Prime time for immune-checkpoint targeted therapy at ASCO 2015

Aurélien Marabelle\textsuperscript{a,b}, Bertrand Routy\textsuperscript{a,b}, Judith Michels\textsuperscript{a,b}, Guido Kroemer\textsuperscript{c,d,e,f,g}, and Laurence Zitvogel\textsuperscript{a,b}

\textsuperscript{a}Gustave Roussy Cancer Campus, Villejuif, France; \textsuperscript{b}INSERM, U1015, Villejuif, France; \textsuperscript{c}INSERM U848, Villejuif, France; \textsuperscript{d}Metabolomics Platform, Institut Gustave Roussy Villejuif, France; \textsuperscript{e}Equipe 11 labellisée Ligue contre le Cancer, Centre de Recherche des Cordeliers, INSERM U1138, Paris, France; \textsuperscript{f}Pôle de Biologie, Hôpital Étuniens Georges Pompidou, AP-HP, Paris, France; \textsuperscript{g}Université Paris Descartes, Sorbonne Paris Cité, Paris, France

ABSTRACT
Cancer immunotherapy has been one of the dominant topics in oral presentations and abstracts during the 2015 annual meeting of the American Society of Clinical Oncology (ASCO). The renewed interest in immunotherapy is explained by the wide spectrum of activity, the durability of tumor responses and the rapid clinical development of immune-checkpoint targeted monoclonal antibodies. These new drugs are currently revolutionizing the field of oncology. Here we highlight what were to us the most important results announced during the annual meeting of ASCO held in Chicago, IL from May, 29th to June, 2nd 2015. In addition, we searched all the posters/published abstracts pertinent to the field of immunooncology from this year conference. Among more than 400 published abstracts on this topic, we have grouped and briefly summarized the most relevant ones.

Introduction
Cancer immunotherapy has been one of the dominant topics in oral presentations and abstracts during the 2015 annual meeting of the American Society of Clinical Oncology (ASCO). The renewed interest in immunotherapy is explained by the very rapid clinical development of immune-checkpoint targeted monoclonal antibodies (imAbs) such as the anti-CTLA-4 imAb ipilimumab (BMS, FDA approved in 2011) and the anti-PD-1 imAbs nivolumab and pembrolizumab (BMS and Merck MSD respectively, FDA approved in 2014). These new drugs are currently revolutionizing the field of oncology for three reasons. First, imAbs bring a disruptive innovation in cancer therapy where drugs are designed to target immune cells as opposed to cancer cells, with the aim of helping patients to fight their own cancer with their immune system. Second, the same imAbs show a broad spectrum of activity with objective tumor responses (ORR) across many cancer types, despite their many histology and site differences. Third, they provide benefits in overall survival (OS) in a significant proportion of patients whereas most of the progress obtained over the last decade with tumor-targeted therapies provided benefits in progression-free survival (PFS) in very genomically selected subsets of patients. Here we will highlight what were to us the most important imAbs results announced during the annual meeting of ASCO held in Chicago, IL from May, 29th to June, 2nd 2015.

In addition, we searched all the posters/published abstracts pertinent to the field of immuno-oncology and imAbs from this year conference. Among more than 400 published abstracts on these topics, we have grouped and briefly summarized the most relevant in three different categories: (1) Results from ongoing clinical trials using imAbs. (2) Preclinical analysis of novel immune therapies. (3) Determination of new biomarkers for patients treated with imAbs. (Tables 1–3)

Confirmation of efficacy in anti-PD-1 sensitive cancers
During the meeting, results from large clinical trials (# of patients > 100) have been reported in cancer types with previously demonstrated activity of anti-PD-1/PD-L1 imAbs.

Metastatic melanoma
The activity and benefits in OS provided by anti-PD-1 imAbs have been confirmed in patients with Metastatic Melanoma (MM). Dr Adil Daud (University of California, San Francisco, CA) reported in a pooled analysis of 655 patients, the long-term efficacy of pembrolizumab in patients with advanced melanoma enrolled in the KEYNOTE-001 study (NCT01295827). The objective response rate (ORR) was 34% (29% in patients previously treated with ipilimumab, 38% in ipilimumab naïve patients), with a 6% CR rate. The 2 y overall survival was 50% (46% in ipilimumab pre-treated patients, 53% in ipilimumab naïve patients).\textsuperscript{1}

