Highlights in genitourinary cancers

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From May 29th till June 2nd, Chicago was host for the 2015 ASCO annual meeting. The theme for this year's congress was 'Illumination and Innovation: Transforming Data into Learning'. With over 30,000 registered attendees from over 120 countries worldwide and more than 6,000 submitted abstracts, this year's meeting was a great success. This report will highlight 12 key studies concerning genitourinary cancers presented during the meeting.

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Efficacy of androgen deprivation therapy (ADT) + docetaxel (D) for men with biochemical relapse after prostatectomy

The optimal treatment for men with castration-sensitive prostate cancer (CSPC) who biochemically recur after radical prostatectomy is not known. As it has been reported that men with metastatic (m) CSPC live longer if they receive D in addition to ADT, this phase III trial tested the efficacy of ADT + D compared to ADT alone in a non-metastatic setting. A total of 413 patients who suffered from biochemical relapse after radical prostatectomy were eligible (PSA ≥ 1 ng/mL and testosterone ≥100 ng/dL) and were randomized 1:1 to receive leuprolide 22.5 mg q3m for 18 months, bicalutamide 50 mg for 30 days, with D at 75 mg/m^2 q3w for 10 cycles (arm A, n=207) or without D (arm B, n=206). Median follow-up time in the intent to treat population was 31.5 months (0.0-60.2). Median progression free survival (mPFS) in arm A was 25.6 months (range 25.0-27.8) compared to 23.1 months (range 22.6-25.0) for arm B (HR[95%CI]: 1.27 [1.01-1.60], p= 0.044). Although there is a marginal clinical benefit, authors remain skeptical about the results and the question remains in which patients we should give this combination.[1]

Efficacy of radium-223 (Ra-223) + D in metastatic castration-resistant PC (CRPC)

Ra-223 is an approved α-emitter that prolongs survival in mCRPC. Previously, it was demonstrated that Ra-223 + D is safe and well tolerated (ESMO 2014).[2] Here, the effect of Ra-223 + D versus D alone on bone alkaline phosphatase and prostate specific antigen (PSA) dynamics was reported. In this phase I/IIa study, 46 patients with progressing CRPC and ≥ 2 bone metastases were randomized 2:1 to Ra-223 (50 kBq/kg q6w for 5 cycles) + D (60 mg/m^2 q3w for 10 cycles, arm A, n=33) or D (75 mg/m^2 q3w with a step-down option to 60 mg/m^2, arm B, n=13). Median (range) baseline PSA was 99 µg/L (3 µg/L-1000 µg/L) for Ra-223 + D patients and 43 µg/L (4 µg/L-1042 µg/L) for D patients. Although not significant, Ra-223 + D appears to favorably impact post-treatment declines in PSA and normalizes bone alkaline phosphatase concentrations. Due to the small study population, validation of these findings in larger cohorts is warranted.[3]

Combination statin/metformin and effect on PC specific mortality

An association exists between obesity/metabolic syndromes and an increased risk of PC. Recently, the combination of statin and metformin proved less toxic and more effective in inhibiting metastases compared to D in mice.[4] In this population-based study, the association between treatment with statin + metformin and PC specific mortality by obesity/metabolic syndromes status was examined. SEER-Medicare linked data were

