. DR. MIHAELA ZAVOLAN (University of Basel and Swiss Institute of Bioinformatics) – “Analiza transcriptomului cancerelor umane “
- 10:30-11:00 PROF. DR. IRINEL POPESCU (Institutul Clinic Fundeni, Universitatea de medicina “Titu Maiorescu”, Bucuresti) - “Medicina translationala, cheia descifrării mecanismelor patogene ale cancerelor hepatobiliopancreatice”

**11:00-11:15 PAUZĂ DE CAFEA** 

**11:15-12:00 SIMPOZION ”JANSSEN”**

- DR. NINA TUNARIU (Royal Marsden Hospital & Institute of Cancer Research, Londra) – “Răspuns sau progresie? Provocări în evaluarea imagistică a pacienților cu cancer de prostată”

**12:00-13:30 DIAGNOSTIC MOLECULAR/ BIOINFORMATICĂ**  
**Moderatori: PROF. DR. MIHAELA ZAVOLAN, DR. EDUARD NEDEA**

- 12:00-12:30 DR. EDUARD NEDEA (The Laboratory of Personalized Genomic Medicine, Columbia University, New York) – “Aplicatiile tehnologiei Next Generation Sequencing in oncologia clinica”

- 12:30-13:00 PROF. ASISTENT DR. ANDREI DUMITRU IACOBAS (New York Medical College & Researcher of the Center for Computational System Biology at Prairie View A&M University) – “Utilizarea genelor de comanda in tratamentul cancerului”
- 13:00-13:30 DR. RĂZVAN LĂPĂDAT (Loyola University Medical Center, Maywood, Illinois) –”Implementarea telepatologiei si evaluarea datelor la distanta in practica clinica-unde ne gasim?”

13:30-14:20 **PAUZĂ DE PRÂNZ** 

**14:20-15:40 CANCERE ORL**

**Moderatori: CONF. DR. GABRIEL KACSO, PROF. ASISTENT DR. DORU PAUL**

- 14:20-14:40 DR. CRISTINA IOSIF (Onco Team Diagnostic, Spitalul Sf. Maria, București) – “HPV- indicator de predictie si prognostic in tumorile de cap gat”
- 14:40-15:10 PROF. DR. LAURA MARCU (Biomedical Engineering and Neurological Surgery, University of California-Davis) – “Tehnici de autofluorescenta in vivo pentru imagistica chirurgicală, orientare și realitate augmentată”
- 15:10-15:40 PROF. ASISTENT DR. DORU PAUL (Northwell Health-Hofstra University, New York, SUA) – “Imunoterapia cancerelor ORL”

**15:40-16:00 SIMPOZION “ROCHE DIAGNOSTICS”-**

SEF LUCRARI DR. FLORINEL POP (Spitalul Clinic de Nefrologie „Carol Davila”, UMF “Carol Davila”, Bucuresti)- ”Portofoliul Roche PD-L1: decizii informate in imuno-oncologie”

16:00-16:15 **PAUZA DE CAFEA** 

**16:15-18:25 CANCERE PULMONARE**

**Moderatori: PROF. DR. ION-CHRISTIAN CHIRICUTA, DR. ADRIAN UDREA**

- 16:15-16:35 DR. FLORINA VASILESCU (Onco Team Diagnostic, Spitalul Militar Central”Dr. Carol Davila”, Bucuresti) – “Diagnosticul tumorilor pulmonare prin metode minim invazive”
- 16:35-16:55 DR. BOGDAN TANASE, SEF LUCRARI DR. NATALIA MOTAȘ, AS. UNIV. DR. MIHNEA DAVIDESCU, DR ALIN BURLACU, DR CORINA BLUOSS, DR OVIDIU RUSS, PROF. DR. TEODOR HORVAT (Institutul Oncologic București, UMF “Carol Davila”, Bucuresti) – “Rezectiile pulmonare toracoscopice (VATS) in tratamentul cancerului bronhopulmonar”
- 16:55-17:15 DR. MIRCEA DEDIU (Spitalul Clinic Sanador, Bucuresti) – “Imunoterapia in cancerul bronhopulmonar nonmicrocelular stadiul III: Avem un nou standard terapeutic?”
- 17:15-17:35 DR. Abil. ALEXANDRU GRIGORESCU (Institutul Oncologic București) -”Terapia targetata in carcinomul pulmonar nonmicrocelular-experienta IOB”
- 17:35-17:55 CONF. DR. GABRIEL KACSO (Clinica Amethyst, UMF ”Iuliu Hatieganu”, Cluj) - ”Radioterapia stereotaxica in cancerul pulmonar incipient”
- 17:55-18:25 PROF. DR. ALINA MIHAI (Beacon Hospital-University College Dublin, Medisprof Cancer Center Cluj)-”Radioterapia stereotaxica in cancerul pulmonar oligometastatic”



**18:25-18:55 SIMPOZION "LILLY"**

**DR. Abil. ALEXANDRU GRIGORESCU** (Institutul Oncologic București)- "Alimta – O alegere pe care va puteți baza"

**18:55-19:15 SIMPOZION "ASTRA ZENECA"**

**DR. MIRCEA DEDIU** (Spitalul Clinic Sanador, Bucuresti) -"Cancerul bronhopulmonar nonmicrocelular avansat: inovatie si progres pentru pacientii cu mutatie EGFR"

**19:15-21:00 CINA FESTIVA**



**Ziua 3, 15 Aprilie 2018**

**9:00-10:00 CANCERE UROLOGICE**

**Moderatori: PROF. DR. FLORINEL BADULESCU, PROF DR. CARMEN ARDELEANU**

**9:00-9:20** PROF. DR. CARMEN ARDELEANU, DR. HORATIU MURESAN (Onco Team Diagnostic, Bucuresti) – "Probleme de diagnostic in tumorile de tract genito-urinar; prezentare de cazuri"

**9:20-9:40** PROF. DR. GHEORGHE IANA (Spitalul Universitar de Urgenta, UMF "Carol Davila", Bucuresti) – "Evaluarea imagistica moderna in determinarile secundare vertebro-medulare"

**9:40-10:00** SEF LUCRARI, DR. MICHAEL SCHENKER (UMF Craiova) – "Imunoterapia in tumorile uroteliale"

**10:00-10:20 PAUZA DE CAFEA**



**10:20-12:10 SESIUNEA: VARIA, CALITATEA VIETII PACIENTULUI ONCOLOGIC**

**Moderatori: CONF. DR. DANA STANCULEANU, SEF LUCRARI DR. MICHAEL SCHENKER**

**10:20-10:50** ELIZABETH CONNELLY NURSE PRACTITIONER ( Monter Cancer Center, Lake Success, New York) – "Efectele secundare ale imunoterapiei- experienta americana"- "Side effects of immunotherapy, american experience"

**10:50-11:10** DRD. OTILIA NICULITA (Institutul Clinic Fundeni, UMF "Carol Davila", Bucuresti) – "Rolul asistentei medicale de hemato-oncologie in Romania"

**11:10-11:30** PROF. DR. XIAO G WANG – "Acupunctura pentru pacienții cu cancer"

**11:30-11:50** PSIHOLOG ADRIAN CALOMFIRESCU (Clinica Medlife-Bucuresti) – "Reabilitarea sexualitatii dupa tratamentul oncologic"

**11:50-12:10** PROF. GABI DIACONU(Centrul de psihiatrie si Psihoterapie Mind Care, Bucuresti) – "Burn-out-ul medical, teama pacientului și blestemul cancerului"

**12:10-12:30** Concluzii

**12:30-13:30 PRANZ**



## COMITET STIINTIFIC:

DR. ION FLORIN ACHIM  
PROF. DR. CARMEN ARDELEANU  
CONF. DR. GABRIEL BECHEANU  
DR. CORINA BLUOSS  
PROF. DR. ROBERT BOTA  
DR. ALEXANDRU BOTAS  
DR. LAURENTIU BUJOR  
DR. ALIN BURLACU  
PROF. DR. GEORGE CĂLIN  
PSIHOLOG ADRIAN CALOMFIRESCU  
DR. MARIA COMANESCU  
ELIZABETH CONNELLY NURSE PRACTITIONER  
PROF. DR. SILVIU CONSTANTINOIU  
PROF. DR. DANIEL CORIU  
CONF. DR. ADINA CROITORU  
AS. UNIV. DR. MIHNEA DAVIDESCU  
DR. MIRCEA DEDIU  
PROF. GABI DIACONU  
DR. CAMELIA DOBREA  
PROF. ASOCIAT DR. ROXANA DRONCA  
PROF. ASISTENT DR. GABRIELA GHEORGHE  
PROF. ASISTENT DR. CRISTINA GHIUZELI  
DR. DANA GRECEA  
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CONF. DR. GABRIEL KACSO  
DR. RĂZVAN LĂPĂDAT  
PROF. DR. ANCA LUPU  
PROF. DR. LAURA MARCU  
PROF. DR. ALINA MIHAI  
PROF. DR. LUCIAN MIRON  
DR. RALUCA MITITELU  
SEF LUCRARI DR. NATALIA MOTAȘ  
DR. HORATIU MURESAN  
DR. EDUARD NEDEA  
CONF. DR. ȘERBAN NEGRU  
DRD. OTILIA NICULITA  
PROF. ASISTENT DR. DORU PAUL  
CONF. DR. DIANA PĂUN  
DR. CATALINA POIANA  
DR. BOGDAN POPESCU  
PROF. DR. IRINEL POPESCU  
DR. VIOLA POPOV  
DR. FLAVIA PORCESCU  
DR. DRAGOS PREDESCU  
DR. GABRIEL RICU  
DR. OVIDIU RUSS  
PROF. DR. ADRIAN SALIC  
SEF LUCRARI, DR. MICHAEL SCHENKER  
CONF. DR. DANA STANCULEANU  
CONF. DR. ALINA TĂNASE  
DR. BOGDAN TANASE  
DR. FLORINA VASILESCU  
DR. ANA-MARIA VLADAREANU  
PROF. DR. XIAO G WANG  
PROF. DR. MIHAELA ZAVOLAN  
CONF. DR. MIHNEA ZDRENGHEA



# REZUMATE SIMPOZION

## Doru Paul, MD, PhD

Northwell-Hofstra University  
Northwell Health Monter Cancer Center, New York, USA

### The immune concert: an introduction

Cancer immunotherapy has advanced tremendously in the last decade, and can be now considered a “fifth column” of cancer treatment, joining the ranks of surgery, cytotoxic chemotherapy, radiation, and targeted therapy. Worldwide, until 2017, more than 20,000 cancer patients that have been treated with immunotherapy. The data from the clinical studies already completed, suggest that immunotherapy can lead to durable responses that few other cancer therapies can approximate. In some cancer types, immunotherapy has proven that is able to fulfill, at least for some patients, the golden goal of cancer treatment which is cancer cure.

Similar to an orchestra, the immune system functions in a finely, coordinated way in its response to stimuli. In the presence of a malignant tumor, in order for the immune system to fight it robustly, there are several key elements, as following:

1. **Appropriate stimuli:** a powerful antigen stimulus.
2. **The presence of the right players:** cells belonging to both the innate and the adaptive immune arms.
3. **Balance** between stimulatory and inhibitory cytokines and the immune cells.
4. **Timing of the immune attack:** coordination between the different immune cells (i.e. antigen presenting cells, different subtypes of T cells, etc).

Akin to a piece of classical concerto, for the immune system to lead to effective killing of cancer cells, a series of stepwise events must be initiated and proceed in an orderly manner named the “cancer immunity cycle” [1].

1. Release of cancer antigens
2. Antigen presentation
3. Priming and activation
4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
6. Recognition of cancer by T cells
7. Killing of cancer cells.

Each step of this process requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors enhance immunity, whereas inhibitors keep the process in check and reduce immune activity and/or prevent autoimmunity.

The type of cancer immunotherapy which has raised the most interest recently involves antibodies to inhibitory immune checkpoint molecules.

Immune checkpoint proteins, such as CTLA4, can inhibit the development of an active immune response by acting primarily at the level of T cell development and proliferation (step 3 above). Anti-CTLA4 antibodies such as ipilimumab or tremelimumab remove the brake placed on the T cells activation. Other factors present on the surface of the tumor, such as PD-L1, can have an inhibitory effect on the T cells that primarily acts to modulate active immune responses in the tumor bed (step 7 above). Anti-PD-1 (i.e. nivolumab and pembrolizumab) and anti-PD-L1 antibodies (i.e. atezolizumab and durvalumab) remove this inhibition allowing the T cells to attack the tumor. These five agents: ipilimumab (CTLA4 inhibitor), nivolumab (PD-1 inhibitor), pembrolizumab (PD-1 inhibitor), atezolizumab (PD-L1 inhibitor), and durvalumab (PD-L1 inhibitor) are currently approved in USA for use in different tumor types.

In a meta-analysis published in *The Journal of Clinical Oncology*, the survival curve of the patients receiving ipilimumab was flattening after 3 years and approximately 20% of patients with metastatic melanoma who received a single round of treatment were alive 10 years after receiving the first dose of ipilimumab with no evidence of disease [2]. Before ipilimumab became available, the 10-year survival rate in metastatic melanoma was less than 10%.