Non-small cell lung cancer
Two randomized phase III trial results were reported during the meeting with the anti-PD-1 nivolumab in second line Non-Small Cell Lung Cancer (NSCLC), meaning after platinum-based doublet chemotherapy failures. Dr David R Spigel (Sarah
| Clinical trial | Number of patients | Conclusions | Abstract # and authors |
|----------------|--------------------|-------------|------------------------|
| Melanoma       |                    |             |                        |
| Vemurafenib+Ipi | 10 MM              | *2 Gr 3 elevation transaminase *5 PR, 2 SD, 3 PD | e20075 (Hassel JC) |
| Phase II Ipi+LPI vs. Ipi alone | In transit stage IIIb-IIIc mel n = 100 | Wiederdink Gr I–2 limb toxicity 4 patients enrolled | e20107 Cavalcanti A |
| Single arm Phase II Ipi 10mg/kg | Stage III-IV MM with preexisting anti-NY-ESO-1 Ab | 22 evaluable pts 23% irPR, 27%irSD, 32% irPD, 18% stopped (irAEs) | e20061 Haag GM |
| Multicenter Turkish study Ipi 3mg/kg x 4 doses | MIPI-TURK Survival rate of 97 turkish MM | 19.2% survival at 30 months (no CR) median OS: 6 months 3 Gr 3 irAE, 4 Gr4 irAE 2 deaths (hepatic toxicity) | e20072 Sevinc A |
| Ipi+radiotherapy vs. Ipi alone | 18 metastatic uveal melanoma | 13/15 SD of liver mets 8/13 secondary failure | e20015 Orloff MM |
| Retrospective study I in MM in a population excluded from clinical trials | Retrospective analysis of MM N = 22 | 29% CR in Ipi+RT versus 8% Ipi alone | e20048 |
| Pembrolizumab 10mg/kg/2 weeks (10/17 previously Ipi treated) | N = 248 MM, South Africa | In 119 pts, median OS = 8.8 months, 3 year survival rate: 12% | e20112 |
| BRAFI+/- IC (sequential) retrospective | 17 MM with brain mets | 12 evaluated: 3 PR, 2 SD, 7 PD (2 mixed, 1 pseudoprogression) BrM response duration: 7+, 6+, 3+ months | e9009 |
| Phase II BRAF-inhibitor followed by Ipi 10mg/kg Q3W '4 to prevent hepatotoxicity in MM | 26 Pts MM BRAF600-mutant : 23 pts : BRAFi prior to ICB and 9 pts : ICB prior to BRAFi | RR with the sequence BRAFi+ICB> RR ICB+BRAFi but survival at 24mo identical (50%) | e20030 Aya F |
| Phase II: P 10mg/kg Q2W in untreated brain metastasis from MM or lung cancer | RR with the sequence BRAFi+ICB> RR ICB+BRAFi but survival at 24mo identical (50%) | 9032. A. Amin |
| Phase 1b/2: T-VEC + P vs. P in MM | 46 Phase II BRAFi-inhibitor followed by Ipi 10mg/kg Q3W '4 to prevent hepatotoxicity in MM | Unlike the combination of both medications, sequentially VEM + Ipi had no evidence of hepatotoxicity and satisfactory response (ORR: 30%) | 9009. H.M. Kluger |
| Retrospective study I in MM in a population excluded from clinical trials | 12 - Interim analysis. PR 3/12, SD 2/12. Anticonvulsant and short course of prednisone were required for couple patients | Incidence of IAE in patients with known autoimmune disorders on I. 50% experienced a flare of their underlying condition during treatment. | TPS9081. A. Ribas |
| Talimogene laherparepvec (T-VEC) enhanced OS in MEL. Combination with I may lead to a synergetic effect in MM | 19 pts MM: T-VEC IL-2< 4 mL 10⁶ PFU/mL week 1, then 10³PFU/mL week 4 then q2weeks + starting at 6th week I 3mg/kg Q3W '4 | -2/3 patients were alive at 18-month -PFS:10.6 -irAE grade: > 3: 32% | 9019: D.B. Johnson |
| Double T cells unloading with Peg-IFN + PD-1 in MM | 12 pts P 2mg/kg Q3W + Peg-IFN SC (1.2 & 63mg/kg) at escalating dose | - No evidence of early toxicity in dose escalation of Peg-IFN + P | e20018. H. M. Zarour |
| MEL brain metastasis with Ipi+ brain radiosurgery (SRS) and/ or whole brain treatment (WBRT) to assess radionecrosis | 34 pts: I + SRS vs. I + WBRT vs. I + SRS + WBRT | - The incidence of radionecrosis was higher in SBS compared to WBRT (41% vs. 0%). One patient required surgery despite prednisone to treat the RN. | e20019: L. Khoja |
| Ipi trial of SCB1, a DNA vaccine targeting DC in melanoma pts | n = 16 resected stage III or IV melanoma i.m. electroproporation | Epitope specific proliferation, γ/IFN Elispot response, PFS 78% and 72% for stage III and IV, OS 100%, little associated toxicity | 9035 Poulam M |
| PROCLAIM national registry, prospective cohort: HD IL-2 followed by Ipi and/or anti-PD-1/ PD-1 inhibitor therapy | n = 240 MM | 1 y survival rate of 100%, 68% and 58%, mOS of 25.1 (n = 20), 18.4 (n = 75) and 14 mo (n = 112) for PD1x, Ipi after HD IL-2 and IL-2 only group. High grade irAE for Ipi (n = 2) and PD1x (n = 2). | e20071 Wong MKK |
| CALM: open-label, multicentre phase II of Coxackievirus A21 oncolytic virus in pts with advanced melanoma | N = 57, i.t., treated or untreated unresectable stage IIIc-IV M1c melanoma, primary endpoint irPFS at 6mos | irPFS at 6mos: 38.6% (21/57), median irPFS of 4.2 mos, irRECIST 28.1% (6/57), irRECIST ≥ 6 mo 19.3% (11/57), median time to response 2.8mos, 1-year survival rate 75.4% (43/57), median OS not reached (follow-up 16.5 mos), no grade 3 or 4 AE | 9030 Andtbacka RH |
| CheckMate 066: randomized, double-blind phase III of Nivo vs. DTIC in treatment- | n = 418 QoL questionnaire at baseline and Q6W: EORTC QL-D-C30 EQ-5D | EORTC QLQ-C30 70.0% with NIVO, 64.9 with DTIC EQ-5D 69.5% with NIVO, 64.9 with DTIC Improvements from baseline for NIVO from week 7 (p = 0.011) through week 49 (p = 0.034), No change for DTIC from baseline, | 9027 Long GV |