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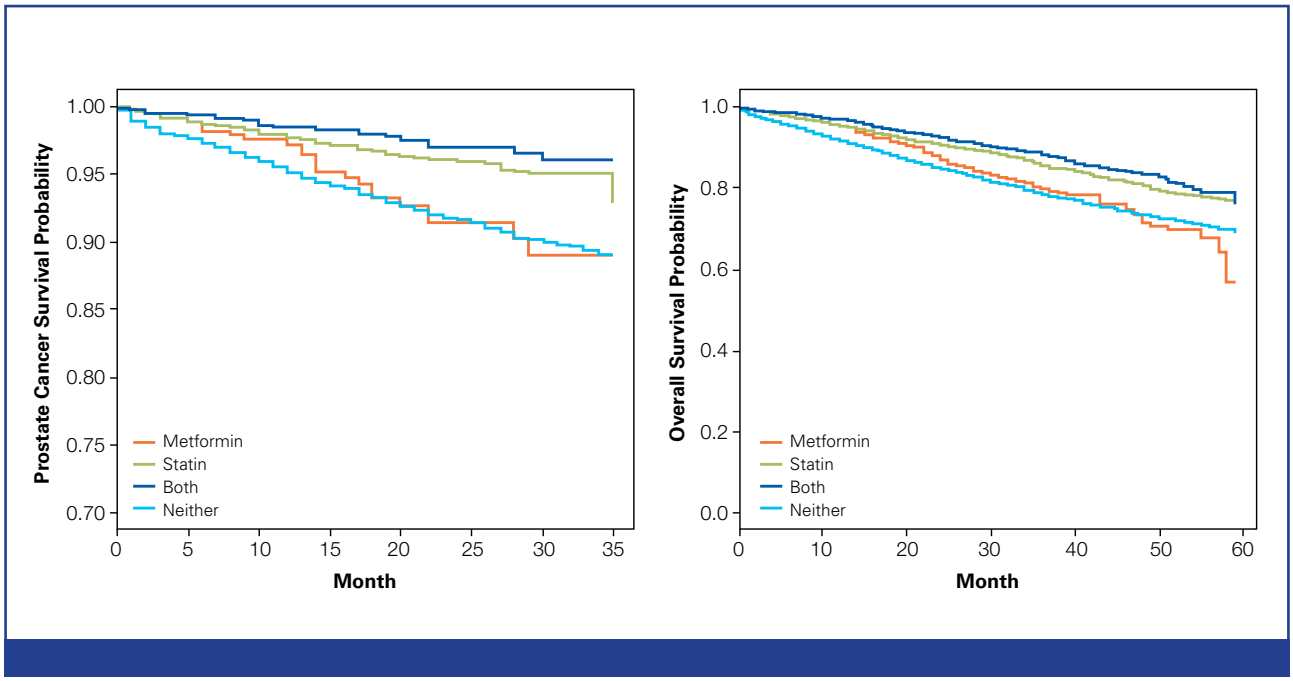

Figure 1. Survival analysis between different types of medication and effect on PC mortality.
A. PC specific mortality showed prolonged survival for patients receiving statin alone or combination statin+metformin.
B. No difference in OS was observed between medication groups.[5]

used to identify 20,972 patients with high-risk PC of which 1,365 died of PC. Use of statin + metformin was associated with a 43% reduction in PC specific mortality compared to patients that did not receive statin+ metformin (HR[95%CI]: 0.57 [0.38–0.87]; *Figure 1*). These results were even more pronounced in patients receiving statin alone when comparing men with obesity/metabolic syndromes (HR[95%CI]: 0.09 [0.01–0.66]) to men without obesity/metabolic syndromes (HR[95%CI]: 0.64 [0.50–0.82]), indicating a potential benefit of statin in this population. No significant difference was observed in overall survival (OS). Further studies are required to confirm these results.[5]

First OS results from the STAMPEDE-trial

Standard of care (SOC) for high-risk locally advanced or mPC is hormone therapy for 3 years or more and radiation therapy for non-metastatic patients. STAMPEDE is a randomised controlled multi-arm multi-stage trial recruiting 2,962 patients with high-risk locally a/mPC that were randomized 2:1:1:1 to SOC (control, n= 1184), SOC+D (75 mg/m^2 q3w for 6 cycles with prednisolone 10mg daily, n=592), SOC+ zoledronic acid (ZA, 4 mg q3w for 6 cycles followed by 4 mg q4w until 2 years, n=593) or SOC+D+ZA (n= 593). At ASCO 2015, primary survival results were reported. Median follow-up time was 42 months. Survival data showed a clinically and statistically significant improvement in OS from adding D but not from adding ZA to SOC, when starting hormone therapy for the first time: HR= 0.76 ([0.63-0.91], P=0.003) for SOC+D; 0.93 ([0.79- 1.11],P=0.437) for SOC+ZA; and 0.81 ([0.68-0.97],P=0.020) for SOC+D+ZA. Median OS was increased from 67 months on SOC to 77 months on SOC+D. Also, a subanalysis for mPC patients revealed that SOC+D improved the OS cohort compared to SOC alone (HR=0.73 [0.59-0.89], P=0.002) increasing OS from 43 to 65 months. These results indicate that docetaxel could be useful in treatment of metastatic PC and even in high-risk non-metastatic disease.[6]

Characterization of neuroendocrine prostate cancer (NEPC) in mCRPC patients

The mechanisms on how PC patients develop resistance to androgen signalling inhibitors such as abiraterone (Abi) or enzalutamide (Enz), are poorly understood. As an increasing percentage of mCRPC patients develop NEPC, this characterization study of NEPC patients was conducted to identify genetic pathways leading resistance to Abi and Enz. Metastasis biopsy was performed in 124 mCRPC patients to determine a NEPC expression signature. Histological differentiation consisted of: 13% small cell cancer, 35% adenocarcinoma,