Currently, there is a plethora of immunotherapy strategies under development that act at different levels of the cancer immunity cycle (step 1-7) depicted above, in an attempt to improve the response rates seen with the checkpoint inhibitors.

In the near future, a better understanding of tumor immunology and the discovery of specific biomarkers for different types of immunotherapies will lead to the development of the new field of **precision immuno-oncology** and, hopefully, better tailored specific immune therapies will be soon administered with greater benefit and less toxicity to individual patients.

[1]. Chen DS and Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1-10.

[2]. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Patt D, Chen TT, Berman DM, Wolchok JD. Pooled analysis of long-term survival data from phase ii and phase iii trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol* 2015;33:1889-94.

## Șerban Negru, MD, PhD

Universitatea de Medicina si Farmacie “Victor Babes” Timisoara  
Centrul de Oncologie OncoHelp Timisoara

### **Basic concepts of immunology and immunotherapy**

Medicine faced a spectacular revolution during the last few years regarding the treatment of cancer. Immunotherapy represents a complete change in the philosophy of cancer approach. The immune system became the primary target of treatment instead of the malignant cell.

In the same time, new treatments are coming together with new mechanisms of action, new side effects and different patterns of response. Each oncologist is confronted to the dilemma of becoming more and more involved in a very complex field which requires a lot of new and different basic knowledge. Understanding fundamental immunology becomes essential. Basic concepts like antigens, antibodies, major histocompatibility complex molecules should be thoroughly reviewed, as well as the main cells involved in the immune mechanisms of action.

T lymphocytes, primary effectors of anticancer immunity, are activated by various methods to eliminate the tolerance installed during disease progression. Efficient activation of the immune system is a formidable weapon capable of definitively eliminating the tumor and obtaining healing in a significant number of cases. Intravesical BCG therapy followed by systemic cytokine treatments with IL-2 or IFN $\gamma$  were the first promising results. In 2011, Sipuleucel-T, the first autologous immunotherapy for asymptomatic metastatic prostate cancer was approved as a treatment standard in oncology. The procedure aims at ex vivo incubation of T lymphocytes obtained from patients by leukapheresis with a chimeric product. 2017 produced another breakthrough result in this field – the CAR-T cell therapy.

The use of anti-CTLA-4 or anti-PD-1 antibodies in metastatic malignant melanoma therapy produced unprecedented results. Recent studies achieved long-term survival in almost half of cases, in a disease considered incurable and deadly. Encouraging results from melanoma were then reproduced in other locations such as lung or kidney cancer.

Stimulating the immune system to get it to efficiently eliminate cancer cells is an adventure over a century that seduced, mumbled and then disappointed generations of researchers, clinicians, and investors alike. In recent years, however, immunotherapy produced spectacular clinical results and by doing that it became the main direction of research and the most important hope in our fight against cancer.

## Adina Croitoru, MD, PhD

Institutul Clinic Fundeni-Universitatea Titu Maiorescu, Bucuresti

### Imunoterapia in tratamentul cancerelor digestive- Cenusareasa sau...Regina?

Imunoterapia in cancerele digestive este ca un fel de Cenusareasa din cauza imunogenicitatii scazute a acestor tumori si din lipsa raspunsului limfocitelor T efectoare.

In **cancerul gastric**, agentul anti PD-1(pembrolizumabul) din studiile KEYNOTE 012, 061, 062 s-a dovedit a fi sigur si eficace in tratamentul pacientilor cu cancer esogastric(CEG) si gastric(CG) avansat PD-L1+ si este in curs de evaluare in linia II-a de tratament vs taxol si in linia I-a de tratament vs 5FU+derivati de platina.

Alaturi de pembrolizumab, nivolumabul in studiul Attraction-2 vs placebo si-a dovedit eficienta in CG si CEG avansate in linia a2-a si in a 3-a de tratament dovedind un control de lunga durata al bolii, dar si o toxicitate scazuta.

Avelumabul, un agent anti PD-L1 in studiul de faza Ib la pacienti pretratati cu CG sau CEG pretratati a aratat o toleranta buna, dar studiul Javelin 300 ca tratament de linia a 3-a nu si-a dovedit eficienta. Se asteapta rezultatele studiului Javelin 100 cu avelumab ca tratament de mentinere la pacienti cu raspuns partial sau complet dupa fluoropirimidine si derivati de platina.

Studiul Check Mate 032 care combina anticorpilor anti CTLA4 cu anti PD-1 la pacienti pretratati a aratat o eficienta mai mare la pacientii cu PD-L1+ sugerand ca expresia PD-L1 creste rata de raspuns tumoral. Trialul de faza III Check Mate-649 care investigheaza nivolumab +ipilimumab vs FOLFOX/CAPOX in linia I-a este in curs de desfasurare.

In **cancerul colorectal** cu instabilitate microsatelitara inalta (MSI-H) sau cu ineficienta genelor de reparare a ADN-ului, ghidul NCCN din 2017 recomanda, ca urmare a rezultatelor interimare ale studiului KEYNOTE 016 si ale studiului CheckMate 142 pembrolizumabul si nivolumabul. Studiul KEYNOTE 164, studiu de faza II la pacienti cu cancer colorectal metastatic pretratati cu MSI-H s-a terminat si se asteapta rezultatele. Studiul KEYNOTE 177, studiu de faza III la pacienti cu CCR metastazat in linia I-a pe 270 pacienti este in curs de desfasurare. La pacientii cu CCR MSS rezultatele cu tratament imunologic au fost dezamagitoare si ca urmare a eforturilor cumulate s-a observat ca asocierea inhibarii MEK-ului cu anti PD-L1 a determinat rezultate sinergice si regresii tumorale durabile. Astfel pe 23 pacienti tratati cu un inhibitor de MEK cu un anticorp anti PD-L1-atezolizumab rata de raspuns tumoral a fost de 17% cu 4 raspunsuri pariale si 5 stabilizari de boala. In prezent este in curs de desfasurare un studiu de faza III care investigheaza cobimetinibul cu atezolizumabul vs regorafenib la pacienti cu multiple linii de tratament.

In **cancerul hepatocelular(CHC)** cele mai promitatoare rezultate s-au obtinut in studiul cu mai multe cohorte, de faza I/II deschis in 2012 pe pacienti cu CHC avansat -Check Mate 040 in care s-au inrolat 576pacienti tratati cu nivolumab in cohorta de escaladare a dozei si in cohorta de expansiune a determinat o rata de raspuns de 20% indiferent de doza, indiferent de statusul infectiei virale B sau C precum si de expresia PD-L1 in celulele tumorale. Durata medie a raspunsului a fost de 9,9luni si supravietuirea mediana a fost de 15 luni si de 13,2 luni in

cohorta de escaladare si respectiv de expansiune. In prezent un studiu de faza III cu nivolumab vs sorafenib la pacienti cu CHC netratati este in curs de desfasurare. Durvalumabul a dovedit eficienta in CHC intr-un studiu de faza I publicat in 2014; in prezent este in curs de desfasurare un studiu de faza II care compara durvalumabul cu tremelimumabul precum si cu asocierea lor. Pembrolizumabul este in evaluare la pacienti cu CHC intr-un studiu de faza II (KEYNOTE 224) si intr-un studiu de faza III (KEYNOTE 240) in linia a II-a de tratament .

In linie cu determinarile din CRC cu MSI-H, Mlecnic a facut o analiza comprehensiva a mediului inconjurator tumoral prin determinarea imunoscoringului. Un scor imun mare la pacienti cu MSS si la pacienti cu MSI-H se asociaza cu un prognostic favorabil

Se pare ca semnatura mutationala MSI-H determinata prin secventierea intregului genom ar putea fi biomarkerul pentru raspuns la tratamentul imunologic. Deasemenea compozitia microbiotei ca de ex\_Bacteroides pot determina raspunsul la ipilimumab. Astfel administrarea orala de Bifidobacterium combinat cu anti PDL-1 inhiba cresterea tumorală. In prezent in cancerile digestive imunoterapia se afla inca in faza de cercetare.

## **Laurentiu Bujor, MD**

Spitalul Sanador Bucuresti

### **Clinical implications of immunogenic effects of radiotherapy**

The distant effect of the radiation has been observed since 1953 by dr. RH Mole who first coined the *abscopal* („ab”-away from, „scopus”-target) term , but the underlying mechanisms are yet to be discovered.

The hypothesis is that the radiation has also a systemic effects that might trigger in the patient an immune response. Most of the reported cases occurred in immunogenic tumors such as renal carcinoma, melanoma, and hepatocellular carcinoma.

Nowadays there is a body of evidence of the immunogenic mechanisms of radiations and preclinical work has led to some interesting clinical studies.

Once the results become mature we will be able to translate into the clinic the advantages of the immunologic effects of the radiotherapy and to integrate immunotherapy and radiation.

The purpose of the presentation is to highlight some recent clinical developments in this field.

## **Raluca Mititelu, MD, PhD**

Spitalul Universitar de Urgenta Militar Central Bucuresti  
Societatea Romana de Medicina Nucleara si Imagistica Moleculara

### **Tratamentul tumorilor neuroendocrine cu <sup>177</sup>Lu-DOTATATE**

In ultimii ani diagnosticul si terapia cu ajutorul radiofarmaceuticelor a cunoscut o evolutie extraordinara prin introducerea in practica a numeroase molecule si radioizotopi cu un potential imens in diagnosticul tintit si terapia personalizata a cancerului. Administrarea unei molecule radiomarcate cu un radionuclid emitor gamma sau pozitronic permite vizualizarea unui proces oncologic prin scintigrafie sau tomografie cu emisie de pozitroni

(PET). Aceeasi molecula cu tropism catre un anumit receptor de pe suprafata celulei tumorale se va localiza in aceasta celula si o va distruge daca este marcata cu un radionuclid ce emite radiatie beta. Radiatia beta are o energie mare care va determina distrugerea celulara, dar un parcurs mic, de doar cativa milimetri, ceea ce face ca acest proces de distrugere sa aiba loc tintit, cu efecte adverse minime locale. Acest proces de a diagnostica iar apoi trata cu ajutorul aceleiasi substante a fost in mod inspirat denumit « theranostic » si este mentionat in literatura de specialitate ca parte integranta a procesului de terapie personalizata.

Utilizarea radiofarmaceuticelor specifice pentru vizualizarea scintigrafica a receptorilor SSR din cadrul tumorilor neuroendocrine (NET) este posibila de mult timp :  $^{111}\text{In}$ -pentetreotide (Octreoscan) si mai recent  $^{99\text{m}}\text{Tc}$ -EDDA/HYNIC-TOC (Tektrotyd). Mai recent Agentia Europeana a Medicamentului (EMA) a autorizat  $^{68}\text{Ga}$ -edotreotide (DOTATOC) pentru utilizarea in imagistica PET a receptorilor SSR din cadrul tumorilor neuroendocrine.

Membrii comunitatii stiintifice publice de mult timp rezultate extrem de bune ale terapiei radionuclidice cu ajutorul peptidelor radiomarcate cu beta-emitatori. Cu toate acestea doar la sfarsitul anului trecut EMA a autorizat primul compus pentru terapia radionuclidica interna a NET:  $^{177}\text{Lu}$ -oxodotreotide (DOTATATE) (Lutathera).

In aceasta lucrare vom prezenta criteriile pentru selectia pacientilor care pot beneficia de aceasta metoda terapeutica, cateva elemente ale protocolului terapeutic si de monitorizare, accentuand pe abordarea multidisciplinara a intregului proces in care colaborarea dintre medici de diferite specialitati este esentiala pentru un rezultat terapeutic de succes.

## **Diana Loreta Păun, MD, PhD**

Universitatea de Medicină și Farmacie “Carol Davila” București

## **Actualități în genetica feocromocitomului**

Feocromocitomul și paragangliomul sunt tumori neuroendocrine, constituite din celule cromafine, caracterizate prin sinteză, eliberare și metabolizare de catecolamine. Feocromocitoamele sunt tumori neuroendocrine derivate din celulele cromafine adrenomedulare iar paraganglioamele sunt tumori cu originea în ganglionii paravertebrali simpatici sau parasimpatici. Impreună, acestea reprezintă cele mai frecvente tumori endocrine cu transmitere ereditară.

Formele ereditare se caracterizează prin tumori bilaterale, multiple, recurente, clinic manifeste, apar adesea în copilărie și biochimic au niveluri crescute de metoxitiramină. Istoricul familial este adesea pozitiv dar poate fi și negativ în cazul unei penetranțe genetice scăzute. Cele mai frecvente sindroame familiale asociate cu feocromocitom/paragangliom familial sunt: boala Von Hippel-Lindau, sindromul MEN 2, neurofibromatoza, sindroame familiale paragangliom/feocromocitom și complexul Carney. Pe lângă genele deja cunoscute, VHL, RET, NF, SDHx, au fost descrise recent o serie de noi gene susceptibile a produce feocromocitom sau paragangliom familial: HIF 2A, FH, PHD1, MDH2, MAX and TMEM 127.