(Continued)
| Clinical trial | Number of patients | Conclusions | Abstract # and authors |
|----------------|--------------------|-------------|------------------------|
| KEYNOTE-029: phase II study of plus low-dose ipi or PEG-IFN in pts with MM or RCC | Pembrolizumab plus Ipi: n = 18 | DLT 6/19 of grade 3 (1 colitis, 1 uveitis, 2 ALT/AST elevation, 1 lipase plus pneumonitis, 1 elevation pancreatic enzymes plus hyperthyroidism) | 3009 Atkins MB |
| OPTIM, a randomized phase III trial of talimogene laverparevec vs. GM-CSF in unresected stage IIIB/C and IV melanoma, post-hoc review of resectability criteria | T-VEC an oncolytic immunotherapy derived from herpes simplex virus type-1, n = 50 | 50 Pts: 39 unrectectable, 7 deemed resectable, 1 disputed, 3 unevaluable | e20109 Faries MB |
| Lung cancer | Pembrolizumab in PD-L1+ BRM NSCLC (untreated) | N = 10 | 44% OR in BRM (4/9 PR), systemic RR was 34% | 8035 Goldberg SB |
| Randomized 2:1 Phase II in stage IV non-squamous NSCLC: carboplatin + paclitaxel, bevacizumab +/- Imprime PGG (beta 1,3/1,6 glucan : a yeast PAMP) | in 92 pts at 2:1 | Combo with PGG mediated rapid, durable RR (60% vs. 43%, 12 weeks vs. 18 weeks, 10.3 mo vs. 6.6 mo), regardless of tumor location and burden, maintenance of regression after tt stop Safety fine | 3070 Biotera Inc. Engel-Riedel W, Ann Oncol 2014, 25 (S) |
| Phase IIb/IV : Nivo in refractory NSCLC | N = 226, 74% NSQ, 50% >3 prior tt | 179/226 remain on study at 4 mo, 1.8% Gr3–4 Out of 51 evaluable (week 9), 14% PR, OC Rr, 43%SD | 3013 Bauer TM |
| Randomized Phase IIb : TG4010 Pox-MUC1-IL-2 in combination with chemotherapy | N = 222 stage IV NSCLC | PFS improved in low CD56+CD16+CD69+ (TrPAL), in non-squamous NSCLC, OS following these trends Risk reduction RR: 0.61 in low TrPAL/NSQ Vaccine still significant in PD-L1 negative tumors | 3034 Quoix E Transgene |
| Phase I/II Nivo +/- Ipi in SCLC | 75 pts : Nivo 3mg/kg Q2W vs. Nivo (dose escalation)+ Ipi Q3W ‘4 | ORR was 1.6 superior with combination with acceptable safety profile (Only 1 pneumonitis in each arm) | 7503. S.C. Antonia |
| Renal cell Carcinoma | CheckMate 016 (Nivo+Ipi) in mRCC | Nivo = 3mg /kg + Ipi 1mg/kg Q3W ‘3 vs. Nivo+Ipi3 vs. + Nivo3+13/4 then Nivo | - Nivo3+Ipi3 was too toxic - 41 pts in 2 other arms had similar ORR but 2 fold increase IrAE with Nivo1+Ipi3 | 4516. H.J. Hammers |
| Phase 1 Keynote -029: Combination lower Ipi dose + std Pembrol in mRCC and MM | Pembrol 2mg/kg + Ipi 1mg/kg Q3W followed by Pembrol | -19 pts enrolled in the safety run period: 32% of grade 3 IrAE were observed (54% in Postow et al. Nejm 2015;372:2006–17) | 3009. M. B. Atkins |
| Pancreatic cancer | IMAGE1 Randomized trial in advanced pancreatic cancer Mycobacterium obuense (IMM-101)and gemcitabine | N = 92 N = 28 Gem alone N = 68 Gem + IMM-101 | Increase in median OS from 4.4 (Gem) vs. 7 mo in Gem+IMM-101 P = 0.01, HR : 0.64 Survival rate at 12 months : 11.5 % (Gem) vs. 22.4% (Gem+IMM-101) | 3051 Dalgleish A |
| CAR T mesothelin | T-VEC an oncolytic immunotherapy derived from herpes simplex virus type-1, n = 50 | 50 Pts: 39 unrectectable, 7 deemed resectable, 1 disputed, 3 unevaluable | e20109 Faries MB |
| Phase 1 b i + Gem in advanced pancreatic cancer | 13 pts : Gem 750–1000mg/m² Q1W ‘7 then q Q1W ‘3 + Ipi (3–10mg/kg) on weeks 1,4,7 &10 | -Diarrhea and hepatotoxicity DLT lead to MTD I 3 + Gemcitabine 1000 - Encouraging outcome | e15281. N.A. Mohindra |
| Imprime PGG (beta 1,3,5 weeks 1,4,7 &10 then q Q1W followed by Pembro (dose escalation)+ Ipi Q3W) in 92 pts at 2:1 Combo with PGG mediated rapid, durable RR (60% vs. 43%, 12 weeks vs. 18 weeks, 10.3 mo vs. 6.6 mo), regardless of tumor location and burden, maintenance of regression after tt stop Safety fine | - Nivo3+Ipi3 was too toxic - 41 pts in 2 other arms had similar ORR but 2 fold increase IrAE with Nivo1+Ipi3 | 7503. S.C. Antonia |
| Lung cancer | Pembrolizumab in PD-L1+ BRM NSCLC (untreated) | N = 10 | 44% OR in BRM (4/9 PR), systemic RR was 34% | 8035 Goldberg SB |
| Randomized 2:1 Phase II in stage IV non-squamous NSCLC: carboplatin + paclitaxel, bevacizumab +/- Imprime PGG (beta 1,3,5 weeks 1,4,7 &10 then q Q1W followed by Pembro (dose escalation)+ Ipi Q3W) in 92 pts at 2:1 Combo with PGG mediated rapid, durable RR (60% vs. 43%, 12 weeks vs. 18 weeks, 10.3 mo vs. 6.6 mo), regardless of tumor location and burden, maintenance of regression after tt stop Safety fine | - Nivo3+Ipi3 was too toxic - 41 pts in 2 other arms had similar ORR but 2 fold increase IrAE with Nivo1+Ipi3 | 7503. S.C. Antonia |

(Continued)
**Table 1. (Continued)**

| Clinical trial | Number of patients | Conclusions | Abstract # and authors |
|----------------|--------------------|-------------|------------------------|
| **Prostate** | | | |
| PROSTVAC vaccine in advanced HRPC (hormonoresistant prostate cancers): 2 Phase II and 1 Phase I with Ipiilimumab | | | |
| Phase I anti-4-1BB and rituximab in CD20+ NHL | N = 35 pts, 22 FL, 5 mantle cell L, 3 diffuse LBCHL | Increased soluble 4-1 BB, Memory T cells, activated NK, PK PF-05082566 half life: 10 d ORR refractory pts: 29% with 2 CR (FL) | 3004 Kohrt HE |
| **Glioblastoma** | | | |
| Randomized trial Nivo vs. Nivo+i-pi at first recurrence of GBM: CHECKMATE-143 | Report on 20 pts with >6 mo follow up | 80% Gr3–4 tox in combo leading to 50% discontinuation OS at 6 mo: 70% with Nico and 80% with combo | 3010 Sampson JH |
| Phase I trial: HER2- CMVpp65 specific CART T cells in GBM | 15 pts seropositive for CMV | 5/15 with objectives responses: 1 PR, 62% reduction, >8 mo, 4 SD 4–24 mo | 3008 Ahmed N |
| **Gastro-esophageal cancer** | | | |
| Gene therapy Adp53 (endoscopic it route) and chemotherapy (CT) in esophageal cancer | 60 patients randomized in 2 arms CT+ vs. CT | Curative effect of the combo with 80%+/-16% vs. 68+/-17% shrinking at 12 weeks | e15097 Cui H |
| Cell immunotherapy (cytokine-induced autologous killer cells) and chemotherapy in gastric cancer | 83 eligible but 58 analyzed: 30 in CIK +CT vs. 28 in CT | Median PFS significantly longer in CIK+CT (p=0.021) 2 year PFS in stage III GC or N+ GC were 62% vs. 26 and 50% vs. 27% respectively. | e15106 Cui J |
| **Cervical cancer** | | | |
| Phase I/II in second-line therapy of women with cervical cancer treated with 1 10mg/kg Q3W ‘14 Advanced cancers: TLRS agonist Entolimod Phase II trial | 26 pts all comers advanced cancers | Encouraging signal of immunotherapy activity with a PFS of 2.5 months. | 3061. S. Lheureux |
| Maintenance immunotherapy with IL-2 and retinoic acid in advanced cancer | 500 pts, 4400 courses of chemo, 112 months follow up | 3 SD for >12 weeks neutralizing Ab the second week for all pts SNP TLRS dictate transaminisits | 3063 Bakhrhibah H, E14055 Recchia F |
| Phase I trial using CEA-targeted IL-2 variant with no CD25 binding property | 11 advanced CEA+ cancers | ^8Zr-CEA-IL-2v at doses of 30 mg traffic to tumors NK and T cell accumulation in blood and tumors | 3016 Schellens Roche Glycart |
| Phase I RG155 anti-CSF1R Ab in advanced solid cancers and pigmented villonodular synovitis (PVNS) | N = 44 (29 PVNS) | PR and SD by PET-CT in 5/44 and 6/40 pts, 24/28 PVNS had OR, 18% Gr3–4 tox (fatigue, pyrexia), reduction of tumor TAM, CSFR1+ cells in tumors, CD14+CD16+ circulating monocytes | 3005 Gomez-Roca CA, Roche Pharma |