26% intermediate histology distinct from small cell cancer or adenocarcinoma and 26% mixed histologies or not classifiable. After 22 months of follow-up, the median OS was: not reached with adenocarcinoma, 11.9 months with intermediate histology, and 6.6 months with small cell cancer (P=0.041). RNA data was available on 45 biopsies leading to 50 gene signatures allowing to differentiate small cell from non-small cell cancer (88% accuracy) and adenocarcinoma from non-adenocarcinoma (79% accuracy). This technique provides insight into the biology of NEPC and could possibly lead to a targeted therapy for NEPC.[7]

Timing of ADT in PC patients with rising PSA

The TROG 03.06 and VCOG PR 01-03 collaborative randomized, prospective phase III trial, in PC with PSA relapse after definitive therapy, assessed if a difference in OS existed between patients randomized to receive immediate intervention with ADT (arm B, N=142) compared to those that had a delayed ADT introduction (arm A, N=151). Median follow-up was 5 years. OS was higher in arm B than arm A (p= 0.047), with 5-year survival rates of 85% and 76%, respectively. Also, although not significant, overall risk of death was lower in patients receiving immediate ADT compared to those with delayed intervention (HR[95%CI]: 0.54 [0.27-1.06], p= 0.07). Finally, local and distant disease progression was significantly reduced in arm B (HR [95%CI]: 0.51[0.34,0.76], p= 0.001; and HR[95%CI]: 0.54 [0.32,0.90], p= 0.018; respectively). In conclusion, OS appears to benefit from immediate ADT. As the study is under-powered, more patients are needed to achieve significance for risk of death (overall and due to PC).[8]

Updated response and survival data of anti-PD-L1 in urothelial bladder cancer (UBC)

Immunotherapy, especially anti–PD-L1 therapy, is a hot topic in UBC treatment as PD-L1 may contribute to immune escape in UBC by disturbing peripheral immune homeostasis. This phase Ia study focused on objective response rate (ORR) and survival rates in 92 mUBC patients receiving 15 mg/kg or 1200 mg atezolizumab (anti–PD-L1 antibody) intravenously q3w. Patients were classified as IHC0/1 (N=41) and IHC2/3 (N=46). The ORR was 50% (35%-65%; 9 CRs, 14 PRs) for IHC2/3, and was 17% (7%-32%; 7 PRs) for IHC0/1 patients with median response durations not yet reached in both groups. Patients with visceral metastases had ORRs of 38% [21%-56%] for IHC2/3 (N= 32) and 14% [5%-30%] for IHC0/1 (N=36), respectively. Median progression free survival (PFS) was 6 months (0-18 months) for IHC2/3 patients and 1month (0-14 months) for IHC0/1 patients. Median OS was not reached for IHC2/3 and was 8 months (1-15 months) for IHC0/1 patients. Furthermore, responders had lower myeloid gene expression at baseline (eg Cox-2, IL8; IL1B) and decreased circulating inflammatory and tumor markers. These results confirm that atezolizumab has a durable activity in UBC patients. Phase II and III studies are currently ongoing.[9]

Pembrolizumab (anti–PD-1) in advanced urothelial cancer (aUC): updated results from KEYNOTE-012

Pembrolizumab, an anti–PD-1 antibody, had previously demonstrated antitumor activity and acceptable safety in patients with recurrent or mUC.[10] At the ASCO meeting, the updated efficacy and safety data for this phase Ib, as well as the relationship between PD-L1 expression and ORR, was presented. Thirty-three patients with PD-L1–positive a/mUC received pembrolizumab 10mg/kg q2w until CR, progression, or unacceptable toxicity (evaluated every 8 weeks). Median follow-up was 13 months. Grade 3/4 adverse events occurred in 7 patients (21%). The ORR was 28% (13%-47%, 3 CRs, 5 PRs) for all patients while patients with PD-L1–positive UC achieved an ORR of 38%. Median response duration was not reached and 12-month PFS rate was 19%. Analogous to MPDL3280A, pembrolizumab demonstrated durable antitumor activity in patients with aUC. The relationship between response and predictive biomarkers is currently being assessed.[11]

Eribulin in aUC: results from theNCI/CTEP 7435 trial by the California Cancer Consortium