Identificarea mutației genetice poate duce la un diagnostic și un tratament precoce, supraveghere ritmică și un prognostic mai bun pentru pacienți și rudele pacienților cu feocromocitom. În plus, fenotipul biochimic poate să ghideze screeningul genetic: un fenotip adrenergic este de obicei asociat cu o mutație MEN 2, NF-1, MAX and TMEM 127 iar un fenotip noradrenergic este frecvent asociat cu un genotip VHL, SDHx, FH sau MDH2. Ca urmare, testele genetice sunt recomandate astăzi la toți pacienții diagnosticați cu feocromocitom sau paragangliom.

### **Gabriel Becheanu, MD**

Catedra de Morfopatologie, Universitatea de Medicină și Farmacie Carol Davila

Institutul Național de Patologie Victor Babes, Laboratorul de Histopatologie și Imunohistochimie

### **Cancerul de colon cu instabilitate a microsateleților**

Cancerul de colon este al doilea cancer ca frecvență în Europa, cu aproape 500.000 de persoane diagnosticate anual, iar datorită progreselor realizate în metodele de diagnostic și tratament, rata mortalității a fost redusă cu 6% la bărbați și mai mult de 7% la femei din 2012. Screeningul, aspirina și terapia hormonală la femei contribuie probabil la reducerea riscului și a incidenței.

Carcinogeneza în această localizare este complexă și implică anomalii genetice și epigenetice, fiind descrise cel puțin două căi majore: instabilitatea cromozomială și a microsateleților (MSI). Statusul MSI este prezent la 1% din cancerurile colorectale sporadice și la pacienții cu sindrom Lynch (3% din cancerurile colonice, cu transmitere autosomal dominantă). Cancerul colorectal MSI prezintă aspecte morfologice particulare. Macroscopic, sunt localizate preferențial în colonul drept, au aspect vegetant, frecvența mai redusă a metastazelor limfoganglionare și la distanță. Histologic sunt heterogene, prezintă o infiltrare marcată cu limfocite, reacție “Crohn’s like”, grad redus de diferențiere, fenotip medular, mucinos, cu celule în inel cu pecete.

Statusul microsateleților reprezintă un marker important cu rol prognostic și predictiv al evoluției cancerului colorectal. Pacienții MSI în stadiul II au o supraviețuire fără recidivă mai lungă decât cei cu status MSS, iar chimioterapia adjuvantă cu 5FU nu este eficientă. Studiile clinice recente arată că imunoterapia poate fi eficientă la pacienții cu cancer de colon metastatic MSI, caracterizat prin mutații numeroase, un număr crescut de neo-epitopi antigenici și de un infiltrat bogat cu limfocite CD8 citotoxice intratumoral.

Având în vedere că recunoașterea cancerelor colonice MSI are implicații clinice importante, iar evaluarea histopatologică are o sensibilitate redusă în diagnosticul acestui grup, analiza expresiei proteinelor reparatorii ale erorilor de împerechere ale ADN-ului se poate realiza imunohistochimic, facil, într-un laborator de histopatologie și imunohistochimie, fără a necesita un laborator de biologie moleculară. Imunohistochimia este o metoda alternativă testării PCR, cu o sensibilitate bună (>90%) și o specificitate excelentă (100%). Se prezintă experiența Laboratorului de Histopatologie și Imunohistochimie din Institutul Național de Patologie Victor Babes în diagnosticul cancerului de colon cu instabilitate a microsateleților.



## **Silviu Constantinoiu, MD, PhD**

Spitalul Clinic Sfanta Maria

UMF "Carol Davila", Bucuresti

### **Progrese recente în esofagectomia minim invazivă**

**Prof. Silviu Constantinoiu, Dragos Predescu, Ion Florin Achim**

The treatment of esophageal cancer has become more effective due to advances in surgical techniques, multi-disciplinary approach, appropriate use of neoadjuvant therapy and perioperative care at centers of excellence in esophageal surgery. Esophagectomy is one of the most complicated and demanding procedures among all gastrointestinal surgeries with a very long learning curve in which excellence can only be achieved through improvement during all the surgical career. The results of esophagectomy are related not only to the volume of cases operated, but also to the experience of surgeons in the management of postoperative complications. Initially, minimally invasive esophagectomy has encountered barriers to implementation in several centers due to the cost and complexity of esophageal cancer treatment. Several meta-analyses and clinical trials published so far support the feasibility of the minimally invasive approach, the advantages of the post-operative period and the equivalence of oncological outcomes with the open technique, which is an important step in imposing minimally invasive techniques as a standard in the treatment of esophageal cancer. In this paper we aim to analyze recent advances in minimally invasive esophagectomy, the evolution of endoscopic surgical techniques through our personal experience and the results of studies published in the medical literature in the last years.

**Keywords:** esophageal cancer, minimally invasive esophagectomy, open esophagectomy, randomized controlled trial

Tratamentul cancerului esofagian a devenit mai eficient datorită progreselor tehnicilor chirurgicale, abordării multidisciplinare, utilizării adecvate a terapiei neoadjuvante și a îngrijirii perioperatorii în cadrul unor centre de excelență în chirurgia esofagiană. Esofagectomia este una dintre cele mai complicate și exigente proceduri dintre toate intervențiile chirurgicale gastro-intestinale cu o curbă foarte lungă de învățare în care excelența se poate atinge doar prin perfecționare de-a lungul întregii cariere chirurgicale. Rezultatele esofagectomiei sunt legate nu numai de volumul de cazuri operate ci și de experiența chirurgilor în managementul complicațiilor postoperatorii. Inițial, esofagectomia minim invazivă a întâmpinat obstacole în implementarea sa în mai multe centre datorită costurilor și complexității tratamentului cancerului esofagian. Mai multe metaanalize și studii clinice publicate până în prezent susțin fezabilitatea abordului minim invaziv, avantajele procedurii din perioada imediat postoperatorie precum și echivalența rezultatelor oncologice cu tehnica clasică, ceea ce constituie un pas important în impunerea tehnicilor minim invazive ca standard în tratamentul cancerului esofagian. În această lucrare ne propunem să urmărim progresele recente în esofagectomia minim invazivă, evoluția tehnicilor chirurgicale endoscopice prin prisma experienței personale și a rezultatelor studiilor publicate în literatura de specialitate în ultimii ani.

**Cuvinte cheie:** cancer esofagian, esofagectomia minim invazivă, esofagectomia clasică, studiu clinic randomizat

## **Dan-Corneliu Jinga MD, PhD**

Department of Medical Oncology

Neolife Bucharest Medical Center

### **Molecular therapy and Immunotherapy: overall improvement of prognostic in stage III of malignant melanoma**

The incidence of cutaneous malignant melanoma has continued to increase in Romania in the last two decades, in accordance with its continuous increasing incidence in all European countries.

Worldwide, the treatment of advanced melanoma has improved considerably over the last 5 years. The Romanian National Insurance covers only the combination of Dabrafenib and Trametinib or Vemurafenib monotherapy for BRAF-mutated inoperable and metastatic malignant melanoma, and Nivolumab monotherapy for BRAF-mutated or BRAF wild-type advanced melanoma. We are waiting the approval for reimbursement of Ipilimumab monotherapy or combination of Ipilimumab and Nivolumab.

Regarding patients with stage III disease, with regional involvement and with dismal prognosis, the National Guidelines approve only high-dose Interferon alpha-2b after surgical resection of the locoregional disease.

The results from a meta-analysis of 17 randomized, controlled clinical trials showed that Interferon alpha-2b prolongs the time to recurrence, but with only marginal benefit in overall survival.

Hope comes from the results of two studies: the first one, COMBI-AD, addresses stage III BRAF-mutated malignant melanoma, exploring the combination of Dabrafenib and Trametinib in adjuvant setting, and the second one, EORTC 18071, published the results from high-dose Ipilimumab therapy in adjuvant setting.

We also discuss the other recent clinical trials, like: BRIM 8 (adjuvant Vemurafenib), KEYNOTE 054 (adjuvant Pembrolizumab), ChekMate 238 (adjuvant Nivolumab versus Ipilimumab) or ChekMate 915 (adjuvant Ipilimumab in combination with Nivolumab versus each drug separately).

The results of these clinical trials using BRAF inhibitors and MEK inhibitors or immune checkpoint inhibitors are very promising.

Unfortunately for us, in Romania, both molecular therapy and immunotherapy are not reimbursed yet for surgically removed stage III malignant melanoma. The approval of these drugs or the new clinical trials would improve the overall survival of stage III malignant melanoma as we already demonstrated for metastatic malignant melanoma in Romanian Early Access Program for Ipilimumab.

## Roxana S. Dronca, MD

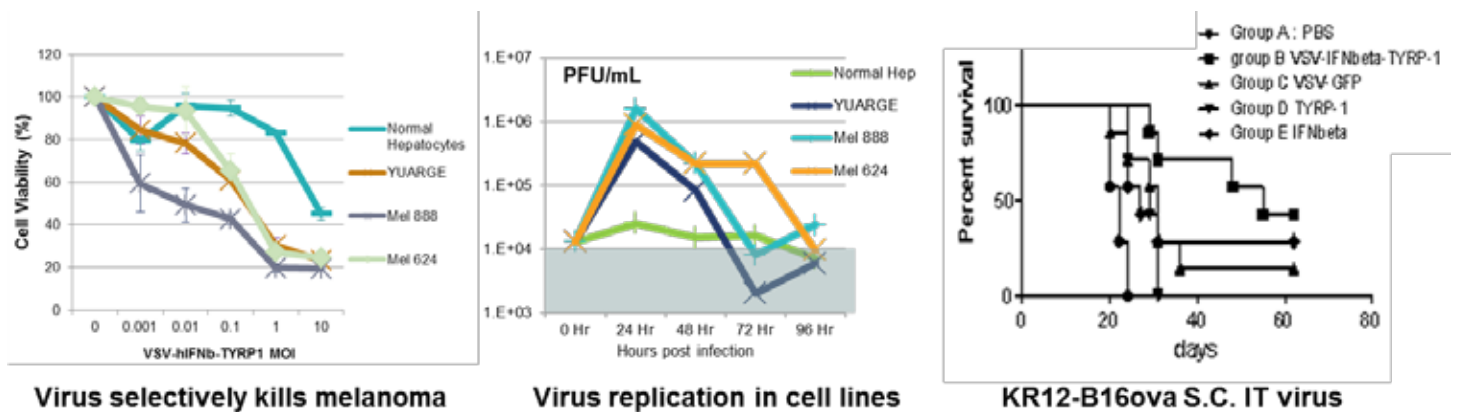
Mayo Clinic College of Medicine

Minnesota, USA

## Terapia cu virusul oncolitic in melanomul malign

Principal Investigator: **Roxana Dronca, M.D.** Co-investigators: **Kah-Whye Peng, Ph.D., Jose Pulido, M.D., Eva Galanis, M.D., Matthew Block, M.D., Ph.D.** Statistician: **Vera Suman, PhD**

This is a phase 1 study evaluating the safety of intratumoral and intravenous administration of VSV-IFN- $\beta$ -TYRP1 administered in combination with pembrolizumab in patients with unresectable advanced melanoma. Preclinical studies by our laboratory have demonstrated the tumor selectivity of the virus for melanoma cells and efficacy of the virus against KR12 B16 tumors in C57B6 mice. These data support the clinical translation of this virus for the treatment of patients with malignant melanoma, including those with uveal melanoma that has metastasized to the liver where no systemic treatment options exist. Moreover, preclinical studies using VSV suggest that VSV-IFN- $\beta$ -administered in combination with anti-PD1 antibody provided enhanced antitumor activity above the activity of either agent alone. (Durham et al. Mol Ther 2017, PMID: 28578991).



An initial evaluation of the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of VSV-IFN- $\beta$ -TYRP1 will be conducted in the phase 1 clinical trial (MC1376) exploring the combined intravenous (IV) and intratumoral (IT) VSV-IFN- $\beta$ -TYRP1 injection in patients with unresectable stage III/IV melanoma who have accessible injectable disease. With VSV, there is the possibility that it can be safely administered at higher titers of replicating oncolytic virus intravenously, which distinguishes it from other oncolytic viruses such as talimogene laherparepvec (T-VEC) which has recently been shown to improve responses when combined with anti-PD1 therapy (Ribas et. all Cell 2017). This may improve the potential for tumor cell infection and oncolysis, as well as priming of the host immune system. As such, we propose to add a second cohort of patients to MC1376, namely, patients who are refractory to immune checkpoint inhibitors (ICI), to assess the safety profile, clinical benefit and immunological responses of VSV-IFN- $\beta$ -TYRP1 in combination with pembrolizumab. A 3 + 3 + 3 dose escalation trial design will be used where VSV-IFN- $\beta$ -TYRP1 is administered IV and IT on Cycle 1 Day 1,

followed by repeat IT injections of VSV-IFN- $\beta$ -TYRP1 in combination with pembrolizumab every 3 weeks until either confirmed complete response (CR) on two subsequent imaging tests, unequivocal progression, or intolerance. Escalation will start with lowest VSV-IFN- $\beta$ -TYRP1 IV+ IT dose tested in MC1376 and at no point will the dose administered in combination with pembrolizumab exceed doses of VSV-IFN- $\beta$ -TYRP1 that have been demonstrated previously to be safe on the monotherapy arm. A cohort of another 4 patients will be enrolled at the MTD (total of 10 patients will be treated at the MTD) to gather additional preliminary data for planning additional studies with this combination. Translational objectives are to assess the status of IFN pathway in tumors pre and post-therapy, to evaluate CD8+ T cell and NK cell responses, as well as and other biomarkers of response to anti-PD1 therapy.