**AE: adverse events, BrM: Brain metastasis, CAR: Chimeric antigen receptor, CMV: Cytomegalovirus, CR: Complete response, DTIC: Dacarbazine, FL: Follicular lymphoma, GBM: Glioblastoma, Gem: Gemcitabine, Gr: grade, GT: gene therapy, HR: Hazard ratio, ILP: isolated limb perfusion, i.m.: intramuscular, Ir: Immune related, Ipi: Ipiilimumab, i.t.: intratumoral, Mel: Melanoma, MM: Metastatic melanoma, mo:month, mRCC: metastatic renal cell carcinoma, Nivo:Nivolumab, NHL: non-Hodgkin lymphoma, NK: Natural killer, NSCLC: Non-small cell lung cancer, ORR: Objective response rate, OS: Overall survival, PD: Progressive Disease, PEG-IFN, pegylated interferon alfa-2b, Pembro: Pembrolizumab, PFS: Progression free survival, PK: Pharmacokinetics, PR: Partial Response QoL: Quality of life, RCC: Renal cell carcinoma, RR: Response rate, RT: Radiotherapy, SCLC: Small cell lung cancer, SD: Stable Disease, TLR: Toll-like receptor, T-VEC: Talimogene laherparepvec |

Cannon Research Institute, Nashville, TN) reported the results of the CheckMate 017 trial (NCT01642004) which randomized nivolumab vs. docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (SQ-NSCLC). The ORR was 20% (27/135 patients) for nivolumab vs. 9% (12/137 patients) for docetaxel. The 1 y OS was 42% in the nivolumab arm vs. 24% in the docetaxel arm (Hazard Ratio = 0.59).2,3

Dr Luis Paz-Ares (Hospital Universitario Virgen Del Rocio, Sevilla, Spain) reported the results of the CheckMate 057 Phase III trial (NCT01673867) which randomized nivolumab (292 patients) vs. docetaxel (290 patients) in advanced non-squamous cell non-small cell lung cancer (non-SQ-NSCLC). The ORR was 19.2% for nivolumab vs. 12.4% for docetaxel. The 1 y OS was 50.5% in the nivolumab arm vs. 39% in the docetaxel arm (HR = 0.73).4

Interestingly, in the randomized nivolumab vs. docetaxel CheckMate 017 Phase III trial in SQ-NSCLC, the OS hazard ratios (HR) favored nivolumab regardless of PD-L1 expression and tumor PD-L1 status was neither prognostic nor predictive for efficacy endpoints compared to docetaxel.2 However, in
non-SQ-NSCLC, the OS HR favored nivolumab only in patients with PD-L1 expression $\geq 1\%$ (Brahmer et al., 2015).

Dr Leora Horn also presented an update of the results of Roche/Genentech anti-PD-L1 atezolizumab (MPDL3280A) in NSCLC (NCT01375842). Out of the 88 patients evaluable for efficacy, the ORR of atezolizumab was 23% and the median duration of response was 17 months. Of interest, patients were concomitantly screened for PD-L1 expression with their internal IHC assay using the SP142 clone. As opposed to Merck (MSD) and BMS, Roche/Genentech scores not only tumor cells for PD-L1 expression but also the immune infiltrative cells. They reported that a subpopulation representing 13.6% (12/88) of patients with NSCLC have high expression of PD-L1 on immune infiltrative cells but no expression of PD-L1 on tumor cells. These patients had an ORR of 50%. The 1 y OS of the whole population was 63%.5

Another report of atezolizumab has been presented by Dr Spigel in PD-L1+ selected NSCLC patients (NCT01846416, phase II FIR trial). The ORR (with mRECIST) was 29% in 1st line (31 patients), 17% in 2nd line NSCLC without brain metastases (92 patients) and and 23% in 2nd line NSCLC with brain metastases (13 patients). The one year OS was 73%, 48% and 35% in 1st line, 2nd line with- and 23% in 2nd line NSCLC with brain metastases (13 patients).