There is a great need for new agents in aUC. Next to anti–PD-L1 antibodies; it was previously reported that eribulin, a microtubule modulator derived from black Pacific sea sponge toxin, is highly active in treatment-naïve and pretreated mUC patients.[12,13] Here, the results of this single phase II trial were presented. Patients were stratified into 3 cohorts: first-line treatment (arm A, N=52), second-line treatment without tubulin exposure (arm B, N=53), or second-line treatment with tubulin exposure (arm C, N=45). Patients received eribulin 1.4 mg/m^2 intravenously on day 1 and 8 q3w. The most

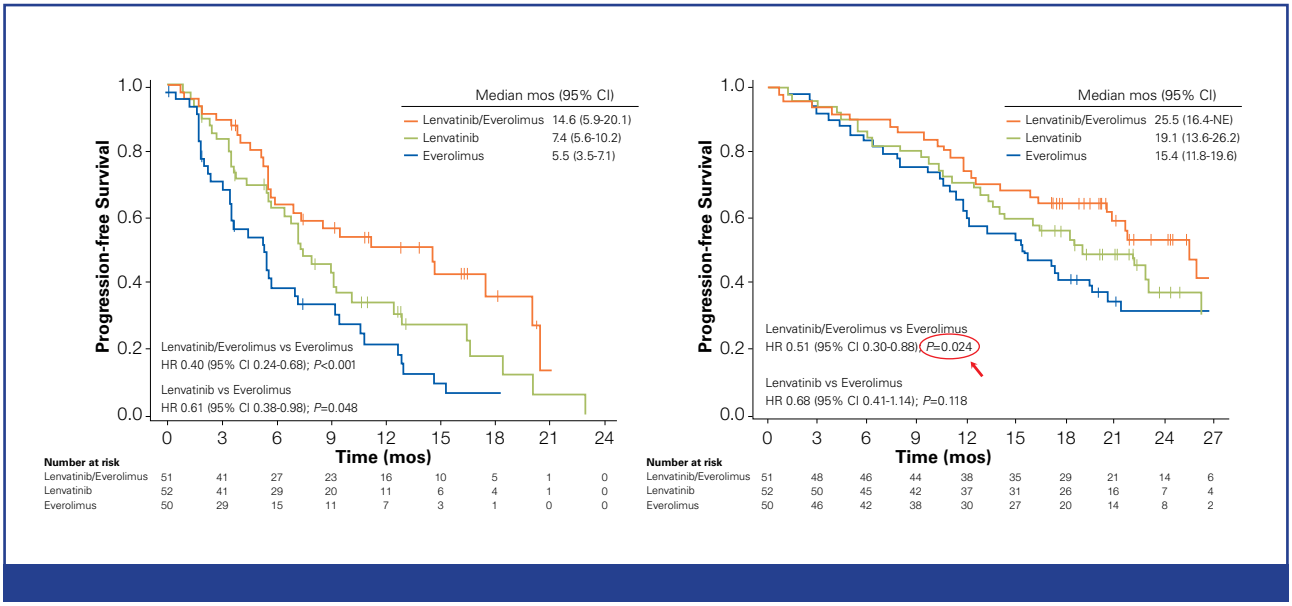

Figure 2. Survival analysis of LEN and EVE in cc mRCC. Kaplan-Meier curves are depicted for A. PFS and B. OS.[15]

common grade 3/4 adverse events were neutropenia (56%), anaemia (21%) and fatigue (7%). Overall responses were: 11 CRs, 41 PRs, 58 SDs and 29 PDs. Median PFS was 4.2 months (3.1-5.6 months), 4.1 months (2.7-6.1 months), and 3.9 months (2.7-5.0 months) for arm A, B, and C; respectively. The median OS was 11.3 months (7.6-18.5 months), 9.7 months (6.2-11.4 months), and 8.4 months (5.3-12.4 months) for arm A, B, and C; respectively. Both PFS and OS were not significantly different between cohorts. These results indicate single agent activity of eribulin in aUC with tolerable toxicities. Phase III evaluation of eribulin is therefore warranted.[14]

Comparative analysis between lenvatinib (LEN), everolimus (EVE), and LEN+EVE in metastatic renal cell carcinoma (mRCC) patients