### **Lucian Miron, MD, PhD**

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### **Soft tissue sarcoma- systemic treatments in advanced stages: what is standard, what is the future?**

Soft tissue sarcomas (STS) in adult are a complex group of neoplasms. The STS biology has made major advancements in understanding of the biology and drivers of several sarcomas. An anthracycline and alkylating agent combination has formed the cornerstone of chemotherapy in STS for more than 30 years, with its value over that of administration of anthracycline as a single agent still being debated.

As single drugs or in combination, anthracyclines yield the best response rates for metastatic sarcomas (rates of 10% to 25% for each drug in various studies). Ifosfamide is particularly active for synovial sarcoma and myxoid liposarcoma appears to be less active for leiomyosarcomas. The combination Dacarbazine has modest activity against leiomyosarcoma, paclitaxel is active against angiosarcomas and desmoid tumors, and sunitinib and cediranib against alveolar soft part sarcoma. The combination of temozolomid and bevacizumab has activity in solitary fibrous tumor.

Recently improved understanding of biology of certain connective tissue tumors has led to clinical introduction of new molecules in the management of disease. *Pazopanib* is an oral multikinase inhibitor that was approved for treatment of patients with locally advanced or metastatic STS after treatment with standard chemotherapy. Pazopanib is approved for treatment for treatment of advanced or metastatic non-GIST soft tissue sarcoma (excluding liposarcoma) after treatment with chemotherapy *Trabectedin is a cytotoxic agent that bind to the minor groove in DNA and affect DNA, RNA, and protein synthesis. Trabectedin was approved for the use in patients with unresectable or metastatic leiomyosarcoma or liposarcoma after prior treatment with anthracycline-containing regimens.*

Eribulin is an antimetabolic agent that inhibits microtubule function and demonstrated improvement in overall survival compared with dacarbazine in patients pretreated, locally advanced or metastatic leiomyosarcoma or liposarcoma.

*Olaratumab* (Lartruvo) is a monoclonal antibody developed for the treatment of solid tumors. It is directed against the platelet-derived growth factor receptor alpha (PDGF). Olaratumab is used in combination with doxorubicin for the treatment of adults with advanced soft-tissue sarcoma (STS) who cannot be cured by cancer surgery or radiation therapy, and who have not been previously treated with doxorubicin.

In a randomised controlled trial with 133 STS patients, olaratumab plus doxorubicin improved the median of progression-free survival from 4.1 to 6.6 months as compared to doxorubicin alone ( $p = 0.0615$ , narrowly missing statistical significance), and overall survival from 14.7 to 26.5 months ( $p = 0.0003$ , highly significant). mTOR inhibitors have been studied in several sarcoma studies with relatively limited success, with the exception of perivascular epithelioid cell tumors, which are rare malignancies characterized by activation of the mTOR pathway. *Everolimus* is an inhibitor of m-TOR with indication in the treatment of patients with angiomyolipomas resulted in an objective tumor response rate of 42% using 10mg everolimus daily comparing with 0% using placebo.

*Tazemetostat* is a small molecule inhibitor of the histone-lysine methyltransferase EZH2, whose activity is enhanced in integrase interactor 1 (INI1)-deficient tumours. Among STS, genetic loss of INI1 has been reported in epithelioid MPNST, extraskeletal myxoid chondrosarcoma, myoepithelial carcinoma and up to 90% of epithelioid sarcoma

Immunotherapy has been one of the major breakthroughs in oncology, for both solid and haematological tumours. Despite historical evidence supporting its role in STS, the results currently reported with adoptive immunotherapy and checkpoint inhibitors remain controversial.

There are a number of ongoing trials in sarcomas investigating immunotherapy, including checkpoint inhibitors as well as T-cell therapy. Tyrosine kinase inhibitors, including imatinib, pexidarartinib, pazopanib, and axitinib have been shown to impact the immune microenvironment within tumors. Subsets of sarcomas overexpress Her2, which has been targeted using chimeric antigen receptor (CAR) T cell.

In the SARC028 phase 2 study, pembrolizumab as a single agent showed activity in unselected STS of all types, with an ORR of 17.5% and a 55% 3-month PFS; undifferentiated pleomorphic sarcoma were the histologies that seemed to benefit the most.

In last years have been seen remarkable growth in the novel treatment strategies for sarcomas, with an increased emphasis on understanding genetic and molecular biology of various sarcoma subtypes to guide design of clinical trials for new targeted therapies. Histologic-specific treatment of soft tissue sarcomas based on defined molecular changes continues to evolve.

## **Tratamentele sistemice in sarcoamele de parti moi avansate- care sunt standardele actuale care este viitorul?**

Sarcoamele de parti moi (SPM) la adulti reprezinta un grup complex de neoplasme cu originea in tesuturile conjunctive. Biologia SPM a facut progrese majore in intelegerea modificarilor genetice si moleculare a mai multor

subtipuri de sarcoame. Asociația de chimioterapie: antraciclina (doxorubicina) și agent alkilant (ifosfamida) a reprezentat standardul de tratament în ultimii 30 de ani, valoarea acesteia față de cea a administrării antraciclinei în monoterapie fiind încă dezbătută!

Ca monoterapie sau în asociații, antraciclinele au obținut cele mai bune rate de răspuns pentru SPM metastatice (RR de la 10% până la 25% în fiecare studiu. Ifosfamida este deosebit de activă pentru sarcomul sinovial, iar liposarcomul mixoid pare să fie mai puțin activă în leiomiosarcomae. Dacarbazina are o activitate modestă împotriva leiomiosarcomului, paclitaxelul este activ împotriva angiosarcomilor și tumorilor desmoide iar *sunitinib* și *cediranib* sunt active împotriva subtipului de sarcom alveolar. Combinația dintre temozolomidă și bevacizumab are activitate în sarcomul fibros solitar.

Progresele recente în domeniul biologiei tumorale a țesutului conjunctiv a condus la introducerea clinică a unor noi molecule-țintite în tratamentul SPM metastazate. *Pazopanib*, un inhibitor oral multikinazic care a fost aprobat pentru tratamentul pacienților cu SPM local-avansate sau SPM metastatice după tratamentul cu chimioterapie standard. *Pazopanib* este aprobat pentru tratamentul sarcomului de țesuturi moi avansate sau metastazice non-GIST (excluzând liposarcomul) după tratamentul cu chimioterapie. *Trabectedin* este un agent citotoxic care se leagă de lanțurile minore ale ADN și ARN afectând sinteza de proteine. *Trabectedin* a fost aprobat pentru utilizare la pacienții cu leiomiosarcom sau liposarcom inoperabil sau metastatic, după tratamentul anterior cu regimuri care conțin antraciclina.

*Eribulin* este un agent antimitotic care inhibă funcția microtubulilor și demonstrează ameliorarea supraviețuirii mai mari comparativ cu dacarbazina la pacienții tratați anterior, indicat în leiomiosarcoame sau liposarcoamele local-avansate sau metastazate.

*Olaratumab (Lartruvo)* este un anticorp monoclonal dezvoltat pentru tratamentul tumorilor solide. Aceasta este îndreptată împotriva receptorului factorului de creștere derivat din plachete alfa (PDGF). *Olaratumab* se utilizează în asociere cu doxorubicină pentru tratamentul adulților cu SPM avansate care nu pot fi vindecați prin chirurgie sau radioterapie și care nu au fost tratați anterior cu doxorubicină.

Într-un studiu randomizat controlat pe 133 pacienți cu SPM tratați cu *olaratumab* și doxorubicina au îmbunătățit supraviețuirea fără progresia bolii de la 4,1 până la 6,6 luni în comparație cu doxorubicina în monoterapie ( $p = 0,0615$ , semnificație statistică) și supraviețuirea globală de la 14,7 până la 26,5 luni ( $p = 0,0003$ , foarte semnificativ). Inhibitorii mTOR au fost studiați în mai multe studii pe SPM cu succes relativ limitat, cu excepția sarcoamelor epiteliale perivasculare, care sunt malignități rare, caracterizate prin activarea căii m-TOR. *Everolimus* un inhibitor al m-TOR cu indicație în tratamentul pacienților cu angiomiolipoame în doză zilnică de 10 mg/zi *per os* determină rate obiective de răspuns tumoral de 42% versus cu 0% cu placebo.

*Tazemetostat* este un inhibitor al moleculei mici de histon-lizină metiltransferază EZH2, a cărei activitate este crescută în tumorile cu integritate interactivă 1 (INI1). La unele subtipuri de SPM s-a identificat pierderea genetică a INI1 (de exemplu în sarcoamele epitelioidale -MPNST, condrosarcomul mixoid extrascheletal, carcinomul mioepitelial și 90% din sarcoamele epitelioidale).

Imunoterapia a reprezentat una dintre descoperirile majore în oncologie, atât pentru tumorile solide, cât și pentru



cele hematologice. În ciuda dovezilor istorice care susțin rolul său în SPM, rezultatele raportate în prezent cu imunoterapia adoptivă și tratamentul cu checkpoint inhibitori rămân controversate.

Există studii în curs de desfășurare care investighează imunoterapia, inclusiv inhibitori ai cu checkpoint inhibitori și terapia cu celule T. Inhibitorii tirozin kinazei, inclusiv tratamentele cu imatinib, pexidarartinib, pazopanib și axitinib, au demonstrat că afectează microclimatul imunitar tumoral în SPM. În subgrupul de sarcoame care supra-exprimă Her2, a fost vizată utilizarea celule T cu receptori de antigen himeric (CAR).

În cadrul studiului SARC028 de fază II, pembrolizumab ca agent unic a prezentat activitate în SPM toate tipurile histologice, determinând ORR de 17,5% și SFP de 55% cu durata de 3 luni;

În ultimii ani s-au observat progrese remarcabile în strategiile noi de tratament SPM bazate pe înțelegerea biologiei genetice și moleculare a diferitelor subtipuri, care să ghideze proiectarea studiilor clinice pentru noile terapii preconizate. Tratamentul specific histologic al sarcoamelor țesuturilor moi bazat pe modificări moleculare identificabile continuă să evolueze!

## **Maria Comănescu, MD**

Universitatea de Medicină și Farmacie Carol Davila, București

### **The heterogeneity of the molecular profile behind the histological types of breast cancer**

Breast carcinoma, despite the advances in research and treatment options, is still a major health problem worldwide. Classification of breast carcinoma relies mainly on their morphological patterns in routine histology, accomplished by their immunohistochemical phenotype.( ER, PR, Her2, CK5/6, ki 67, ecadherin). Further on, they can be grouped based on their gene pattern expression, resulting in molecular subtypes. Breast carcinoma represents a stepwise progression from preneoplastic alterations to invasive carcinoma, under the influence of genetic and epigenetic factors and has different clinical behaviour as well as different clinical options in overlapping histological subtypes. The heterogeneity in genomic variability in primary and secondary breast carcinomas correlated with their morphological pattern has clinical value and is important for developing effective therapies.

## **Dana Grecea, MD**

Universitatea de Medicină și Farmacie Cluj  
Institutul Oncologic Cluj

### **Where Are We with Treatment of Her-2 positive Breast Cancer?**

Approximately 15-20% of breast cancer patients overexpress her-2 protein. The combination of Trastuzumab and Pertuzumab was assessed in Cleopatra trial. The results of this trial established a new first-line standard of metastatic her-2 positive breast cancer with an increase in progression free survival (PFS) of 6 months ( 18.6 vs 12.4 months,  $p < .001$ ) and OS (56.5 vs 40.8 months,  $p = .002$ ). In second line, Emilia study compared T-DM1



vs lapatinib plus capecitabine in patients with locally advanced or metastatic her-2 positive breast cancer who had previously received zero or more than three prior regimens. T-DM showed a significant improvement in median PFS ( 9.0 vs 6.4 months, HR=0.65, p<.001). This established T-DM1 as the new standard for second-line treatment. The Th3resa study reported efficacy of T-DM1 for heavily pretreated population confirming the role of T-DM1 in advanced her-2 positive cancers. The study compared T-DM1 to physician's choice therapy and demonstrated an improved PFS of 6.2 months for T-DM1 compared with 3.3 months for physician's choice therapy (p<.001). CNS metastasis is understood to be a relatively late event in the course of mBC. Historically, mean survival from CNS metastasis diagnosis is 2–16 months. Presence of brain metastasis has a major impact on median OS: without CNS mets: 53.4 months (95% CI 47.6, 63.1) with CNS mets: 37.7 months (95% CI 30.2, 42.7). There is a lack of robust, prospective randomized trial data to support guidance on how to treat patients with CNS metastases from her-2 positive BC. In Kamilla study, patients with CNS metastases at baseline had untreated, asymptomatic CNS metastases or controlled CNS disease previously treated with radiotherapy. These patients were followed for a median of 16.0 (range: 0.3–38.7) months. Median PFS was 5.5 months (95% CI 5.4, 5.7) vs. 7.9 months (95% CI 6.9, 8.1) in patients with and without CNS metastases at baseline, respectively. Of the 399 patients with CNS metastases at baseline, 126 (32%) had measurable CNS target lesions that were evaluated for treatment response. Median time to progression in the brain for the 65 patients who received T-DM1 was 11.3 months (95% CI 8.6, 13.7). Post-progression T-DM1 was permitted in patients whose CNS metastases were amenable to local radiotherapy or surgery

## **Gabriel Ricu, MD**

Clinica "Amethyst", București

## **Cardiac toxicity in early left breast cancer irradiation after breast conserving surgery**

**G. Ricu<sup>1,2</sup>, R. Hepp de Los Rios<sup>3</sup>, R. Galalae<sup>1,3</sup>**

<sup>1</sup> Amethyst Radiotherapy Centre

<sup>2</sup> Medico-Military Scientific Research Centre

<sup>3</sup> Evangelische Kliniken Gelsenkirchenary

**Background.** Adjuvant radiotherapy of the whole breast after breast conserving surgery (BCS) is a well-established indication. It is also known that, at least in the past, treating the left side increases the risk of cardiac mortality. The risk of ischaemic heart disease after radiotherapy for breast cancer seems to increase linearly with the mean dose to the heart.