### Head and neck squamous cell carcinoma

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### Ovarian cancer

Some tumor responses in Ovarian Cancer (OC) patients were seen in early anti-PD-1 phase I trials with a 6% ORR (1/17...
### Table 3. Prognostic parameters or predictors of response to imAbs presented at ASCO 2015.

| Clinical trial design | Predictor(s) | Conclusions | Abstract # and authors |
|-----------------------|--------------|-------------|-------------------------|
| Immunohistochemistry  |              |             |                         |
| PD1 and PD-L1 prognostic values in ccRCC | IHC study in 92 metastatic ccRCC after sunitinib | PD-L1 expression in 71% cases; PD-L1 high associated with shorter PFS and double positive worse clinical outcome | E14002 Brunot A |
| NSCLC                 | PDL1 IHC     | PDL1 expression higher in females, non-squamous, smokers, high PDL1 expression associated with lower risk of recurrence and better OS | e7551 Owonikoko TK |
| 2 series of NSCLC TMA Yale : n = 204 TMA Greece : n = 350 | CD3, CD8, PD-L1, IDO, B7-H4 multiplexed IHC | PD-L1, IDO, B7-H4 differentially expressed Limited prognostic value PD-L1 and IDO1 correlated with increased TILs | e3067 |
| PDL-1 expression and TILs density in Chinese gastric cancer and OS | 398 stage I-IV operable GC, PDL-1 and TIL in IHC PDL-1+ if >5% tumor cells | PD-L1 + in 14% PD-L1 positivity associated with TIL density (p = 0.002), high TIL density correlated with OS (HR : 0.10) | 4042 Geng R |
| CXCR4 expression on tumors and CTC | Randomized Phase II : CXCR4 antagonist (LY2510924) and chemotherapy in SCLC | High levels of CTCs and/or CXCR4 expression on CTC and/or tumor tissues at baseline predict benefit of adding LY to standard chemotherapy | 7567 Salgia R |
| Quantity and quality of TILs predicting pCR/DFS/OS | N = 100 TNBC pre- and post-neoadjuvant chemotherapy (NAC) | TIL in pre-NAC (but not post-NAC) predict pCR and survival CD4/CD3 ratio lower in pre-NAC with pCR and lower in post-NAC with pCR CD8/CD4 ratio higher in pre-NAC with pCR and lower in post- NAC with pCR | 3035 Altamirano C |
| PD-L1 expression in immune infiltrates (IC) vs. tumor cells (TC) in NSCLC | 498 and 706 NSCLC from MPDL3280A and non-trial cohort using SP142 IHC assay | High PD-L1 expression on TC or IC associated with ORR, PFS and OS to anti-PDL1 Ab in NSCLC but different immunological context that may impact clinical outcome further | 3015 and others Gettinger S, Spigel, Spiro, Horn |
| Stromal (S) versus intratumoral infiltrating CD8+ lymphocytes in resected NSCLC | CD8, CD4 and FoxP3 IHC of TMA 507 NSCLC primary tumor | Increased DSS for CD8+ infiltrate (HR 0.45, 95% CI 0.30–0.69; p = 0.04) in N+ pts. Improved OS for PD-L1 (HR 0.71, 95% CI 0.53–1.01; p = 0.06) in N0. | 11051 Ameratunga M |
| TIL classification and survival in primary melanoma | TIL on H&E in 1241 primary cutaneous melanoma (absent, non-brisk and brisk); CD3, CD45 IHC in 200 tumors; 365 SNV in 607 pts, | 24 (28 MSI, 13 D), absent (n = 388 , 31%), non-brisk (n = 330 , 27%), brisk (n = 523 , 42%) TILs. RFS and OS (HR 0.54, 95% CI 0.0017) for brisk TIL. CD3, CD45 not prognostic. Two germline variants of BCL10 associated with TIL grade (rs962409, OR \( < 0.001 \); HR 0.97 ; p = 0.0007) | e20042 Ann Weiss S |
| CXCR4 expression on tumor and CTCs as a predictive response marker for CXCR4 antagonist | IHC H-score ROC curves and their AUCs to determine optimal cutoff n = 90 | High levels of CTCs (HR 0.403, 95% CI 0.151, 1.076) and/or CXCR4 expression on CTCs (HR 0.476, 95% CI 0.147, 1.548) and/or tumor tissue (HR 0.787, 95% CI 0.211, 2.933) at baseline are predictive for the response to the addition of LY to f | 7567 Salgia R |
| Zonal difference in PD-1 expression in center of tumor vs. periphery in MSS and MSI CRC | CD8, PD-1 expression in tumor center and periphery n = 42 (28 MSi, 13 MSS) | MSI: CD8 count in tumor center and periphery correlate with earlier tumor size and stage, PD-1 positivity in the center 61% MSS: no PD-1 positivity in the center | 3574 O'Kane G |
| IHC comparison between 75 breast cancer brain metastasis to 20 primary brain tumor | - Absence of TILs - PD-L1 | - TILs were absent/low in 97% of breast met and significantly reduced compared to primary tumor - PD-L1 expression was negative in both tumors | 2059. N.O. Williams |
| 58 LN s surgical resection from Mel patients to characterize microenvironmental environment Multicenter trial of 78 patients with MM on I | IHC PD-1 in regional LN | - Unlike VEGFA, PD-1 was mostly expressed in pN0 and associated to 5 y survival | 9026. V.L. Vazquez |
| - PD-L1 gene expression ineffective to predictable I effect | Extraction from mRNA from formalin-fixed followed by RT-PCR once again showed no statistical difference in PD-L1 expression and response to I | - | 9044. C. Brueggemann |

(Continued)
Table 3. (Continued)