A phase Ib trial with LEN; a highly potent tyrosine kinase inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT; in combination with EVE has shown manageable toxicity and antitumor activity.[15] This open-label, multicentre phase II trial focused on comparing PFS of LEN+EVE or LEN versus EVE, as well as to determine safety profile, OS and ORR. Progressive VEGF-pretreated clear-cell (cc) mRCC patients were randomized 1:1:1 to LEN 24 mg/day (n=52), EVE 10 mg/day (n=50), or LEN+EVE 18 mg/day+5mg/day (n=51) in 28-day cycles. LEN+EVE and LEN alone prolonged PFS (14.6 and 7.4 months respectively) compared to 5.5 months with EVE (HR[95%CI]= 0.40 [0.24-0.68], p< 0.001; and; HR[95%CI]: 0.61 [0.38-0.98], p= 0.048; respectively) (*Figure 2*). Furthermore, LEN+EVE and LEN improved ORR in comparison to EVE (p< 0.001 and p= 0.007, respectively). The median response duration was longest in the LEN+EVE arm at 13.0 months as compared to 7.5 and 8.5 months in the LEN and EVE treated patients, respectively. Moreover, the median OS was significantly longer in LEN+EVE versus EVE (HR [95%CI]: 0.51 [0.30-0.88], p= 0.024). The combination also showed an acceptable toxicity profile with diarrhoea (20%), hypertension (14%), and fatigue (14%) as most common grade ≥3 adverse events (similar for LEN alone). Due to the promising results of LEN, a randomized phase III trial of the combination LEN+EVE is planned in mRCC patients.[16]

Final clinical results of EVE versus sunitinib (SU) in non ccmRCC (ncc mRCC): ASPEN trial

Although therapeutic models exist for cc mRCC patients, limited evidence exists to guide therapeutic decisions in patients with ncc mRCC. The ASPEN-trial assessed if a difference in PFS could be found when treating ncc mRCC patients (N=108) with EVE or SU. Patient distribution based on histology in this phase II trial was: papillary (65%), chromophobe (15%), or unclassified (20%). Patients were randomized 1:1 to either EVE (N=57) or SU (N=51) until progression. Median PFS for SU was 8.3 months (5.8-11.1 months) compared to 5.6 months (5.5-6.0 months) for EVE (HR[95%CI]: 1.41 [1.03-1.92], p= 0.160 with α=20%). The same effect was

Key messages for clinical practice

1. Firstly, the role of docetaxel as adjuvant therapy with other prostate cancer treatment (Radium-223 or androgen deprivation therapy) seems favorable. Also, an elevated percentage in neuro-endocrine prostate cancers leads to an increased interest in this type of cancer treatment.
2. Secondly, the revival of immunotherapy, by means of PD-L1–inhibition, is clearly ongoing in urothelial cancers with encouraging results. Furthermore, eribulin shows promising effect in the treatment of advanced urothelial carcinoma.
3. Lastly, the new potent target agent lenvatinib (combined with everolimus) is clearly favored in the treatment of metastatic renal cell cancer. Further research in this field is warranted. Moreover, research is conducted to enhance therapy of patients with non-clear cell renal cell carcinoma, showing chromofobe cancers more sensitive to mTOR inhibitors.

noted for papillary mRCC, but not for chromophobe mRCC. Interestingly, SU performed better in good risk patients (median PFS = 14.0 months versus 5.7 months for EVE; HR[95%CI]: 3.07 [1.51-6.28]) while EVE prolonged PFS in poor risk ncc mRCC patients (median PFS = 6.1 months in comparison to 4.0 months for SU; HR[95%CI]: 0.21 [0.06-0.69]). Manageable toxicity was observed with highest toxicity in the SU cohort. These results might allow for an mTOR first-line setting in ncc mRCC, in case of chromophobe and poor risk mRCC patients, although new agents are needed for this population of patients.[17]

Sorafenib (SO) or SU as adjuvant therapy for unfavorable RCC: result of the ASSURE trial