**Methods.** Performing the radiotherapy in deep inspiration breath hold (DIBH) significantly reduces the

planned heart dose. Recently, accelerated partial breast irradiation (APBI) with multicatheter brachytherapy (MBT) has become widely accepted as an alternative for patients with low risk profile breast cancer after BCS.

**Results.** We retrospectively reviewed the treatment plans of our first 20 patients treated with MBT-APBI for left-side breast cancer and compared them with our published data on similar patients treated in DIBH. There were no significant differences in the heart mean dose (mean value: APBI 1,83 Gy vs DIBH 1,85 Gy,  $p=0,48$ ), but a 70% reduction in the dose applied to at least 2 cm<sup>3</sup> (D2cm<sup>3</sup>): mean values 7,44 Gy with APBI vs.23,65 Gy with DIBH,  $p<0.0001$ . Also a marked dose reduction in the mean doses applied to left descending coronary artery (LAD) was noted (mean 4,14 Gy with APBI vs. 10.59 with DIBH).

**Conclusions.** Despite the use of modern techniques in adjuvant radiotherapy after BCS, there still persists a dose delivery to the heart and especially to sensitive regions like LAD or the left ventricle. Dose constraints actually in use are mostly based in retrospective estimations of the heart dose. New markers like brain natriuretic peptide (BNP) can be helpful in defining new dose constraints, but also to define higher risk groups, which should have a more in-depth monitoring after treatment.

## **Camelia Dobrea, MD**

Onco Team Diagnostic

Institutul Clinic Fundeni, București

## **Adult T-cell leukemia–lymphoma in southern Romania – a clinical and pathological approach**

**Camelia Dobrea**<sup>1,2</sup>, **B Popescu**<sup>2,3</sup>, **Al Bardas**<sup>3</sup>, **Flavia Porcescu**<sup>1</sup>, **Viola Popov**<sup>4</sup>, **Ana-Maria Vladareanu**<sup>2,5</sup>, **Anca Lupu**<sup>2,6</sup>, **D Coriu**<sup>2,3</sup>

1 OncoTeam Diagnostic, Bucharest; 2 Carol Davila University of Medicine Bucharest; 3 Fundeni Depart of Hematology, Bucharest ; 4 - Colentina Depart of Hematology, Bucharest , 6- University Emergency Hospital, Depart of Hematology, Bucharest 6 - Coltea Depart of Hematology, Bucharest

Adult T-cell leukemia–lymphoma (ATL) is a rare and aggressive T-cell malignancy caused by human T-cell lymphotropic virus type 1 (HTLV-1). According to Shimoyama criteria, there are four clinical variants of ATL: the acute and lymphoma types (aggressive forms, with dismal prognosis); the chronic and smoldering types have a better outcome. There is no general consensus regarding the optimal treatment. Based on the clinical subtype, the ATL patients can receive chemotherapy, antiretroviral medication or immunotherapy. The allogeneic stem cell transplantation can improve the overall survival in some patients.

ATL often occurs in HTLV-1–endemic areas such as Japan, the Caribbean, South America or Middle East. In Europe, Romania is the only HTLV-1 endemic country; for this reason an ATL workgroup was created. Within the workgroup, a multicentric retrospective analysis of ATL cases between 2010 and 2015 was performed on 88 patients diagnosed in the Hematology departments in Bucharest, Romania (Fundeni Clinical Institute, Coltea

Hospital, Emergency University Hospital of Bucharest and Colentina Hospital). The patients were stratified into clinical subtypes according to Shimoyama classification and into treatment groups. The majority of patients were diagnosed with aggressive forms (54% acute type, 42% lymphoma type) and treated with chemotherapy (56,8% CHOP/CHOP-like regimens, 13,6% LSG15 regimen); only 19,3% received combinations that include antiviral agents. The median survival was 5 months for the aggressive forms, with no difference between the types of treatment received.

The data resulted from this study along with epidemiological data on HTLV-1 high seroprevalence in Romania stand up for the hypothesis that the ATL forms diagnosed in Romanian patients are predominantly aggressive with poor outcome. The accurate diagnosis and therapeutic management of such cases are challenging for the hematopathologist and the clinician.

### **Cristina Ghiuzeli, MD**

Northwell-Hofstra University  
Northwell Health Monter Cancer Center New York, USA

### **Tratamentul contemporan al leucemiei mieloide acute**

This presentation will cover 4 newly approved AML treatments: Midostaurin (Rydapt), Enasidenib (Idhifa), Gemtuzumab ozogamicin (Mylotarg) and Liposomal Daunorubicin/Cytarabine (Vyxeos). The presenter will discuss studies that led to the FDA approval of the treatments, as well as the adverse effects of each drug and context in which they can be used.

### **Alina Daniela Tanase, MD, PhD**

Institutul Clinic Fundeni

### **T Cell-Replete Haploidentical Transplantation with Post-Transplantation Cyclophosphamide for Malignant Lymphoma**

Allogeneic stem cells transplantation (Allo-SCT) is a potentially curative therapeutic strategy for patients with malignant lymphomas that relapse after the autologous stem cell transplant (ASCT), or for selected cases of refractory lymphomas, as first transplant.

Most patients with Hodgkin's lymphoma and aggressive NonHodgkin's lymphomas are cured with first-line chemotherapy, while almost half of those with relapsing or progressive disease respond to rescue chemotherapy, and benefit from dose high dose chemotherapy (HDC) followed by the autologous stem cell transplantation. However, there are a substantial number of patients who need subsequent therapy due to relapse after autologous stem cell transplantation. In this context, after the initial disappointing results obtained with myeloablative regimens

in allo SCT, due to a high transplant mortality rate, the use of Allo-HSCT increased with the development of reduced-intensity conditioning. (RIC). Another limitation of the use of Allo-HSCT is donor availability: half of caucasian population are able to find an identical HLA donor or unrelated voluntary donor (MUD), this percentage being even lower in case of other ethnic population. Alternative sources of stem cells, such as umbilical cord blood or haploidentical donors (50% HLA compatible familial donor), have the potential to extend accessibility to Allo-HSCT for all patients in need. In recent years, encouraging results have been achieved with haploidentical stem cell transplant associated with post-transplant cyclophosphamide (post-Cy).

### **Mihnea Zdrengea, MD, PhD**

UMF "Iuliu Hatieganu" si Institutul Oncologic "Ion Chiricuta" Cluj-Napoca, Romania

#### **Axa PD-1-PD-L1 in limfoamele agresive: promisiuni si certitudini**

Blocarea semnalizarii co-inhibitorii via receptorul programmed death 1 (PD-1) este o abordare extrem de actuala in oncologie. Agentii blocanti ai receptorului sau a liganzilor acestuia fac obiectul unui numar impresionant de trialuri clinice in cancer, unii fiind deja aprobati in tumori solide. Si in cazul hemopatiilor maligne, acesti agenti au suscitau un interes deosebit, iar doi anticorpi monoclonali anti PD-1 sunt actualmente aprobati in limfomul Hodgkin recazut sau refractar. Prezentarea trece in revista mecanismul de actiune al agentilor blocanti ai semnalizarii prin axa PD-1- PD-L, precum si rezultate obtinute cu acestia in limfoamele agresive. De asemenea, relevanta predictiva a expresiei acestor molecule de catre tesutul tumoral, si alti biomarkeri cu valoare predictiva pentru raspunsul la terapie.

### **Gabriela Gheorghe, MD**

Medical College of Wisconsin, USA

#### **Posttransplant lymphoproliferative disorders: Too much splitting, not enough lumping? Why the 2017 WHO classification is clinically relevant.**

Posttransplant lymphoproliferative disorders (PTLD) are serious complications of organ transplantation as a result of the overall increase in the number of solid organ or allogeneic hematopoietic stem cell transplantations, more potent immunosuppressive regimens and overall improved long-term survival. While the recognition of the disease is increasing, the diagnosis and accurate classification of PTLD cases remains challenging. The 2017 WHO classification provides an international standard for oncologists and pathologists alike.

PTLD comprise a spectrum ranging from early and polyclonal lesions to EBV positive or EBV negative proliferations indistinguishable from lymphomas that occur in immunocompetent individuals. Early/nondestructive lesions often regress spontaneously or with reduction in immunosuppression. Polymorphic PTLD are morphologically polymorphic lesions that efface the architecture but do not fulfill criterias for any recognized type of

lymphoma. It is important to differentiate classical Hodgkin lymphomas from Hodgkin-like polymorphic PTLD lesions.

Reduction of immunosuppression leads to regression in a subset of cases but some may progress and require therapy. Monomorphic PTLD should be further characterized based on the WHO classification of hematopoietic malignancies. Numerous hematopoietic malignancies, including multiple myelomas, have been described in the posttransplant setting.

The presence or absence of molecular evidence of clonality is not completely predictive of prognosis. Polyclonal lymphoproliferative disorders can be clinically aggressive and fatal.

PTLD accounts for a high rate of graft loss and significant mortality. The management of PTLD remains challenging and generally there is no standardized therapeutical approach that can be applied to all patients. Treatment guidelines require reduction in immunosuppression, rituximab, chemotherapy and immunological agents. Many oncologists now consider rituximab as first line therapy after reduction of immunosuppression.

It is well known that PTLD can present with morphologically different lesions at different sites.

Since this might lead to different treatment strategies, biopsy of any new lesion is essential and close collaboration between the clinician and the pathologist is paramount.

## **Robert G. Bota, MD**

Department of Psychiatry and Human Behavior, University of California, Irvine

## **The effect of cancer and cancer treatment on the brain: the interface between cancer care and psychiatry**

### **Fast Facts**

- \_ The most common psychiatric disorder observed in cancer patients is adjustment disorder with depression, anxiety or both.
- \_ Patients with cancer have a high rate of psychiatric comorbidity; approximately one-half exhibit emotional difficulties.
- \_ Cancer and cancer treatment might impede brain's cognitive abilities as blood brain barrier is breached, by cytokine suppression, decreased BDNF levels amongst others

### **Overview**

Psycho-oncology is a complex discipline that addresses the psychological, behavioral, and ethical aspects of cancer. In major cancer programs, the psychiatrists involved in the psycho-oncology practice address two major dimensions of cancer: (1) the psychological responses of patients to cancer at all stages of the disease, including the treatment of psychiatric morbidities such as depression and anxiety, and (2) the psychological and be-

behavioral factors that may influence patient adherence to treatment as well as the patient's response to treatment. The practice of psycho-oncology has changed greatly in the last twenty years, as more children and adults have earned the title of cancer survivor. However, the quality of their survival is greatly affected by a myriad of neurological and cognitive impairments. Many cancer patients remain out of sight of the health services due to societal stigma and a lack of resources to diagnose, treat, and support these cases. Regardless of the prognosis, cancer is a cause of anxiety and depression in more than one-third of cancer patients. Furthermore, depression causes reduced immune responses, and the presence of untreated depression directly correlates with poor prognosis. Treatment of depression in cancer patients is very intricate, as many antidepressants can lower the efficacy of cancer drugs by interfering with their metabolism. Psycho-oncology is a highly multi-disciplinary effort, and as such it requires a multi-disciplinary team approach and the ability to speak a common language with the major oncological specialties (such as hematology-oncology, oncological surgery and radiation oncology). Psycho-oncology research interacts with cancer epidemiology, immunology, endocrinology, cancer biology, pathology, bioethics, palliative care, rehabilitation medicine, clinical trials research, experimental design, clinical decision making, and, of course, psychiatry and psychology. Cancer is, after all, a disease of both the body and the mind – a concept which will be extensively explored in this presentation.

### **Challenge**

Physicians need to be aware of how to diagnose and treat psychiatric conditions in patients with cancer, as the risk of having a psychiatric diagnosis is 30 to 40 percent and untreated, those conditions will decrease the quality of life and will also reduce the survival rate from the cancer.