| Clinical trial design | Predictor(s) | Conclusions | Abstract # and authors |
|-----------------------|--------------|-------------|------------------------|
| Preclinical analysis looking at the PD-L1 expression in EBV+ associated nasopharyngeal carcinoma | -IHE evaluation of PD-L1 | - Using a IHE PDL-1 cut-off of > 1%, 70% of EBV positive NPC expressed in a cohort of 119 patients | 6070. K. Mahaprom |
| Stromal (S) vs. tumoral PD-L1 expression with CD8+ cell count in gastro-esophageal cancer | n = 34 PD-L1 (SH1 clone) status (5% cutoff) at the tumor cell and TIL/TAMs and stromal CD8+ density (50% cutoff) in gastric and gastroesophageal junction AC | 12% tumors PD-L1+, 45% TIL PD-L1+, high stromal CD8+ density (>500 cells/m2) is associated with PD-L1 positivity (89%, p = 0.004) and worse prognosis (PS, HR 3.91 95%CI 1.32–11.59 p = 0.01; OS, HR 3.46 95%CI 1.09–10.06 p = 0.03) | 4031 Kelly RJ |
| ELISA Detectable soluble PD-L1 in LG or HG glioma patients or brain mets of solid cancers | EDTA plasma from 16 LG and 68 HG glioma (sandwich ELISA using Millipore ABF133 and clone SH1) | Detectable in 37% LGG and 52% HGG but ns for concentrations Detectable in 10–50% of brain mets in breast, lung cancers, not in RCC, not in tumors with high PD-L1 membrane expression | e13039 and e13026 Berghoff AS |
| Plasma soluble PD-L1 in glioma pts and in brain metastatic (BM) pts from solid tumors (melanoma, lung, breast, RCC) | EDTA plasma, sandwich ELISA, rabbit polyclonal anti-PD-L1/CD274 ab on a PD-L1 monoclonal ab (clone SH1), limit of detection PD-L1 50pg/ml. | 37.5% (6/16) low-grade and 52.9% (36/68) high-grade glioma, median (1232 vs. 411 pg/mL; p > 0.05), young age (50 vs. 61 ys; p = 0.006). Melanoma (n = 43), (2/4, 50%), breast (1/4, 25%), lung (3/29, 10.3%), RCC (0/6, 0%). | e13039 and e13026 Berghoff AS |
| Flow cytometry Predicting response to Pembrolizumab in MM | Bim+PD1+ CD11a+b+CD8+ circulating T cells | Higher frequencies at Baseline associated with clinical benefit at 4 cycles, dynamic decrease in serial PB samples in OR | 9013 Dronca S |
| IFN-α2b dose reduction in melanoma: a pilot study | Jak-STAT pathway activation: pSTAT1 via flow cytometry, activation of ISGs via PCR analyses | Induction of pSTAT1 and ISGs are similar for IFN-α2b dose reduction | e20035 Levine KM |
| MHC-II expression to predict response to anti-PD1 therapy | MHC-I/II mRNA (Gene Set Analysis), flow cytometry, IHC (MHC-I, MHC-II, SOX10, CD4, CD8) basal and stimulated (IFN) 60 melanoma cell lines 26 pts’ tumor samples | MCH-I (n = 16) is not associated with response. MCH-II (n = 10) is associated with response and CD4/CD8 infiltrate | 9041 Balko JM |
| 29 MM patients on Pembrolizumab 2mg/kg on EAP | - BIM (BCL 2 interacting mediator of cell death) | - Flow cytometry evaluation of BIM on CD11a+,PD1+,CD8+. Responders after 4 P cycles could be discriminated based on a higher baseline BIM | 9013. R.S. Dronca |
| Sequencing Immune gene signatures and efficacy of MK-368 (anti-PD-1 Ab) in PDL1+ gastric cancers | 33 RNA expression profiling of advanced gastric cancers (Phase I KEYNOTE 012) Integrated analysis of gene expression profiling in 2 large data sets from MD Anderson (PROSPECT, BATTLE-1) and TCGA | IFNg, TCR signaling, expanded immune and denovo signatures all predicted ORR and PFS to anti-PD1 Ab EMT phenotype (mir-200/ZEB1) coexist with PD-L1, PD-L2, PD1, Tim3, BTLA, CTLA4 gene expression, and FoxP3 Treg infiltration In 36% cases, high TIL infiltrates: Expression of CDA8 positively correlated with PDL1, IDO1, FOXP3, TIM3, LAG3 In 33% T cell exclusion associated with activation of b catenin, PPAR, FGFR pathways Mutational burden does not vary between these subsets | 3026 Shankaran V 3030 Lou Y 4511 Sweis RF |
| Molecular drivers and TILs in urothelial bladder cancer | 267 samples: RNA sequencing and exome somatic mutation data | Mutational burden does not vary between these subsets T-cell exclusion by tumor-intrinsc β-catenin signaling, via failed production of CCL4, with failed recruitment of Batf3-lineage DC, resistance to anti-CTLA4/anti-PD-L1 mAb in mice | 9014 Spranger S |
| Intrinsic β-catenin signaling in melanoma | Exome sequencing and gene expression profiling (TCGA), genetically engineered mouse melanoma models (BrafV600E/PTEN−/− active β-catenin) | Exome sequencing and gene expression profiling from circulating exosomes offers the ability to monitor changes in immune pathway genes | 22159 Hurley J |
| Profiling exosomal mRNAs in IPI treated pts for malignant melanoma | Exosome RNA profile, RNA extraction using exorNeasy columns, from plasma baseline, 2 and 4 weeks, and 4 mos Sb6 mRNAs associated with inflammation and 21 mRNA controls by RT-qPCR using the OpenArray technology | n = 450 genes detected, differential expression in responding and non-responding pts, current candidate genes of interest include BMP2, PLCG1 and PDGFB, RNA expression profiling from circulating exosomes offers the ability to monitor changes in immune pathway genes | (Continued) |
Table 3. (Continued)

| Clinical trial design | Predictor(s) | Conclusions | Abstract # and authors |
|-----------------------|--------------|-------------|------------------------|
| Expression of immune related genes in metastatic mesothelioma to address immune escape mechanism | Immune profile for potential patient that would benefit from ICB | Out of 75 mesotheliomas, 2 clusters were described (High/Low) based on their immune cell related genetic signature. | 7566. A. Khattri |
| 41 PBMCs pre/post were obtained from different MM trials | TCR diversity post Pembro | Unlike Anti-CTLA4, TSC sequencing revealed a greater diversity post-P, which correlated with patients’ outcome. | 3027. J.M. Zaretsky |
| Functional | |
| Ipi treatment in 10 pts with MM to evaluate effect on NK cells | Off target effect on NK from baseline and after 2nd and 4th dose | -2 folds upregulation of IL-2Rα chain and improvement of in vitro cytotoxic NK activity in responder patients | 9065. I.E.D.P Da Silva |
| T cell responses to anti-GD2 CH14.18 antibody in NB children | T cell and Ab responses to GD2 mimotopes and TAA antigens | Robust T cell responses to distinct TAA and GD2 mimotopes (not found in healthy volunteers) in 17 NB long term responders. No Ab responses. | 3029 Kayser S |
| Blood biomarker | |
| Early changes in LDH a marker of response to PD-1, PD-L1 inhibitors | Retrospective analysis of MM pts’ fluctuation in LDH from baseline to cycle 2 n = 65 | Higher LDH at cycle 2 associated with non-respose (64 vs. 36%) Similarly for patients with high baseline LDH level. (93 vs. 7%) | e20045 Shreders A |
| Retrospective observational study of 29 patients with MM treated with anti-PD-1 | -Eosinophil count > 100/mm³ at 3 weeks | Eosinophil counts incremental of >100/mm³ and >400/mm³ at 3 weeks and 12 weeks respectively after PD-1 injection correlated with a superior clinical outcome | 9069. L. Gaba |
| 720 MM treated with Ipi 3mg/kg in an EAP | - neutro >7500 - neutro/lympho | - Non-responders could be predicted by an elevated baseline neutrophil count and neutro/lympho | 9034. P.F. Ferrucci |
| MM on PD-1/PDL-1 blockage therapy NCT01295827 | -Normal baseline LDH | According to these 2 trials of 110 and 54 pts respectively, normal baseline LDH is the most important clinical predictive marker of good response | 9031 K.K. Tsai + e20029 D.W.Kim |
| Pharmacokinetic | |
| KEYNOTE-001and-002 pharmacokinetic study to determine the incidence of anti-drug antibody | - Absence of anti-drug antibody | - Prembro resistance is not linked to formation of autoimmune antibody based in the analysis of 268 patients where less <1% developed antidrug antibody | 3058. T.C. Gangadhar |