This ECOG-ACRIN-led, NCTN phase III trial determined if a difference existed in drug dosing, toxicity and outcome when starting doses of SO and SU were reduced in patients with completely resected locally aRCC. A total of 1.943 patients were enrolled and randomized 1:1:1 to SU 50mg/day q4/6w (N=647), SO 800mg/day (N=649) or PB (N=647) for up to 1 year. For 1.322 patients, starting doses of SU and SO were reduced from 50mg to 37.5mg (25%) and from 800mg to 400mg (50%), respectively, with mandatory escalation to full dose after the first 2 cycles when tolerated. Three-month patient discontinuation rates from adverse events or refusal was 25% for SU and 30% for SO when receiving full dose. The redesign significantly reduced the 3-month patient discontinuation rates to 17% (p= 0.01) and 11% (p< 0.001), respectively, without difference in total dose over 1 year for both groups. Furthermore, no difference in overall 5-year disease-free survival (DFS) was observed for SU (53.8% [49.0%-59.1%]) or SO (52.8% [48.0%-58.0%]) compared to placebo (55.8% [51.2%-60.9%]; HR[95%CI]: 1.01 [0.83-1.23] and HR[95%CI]: 0.98 [0.81-1.20], respectively). These data raises the concern about the differential effects of multi-kinase inhibitors across a range of doses and contradict the use of SO or SU as adjuvant therapy in locally aRCC.[18]

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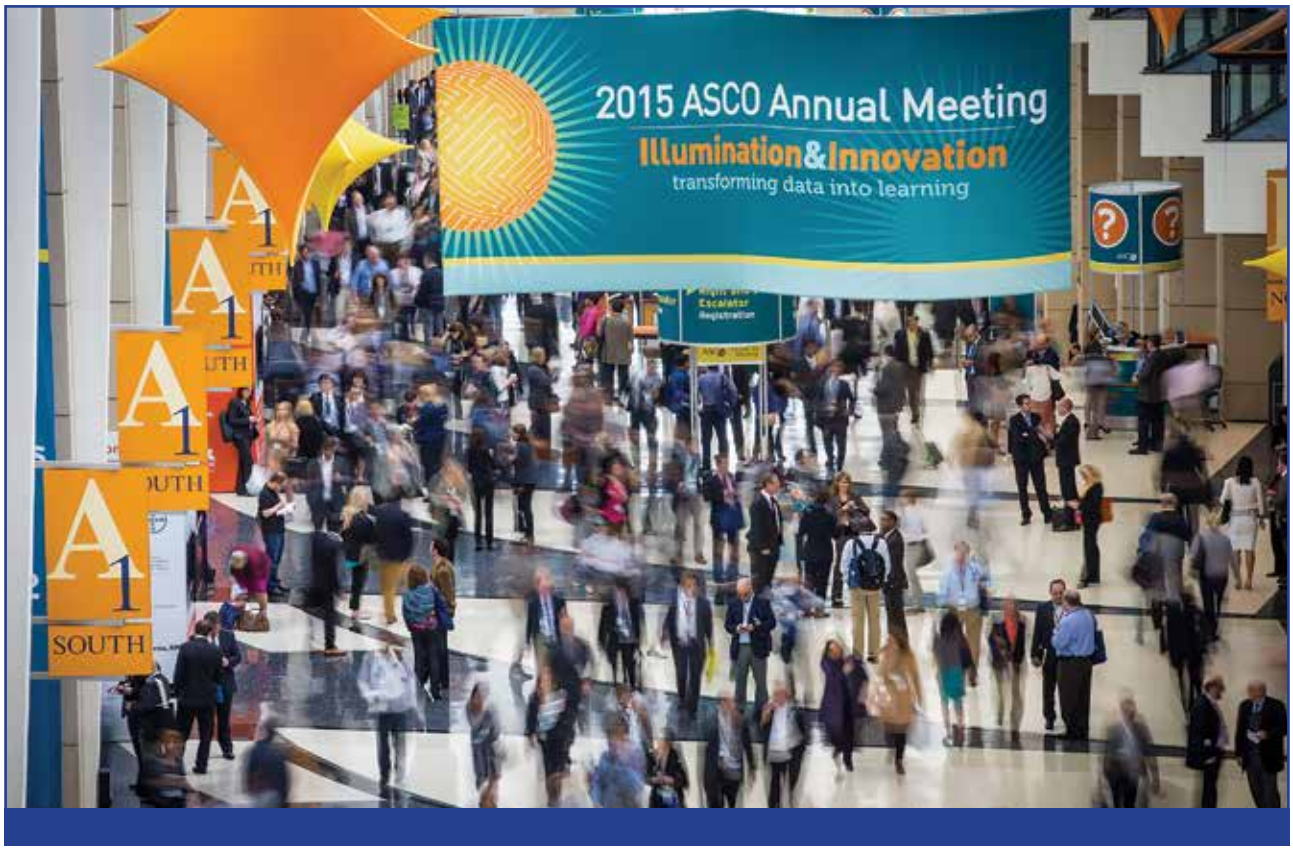

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