**Target audience:** Primary care physicians, family medicine, internal medicine, psychiatrists, hematology-oncology, oncology surgeons and radiation oncology.

### **Learning Objectives**

- \_ Evaluate psychiatric diagnosis in patients with cancer.
- \_ Recognize how psychiatric manifestations are different in patients with cancer.
- \_ Discuss treatment algorithms for common psychiatric conditions in patients with cancer.

## **George A Călin, MD, PhD**

University of Texas MD Anderson Cancer Center  
Texas, USA

## **Despre genomul ultraconservat si RNA-uri non-codificante: implicatii pentru pacientii cu cancer**

The newly discovered differential expression in numerous tissues, key cellular processes and multiple diseases for several families of long and short non-codingRNAs (ncRNAs, RNAs that do not codify for proteins but for RNAs with regulatory functions), including the already famous class of microRNAs (miRNAs) strongly suggest that the scientific and medical communities have significantly underestimated the spectrum of ncRNAs whose altered expression has significant consequences in diseases. MicroRNA and other short or long non-codingRNAs

alterations are involved in the initiation, progression and metastases of human cancer. The main molecular alterations are represented by variations in gene expression, usually mild and with consequences for a vast number of target protein coding genes. The causes of the widespread differential expression of non-codingRNAs in malignant compared with normal cells can be explained by the location of these genes in cancer-associated genomic regions, by epigenetic mechanisms and by alterations in the processing machinery. MicroRNA and other short or long non-codingRNAs expression profiling of human tumors has identified signatures associated with diagnosis, staging, progression, prognosis and response to treatment. In addition, profiling has been exploited to identify non-codingRNAs that may represent downstream targets of activated oncogenic pathways or that are targeting protein coding genes involved in cancer. Recent studies proved that miRNAs and non-coding ultraconserved genes are main candidates for the elusive class of cancer predisposing genes and that other types of non-codingRNAs participate in the genetic puzzle giving rise to the malignant phenotype. Last, but not least, the shown expression correlations of these new ncRNAs with cancer metastatic potential and overall survival rates suggest that at least some member of these novel classes of molecules could potentially find use as biomarkers or novel therapeutics in cancers and other diseases.

## **Adrian Salic, MD, PhD**

Harvard Medical School, Harvard University

### **Targeting the Hedgehog signaling pathway in cancer**

The Hedgehog cell-cell signaling pathway is essential for animal embryonic development and for adult stem cell maintenance. Impaired Hedgehog signaling during development leads to many birth defects, while uncontrolled activation is deeply implicated in cancer.

Hedgehog signals are relayed across the plasma membrane of cells by the seven transmembrane-spanning (7TM) protein Smoothed. In the absence of Hedgehog stimulation, Smoothed adopts an inactive conformation, which ensures that signaling is off. When the Hedgehog pathway is stimulated, cholesterol binds to the extracellular domain of Smoothed, causing the protein to adopt an active conformation, which, in turn, triggers the downstream cytoplasmic steps of the Hedgehog signal transduction cascade.

Smoothed plays key roles in several cancers, including basal cell carcinoma and medulloblastoma. Oncogenic activation of Smoothed can occur either by mutation, or by loss of the inhibitory effect that the tumor suppressor membrane protein Patched exerts normally on Smoothed. Given its critical role in cancer, numerous small molecule inhibitors have been developed against Smoothed, including drugs approved for clinical use, such as Vismodegib (Roche) and Sonidegib (Novartis).

I will present findings from our lab concerning the biochemical and cell biological mechanisms that govern Smoothed activity during Hedgehog signaling. I will also discuss results obtained through X-ray crystallog-



raphy, that elucidate how various drugs inhibit Smoothed, how mutations activate Smoothed in cancer, and how drug-resistant Smoothed mutants emerge during cancer relapse.

## **Mihaela Zavolan, PhD**

Computational and System Biology Unit, Biozentrum, University of Basel and Swiss Institute of Bioinformatics.

### **Transcriptome analyses of human cancers**

Cancer is a very complex disease, with alterations at multiple levels. The Cancer Genome Atlas (TCGA) project initiated by the NIH has compiled molecular profiles for tens of human cancers with the aims of improving diagnostic methods and preventive strategies. Our group develops computational approaches to uncover novel gene expression signatures, as well as the responsible regulators, from RNA sequencing data. In particular, we found that the expression of specific ribosomal proteins is perturbed in cancers due to copy number variations, and these perturbations are predictive for the cancer-free survival of the patients. Cancer cells also express transcripts with shortened 3' untranslated regions, and therefore, with different susceptibilities to a variety of regulators. Combining the inference of 3' UTR usage with analysis of sequence motifs, we found that the polypyrimidine tract binding protein 1 (PTBP1) is overexpressed in glioblastoma, where it leads to expression of transcripts with shortened 3' UTRs.

### **Analiza transcriptomului cancerelor umane**

Cancerul este o afecțiune complexă, cu alterări la nivele multiple. Atlasul Genomic al Cancerului (TCGA) este un proiect inițiat de NIH, ce a compilat profiluri moleculare pentru 10 cancere umane, cu perspectiva de a îmbunătăți metodele de diagnostic și strategiile de prevenție. Grupul nostru dezvoltă metode computaționale care permit descoperirea de noi amprente de expresie a genelor, precum și a reglatorilor responsabili, pornind de la ARN-ul secvențat din celule canceroase și celule de control. În particular, am descoperit că expresia anumitor proteine ribozomale este perturbată în cancer, ca urmare a schimbărilor care au loc în numărul locilor genomici care codifică diverse proteine ribozomale. Aceste perturbări sunt predictive pentru supraviețuirea pacienților. În același timp, studiem expresia regiunilor netranslate ale ARN-urilor mesager (3' UTRs), care sunt substanțial mai scurte în celule canceroase comparativ cu celulele normale. Această modificare are ca rezultat diferențe în susceptibilitate transcriptelor corespunzătoare pentru o multitudine de reglatori. Combinând date despre exprimarea 3'UTRs cu analize ale motivelor ce se găsesc în aceste secvențe, am descoperit că supraexprimarea proteinei care interacționează cu tracturi de polipirimidine (PTBP1) în glioblastom, duce la expresia de transcripți cu regiune netranslatată scurtă (short 3'UTRs).

## **Eduard Nedeia**

The Laboratory of Personalized Genomic Medicine, Columbia University, New York

### **Applications of the Next Generation Sequencing technology in clinical oncology**

Precision medicine aims to match individuals sharing a common molecular biomarker to an efficient preventive approach or targeted therapy. The field of oncology witnessed the benefits of targeted therapy more than 15 years ago with the discovery of Imatinib, a relatively specific inhibitor of the Abl1 tyrosine kinase, which was able to induce an unparalleled response in chronic myelogenous leukemia patients who harbor a specific translocation that constitutively activates Abl1.

The advent of the next generation sequencing (NGS) technology and the staggering advances that made it affordable, have allowed the scrutinizing at base resolution of the genome and transcriptome of various cancer types and the identification of many biomarkers. Some of these molecular signatures has empowered the clinical oncologist with new tools for a precise molecular diagnosis and for a potential tailored treatment of certain malignancies.

In my presentation, I will illustrate the benefits and limitations of the current NGS-based genomic tests that are made available by the modern clinical diagnostic laboratories to support the clinical oncologist in making the most informed decisions for the personalized management of the cancer patients.

Medicina de precizie isi propune sa asigure o strategie eficienta de profilaxie sau de tratament tintit conform unui biomarker molecular comun unei cohorte de indivizi. In domeniul oncologic, acest principiu a fost ilustrat cu succes de mai mult de 15 ani, odata cu introducerea in clinica a inhibitorului relativ specific al tirozin kinazei Abl1, Imatinib. Acesta induce un raspuns spectaculos in pacientii cu leucemie mielogena cronica care posedea o translocatie ce activeaza constitutiv aceasta kinaza.

Aparitia tehnologiei de secventiere de noua generatie si avansurile tehnologice uimitoare care au facut-o accesibila financiar, au permis interogarea cu o rezolutie mare a modificarilor prezente in celulele canceroase, atat la nivelul materialului genetic cat si al expresiei acestuia. Identificarea unor amprente biologice specifice anumitor cancere, permite medicului oncolog sa faca un diagnostic molecular si, in anumite cazuri, sa actioneze terapeutic intr-un mod tintit si precis.

Voi prezenta beneficiile si limitarile testelor genetice oferite in prezent de laboratoarele moderne de diagnostic care sprijina medicul oncolog in a oferi pacientilor o solutie optimizata si personalizata bazata pe identificarea defectelor moleculare prezente in celulele canceroase.

## **Andrei Dumitru Jacobas, PhD**

Associate Professor of Pathology - New York Medical College & Researcher of the Center for Computational System Biology at Prairie View A&M University

### **Gene Master Regulators in Cancer Gene Therapy**

We prove that cancer nodules and surrounding normal tissue are governed by distinct Gene Master Regulators (GMR) and that smart manipulation of a GMR expression selectively destroys cancer cells. The method relies on profiling the gene expression in tumor biopsies and comparing the transcriptomes of the cancer and normal subdivisions of the sample. An original mathematical algorithm establishes the gene hierarchy in each part of the tumor based on their Gene Commanding Height, a composite measure of gene expression control and coordination. For now, the algorithm is implemented on our Illumina sequencers (MiSeq and NexSeq550) and Agilent and Illumina gene expression microarray platforms, and tested for cancer in humans and animal (mouse, rat, rabbit, dog and chicken embryo) models of human cancers. The method is illustrated in <https://doi.org/10.18632/oncotarget>, presenting applications to thyroid anaplastic and papillary carcinoma and in [http://www.hrpub.org/journals/article\\_info.php?aid=6128](http://www.hrpub.org/journals/article_info.php?aid=6128) with an application to a case of clear cell renal cell carcinoma.

## **Razvan Lapadat, MD**

Loyola University Medical Center, Department of Pathology  
Maywood, Illinois, United States

### **Implementation of Telepathology and Remote Data Assessment in Clinical Practice: Are We There Yet?**

In April of 2017, the digital pathology world reached a major milestone: the FDA approved the first digital pathology solution for primary diagnostic use in the United States. Ten years ago, it took slide scanners 30 to 60 minutes to scan a single slide. Today, not only are they much faster – with scanning times as short as 30 seconds – but the quality of images is significantly better.

Telepathology holds the promise of moving beyond the usual diagnosis process to truly collaborative pathology. Furthermore, the model of sending glass slides to a single consultant is giving way to a broadly-linked digital network of experts. Diagnosis using remote pathology examination can be performed regardless of continent or time zone. Additionally, the histological images approach the quality of the ones examined using a light microscope in a time that is significantly shorter.

Telepathology has a tremendous growth path due to rapid advances in information and technology. It has a wide variety of applications: remote primary diagnosis, specialist referrals, secondary opinions, remote teaching and research. The practice requires minimal hardware and skilled staff availability as prerequisites for

successful implementation.

At our institution we recently implemented a digital pathology frozen section and cytology diagnostic system. This allows attending pathologists, trainees and our clinical colleagues to better collaborate in each case. The system spans several different hospitals in our area, thus allowing for a fast diagnosis even in the most challenging cases.

We aim to see how telepathology bridges the existing gaps in the classical slide diagnosis process, contributing to effective healthcare and addresses possible constraints to telepathology and the solutions to overcome them.

### **Cristina Iosif, MD**

Onco Team Diagnostic, Spitalul Sf Maria, București

### **HPV – indicator de predictie si prognostic in tumorile de cap si gat**

**Cristina Iosif, Roxana Nicolae**

Onco Team Diagnostic

Carcinomul scuamos al regiunii cap-gat este al 6-lea cancer ca frecventa in lume si reprezinta >90% din malignitatile cu aceasta localizare.

Recent, considerarea statusului HPV (sau “p16 status”/ marker “surogat” pentru infectia HPV)ca factor important de prognostic in cancerul scuamos orofaringian a condus la subclasificarea moleculara a acestuia in carcinoame scuamoase HPV positive si carcinoame scuamoase HPV negative cu caracteristici clinico-biologice diferite ; noua clasificare prezenta atat in noul WHO 2017 cat si in AJCC 8<sup>th</sup> ed are implicatii diagnostice, prognostice si de predictive; metode de evaluare a statusului HPV in cancerul de cap-gat, accesibilitatea acestora, avantaje/dezavantaje, aplicatii practice, orientare terapeutica.

### **Laura Marcu, PhD**

University of California-Davis

### **Autofluorescence lifetime techniques for surgical imaging, guidance and augmented reality**

### **Tehnici de autofluorescenta rezolvata in timp pentru imagistica chirurgicală, orientare și realitate augmentată**

This presentation overviews fluorescence lifetime spectroscopy and imaging techniques for label-free *in vivo* characterization of biological tissues. Numerous studies have shown that tissue autofluorescence properties have the potential to assess biochemical features associates with distinct pathologies in tissue and to distinguish var-

ious cancers from normal tissues. However, despite these promising reports, autofluorescence techniques have been sparsely adopted in clinics. Moreover, when adopted they were primarily used for pre-operative diagnosis rather than surgery guidance. This presentation overviews clinically-compatible multispectral fluorescence lifetime imaging (FLIM) techniques developed in our laboratory and their ability to operate as stand-alone tools, integrated in a biopsy needle and in conjunction with the da Vinci surgical robot. We present clinical studies in patients undergoing surgery that demonstrate the potential of these techniques for intraoperative delineation of brain tumors and brain radiation necrosis as well as head and neck cancer including image-guided augmented reality during trans-oral robotic surgery (TORS). Challenges and solutions in the clinical implementation of these techniques are discussed.