Abbreviations: Refer to Table 1 with the addition of: ccRCC: clear cell Renal cell carcinoma, CRC: colorectal cancer CTC: Circulating tumor cells, EAP: extended access program, EBV: Epstein-Barr virus, EMT: Epithelial-mesenchymal transition, IHC: immunohistochemistry, LDH = Lactate dehydrogenase, Lympho: Lymphocyte, MSI: microsatellite unstable, MSS: microsatellite stable, Neutro: Neutrophils, PBMC: Peripheral blood mononuclear cell, RFS: relapse free survival, TCR: T cell receptor.

patients) reported (Brahmer et al., 2012). Additional data have been presented this year. Dr Disis (University of Washington School of Medicine, Seattle, WA) reported the results of the anti-PD-L1 imAb avelumab (MSB0010718C/ PF-06834635) currently co-developed by Merck KGaA (EMD Serono) and Pfizer in patients with OC. Of note this anti-PD-L1 is a fully human, non-modified, IgG1 imAb with abilities to perform antibody derived cell cytotoxicity/phagocytosis (ADCC/ADCP) via FcγR positive cells (NK cells, myeloid cells,…). Patients with a median of four prior lines of therapy were treated with avelumab 10mg/kg Q2W (NCT01772004). Out of 75 patients without PD-L1 screening, avelumab showed a 10.7% ORR (8/75 patients) and a stable disease (SD) in 44% patients (33/75).

Dr Andrea Varga (Gustave Roussy, Villejuif, France) reported the results of the anti-PD-1 pembrolizumab (MK3475, Merck, MSD) in patients with OC (NCT02054806). Patients were selected for PD-L1 expression using an immuno-histo-chemistry (IHC) assay based on 1% threshold positivity with the anti-PD-L1 22C3 clone. In this cohort and with this assay/threshold, 51% of patients (49/96) were PD-L1+. In these PD-L1+ patients, an ORR of 11.5% (3/26) has been reported and a stable disease in 23.1% (6/26) of patients.

Identification of new anti-PD-1 sensitive cancers

During this ASCO, four additional histologies have been added to the growing list of cancers with demonstrated sensitivity to anti-PD-1/PD-L1 therapy: Small Cell Lung Cancer (SCLC), Hepatocarcinoma (HCC), Colo-Rectal Cancers (CRC) with Micro-Satellite Instability (MSI), and Esophageal Cancers (ESCC) (Fig. 1).

Small cell lung cancer

Dr Patrick Ott (Dana-Farber Cancer Institute, Boston, MA) presented the results of pembrolizumab therapy in second line SCLC patients (NCT02054806). Patients were screened and selected for PD-L1 expression. Out of the 147 patients with Small Cell Lung Cancer (SCLC) screened, 42 (28.6%) had PD-L1+ tumors. Only 20 patients were subsequently eligible for the
trial. The ORR was 35% (7/20) and stable disease of 5% (1/20).10

**Hepatocarcinoma**

Intra-tumoral PD-L1 expression was known to have a negative impact on survival of patients with HCC (Gao et al., 2009; Shi et al., 2011). This data supported the development of an anti-PD-1 based therapy in Hepatocarcinoma (HCC). Dr Anthony B. El-Khoueiry (University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA) reported the results of the CA209–040 trial testing nivolumab in patients with histologically confirmed advanced HCC with Child-Pugh (CP) score ≤ B7 and progressive disease (PD) on, intolerant of, or refusing sorafenib in patients with either no active hepatitis virus infection or virus-infected HCC patients. The ORR was 19% (8/42 patients) and the DCR was 67%. The 1 y OS (out of 47 patients) was 62%. Overall, in this small cohort of patients, there was no efficacy or safety difference between uninfected and HCV/HBV infected patients.11

**Esophageal cancer**

Dr Toshihiko Doi (National Cancer Center Hospital East, Chiba, Japan) reported the results of the EC cohort of the KEYNOTE-028 (NCT02054806) trial. This cohort included squamous cell carcinoma (SCC) or adenocarcinoma of the esophagus or gastro-esophageal junction. Patients were selected for PD-L1 expression. With a 1% cancer cells PD-L1 positivity threshold (22C3 clone), 44.6% (37/83) of Esophageal Cancer (EC) were PD-L1 positive. The ORR was 30.4% (7/23) and the DCR was 43.4% (10/23). The median duration of response was ~10 months.12

**Mismatch repair deficiency**

Recent data has suggested that the level of somatic mutations could be correlated to the immunogenicity of tumors and chances of response to single imAbs.13-15 This hypothesis is supported by the excellent results of anti-PD-1 therapy in cancers with Mismatch repair deficiency (MMR) defects. Dr Dung Le (The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) reported the results of a phase II trial of pembrolizumab in colorectal cancer patients (CRC) with either MMR-proficient (n = 25) or MMR-deficient (n = 25) cancers, but also in non-CRC with MMR-defects (n = 21) (NCT01876511). The MMR-deficient non-CRC cohort was made of four cholangiocarcinoma, two endometrial cancers, two small bowel cancers, one prostate and one gastric cancer. The ORR in MMR-deficient cancers was 62% and 60% in CRC and non-CRC respectively, whereas it was 0% in MMR-proficient CRC.16
tumor as compared with 73 MMR-proficient tumors. The high somatic mutation loads were associated with prolonged progression-free survival.17

How to overcome immune checkpoint blockade resistance

Combination with chemotherapy

Response rates obtained with atezolizumab (MPDL3280A) in 2nd line NSCLC are around 20%, whereas first line platinum-based doublet chemotherapy usually gives ORR around 30%. Dr Stephen Liu (Georgetown Univ Hosp, Washington, DC) reported the results of the Phase Ib study evaluating atezolizumab combined with 4–6 cycles carboplatin + either paclitaxel (Arm C), pemetrexed (Arm D) or weekly nab-paclitaxel (Arm E) in patients with first line locally advanced or metastatic NSCLC (NCT01633970). In this cohort of patients, 81% had non-squamous and 19% had squamous NSCLC. Thirty (30) patients were evaluable for efficacy (Arm C, 5; Arm D, 12; Arm E, 13). The ORR was 67% across all arms: 60% in Arm C (3 PRs), 75% in Arm D (9 PRs) and 62% in Arm E (6 PRs and 2 CRs). Tumor responses were seen in each arm independently of PD-L1 expression.18

The safety and efficacy of combining an anti-PD-1/PD-L1 imAb with chemotherapy in NSCLC has also been reported by Dr Vassiliki Papadimitrakopoulou (University of Texas MD Anderson Cancer Center, Houston, TX). The KEYNOTE-021 trial evaluated the safety, tolerability and efficacy of pembrolizumab in combination with four cycles of platinum-doublet chemotherapy in NSCLC with Wild-type EGFR and negative ALK translocation status and any PD-L1 status (NCT01740297). Cohort A (n = 25) was treated with pembrolizumab, carboplatin and paclitaxel. Cohort C (n = 24) was treated with pembrolizumab, carboplatin and pemetrexed. Cohort A was composed of 52% (13/25) adenocarcinoma and 36% (9/25) squamous cell carcinoma, and 92% (23/25) current/former smokers. Cohort C was composed of 79% adenocarcinoma (19/24) but no squamous cell carcinoma, and 83% (20/24) current/former smokers. The ORR was 28% and DCR 84% in cohort A. The ORR was 58% and the DCR was 100% in cohort C.19

Although these two reports contained a limited number of patients they both suggest that combination with pemetrexed might be more synergistic with an anti-PD-1/PD-L1 imAb than with (nab) paclitaxel. However, we need to wait for data with more patients and longer survival follow-up to draw any conclusion.

Anti-PD-1 + anti-CTLA-4 combination therapy

Dr Amita Patnaik (START, San Antonio, TX) presented the results of the pembrolizumab + ipilimumab combination in patients with NSCLC. Patients with stage IIIIB/IV NSCLC that recurred after ≤ two prior regimens received pembrolizumab + ipilimumab every 3 weeks for 4 cycles followed by maintenance pembrolizumab (NCT02039674). The population was composed of 56% adenocarcinoma and 22% squamous cell carcinoma (22% NOS). The ORR was 39% (7/18) and the DCR 83% (15/18 patients). No data were presented with further follow up (to see if additional SD transform into PR), notably no survival data was presented.20

Dr Scott Antonia ( Moffitt Cancer Center, Tampa, FL) reported the results of the nivolumab + ipilimumab combination trial in SCLC patients (Checkmate 032, NCT1928394). In the nivolumab alone arm (40 patients) the ORR was 18% and the DCR was 38%. In the nivolumab+ipilimumab arm (46 patients) the ORR was 17% and the DCR of 54%. Of note, out of the 17 patients with SD, 7 had subsequently a confirmed PR resulting in an updated ORR of 32.6% in the nivolumab + ipilimumab arm (no additional responses occurred in the nivolumab alone arm).21

In-situ immunization

In situ immunization consists in injecting immunostimulatory products into a tumor site in order to prime the antitumor immune response. Oncolytic viruses are versatile biotherapies with multiple antitumor effects into a single product: tumor cell cytotoxicity, immune adjuvant effect thanks to the viral pathogen associated molecular patterns and pro-inflammatory cytokines encoded by transgenes. T-VEC is an HSV derived oncolytic virus genetically modified to express GM-CSF. Dr Igor Puzanov (Vanderbilt University Medical Center, Nashville, TN) reported an update on the IV ipilimumab + IT T-VEC phase 1b/2 trial in stage IIIB-IV melanoma (NCT01740297). Out of 18 patients treated with more than 17 months of follow-up, the ORR was 56% (33% of CR) with 44% having responses during more than 6 months. On a per lesion level, 68.5% (24/35) injected index lesions and 50% (8/16) un.injected index lesions regressed more than 50%.22

Another in situ strategy has been followed by the team of Dr Randy Christopher Bowen (University of Utah, Salt Lake City, UT) with intra-tumoral (IT) interleukin-2 and IT ipilimumab in patients with III/IV unresectable melanoma with at least one injectable lesion (NCT01672450). Twelve patients were treated, 10 were evaluable for response by irRC. The ORR was 40% although one PD was later found to be a CR by resection. The two non-evaluable patients had regression of multiple skin lesions. A response in at least one non-injected lesion (abscopal effect) was seen in 9/12 patients (75%).23

Conclusion

Besides these major announcements, smaller results with significant impact on clinical practice have been presented. For instance, experiencing a severe irAE from anti-CTLA-4 might not preclude a patient with melanoma from subsequently receiving an anti-PD-1.24 On the other hand, treating a melanoma patients with anti-CTLA4 after anti-PD-1 failure still have antitumor activity and do not provide additional protection.25 Against common dogma, anti-PD-1 therapy might be also active in metastatic uveal melanoma. Out of small cohort of seven patients treated with anti-PD-1, 1 presented a CR, 1 a PR and 1 a SD.26 Desmoplastic melanoma, another rare subtype of melanoma comprising approximately 1% of cases and with higher mutational load than other sub-types of melanoma presented an ORR of 70% with PD-1/PD-L1 imAbs in a retrospective analysis of over 1,000 melanoma patients.27 Altogether,
this additional set of data reinforces the validity of using imAb to treat multiple types of advanced cancers. Although some patients can respond to these new immunotherapies, a significant proportion of them do not respond and new combination therapies have to be found to address such primary refractoriness. Also, responding patients can subsequently relapse and it is not clear what is at stake biologically to explain these secondary immune resistances. These first immune targeted therapies have demonstrated that the most immunogenic cancers can be treated with a single immune checkpoint blockade and that combination of imAbs can overcome monotherapy resistance. Now the question is not to know if this immunotherapy phenomenon is limited to a subset of highly mutated cancers but rather to identify which additional immune checkpoints are critical for the tolerance of primary resistant or less mutated cancers. And these yet to be discovered immune checkpoints might not only be on T-cells but also on other subsets of the adaptive and innate immune cells.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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