## **Doru Paul, MD, PhD**

Northwell-Hofstra University  
Northwell Health Monter Cancer Center  
New York, USA

## **Head and neck immunotherapy**

Over the last decade, immunotherapy treatment for malignant tumors has been progressing very fast. The most remarkable advance in the field of cancer immunotherapy is the clinical development and approval of immunomodulators, also known as immune checkpoint inhibitors. The role of immune checkpoint inhibitors is to restore and augment the antitumor immune action of cytotoxic T cells by blocking immune checkpoint molecules on T cells or their ligands on antigen presenting cells and tumor cells. The first in class approved immune checkpoint inhibitor is ipilimumab, an anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) monoclonal antibody that has been used initially in the treatment of advanced melanoma. The second class of immune check point inhibitors are PD-1 and PD-L1 inhibitors. The most significant results in the last two years regarding the treatment of head and neck cancers have been the validation of the use of pembrolizumab and nivolumab, PD-1 inhibitors, as second line treatments in squamous cell cancers of head and neck. In USA, both pembrolizumab and nivolumab are FDA approved for this indication. Three studies, KEYNOTE-012, KEYNOTE-055 and KEYNOTE-040 established the efficacy of pembrolizumab in second line head and neck cancer treatment. The overall response rate (ORR) to pembrolizumab has been approximately 18% in these studies and the agent has been well tolerated in general with  $\geq$ Grade 3 adverse events of approximately 9%. In the KEYNOTE-040, a Phase 3 randomized study, in the intent to treat population, the overall survival was not statistically improved in the pembrolizumab arm versus the standard of care chemotherapy arm. A post-hoc analysis presented at ESMO in 2017, showed that in patients bearing tumors with either positive PD-L1 expression in tumor or immune cells ( $\geq 1\%$ ) had a statistically significant improvement in overall survival (8.7 vs 7.1 months  $p=0.0078$ ). Also, in patients bearing tumors with strongly positive PD-L1 expression ( $\geq 50\%$ ), the overall survival was significantly improved (11.6 vs 7.9 months  $p=0.0017$ ). CheckMate-141, a pivotal Phase 3 randomized study, demonstrated significant median overall survival improvement using nivolumab immunotherapy in second line compared with standard of care chemotherapy

(7.5 vs 5.1 months  $P=0.01$ ). The response rate was 13% in the immunotherapy arm. The median progression free survival was not increased in the nivolumab arm. Also, the greatest improvement in median overall survival (8.7 vs 4.6 months) was noticed in patients bearing tumors with positive PD-L1 expression ( $\geq 1\%$ ). Grade 3 or 4 toxicities occurred in approximately 13% of the patients. For the patients bearing tumors with negative ( $< 1\%$ ) PD-L1 expression (45% of the patients) the median overall survival was the same with the chemotherapy control arm. Recently, durvalumab, a PD-L1 inhibitor, showed an overall response rate of 18% when used in second line in patients bearing tumors with moderately strong PD-L1 expression ( $\geq 25\%$ ). There were 8%  $\geq$  Grade 3 adverse events. Overall, the response rate to check point inhibitors in head and neck cancer is 13-18%. The lack of response in the remaining majority of cases may be related among other factors to the hypoxia and strong local inflammation present in these tumors that may have an inhibitory effect.

### **Florina Vasilescu, MD**

Spitalul Militar Central Dr Carol Davila, Bucuresti

### **Diagnosticul tumorilor pulmonare prin metode minim invasive**

**Dr Florina Vasilescu, Dr Natalia Motas, Dr. biolog Aura Buburuzan**

Oncoteam Diagnostic, Institutul Oncologic Fundeni

Carcinomul pulmonar continua sa ocupe primele locuri atat in ceea ce priveste numarul de noi cazuri diagnosticate anual cat si datorita ratei foarte crescute a mortalitatii.

Diagnosticul cancerului pulmonar se face, in functie de stadiul tumoral, fie prin evaluarea histopatologica a tesutului obtinut prin excizie chirurgicala, fie prin evaluarea biopsiilor mici sau a specimenelor citologice atat din tumora primara cat si din determinari metastatice.

De asemenea stadiul tumoral influenteaza metoda terapeutica abordata : chirurgicala ( stadiul I), chirurgicala si terapie adjuvanta ( stadiul II,III), chimioterapie/radioterapie si terapie moleculara tinta ( stadiile IIIb, IV)

Majoritatea pacientilor fiind insa diagnosticati in stadii avansate IIIb, IV patologul are la dispozitie pentru diagnostic doar specimene tisulare sau citologice obtinute prin metode minim invasive in functie de caz : biopsii bronșice, biopsii pleurale ,EBUS -TBNA, punctia biopsie in nodulii tumorali ghidata CT, specimene citologice : lichid pleural, aspirate bronșice.

Lucrarea prezentata va arata problemele de diagnostic intalnite la aceste cazuri in cadrul laboratorului de anatomie patologica : diagnostic diferential adenocarcinom pulmonar / carcinom scuamos; carcinom primitiv pulmonar/ metastaze; incidenta mutatiilor EGFR, a translocatiei ALK, a statusului PDL1 pe aceste specimene recoltate prin metode minim invasive, utilitatea citoblocurilor realizate din lichide si aspirate in diagnostic.

O alta metoda minim invaziva o reprezinta biopsia lichida, metoda utilizata in special in detectia mutatiei EGFR dar si pentru monitorizarea bolii si a detectiei rezistentei primare sau dobandite la terapia anti-EGFR.

**Dr. Bogdan Tănase, Dr. Natalia Motaș, Dr. Mihnea Davidescu, Dr. Alin Burlacu,  
Dr. Corina Bluoss, Dr. Ovidiu Rus, Prof. Dr. Teodor Horvat**

Clinica de Chirurgie Toracică, Institutul Oncologic București

## **Rezecțiile pulmonare toracoscopice (VATS) în tratamentul cancerului bronhopulmonar**

Chirurgia toracică minim invazivă este o cale de abord de actualitate în cadrul tratamentului chirurgical al cancerului bronhopulmonar de care poate beneficia un număr mare de pacienți având rezultate oncologice cel puțin comparabile cu pacienții tratați prin chirurgia clasică, dar și o gamă largă de beneficii precum reintegrarea socială rapidă, posibilitatea începerii tratamentului oncologic adjuvant imediat postoperator, lipsa sindromului algic post toracotomie precum și criteriul estetic.

De asemenea chirurgia toracică video asistată aduce un beneficiu real pacienților cu rezervă pulmonară marginală care nu suportă un tratament chirurgical de rezecție pulmonară prin toracotomie (toracotomia în sine reduce temporar rezerva funcțională respiratorie cu aproximativ 25%) devenind astfel eligibili pentru un tratament chirurgical cu viză curativă.

În tratamentul cancerului bronhopulmonar se poate utiliza abordul minim invaziv pentru rezecții non-anatomice cu stapler sau LASER, precum și pentru rezecții reglate: segmentectomii, lobectomii, bilobectomii sau pneumonectomii.

În lucrarea propusă prezentăm avantajele chirurgie toracice minim invazive cu exemple de cazuri operate în clinica noastră, considerând astfel chirurgia toracică minim invazivă o metodă de abord care prin beneficiile pe care le oferă devine o chirurgie a prezentului pentru cazurile selecționate fără a exclude calea clasică de abord.

**Mircea Dediu, MD**

Spitalul Clinic Sanador, București

## **Immune therapy is stage III NSCLC: Do we have a new standard of care?**

Concurrent chemoradiation was consecrated as standard of care for inoperable stage III non-small cell lung cancer, more that 15 years ago. Since, many strategies were attempted in order to improve clinical outcome of the patients, but unfortunately none was proved to be successful. Recently the immune therapy tsunami, profoundly altered the classical chemotherapy approach in metastatic non-oncogene driven NSCLC. Nowadays, immune therapy represents the preferred option in first line for patients with > 50% P-DL1 expression, and for virtually all patients in second line setting. Last year at ESMO congress, the PACIFIC trial results were presented. PACIFIC,



used durvalumab, a PD-L1 inhibitor, as consolidative treatment upon concurrent chemoradiation, and was the first trial communicating a substantial improvement in the outcome of stage III NSCLC patients. As a result, the NCCN guidelines included the PACIFIC trial strategy as the only recommended treatment for this patient sub-category. This presentation will briefly review the previous failing approaches attempted to improve treatment efficacy in non operable stage III patients along with the major advances reported with immune therapy in the PACIFIC trial.

### **Gabriel Kacsó, MD**

UMF „Iuliu Hatieganu”, Cluj-Napoca;

RTC Amethyst Cluj

### **Stereotactic ablative radiotherapy for NSCLC**

Stereotactic ablative radiotherapy (SART) is a remarkable progress of irradiation as curative or palliative treatment of a large variety of malignant or benign tumors, as well as other particular conditions (arterio-venous malformations for example).

Accurate, safe and effective, SART has recently become a recognized alternative to surgery as curative approach for early stages of non-small cell lung cancers (NSCLC). A combined analysis of the two published randomized trials (each one not completing accrual) comparing SART vs lobectomy in operable cancers showed superiority of SABRT in terms of 3 years overall survival 95 vs 79 %, (HR=0.14, p=0.037) with less severe toxicity, including treatment related deaths.

In our clinic, we developed the SART program since last year as curative or palliative scenario, including NSCLC, with particular interest for the oligo-metastatic setting (any cancer) and re-irradiation. To our knowledge, we are the only centre performing it in Romania.

We present our SART clinical and technical protocol for early NSCLC. Due to limited number of patients and short follow-up, conclusions are premature on survival, but so far none of our patients experienced progression or severe toxicity.

### **Alexandru C. Grigorescu, MD, PhD**

Fundeni Institute of Oncology Bucharest

### **TKI treatment in NSCLC Experience of an IOB clinical study site**

Despite the fact that IOB's experience is limited to the use of new drugs because of financial restrictions, restric-

tions that affect in some countries even richer countries, initiation of studies, even small scale, at the proposal of the investigator are welcome for the development of clinical research that must start from the clinician.

In this respect I will present the:” Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer patients” and “Short Review of “Phase II Study of Erlotinib Plus Gemcitabine in First-Line Treatment of Poor Prognosis, Advanced Non-Small Cell Lung Cancer(NSCLC) Patients”- 8 Years Letter” published in oncology journals.

The proposal of the first study was to investigate whether clinical benefit can be obtained by concurrent administration of erlotinib with gemcitabine as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2. The conclusion of this study was positive: gemcitabine plus erlotinib achieve superior response rate and comparable overall survival with acceptable toxicity compared to monochemotherapy with gemcitabine. This combination represents a treatment option for patients with advanced NSCLC and ECOG PS 2.

The second part of presentation is the situation of target therapy after 8 years from the beginning of our study “Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer (NSCLC) patients”, the things are not enough clear regarding the combination of target therapy or immunotherapy for patients with advanced NSCLC. This review tries to discuss some important meta-analysis and some important study which give us more information and solutions to resolve this matter.

Finally, is presented the study “TITAN” where IOB participated confirm the value of target therapy in advanced lung cancer. Authors concluded that:” No significant differences in efficacy were noted between patients treated with erlotinib and those treated with docetaxel or pemetrexed. Since the toxicity profiles of erlotinib and chemotherapy differ, second-line treatment decisions should take into account patient preference and specific toxicity risk profiles”.

Conclusions are that clinical research by investigators initiative should be stimulated and the new approaches, and we point out in this way the discussions at ESMO 2017, are based to the previous research which should not be neglected.

## **Alina Mihai, MD**

Beacon Hospital, Sandyford, Dublin

Medisprof Cancer Center Cluj

## **Stereotactic radiosurgery and stereotactic ablative radiotherapy in oligometastatic NSCLC**

This presentation will focus on current indications of SRS/SABR in patients with oligometastatic NSCLC, challenges in patient selection and the future of this technology in the era of immune and targeted therapies. Technical challenges in the treatment of oligometastases will be shortly discussed.

## **Carmen Ardeleanu, MD, PhD**

UMF “Carol Davila” București

Onco Team Diagnostic București

## **Probleme de diagnostic in tumorile de tract genito-urinar; prezentare de cazuri**

### **Prof. Dr Carmen Ardeleanu, Dr. Horatiu Muresan (Onco Team Diagnostic Bucuresti)**

Patologia tumorală a tractului genitourinar ridică adesea probleme dificile de diagnostic diferențial. Stabilirea diagnosticului corect oferă medicului curant posibilitatea alegerii atitudinii terapeutice corecte. În prezentarea noastră am selectat câteva astfel de cazuri mai puțin frecvente în practica curentă, al cărui diagnostic poate fi adesea dificil:

**Carcinomul mucinos tubular cu celule fusiforme** (Mucinous tubular and spindle cell carcinoma) este o variantă rară de carcinom renal, relativ recent descrisă și acceptată de OMS. Majoritatea acestor tumori au o evoluție blândă, fără recidive sau metastaze dar au fost raportate și cazuri cu grad înalt de malignitate.

**Carcinomul Cromofob** reprezintă aproximativ 5% din carcinoamele renale și în general are un prognostic favorabil, cu o rată de supraviețuire la 5 ani de peste 80%. Prezența diferentierii sarcomatoide, în aproximativ 9% din cazuri, alterează semnificativ prognosticul acestor pacienți. Diagnosticul diferențial între carcinomul cromofob și carcinomul renal cu celule clare cu citoplasmă granulară eozinofilă este deseori o problemă pentru anatomopatolog.

**Nefroblastomul** este cea mai frecventă tumoră renală în patologia pediatrică, având în mod tipic trei componente: blastemala, epitelială și stromală. Nefroblastomul trifazic rareori ridică probleme de diagnostic dar în situația prezenței unei singure componente, mai ales în cazul biopsiilor mici, diagnosticul poate fi unul extrem de dificil.

**Tumora Sertoli cu celule mari calcifiante** (Large-cell calcifying Sertoli cell tumor -LCCSCT) este o tumoră rară de cordoane sexuale stromale întâlnită la pacienți tineri, principala problemă de diagnostic diferențial fiind cu Tumora cu celule Leydig.

**Chistadenocarcinomul seros testicular de tip ovarian** este o tumoră ce apare foarte rar în testicul sau paratesticular interesând suprafața testiculară sau epididimul. Principalul diagnostic diferențial este cu mezoteliomul tunicii vaginale.

## **Michael Schenker, MD, PhD**

UMF Craiova

### **Imunoterapia in tumorile uroteliale**

Ultimele 24 de luni au adus progrese deosebite in tratamentul carcinoamelor uroteliale, local avansate sau metastatice, care prezinta progresia bolii in timpul sau dupa chimioterapia pe baza de saruri de platina sau care prezinta evolutie a bolii in primele 12 luni de la incheierea chimioterapiei pe baza de platina administrate in scop neo-adjuvant sau adjuvant.

Astfel, in mai 2016, FDA ofera aprobare accelerata pentru atezolizumab (Tecentriq) pentru aceasta indicatie, pe baza rezultatelor unui studiu clinic de faza IIb ce a inclus 310 pacienti si care a aratat o rata de raspuns obiectiv (ORR) de 14,8% si o durata a raspunsului cuprinsa intre 2,1 si 13,8 luni.

A fost primul imunoterapic aprobat pentru aceasta indicatie, pentru ca, in 2017, nu mai putin de 4 produse diferite sa fie aprobate, in procedura accelerate, de catre FDA pentru aceasta indicatie: nivolumab (Opdivo), in februarie 2017, durvalumab (Imfinzi), avelumab (Bavencio) si pembrolizumab (Keytruda), toate in mai 2017. Este o situatie singular, in care toate cele 5 imunoterapice anti PD1/PDL1 au fost inregistrate succesiv pentru aceeasi indicatie.

In acest moment, sunt in derulare trialuri clinice pentru alte indicatii in carcinoamele uroteliale : prima linie de tratament pentru boala avansata sau terapie adjuvanta, dupa chirurgie radicala, la pacienti cu risc pentru recidiva (ex: WO30070, SAUL, CA209-274 trialuri clinice in care este implicat si centrul nostru, Centrul de Oncologie Sf Nectarie Craiova).

## **Gabriel Diaconu, MD**

Centrul de psihiatrie si psihoterapie Mind Care, București

### **Burn-out-ul medical, teama pacientului și blestemul cancerului**

#### **Medical burn-out, patient fright and the doom of cancer**

It is the uneasy task of the psychiatrist to shine a light in the dark for a patient coping with a diagnosis of cancer. I will say "cancer" as it is understood by common-folk, the only word they memorize in a long line of technical words. Here is a burden on the doctor, the bearer of bad news. More burden is to foretell a future, and there there is danger of either being too much, or too little, of an optimist.

It is worth noting to the patient, while in counselling, that we are also humans. They tend to idealize us, and when disappointed demonize us. And from burden from burn-out a small step is needed. Doctors are courageous individuals. Or so says the legend. So we make the step. I will argue in my talk that this is wrong. Frightfully so.

I will argue that patient fright is modulated by a doctors beliefs, and attitudes, when these are not supported by facts. And I will also discuss the curse of cancer as a psychological archetype. We need to understand it in order to adress the deep connection between healer, and the sick.

Psihiatrul are o sarcină dificilă, cea de-a fi o lumină în întuneric pentru pacientul care se confruntă cu un diagnostic de cancer. Spun ”cancer” așa cum este înțeles termenul de omul de rând, singurul pe care îl memorează într-un lung șir de termeni tehnici. Aici e povara medicului, vestitorul de vești rele. Și mai apăsător e să prezici viitorul, și-aici e aidoma periculos să fii prea mult, sau prea puțin, optimist.

Merită amintit pacientului, când vine spre consiliere, că și noi suntem oameni ca și el. Asta pentru că tinde să ne idealizeze, și când îl dezamăgim ne demonizează. Iar de la povară la oboseală e nevoie de un singur pas. Doctorii sunt curajoși. Sau așa spune povestea. Astfel că facem acel pas. Am să argumentez, în discuția mea, că e greșit. Înfricoșător de greșit. Mai mult, am să argumentez că spaima pacientului e modulată de credințele, atitudinea doctorului, când acestea nu sunt sprijinite de fapte. Și am să discut de asemenea blestemul cancerului ca arhetip. Avem nevoie să îl înțelegem încât să adresăm legătura adâncă ce se creează între vindecător, și bolnav.

## **Adrian Calomfirescu, Psiholog**

Clinica Medlife-București

### **Reabilitarea sexualitatii dupa tratamentul oncologic**

Medicina a avansat in timp imbunatatind tratamentele pentru cancer si rata de supravietuire a pacientilor. Multe tipuri de cancer au evoluat dintr-o boala acuta intr-una cronica, iar cu populatia care imbatraneste, numarul supravietuitorilor este in crestere. Cancerul ca si boala, diagnostic si terapii, toate au un efect engativ asupra calitatii vietii pacientului dar si a partenerului (si a celorlalti membri ai familiei). Impactul acestor elemente variate ale procesului bolii scad nivelul de functionare a pacientului si abilitatea lui de a mentine o intimitate si viata sexuala sanatoasa. Acest declin poate continua ani dupa ultimul tratament oncologic. Din aceasta cauza atitudinea in oncologie se muta la o focalizare asupra tratamentului si supravietuirii catre o grija si imbunatatire a calitatii vietii. Disfunctiile sexuale apar in majoritatea pacientilor oncologici, in special cei diagnosticati cu cancer urologic sau ginecologic. Studiile arata ca cel putin 35-50% dintre supravietuitori de cancer pot dezvolta o disfunctie sexuala in urma tratamentului. Desi prevalenta este ridicata, foarte putini profesionisti, medici si psihologi sunt atenti asupra acestui aspect al vietii pacientului. Atentia asupra supravietuirii este inca principala, iar latura intimitatii si sexualitatii nu este privita ca fiind importanta. Datorita acestui fapt pacientii primesc foarte putina informatie legata de dificultatile sexuale ce survin in urma tratamentului primit. Desi si-ar dori sa fie intrebati, informati si ajutati, deoarece uneori nevoile pacientului nu sunt aceleasi cu nevoile specialistului.

## **Elizabeth Connelly, Nurse Practitioner**

Northwell Health Imbert Cancer Center  
New York, USA

### **Immunotherapy Treatment for Cancer: The American Experience**

In caring for oncology patients and their families, Nurse Practitioners and Registered Nurses have a vital role in recognizing both chemotherapy and immune-related adverse events and guiding management. The traditional use of antineoplastic regimens with chemotherapy, suppress the immune system, increasing the risk of bone marrow suppression including; infections, sepsis, anemia and thrombocytopenia. Chemotherapy also attacks cells that are in active growth and repair. Side effects, including, but not limited to; fatigue, mucositis and diarrhea, are a common management focus.

In contrast, immunotherapy agents activate the immune system, which can lead to cancer response and potential immune related adverse events, due to enhanced T cell responses. The most commonly used immunotherapy agents are antibodies against the checkpoints i.e checkpoint inhibitors directed against CTLA4, PD-1 and PD-L1 respectively. In several solid tumors (i.e. Melanoma and Non-Small Cell Lung Cancers) CTLA4 and PD-1 inhibitors may be used in combination. A plethora of immune related side effects can be associated with these compounds, the most common ones being, skin rashes, diarrhea and hypo or hypothyroidism but any symptom related to development of auto-immune like conditions may occur.

Patient and family education is of paramount importance to understand these drug actions and potential side-effect recognition and management. Cancer care is always best managed by a multidisciplinary approach, and nurses are essential for education, early recognition, management and especially, patient advocacy in achieving the best outcomes.

The goals of this program are:

- 1.To review immunotherapy side-effects, specifically, recognizing oncologic emergencies.
- 2.Discuss pathophysiology of check-point inhibitors.
- 3.Recognition of potential side-effects and the management thereof, to prevent toxicities.
- 4.Discuss the challenges.

## **Oana Otilia Niculita, Drd. As. Med. Lic.**

Institutul Clinic Fundeni, București

### **Rolul asistentei medicale de hemato-oncologie in Romania**

Cancerul este o problemă majoră de sănătate la nivel mondial și o cauză semnificativă a mortalității și a morbidității la toate grupele de vârstă, deși o proporție mai mare este la persoanele în vârstă, în comparație cu celelalte grupe de vârstă, suferă de cancer. În multe țări, prevenirea și tratamentul cancerului este o prioritate națională în domeniul sănătății. Dezvoltarea cunoștințelor științifice și a progreselor tehnologice, împreună cu creșterea cunoștințelor pacienților cu privire la boala și tratamentul acestora, au dus la creșterea așteptărilor publicului în ceea ce privește îngrijirea cancerului.

Funcția asistentei medicale în îngrijirea cancerului este acum foarte solicitantă - și în următorii câțiva ani această presiune ar putea fi amplificată de o lipsă de personal medical.

O asistentă medicală de hemato-oncologie lucrează în momentul de față într-o varietate de roluri noi, pentru care nu care a fost instruită pe bancile școlii, dar acum sunt din ce în ce mai obișnuite, îngrijește și educă pacienții cu cancer.

Asistentele hemato-oncologice lucrează într-o echipă multidisciplinară, într-o varietate de activități, de la secția de spitalizare de zi sau ambulatoriu, până la unitatea de transplant de măduvă osoasă unde se oferă servicii precum îngrijirea pe termen lung a pacienților cu cancer, până la comunitate. Acestea pot lucra cu o varietate de pacienți, de la copii la vârstnici, de la pacienți externi până la îngrijiri paliative și realizând de la screeningul dinaintea administrării chimioterapiei, gestionarea oboselii sau managementul general al simptomelor și îngrijirea de susținere până la educația pacientului, coordonarea îngrijirii sau îngrijirea directă a pacienților.

Asistența medicală trebuie pregătită pentru a promova confortul pacientului, pentru a furniza pacienților și familiilor acestora informațiile referitoare la controlul durerii, informații și asistență cu intervenții comportamentale și fizice, pentru a preveni și a atenua efectele secundare ale terapiei farmacologice și pentru a promova respectarea de către pacient a terapiei recomandate. Asistenta de hemato-oncologica ar trebui să explice raționamentul intervențiilor și să ofere timp pentru întrebările pacientului și familiei. Educația pentru pacienți trebuie să includă numele agenților farmacologici, schemele de dozare, efectele secundare, intervențiile pentru a atenua greața și vărsăturile, cum ar fi antiemeticele și intervențiile pentru atenuarea constipației. Asistența medicală trebuie să monitorizeze eficacitatea și efectele secundare ale intervențiilor terapeutice, ale stării respiratorii și ale funcționării intestinului, precum și asupra funcționării mentale și cognitive. Pacientul și familia trebuie să știe cum să contacteze personalul medical în caz de urgență și ar trebui să aibă libertatea de a face acest lucru.

Asistenții medicali se alătură profesiei pentru un motiv, pot influența semnificativ calitatea îngrijirii oferite și, în cele din urmă, rezultatele pacientului. Ei sunt vindecătorii, ajutoarele, îngrijitorii lumii. Când asistentele aleg să lucreze într-un cadru hemato-oncologic, înțeleg că vor exista provocări și o fac oricum. Ei fac sacrificii pentru pacienții lor în fiecare zi. Într-o perioadă în care ai nevoie cel mai mult de ajutor, este o asistentă medicală care te va ajuta.



# A 2-a ediție a Simpozionului Translațional de Oncologie Personalizată pentru combaterea cancerului

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## Platină



## Aur



## Bronz



## Parteneri



## Argint



## Parteneri media



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